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The Chemistry of Carbanions. XIV. Factors Influencing the Rate of Addition of Dimethylmagnesium to Benzophenone[1]

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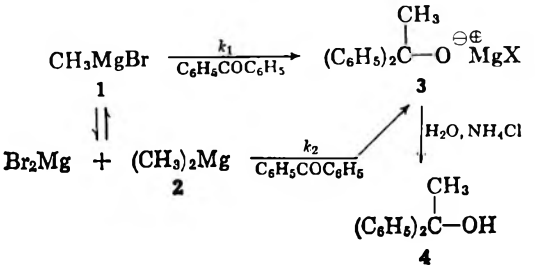
The rate of reaction of benzophenone with dimethylmagnesium in ether solution has been found to fit the bimolecular kinetic expression rate = $k_2[Me_2Mg][C_6H_5COC_6H_5]$. The addition of donor ligands to the reaction mixture may either accelerate or retard the rate of this addition reaction. The most effective additives are bidentate ligands such as N,N,N′,N′-tetramethylethylenediamine (**25**, retards the rate of addition) and β-methoxyethyldimethylamine (**28**, accelerates the rate of addition) which form 1:1 complexes with dimethylmagnesium in ether solution. The data are interpreted as indicating that addition occurs *without* a prior dissociation of the ligands from dimethylmagnesium. Instead, the addition is suggested to proceed *via* a transition state (or an intermediate) involving a pentacoordinated magnesium species such as structure **32**.

Although a number of studies of rate of reaction of Grignard reagents with ketones have been published,[2,3] there remains a striking diversity of opinion as to how these data should be interpreted. These difficulties in interpretation arise, at least in part, from the facts that most, if not all, Grignard reagents (*e.g.*, **1**) are in rapid equilibrium with the corresponding dialkyl- or diarylmagnesium compounds (*e.g.*, **2**)[4] and both magnesium reagents (*e.g.*, **1** and **2**) are probably capable of addition to carbonyl functions to form alkoxides (*e.g.*, **3**). Furthermore, there is general agreement[2] that the addition of dialkylmagnesium reagents to ketones is more rapid than addition of the corresponding alkylmagnesium halides (*i.e.*, $k_1 < k_2$ in Scheme I). Consequently, many supposed studies of the addition of alkylmagnesium halides may in fact be studies of only the addition of dialkylmagnesium compounds or of some combination of two different addition reactions.

SCHEME I



In continuing our study of this reaction, we have chosen to bypass the question of whether the dialkylmagnesium, the alkylmagnesium halide, or both of them are the actual reactants. Instead, we have focused our attention on the reaction of dimethylmagnesium with benzophenone. In ether solution, dimethylmagnesium,[4b] like diethylmagnesium[3d,3e,4a,5] is monomeric in the concentration range up to 0.1–0.2 *M* so that the additional complication of association to larger molecular aggregates seen[3d,3e,4a,5] with alkylmagnesium halides and magnesium halides is also avoided. Both earlier work[2] and the present study have established that the "methylmagnesium alkoxides"[4b] formed from reaction of equivalent amounts of

(1) This research has been supported by Grant No. AF-AFOSR-573 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research.

(2) For examples, see (a) J. G. Aston and S. A. Bernhard, *Nature*, **165**, 485 (1950); (b) N. M. Bikales and E. I. Becker, *Can. J. Chem.*, **41**, 1329 (1963); (c) M. Anteunis, *J. Org. Chem.*, **26**, 4214 (1961); *ibid.*, **27**, 596 (1962); (d) R. D'Hollander and M. Anteunis, *Bull. Soc. Chim. Belges*, **74**, 71 (1965); (e) H. O. House and D. D. Traficante, *J. Org. Chem.*, **28**, 355 (1963); (f) A. V. Tuulmets, *Kinetika i Kataliz*, **5**, 71 (1964); (g) A. V. Tuulmets, *Reaktsionnaya Sposobnost Organ. Soedin. Tartusk. Gos. Univ.*, **1**, 89, 196, 212, 220 (1964); *Chem. Abstr.*, **61**, 11,866, 13,154, 13,155 (1964); (h) A. V. Tuulmets, *ibid.*, **2**, 391 (1965); *Chem. Abstr.*, **65**, 3691 (1966); (i) T. Holm, *Acta Chem. Scand.*, **19**, 1819 (1965); *ibid.*, **20**, 1139 (1966); (j) T. Holm, *Tetrahedron Lett.*, No. 28, 3329 (1966); (k) S. G. Smith and G. Su, *J. Amer. Chem. Soc.*, **88**, 3995 (1966); (l) S. G. Smith and G. Su, *Tetrahedron Lett.*, 4417 (1966); (m) S. G. Smith and J. Billet, *J. Amer. Chem. Soc.*, **89**, 6948 (1967); (n) E. C. Ashby, R. B. Duke, and H. M. Neumann, *ibid.*, **89**, 1964 (1967); (o) M. Oki, M. Hirota, H. Satonaka, and T. Hagiwara, *Tetrahedron Lett.*, 1785 (1967); (p) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(3) For recent reviews including this subject, see (a) R. M. Salinger in "Survey of Progress in Chemistry," Vol. 1, A. F. Scott, Ed., Academic Press Inc., New York, N. Y., 1963, pp 301–324; (b) B. J. Wakefield, *Organometal. Chem. Rev.*, **1**, 131 (1966); (c) W. Tochtermann, *Angew. Chem. Intern. Ed. Engl.*, **5**, 351 (1966); (d) R. E. Dessy and W. Kitching in "Advances in Organometallic Chemistry," Vol. 4, F. G. A. Stone and R. West, Ed., Academic Press Inc., New York, N. Y., 1966, pp 280–289; (e) E. C. Ashby, *Quart. Rev.* (London), **21**, 259 (1967).

(4) (a) M. B. Smith and W. E. Becker, *Tetrahedron*, **22**, 3027 (1966); (b) H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, **32**, 2481 (1967).

(5) (a) A. D. Vreugdenhil and C. Blomberg, *Rec. Trav. Chim.*, **82**, 453 (1963); (b) E. C. Ashby and M. B. Smith, *J. Amer. Chem. Soc.*, **86**, 4363 (1964).

TABLE I

RATES OF ADDITION OF DIMETHYLMAGNESIUM TO BENZOPHENONE IN ETHER SOLUTION

Me_2Mg concn, M	$C_6H_5COC_6H_5$ concn, M	% reaction after 0.14 sec at *ca.* 25°	k_2,[a] M^{-1} sec^{-1}	$10^{-2}k_3$,[b] M^{-2} sec^{-1}	k_1, sec^{-1} [c]	k_1', sec^{-1} [d]
0.048	0.024	14	23	4.2	0.46	0.95
0.072	0.024	16	17	2.8	0.41	1.3
0.096	0.024	20	17	2.0	0.40	1.7
0.144	0.024	26	15	1.1	0.31	2.1
0.192	0.024	34	16	0.85	0.31	2.9
0.384	0.024	63	19	0.48	0.30	7.0
0.096	0.012	25	22	2.3	0.23	2.0
0.096	0.036	25	23	3.9	0.70	2.6
0.096	0.048	25	23	2.6	0.96	2.1
0.158	0.083	32	19	1.4	1.3	2.7
0.198	0.104	39	20	1.2	1.7	3.6
0.258	0.135	46	20	0.92	2.0	4.4
		Average	20 ± 2	1.8 ± 0.9	0.76 ± 0.5	2.8 ± 1

[a] Rate = $k_2[Me_2Mg][C_6H_5COC_6H_5]$. [b] Rate = $k_3[Me_2Mg]^2[C_6H_5COC_6H_5]$. [c] Rate = $k_1[Me_2Mg]$. [d] Rate = $k_1'[C_6H_5COC_6H_5]$.

ketone and dimethylmagnesium are substantially less reactive in addition reactions than the starting dimethylmagnesium. Therefore, by limiting our studies to reactions of benzophenone with at least a twofold molar excess of dimethylmagnesium, we believe that we are studying the process by which a methyl group is transferred from dimethylmagnesium to benzophenone without serious competition from other reactions.

Our rate studies utilized the previously described[2e,p] flow reactor in which ether solutions of benzophenone and dimethylmagnesium were mixed in a capillary tube and then quenched 0.14 sec after mixing. Gas chromatographic analysis of the quenched reaction mixture provided a measure of the amount of carbinol **4** produced. By utilizing various initial concentrations of reactants, the data summarized in Table I were obtained. Among the simple kinetic expressions, which might be written for this reaction, our data fit best the simple bimolecular relationship (eq 1) rather

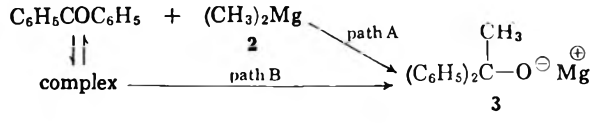
$$\text{rate} = k_2[CH_3MgCH_3][C_6H_5COC_6H_5] \quad (1)$$

than a dependence on only the concentration of one reactant or on a higher order in one of the reactants. Although other, more elaborate kinetic expressions could probably be derived which would fit our data, we question that the quality of our data justifies such treatments. In particular, our measurements were necessarily performed under adiabatic conditions with the result that the reaction temperatures could not be controlled after the reactants were mixed.[6]

The same type of first-order kinetic dependence on each of the reactants has been observed for the reaction of dimethylmagnesium with benzophenone in tetrahydrofuran solution[2b] and with 4-methylmercaptoacetophenone.[2m] In another study of the reaction of benzophenone with dimethyl magnesium in an ether–benzene mixture,[2c] an order higher than one was suggested for the dimethylmagnesium dependence. These data, which did not appear to fit any simple kinetic relationship, suffered from several deficiencies[2b] including the use of *almost* equal concentration of reactants so that all of the rate constant calculations employed the small differences between two relatively large numbers. In all cases,[2b,c,e,i,m] there appears to be agreement that the reaction rate is dependent on both the concentration of the dialkylmagnesium and the concentration of the ketone. We believe the present data are most consistent with the presence of one molecule of the dialkylmagnesium compound and one molecule of ketone in the rate-limiting step of this addition reaction.

Even in the early discussions[3e,7] of the mechanism of addition of organomagnesium compounds to ketones, the idea was often expressed that the organometallic reagent and the ketone formed an intermediate complex which then underwent further reaction to form the alkoxide product (*e.g.*, **3**). Only very recently has there been quantitative evidence[2i–m] for the extremely rapid formation of a complex between organomagnesium reagents and ketones. Many workers[2c,2e,8] have observed the formation of transient colors which appeared to persist in reaction mixtures only as long as both unchanged organomagnesium reagent and unchanged ketone were present in the reaction. However, early claims to have isolated intermediate complexes as precipitates have been refuted.[2b,9] The general questions raised by observation of transient complexes in this reaction mixture (illustrated in Scheme II) are about the actual nature of

SCHEME II



these complexes and whether these complexes are intermediates in product formation (*i.e.*, path B) or if they are merely side equilibria competing with the formation of the product (*i.e.*, path A). Since the formation of these spectroscopically (and sometimes

(6) As a result, all of our "per cent reaction at 25° " measurements (Tables I–III) are influenced by a systematic error which causes them to be too large. The reported[2b] value of the activation energy for reaction of benzophenone with methylmagnesium bromide is 10–13 kcal/mol and the maximum temperature rise for complete reaction with solutions more concentrated than those employed in this study was 10°.[2e] From these data we estimate that none of our data is too large by more than a factor of 1.5. Since most of our measurements involved reactions which proceed only 20–40% to completion, the actual systematic error in these measurements is probably substantially smaller and remains relatively constant.

(7) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp 138–142.

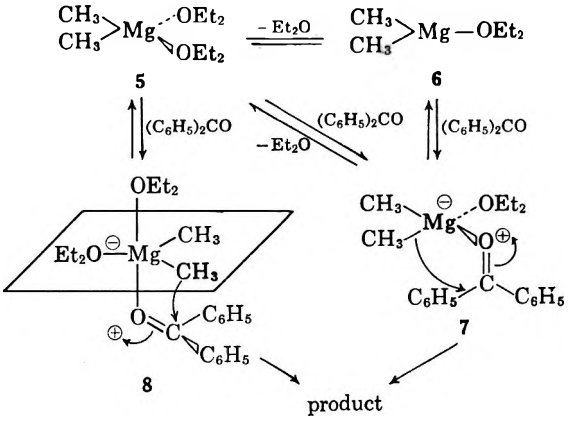
(8) (a) H. Gilman and R. E. Fothergill, *J. Amer. Chem. Soc.*, **51**, 3149 (1929); (b) R. MacLeod and coworkers, "Petroleum Research Fund Reports," 1959, p 93; 1961, p 50.

(9) D. O. Cowan and L. A. Dolak, *J. Org. Chem.*, **31**, 4296 (1966).

visually) observable complexes is much faster[2i-m] than the formation of addition products (*i.e.*, **3**), a rigorous differentiation between these possibilities will be exceedingly difficult.[10]

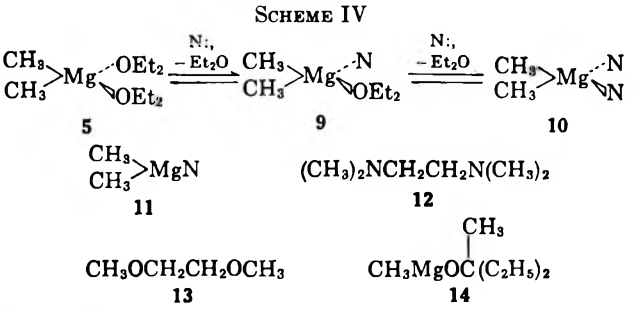
However, it did appear possible to get information about whether it was necessary to dissociate one[11] of the solvent ligands from the organomagnesium reactant[12,13] (*e.g.*, **5** → **6** → **7** in Scheme III) prior to addition.

SCHEME III



Alternative possibilities would involve formation of a pentacoordinate intermediate[14] such as **8** without loss of one of the initial solvating ligands, or the direct displacement of one of the ligands by the ketone (*i.e.*, **5** → **7**) without the intervention of the tricoordinate species **6**. We have noted earlier[4b] that the rate of exchange of alkyl groups between two different dialkylmagnesium derivatives can be retarded substantially by the addition of materials which are better donor ligands than diethyl ether. Addition of the same materials has been found to enhance the rate of reaction of organomagnesium compounds with alkyl halides,[15] and to retard the rate of abstraction of the acidic hydrogen atom from terminal acetylenes.[16]

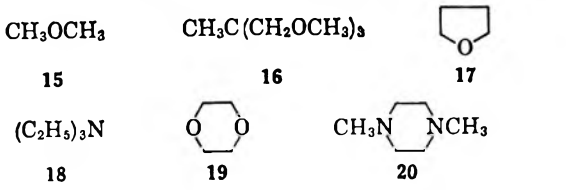
SCHEME IV



The addition of these donor ligands (*e.g.*, N: in Scheme IV) presumably favors the formation of coordination complexes such as **9** and **10** and reduces the probability of forming tricoordinated magnesium species such as **6** and **11**. In the case of certain bidentate ligands such as **12** and **13** it has been possible to isolate crystalline complexes corresponding to structure **10** from ether solutions.[13a,17] It appears reasonable to expect that reactions which require prior dissociation of one of the ligands bound to magnesium will be retarded by the presence of these good donor ligands since the concentration of partially coordinated forms such as **6** and **11** will be lowered. Reactions which do not require such prior dissociation may be accelerated by such ligands especially in cases where the C–Mg bond is undergoing heterolytic cleavage in the sense that $Mg-CH_3 \rightarrow Mg^{\oplus}CH_3^{\ominus}$.

With this view in mind we have examined the effect on the rate of addition of excess dimethylmagnesium to benzophenone in ether solution, when a number of additives have been added in concentrations comparable to the concentration of the organometallic reagent. The data are summarized in Table II along with the corresponding data for the reaction with methylmagnesium bromide and with the previously studied[4b,18] methylmagnesium alkoxide **14**.

In general, the donor ligands studied fell into three classes. The ligands **15**–**20**, which probably all function as monodentate ligands under the conditions studied,[19] had little if any effect when only 1–2 mol of the material was present per mole of the magnesium reagent. Although the addition of a 50- to 100-fold excess of tetrahydrofuran did retard the rate of addition significantly,[2j] it is not clear how much of this effect is to be attributed to a change in the bulk properties of the solvent, rather than to a change in the donor ligands surrounding magnesium. The second group of additives studied, **21**–**24**, had various effects (see Experimental Section) but all suffered from the defect that insoluble materials were formed when these materials were added to ethereal solutions of dimethylmagnesium. Consequently, we were unable to examine the effects of these materials over a useful range of



(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, pp 127–194.

(11) W. French and G. F. Wright [*Can. J. Chem.*, **42**, 2474 (1964)] have presented evidence that at least one ether ligand is present in the transition state by demonstrating induced asymmetry in the product from dimethylmagnesium and benzaldehyde when an optically active ether was used as part of the solvent.

(12) The presently available X-ray data suggest that each magnesium atom in organomagnesium reagents is normally surrounded by four ligands arranged tetrahedrally around the metal atom. See (a) E. Weiss, *J. Organometal. Chem.*, **2**, 314 (1964); (b) G. Stucky and R. E. Rundle, *J. Amer. Chem. Soc.*, **85**, 1002 (1963); **86**, 4821, 4825 (1964); (c) L. J. Guggenberger and R. E. Rundle, *ibid.*, **86**, 5344 (1964).

(13) The stoichiometries and molecular weights of the amine and ether complexes derived from organomagnesium compounds are also consistent with the idea that these substances are normally tetracoordinate: (a) G. E. Coates and J. A. Heslop, *J. Chem. Soc., Sect. A*, 26 (1966); (b) G. E. Coates and D. Ridley, *J. Chem. Soc.*, 56 (1967).

(14) Although the organomagnesium compounds appear normally to exist as tetracoordinate species[12,13] the existence of hexacoordinate derivatives of magnesium with octahedral symmetry has been demonstrated for the magnesium halide hexahydrates [R. W. G. Wyckoff, "Crystal Structures," Vol. 3, 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1965, p 785] and suggested for the magnesium cation solvated with methanol [S. Nakamura and S. Meiboom, *J. Amer. Chem. Soc.*, **89**, 1765 (1967)]. In an oxymagnesium bromide–ether complex, each magnesium atom is pentacoordinate (ref 12b). Also the magnesium atom in porphyrins is believed to be pentacoordinate: J. N. Phillips, "Comprehensive Biochemistry," Vol. 9, M. Florkin and E. H. Stotz, Ed., Elsevier Publishing Co., New York, N. Y., 1963, pp 34–72.

(15) (a) L. I. Zakharkin, O. Y. Okhlobystin, and B. N. Strunin, *J. Organometal. Chem.*, **4**, 349 (1965); (b) L. I. Zakharkin, O. Y. Okhlobystin, and K. A. Bilevitch, *Tetrahedron*, **21**, 881 (1965); (c) H. F. Ebel and R. Schneider, *Angew. Chem. Intern. Ed. Engl.*, **4**, 878 (1965).

(16) J. H. Wotiz and G. L. Prcffitt, *J. Org. Chem.*, **30**, 1240 (1965).

(17) L. I. Zakharkin, *J. Gen. Chem., USSR*, **34**, 3166 (1964).

(18) H. O. House and W. L. Respess, *J. Org. Chem.*, **30**, 301 (1965).

(19) We presume that for reasons of unfavorable geometry the triether **16** and the heterocycles **19** and **20** are not apt to function as bidentate ligands when an excess of a second donor solvent, diethyl ether, is present.

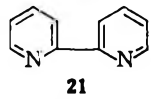
TABLE II

RATES OF ADDITION OF METHYLMAGNESIUM DERIVATIVES TO BENZOPHENONE IN THE PRESENCE OF VARIOUS ADDITIVES

Organometallic reagent (concn, *M*)	Additive (concn, *M*)	Concn of benzophenone, *M*	% reaction after 0.14 sec at *ca.* 25°
Me_2Mg (0.047)[a]		0.024	22
Me_2Mg (0.047)[a]	THF (**17**, 0.047)	0.024	19[b]
	THF (**17**, 0.094)		20[b]
	THF (**17**, 0.23)		17[b]
	THF (**17**, 0.47)		16[b]
	THF (**17**, 2.3)		6[b]
	THF (**17**, 4.7)		3[b]
Me_2Mg (0.053)[a]	Me_2O (**15**, 0.051)	0.024	20[b]
	Me_2O (**15**, 0.15)		23[b]
	Me_2O (**15**, 0.20)		24[b]
Me_2Mg (0.047)[a]	Triether **16** (0.047)	0.024	20
	Triether **16** (0.094)		23
Me_2Mg (0.055)[a]		0.038	36[b]
Me_2Mg (0.055)[a]	Et_3N (**18**, 0.73)	0.038	38[b]
Me_2Mg (0.047)[c]		0.024	15
Me_2Mg (0.047)[c]	Dioxane (**19**, 0.047)	0.024	15
Me_2Mg (0.047)[c]	Diamine (**20**, 0.047)	0.024	15
Me_2Mg (0.047)[c]	Triamine **23** (0.024)	0.024	30[b,d]
	Triamine **23** (0.047)		30[b,d]
	Triamine **23** (0.094)		14[e]
Me_2Mg (0.055)[c]	Triether **22** (0.055)	0.024	17[d]
Me_2Mg (0.047)[a]	HMP (**24**, 0.023)	0.024	36
	HMP (**24**, 0.047)		56–67
	HMP (**24**, 0.070)		74[b]
	HMP (**24**, 0.094)		38–67[e]
	HMP (**24**, 0.18)		11–14[e]
$MeMgOC(C_2H_5)_2$[c] (0.037)		0.024	1.7
MeMgBr (0.047)		0.024	1.5
MeLi (0.050)	$MgBr_2$ (0.025)	0.024	30
MeLi (0.050)	$MgBr_2$ (0.028)	0.024	26
Me_2Mg (0.047)[a]	DME (**27**, 0.047)	0.024	29
	DME (**27**, 0.094)		29
	DME (**27**, 0.23)		45
	DME (**27**, 0.47)		54
Me_2Mg (0.047)[a]	Diamine **25** (0.012)	0.024	20
	Diamine **25** (0.023)		15
	Diamine **25** (0.037)		15
	Diamine **25** (0.047)		7
	Diamine **25** (0.094)		7
	Diamine **25** (0.23)		7
Me_2Mg (0.055)[c]	Amino ether **26** (0.055)	0.024	3[b]
	Amino ether **26** (0.11)		3[b]
Me_2Mg (0.038)[c]		0.024	13[b]
Me_2Mg (0.038)[c]	Amino ether **28** (0.018)	0.024	29[b]
	Amino ether **28** (0.028)		37[b]
	Amino ether **28** (0.038)		36
	Amino ether **28** (0.055)		45
	Amino ether **28** (0.075)		40
	Amino ether **28** (0.15)		40[b]
	Amino ether **28** (0.18)		41[b]
	Amino ether **28** (0.37)		36[b]

[a] This dimethylmagnesium solution was from preparation no. 1. [b] These data were obtained from a single run. [c] This dimethylmagnesium solution was from preparation no. 2. [d] In this experiment the reacting solutions were mixed rapidly before a precipitate began to form in the organomagnesium solution. [e] In this experiment, a precipitate began to form in the organomagnesium solution before the reactants could be mixed.

concentrations. The final group of additives were the bidentate ligands, **25**–**28**, which differed from the earlier additives, **15**–**20**, in that the addition of 1–2 mol of these materials per mole of dimethylmagnesium had a substantial effect on the rate of addition but addition of excess material produced relatively little if any further change. These observations argue strongly, as do the isolation experiments,[13a,17] that these additives, **25**–**28**, have converted the dimethylmagnesium largely into the monomeric[13a] complexes such as **29**–**31** when even 1 molar equiv of the additive was present in ether solution. The two diamine additives **25** and **26** retarded the rate of addition by about a factor of 4 while the ethereal additives **27** and **28** accelerated the rate of addition by a factor of 2–3. The ability of added 1,2-dimethoxyethane to enhance the rate of addition of methylmagnesium bromide has been noted previously.[2p] A brief investigation (Table III) of



21

$CH_3OCH_2CH_2OCH_2CH_2OCH_3$

22

23

$[(CH_3)_2N]_3P{=}O$

24

$(CH_3)_2NCH_2CH_2N(CH_3)_2$

25

$(CH_3)_2NCH_2CH_2OCH_2CH_2N(CH_3)_2$

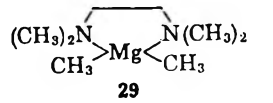
26

$CH_3OCH_2CH_2OCH_3$

27

$CH_3OCH_2CH_2N(CH_3)_2$

28



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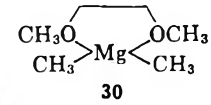

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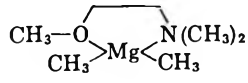


31

TABLE III

RATES OF ADDITIONS OF THE COMPLEX FROM DIMETHYLMAGNESIUM AND β-METHOXYETHYLDIMETHYLAMINE (**28**) TO BENZOPHENONE IN ETHER SOLUTION

Concn of Me_2Mg + $CH_3OCH_2CH_2N(CH_3)_2$, *M*	PhCOPh concn, *M*	% reaction after 0.14 sec at *ca.* 25°	$10^{-2}k_2$,[a] M^{-1} sec^{-1}	k_1,[b] sec^{-1}
0.038	0.024	36	1.0	1.9
0.038	0.018	39	1.1	1.5
0.038	0.012	39	1.0	0.95

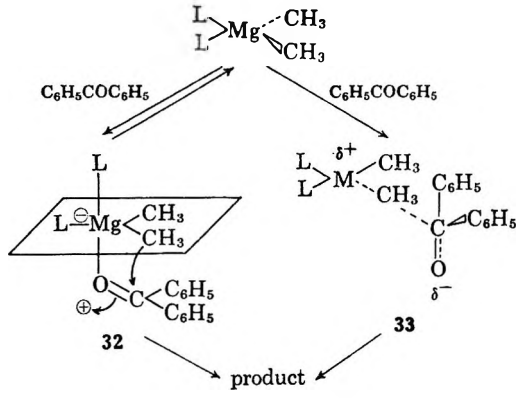
[a] Rate = k_2[Me_2Mg complex][$C_6H_5COC_6H_5$]. [b] Rate = k_1[Me_2Mg complex].

the effect of concentration changes on the rate of addition in the presence of the amino ether **28** indicated that the reaction was still following bimolecular kinetics rather than an alternative process dependent on the concentration of only one of the reactants. In an accompanying study of the stereochemistry of the addition process,[20] the relative proportions of *cis* and *trans* isomers produced from the addition of an ethereal solution of dimethylmagnesium to the carbonyl group of 5-methyl-2-cyclohexenone were essentially the same irrespective of whether the reaction was run without an additive or in the presence of the diamine **25** or the amino ether **28**.

The foregoing data are most consistent with the idea that addition of the dimethylmagnesium to ketones follows the same general reaction path irrespective of whether the ligands bound to magnesium are two ether molecules (*i.e.*, **5**) or a bidentate ligand (*e.g.*, **29**–**31**). However, the activation energy for the transfer of a methyl group from magnesium to the carbon atom of the carbonyl group is altered by the nature of the donor ligands bound to magnesium. As a result the methyl transfer can either be accelerated or retarded when the ether ligands are replaced by other species. These observations then argue that the donor

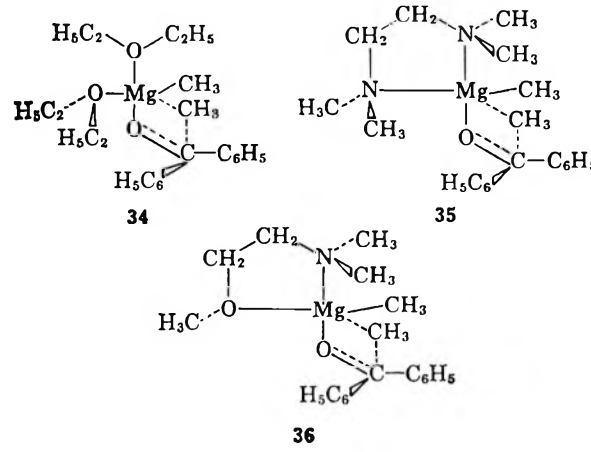
(20) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).

ligands are *not* dissociated from the magnesium prior to ketone addition (as in **5** → **6** → **7** in Scheme III) but rather that the addition involves a pentacoordinate intermediate (as in **8** and **32**), the direct displacement of a donor ligand by the ketone (*i.e.*, **5** → **7**), or the transfer of a methyl group to the carbonyl carbon atom without concurrent association of the oxygen and magnesium atoms (as in **33**). We regard the process **33**



as unlikely for two reasons. In the relative nonpolar reaction medium employed, formation of the indicated alkoxide ion without aid from solvation by a second magnesium species seems unlikely. This alternative process would also suggest that the configuration of the alkyl group should be inverted during its transfer to the carbonyl carbon atom. Although we do not yet have direct evidence bearing on the stereochemical outcome of adding an alkylmagnesium reagent to a ketone, both the addition of a cyclopropylmagnesium derivative to carbon dioxide[21] and the transfer of a primary alkyl group from one magnesium atom to another[4b] are known to occur with retention of configuration. It seems likely that a comparable stereochemical result will be found for the ketone addition. Our data do not allow a choice to be made between the formation of a pentacoordinate intermediate (*e.g.*, **32**) and the direct displacement of a donor ligand to form a tetrahedral intermediate (*e.g.*, **5** → **7**). However, the observations[2i-m] indicating a rapid formation of a ketone–organomagnesium complex followed by the rate-limiting formation of the addition product appear to us to be more consistent with the formation of a pentacoordinate intermediate such as **32** in which no bond breaking is required. Subsequent rate-limiting decomposition of this pentacoordinate intermediate would then yield the tetracoordinate addition product.

The reasons for the differing rates of reaction (retarded with **29** and accelerated with **30** and **31**) when the bidentate complexes are employed as reactants are open to speculation. However, it is appropriate to note that in pentacoordinate transition states **34**–**36** for the transfer of a methyl group to benzophenone, both the diethyl ether ligands in **34** and the relatively rigid diamine ligand in **35** have alkyl groups which may interfere sterically with the approach of the benzophenone. By contrast, the amino ether complex in **36** has a conformation in which the O-methyl group lies away from the direction of approach of the benzophenone. The same possibility exists for the 1,2-dimethoxyethane com-



plex **30** which was also found to add to benzophenone more rapidly than the diethyl ether complex **5**.

Experimental Section[22]

Preparation of Reagents.—Ethereal solutions of dimethylmagnesium were prepared from dimethylmercury and triply sublimed magnesium and standardized by reaction with dimethylphenylsilyl chloride.[23] Ethereal solutions of methyllithium and of methylmagnesium bromide were either commercial samples or were prepared by the reaction of methyl bromide with lithium or triply sublimed magnesium and standardized by the same procedure.[23] Benzophenone was recrystallized from aqueous ethanol, dried under reduced pressure, and sublimed, mp 48–49°. Reagent samples of ether and tetrahydrofuran (**17**) were distilled from $LiAlH_4$ prior to use. 1,2-Dimethoxyethane (**27**) was refluxed with sodium overnight and then distilled and redistilled from $LiAlH_4$. N,N,N′,N′-Tetramethylethylenediamine (**25**) was distilled and then redistilled from $LiAlH_4$, bp 120–121°. Hexamethylphosphoramide (**24**) was stirred over molecular sieves (Linde type 4A) for 2 days, and then filtered, stirred with sodium overnight, and distilled under reduced pressure, bp 67° (0.6 mm). Bis(N,N-dimethylaminoethyl) ether (**26**, obtained from Union Carbide Chemicals Corp., Charleston, W. Va.) was stirred overnight with BaO and then distilled, bp 77–78° (12–13 mm). A sample of the triamine **23** was distilled, from $LiAlH_4$ and then redistilled, bp 80° (12 mm). The triether **22** was stirred successively over KOH and BaO and then distilled and redistilled from $LiAlH_4$, bp 65° (20 mm). N,N′-Dimethylpiperazine (**20**) was distilled from $LiAlH_4$, bp 128–130°. Dioxane (**19**) was refluxed over KOH, distilled, and redistilled from $LiAlH_4$, bp 100.5°. The material was degassed by five cycles of freezing and thawing at 0.1 mm and then used promptly. 2,2′-Bipyridyl (**21**) was crystallized from hexane and then dried under reduced pressure, mp 70.5–71°. Triethylamine (**18**) was distilled from $LiAlH_4$, bp 88–89.5°. Dimethyl ether was distilled from a commercial cylinder (Matheson) into a cold trap under a nitrogen atmosphere.

A mixture of 100 ml of aqueous 37% formaldehyde and 100 ml of aqueous 90% formic acid was added, dropwise and with stirring, to 25.0 g of 2-methoxyethylamine. The exothermic reaction which occurred during the addition was moderated with an ice bath. After the addition was complete, the mixture was heated on a steam bath overnight and then 25 ml of concentrated aqueous HCl was added and the mixture was concentrated under reduced pressure. The residual crude amine hydrochloride (55.8 g of yellow oil) was mixed with 200 ml of saturated aqueous K_2CO_3 and continuously extracted with pentane. The pentane extract was dried, concentrated, and distilled to separate 21.3 g

(21) H. M. Walborsky and A. E. Young, *J. Amer. Chem. Soc.*, **86**, 3288 (1964).

(22) 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 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 (cps) or δ values (ppm) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a Hitachi (Perkin-Elmer) mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates. All transfers and reactions of organometallic reagents were performed under a nitrogen atmosphere.

(23) H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965).

(63%) of the amino ether **28** as a colorless liquid, bp 98–100°. Redistillation from $LiAlH_4$ afforded the pure[24] amino ether **28**: bp 98–100°; $n^{26}D$ 1.3972; nmr ($CDCl_3$), δ 3.47 (2 H triplet, J = 5.5 cps, CH_2–O), 3.35 (3 H singlet, CH_3O), 2.48 (2 H triplet, J = 5.5 cps, CH_2–N), and 2.27 (6 H singlet, CH_3N); mass spectrum, molecular ion, m/e 103, abundant fragment peaks, m/e 58, 45, and 42.

Anal. Calcd for $C_5H_{13}NO$: C, 58.21; H, 12.70; N, 13.58. Found: C, 58.33; H, 12.61; N, 13.35.

A mixture of 90.0 g (0.751 mol) of 1,1,1-tris(hydroxymethyl)-ethane, 57.5 g (2.50 mol) of sodium hydride (from washing an oil dispersion with pentane), and 1500 ml of tetrahydrofuran was heated under reflux for 12 hr. To the resulting suspension was added, dropwise and with stirring, over a 6-hr period, 400 g (2.85 mol) of methyl iodide. The resulting mixture was stirred at room temperature for 140 hr and then filtered and the residue was washed with tetrahydrofuran. The combined filtrates were concentrated under reduced pressure and the residue was dissolved in 500 ml of pentane and again filtered to remove additional amounts of NaI which separated. After this filtrate had been concentrated, the residual yellow liquid (104 g) was distilled from $LiAlH_4$ to separate 97.2 g (80%) of 1,1,1-tris(methoxymethyl)ethane (**16**)[25] as a colorless liquid: bp 61–62° (13 mm), $n^{26}D$ 1.4701; nmr (CCl_4), δ δ 3.22 (9 H singlet, OCH_3, 3.12 (6 H singlet, O–CH_2) and 0.84 (3 H singlet, CH_3–C); mass spectrum, weak molecular ion peak at m/e 162, abundant fragment peaks, m/e 85, 75, 71, 55, and 45.

Anal. Calcd for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.11; H, 10.99.

Procedure for Kinetic Studies.—An ether solution (*ca.* 19 ml) containing known concentrations of benzophenone and phenanthrene (an internal standard for gas chromatographic analysis) was mixed with an ether solution (20.0 ml) containing known concentrations of dimethylmagnesium and any additives under a positive nitrogen pressure of 5 cm of Hg in the previously described[2e,2p] flowing-stream reactor fitted with a 30-cm reaction tube. The volumes of solution were adjusted so that an excess of the organometallic solution was always present. Control experiments established that the changes in viscosity (and corresponding changes in flow rate and mixing ratio) caused by the concentrations of reactant and additives we employed were less than the experimental error of our analytical method and could be neglected. Repetition of previously described[2e,p] calibration procedures established the flow rate (11.7 ml/sec), the mixing ratio, and the reaction time (0.14 sec) for all of the rate measurements made. The temperature of the initial reaction solutions before mixing were brought to 22–26°, but no effort was made to thermostat the flowing-stream apparatus. The reaction mixtures were quenched in cold (0–5°) aqueous methanol (3:4 v/v) and the resulting solutions were mixed with saturated, aqueous NH_4Cl to cause separation of the ether phase. The aqueous phase was extracted with ether and the combined ether solutions were washed with aqueous NaCl, dried, and concentrated under reduced pressure to a volume of 4–5 ml. After these concentrated solutions had been mixed with *ca.* 1 mg of *p*-toluenesulfonic acid and *ca.* 0.1 g of $CaSO_4$ to adsorb any residual water, the solutions were analyzed by gas chromatography[26] employing equipment which had been calibrated with known mixtures of authentic samples. As demonstrated previously,[4b] the diphenylmethylcarbinol (**4**) present in the reaction mixtures was converted quantitatively into 1,1-diphenylethylene when the acidified reaction mixture was injected into the heated inlet system of the gas chromatograph. The retention times of the components being analyzed follow: 1,1-diphenylethylene, 2.8 min; benzophenone, 8.4 min; and phenanthrene, 15.6 min. Benzhydrol (corresponding retention time 18 min) was not detected in any of the reactions. The average analytical values from three gas chromatograms were employed for each run. In all cases the material balances exceeded 95% and control experiments demonstrated that the quenching, isolation, and analysis procedures did not alter the composition of known mixtures of authentic samples. The "per cent reaction" figures listed in Tables I, II, and III were obtained by dividing the corrected area of the diphenylethylene peak by the total corrected area of the diphenylene and benzophenone peaks. Unless otherwise noted, all of the "per cent reaction" values listed in Table II are average values from duplicate runs which agreed with one another to within 3% or less. The estimated errors in measuring volumes and concentrations of reaction solutions are 3% or less. The molar concentrations of reactants listed in Tables I, II, and III refer to the initial concentrations of reactants after the solutions have been mixed. The extent of reaction in the standard reactions of dimethylmagnesium with benzophenone in ether solution were found to vary somewhat with different lots of dimethylmagnesium. This effect presumably arose because the different lots of reagent contained slightly different amounts of alkoxide impurities. Although a single lot of dimethylmagnesium was used for all of the concentration studies listed in Tables I and III, two different lots of reagent were used for the data listed in Table II. A set of standard reactions (dimethylmagnesium plus benzophenone in ether) was run for each lot of dimethylmagnesium. Data concerned with the effect of additives should be compared with the standard reaction utilizing the same lot of dimethylmagnesium. The methylmagnesium 3-methyl-3-pentoxide solutions were prepared by the addition of 3-methyl-3-pentanol to an ether solution containing an equimolar amount of dimethylmagnesium as previously described.[4b]

Because of the immediate formation of a light orange-brown precipitate when 2,2′-bipyridyl (**21**) was mixed with ethereal dimethylmagnesium no rate measurements were possible with this additive. The slower formation of precipitate with the additives **22**–**24** permitted us to obtain crude estimates of their effect which are summarized in Table II. The results with hexamethylphosphoramide varied substantially depending on whether the formation of a precipitate had started before the solutions of benzophenone and the methylmagnesium derivative were mixed. In general the addition of 0.5–1.5 molar equiv of the phosphoramide to an ethereal solution resulted in the slow separation of a white solid. Addition of 2 molar equiv of the phosphoramide resulted in the rapid separation of a white solid. Collected samples of this white solid did not melt below 350° and were insoluble in water, tetrahydrofuran, and hexamethylphosphoramide but did dissolve in dilute, aqueous HCl.[27] No precipitate was observed after several hours when equal volumes of hexamethylphosphoramide and ethereal 0.46 *M* dimethylmagnesium were mixed. Several runs were made with organometallic reagents prepared from 2 molar equiv of ethereal methyllithium and 1 molar equiv of anhydrous magnesium bromide since earlier experiments[4b] suggested that the reagent formed in this mixture was equivalent to dimethylmagnesium. The reagent prepared in this fashion appears to be slightly more reactive than an equivalent concentration of ethereal dimethylmagnesium which is free from lithium bromide.

Preparation of Complexes from Dimethylmagnesium. A. With N,N,N′,N′-Tetramethylethylenediamine (25).—Following the previously described procedure,[13a] a solution of 3.2 mmol of dimethylmagnesium in 5.0 ml of ether was treated with 0.60 ml (*ca.* 6 mmol) of the diamine **25** and the resulting solution was concentrated to dryness under reduced pressure. Sublimation of the residual white solid at 80° and 0.1 mm afforded the complex **29** as white solid which was soluble in ether at room temperature to the extent of at least 0.5 *M*. The complex crystallized from solution when the ether solution was cooled below 0°. However, solutions of the complex in chlorobenzene[28] could be cooled to *ca.* −60° without separation of the complex from solution. The nmr spectrum of a chlorobenzene solution of the complex **29** at *ca.* 30° exhibited, in addition to solvent absorption, two singlets at δ 1.97 (CH_3N and CH_2N) and −1.30 (78 cps above TMS, CH_3Mg) in a ratio of about 8:3. For comparison, the spectrum of a chlorobenzene solution of the diamine **25** exhibited two singlets (separation 11.5 cps) at δ 2.22 (4 H, CH_2N) and 1.95 (12 H, CH_3N). The nmr spectrum of the diamine solution was essentially the same at *ca.* 30° and at *ca.* −63°. A cold (−54°) solution of the complex **29** in chlorobenzene retained the highfield singlet attributable to the CH_3–Mg protons. However, the signal for the CH_2N and CH_3N protons separated into two singlets separated by 4.5 cps with the higher field peak being of lower intensity. These peaks may represent the separate signals for

(24) A gas chromatographic column packed with 1,2,3-tris(β-cyanoethoxy)propane (TCEP) suspended on Chromosorb P was employed for this analysis.

(25) The preparation and characterization of this substance was performed in our laboratories by Mr. W. F. Fischer, Jr.

(26) A gas chromatographic column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis.

(27) This material may be the insoluble, presumably polymeric bisdimethylaminomagnesium described previously by Coates and Ridley.[13b]

(28) The complex was previously reported[13a] to give monomeric solutions in benzene.

the CH_2N and CH_3N protons which are no longer accidentally equivalent at low temperatures. A chlorobenzene solution containing approximately equimolar amounts of the diamine **25** and the complex exhibited, in addition to solvent absorption and the high field singlet for the CH_3–Mg protons, two singlets (separation 5 cps) with the higher field absorption being the more intense as would be expected if the free diamine **25** were exchanging rapidly with the diamine in the complex **29**. This pattern persisted down to *ca.* −30°. Below this temperature the less intense, lower field peak broadened. However, at no point down to −63°, was there evidence for two different sets of peaks attributable to free and complexed diamine. We therefore concluded that exchange of this ligand on dimethylmagnesium is relatively rapid at or above −30°.

The diamine complex **29** was also prepared from methylmagnesium bromide by the following procedure. To 50 ml of an ethereal solution containing 0.15 mol of methylmagnesium bromide was added 15 ml (0.18 mol) of dioxane. The resulting mixture was diluted with 50 ml of ether and stirred at room temperature for 30 min after which the ether solution was separated from the insoluble dioxane complex by filtration through a filter stick. The residual solid was washed with ether and the combined ether filtrates were treated with 12 ml (*ca.* 0.1 mol) of the diamine **25**. The resulting solution was concentrated under reduced pressure and the residual white solid was sublimed (0.1–0.2 mm and 80–100°) to separate 2.4 g (21%) of the diamine complex **29**, mp 94.5–96.5° in a sealed evacuated tube (lit.[13a] mp 97–98°). This complex appears not to decompose at its melting point since the resolidified sample from the melting point determination had the same melting point as the original sample.

B. With 1,2-Dimethoxyethane (27).—A solution prepared from 3.2 mmol of dimethylmagnesium and 1.0 ml of 1,2-dimethoxyethane in 5.0 ml of ether was cooled in a Dry Ice–acetone bath and then allowed to warm to room temperature. Once crystallization of the complex **30** had been initiated at low temperatures, it continued at room temperature in agreement with an earlier report.[13a] The solid was separated (centrifugation followed by removal of the supernatant liquid through a cannula), washed with a 5-ml portion of ether, and then dried under reduced pressure. During this drying process partial decomposition of the complex appeared to occur. The portion of the residue which was still soluble was taken up in benzene[28] for nmr examination. Apart from absorption attributable to benzene and small amounts of ether, the sample exhibited singlets at δ 3.21 (OCH_2), 3.12 (OCH_3), and −0.90 (54 cps above TMS, CH_3–Mg). The ratio of peak areas corresponded approximately to the 1:1 complex **30**. For comparison, the nmr spectrum of a benzene solution of 1,2-dimethoxyethane has singlets at δ 3.37 (OCH_2) and 3.18 (OCH_3).

C. With β-Methoxyethyldimethylamine (28).—To 4.4 ml of an ether solution containing 2.8 mmol of dimethylmagnesium was added 0.55 ml (5 mmol) of the methoxyamine **28** and the resulting solution was concentrated to dryness under reduced pressure. The residual crystalline complex **31** was soluble in ether at room temperature to the extent of at least 0.5 *M* but crystallized from solution when the solution was cooled below 0°. Attempts to sublime the complex at 80–90° and 0.08 mm were not successful; the complex appeared to dissociate leaving polymeric dimethylmagnesium behind in the manner noted previously[13a] for the 1,2-dimethoxyethane complex **30**. A chlorobenzene solution of the amino ether complex **31** has nmr signals at δ 3.28 (2 H triplet, J = 5.5 cps, CH_2O), 3.21 (3 H singlet, CH_3O), 2.31 (2 H triplet, J = 5.5 cps, CH_2N), 2.12 (6 H singlet, CH_3N) and −1.25 (75 cps above TMS, 6 H singlet, CH_3Mg). For comparison, a chlorobenzene solution of the amino ether **28** has nmr peaks at δ 3.39 (2 H triplet, J = 6 cps, CH_2O), 3.22 (3 H singlet, OCH_3), 2.41 (2 H triplet, J = 6 cps, CH_2N), and 2.17 (6 H singlet, CH_3N).

Registry No.—Dimethylmagnesium, 2999-74-8; benzophenone, 119-61-9; **16**, 15476-20-7; **25**, 110-18-9; **28**, 3030-44-2; **29**, 15405-88-6; **30**, 15405-89-7; **31**, 15405-87-5.

Acknowledgments.—The authors are indebted to Dr. Francis Johnson of the Dow Chemical Co. for a generous sample of triply sublimed magnesium, to the Union Carbide Chemicals Co. for a sample of bis (N,N-dimethylaminoethyl) ether, and to Professor Stanley G. Smith for providing us with a preprint of his manuscript prior to publication.

The Chemistry of Carbanions. XV. The Stereochemistry of Alkylation of 4-*t*-Butylcyclohexanone[1a]

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Alkylation of the enolate anion **1** of 4-*t*-butylcyclohexanone with triethyloxonium fluoroborate yielded a mixture of O-alkylated product and a mixture of approximately equal amounts of the stereoisomeric 2-ethyl-4-*t*-butylcyclohexanones. A comparable mixture of C-alkylated products was obtained from reaction of the enolate anion with ethyl iodide for short periods of time. Quenching the enolate anion **1** in a mixture of deuterium oxide and deuterioacetic acid yielded a mixture of the axial deuterio ketone (*ca.* 70%) and the equatorial deuterio ketone (*ca.* 30%). These results are interpreted as evidence that the transition states for alkylation and protonation have geometries resembling the enolate anion **1** rather than the products.

With specific methods in hand for generating the enolate anions of simple ketones,[2] we were interested in examining the preferred direction of alkylation of an enolate anion derived from a simple cyclohexanone.[3,4] For this purpose we elected to study the alkylation and the protonation of the enolate anion **1** derived from 4-*t*-butylcyclohexanone (**2**). Solutions of this enolate anion **1** in 1,2-dimethoxyethane (DME) were obtained either by reaction of the ketone **2** with triphenylmethyllithium or by reaction of the enol acetate **3** with 2 equiv of methyllithium. The latter

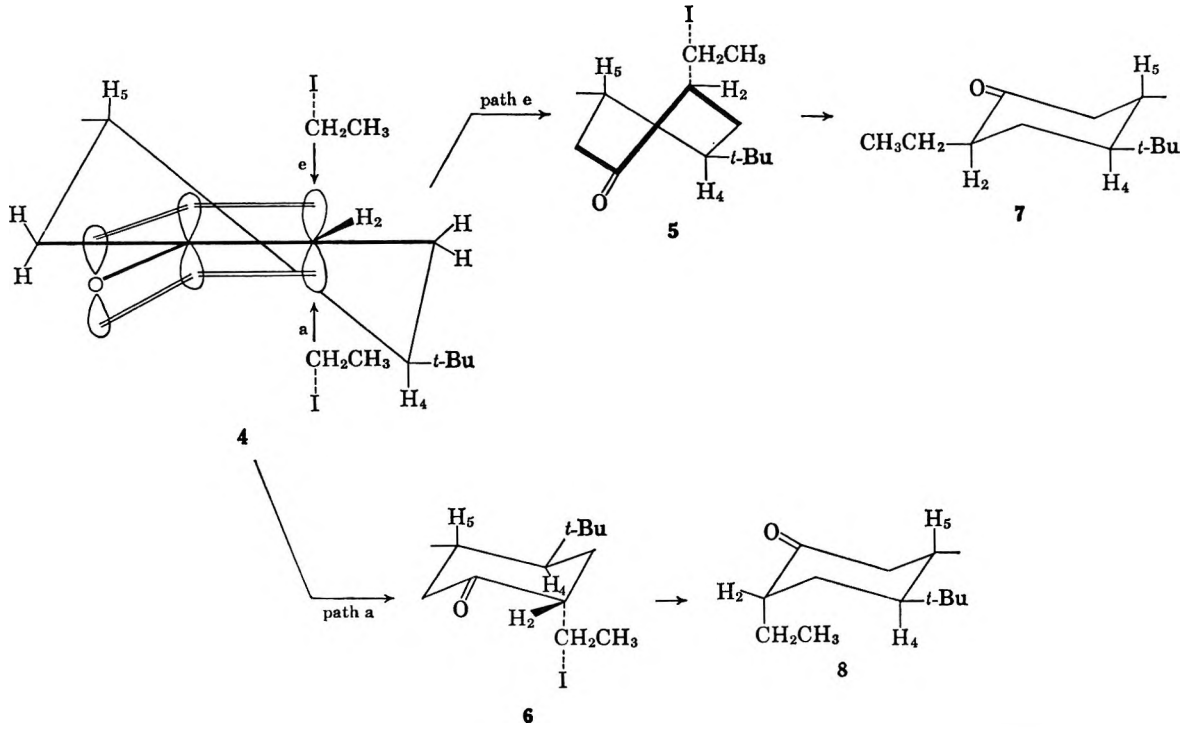
(1) (a) This research has been supported by research grants from the National Institutes of Health (Grant No. GM-08761) and the Directorate of Chemical Sciences, Air Force Office of Scientific Research (Grant No. AF-AFOSR-573); (b) National Institutes of Health Predoctoral Fellow, 1963–1965; (c) National Institutes of Health Predoctoral Fellow, 1965–1966.

(2) (a) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); (b) H. O. House and B. M. Trost, *ibid.*, **30**, 1341, 2502 (1965).

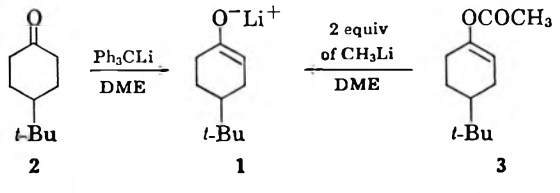
(3) For recent reviews of the stereochemistry of C alkylation, see (a) L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965); (b) J.-M. Conia, *Rec. Chem. Progr.* (Kresge-Hooker Sci. Lib.), **24**, 43 (1963).

(4) For recent studies pertinent to the stereochemistry of alkylation of simple cyclohexanone derivatives, see (a) R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 1194 (1958); (b) E. J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 3476 (1960); C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *ibid.*, **83**, 4433 (1961); M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967); (c) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **84**, 2611 (1962); (d) J. M. Conia and P. Briet, *Bull. Soc. Chim. Fr.*, 3881, 3888 (1966).

SCHEME I



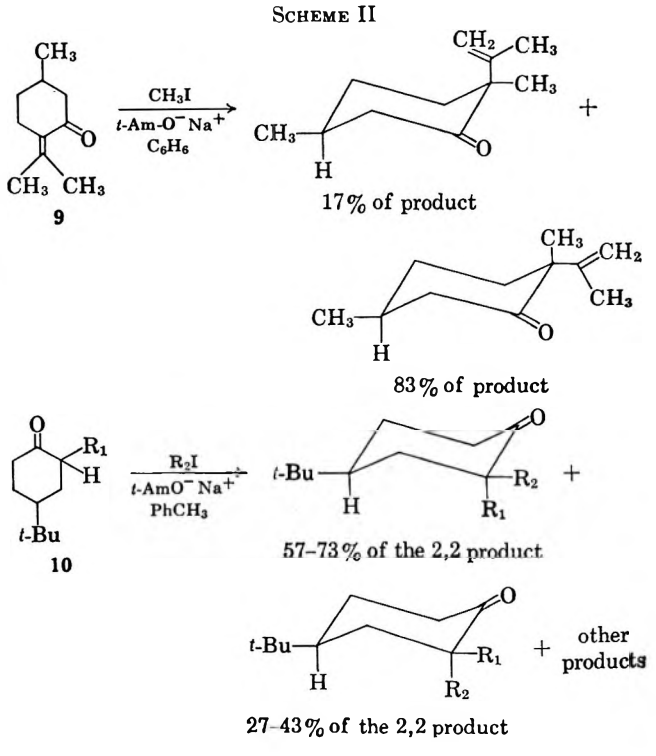
procedure[2] afforded a solution which contained equivalent amounts of the enolate anion 1 and lithium *t*-butoxide.



For stereoelectronic reasons, the enolate anion must be attacked by the alkylating agent at carbon from directions (labeled a and e in structure **4**) perpendicular to the plane of enolate anion (Scheme I). As carbon–carbon bond formation progresses (with attendant bending of the originally planar array of bonds surrounding the α-carbon atom) along path e (**4** → **5** → **7**) the cyclohexane ring is obliged to adopt a twist-boat conformation **5**; subsequent conformational change leads to the *cis*-diequatorial product **7**. The same considerations applied to reaction path a (**4** → **6** → **8**) lead directly to a chair conformation **6** of the cyclohexane ring with the formation of the *trans*-alkylated product **8**. If the assumption is made that a chairlike transition state (*e.g.*, **6**) will have lower energy than the twist-boat alternative (*i.e.*, **5**),[5] the aforementioned considerations have led to the general conclusion[3] that reaction *via* a chairlike transition state (*e.g.*, **6**) to introduce an axial alkyl group (*e.g.*, **8**) should be the favored reaction path in the absence of opposing steric and conformational interactions. The magnitude of this energy difference may be expected to depend upon the extent to which the transition states resemble the chair and boat conformations of a cyclohexanone rather than an enolate anion.

Two previous studies of simple cyclohexanone derivatives which bear on this question are the indicated methylation of pulegone (**9**)[4b] and related compounds and the alkylation of several 2-alkyl-4-*t*-butylcyclohexanones **10**.[4d] Recent studies, correcting an earlier report, have indicated that the major alkylated product from pulegone (**9**) corresponds to reaction path a but the reverse stereochemical result (path e favored) is found with saturated derivatives of pulegone (**9**).[4b] In alkylation of the 4-*t*-butyl derivatives **10**, reaction path e was favored slightly over reaction path a[4d] (Scheme II). One might argue that these latter cases

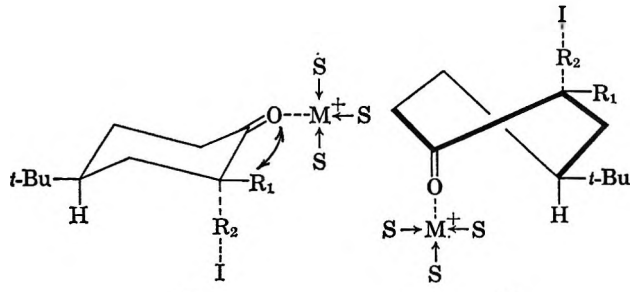
SCHEME II



are exceptional in that the expected reaction path (*i.e.*, path a *via* a transition state such as **6**) is dis-

(5) *Cf.* N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, **88**, 2999 (1966).

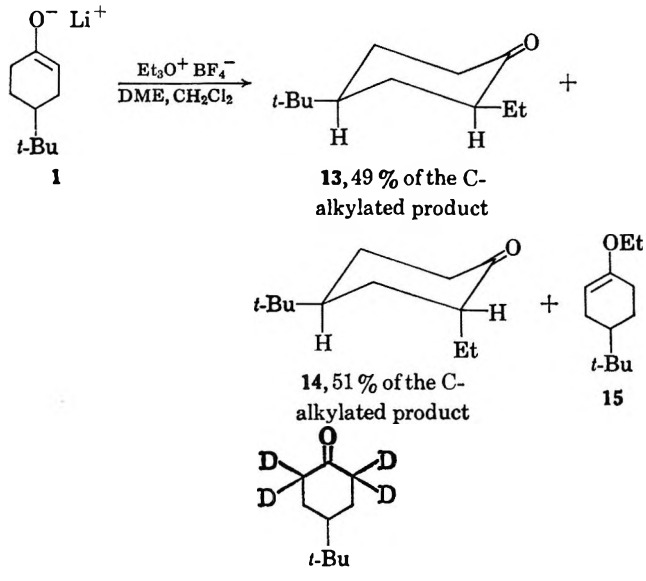
favored by a nonbonding steric interaction in the transition state between the equatorial 2 substituent (R_1 in structure **11**) and the solvated metal–oxygen bond. This particular interaction can be lessened in a conformation approaching the geometry of a twist-boat (*i.e.*, **12**) which would lead to the observed pre-



11 **12**

dominant product. However, this argument loses much of its appeal when considered in light of our current finding that the alkylation of the unsubstituted 4-*t*-butylcyclohexanone enolate anion, **1**, also leads to an approximately equal mixture of *cis* and *trans* isomers **13** and **14**. In this case the interaction indicated in structure **11** (R_1 = H) certainly is not a serious deterrent to the formation of the *trans* product **14** (Scheme III).

SCHEME III



In these alkylation experiments the absence of equilibration of the products **13** and **14** was demonstrated by alkylating the enolates derived from a mixture of the ketone **2** and its tetradeuterio derivative **16** to form a mixture of ketone products **13** and **14** containing primarily d_0 and d_3 species. The formation of the O-alkylation product **15** as a by-product when the reactive alkylating agent, the triethyloxonium ion, was employed is also of interest. This side reaction, suspected earlier,[2b] has been reported elsewhere in the intervening period.[6] None of this O-alkylated product **15** was observed when the enolate anion was alkylated with the less reactive alkylating agent, ethyl iodide. Interestingly, the composition of the monoalkylated product recovered after short reaction times (54% of **14** and 46% of **13**) with ethyl iodide was not appreciably different from the composition of alkylated product obtained with triethyloxonium ion.

In view of the present stereochemical results and of results obtained on alkylation of the enolate anions from various bicyclic and polycyclic ketones,[2b,3,7] we conclude that there is no inherent factor which strongly favors the alkylation of a cyclohexanone enolate anion from that direction which will form a product with an axial alkyl substituent. Accordingly, we must also conclude that the energies of the two transition states for alkylation are approximately equal; in other words, some error exists in the previously presented argument that the transition state for path a will be of significantly lower energy than the transition state for path e. All of our presently available data are most consistent with the idea that relatively little new C–C bond formation has occurred at the transition state for the alkylation of enolate anions. For this reason, we believe that the geometries of the six-membered rings in the transition states resemble much more closely the geometry of the planar enolate ion (*e.g.*, **4**) than the geometries of chair (*e.g.*, **6**) or twist-boat (*e.g.*, **5**) cyclohexane rings.[2b,8] An examination of molecular models failed to reveal any obvious steric factors in the enolate anion **1** which would favor attack of the alkylating agent from one of the directions a or e (structure **4**). Consequently, if the geometries of the transition states for alkylation resemble the enolate ion **4** rather than structures such as **5** and **6**, the energy difference between the two transition states would be expected to be small.

Although the previously observed[2b] enhancement of the proportion of *cis*-fused product when the $\Delta^{1,9}$-enolate from 1-decalone was alkylated with trimethyloxonium ion rather than the less reactive methyl iodide is consistent with the idea that the transition state resembles the enolate anion, especially with reactive alkylating agents, other explanations are possible.[9] As noted in accompanying studies[10] of the alkylation of methyl 4-*t*-butylcyclohexyl ketone and 1-cyano-4-*t*-butylcyclohexane, the formation of *cis*-fused products

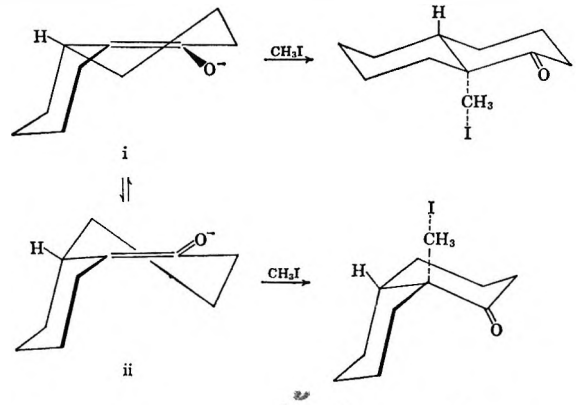
(6) G. J. Heiszwolf and H. Kloosterziel, *Chem. Commun.*, 51, 767 (1966).

(7) In the absence of opposing steric or conformational effects, both 1-ketodecalin and 1-ketoperhydroindanone systems are alkylated at the bridgehead to form predominantly *cis*-fused products. For discussion of the perhydroindanone case, see ref 3a; H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964); H. O. House and C. J. Blankley, *ibid.*, **32**, 1741 (1967).

(8) W. S. Johnson, D. S. Allen, Jr., R. R. Hindersinn, G. N. Sausen, and R. Pappo, *J. Amer. Chem. Soc.*, **84**, 2181 (1962).

(9) The alkylation of 1-decalone at C-9 is ambiguous in that suitable conformations of the starting enolate anion i and ii can provide reaction paths which lead to initial products where both cyclohexane rings are in chair conformations irrespective of the stereochemistry of alkylation.

(10) H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).



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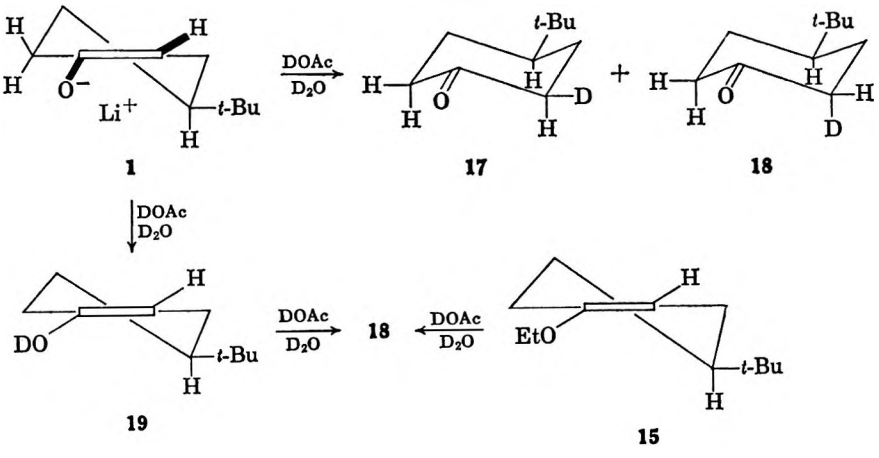
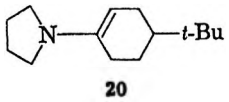
SCHEME IV



in the alkylation of 1-decalones can be regarded as an example of the preference for introduction of an equatorial alkyl group in the alkylation of a cyclohexyl ketone enolate.

In an ancillary study, we have also examined the protonation of the enolate anion **1** in a deuterium oxide–deuterioacetic acid mixture (Scheme IV). In principle, this protonation process could provide information about the stereochemistry of forming bonds to the α carbon of the enolate anion **1** in a situation where the transition state of this very rapid reaction presumably resembles the enolate anion. In practice, this goal is complicated by the fact that protonation of this strongly basic anion at either carbon (to form **17** or **18**) and at oxygen (to form **19**) are diffusion-controlled reactions[11] so that comparable amounts of the ketones **17** and **18** and the enol **19** are produced in the quenching process. Further reaction of the enol **19** with aqueous acid can also yield one or both of the ketones **17** or **18**. In an effort to learn the stereochemical course of ketonization of the enol **19**, the related enol ether **15** was subjected to the same reaction conditions to yield a ketone product calculated to contain more than 90% of the ketone **18** with axial deuterium. A comparable result was reported for the carefully controlled (see Experimental Section) acidic hydrolysis of the enamine **20**.[12] The nmr spectrum of the ketone



20

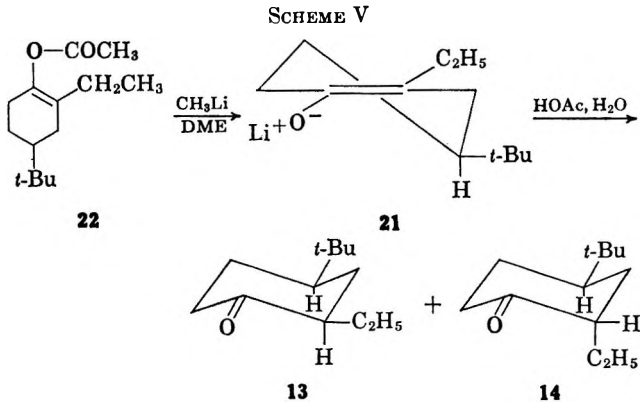
mixture obtained from quenching the enolate anion **1** in deuterated aqueous acetic acid was consistent with the presence of *ca.* 70% of the axial deuterated ketone **18** and *ca.* 30% of the equatorial isomer **17**. Supporting evidence for the validity of this result was obtained by quenching the enolate anion **21** in aqueous acetic acid to obtain a mixture of the ketone **13** (80%, axial proton) and **14** (20%, equatorial proton) (Scheme V).

Since the composition of the monodeuterated ketone mixtures obtained from the enol **19** and the enolate **1** are different, one must conclude that at least part of the enolate anion **1** reacts with a deuteron to form a C–D bond directly. Furthermore, at least 20–30% of the new C–D bonds formed by reaction of the enolate

(11) M. Eigen, *Angew. Chem., Intern. Ed. Engl.*, **3**, 1 (1964).

(12) J. P. Schaefer and D. S. Weinberg, *Tetrahedron Lett.*, 1801 (1965).

SCHEME V



anion **1** with a deuteron occur by attack of the deuteron donor from the direction labeled e in structure **4**. If the crude assumption is made that one-half of the enolate anion is protonated on oxygen and one-half is protonated on carbon, it would then appear that protonation at carbon occurs with approximately equal ease from either side of the enolate anion **1**. The results of these protonation experiments, like the stereochemical results obtained from alkylating the enolate anion **1**, are most readily explicable if the transition state geometries for both reactions resemble the geometry of the enolate anion so that energy differences between the directions of attack on the enolate (*e.g.*, a or e in structure **4**) are small.

Experimental Section[13]

Preparation of Starting Materials.—Pure[14] 4-*t*-butylcyclohexanone (**2**), mp 47–48°, bp 110–113° (16 mm), was obtained by conversion of the crude ketone into its $NaHSO_3$ addition product which was separated and reconverted into the ketone with aqueous Na_2CO_3. A mixture of 26 g (0.17 mol) of the ketone **2** and 40 ml of D_2O containing 400 mg of Na_2CO_3 was heated to 70–80° with stirring for 24 hr and then cooled and extracted with

(13) 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; tetramethylsilane was used as the internal standard. The mass spectra were obtained with a CEC Model 21-130 mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. All solutions of enolate anions were prepared and transferred under a nitrogen atmosphere.

(14) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb W was employed for this analysis.

ether. After the ethereal extract had been dried and concentrated, the crude recovered ketone was subjected to the same exchange procedure five additional times. In the final exchange, 5 ml of 1,2-dimethoxyethane was added to the D_2O as a cosolvent. The final crude ketone was distilled to separate 7.0 g (27%) of the tetradeuterio ketone **16**; the mass spectrum of the product indicated the presence of 6% d_3 species and 94% d_4 species.

Samples of the ketone **16**, injected on and recollected from our gas chromatography columns,[15,16] lost 5% or less of their d_4 species during this treatment. The sample also slowly lost deuterium when allowed to stand in the heated inlet system of the mass spectrometer; however, this complication was not significant when times no longer than 15 min elapsed between introduction of the sample and completion of the measurements. The infrared spectrum (CCl_4)[17] of the tetradeuterio ketone **16** has a carbonyl peak at 1710 cm^{-1} with peaks attributable to C–D stretching at 2110 (m), 2125 (m), 2180 (shoulder), and 2225 cm^{-1} (s). The infrared absorption in the finger print region differed from the spectrum of the nondeuterated ketone **2** in a number of places. The nmr spectrum ($CDCl_3$) of the nondeuterated ketone **2** has a singlet at δ 0.93 (9 H, $(CH_3)_3C$–) with a multiplet in the region 1.1–1.92 (4 H, CH_2 groups at C-3 and C-5) and two partially resolved multiplets in the regions 1.92–2.17 (*ca.* 1 H, CH at C-4) and 2.17–2.63 (*ca.* 4 H, CH_2 at C-2 and C-6). In the same solvent, the tetradeuterio ketone **16** has the multiplets in the regions 1.1–1.92 and 1.92–2.17, but lacks absorption in the lower field (2.2–2.7) region. In benzene solution,[18] the nmr spectrum of the nondeuterated ketone **2** has the *t*-butyl singlet at δ 0.75 with multiplets in the regions 0.87–1.47 (4 H, CH_2 at C-3 and C-5), 1.47–1.98 (3 H, CH at C-4 and axial[18] CH at C-2 and C-6), and 1.98–2.40 (2 H, equatorial CH at C-2 and C-6). The nmr absorption of a benzene solution of the tetradeuterio ketone **16** differs in having a multiplet in the region δ 1.47–1.98 attributable to only one proton (CH at C-4) and in lacking absorption in the region 1.98–2.40.

Ethereal solutions of methyllithium were prepared from methyl bromide in the usual way and standardized either by a double titration procedure employing 1,2-dibromoethane or by use of the chlorodimethylphenylsilane procedure.[19] Triethyloxonium fluoroborate, prepared as previously described,[20] was washed thoroughly with ether, recrystallized from a methylene chloride–ether mixtur, dried under reduced pressure, and stored under nitrogen.

1-Acetoxy-4-*t*-butylcyclohexene (3).—A solution of 25.163 g (0.163 mol) of the ketone **2** in 152 ml (1.32 mol) of isopropenyl acetate containing several milligrams of *p*-toluenesulfonic acid was refluxed for 24 hr and then cooled and partitioned between pentane and aqueous Na_2CO_3. The pentane extract was dried, concentrated, and distilled to separate 24.998 g (78.6%) of the pure[15] enol ester **3**: bp 135° (21 mm); $n^{25}D$ 1.4602 (lit.[21] bp 85–86° (2.5–3 mm); $n^{20}D$ 1.4640); ir (CCl_4), 1755 (ester C=O) and 1685 cm^{-1} (C=C); nmr ($CDCl_3$), δ 5.38 (1 H multiplet, vinyl CH), 0.88 (9 H singlet, $(CH_3)_3C$–), 2.09 (singlet, CH_3CO–), and 1.1–2.4 (multiplet, aliphatic CH); mass spectrum, molecular ion peak at *m/e* 196, abundant fragment peaks at *m/e* 154 (M − CH_2=C=O), 139, 97, 70, 57, 55, 43, and 41.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.48; H, 10.26.

(15) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis.

(16) The gas chromatography column employed was packed with 1,2,3-tris(β-cyanoethoxy)propane suspended on Chromosorb W which had been neutralized and then treated with dichlorodimethylsilane prior to use.

(17) Because of the relatively low intensities of the peaks in the region 2100–2300 cm^{-1} attributable to C–D stretching vibrations, this region of the spectrum was measured both as a 10–20% solution in a 0.1-mm cell and as a 5–8% solution in a 5-mm cell.

(18) For cyclohexanone derivatives, it has been found that changing the solvent from deuteriochloroform to benzene causes an upfield shift of the axial α protons of 0.3–0.4 ppm relative to the equatorial α protons. For discussion and examples, see (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, pp 159–176; (b) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 1641, 2021 (1965); (c) D. H. Williams, *Tetrahedron Lett.*, 2305 (1965). In the present case, use of pyridine as a solvent for the ketone **2** did not lead to a useful separation of the nmr signals attributed to the axial and equatorial α protons.

(19) H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965).

(20) H. Meerwein in "Methoden der organischen Chemie" (Houben–Weyl), Vol 6, Part 3, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, Germany, 1965, p 329.

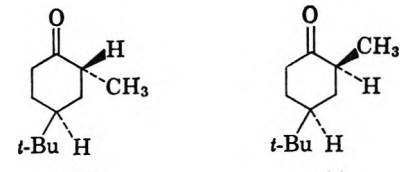
(21) M. M. Rogic, *Tetrahedron*, **21**, 2823 (1965).

1-Ethoxy-4-*t*-butylcyclohexene (15).—A mixture of 6.0 g of ethanol, 7.0 g (45 mmol) of the ketone **2**, 8.8 g (59 mmol) of ethyl orthoformate, and 50 mg of *p*-toluenesulfonic acid was stirred at 25° for 48 hr and made basic with sodium ethoxide and distilled. After the ethanol had been separated at atmospheric pressure, the residual liquid was distilled under reduced pressure to separate 6.5 g (57%) of 1,1-diethoxy-4-*t*-butylcyclohexane: bp 67–70° (0.1 mm); $n^{25}D$ 1.4443; ir (CCl_4), no absorption in the 6-μ region, three intense peaks at 1060, 1090, and 1120 cm^{-1} (CO of ketal); nmr ($CDCl_3$), overlapping quadruplets (J = 7 cps for each) centered at δ 3.38 and 3.48 (4 H, CH_2 of ethoxyl groups), 0.87 (9 H singlet, $(CH_3)_3C$), two overlapping triplets (J = 7 cps for each) centered at 1.14 and 1.17 (CH_3 of ethoxyl groups) superimposed on complex absorption in the region δ 1.0–2.3 (aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 228, abundant fragment peaks at *m/e* 98, 97, 70, 55, 45, 43, and 41. The ketal (6.5 g) was mixed with 0.50 g of ammonium dihydrogen phosphate and heated to 170° for 2 hr allowing the ethanol to distil from the mixture as it formed. Distillation of the residual liquid afforded 5.0 g (61%) of the enol ether **15**: bp 114–117° (11 mm); $n^{23}D$ 1.4629; ir (CCl_4), 1670 cm^{-1} (C=C); nmr ($CDCl_3$), δ 4.53 (1 H multiplet, vinyl CH), 3.64 (2 H quadruplet with J = 7 cps, CH_2 of ethoxyl group), 1.25 (triplet with J = 7 cps, CH_3 of ethoxyl group), 0.89 (9 H singlet, $(CH_3)_3C$–), 1.0–2.4 (multiplet, aliphatic CH); mass spectrum, molecular ion peak at *m/e* 182, abundant fragment peaks at *m/e* 98, 97, 70, 55, 43, and 41.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.16; H, 12.20.

The Pyrrolidine Enamine of 4-*t*-Butylcyclohexanone (20).—A solution of 12.005 g (78 mmol) of the ketone **2**, 12 g (0.17 mol) of pyrrolidine, and several milligrams of *p*-toluenesulfonic acid in 30 ml of benzene was refluxed for 6 hr with continuous separation of water. Distillation of the resulting solution separated 10.84 g (68%) of the enamine **20**: bp 110–115° (0.03 mm); ir ($CHCl_3$), 1640 (C=C) and 1705 cm^{-1} (weak, probably a small amount of the starting ketone present as an impurity); nmr ($CDCl_3$), δ 4.18 (1 H multiplet, vinyl CH), 0.86 (9 H singlet, $(CH_3)_3C$–), 2.8–3.2 (4 H multiplet, $-CH_2N$) and 1.0–2.4 (11 H multiplet, aliphatic CH).

Preparation of the Stereoisomeric 4-*t*-Butyl-2-methylcyclohexanones (23 and 24). A. Methylation of the Enamine.—A



23 **24**

solution of 17.38 g (83.7 mmol) of the enamine **20** and 17.00 g (119.5 mmol) of methyl iodide in 150 ml of benzene was refluxed for 20 hr and then hydrolyzed with water and concentrated. Distillation of the crude neutral product afforded 10.657 g of colorless liquid, bp 110–113° (14 mm), $n^{25}D$ 1.4583, which contained, in order of elution on gas chromatography,[16] 21% of a mixture of dialkylated products, 9% of the *cis* isomer **24**, 25% of the *trans* isomer **23**, and 45% of the unmethylated ketone **2**.[22–24] A sample of the *trans* ketone **23**[23,24] was collected:[16] ir (liquid film), 1705 cm^{-1} (C=O); mass spectrum, molecular ion peak at *m/e* 168, abundant fragment peaks at *m/e* 112, 83, 69, 57, 55, 43, 41, and 39; nmr ($CDCl_3$), δ 1.3–2.8 (8 H multiplet, aliphatic CH), 0.95 (9 H singlet, $(CH_3)_3C$–), and 1.19 (3 H doublet with

(22) The presence of a substantial quantity of the less stable[23,24] *trans* ketone **23** in this product mixture in spite of the fact that partial equilibration has presumably occurred during the isolation procedure reflects the stereospecificity previously observed in the alkylation and hydrolysis of the intermediate enamine. See F. Johnson and A. Whitehead, *Tetrahedron Lett.*, 3825 (1964); S. Karady, M. Lenfant, and R. E. Wolff, *Bull. Soc. Chim. Fr.*, 2472 (1965).

(23) The preparation and various spectroscopic properties of the stereoisomeric ketones **23** and **24** have been described briefly in several places (ref 5, 22, and 24). Equilibration[5,24a] of these epimers led to mixtures which contained 93–94% of the *cis* isomer **24** (equatorial methyl group) and 6–7% of the *trans* isomer **23** (axial methyl group).

(24) (a) C. Beard, C. Djerassi, J. Sicher, F. Šipoš, and M. Tichý, *Tetrahedron*, **19**, 919 (1963); (b) F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).

J = 7 cps, CCH_3).[25] This material was identified with a previously described sample[22,24b] by comparison of infrared spectra.

A portion of the mixture from the enamine alkylation was stirred with aqueous sodium bisulfite for 12 hr; the unchanged ketonic material, separated from the bisulfite adduct, contained[16] 65% of dialkylated material and 35% of the monoalkylated ketones **23** and **24**. A sample of the dialkylated product was collected:[15] nmr ($CDCl_3$), δ 1.2–2.8 (*ca.* 7 H multiplet), 0.93 (*ca.* 9 H singlet, $(CH_3)_3C$–), and 1.04 (*ca.* 6 H, apparently a doublet with J = 7 cps, CH_3C); mass spectrum, molecular ion peak at *m/e* 182, abundant fragment peaks at *m/e* 126, 97, 85, 69, 57, 55, 43, and 41. These data suggest that the dialkylated product from this reaction is primarily a 2,6-dimethyl-4-*t*-butylcyclohexanone rather than the 2,2-dimethyl isomer.

B. Methylation of 2-Carboethoxy-4-*t*-butylcyclohexanone.—Following previous procedures,[5,26] the ketone **2** was converted into **2-ethoxalyl-4-*t*-butylcyclohexanone** (bp 190–195° (17 mm), yield 75%) and subsequently to **2-carboethoxy-4-*t*-butylcyclohexanone**: yield 51%; bp 160–165° (25 mm); $n^{25}D$ 1.4747 (lit.[5] bp 128.5–129° (6 mm); $n^{25}D$ 1.4768); ir ($CHCl_3$), 1735 (shoulder), 1715, 1655, and 1615 cm^{-1} (both enol and keto forms of β-keto ester). Methylation yielded **2-carboethoxy-2-methyl-4-*t*-butylcyclohexanone**: yield 84%; bp 120–123° (2 mm); $n^{25}D$ 1.4614 (lit.[5] bp 105.5° (1.3 mm); $n^{25}D$ 1.4610); ir ($CHCl_3$), 1735 (ester C=O) and 1715 cm^{-1} (ketone C=O). Hydrolysis and decarboxylation of 19.82 g (0.0826 mol) of this methylated β-keto ester with 150 ml of refluxing aqueous 4 *M* hydrochloric acid yielded a crude product (14.19 g, bp 156–159° (16 mm)) which contained[16] primarily the *cis* isomer **24** accompanied by lesser amounts of the *trans* isomer **23** and the ketone **2**. Fractional distillation with a 40-cm spinning-band column separated the *cis* ketone **24** as 4.233 g (30%) of colorless liquid: bp 158–159° (16 mm); $n^{26}D$ 1.4595 (lit.[5] for mixture of *cis* and *trans* isomers, bp 75° (3.2 mm), $n^{25}D$ 1.4586); this material was identified with a previously described[22,24b] sample by comparison of infrared spectra—ir (liquid film), 1710 cm^{-1} (C=O); mass spectrum, molecular ion peak at *m/e* 168, abundant fragment peaks at *m/e* 112, 97, 83, 69, 57, 55, 43, 41, and 39; nmr ($CDCl_3$), δ 1.2–2.7 (8 H multiplet), 0.96 (9 H singlet, $(CH_3)_3C$–), and 1.06 (3 H doublet with J = 6 cps, CCH_3).[25]

Alkylation of 4-*t*-Butylcyclohexanone (1). A. With Methyl Iodide.—Following previously described procedures,[2] a solution of 21 mmol of methyllithium in 30 ml of 1,2-dimethoxyethane was treated with 2.2 g (10 mmol) of the enol acetate **3**. The resulting solution of the enolate anion **1** was cooled to 0° and treated, rapidly and with stirring, with 1.9 ml (34 mmol) of methyl iodide. After the resulting mixture had been stirred for 5 min, it was diluted with aqueous hydrochloric acid and extracted with ether. The ethereal extract was dried, concentrated, and distilled to separate 1.3 g (*ca.* 70%) of fractions boiling in the ranges 110–130° (18 mm) and 90–95° (0.05 mm). The fractions contained[16] *ca.* 25% of dimethylated product, *ca.* 50% of the *cis*-monomethyl ketone **24**, and *ca.* 25% of material corresponding in retention time to the unalkylated ketone **2**. Although a small amount of the *trans* ketone **23** could be detected,[16] its gas chromatographic peak was not sufficiently well resolved to permit a reliable estimate of the amount of material. A sample of the *cis* ketone **24** was collected[16] and identified with the previously described sample by comparison of infrared and mass spectra. The polyalkylated material had infrared absorption (CCl_4) at 1710 cm^{-1} (C=O) with a molecular ion peak in the mass spectrum at *m/e* 182. The mass spectrum of this sample is similar to, but not identical with, the mass spectrum of the dialkylated product from the enamine **20** suggesting that the two samples contain differing proportions of 2,2 and 2,6 isomers. Because of the difficulties in analyzing mixtures of these methylated products, no further work was done to learn the composition of kinetically controlled mixtures of the monomethylated ketones **23** and **24**.

B. With Triethyloxonium Tetrafluoroborate.—For experiments in which the enolate anion **1** was generated from the enol acetate **3**, solutions of 2.8 mmol of methyllithium in 2.8–3.0 ml of 1,2-dimethoxyethane containing a few milligrams of triphenylmethane were prepared as previously described.[2] A weighed amount of durene was added as an internal standard and then the solutions were treated with the enol acetate **3** until the red color was almost discharged. Each enolate anion solution was treated, rapidly and with vigorous stirring, with a solution of excess triethyloxonium tetrafluoroborate in 3.5 ml of methylene chloride.[27] The resulting solutions were stirred for 2 min and then diluted with 30 ml of water containing 3 g of sodium acetate. After the organic products had been extracted with ether, the organic extracts were dried, concentrated, and analyzed by gas chromatography.[15] The gas chromatography equipment was calibrated with known mixtures prepared from pure samples. The retention times of the materials follow: durene, 12.3 min; enol ether **15**, 19.9 min; ketone **2**, 31.5 min; *cis* ketone **13**, 38.4 min; *trans* ketone **14**, 44.5 min. The results of these alkylations are summarized in Table I, the product yields being calculated based on the internal standard.

A sample of the enol ether **15** was collected[15] and identified with the previously described sample by comparison of infrared and mass spectra; a collected[15] sample of the ketone **2** was identified with an authentic sample by comparison of infrared spectra. The *cis* ketone **13**[28] was collected:[15] ir (CCl_4), 1715 cm^{-1} (C=O); nmr (pure liquid), δ 0.7–1.0 (12 H multiplet, superimposed signals for $(CH_3)_3C$– and CH_3C) and 1.0–2.5 (10 H, multiplet); mass spectrum, molecular ion peak at *m/e* 182, abundant fragment peaks at *m/e* 111, 83, 57, 55, 43, and 41. A sample of the *trans* ketone **14**[28] was collected:[15] ir (CCl_4), 1710 cm^{-1} (C=O); nmr (pure liquid), δ 0.7–1.0 (12 H multiplet, superimposed signals for $(CH_3)_3C$– and CH_3C) and 1.0–2.5 (10 H multiplet); mass spectrum, molecular ion peak at *m/e* 182, with abundant fragment peaks at *m/e* 111, 83, 57, 55, 43, and 41. To establish which of the epimeric ketones **13** and **14** was which, a solution of 60 mg of amixture of approximately equal amounts of the ketones in 2 ml of ethanol containing 10 mg of Na_2CO_3 was heated to 70° for 15 hr. The resulting ketone mixture contained[15] 82% of the *cis* isomer **13** and 18% of the *trans* isomer **14** in agreement with previous data.[5,28]

In an additional set of alkylation experiments, solutions of 1.4 mmol of triphenylmethyllithium in 1.3 ml of 1,2-dimethoxyethane were prepared from methyllithium and triphenylmethane.[2] Weighed samples of durene or tetralin (internal standards) were added. In certain cases 1 molar equiv of lithium *t*-butoxide was also generated in the reaction solution by reaction of methyllithium with *t*-butyl alcohol. Then these solutions were titrated with solutions of either the ketone **2** or a mixture of the ketone **2** and the tetradeuterio ketone **16** in 4–5 ml of 1,2-dimethoxyethane until the red color of the triphenylmethyl anion was just discharged. The resulting solutions of enolate anions were then treated with excess triethyloxonium tetrafluororate in 3.5 or 10 ml of methylene chloride. After the resulting mixtures had been stirred for 2 min, they were diluted with 30 ml of water containing 3 g of sodium acetate and then subject to the previously described isolation and analysis procedures. In the case of experiments employing mixtures of the d_0 ketone **2** and d_4 ketone **16**, samples of the *cis* ketone **13** were collected[16] and analyzed for deuterium content by mass spectrometry. Repassing these collected samples through the same gas chromatography column resulted in the loss of 5% or less of the various deuterated species present.

C. With Ethyl Iodide.—A solution of the enolate anion **1**, prepared in the usual way from 2.8 mmol of methyllithium in 2 ml of 1,2-dimethoxyethane containing a weighed sample of durene (internal standard) and 196 mg (1.00 mmol) of the enol acetate **3**, was added, dropwise and with stirring, to 1.190 g (7.6 mmol) of ethyl iodide. The resulting mixture was stirred for 5 min at 25° and then quenched in aqueous 1 *M* hydrochloric acid and extracted with pentane. The pentane solution was dried, concentrated, and analyzed[15] as previously described. The calculated yields of products were 48% of the unalkylated ketone **2**, 12%

(25) As noted previously,[24b] the axial 2-methyl group of the *trans* ketone **23** occurs at *ca.* 0.13 ppm lower field than the equatorial 2-methyl group of the *cis* ketone **24** in deuteriochloroform solution.

(26) E. Arnal, G. Lamaty, C. Tapiero, P. F. Winternitz, J. Wylde, and R. Wylde, *Bull. Soc. Chim. Fr.*, 952 (1963).

(27) In preliminary experiments where the triethyloxonium fluoroborate was mixed with 1,2-dimethoxyethane prior to adding this alkylating agent to the solution of the enolate, substantial quantities of the *methylated* ketones **23** and **24** were produced. Evidently the known[29] exchange of alkyl groups between ethers and trialkyloxonium salts occurs very rapidly when 1,2-dimethoxyethane and this triethyloxonium salt are mixed. Unless otherwise noted, the formation of the methyl ketone by-products **23** and **24** was not a problem when a methylene chloride solution of the triethyloxonium salt was added to a solution of the enolate **1** in 1,2-dimethoxyethane.

(28) The 2-ethyl-4-*t*-butylcyclohexanone epimers **13** and **14** have been reported previously;[5] a mixture of the isomers boils at 88° (2.7 mm), $n^{25}D$ 1.4592. Equilibration of these epimers in alcohol at 25° was reported to give a mixture containing 86% of the *cis* isomer **13** (equatorial ethyl group) and 14% of the *trans* isomer **14** (axial ethyl group); at 65°, the composition was 82% of **13** and 18% of **14**.

TABLE I
THE ALKYLATION OF THE LITHIUM ENOLATE ANION OF 4-*t*-BUTYLCYCLOHEXANONE WITH TRIETHYLOXONIUM TETRAFLUOROBORATE

Compd (mmol)	$Et_3O^+ BF_4^-$, mmol	Product yields, %				Compn of monoalkylated product, %	
		Enol ether **15**	Ketone **2**	*trans* ketone **14**	*cis* ketone **13**	*trans* **14**	*cis* **13**
3 (1.05)	7.5	17	0	28	30	48	52
3 (0.89)	7.7	18	4	26	28	48	52
3 (0.82)	7.5	12	12	26	26	50	50
2 (0.58)[a]	7.6	19	7	31	29	52	48
2 (0.82)	7.6	19	19	21	21	50	50
2 + **16** (1.25)[b,c]	7.4	*f*	*Ca.* 10	*Ca.* 24	*Ca.* 23[d]	51	48
2 + **16** (1.20)[b]	7.4	*f*	*Ca.* 27	*Ca.* 30	*Ca.* 28[e]	52	48

[a] This enolate anion solution also contained 1.22 mmol of added lithium *t*-butoxide. [b] An aliquot of a solution prepared from 386.3 mg of the nondeuterated ketone **2** and 438.5 mg of the tetradeuterio ketone **16** (6% d_3 and 94% d_4) was employed. [c] This enolate anion solution also contained 1.25 mmol of added lithium *t*-butoxide. [d] A collected sample[16] of this product contained 47% d_0, 1% d_1, 10% d_2, and 42% d_3 species. The calculated values in the absence of exchange are 47% d_0, 0% d_1, 3% d_2, and 50% d_3 species. [e] A collected sample[16] of this product contained 45% d_0, 1% d_1, 7% d_2, and 47% d_3 species. The calculated values in the absence of exchange are 47% d_0, 0% d_1, 3% d_2, and 50% d_3 species. [f] These analyses were obtained with a different gas chromatography column[16] and a different internal standard (tetralin) from the general procedure described in the Experimental Section. With this analytical procedure the enol ether was decomposed on the gas chromatography column and the reliability of the other analyses was lower. This gas chromatographic method[16] was used primarily to facilitate collection of the *cis* ketone **13** with a minimum of hydrogen–deuterium exchange.

of the *cis* ketone **13**, 14% of the *trans* ketone **14**, and 1% of one or more dialkylated products; no enol ether **15** was detected. These results correspond to a monoalkylated product mixture having the composition 54% of *trans* isomer **14** and 46% of *cis* isomer **13**. This experiment was repeated employing 2.8 mmol of methyllithium, 184 mg (0.942 mmol) of the enol acetate **3**, and 1.159 g (7.4 mmol) of ethyl iodide. However, the solution containing the enolate anion and ethyl iodide was stirred for 30 min at 25° in order to obtain more nearly complete reaction of the enolate anion. The calculated[15] yields of products were 19% of the unalkylated ketone **2**, 28% of the *cis* ketone **13**, 13% of the *trans* ketone **14**, and 5% of one or more dialkylated products. These latter results are almost certainly complicated by partial equilibration of the *cis*- and *trans*-monoalkylated ketones during this reaction. As in the previous experiment, none of the enol ether **15** was detected.[15] Collected[16] samples of the ketones **2**, **13**, and **14** were identified with the previously described samples of these materials by comparison of mass spectra. The mass spectrum of a collected[16] sample of the dialkylated product has a molecular ion peak at *m/e* 210 with abundant fragment peaks at *m/e* 111, 98, 83, 71, 69, 57, 55, 43, and 41.

Formation of the Monodeuterio Ketones 17 and 18. A. From the Enolate Anion 4.—Reaction of 3.9 mmol of methyllithium with 379 mg (1.9 mmol) of the enol acetate **3** in 4.0 ml of 1,2-dimethoxyethane yielded a solution of the enolate anion **1** which was added, dropwise and with vigorous stirring, to a solution of deuterioacetic acid in deuterium oxide (from 218 mg (2.1 mmol) of acetic anhydride and 20 ml of deuterium oxide). The ether extract of this reaction mixture was dried, concentrated, and distilled to separate 208 mg (70%) of the monodeuterated ketone **17** and/or **18**, mp 46.5–48.5°, which contained 6% d_0 species, 89% d_1 species, and 5% d_2 species. From two comparable reactions, the monodeuterated ketone **17** and/or **18** was obtained in yields of 71 and 69% and contained, respectively, 7% d_0, 85% d_1, and 8% d_2 species and 3% d_0, 94% d_1, and 3% d_2 species. The infrared spectra (CCl_4)[17] of the three samples exhibit no significant differences and have carbonyl absorption at 1715 cm^{-1} with the following bands attributable to C–D stretching vibrations:[29] 2215 (medium), 2190 (shoulder), 2150 (strong), 2140 (shoulder), and 2130 cm^{-1} (shoulder). The general pattern of the spectrum in the 2100–2250-cm^{-1} region is very similar to that observed[2b] for the 2-deuterio-*trans*-1-decalone obtained previously by quenching the corresponding enolate anion in a deuterium oxide–deuterioacetic acid mixture. The nmr spectrum of a benzene solution of the monodeuterated ketone was measured and the areas under the multiplets in the regions δ 1.47–1.98 and 1.98–2.40 were determined. These areas (average of three determinations) corresponded, respectively, to 2.3 protons and 1.7 protons (*cf.* the nmr spectra of ketones **2** and **16**) indicating that the monodeuterated sample contains approximately 70% of the axial deuterio ketone **18** and approximately 30% of the equatorial deuterio ketone **17**. The enolate anion **1**, prepared as previously described, was also quenched in more basic medium (pH 11) obtained from solution of 160 mg of Na_2CO_3 in 20 ml of deuterium oxide. However, the recovered ketone (75% yield) had substantial polydeuteration (17% d_0, 59% d_1, 20% d_2, and 4% d_3 species) in spite of the fact that the ketone was removed from the mixture by pentane extraction as rapidly as conventional manipulations would permit.

B. From the Enol Ether 15.—A solution of 435 mg (2.38 mmol) of the enol ether **15** in 4 ml of 1,2-dimethoxyethane was mixed with 2 ml of a mixture of equal weights of deuterioacetic acid (O-D) and deuterium oxide. The resulting solution was heated on a steam bath for 10 min and then cooled, diluted with excess aqueous $NaHCO_3$, and extracted with ether. The ethereal extract was dried, concentrated, and sublimed (80° at 10 mm) to separate 211 mg (58%) of the monodeuterio ketone **17** and/or **18**, mp 46–48.5°, which contained 13% d_0, 81% d_1, and 6% d_2 species. From a comparable run, the recovered ketone (56% yield) contained 12% d_0, 84% d_1, and 4% d_2 species. The infrared spectra (CCl_4)[17] of these samples differ from the spectra of the previous monodeuterated samples obtained from the enolate anion only in a slight difference in the intensity of a weak band at 1196 cm^{-1}. No difference is apparent among any of these spectra in the region 2100–2250 cm^{-1} where the C–D stretching bands occur.[29] The nmr absorption of a benzene solution of this monodeuterated sample was determined in the regions δ 1.47–1.98 and 1.98–2.40. The areas of these multiplets (two determinations) are equivalent (*i.e.*, 2 H each), suggesting that this monodeuterated sample is composed of more than 90% of the axial isomer **18** and less than 10% of the equatorial isomer **17**.

(29) The stretching frequencies of axial and equatorial C–D bonds of cyclohexane derivatives were studied initially by (a) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956); (b) E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *ibid.*, **78**, 5036 (1956), and have been used subsequently by (c) S. K. Malhotra and H. J. Ringold, *ibid.*, **85**, 1538 (1963); **86**, 1997 (1964). The general frequency differences have been summarized by (d) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N.Y., 1962, p 217, and the possibilities of using these frequency differences for analysis were recently reviewed by (e) E. L. Eliel, *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965). Although the generalization has been made that equatorial C–D bonds will usually have stretching frequencies at higher frequencies (2150–2180 cm^{-1}) than the stretching frequencies (2115–2155 cm^{-1}) of axial C–D bonds, the ranges of these frequencies often overlap and the positions are altered by structural changes in the molecule being studied. Furthermore, whenever the C–D bond is part of a >CHD grouping, at least two C–D stretching bands (symmetric and antisymmetric) are to be expected. Thus, the assignment of observed infrared bands to either axial or equatorial C–D stretching in the absence of other data (such as authentic samples of *both pure monodeuterated* compounds) is most hazardous. For purposes of analysis, the further problem arises that any assumption that the extinctions of equatorial and axial C–D stretching vibrations will be equal is very apt to be erroneous requiring again that *both pure monodeuterated* compounds be available if gross errors in composition estimates are to be avoided. This point is clearly illustrated by the published[29a] spectra of two stereoisomeric monodeuterio ketones and has been discussed in more general terms in ref 29e. For at least the cases studied here the infrared absorption of the axial monodeuterio ketone **18** appeared to be very insensitive to the presence of substantial amounts of equatorial isomer **17** present as an impurity. Therefore, we have concluded that the infrared data would not provide us with a reliable method for estimating the composition of mixtures of monodeuterated ketones **17** and **18**.

C. From the Enamine 20.[30]—A solution prepared from 1.25 g (8.0 mmol) of freshly distilled $POCl_3$ and 10 ml of deuterium oxide was cooled to 0°, covered with 5 ml of pentane, and then 1.03 g (5.0 mmol) of the enamine **20** was added dropwise with stirring. A precipitate formed in the aqueous layer and then redissolved over a 5-min period. After the mixture had been stirred for 20 min, the pentane layer was separated and the aqueous layer was extracted with two additional portions of pentane. Concentration of the combined pentane extracts left only 5 mg of residue which was not investigated further. The remaining aqueous phase was diluted with 300 ml of water (not deuterium oxide) and then stirred with 150 ml of pentane for 15 hr. This pentane layer was separated, combined with two additional pentane extracts of the aqueous layer, dried, and concentrated. Sublimation of the residual solid afforded 453 mg (59%) of the monodeuterated ketone **17** and/or **18**, mp 46.5–48°, which contained 3% d_0, 87% d_1, 8% d_2, and 2% d_3 species. The infrared spectrum (CCl_4)[17] of the sample closely resembles the spectra for the monodeuterated products from the enolate anion **1** and the enol ether **15** except that the band at 2215 cm^{-1} is more intense and the band at 1196 cm^{-1} is less intense. These differences could be attributable to the differing amounts of d_0 and d_2 species in these various samples. The nmr spectrum of a benzene solution of this sample has equivalent areas (*i.e.*, 2 H each) under the multiplets in the regions δ 1.47–1.98 and 1.98–2.40, suggesting that the sample is composed of more than 90% of the axial isomer **18** and less than 10% of the equatorial isomer **17**.

A variety of attempts was made to perform the hydrolysis of the enamine **20** at the level of acidity (pH < 1) originally specified.[12] However, we invariably found that the product remained in the aqueous phase (presumably as the immonium salt) even after the aqueous layer had been stirred with pentane for periods of 24 hr. A mixture prepared from 50 ml of 0.1 *M* deuterium chloride in deuterium oxide (pH ~ 1), 100 ml of pentane, and 200 mg of the enamine was stirred at 25° for 24 hr (only 5 mg of material was in the pentane after 5 min). This pentane extract was dried, concentrated, and sublimed to separate 43 mg (29%) of partially deuterated ketone, mp 46–48°, which contained 2% d_0, 76% d_1, 18% d_2, 3% d_3, and 1% d_4 species. To examine the effect of using a less acidic aqueous solution, a solution of 400 mg (1.9 mmol) of the enamine in 100 ml of pentane was shaken with a mixture of 1 ml of deuterioacetic acid (O–D) and 9 ml of deuterium oxide (pH ~ 4) for 1 min and then the organic layer was separated, dried, and concentrated. Sublimation (80° at 10 mm) afforded 232 mg (58%) of the partially deuterated ketone, mp 46–48°, which contained 8% d_0, 17% d_1, 24% d_2, 28% d_3, and 23% d_4 species. Thus, it would appear that a deuterium oxide solution buffered to a pH in the range <4 and >1 would be optimum for hydrolysis at a reasonably rapid rate with a minimum of hydrogen–deuterium exchange in the immonium salt. However, in our opinion the hydrolysis of the enol ether **15** provides a simpler preparation for the monodeuterated ketone **18**.

Preparation of the Enol Acetate 22.—A mixture of 1.823 g (10 mmol) of the ketones **13** and **14** (mixture of stereoisomers), 10.25 g (100 mmol) of acetic anhydride, 30 ml of carbon tetrachloride, and 0.05 ml of aqueous 70% perchloric acid was stirred at room temperature for 1 hr. The reaction mixture was extracted with ether, washed repeatedly with aqueous sodium carbonate, and then dried, concentrated, and distilled. The enol acetate **22** was collected as 1.831 g (82%) of colorless liquid fractions: bp 108–115° (10 mm); $n^{27}D$ 1.4665–1.4678; ir (CCl_4), 1750 (enol ester C=O) and 1695 cm^{-1} (enol ester C=C); uv (EtOH), end absorption, 210 mμ (ϵ 2340); nmr (CCl_4), δ 2.02 (3 H singlet, CH_3CO), 0.87 (9 H singlet, $(CH_3)_3C$), and 0.7–2.2 (12 H multiplet, aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 224, relatively abundant fragment peaks at *m/e* 182 (M − CH_2=C=O), 125, 98, 82, 57, 55, 43, and 41. The sample exhibited a single gas chromatographic peak[31] accompanied in the earlier distillation fractions by 1–2% of the starting ketone **2**.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.90; H, 10.79.

Protonation of the Enolate Anion 21.—The reaction of 207.8 mg (0.928 mmol) of the enol acetate **22** with 2.0 mmol of methyllithium in 3.0 ml of 1,2-dimethoxyethane was conducted in the usual way to give a solution of the enolate anion **21** containing a slight excess of methyllithium (the red color of the triphenylmethyl carbanion was still present). The solution, which also contained a weighed amount of durene as an internal standard, was added, dropwise and with vigorous stirring, to a solution prepared from 166.5 mg of acetic anhydride (corresponding to 3.3 mmol of acetic acid) and 1.001 g (10 mmol) of sodium acetate in 10.0 ml of water. The resulting solution (pH 5–6) was stirred for 10 min and then extracted with either ether or pentane. After the organic extract had been washed with aqueous $NaHCO_3$, dried, and concentrated, it was analyzed on a gas chromatograph[15] which had been previously calibrated with known mixtures of authentic samples. The composition[15] of the recovered ketone (average value from two runs) was 78% of the *cis* isomer **13** and 22% of the *trans* isomer **14**. Corresponding experiments were performed in which 1,2-dimethoxyethane solutions of the enolate anion **21** were quenched in deuterium oxide containing acetic acid-d_1 and sodium acetate. The recovered ketone contained[15] (average of two runs) 80% of the *cis* isomer **13** and 20% of the *trans* isomer **14**. A collected[15] sample of the ketone (mixture of **13** and **14**) was analyzed for deuterium content by mass spectrometry and found to contain 16% d_0 species, 80% d_1 species, and 4% d_2 species. Control experiments indicated about 5% loss of deuterium d_3 species when trideuterated 2-ethyl-4-*t*-butylcyclohexanone was passed through the column[15] used for collection and analysis. The absence of d_3 species and substantial amounts of d_2 species in these experiments indicates the absence of extensive equilibration after the enolate anion **21** had been protonated at carbon and indicates that the composition of ketones derived from this protonation process is *ca.* 80% of the *cis* ketone **13** (axial C-2 proton) and *ca.* 20% of the *trans* ketone **14** (equatorial C-2 proton).

Registry No.—**2**, 98-53-3; **3**, 7360-39-6; **15**, 3393-97-3; **16**, 15649-46-4; **20**, 4147-00-6; **22**, 15649-48-6; **23**, 15649-49-7; **24**, 15649-50-0.

(30) (a) The hydrolysis of the morpholine enamine (corresponding to **20**) in a medium prepared from deuterium oxide and phosphorus oxychloride has been reported previously (ref 12). We are grateful to Dr. Schaefer for providing us with their exact experimental procedures. (b) The hydrolysis of the pyrrolidine enamine of 2-methylcyclohexanone in a deuterioacetic acid–deuterium oxide mixture was found to be complete within 5 min and to give a mixture of 7% d_0, 57% d_1, 34% d_2, and 2% d_3 species: S. K. Malhotra and F. Johnson, *Tetrahedron Lett.*, 4027 (1965).

(31) A gas chromatography column packed with LAC-728 (diethylene glycol succinate) suspended on Chromosorb P was employed for this analysis.

The Chemistry of Carbanions. XVI. The Stereochemistry of Alkylation of the 1-Acetyl and 1-Cyano Derivatives of 4-(*t*-Butyl)cyclohexane[1a]

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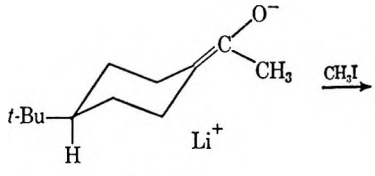
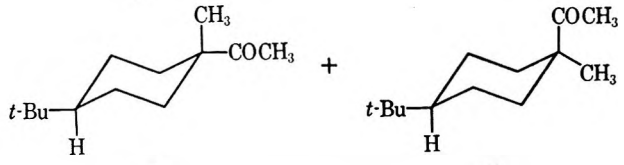
The lithium enolate anions **1** and **26** from methyl 4-*t*-butylcyclohexyl ketone (**9**) and 1-cyano-4-*t*-butylcyclohexane (**21**) were alkylated with methyl iodide in 1,2-dimethoxyethane solution. In each case, the major monoalkylated product was the material containing an equatorial methyl group. These results are discussed in light of earlier N-methylation of 1-ethyl-4-*t*-butylpiperidine (**4**) to form a mixture of salts in which the stereoisomer with an axial methyl group predominated.

As part of an exploration of the various structural features which control the stereochemistry of enolate anion C alkylation,[2] we have examined the stereochemistry of methylation of the enolate **1** to form

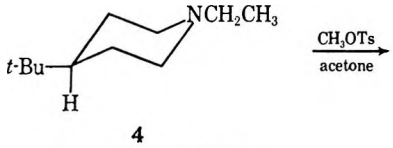


1

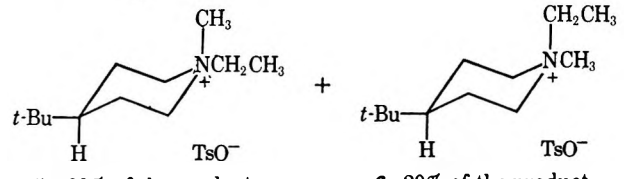


2 **3**

ketones **2** and **3**. The stereochemical problem posed by this reaction differs from the extensively studied[2b] alkylation of cyclohexanone derivatives in that the only portion of the enolate anion contained within the cyclohexane ring is the carbon atom undergoing alkylation. Consequently, the steric interactions incurred by an alkylating agent approaching the enolate anion **1** are related to those which influence the previously studied[3] methylation of the piperidine derivative **4** in which the



4

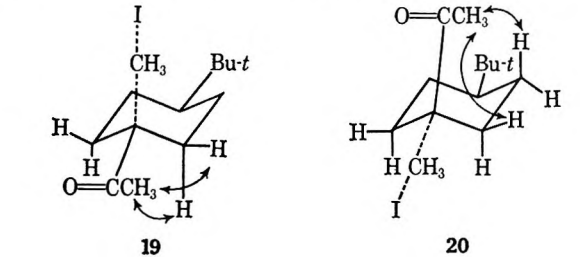


5, 80% of the product **6**, 20% of the product

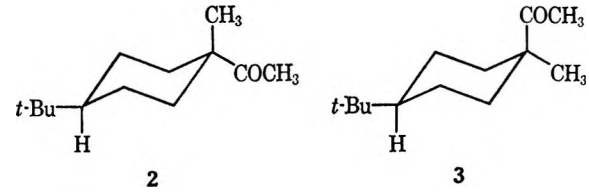
introduction of an axial methyl group to form **5** is approximately four times as rapid as the introduction of a methyl group to form **6**.

A solution of the enolate anion **1** was obtained by reaction of the enol acetate **7** with methyllithium in 1,2-dimethoxyethane (DME)[4] as illustrated in Scheme I. Under these conditions, varying amounts of the dialkylated by-products **13** and **14** were obtained. However, neither of the ethyl ketones **11**, the products expected if equilibration of the enolate anion **1** had occurred prior to alkylation, could be detected. The equations in Scheme II illustrate the procedures used to establish the stereochemistry of the alkylated products **2** and **3** by conversion into the known[5] alcohols **15** and **16**. The stereochemistry of the major dialkylated product **13** was established by the indicated synthesis from the known[6] acid **17**. The results indicate that introduction of an equatorial methyl group to form **3** is approximately five times as fast as introduction of an axial methyl group to form **2**.

It seemed possible that different stereochemical preferences found for the alkylation of the piperidine derivative **4** (introduction of an axial methyl group favored) and the enolate anion **1** (introduction of an equatorial methyl group favored) could be attributed to the stereoelectronic factor requiring a specific orientation of the acetyl group during alkylation of the enolate **1**. In particular, the necessity for the acetyl group to lie in a plane perpendicular to the forming methyl–carbon bond[2] leads to the conclusion that the transition states for alkylation should be portrayed by structures **19** and **20**. In these structures nonbonding



19 **20**



2 **3**

(1) (a) This research has been supported by research grants from the National Institutes of Health (Grant No. 08761) and from the Directorate of Chemical Sciences, Air Force Office of Scientific Research (Grant No. AF-AFOSR-573); (b) National Institutes of Health Predoctoral Fellow, 1965–1966.

(2) For reviews of this subject, see (a) J. M. Conia, *Rec. Chem. Progr.* (Kresege-Hooker Sci. Lib.), **24**, 43 (1963); (b) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965).

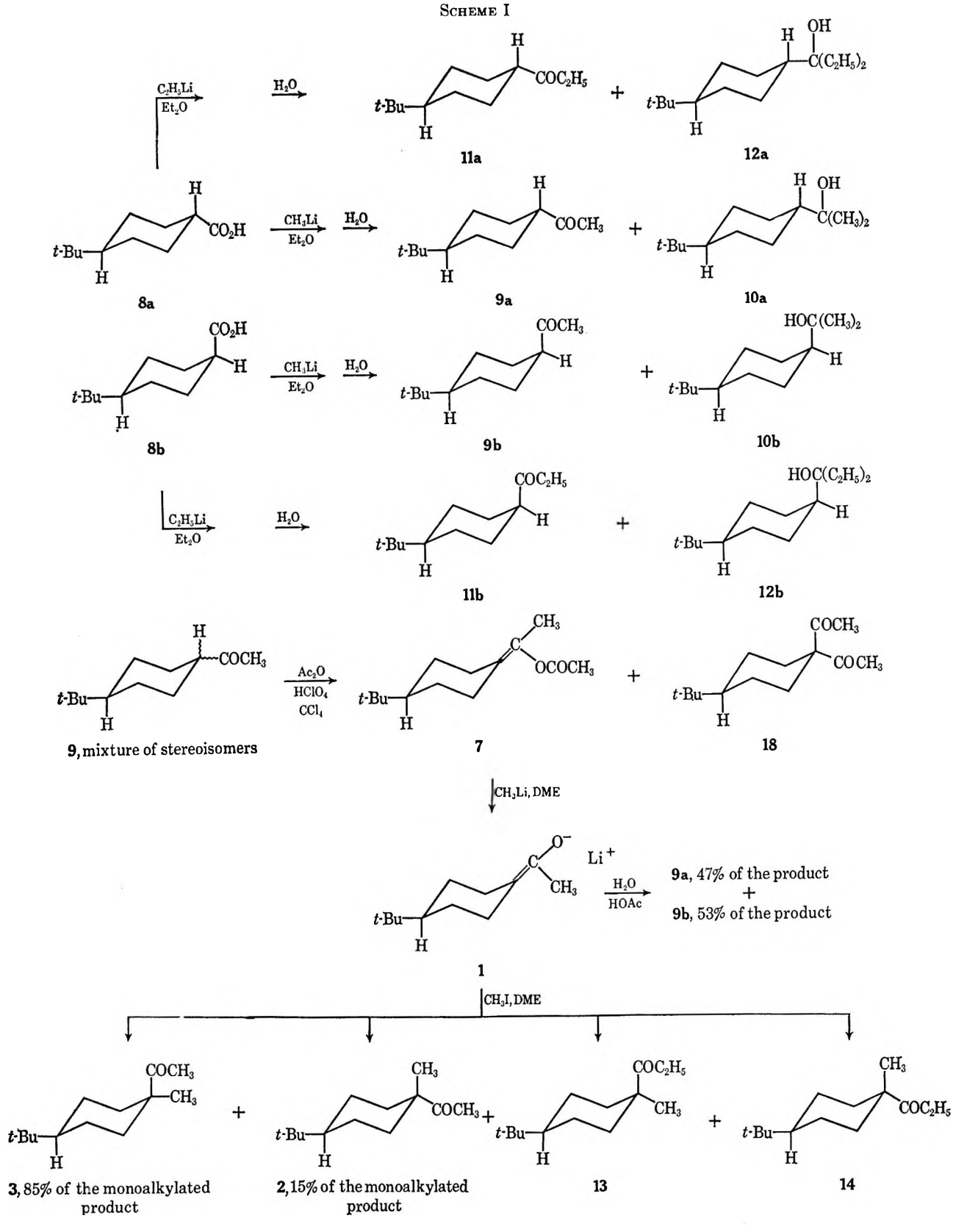
(3) (a) H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.*, **31**, 1073 (1966); (b) also see D. R. Brown, B. G. Hutley, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 719 (1966); (c) D. R. Brown, J. McKenna, J. M. McKenna, J. M. Stuart, and B. G. Hutley, *ibid.*, 380 (1967).

(4) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 2502 (1965); (b) H. O. House and C. J. Blankley, *ibid.*, **32**, 1741 (1966); (c) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *ibid.*, **32**, 935 (1966).

(5) For leading references, see H. O. House and W. L. Respess, *J. Org. Chem.*, **30**, 301 (1965).

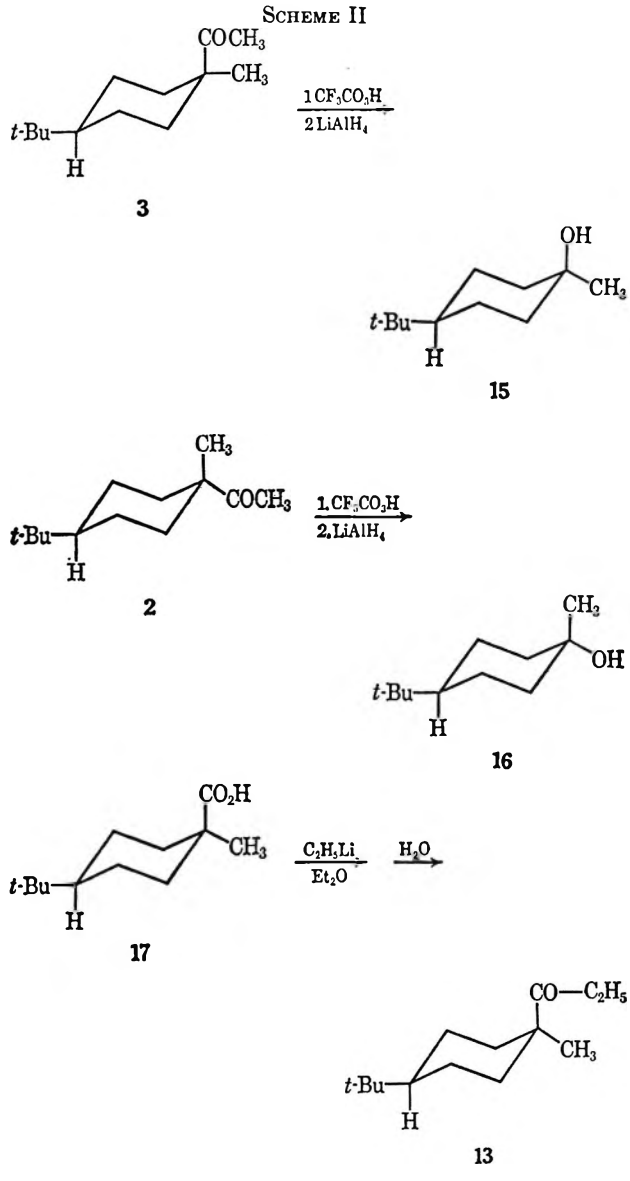
(6) F. D. Greene and A. Fang, unpublished work.

SCHEME I

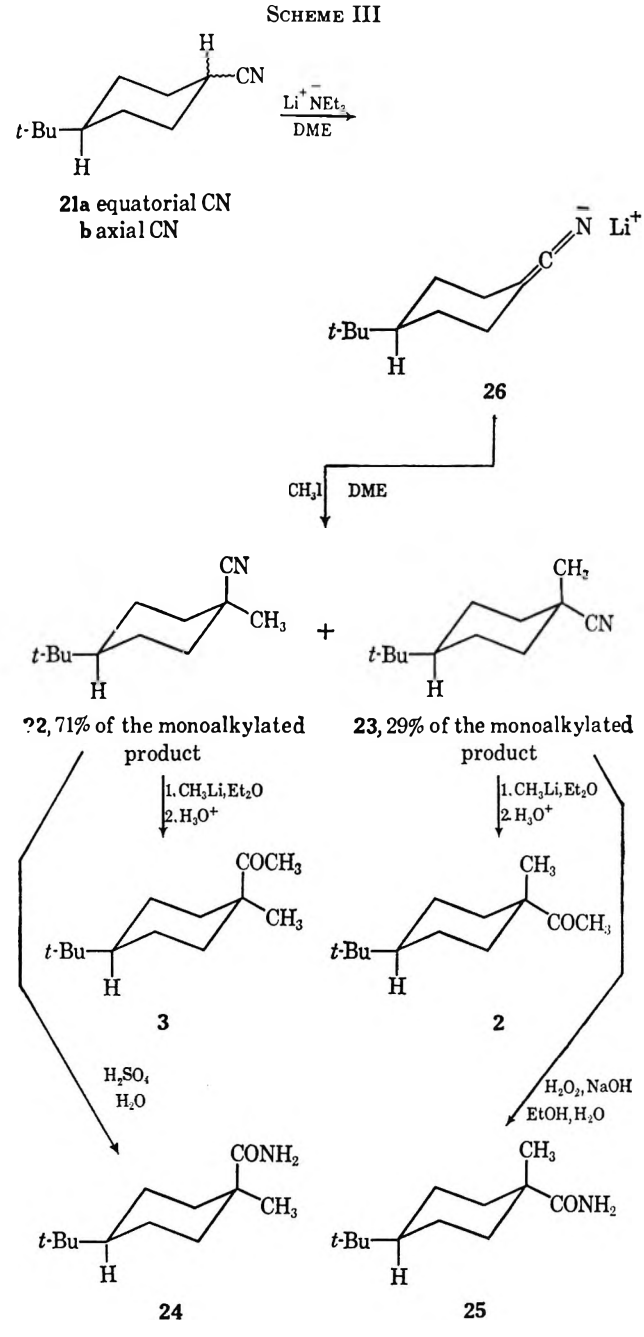


interactions which interfere with the necessary conformation of the acetyl group (represented by heavy arrows in **19** and **20**) appear to be more severe in structure **19** leading to the ketone **2** with an axial methyl group. This consideration does not arise in the alkylation of the related N-ethylamine **4** since no particular orientation of the N-ethyl group is required. To test this hypothesis, the related nitrile **21** was alkylated under comparable conditions. The relatively small, linear cyano function would appear much less subject to the types of nonbonding interactions represented in structures **19** and **20** and, consequently, might be expected to exhibit a stereochemical preference in alkylation similar to that seen for the amine **4**. In fact, the stereochemical results of this alkylation (Scheme III) correspond to the results obtained on alkylation of the

SCHEME II



SCHEME III



enolate anion **1** in that introduction of an equatorial methyl group was approximately three times as rapid as introduction of an axial methyl group.[7] The reactions used to establish the stereochemistry of the alkylated products **22** and **23** are summarized in Scheme III.

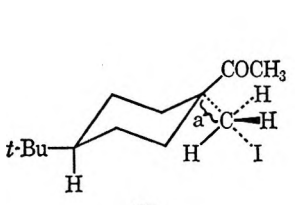
These results indicate that, in the absence of serious opposing steric factors, the methylation of stabilized cyclohexyl carbanion derivatives such as **1** and **26** gives predominantly products with equatorial methyl groups. The corresponding amine **4**, which might be considered as a crude model for such carbanions, yields predominantly the product with an axial methyl group and protonation of the enolate **1** with aqueous acetic acid shows little evidence of any stereoselectivity.[8]

The equilibrium concentrations of the ketones **9** (90% of **9a** and 10% of **9b** in 1,2-dimethoxyethane at 25°) indicate that the free-energy difference between axial and equatorial acetyl groups is approximately 1.3 kcal/mol. The energy difference between these values and the value (1.8 kcal/mol)[7b] for an ethyl group is not sufficient that one can account for the different stereochemical paths for C and N alkylation with differences in stabilities of alkylated products. Consequently, the energy differences between axial and equatorial alkylation at carbon or at nitrogen must be greater in the transition states than in the alkylated products. More specifically, the results suggest that an entering pentacoordinate methyl group has a greater effective steric bulk than an acetyl or nitrile function when it is becoming bonded to carbon (*i.e.*, **27a** of lower energy than **27b**) but has a smaller effective steric bulk than a fully

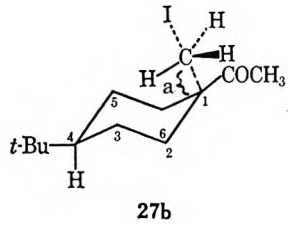
(7) (a) Methylation of the enolate anion derived from a cyclohexanecarboxaldehyde derivative has also been found to result in predominant formation of the product with an equatorial methyl group: R. E. Ireland and L. N. Mander, *Tetrahedron Lett.*, 3453 (1964). (b) The free-energy differences between axial and equatorial substituents are reported to be 1.7 kcal/mol for a methyl group (E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N.Y., 1966, p 44) and 1.3–1.4 kcal/mol for a formyl group (G. W. Buchanan and J. B. Stothers, *Chem. Commun.*, 179 (1967)).

(8) Studies of the stereochemistry of enolate protonation are complicated by the fact that the rates of protonation at carbon and at oxygen are presumably both diffusion controlled and, consequently, approximately equal; see M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964). As a result, approximately half of the mixture of stereoisomeric ketones **9** is derived not from the enolate but from subsequent protonation of the enol at carbon.

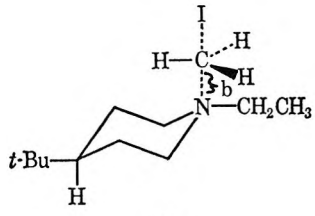
bonded alkyl group (*e.g.*, methyl, ethyl, benzyl)[3] when it is becoming bonded to nitrogen (*i.e.*, **28a** of lower energy than **28b**). Two general explanations for



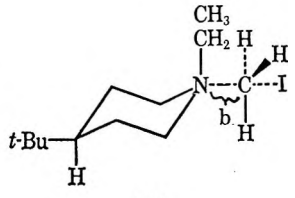
27a



27b



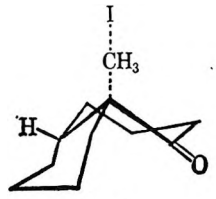
28a



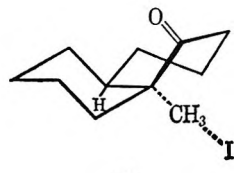
28b

this apparent difference in the effective size of an entering methyl group can be considered. (1) The forming bond to the alkylating agent is more completely formed, and consequently shorter, in carbon alkylation (bond a in **27**) than is the case in the nitrogen alkylation (bond b in **28**). (2) The direction of attack by the entering methyl group is different in the two types of alkylation. Specifically, in the axial nitrogen alkylation the entering group presumably approaches the tetrahedral nitrogen atom from a direction essentially perpendicular to the plane of the piperidine ring as indicated in structure **28a**. Since the nucleophilic centers in initial enolate anions **1** and **26** (and their associated cations) are not tetrahedral but planar, the entering axial methyl group will presumably approach C-1 on a path which is not perpendicular to the plane of the cyclohexane ring but rather tilted back toward C-3 and C-5 as illustrated in structure **27b**. This reaction path will bring the entering methyl group closer to the axial hydrogens at C-3 and C-5 (structure **27b**) than is the case in the corresponding N alkylation (structure **28a**) and would serve to destabilize this reaction path leading to axial C alkylation. As formation of the new C–C bond at the transition state becomes more complete, this latter factor will become less important since with complete C–C bond formation the C-1 carbon will be tetrahedral and the methyl group will be perpendicular to the cyclohexane ring. At the present time our available data[4] are most consistent with the idea that the transition states for both amine and enolate alkylations resembled the starting materials more than the products. Consequently, we favor the second explanation in which the orientation of the entering alkyl group rather than the length of the forming bond is assigned primary importance. We hope to obtain information bearing on these questions from experiments currently in progress.

Finally, it should be noted that the preference for alkylation of a cyclohexyl ketone to introduce an equatorial alkyl group agrees very well with the observation that bridgehead alkylation of 1-decalone derivatives[2,4a] and 1-keto perhydroindan derivatives[2,4b] favors the production of *cis*-fused products. In either of the probable[4c] transition states (**29** or **30**)



29



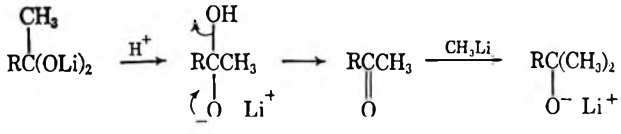
30

leading to 9-methyl-*cis*-1-decalone, it will be noted that the entering methyl group is equatorial with respect to the nonoxygenated cyclohexane ring.

Experimental Section[9]

Preparation of the Starting Materials.—The *cis* (**8b**, mp 116–117.5°, lit.[10a] mp 117–118°) and *trans* (**8a**, mp 175–176°, lit. mp 176–177°,[10b] 174.5–175°[10a]) acids were prepared and separated as previously described.[10] The purity of each acid was verified by esterification of each isomer with excess ethereal diazomethane followed by gas chromatographic analysis;[11,12] the *cis*-methyl ester was eluted more rapidly than the *trans* isomer. Ethereal solutions of methyllithium were prepared and analyzed as previously described.[13]

Preparation of the Ketones 9 and 11.—Since our initial reaction of the acid **8** with ethereal methyllithium led to mixtures which contained both the expected ketones **9** and variable amounts of the alcohols, we studied various methods to diminish the proportion of alcohol formed in the reaction. We concluded that the bulk of the alcohol by-product was formed during the quenching procedure when the ether solution containing the lithium alkoxide[14] and methyllithium was added to aqueous acid. Evidently the indicated reactions occur sufficiently rapidly that they may compete with the rate of mixing of the ethereal solution containing excess methyllithium with aqueous acid. The



initial addition of methyllithium to the carboxylic acid was less critical since small amounts (1–3%) of alcohol were formed by dropwise addition of methyllithium to either the free acid **8** or to its lithium salt (prepared from **8** and lithium hydride), provided that mixing was sufficiently rapid during the subsequent quenching procedure. The following procedure was found to be reproducible and to give small amounts of alcohol by-product.

To a cold (0°), vigorously stirred solution of 7.235 g (37.9 mmol) of a mixture of stereoisomeric acids **8** in 250 ml of ether was added, dropwise over a period of 0.75 hr, 60 ml of an ethereal solution containing 76.9 mmol of methyllithium. During the addition a voluminous white precipitate (the lithium salt of the acid) separated and then redissolved as the addition was continued. The resulting faintly turbid solution was stirred at

(9) 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 with a CEC Model 21-130 mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. All reactions utilizing organolithium reagents were conducted under a nitrogen atmosphere.

(10) (a) H. H. Lau and H. Hart, *J. Amer. Chem. Soc.*, **81**, 4897 (1959); (b) R. D. Stolow, *ibid.*, **81**, 5806 (1959); (c) M. Tichý, J. Jonas, and J. Sicher, *Coll. Czech. Chem. Commun.*, **24**, 3434 (1959).

(11) A gas chromatography column packed with silicone fluid, no. 710, suspended on Chromosorb P was employed for this analysis.

(12) The *cis*-methyl ester is reported to melt at 26.1–26.7° and the *trans*-methyl ester is reported to boil at 84° (0.9 mm): E. A. S. Cowell, N. B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960).

(13) H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965).

(14) H. F. Bluhm, H. V. Donn, and H. D. Zook, *J. Amer. Chem. Soc.*, **77**, 4406 (1955).

room temperature for 4 hr and then 50-ml aliquots were removed from the reaction mixture and added, dropwise and with stirring, to fresh portions of ice and dilute aqueous hydrochloric acid. The combined ether layers were washed with aqueous sodium carbonate and with water and then were dried and concentrated. Distillation of the residual liquid (6.59 g) separated 6.54 g (94.8%) of colorless liquid, bp 67–72° (0.57 mm), $n^{25}D$ 1.4593, which contained[15] 9% of the *cis* ketone **9b** (eluted first) and 91% of the *trans* ketone **9a** (eluted second). Neither of the alcohols **10** was detected. Acidification of the aqueous sodium carbonate washings afforded 0.24 g of the starting acid **8**.

The reaction of 165.7 mg (0.90 mmol) of the *trans* acid **8a** with 3.46 mmol of methyllithium in 6.7 ml of ether was performed following the above procedure except that special precautions to obtain rapid mixing during the addition and quenching steps were not observed. The crude neutral product, an oil, contained[16] the *trans* ketone **9a** (46%, first eluted) and the *trans* alcohol **10a** (54% eluted second). Samples of each of these components were collected.[16] The *trans* **ketone 9a** was obtained as a colorless liquid: ir (CCl_4), 1710 cm^{-1} (C=O); nmr ($CDCl_3$), δ 0.88 (9 H singlet, $(CH_3)_3C$), 2.20 (3 H singlet, $COCH_3$), and 1.0–2.5 multiplet (10 H, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 57 ($(CH_3)_3C^+$), 43 ($CH_3C{\equiv}O^+$), and 41.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.14; H, 12.16.

The *trans* **alcohol 10a** was obtained as a solid which was sublimed (75° at 0.15 mm) to separate white needles: mp 101–102°; ir (CCl_4), 3590 cm^{-1} (OH); nmr ($CDCl_3$), δ 0.87 (9 H singlet, $(CH_3)_3C$), and 1.19 (6 H singlet, $(CH_3)_2C$); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 59 ($(CH_3)_2C{=}O^+H$) and 57 ($(CH_3)_3C^+$).

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.83; H, 13.21.

Similarly, reaction of 111.2 mg (0.603 mmol) of the *cis* acid **8b** with 2.18 mmol of methyllithium in 4.7 ml of ether yielded a crude neutral product which contained[16] the *cis* ketone **9b** (58%, eluted first) and the *cis* alcohol **10b** (42%). A collected[16] sample of the *cis* **ketone 9b** was a colorless liquid: ir (CCl_4), 1710 cm^{-1} (C=O); nmr ($CDCl_3$), δ 0.84 (9 H singlet, $(CH_3)_3C$), 2.22 (3 H singlet, CH_3CO), and 1.0–2.8 multiplet (10 H, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 71, 57 ($(CH_3)_3C^+$), 43 ($CH_3C{\equiv}O^+$), and 41.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.85; H, 12.08.

A collected[16] sample of the *cis* **alcohol 10b** was a colorless oil: ir (CCl_4), 3600 (unassociated OH) and 3420 cm^{-1} (broad, associated OH); nmr ($CDCl_3$), 0.87 (9 H singlet, $(CH_3)_3C$) and 1.22 (6 H singlet, $(CH_3)_2C$); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 59 ($(CH_3)_2C{=}{}^+OH$) and 57 ($(CH_3)_3C^+$).

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.69; H, 13.15.

After a mixture of 99.4 mg (0.54 mol) of the *trans* acid **8a** and 1.08 mmol of ethyllithium in 5.3 ml of benzene had been allowed to react for 2 hr, the resulting solution was added, dropwise and with stirring, to dilute aqueous hydrochloric acid. The crude neutral product, isolated as previously described, contained[15] the *trans* ketone **11a** (*ca.* 60%, eluted first) and a product thought to be the *trans* alcohol **12a** (*ca.* 40%, eluted second): ir (CCl_4), 3600 and 3460 cm^{-1} (OH). A collected[15] sample of the *trans* **ketone 11a** was obtained as a colorless liquid: ir (CCl_4), 1715 cm^{-1} (C=O); nmr (CCl_4), δ 2.37 (2 H quadruplet, J = 7 cps, $COCH_2$–), 0.97 (3 H triplet, J = 7 cps, CH_3C), and 0.84 (9 H singlet, $(CH_3)_3C$–); mass spectrum, molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 139, 83, 57, 55, and 41.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.60; H, 12.41.

The same procedure was repeated with 47.6 mg (0.258 mmol) of the *cis* acid **8b** and 0.516 mmol of ethyllithium in 4.1 ml of benzene to yield a crude neutral product which contained[15] the *cis* ketone **11b** (*ca.* 70%, eluted first) and a component believed to be the *cis* alcohol **12b** (*ca.* 30%, eluted second): ir (CCl_4), 3600 and 3470 cm^{-1} (OH). A collected sample of the *cis* **ketone 11b** was obtained as a colorless liquid: ir (CCl_4), 1715 cm^{-1} (C=O); nmr (CCl_4), δ 2.38 (2 H quadruplet, J = 7 cps, $CO-CH_2$–), 0.99 (3 H triplet, J = 7 cps, CH_3C), and 0.81 (9 H singlet, $(CH_3)_3C$–); mass spectrum, molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 139, 111, 85, 83, 57, 55, and 41.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.65; H, 12.39.

Examination of the gas chromatographic behavior[16] of the ethyl ketones **11** established that the *cis*-ethyl ketone **11b** was eluted more rapidly than the *trans*-ethyl ketone **11a** and that each of the ethyl ketones **11** was resolved from the subsequently described alkylation products **2**, **3**, **13**, and **14**.

Preparation of the Enol Acetate 7.—A solution of 19.19 g (0.0968 mol) of the ketone **9** (a mixture of stereoisomers), 100 g (0.978 mol) of acetic anhydride, and 0.5 ml of aqueous 70% perchloric acid in 300 ml of carbon tetrachloride was stirred at room temperature for 1.5 hr and then diluted with 500 ml of pentane. The resulting solution was stirred with 200 ml of saturated aqueous sodium bicarbonate to which additional portions of solid sodium bicarbonate were added periodically until the evolution of carbon dioxide ceased. After the organic layer had been separated, dried, and concentrated, the residual oil (22.3 g) was distilled through a 90-cm spinning-band column. Fractions collected at 143–148° (10 mm), $n^{29}D$ 1.4689, amounted to 10.26 g (47%) and contained[15] the **enol acetate 7** (eluted first) contaminated with 1.5% of the diketone **18** (eluted second). The spectra of the enol acetate **7** indicate it to be the more highly substituted isomer: ir (CCl_4), 1755 (enol ester C=O) and 1690 cm^{-1} (enol C=C); nmr (CCl_4), δ 2.06 (3 H singlet, CH_3COO–), 1.82 (3 H broad singlet, $CH_3C{=}C$), 0.86 (9 H singlet, $(CH_3)_3C$–), and 1.0–2.7 multiplet (9 H, aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 224 with abundant fragment peaks at *m/e* 182 (M − $CH_2{=}C{=}O$), 57, 43, and 41.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.77; H, 10.84.

The later fractions from the fractional distillation contained increasing amounts of the solid diketone **18** which could be separated by recrystallization from methanol. The pure **diketone 18** separated as white plates: mp 82.0–82.5°; ir (CCl_4), 1695 and 1715 cm^{-1} (shoulder) (C=O of nonenolized β-diketone); nmr ($CDCl_3$), δ 2.10 and 2.05 (two 3 H singlets, CH_3CO–), 0.80 (9 H singlet, $(CH_3)_3C$–), and 1.0–2.7 multiplet (9 H, aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 224 with abundant fragment peaks at *m/e* 182, 57, 43, and 41.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.77; H, 10.60.

From reactions of the methyl ketone **9** with isopropenyl acetate and *p*-toluenesulfonic acid,[4] mixtures of enol acetates were obtained which contained[16] both the more highly substituted enol acetate (eluted first) and a more slowly eluted component believed to be a mixture of the stereoisomeric less highly substituted enol acetates. The infrared and nmr spectra of this mixture were consistent with this assignment. Acid-catalyzed isomerization[4] of this mixture converted the material into a mixture of enol acetates which contained[16] *ca.* 95% of the more highly substituted enol acetate **7**. As had been noted previously,[4b] formation of the C-acetylated product **18** was not a significant side reaction when the isopropenyl acetate procedure was employed for the preparation of the enol acetate.

Methylation of the Enolate Anion 1.—Following previously described procedures,[4] the enol acetate **7** was added to solutions of methyllithium in 1,2-dimethoxyethane until the triphenylmethyl anion indicator was almost decolorized. The resulting solutions of enolate anion were stirred vigorously at room temperature and methyl iodide was added in one portion. After each reaction mixture was stirred for the time specified in Table I,

TABLE I

METHYLATION OF THE ENOLATE ANION 1 IN DIMETHOXYETHANE SOLUTION

Concn of enolate anion, *M*	Concn of methyl iodide, *M*	Reaction time, sec	Products, % yield					
			9a	**9b**	**2**	**3**	**14**	**13**
0.088	0.36	30	3.3	2.1	7.2	54.8	1.8	15.5
0.096	0.44	10	4.6	5.0	10.2	56.8	1.9	8.3
0.089	0.35	*Ca.* 2	13.2	13.2	8.1	47.2	...	2.5

a 10-ml aliquot of dilute, aqueous hydrochloric acid was added, followed by a weighed sample of tetralin (as an internal standard). The reaction mixtures were partitioned between water and ether

(15) A gas chromatography column packed with LAC-728 (diethylene glycol succinate) suspended on Chromosorb P was employed for this analysis.

(16) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis.

and the ethereal layer was washed with aqueous sodium bicarbonate, dried, concentrated, and analyzed by gas chromatography.[16] The gas chromatography equipment was calibrated with known mixtures of collected samples to permit the yield calculations listed in Table I. The retention times[16] of the components being analyzed follow: tetralin, 27.2 min; monoalkylated ketone **3**, 38.2 min; starting ketone **9b**, 41.4 min; dialkylated ketone **13**, 43.2 min; starting ketone **9a**, 51.6 min; monoalkylated ketone **2**, 56.4 min; and dialkylated ketone **14**, 68.0 min.

In another experiment a solution of the enolate anion **1**, from 0.568 mmol of the enol acetate **7** and 1.32 mmol of methyllithium, in 6.6 ml of 1,2-dimethoxyethane containing a weighed amount of tetralin was added dropwise to a solution of 1.29 mmol of acetic acid in 63 ml of water. The ethereal extract from this mixture contained[15] (average values from two runs) 47% of the equatorial ketone **9a** and 53% of the axial ketone **9b**; the calculated recovery of the ketone **9** was 72%.

To determine the equilibrium composition of the ketones **9**, a weighed sample (*ca.* 0.1 mmol) of each pure ketone was added to 2.00 ml of 1,2-dimethoxyethane which contained a weighed amount (*ca.* 10 mg) of tetralin as an internal standard and 0.05 mmol of alcohol-free potassium *t*-butoxide. Each solution was stirred at room temperature for 2 hr and then partitioned between ether and dilute aqueous hydrochloric acid. The neutral product recovered from each ether solution contained[15] 90% of the equatorial ketone **9a** and 10% of the axial ketone **9b**; the calculated recovery of ketones **9** exceeded 90% in each case.

Identification of the Alkylation Products from Ketone 9.—Each component was collected from the gas chromatograph[15,16] of an appropriate alkylation reaction. The monoalkylated ketone **3** was separated as a crystalline solid which was sublimed (40° at 10 mm) to separate white needles: mp 46.5–47°; ir (CCl_4), 1705 cm^{-1} (C=O); nmr ($CDCl_3$), δ 2.05 (3 H singlet, CH_3CO), 0.98 (3 H singlet, CH_3C), and 0.73 (9 H singlet, $(CH_3)_3C$–); mass spectrum, weak molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 97, 57, 55, 43, and 41.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.52; H, 12.21.

The monoalkylated ketone **2**, a crystalline solid, was sublimed (60° at 20 mm) to afford white plates: mp 45.5–46.5°; ir (CCl_4), 1705 cm^{-1} (C=O); nmr ($CDCl_3$), δ 2.10 (3 H singlet, CH_3CO), 1.10 (3 H singlet, CH_3C), and 0.85 (9 H singlet, $(CH_3)_3C$–); mass spectrum, weak molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 97, 83, 69, 57, 55, 43, and 41.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.77; H, 12.35.

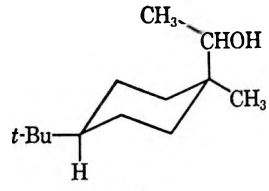
The dialkylated ketone **13** was obtained as a colorless liquid: ir (CCl_4), 1710 cm^{-1} (C=O); nmr ($CDCl_3$), δ 2.48 (2 H quadruplet, J = 7 cps, $-CH_2CO-$), 1.03 singlet superimposed on the center peak of a triplet with J = 7 cps, (6 H, two CH_3C groups), and 0.81 (9 H singlet, $(CH_3)_3C$–); mass spectrum, weak molecular ion peak at *m/e* 210 with abundant fragment peaks at *m/e* 97, 83, 69, 57, 55, and 41.

Anal. Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.95; H, 12.37.

A previously characterized[6] sample (65.4 mg or 0.329 mmol) of the *cis* acid **17** (mp 129–130.5°) was allowed to react with 0.658 mmol of ethyllithium in 4.4 ml of benzene following the previously described procedure. The crude neutral product exhibited only a single gas chromatographic peak[15] corresponding to the ketone **13**. A collected[15] sample was identified with ketone **13** by comparison of infrared spectra.

The minor dialkylated ketone **14** was separated as a colorless liquid which still contained an impurity which was only partially resolved by gas chromatography.[15,16] Although we were unsuccessful in obtaining a pure sample of this minor product, the spectroscopic properties of the crude material leave little doubt as to its identity: ir (CCl_4), 1705 cm^{-1} (C=O); nmr (CCl_4), δ 2.41 (2 H quadruplet, $-CH_2CO-$), 0.86 (9 H singlet, $(CH_3)_3C$–), and 0.8–2.0 multiplet (aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 210 with abundant fragment peaks at *m/e* 97, 83, 69, 57, 55, and 41.

Baeyer–Villiger Oxidation of the Ketones 2 and 3.—A mixture of 76.3 mg (0.39 mmol) of the ketone **3**, 447 mg of disodium hydrogen phosphate, and *ca.* 1.9 mmol of peroxytrifluoroacetic acid[17] in 1.2 ml of methylene chloride was stirred at room temperature for 3 days. Since the crude neutral product had infrared absorption indicative of a mixture of trifluoroacetate (1780 cm^{-1}), acetate (1730 cm^{-1}), and ketone (1700 cm^{-1}) functions, the material was treated with additional portions of peroxytrifluoroacetic acid and disodium hydrogen phosphate and stirring was continued for an additional 2 days. The resulting neutral product, which still contained some unchanged ketone, was treated with a mixture of 34.5 mg (0.908 mmol) of lithium aluminum hydride and 1.6 ml of ether. The resulting mixture was stirred at room temperature for 1.5 hr and then treated with sufficient dilute aqueous sodium hydroxide to precipitate the aluminum and lithium salts as a granular precipitate. After the precipitate had been separated and washed with ether, the combined ether solutions were concentrated. The residual liquid contained[15] a mixture of the tertiary alcohol **15** (eluted first) and the secondary alcohol **31** (eluted second, from reduction of the unchanged ketone **3**). A sample of the alcohol **31**, obtained by reduction of the



31

ketone **3** with ethereal lithium aluminum hydride, was identified with a collected[15] sample of the above component by comparison of infrared spectra, mass spectra, and gas chromatographic retention times. A collected[15] sample of the tertiary alcohol **15** was identified with a previously described[5] sample by comparison of gas chromatographic retention times and infrared spectra.

Reaction of 22.1 mg (0.113 mmol) of the ketone **2** with *ca.* 0.67 mmol of peroxytrifluoroacetic acid[17] and 129 mg of disodium hydrogen phosphate in 0.43 ml of refluxing methylene chloride for 1.5 hr afforded a crude neutral product which no longer contained any starting ketone. Reduction with 25.6 mg (0.676 mmol) of lithium aluminum hydride in 1.0 ml of ether as previously described yielded a crude neutral product which exhibited a single gas chromatographic peak[15] corresponding to the tertiary alcohol **16**. A collected sample was identified with a previously described[5] sample of the alcohol **16** by comparison of gas chromatographic retention times and infrared spectra.

Preparation of the Nitrile 21.—Following previously described procedures,[18] 6.0 g of a mixture of stereoisomeric acids **8** was converted into 5.35 g (89.5%) of a mixture of stereoisomeric amides, mp 156.5–159° (lit.[18] melting point of *cis* isomer, 162.7–163.9°; *trans*, 134.2–135.8°), and 3.00 g of this amide mixture was dehydrated to yield 2.50 g (92.3%) of a mixture of stereoisomeric nitriles **21**, bp 117.5–119° (12 mm). This mixture contained[15] *ca.* 58% of the axial nitrile **21b** (eluted first) and *ca.* 42% of equatorial nitrile **21a** (eluted second). Collection[15] from the gas chromatograph afforded pure samples of the *cis*-nitrile **21b**, mp 54–55° (lit.[18] mp 56.3–57.3°) and the *trans*-nitrile **21a**, mp 31–32° (lit.[18] mp 33.4–34.7°).

Methylation of the Nitrile 21.—To a solution of 21.6 mmol of methyllithium and several milligrams of triphenylmethane (as an indicator) in 35 ml of 1,2-dimethoxyethane was added 2.15 ml (20.4 mmol) of diethylamine. To the resulting red solution was added a solution of 2.80 g (17.0 mmol) of the nitrile **21** (mixture of stereoisomers) in 3.0 ml of 1,2-dimethoxyethane. After the pale red solution had been warmed to 50° for 10 min and then cooled to room temperature, 5.45 ml (87.2 mmol) of methyl iodide was added to the mixture rapidly with stirring. After the exothermic reaction subsided, the mixture was stirred for 25 min and then partitioned between ether and aqueous hydrochloric acid. The ethereal layer was washed with water and aqueous sodium thiosulfate, dried, and concentrated. Distillation in a short-path still separated 2.92 g (95.7%) of alkylated product which contained (in order of increasing retention time)[15] the axial nitrile **22** (*ca.* 68%), the axial nitrile **21b** (*ca.* 2%), the equatorial nitrile **23** (*ca.* 29%), and the equatorial nitrile **21a** (*ca.* 3%). This alkylation was repeated on a smaller scale in the presence of an internal standard (biphenyl). Utilizing previously calibrated gas chromatography apparatus,[15] the calculated yields were 68% of the *cis*-nitrile **22** and 28% of the

(17) W. D. Emmons and G. B. Lucas, *J. Amer. Chem. Soc.*, **77**, 2287 (1955).

(18) B. Rickborn and F. R. Jensen, *J. Org. Chem.*, **27**, 4608 (1962).

trans-nitrile **23** corresponding to a 71:29 ratio of the monoalkylated products.

To examine the effect of using a less reactive alkylating agent, a cold (−70°) solution of methyl chloride (*ca.* 16 mmol) in 2.0 ml of 1,2-dimethoxyethane was treated with a solution of the anion **26**, prepared from 1.08 mmol of the nitrile **21** and 1.40 mmol of lithium diethylamide in 3.8 ml of 1,2-dimethoxyethane. After the addition was complete, the solution was allowed to warm to room temperature and was stirred for 23 hr and then subjected to the previously described isolation procedure. After a weighed amount of internal standard had been added, analysis[15] indicated the yields of alkylated products to be 67% of **22** and 13% of **23** corresponding to an 84:16 ratio of monoalkylated products.

Samples of each of the alkylated nitriles **22** and **23** were collected[15] for characterization. Sublimation (65° at 10 mm) of the axial nitrile **22** afforded the material as white plates: mp 48.5–49.5°; ir (CCl_4), 2230 cm^{-1} (C≡N); nmr (CCl_4), δ 1.1–2.3 (9 H multiplet, aliphatic CH), 1.37 (3 H singlet, CH_3C), and 0.94 (9 H singlet, $(CH_3)_3C$); mass spectrum, weak molecular ion at *m/e* 179 with abundant fragment peaks at *m/e* 123, 108, 95, 57, 41, and 39.

Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81. Found: C, 80.62; H, 12.04.

The equatorial nitrile **23** sublimed (80° at 10 mm) as white needles: mp 49.5–50°; ir (CCl_4), 2235 cm^{-1} (C≡N); nmr (CCl_4), δ 1.0–2.2 (9 H multiplet, aliphatic CH), 1.40 (3 H singlet, CH_3C), and 0.90 (9 H singlet $(CH_3)_3C$); mass spectrum, weak molecular ion peak at *m/e* 179 with abundant fragment peaks at *m/e* 124, 108, 95, 57, 56, 55, 41, and 39.

Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81. Found: C, 80.55; H, 11.89.

The Stereochemistry of Nitriles 22 and 23. A. Conversion into Ketones 2 or 3.—A solution of 62.7 mg (0.35 mmol) of the nitrile **22** and 1.44 mmol of methyllithium in 3.6 ml of ether was refluxed with stirring for 15 hr and then poured into 50 ml of dilute, aqueous hydrochloric acid. The resulting mixture was heated on a steam bath overnight and then extracted with ether. The ethereal solution was dried and concentrated to leave the crude ketone **3**[15] as a residual solid. Sublimation (70° at 0.12 mm) afforded 62.1 mg (91.7%) of the ketone **3**, mp 47.5–48°, identified with the previously described sample by a mixture melting point determination and by comparison of gas chromatographic retention times[15] and infrared and mass spectra.

The comparable reaction of 46.3 mg (0.26 mmol) of the nitrile **23** with 1.3 mmol of methyllithium and subsequent hydrolysis yielded, after sublimation (70° at 10 mm), 44.1 mg (87%) of the ketone **2**, mp 45–46°, identified with the previous sample by all of the criteria listed above.

B. Conversion into Amides 24 and 25.—A mixture of 42.0 mg (0.23 mmol) of the nitrile **23**, 0.1 ml (0.87 mmol) of aqueous 30% hydrogen peroxide, 0.15 ml of absolute ethanol, and 9.6 μl (0.06 mmol) of aqueous 6 *N* sodium hydroxide was stirred at room temperature for 1 hr and at 50° for 2 hr. Upon dilution with water, the amide separated as a crystalline solid, mp 137–139°, yield 39.8 mg (86%). Recrystallization from aqueous ethanol afforded the pure equatorial amide **25** as white needles: mp 139.5–140° (lit.[6] mp 139.5–140°); ir ($CHCl_3$) 3510, 3480, and 3390 (NH), 1670 (amide C=O), and 1580 cm^{-1} (NH_2 bending).

Attempts to hydrolyze the axial nitrile **22** by the same procedure resulted in recovery of the starting nitrile, a result consistent with the more hindered nature of the axial cyano group. Consequently, an alternative hydrolysis procedure[19] was employed in which a solution of 26 mg (0.15 mmol) of the nitrile **22** in 0.17 ml of concentrated sulfuric acid was stirred at 60° for 6.5 hr and then diluted with water and extracted with ether. The crude neutral product was recrystallized from aqueous ethanol to separate 18.2 mg (64%) of the amide **24** as white needles: mp 131–132° (lit.[6] mp 129–130°); ir ($CHCl_3$), 3510, 3480, and 3390 (NH), 1670 (amide C=O), and 1585 cm^{-1} (NH_2 bending).

Registry No.—**2**, 15619-08-6; **3**, 15619-21-3; **7**, 15619-09-7; **9a**, 15619-10-0; **9b**, 15619-11-1; **10a**, 15619-12-2; **10b**, 15619-13-3; **11a**, 15619-14-4; **11b**, 15619-15-5; **13**, 15619-16-6; **18**, 15619-17-7; **21a**, 15619-18-8; **21b**, 15619-19-9; **22**, 15619-22-4; **23**, 15619-20-2.

(19) N. Sperber, D. Papa, and E. Schwenk, *J. Amer. Chem. Soc.*, **70**, 3091 (1948).

The Chemistry of Carbanions. XVII. The Addition of Methyl Organometallic Reagents to Cyclohexenone Derivatives[1a]

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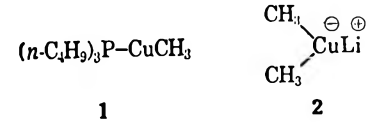
The additions of methylmagnesium and methylcopper derivatives to the α,β-unsaturated ketones **8**, **19**, and **21** have been studied. The stereochemistry of conjugate addition to the ketone **8** differs for methylcopper and methylmagnesium derivatives. When mixtures of these two metal derivatives are present, both contribute to the over-all stereochemistry of addition. Use of trimethylphosphite as a ligand for methylcopper to give relatively stable, ether-soluble complexes has been found advantageous in certain cases. Although the conjugate addition of lithium dimethylcuprate to α,β-unsaturated ketones appears to require no other species in the reaction solution, trimethyl phosphite and tri-*n*-butylphosphine complexes of methylcopper will undergo conjugate addition only if various salts such as lithium iodide, lithium bromide, magnesium bromide, or lithium cyanide are present in the reaction medium. A possible interpretation of this observation is presented.

Earlier studies of the copper-catalyzed conjugate addition of organomagnesium compounds and organolithium compounds to α,β-unsaturated ketones[2] had provided evidence supporting the idea that the actual reactants in these conjugate addition reactions are organocopper(I) compounds such as the materials



1 **2**

with the stoichiometric compositions **1** and **2**. Although it is probable that these copper(I) derivatives actually exist as associated structures (*e.g.*, tetramers) which may be bonded to solvent molecules as additional ligands, no compelling experimental evidence relating to these questions is currently available. The early data led to the hypothesis that the conjugate addition of the organocopper(I) reactants proceeded *via* a one-electron

(1) (a) This research has been supported by Grant No. AF-AFOSR-573 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research; (b) National Institutes of Health Predoctoral Fellow, 1966–1967.

(2) (a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966), and references cited therein; (b) H. O. House, R. A. Latham and C. D. Slater, *ibid.*, **31**, 2657 (1966); (c) H. O. House and H. W. Thompson, *ibid.*, **28**, 360 (1963); (d) H. O. House, D. D. Traficante, and R. A. Evans, *ibid.*, **28**, 348 (1963); (e) H. O. House and J. E. Oliver, *ibid.*, **33**, 929 (1968).

TABLE I

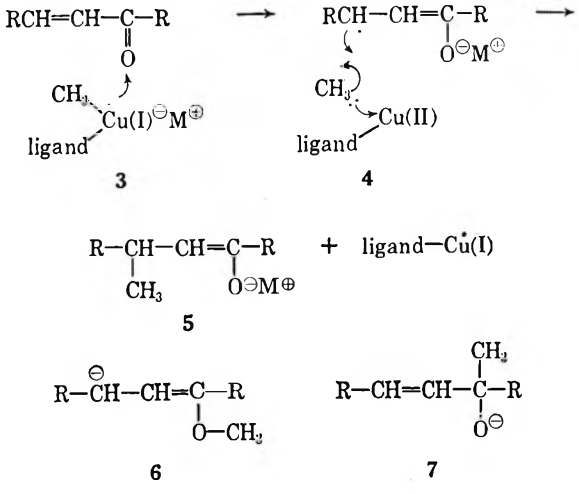
THE PRODUCTS OBTAINED FROM ADDITION OF METHYLMAGNESIUM REAGENTS TO 5-METHYL-2-CYCLOHEXENONE (8) IN ETHER SOLUTION

Organometallic reagent and any additives (concn, *M*)	Ketone 8, concn, *M*	Product composition[a] 1,4 addition: % of total product	1,4 addition: *cis* 10, %	1,4 addition: *trans* 9, %	1,2 addition: % of total product	1,2 addition: *cis* 11, %	1,2 addition: *trans* 12, %
CH_3MgBr (0.50–0.54)	0.38–0.41	21	8	92	79	13	87
$(CH_3)_2Mg$ (0.40–0.49)	0.25–0.38	3	10	90	97	12	88
CH_3Li[c]	*c*	<1			>99[b]	33	67
$(CH_3)_2Mg$ (0.51) + $[(CH_3)_2N]_3PO$ (0.51)	0.36	<1			>99[b]	13	87
$(CH_3)_2Mg$ (0.38) + $(CH_3)_2NCH_2CH_2OCH_3$ (0.38)	0.33	2			98[b,d]	15	85
$(CH_3)_2Mg$ (0.38) + $(CH_3)_2NCH_2CH_2OCH_3$ (1.9)	0.33	7			93[b,d]	15	85
$(CH_3)_2Mg$ (0.40) + $(CH_3)_2NCH_2CH_2N(CH_3)_2$ (0.40)	0.33	5			95[d]	13	87
$(CH_3)_2Mg$ (0.50) + CuI (0.005)	0.42	>99	9	91	<1		
CH_3MgBr (0.54–0.55) + CuI (0.005)	0.38–0.43	99	7	93	1		

[a] Unless otherwise noted the values listed are average values obtained from two or more reactions and the calculated yields of products exceeded 90%. [b] These data are derived from a single run. [c] A description of this reaction is given in the Experimental Section. [d] In this case the calculated yields were in the range 80–84%.

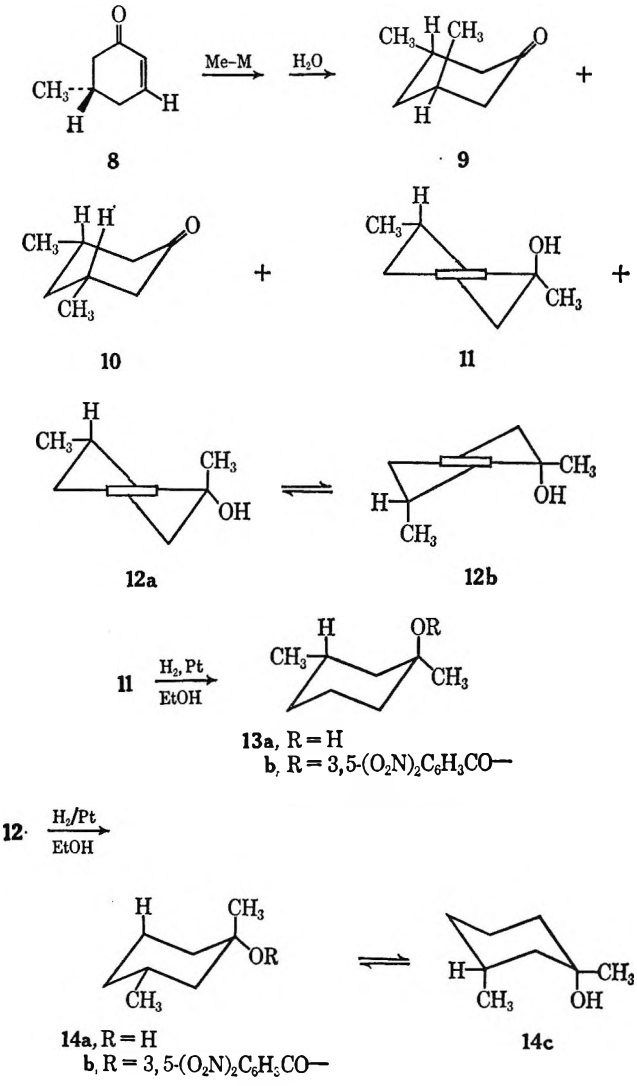
transfer **3** followed by transfer of an alkyl radical **4** as indicated in Scheme I. This hypothesis presumes that the transition state for the indicated (**4**) transfer of an alkyl radical to the end of the conjugated anion radical to form an enolate anion **5** will be energetically more favorable than formation of the allylic anion **6** or disruption of the conjugated radical ion system by attack at the carbonyl carbon atom to form **7**.

SCHEME I



The further question exists of what relationship, if any, exists between the mechanisms of the copper-catalyzed conjugate additions and the presumably uncatalyzed conjugate additions of organomagnesium compounds to α,β-unsaturated ketones. In an earlier study of asymmetric induction, Inouye and Walborsky[3a] provided evidence for different stereochemical requirements in the copper-catalyzed and the uncatalyzed additions of phenylmagnesium bromide to an α,β-unsaturated ester. Some preliminary data from a study by Marshall and Anderson[3b] suggested that different stereochemical outcomes might be observed in the copper-catalyzed and uncatalyzed additions to an α,β-unsaturated ketone. Our earlier study[2c] of an α,β-unsaturated ketone where small differences in stereochemical outcome would not have been detected had indicated that the major stereochemical pathway was the same in the catalyzed and uncatalyzed reactions. To examine this stereochemical question in more detail, we chose to study the reactions of methyl organometallic reagents with 5-methyl-2-cyclohexenone (**8**, Scheme II).

SCHEME II



A mixture[4] containing 94–96% of the *trans* ketone **9** and 4–6% of the *cis* ketone **10** had been obtained earlier when the unsaturated ketone **8** was treated with ethereal

(3) (a) Y. Inouye and H. M. Walborsky, *J. Org. Chem.*, **27**, 2706 (1962); (b) J. A. Marshall and N. H. Anderson, *ibid.*, **31**, 667 (1966).

(4) N. L. Allinger and C. K. Riew, *Tetrahedron Lett.*, No. 12, 1269 (1966).

TABLE II

THE PRODUCTS OBTAINED FROM ADDITION OF METHYLCOPPER(I) DERIVATIVES TO 5-METHYL-2-CYCLOHEXENONE (8)

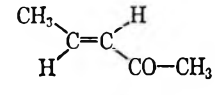
Methylcopper reagent (concn, M)	Additive (concn, M)	Concn of ketone 8, M	Solvent	Product Yield, %	Composition[a] cis 10, %	trans 9, %	Ketone 8 recovery, %
CH_3Cu (0.48–0.58)[b]	LiI (0.48–0.58)[c]	0.22–0.35	Et_2O	92–99	1	99	
CH_3Cu (0.41)[b]	$(CH_3)_2Mg$ (0.41) + LiI (0.41)[c]	0.31	Et_2O	97	5[d]	95[d]	
CH_3Cu (0.41)[b]	$MgBr_2$ (0.41) + LiI (0.41)[c]	0.31	Et_2O	97	2[d]	98[d]	
CH_3Cu (0.48)[b]	None	0.27	Et_2O	<1[d]			45
CH_3Cu (0.44)[b]	LiI (0.43)[e]	0.36	Et_2O	11[d]	g		f
CH_3CuPBu_3 (0.37–0.54)	LiI (0.37–0.54)[c]	0.26–0.43	Et_2O	34	2	98	f
$(CH_3)_2CuLi$ (0.51–0.54)	LiI (0.51–0.54)[c]	0.33–0.43	Et_2O	90–92	2	98	
$(CH_3)_2CuLi$ (0.47)	None	0.40	Et_2O	98	2[d]	98[d]	
$(CH_3)_2CuLi$ (0.47)	LiI (0.47)[e]	0.40	Et_2O	97	2[d]	98[d]	
$CH_3Cu[P(OBu)_3]_3$ (0.46)	LiI (0.46)[c]	0.34	Et_2O	88[d]	g		
$CH_3Cu[P(OMe)_3]_3$ (0.47–0.48)	LiI (0.47–0.48)[c]	0.30–0.43	Et_2O	90–91	2	98	
$CH_3Cu[P(OMe)_3]_3$ (0.34)	LiI (0.34)[c]	0.29	1,2-Dimethoxyethane	82	2[d]	98[d]	
$CH_3Cu[P(OMe)_3]_3$ (0.38–0.53)	None	0.30–0.43	Et_2O	<1			f
$CH_3Cu[P(OMe)_3]_3$ (0.47)	None	0.40	THF	<1[d]			25[f]
$CH_3Cu[P(OMe)_3]_3$ (0.38–0.47)	LiI (0.36–0.48)[e]	0.30–0.40	Et_2O	71–97	g		
$CH_3Cu[P(OMe)_3]_3$ (0.47)	$MgBr_2$ (0.47)	0.40	Et_2O	73–87	2	98	
$CH_3Cu[P(OMe)_3]_3$ (0.47)	LiBr (0.47)	0.40	Et_2O	35[d]	g		
$CH_3Cu[P(OMe)_3]_3$ (0.47)	CH_3Li (0.02)	0.40	Et_2O	<1[d]			
$CH_3Cu[P(OMe)_3]_3$ (0.47)	LiI (0.47)[e]	0.40	THF	48	1[d]	99[d]	
$CH_3Cu[P(OMe)_3]_3$ (0.47)	LiBr (0.47)	0.40	THF	20[d]	g		8
$CH_3Cu[P(OMe)_3]_3$ (0.47)	$(n\text{-}C_6H_{13})_4NI$ (0.47)	0.40	THF	<1[d]			<1[f]

[a] Unless otherwise noted the product compositions listed are average values obtained from two or more reactions. [b] A suspension of the organocopper reagent was employed. The concentration value listed is the calculated value if all the organocopper reagent had been in solution. [c] This LiI was formed in the reaction mixture from methyllithium and copper(I) iodide or its phosphine or phosphite complex. [d] These data are derived from a single run. [e] This LiI was added to methylcopper which had previously been washed free of halide salts. [f] Uncharacterized higher molecular weight material was also formed in this reaction. [g] The composition of the mixture of stereoisomeric ketones 9 and 10 was not determined in this case.

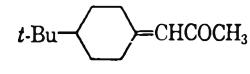
methylmagnesium iodide in the presence of copper(I) chloride. In the present investigation, we determined the yields of conjugate addition (**9** and **10**) and 1,2 addition (**11** and **12**) products and the proportions of stereoisomeric ketones and alcohols. The stereochemistry of the previously unknown alcohols **11** and **12** was established by hydrogenation to form the known[5] saturated alcohols **13a** and **14a**. The results of these product studies are summarized in Tables I and II.

Briefly we found that methylmagnesium derivatives (Table I) gave mixtures of conjugate addition products **9** and **10** in which the less abundant diequatorial *cis* isomer **10** comprised 7–10% of the mixture both in the absence of copper and in the presence of small amounts (1–2 mol %) of a copper catalyst. This result is interesting when considered in the light of our earlier finding[2a] that the conjugate addition reaction is accelerated 10- to 100-fold by the presence of 1–2 mol % of a copper(I) species. The addition of methylcopper derivatives in equimolar amount (Table II) gave mixtures in which the less abundant *cis* isomer **10** comprised 1–2% of the mixture and a mixture of equimolar amounts of methylcopper and dimethylmagnesium gave a value (5% of ketone **10**) midway between these two extremes. Thus, it would appear that both metal atoms (magnesium and copper) are present in the aggregate which transfers a methyl group to the β-carbon atom of the α,β-unsaturated ketone and the predominant metal present appears to exert some control over the stereochemistry of addition. However, even in this system we have not detected a stereochemical difference between the apparently uncatalyzed and copper-catalyzed additions of methylmagnesium derivatives which would be analogous to the difference reported by Inouye and Walborsky. Also of interest was the observation that the stereochemistry of 1,2 addition of various methylmagnesium reagents to the ketone **8** is essentially independent of the other ligands bound to magnesium. A discussion of this observation is presented elsewhere.[2e]

In our earlier studies[2a] involving conjugate additions of methylcopper(I) derivatives to the unsaturated ketones **15** and **16**, high yields of conjugate addition



15



16

products were obtained with ether solutions of either of the methylcopper(I) complexes **1** or **2** or with the slurry of yellow, insoluble (and presumably polymeric) methylcopper(I) obtained from treatment of copper(I) iodide with 1 equiv of methyllithium in ether solution. We were therefore surprised to find that, though reaction of the ketone **8** with the dimethylcuprate **2** gave the conjugate addition products **9** and **10** in good yield, the corresponding reaction with the tributylphosphine complex **1** gave relatively poor yields (34%, Table II) accompanied by a viscous, apparently polymeric, material as the major product. We were initially inclined to the view that this polymer formation was the result of the recently described[6] initial conjugate addition of tri-*n*-butylphosphine to the cyclohexenone followed by

(5) A. V. Kamernitskii and A. A. Akhrem, *J. Gen. Chem. USSR*, **30**, 772 (1960).

(6) (a) R. F. Hudson and P. A. Chopard, *Helv. Chim. Acta*, **46**, 2178 (1963); (b) F. Ramirez, O. P. Madan, and C. P. Smith, *Tetrahedron*, **22**, 567 (1966); (c) R. G. Harvey, *ibid.*, **22**, 2561 (1966); (d) R. G. Harvey and E. V. Jensen, *Tetrahedron Lett.*, 1801 (1963); (e) R. Oda, T. Kawabata, and S. Tanimoto, *ibid.*, 1653 (1964); (f) S. Trippet, *Chem. Commun.*, 468 (1966).

further reaction of the intermediate ylide to form high molecular weight products. Although this possibility is difficult to disprove rigorously in the absence of a knowledge of the polymer structure, it was rendered unlikely by control experiments in which the unsaturated ketone **8** was stirred with ether solutions of tri-*n*-butylphosphine or trimethyl phosphite both in the presence and in the absence of copper(I) iodide for periods of time equivalent to the reaction times with methylcopper. In all cases, more than 90% of the unchanged cyclohexenone derivative **8** was recovered.

We subsequently found that an ether-soluble complex of methylcopper(I) could be obtained by reaction of 1 molar equiv of methyllithium with 1 molar equiv of copper(I) iodide in the presence of 3 molar equiv of either tri-*n*-butyl phosphite or trimethyl phosphite. The trimethyl phosphite ester has proved to be a more satisfactory complexing agent than either tri-*n*-butyl phosphite or tri-*n*-butylphosphine because of its volatility (bp 110–111°) and partial water solubility permitting this reagent to be removed readily from the crude reaction products. We have observed that copper(I) iodide can be converted into a crystalline, ether-soluble complex by treatment with 2 molar equiv of trimethylphosphite. This complex has the stoichiometric composition indicated in structure **17**. A cryoscopic determination of the apparent molecular weight of this complex **17** in benzene solution gave a value of 708 corresponding to 1.62 times the weight of the monomer **17**. This value would be consistent with a dimeric structure (presumably with two halogen bridging atoms) for the complex with partial dissociation in benzene solution. Of course other states of aggregation with partial dissociation could also lead to the observed value.

$$\mathrm{CuI} + 2(\mathrm{MeO})_3\mathrm{P} \xrightarrow[\mathrm{Et_2O}]{} \underset{\mathbf{17}}{[(\mathrm{MeO})_3\mathrm{P}]_2\mathrm{CuI}}$$

$$\mathrm{MeCu} + 3(\mathrm{MeO})_3\mathrm{P} \longrightarrow \underset{\mathbf{18}}{[(\mathrm{MeO})_3\mathrm{P}]_3\mathrm{CuMe}}$$

The observation that 3 molar equiv of trimethyl phosphite are required to obtain complete solution of methylcopper as its complex and that a solution is obtained when equimolar quantities of the copper(I) iodide complex **17**, methyllithium, and trimethyl phosphite are mixed both suggest that the methylcopper complex may have the stoichiometry indicated in structure **18**.[7] Since we have thus far been unable to isolate a pure sample of this complex, it has not been possible to obtain meaningful molecular weight data for a solution of this material. Consequently, the state of aggregation of these soluble phosphite complexes, like the tri-*n*-butylphosphine complex of methylcopper, is not known.

Of interest was the finding that an ether solution of the trimethyl phosphite–methylcopper complex **18** formed from the phosphite, methyllithium, and copper(I) iodide, unlike the phosphine complex **1**, added to the cyclohexenone **8** to form the conjugate addition products **9** and **10** in good yield accompanied by little polymeric material. This observation supports our earlier tentative conclusion that the polymer-forming side reaction with the complex **1** is not the result of the aforementioned conjugated addition of tri-*n*-butylphosphine to the unsaturated ketone **8** since trimethyl phosphite might be expected to undergo a similar side reaction.[6c] In examining this reaction further we were led to prepare an ether suspension of methylcopper(I) from copper(I) iodide and methyllithium and then to separate the insoluble methylcopper. This precipitate was washed with ether at low temperatures until it was free from the lithium iodide which had been present in equimolar amounts in all of the previously studied[2a] ether solutions of copper reagents. Reaction of the unsaturated ketone **8** with an ethereal suspension of this halide-free methylcopper led to the formation of polymeric material; neither of the addition products **9** and **10** could be detected in the crude reaction product. Surprisingly, the same result was obtained when an *ether solution* of the complex **18** from halide-free methylcopper and 3 molar equiv of trimethyl phosphite was allowed to react with the ketone. Only in the reaction of the unsaturated ketone **8** with the dimethylcuprate **2** were high yields of the conjugate addition products **9** and **10** formed when no lithium iodide was present in the reaction mixture. As indicated in Table II, this tendency of the halide-free methylcopper reagent to polymerize the ketone **8** could be partially avoided by adding 1 molar equiv of lithium iodide to an ether slurry of methylcopper and high yields of conjugate addition products **9** and **10** were obtained when 1 molar equiv of lithium iodide was added to an ether solution of the halide-free phosphite complex **18**. Although added lithium bromide appeared to give poorer yields than lithium iodide, magnesium bromide and lithium iodide were approximately equally effective. In tetrahydrofuran solution similar results were obtained except that poorer yields of addition products **9** and **10** were obtained by adding lithium iodide and lithium bromide to the phosphite complex **18**. However, it was of interest to find that the presence of tetra-*n*-butylammonium iodide in the reaction solution did not lead to the formation of the conjugate addition products **9** and **10**.

Studies of reactions of the unsaturated ketones **19** and **21** with methylcopper derivatives (see Scheme III), summarized in Tables III and IV, offer further evidence for the necessity of some metal derivative (*e.g.*, LiI, $MgBr_2$, or CH_3Li) in the reaction mixture for the successful conjugate addition of a methyl group to an α,β-unsaturated ketone. With ketones **19** and **21**, the absence of such a salt results not in polymerization of the ketone, but in its recovery. Even the solution, presumably containing a complex with the stoichiometry represented by **25**, obtained by reaction of the copper(I) cyanide complex **24**[8] with methyllithium, was capable of adding a methyl group to the end of the conjugated system in ketone **21**. These observations are consistent with our currrent mechanistic hypothesis (Scheme I) if the further requirement is made that the methylcopper(I) must be complexed (as in **3**) with at least one ligand (*e.g.*, $I^{\ominus}$, $CN^{\ominus}$, $CH_3^{\ominus}$) which places a net negative charge on the copper complex. This additional electron pair supplied by the ligand should facilitate both an electron-donation process (*e.g.*, **3**) and the subsequent transfer of a methyl radical (*e.g.*, **4**).

(7) The alternative possibility exists that the formation constants for these complexes are sufficiently small that an excess of trimethyl phosphite is required in the solutions to prevent separation of the ether-insoluble uncomplexed copper(I) reagents.

(8) Y. Nishiyama, M. Nakagawa, and Y. Suzuki, Japanese Patent 21,321 (Nov 6, 1961); *Chem. Abstr.*, **48**, 4425 (1963).

SCHEME III

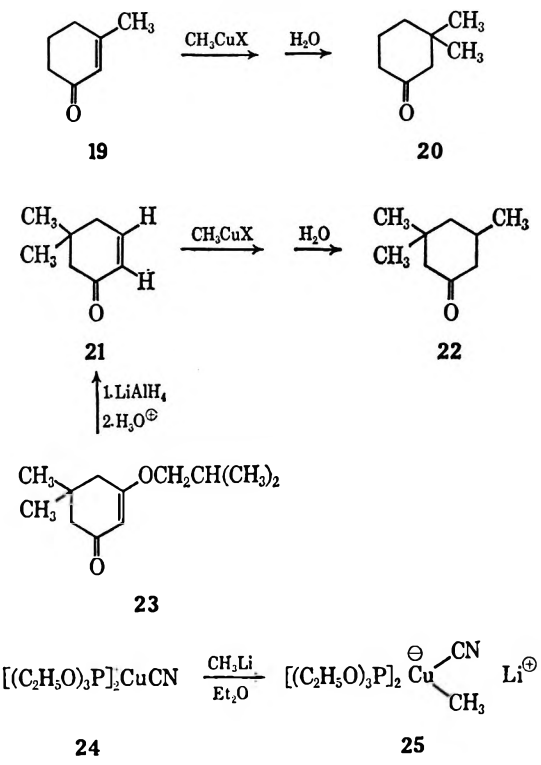


TABLE III

THE PRODUCTS OBTAINED FROM ADDITION OF METHYLCOPPER DERIVATIVES TO 3-METHYL-2-CYCLOHEXENONE (19) IN ETHER SOLUTION

Methylcopper reagent (concn, *M*)	Concn of lithium iodide, *M*	Concn of ketone **19**, *M*	Product **20** yield, %	Ketone **19** recovery, %
$(CH_3)_2CuLi$ (0.26)	0.26	0.24	98	1
CH_3CuPBu_3 (0.31)	0.31	0.24	97	3
CH_3CuPBu_3 (0.31)		0.24	<1	81
$CH_3Cu[P(OMe)_3]_3$ (0.31)	0.31	0.24	88	9
$CH_3Cu[P(OMe)_3]_3$ (0.31)		0.24	<1	70

TABLE IV

THE PRODUCTS OBTAINED FROM ADDITION OF METHYLCOPPER DERIVATIVES TO 5,5-DIMETHYL-2-CYCLOHEXENONE (21) IN ETHER SOLUTION

Methylcopper reagent (concn, *M*)	Concn of lithium iodide, *M*	Concn of ketone **21**, *M*	Product **22** yield, %	Ketone **21** recovery, %
CH_3CuPBu_3 (0.39)	0.39	0.25	92	<1
$CH_3Cu[P(OMe)_3]_3$ (0.39)	0.39	0.35	93	<1
$CH_3Cu[P(OMe)_3]_3$ (0.44)		0.33	<1	86
$CH_3Cu^{\ominus}(CN)[P(OEt)_3]_2\,Li^{\oplus}$ (0.15)		0.11	75	19

The nmr methyl signals for the various methylcopper complexes are summarized in Table V. As would be expected, the methyl signal is found at highest field in those complexes **2** and **25** believed to carry at least a partial negative charge. The observation that the methyl signal is shifted to higher field when lithium iodide is added to the phosphine complex **1** is consistent with the above suggestion that the iodide anion serves to enhance the electron density in the methylcopper complex. The failure to observe any significant shift in the methyl signal of the phosphite complex **18** with added lithium iodide presumably reflects the fact that the metal atom is already tetracoordinate. As a result, coordination of the copper with iodide ion would probably require loss of one of the phosphite ligands.

TABLE V

NUCLEAR MAGNETIC RESONANCE METHYL SIGNALS FOR ETHER SOLUTIONS OF VARIOUS METHYLCOPPER DERIVATIVES

Methylcopper complex[a]	Concn, *M*	Nmr methyl signal, Hz above TMS at 60 MHz
$(CH_3)_2Cu^{\ominus}\,Li^{\oplus}$ (**2**)	0.69	82
$[(EtO)_3P]_2Cu^{\ominus}(CN)CH_3\,Li^{\oplus}$ (**25**)	0.74	80
$[(CH_3O)_3P]_4CuMe$ (**18**) + LiI[b]	0.70	52
$[(CH_3O)_3P]_4CuMe$ (**18**)	0.70	55
n-Bu_3PCuMe (**1**) + LiI[b]	0.74	47
n-Bu_3PCuMe (**1**)	0.62	37

[a] The complexes are written as the simplest formulas which appear to correspond to the correct stoichiometry for formation of the complexes. [b] This lithium iodide was formed during the preparation of the methylcopper.

Experimental Section[9]

Preparation of the Starting Materials.—The previously described[10,11] condensation of ethyl crotonate with the sodium enolate of ethyl acetoacetate gave **5-methylcyclohexane-1,3-dione** (yield 25%) as white needles from ethyl acetate: mp 126–128° (lit.[11] mp 128–129°); ir ($CHCl_3$), 1720 (shoulder), 1705, and 1585 (broad) cm^{-1} (partially enolic β-diketone); uv maximum, 254 mμ (ε 18,000); nmr ($CDCl_3$), δ 10.98 (1 H singlet, OH), 5.47 (1 H singlet, vinyl CH), 1.7–2.8 (5 H multiplet, aliphatic CH), and 1.08 (1 H multiplet, CH_3–C).[12] This diketone was converted[10] into **3-ethoxy-5-methyl-2-cyclohexenone** isolated in 67% yield as a colorless liquid: bp 78–79.2° (0.3 mm), $n^{28}D$ 1.4891 (lit.[10] bp 83° (0.1 mm)); ir (CCl_4), 1655 (conjugated C=O) and 1610 cm^{-1} (conjugated C=C); uv maximum 249 mμ (ε 17,300); nmr (CCl_4), δ 5.18 (1 H singlet, vinyl CH), 3.92 (2 H quadruplet, J = 7 Hz, CH_2O), 1.5–2.5 (5 H multiplet, aliphatic CH), 1.37 (3 H triplet, J = 7 Hz, ethoxyl CH_3), and 1.10 (3 H multiplet, CH_3C); mass spectrum, molecular ion, m/e 154, abundant fragment peaks, m/e 112, 84, 69, 68, 43, 29, and 27.[12] Reduction of this enol ether with $LiAlH_4$ and subsequent acid-catalyzed hydrolysis[10] afforded the **unsaturated ketone 8** in 83% yield: bp 55.5–60° (4.5 mm); $n^{25}D$ 1.4742 (lit.[10] bp 60° (8 mm); $n^{25}D$ 1.4739); ir (CCl_4), 1680 (conjugated C=O), 1635, and 1615 cm^{-1} (conjugated C=C); uv maximum, 225 mμ (ε 10,900); nmr (CCl_4), δ 6.7–7.1 (1 H multiplet, vinyl CH), 5.88 (1 H doublet (J = 10 Hz) of partially resolved multiplets, vinyl CH), 1.7–2.7 (5 H multiplet, aliphatic CH), and 1.09 (3 H multiplet, CH_3C); mass spectrum, molecular ion, m/e 110, abundant fragment peaks, m/e 68, 41, 40, 39, and 27.[12]

Ethereal solutions of dimethylmagnesium (from dimethylmercury), methylmagnesium bromide, and methyllithium (from methyl bromide) were prepared and standardized (with dimethylphenylsilyl chloride) as described previously.[2] Commercial halide-free ethereal solutions of methyllithium were also employed.[13] An ether solution of anhydrous magnesium bromide

(9) 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. Unless otherwise stated, the ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 MHz with a Varian Model A-60 nmr spectrometer. The chemical shift values are expressed either in Hz or δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a CEC Model 21-130 or a Hitachi (Perkin-Elmer) mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates. All transfers and reactions involving organometallic reagents were performed under a nitrogen atmosphere.

(10) J. P. Blanchard and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 5863 (1951).

(11) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **107**, 602 (1915).

(12) The characterization of this material in our laboratory was performed by Mr. R. W. Giese.

(13) These solutions, purchased from Foote Mineral Co., were found to be 1.33–1.55 *M* in methyllithium (ethylene dibromide standardization procedure) and to be 0.04–0.06 *M* in halide (Volhard titration).

(from ethylene dibromide) was prepared and standardized as previously described.[2] Ethereal solutions of anhydrous lithium iodide and anhydrous lithium bromide, standardized by Volhard titrations, were prepared by a modification of a previously described procedure.[14] To a suspension of 2.46 g (0.310 mol) of lithium hydride in 100 ml of ether was added, dropwise and with stirring over a 45-min period, a solution of 31.7 g (0.125 mol) of iodine in 250 ml of ether. The resulting mixture was stirred for 10 hr and then filtered to give a clear, colorless solution of lithium iodide which was 0.672 *M* in iodide ion. The solution remained colorless when it was stored in the dark over a small amount of lithium hydride. A comparable reaction of 4.00 g (0.504 mol) of lithium hydride with 28.0 g (0.175 mol) of bromine in 250 ml of ether gave, after filtration, a pale orange solution of lithium bromide which was 1.202 *M* in bromide ion. The preparation and/or purification of the complexing agents N,N,N′,N′-tetramethylethylenediamine and β-methoxyethyldimethylamine is described elsewhere.[2e] Commercial trimethyl phosphite was distilled twice and then stored over Linde Molecular Sieves, No. 5A: bp 110–111°; n^{25}D 1.4070 (lit. bp 110° (737 mm);[15] n^{18}D 1.4094[16]). Commercial tri-*n*-butyl phosphite was purified by distillation, bp 138–140° (20 mm) (lit.[17] bp 122° (12 mm)).

Copper(I) iodide was purified according to a previously described procedure;[18a] the reprecipitated salt was washed successively with water, ethanol, and pentane and then dried under reduced pressure. The following procedure was employed to obtain suspensions of halide-free methylcopper. To a cold (−70°) solution of 1.28 g (1.00 ml, 2.65 mmol) of the crude bis(di-*n*-butyl sulfide) complex[18b] of copper (I) iodide in 10 ml of ether was added 2.0 ml of an ethereal solution containing 2.36 mmol of methyllithium. The precipitate of methylcopper was separated by centrifugation and the supernatant liquid was removed through a cannula employing a positive nitrogen pressure. The residual methylcopper was washed with four 10-ml portions of cold (0°) ether. Titration for halogen content indicated that 0.9% of the total halide ion remained in the precipitated methylcopper and 98.5% of the total halide ion was in the ethereal solutions. In a second preparation, a cold (−70°) slurry of 315 mg (1.64 mmol) of copper(I) iodide in 10 ml of ether was treated with 1.65 ml of an ethereal solution containing 1.64 mmol of methyllithium. The precipitated methylcopper was separated and washed with four 10-ml portions of cold (0°) ether as previously described. The methylcopper was quenched with water and then dissolved in dilute aqueous HNO_3; the combined ethereal solutions were concentrated; and the residue was dissolved in dilute, aqueous HNO_3. Aliquots of each aqueous solution were analyzed for halide ion content (Volhard titration) and for copper content. The copper analyses were performed by conversion of the copper into an aqueous solution of the copper(II)–ammonia complex which was determined photometrically by measuring the optical density of the solution at 650 mμ.[18c] These results indicated the presence of 1.49 mmol of copper and 0.0151 mmol of halide ion in the precipitate and 0.348 mmol of copper and 1.66 mmol of halide ion in the ether solution.

The tri-*n*-butylphosphine complex of copper(I) iodide and lithium dimethylcuprate (2) were prepared as previously described.[2a] Cryoscopic determination of the molecular weight of a benzene solution (0.135 to 0.359 *m*) of the copper(I) iodide–tri-*n*-butylphosphine complex gave a value of 1206 corresponding to 3.07 times the molecular weight (lit.[19a] 3.36). Ether solutions of the tri-*n*-butylphosphine–methylcopper complex (1) were prepared either by treatment of an ether solution of the copper(I) iodide complex with methyllithium or by treatment of an ether slurry of methylcopper with 1 molar equiv of the phosphine.

(14) M. D. Taylor and L. R. Grant, *J. Amer. Chem. Soc.*, **77**, 1507 (1955).

(15) A. W. Reitz and R. Sabathy, *Z. Phys. Chem.* (Leipzig), *B*, **41**, 154 (1938).

(16) D. Voigt, *Ann. Chim.* (Paris), [4] **12**, 429 (1949).

(17) W. Gerrard, *J. Chem. Soc.*, 1464 (1940).

(18) (a) G. B. Kauffman and L. A. Teter, *Inorg. Syn.*, **7**, 9 (1963). (b) This crude, ether-soluble complex was prepared according to the unpublished directions of Professor G. M. Whitesides. Addition of 19.0 g (0.10 mol) of purified copper(I) iodide to 29.2 g (0.20 mol) of di-*n*-butyl sulfide led to solution of the copper salt accompanied by the evolution of heat. The resulting deep red-orange liquid was filtered and stored under a nitrogen atmosphere. (c) A. R. Olson, C. W. Koch, and G. C. Pimentel, "Introductory Quantitative Chemistry," W. H. Freeman and Co., San Francisco, Calif., 1956, p 426.

(19) (a) F. G. Mann, D. Purdie, and A. F. Wells, *J. Chem. Soc.*, 1503 (1936). (b) A. E. Arbuzov, *Zh. Russ. Fiz. Khim. Obshchest.*, **38**, 293 (1906); *Chem. Zent.*, **77**, 750 (1906).

To a suspension of 1.62 g (8.5 mmol) of copper (I) iodide in 14 ml of ether was added, dropwise with stirring, 2.12 g (2.00 ml, 17 mmol) of trimethyl phosphite. When the resulting mixture was heated to reflux, a colorless solution resulted. When cooled to 0°, this solution deposited 3.16 g (85%) of the complex **17** as white prisms, mp 68–70.4°. Recrystallization from a small volume of ether afforded 2.81 g (75%) of pure complex **17**: mp 70.2–71.4° (lit.[19b] mp 69–70°); nmr (CCl_4), δ 3.72 (doublet with J = 11.2 Hz, $POCH_3$). For comparison, pure trimethyl phosphite has an nmr (CCl_4) doublet (J = 11.4 Hz) at δ 3.46.

Anal. Calcd for $C_6H_{18}CuIO_6P_2$: C, 16.43; H, 4.14; Cu, 14.49; I, 28.94; P, 14.12; mol wt, 439. Found: C, 16.51; H, 4.08; Cu, 14.15; I, 28.67; P, 13.90; mol wt, 708 (1.62 times monomer, cryoscopic in benzene, 0.095–0.0206 *m*).

A cold (0°) ether solution of the complex **17**, prepared from 1.40 g (7.3 mmol) of copper(I) iodide, 1.808 g (14.5 mmol) of trimethyl phosphite, and 15 ml of ether, was treated with 6 ml of an ether solution containing 7.2 mmol of methyllithium. An immediate bright yellow precipitate of methylcopper separated and did not redissolve after stirring for 10 min. However, when an additional 904 mg (7.2 mmol) of trimethyl phosphite was added, the precipitated methylcopper dissolved immediately to give a colorless solution of the methylcopper complex **18**. Alternatively, a cold (0°) ethereal suspension of methylcopper, prepared from 296 mg (1.56 mmol) of copper(I) iodide and 1.54 mmol of methyllithium in 5 ml of ether was treated, portionwise, with 580 mg (4.68 mmol) of trimethyl phosphite. Although it was evident that part of the methylcopper had dissolved after 1 and 2 molar equiv of the phosphite had been added, it was necessary to add the third molar equivalent of the phosphite before complete solution of the methylcopper was achieved. In trial experiments employing tri-*n*-butyl phosphite, similar behavior was observed. However, since the butyl phosphite complex appeared to offer no advantages over the methyl phosphite complex **18**, it was not investigated further. Ether solutions of the methyl phosphite complex **18** were stable at 0° for 5–10 min after which time they began to develop a turbidity.

To a solution of 16.6 g (0.100 mol) of redistilled triethyl phosphite (bp 157–158°) in 25 ml of benzene was added, portionwise with stirring and cooling, 4.45 g (49.8 mmol) of copper(I) cyanide. After the resulting mixture had been stirred for 15 min, it was filtered to remove a small amount of insoluble material and then concentrated under reduced pressure. The residual tan solid (20.8 g or 98%) was recrystallized from hexane to separate the pure copper(I) complex **24** as white prisms: mp 120–120.9° (lit.[8] mp 120°); ir (CCl_4), 2125 cm^{-1} (C≡N); nmr (CCl_4), δ 3.99 (12 H broadened quintet, both J values of ~7 Hz, P–O–CH_2) and 1.23 (18 H triplet, J = 7 Hz, ethoxyl CH_3). A sample of triethyl phosphite has nmr (CCl_4) peaks at δ 3.80 (quintet with both J values of ~7 Hz) and 1.22 (triplet, J = 7 Hz).

Anal. Calcd for $C_{13}H_{30}CuNO_6P_2$: C, 37.01; H, 7.17; Cu, 15.06; N, 3.32; P, 14.68; mol wt 422. Found: C, 37.20; H, 7.14; Cu, 14.97; N, 3.31; P, 14.40; mol wt, 1462 (3.48 times monomer, cryoscopic in benzene, 0.111–0.172 *m*).

To prepare the methylcopper complex **25**, a cold (0°) solution of 1.300 g (3.08 mmol) of the bis(triethyl phosphite) complex (**24**) of copper(I) cyanide in 10 ml of ether was treated with 2.00 ml of an ether solution containing 3.08 mmol of methyllithium. The resulting colorless solution of the complex **25** is the most stable complex of methylcopper that we have encountered thus far; the ether solution is stable for at least several hours at 25° and for several days at 0°.

The nmr methyl signals for ether solutions of the various methylcopper derivatives at *ca.* 25° are listed in Table V. In each case, the methyl signal appears as a sharp singlet.

Preparation of the Epimeric Ketones 9 and 10. A. The *cis* Isomer 10.—Following a previously described procedure,[20] a solution of 100 g of 3,5-dimethylphenol in ethanol was hydrogenated over Raney nickel catalyst at 190° and 2100 psi. Distillation of the crude product gave 98 g (95%) of epimeric alcohols as a colorless liquid, bp 71–75° (5 mm), n^{25}D 1.4527 (lit.[20] bp 75–76° (10 mm), n^{25}D 1.4530), which solidified on cooling. Two recrystallizations from petroleum ether (bp 30–60°) separated 71.8 g (69.5%) of one or more of the epimeric 3,5-dimethylcyclohexanols as white needles, mp 36–38.2° (lit.[20] 38–38.5°). Oxidation of 13.0 g of the crystalline alcohol with aqueous chromic acid yielded 6.20 g (51%) of the crude *cis* ketone **10** as a pale

(20) L. Alquist and coworkers, *Ark. Kemi*, **14**, 171 (1958).

yellow liquid: bp 82–83° (35 mm); $n^{25}D$ 1.4547 (lit.[20] bp 102° (65 mm); $n^{25}D$ 1.4530). A 5.0-g sample of the crude ketone was converted to the oxime of the *cis* ketone **10** which separated from petroleum ether as 3.05 g (56.6%) of white needles, mp 76.5–77.6° (lit.[20] 76.4–77.2°). Hydrolysis of 2.0 g of this oxime with aqueous oxalic acid followed by distillation of the crude product afforded 1.41 g (79%) of the pure[21] *cis* ketone **10**: bp 79° (22 mm); $n^{25}D$ 1.4412 (lit.[20] bp 102° (60 mm); $n^{25}D$ 1.4398); ir (CCl_4), 1715 cm^{-1} (C=O); nmr (CCl_4), δ 1.00 (multiplet, CH_3C) superimposed on a multiplet at 1.1–2.5 (aliphatic CH); mass spectrum, molecular ion, *m/e* 126, abundant fragment peaks, *m/e* 111, 69, 56, 55, 42, 41, and 39.

B. The *trans* Isomer 9.—Employing a modification of the previously described procedure,[4] a cold (0°) solution of lithium dimethylcuprate (2), from 1.30 g (6.7 mmol) of copper(I) iodide and 12 mmol of methyllithium in 23 ml of ether, was treated with a solution of 370 mg (3.35 mmol) of the ketone **8** in 3 ml of ether. After the mixture had been stirred for 15 min, it was poured into an aqueous solution (pH 8) of NH_4Cl and NH_3. The organic phase was combined with the ethereal extract of the aqueous phase and then washed successively with aqueous NH_4Cl, water, and aqueous NaCl. After the ethereal solution had been dried and concentrated, distillation in a short-path still separated 368 mg (87%) of the *trans* ketone **9**, $n^{25}D$ 1.4470 (lit.[22] $n^{25}D$ 1.4465) which contained[21] 2% of the *cis* isomer **10** (eluted first) and 98% of the *trans* isomer **9** (eluted second). A collected[21] sample of the *trans* ketone **9** was used for further characterization: ir (CCl_4), 1715 cm^{-1} (C=O); nmr (CCl_4), δ 1.8–2.6 (6 H mulitplet, aliphatic CH), 1.57 (2 H triplet, J = 5 Hz, CH_2 at C-4), and 0.97 (6 H doublet, J = 6 Hz, CH_3–C); mass spectrum, molecular ion, *m/e* 126, abundant fragment peaks, *m/e* 111, 69, 56, 55, 42, 41, and 39. A 103-mg sample of this *trans* ketone **9** was converted into 178 mg (71%) of the crude 2,4-dinitrophenylhydrazone which was recrystallized from ethanol to separate 129 mg (52%) of the pure **2,4-dinitrophenylhydrazone** as orange needles, mp 108.4–110° (lit.[22] mp 109.6–110.3°).

Preparation of the Epimeric Alcohols 11 and 12.—To a cold (0°) solution of 90 mmol of methyllithium in 80 ml of ether was added, dropwise and with stirring over a 30-min period, a solution of 6.00 g (54.6 mmol) of the unsaturated ketone **8** in 10 ml of ether. The resulting mixture was poured into water and the resulting aqueous phase was extracted with ether. After the combined ether solutions had been washed with water and aqueous NaCl, they were dried and concentrated to leave 6.20 g of crude product which was composed[23,24] of 33% of the *cis* alcohol **11** (eluted first) and 67% of the *trans* alcohol **12** (eluted second). Samples of each of the alcohols **11** and **12** were collected[24] for characterization. The *cis* alcohol **11** was obtained as a colorless liquid: ir (CCl_4), 3620 and 3475 cm^{-1} (unassociated and associated OH); nmr (CCl_4), δ 5.5–5.7 (2 H multiplet, vinyl CH), 1.1–2.4 (5 H multiplet, aliphatic CH), 1.20 (3 H singlet, CH_3–C–O) and 0.97 (3 H doublet, J = 5.5 Hz, CH_3–C); mass spectrum, molecular ion, *m/e* 126, abundant fragment peaks, *m/e* 108, 93, 91, 79, 77, and 39.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.80; H, 11.33.

The *trans* alcohol **12**, a colorless liquid, has the following spectral characteristics: ir (CCl_4), 3610 and 3425 cm^{-1} (unassociated and associated OH); nmr (CCl_4), δ 5.3–5.5 (2 H multiplet, vinyl CH), 1.2–2.4 (5 H multiplet, aliphatic CH), 1.20 (3 H singlet, CH_3–C–O), and 0.95 (3 H multiplet, CH_3–C); mass spectrum, molecular ion, *m/e* 126, abundant fragment peaks, *m/e* 106, 105, 93, 91, 78, 77, 44, and 39.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.06; H, 11.02.

The *cis* alcohol **11** would be expected to exist primarily in the indicated conformation with both methyl groups in equatorial or pseudo-equatorial positions. The two conformations **12a** and **b** for the *trans* alcohol **12** are probably of similar energy with some preference for conformation **12a** which avoid the 1,3 interaction between an axial methyl group and a pseudo-axial hydroxyl function. The observations that the *cis* alcohol, with a relatively hindered pseudo-axial hydroxyl function, is eluted more rapidly from gas chromatography[23,24] and has a more abundant fragment peak in its mass spectrum at 108 ($M^+ - H_2O$) both are in keeping with the assigned stereochemistry. To establish the stereochemical assignments, a solution of 6.20 g (49.3 mmol) of the mixture of unsaturated alcohols **11** and **12** from the above reaction in 50 ml of ethanol was hydrogenated at 24° and atmospheric pressure over the catalyst from 325 mg of PtO_2 in the presence of 8 mg of $NaNO_2$.[25] After 9.0 hr the hydrogen uptake (1100 ml, 45.0 mmol or 0.93 equiv) ceased and the reaction mixture was filtered and concentrated to leave 6.11 g of the crude product as an orange oil: ir (CCl_4), 3600 and 3350 cm^{-1} (unassociated and associated OH). This crude product was composed[24] of the *cis* alcohol **13a** (*ca.* 29%, first eluted) and the *trans* alcohol **14a** (*ca.* 71%, eluted second). Pure samples of each of the saturated alcohols were collected for characterization. The *cis* alcohol **13a** was a colorless liquid: $n^{25}D$ 1.4515 (lit.[5] $n^{20}D$ 1.4527); ir (CCl_4), 3600 and 3450 cm^{-1} (unassociated and associated OH); nmr (CCl_4), δ 1.90 (1 H singlet, OH), 1.0–2.0 (9 H multiplet, aliphatic CH), 1.16 (3 H singlet, CH_3–C–O) and 0.87 (3 H doublet, J = 5.5 Hz, CH_3–C); mass spectrum, molecular ion, *m/e* 128, abundant fragment peaks, *m/e* 95, 85, 71, 58, 43, 41, and 39. Reaction of a 32-mg sample of this *cis* alcohol **13a** with the anhydride from 3,5-dinitrobenzoic acid[26] yielded 69.1 mg (85%) of the crude ester **13b**. Recrystallization from petroleum ether afforded 51.3 mg (64%) of the pure **3,5-dinitrobenzoate 13b** as white needles: mp 119–120° (lit.[5] mp 118–119°); ir (CCl_4), 1730 (ester C=O), 1545, and 1330 cm^{-1} (NO_2).

The *trans* alcohol **14a** was a colorless liquid: $n^{25}D$ 1.4575 (lit.[5] $n^{20}D$ 1.4594); ir (CCl_4), 3600 and 3350 cm^{-1} (unassociated and associated OH); nmr (CCl_4), δ 3.39 (1 H singlet, OH), 1.0–1.9 (9 H multiplet, aliphatic CH), 1.17 (3 H singlet, CH_3–C–O) and 0.89 (3 H doublet, J = 5 Hz, CH_3–C); mass spectrum, molecular ion, *m/e* 128, abundant fragment peaks, *m/e* 95, 85, 71, 58, 43, and 41. Reaction of 35 mg of the *trans* alcohol **14a** with the 3,5-dinitrobenzoic anhydride[26] gave 76 mg (85%) of the crude ester **14b** as a yellow oil. Recrystallization from petroleum ether separated 60.7 mg (68%) of the **3,5-dinitrobenzoate 14b** as white needles: mp 56–59° (lit.[5] mp 59.5–61°); ir (CCl_4), 1720 (ester C=O), 1540, and 1340 cm^{-1} (NO_2).

In an additional experiment, a solution of 20 mg (0.17 mmol) of the pure[24] *trans* unsaturated alcohol **12** in 0.60 ml of ethanol containing 1 μl of aqueous 80% $NaNO_2$[25] was hydrogenated at 25° and atmospheric pressure over the catalyst from 10 mg of PtO_2. After 1.3 hr the hydrogen uptake (3.5 ml or 0.94 equiv) ceased and the crude product was isolated as previously described. A collected[24] sample of the single component detected in the crude product was identified with the previously described sample of the *trans* alcohol **14a** by comparison of gas chromatographic retention times and infrared and mass spectra. Under conditions where the nmr peak width at half-height was 1.2 Hz for internal tetramethylsilane, the value for the singlet methyl peak in the *cis* alcohol **13a** was 1.6 Hz and the corresponding value for the *trans* alcohol **14a** was 1.9 Hz. As noted elsewhere,[27] long-range coupling should cause this peak to be broader for an axial methyl group than for an equatorial methyl group. As noted earlier for the unsaturated alcohols **11** and **12**, the *cis* alcohol **13a** would be expected to exist predominantly in the indicated conformation with two equatorial methyl groups, whereas the *trans* isomer **14a** would presumably be composed of a mixture of conformers **14a** and **14c** in which one of the two methyl groups is axial. Thus, this observation is consistent with the stereochemistry assigned[5] to the two alcohols **13a** and **14a** for other reasons.

Reaction of 5-Methyl-2-cyclohexenone (8) with Methyl Organometallic Reagents.—The results of quantitative product analyses for the mixtures obtained from reaction of the conjugated ketone **8** with methylmagnesium derivatives and methylcopper derivatives are summarized in Tables I and II. In these experiments, a solution (or in certain cases, a suspension) of the organometallic reagent and any additives was prepared in the solvent indicated in the tables. To this cold (0°) solution of organometallic reagent was added with stirring, a solution containing a weighed amount of *n*-butylbenzene (an internal standard for gas chromatographic analysis) and a weighed sample of the ketone **8**. The

(21) A gas chromatography column packed with 1,2,3-tris(β-cyanoethoxy)propane (TCEP) suspended on Chromosorb P was employed for this analysis.

(22) N. L. Allinger, *J. Amer. Chem. Soc.*, **81**, 232 (1959).

(23) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis.

(24) A gas chromatography column packed with silicone fluid, no. XE-60 suspended on Chromosorb P was employed for this analysis.

(25) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).

(26) The esterification procedure of J. H. Brewster and C. J. Ciotti, Jr. (*J. Amer. Chem. Soc.*, **77**, 6214 (1955)) was employed.

(27) C. W. Shoppee, F. D. Johnson, R. E. Lack, and S. Sternhall, *Chem. Commun.*, 347 (1965).

inital concentrations of the organometallic reagent, any additives, and the ketone **8** after the solutions (total volume 7–15 ml) had been mixed are specified in Tables I and II. The resulting solutions were stirred at 0° for 5–10 min and then poured into saturated aqueous NH_4Cl adjusted to pH 8–9 by the addition of aqueous NH_3. After the resulting mixtures had been extracted with ether, the ethereal solutions were washed with aqueous NaCl, dried, concentrated, and analyzed by gas chromatography.[21,24] The gas chromatography equipment was calibrated with known mixtures of authentic samples of the internal standard, the alcohols **11** and **12**, and the ketones **8**, **9**, and **10**. On one column,[21] the alcohols were dehydrated and the ketones and standard were eluted with the following retention times: *n*-butylbenzene, 9.0 min; *cis* ketone **10**, 21.6 min; *trans* ketone **9**, 24.6 min; and unsaturated ketone **8**, 40.4 min. The second column[24] which did not completely resolve the ketones **9** and **10** was used to determine yields and to analyze the mixture of alcohols **11** and **12**. On this column,[24] the following relative retention times were obtained: *n*-butylbenzene, 7.0 min; *cis* alcohol **11**, 10.2 min; *trans* alcohol **12**, 13.2 min, and the mixture of ketones **9** and **10**, 20.3 min. Unless otherwise noted in Table I the calculated yields of products exceeded 90% and in Tables I and II the product compositions are average values from two or more reactions. In all cases the individual values differed from the average values listed by less than 2%.

In order to examine the higher molecular weight products formed when halide-free methylcopper derivatives were mixed with the unsaturated ketone **8**, a cold (0°) solution of the complex **18** (0.52 *M* concentration), from 20.8 mmol of halide-free methylcopper and 7.74 g (62.4 mmol) of trimethyl phosphite, in 40 ml of ether was treated with 1.65 g (15 mmol) of the ketone **8** and the resulting mixture was stirred at 0° for 20 min. After the reaction solution had been quenched in aqueous NH_4Cl and NH_3, the crude organic product, isolated as previously described, was 2.01 g brown viscous oil. Distillation in a short-path still afforded no significant amount of material boiling in the range of ketones **8**–**10**. A fraction of the crude product did distill at higher temperatures as 102 mg of a pale yellow viscous oil (0.1 mm and 150–185° bath) and 120 mg of a pink glassy material (0.1 mm and 185–195° bath). The higher boiling of these two fractions had infrared peaks (CCl_4) at 1710 (strong), 1685 (shoulder), and 1620 (weak) cm^{-1} with broad nmr absorption in the regions δ 1.2–3.0 and 0.7–1.2.

As control experiments, solutions containing weighed samples of *n*-butylbenzene (an internal standard), 0.500 mmol of the unsaturated ketone **8**, and 0.500 mmol of the phosphorus derivative to be tested were stirred for 15 min at 25° and subjected to the isolation and analysis procedures described above. The following phosphorus derivatives gave the per cent recovery of unchanged ketone **8**: tri-*n*-butylphosphine, 100% recovery; tri-*n*-butylphosphine complex of copper(I) iodide, 96% recovery; trimethyl phosphite, 98% recovery; bis(trimethyl phosphite) complex of copper(I) iodide, 94% recovery.

3,3-Dimethylcyclohexanone (20).—To a cold (0°) solution of lithium dimethylcuprate (**2**), prepared from 9.00 g (47 mmol) of copper(I) iodide and 111 mmol of methyllithium in 138 ml of ether, was added, dropwise and with stirring over a 15-min period, a solution of 5.00 g (45.5 mmol) of redistilled 3-methyl-2-cyclohexenone (**19**), bp 84.5–85° (13 mm), during which some methylcopper separated from the reaction mixture as a yellow precipitate. The resulting mixture was stirred at 25° for 15 min and then poured in an aqueous solution (pH 8–9) of NH_3 and NH_4Cl. The ethereal extract of the mixture was washed with aqueous NaCl, dried, concentrated, and distilled to separate 4.8 g of colorless liquid, bp 71–71.5° (19 mm), which contained[24] *ca.* 10% of an unknown component eluted first and *ca.* 90% of the saturated ketone **20**.[28] A collected[24] sample of the pure ketone **20** has the following spectral peaks: ir (CCl_4), 1715 cm^{-1} (C=O); nmr (CCl_4), δ 1.2–2.4 (8 H multiplet, aliphatic CH) and 0.96 (6 H singlet, CH_3C); mass spectrum, molecular ion peak, *m/e* 126, abundant fragment peaks, *m/e* 111, 83, 69, 56, 55, 42, 41, and 39.

(28) G. Buchi, O. Jeger, and L. Ruzicka (*Helv. Chem. Acta*, **31**, 245 (1948)) report the ketone **20** to boil at 62–65° (13 mm).

Reaction of 110 mg of this ketone **20** with excess 2,4-dinitrophenylhydrazine in acidic methanol yielded 213 mg (86%) of the **2,4-dinitrophenylhydrazone** as orange needles from ethanol, mp 139.6–140.6° (lit.[28] mp 139°).

5,5-Dimethyl-2-cyclohexenone (21).—Following the general procedure described earlier,[29] reaction of 50 g (0.357 mol) of 5,5-dimethylcyclohexane-1,3-dione with 10 ml of isobutyl alcohol and 1.1 g of *p*-toluenesulfonic acid in 275 ml of refluxing benzene for 3.5 hr yielded 63.0 g (90%) of **3-isobutoxy-5,5-dimethyl-2-cyclohexenone (23)** as a colorless liquid: bp 79–83° (0.07 mm); $n^{26}D$ 1.4777 (lit.[29c] bp 76° (0.1 mm); $n^{18}D$ 1.4810); ir (CCl_4), 1665 (conjugated C=O) and 1615 cm^{-1} (conjugated C=C); nmr (CCl_4), δ 5.15 (1 H singlet, vinyl CH), 3.58 (2 H doublet, J = 6 Hz, CH_2O), 1.5–2.5 (5 H multiplet, aliphatic CH); 1.03 (6 H singlet, CH_3C) and 0.96 (3 H doublet, J = 6 Hz, CH_3C); mass spectrum, weak molecular ion peak at *m/e* 196, abundant fragment peaks at *m/e* 124, 68, 58, 44, and 43.

Reduction of 60 g (0.306 mol) of this enol ether **23** with 5.00 g (0.132 mole) of $LiAlH_4$ in 350 ml of ether and subsequent hydrolysis with aqueous sulfuric acid following previously described procedures[10,29a,30] yielded 33.6 g (88%) of crude neutral product. Fractional distillation through a 90-cm spinning-band column separated 27.1 g of pure[24] material, bp 74–75° (11 mm), and $n^{26}D$ 1.4680 (lit. bp 75° (15 mm),[29a] $n^{25}D$ 1.4710,[29a] $n^{22}D$ 1.4699[29c]), as well as 6.45 g of higher boiling fractions which were contaminated[11] with a higher boiling impurity. The pure unsaturated ketone **21** has the following spectral peaks: ir (CCl_4), 1710 (shoulder), 1680 (conjugated C=O), 1640 and 1615 cm^{-1} (conjugated C=C); nmr (CCl_4), δ 6.76 (1 H doublet of triplets, J = 10.5 and 4 Hz, vinyl CH), 5.89 (1 H doublet of triplets, J = 10.5 and 2 Hz vinyl CH), 2.1–2.5 (4 H multiplet, aliphatic CH), and 1.05 (6 H singlet, CH_3C); mass spectrum, molecular ion peak at *m/e* 124, abundant fragment peaks at *m/e* 68, 58, and 43.

Addition of Methylcopper Derivatives to 3-Methyl-2-cyclohexenone (19) and to 5,5-Dimethyl-2-cyclohexenone (21).—The product data for these additions are summarized in Tables III (ketone **19**) and IV (ketone **21**). Solutions of the methylcopper reagents in ether were prepared as previously described; in certain cases the methylcopper was washed free of lithium iodide prior to addition of the complexing ligand. Ether solutions of the ketone **19** or **21** and pentamethylbenzene (an internal standard) were added to cold (0°) solutions of the methylcopper derivative. The concentrations of reactants listed in Tables III and IV are the initial concentrations after mixing. After the reaction solutions had been stirred at 0° for 10–15 min, they were poured into an aqueous solution (pH ~8) of NH_4Cl and NH_3. The combined ether phase and ethereal extract of the aqueous phase were washed with aqueous NaCl, dried, concentrated, and analyzed by gas chromatography[24] employing equipment which had been previously calibrated with known mixtures of authentic samples. For reactions with the ketone **19**, the retention times[24] were as follows: saturated ketone **20**, 18.3 min; pentamethylbenzene, 31.3 min; and unsaturated ketone **19**, 35.9 min. For reactions with the ketone **21**, the retention times[24] were as follows: saturated ketone **22**, 21.1 min; triethyl phosphite (present in certain reactions), 22.5 min; the unsaturated ketone **21**, 24.2 min; and pentamethylbenzene, 32.0 min. A collected[24] sample of the product ketone **22** was identified with an authentic sample[31] by comparison of gas chromatographic retention times and infrared spectra.

Registry No.—**8**, 15466-88-3; **9**, 15466-89-4; **10**, 15466-90-7; **11**, 15466-91-8; **12**, 15466-92-9; **13a**, 15466-93-0; **14a**, 15466-94-1; **17**, 15523-81-6; **19**, 1193-18-6; **20**, 2979-19-3; **21**, 4694-17-1; **22**, 873-94-9; **23**, 15466-96-3; **24**, 15523-82-7; **25**, 15523-83-8.

(29) (a) R. Frank and H. Hall. *J. Amer. Chem. Soc.*, **72**, 1645 (1950); (b) A. Eschenmosher, J. Schreiber, and S. Julia, *Helv. Chim. Acta*, **36**, 482 (1953); (c) A. W. Allan, R. P. A. Sneeden, and J. M. Wilson, *J. Chem. Soc.*, 2186 (1959).

(30) W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 14 (1960).

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

Perhydroindan Derivatives. IX. The Diels–Alder Reaction with 7-Methylindene Derivatives[1a]

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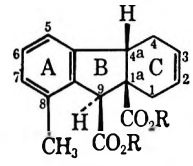
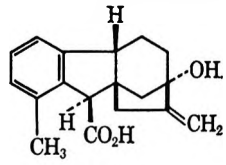
1,2-Dicarbomethoxy-7-methylindene (**3**) has been synthesized. The Diels–Alder reaction of this indene derivative **3** with butadiene has been found to occur without migration of the carbon–carbon double bond to form the tetrahydrofluorene derivative **1**.

In continuing our study of synthetic routes to the gibberellins and related molecules,[2] we wished to prepare the unsaturated diacid **1a** since model studies[2a] had suggested that this intermediate might be a suitable precursor for epiallogibberic acid **2**. A useful synthesis of this diacid **1a** has been accomplished and



1a, R = H
b, R = CH_3



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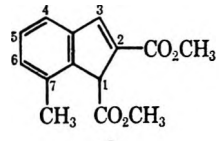

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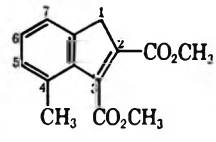

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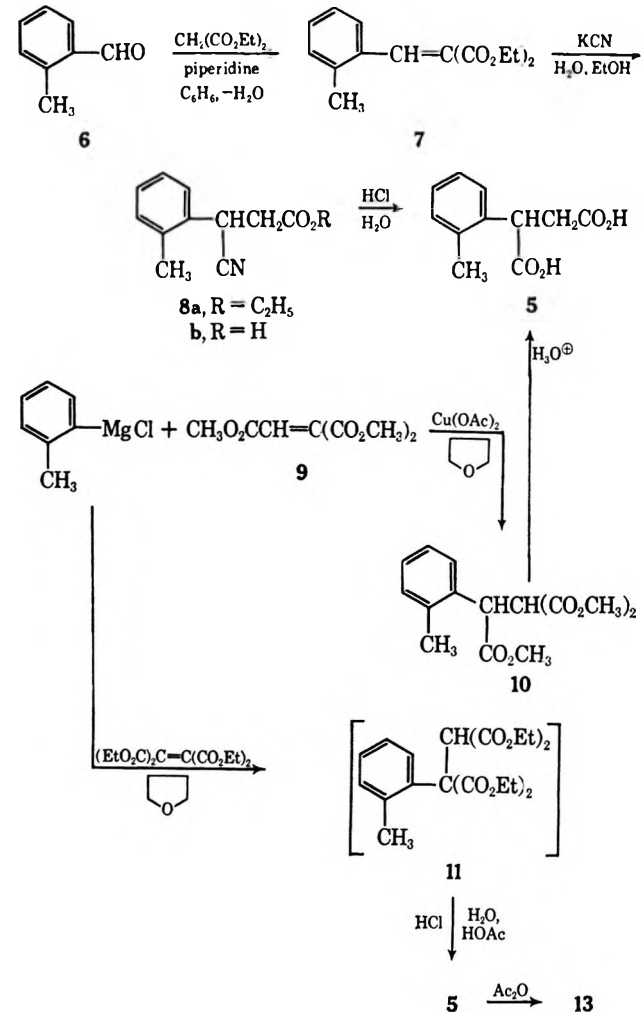
is described in this paper. At the same time, we initiated studies directed toward the synthesis of a diacid analogous to **1a** except that the 8-methyl group is replaced by a 7-methoxyl function. These studies, described in an accompanying paper,[3] led to an interesting complication in the Diels–Alder reaction used to add the C ring.

Our synthetic plan was to use a Diels–Alder reaction between butadiene and the indene diester **3** to obtain the diacid derivative **1** with a *cis* fusion between the B and C rings. Since it was not clear at the outset which of the unsaturated esters **3** or **4** would be more stable, we sought a synthetic route which would hopefully allow us to obtain the diester **3** even if it was less stable than its double-bond isomer **4**. Scheme I summarizes several routes which were used to obtain the succinic acid intermediate **5** required in subsequent steps. This diacid **5** was converted into keto diester **12** (Scheme II) employing a modification of a previously described procedure.[4] Attempts to reduce the carbonyl function of this enolic keto diester **12** to an alcohol were unsuccessful in spite of the fact that a comparable reaction was successful in the analogous methoxyindanone series.[3] This problem was overcome by catalytic hydrogenation of the related enol acetate **15** over a platinum catalyst. The resulting acetoxy diester underwent an acid-catalyzed elimination of acetic acid

SCHEME I



to form the unsaturated ester **3**. Treatment of this ester **3** with acid catalysts under conditions known to effect equilibration of double-bond isomers in related compounds[3] lead to recovery of the diester **3** in which not more than 5% of the isomeric diester **4** could have been present. We therefore conclude that the desired olefin **3** is substantially more stable than its double-bond isomer **4**.

Reaction of the unsaturated ester **3** with 1,3-butadiene at elevated temperatures yielded the desired Diels–Alder adduct **1** (Scheme III). Base-catalyzed hydrogen–deuterium exchange at C-9 of the diester **1b** demonstrated that the product isolated has the more stable configuration at this center. Heating the diacid **1a** readily formed a cyclic anhydride **17**. Since the five-membered cyclic anhydride is formed under equilibrating conditions, the product formed will clearly be the more stable epimer **17** with the two five-membered

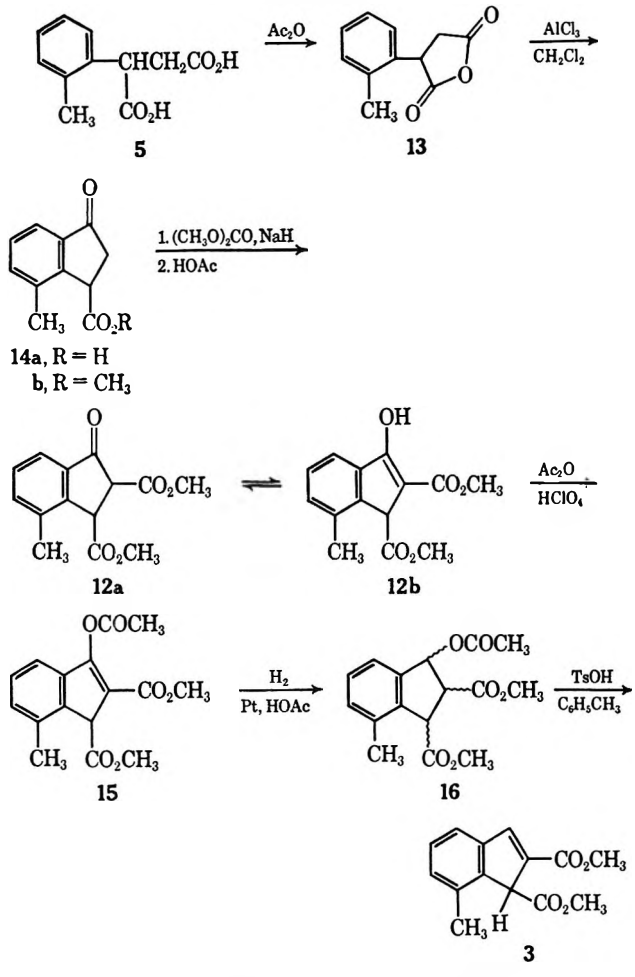
(1) (a) This research has been supported by grants from the National Science Foundation (Grant No. GP-5685) and the Directorate of Chemical Sciences, Air Force Office of Scientific Research (Grant No. AF-AFOSR-573); (b) National Science Foundation Predoctoral Fellow, 1965–1967.

(2) (a) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 448 (1968); (b) H. O. House and R. Darms, *ibid.*, **30**, 2528 (1965), and references therein.

(3) H. O. House, J. K. Larson, and H. C. Müller, *ibid.*, **33**, 961 (1968).

(4) K. Mori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem.* (Tokyo), **27**, 27 (1963).

SCHEME II



rings *cis* fused. Reconversion of this anhydride into the diester **1b** under neutral conditions allowed us to assign the indicated configurations at C-9 to the acid derivatives **1**. Since the diester **1b** was not epimerized when treated with methanolic sodium methoxide, the indicated stereochemical arrangement with both carbomethoxy groups *cis* is also the more stable epimer.

The fact that the Diels–Alder adduct had the structure **1** (from unsaturated ester **3**) and not the isomeric structure **20** which would result from reaction of butadiene with the double-bond isomer **4** was indicated from the nmr spectrum of **1**. The assignment was verified by decarboxylation and dehydrogenation of the diacid **1a** to form the known 1-methylfluorene **18**. The isomeric adduct would be expected[3] to yield 4-methylfluorene **21** when subjected to this degradation.

Experimental Section[5]

o-**Tolualdehyde (6). A. From *o*-Xylene.**—Following a general bromination procedure described previously,[6] treatment of 64.0 g (0.603 mol) of *o*-xylene with 110 g (0.618 mol) of N-bromosuccinimide and 2.0 g (8.3 mmol) of benzoyl peroxide in 600 ml of carbon tetrachloride yielded 73.6–84.0 g (66–75%) of α-bromo-*o*-xylene, bp 70–72° (2.8 mm) [lit. bp 102° (15 mm),[7] 215–218° (760 mm)[8]]. The procedure of Hass and Bender[9] was applied to α-bromo-*o*-xylene to give a 66–71% yield of o-tolualdehyde (**6**), bp 60–66° (3.5–5.0 mm) [lit.[9] bp 68–72° (6 mm)]; the 2,4-dinitrophenylhydrazone was crystallized as orange needles from an ethanol–ethyl acetate mixture, mp 194–195° (lit.[10] mp 193–194°).

B. From *o*-Toluic Acid.—*o*-Toluic acid was converted into N,N-dimethyl-*o*-toluamide, yield 93%, bp 124–125° (5 mm) [lit.[11] bp 115–118° (4.8 mm)], as previously described.[11] A cold (−10°) solution of 400 g (2.45 moles) of this dimethylamide in 2.0 l. of ether was reduced with the lithium diethoxyaluminum hydride reagent[12] prepared from 51.2 g (1.35 moles) of $LiAlH_4$ and 117 g (1.35 mole) of ethyl acetate. Following the usual isolation procedure,[12] the *o*-tolualdehyde (**6**) was collected as 218.6 g (74.2%) of colorless liquid, bp 70–72° (4.6 mm).

o-**Tolylsuccinic Acid (5). A. From *o*-Tolualdehyde (6).**—Following previous directions,[4] *o*-tolualdehyde (**6**) was condensed with diethyl malonate to give the pure[13] diethyl *o*-methylbenzalmalonate (**7**) in 98% yield: bp 145–150° (*ca.* 1 mm) [lit.[4] bp 148–149° (4 mm)]; ir (CCl_4), 1735 (conjugated ester C=O) and 1630 cm^{-1} (conjugated (C=C); nmr (CCl_4), δ 7.82 (1 H singlet, vinyl CH), 6.9–7.4 (4 H multiplet, aryl CH), 4.24 and 4.13 (4 H, two overlapping quadruplets with J = 7 cps, ethoxy CH_2), 2.36 (3 H singlet, aryl CH_3), and 1.32 and 1.11 (6 H, two overlapping triplets, J = 7 cps, ethoxyl CH_3). Following previous directions,[4] 297.7 g (1.13 moles) of this unsaturated ester **7** was treated with potassium cyanide in aqueous ethanol and the crude mixture of cyano acid **8b** and ester **8a** was hydrolyzed with aqueous HCl to give 181.7 g (77%) of the crude diacid **5** as pale yellow prisms, mp 172–179°. Recrystallization from aqueous ethanol afforded the diacid **5** as white prisms, mp 179.5–180.5°. The material separated from diisopropyl ether as white prisms: mp 184–185° (lit.[4] mp 184–185°); ir (Nujol mull), 2500–3000 (carboxyl OH) and 1700 cm^{-1} (carboxyl C=O).

B. From 1,1,2-Tricarbomethoxyethylene (9).—The reaction of 153 g (1.0 mol) of methyl bromoacetate with the enolate anion formed from 264.2 g (2.0 mol) of dimethyl malonate, 23.0 g (1.0 g-atom) of sodium, and 1.0 l. of methanol yielded, after the usual isolation procedure, 111.9 g (58%) of pure[13] **1,1,2-tricarbomethoxyethane** as a colorless liquid: bp 86–95° (0.2–0.4 mm) [lit. bp 120–122° (5 mm),[14a] 98–102° (0.5 mm),[14b] mp 34°,[14a] 34–35°[15]]; ir (CCl_4), 1750 cm^{-1} (ester C=O). To a cold (0°) solution of 102.1 g (0.50 mol) of this triester in 170 ml of methylene chloride was added, dropwise and with stirring, a solution of 27.2 ml (0.50 mol) of bromine in 71 ml of methylene chloride. After the addition was complete, the mixture was stirred for 30 min at reflux. The resulting solution was washed successively with aqueous Na_2CO_3, with water, and with saturated aqueous NaCl and then dried, concentrated, and distilled. The **1-bromo-1,1,2-tricarbomethoxyethane**, collected at 90–93° (0.15–0.17 mm) [lit.[15] bp 148.5–149.5° (9 mm)], amounted to 130.6 g (92.2%): ir (CCl_4), 1750 and 1775 (shoulder) cm^{-1} (ester C=O); nmr (CCl_4), singlets at δ 3.37 (2 H, $-CH_2-CO$), 3.71 (3 H, $-CO_2CH_3$), and 3.83 (6 H, CO_2CH_3). A solution of 127.3 g (0.45 mole) of this bromo ester in 450 ml of pyridine was heated to 95–100° for 1 hr and then cooled and poured into water. The resulting mixture was extracted with ether and the ethereal extract was washed successively with dilute, aqueous HCl, with aqueous $NaHCO_3$, and with saturated, aqueous NaCl. After the ethereal solution had been dried and concentrated, distillation afforded 57.8 g (64%) of **1,1,2-tricarbomethoxyethylene (9)**, bp 88–90°

(5) 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. Unless otherwise stated, the ultraviolet spectra were determined in 95% ethanol 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 (cps) or δ values (ppm) relative to a tetramethylsilane internal standard. The mass spectra were obtained with either a CEC Model 21-130 or a Hitachi (Perkin-Elmer) mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates. All reactions involving organometallic reagents or other strong bases (metal alkoxides, sodium hydride) were performed under a nitrogen atmosphere.

(6) W. Wenner, *J. Org. Chem.*, **17**, 523 (1952).

(7) S. Dev, *J. Indian Chem. Soc.*, **32**, 403 (1955).

(8) E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **91**, 1687 (1907).

(9) H. B. Hass and M. L. Bender, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 932.

(10) B. O. Field and J. Grundy, *J. Chem. Soc.*, 1110 (1955).

(11) H. O. House and W. M. Bryant, *J. Org. Chem.*, **31**, 3482 (1966).

(12) H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **86**, 1089 (1964).

(13) A gas chromatography column packed with silicone gum, no. SE-30, suspended on Chromosorb P was employed for this analysis.

(14) (a) P. Pino, A. Miglierina, and E. Pietra, *Gazz. Chim. Ital.*, **84**, 443 (1954); (b) R. D. Haworth, H. K. Pindred, and P. R. Jefferies, *J. Chem. Soc.*, 3617 (1954).

(15) T. Gradowska, A. Krynicki, and R. Malachowski, *Bull. Inter. Acad. Polonaise Sci., Classe Sci. Math. Nat.*, **1933A**, 552; *Chem. Abstr.*, **28**, 4383 (1934).

(0.2 mm). This triester **9** crystallized from an ether–pentane mixture as 22 g (24%) of white prisms: mp 39.5–41.5° [lit.[15] mp 40–41°, bp 141° (12 mm)]; ir (CCl_4), 1735 cm^{-1} (conjugated ester C=O); nmr (CCl_4), δ 6.82 (1 H singlet, vinyl C–H) and three partially resolved singlets at δ 3.77, 3.82, and 3.84 (9 H, CO_2CH_3); uv maximum (*n*-heptane), 204 mμ (ϵ 14,500); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 173, 59, 53, 39, 31, 30, 29, and 28.

To a solution of *o*-tolylmagnesium chloride, prepared from 30.38 g (0.24 mol) of *o*-chlorotoluene, 5.35 g (0.22 g-atom) of magnesium, and 200 ml of tetrahydrofuran, was added, dropwise and with stirring, a solution of 20.22 g (0.10 mol) of the unsaturated ester **9** and 2.0 g (0.010 mol) of anhydrous cupric acetate in 230 ml of tetrahydrofuran. After the addition was complete, the reaction mixture was stirred for 1 hr and then hydrolyzed with saturated, aqueous ammonium chloride. The ether layer was combined with the ethereal extract of the aqueous phase and then dried and concentrated. Distillation of the residual liquid separated 17.4 g (59%) of the crude ester **10**, bp 132–133° (0.2 mm). Crystallization of the product from a pentane–ether mixture afforded 11.25 g (39%) of the ester **10** as white crystals: mp 83.5–85° (recrystallization raised the melting point to 84.5–85°); ir (CCl_4), 1745 and 1760 cm^{-1} (ester C=O); uv maxima, series in the region 250–275 mμ (ϵ 430 or less); nmr (CCl_4), δ 7.05 (4 H, aryl C–H), 2.40 (3 H singlet, aryl CH_3), 3.28, 3.53, and 3.67 (three 3 H singlets, CO_2CH_3 functions), and two doublets (J = 12 cps, an AB pattern) with the chemical shift positions estimated to be δ 4.12 and 4.52 (2 H, aliphatic CH); mass spectrum, molecular ion peak at *m/e* 294, abundant fragment peaks at *m/e* 203, 135, 116, 115, 91, 59, and 39.

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.37; H, 6.21.

A mixture of 5.88 g (20 mmol) of this triester **10** and 20 ml of concentrated aqueous HCl was refluxed for 18 hr. The resulting mixture was partitioned between ether and water and the ethereal solution was extracted with aqueous NaOH. Acidification of this aqueous extract precipitated 3.96 g (95%) of the diacid **5**, mp 179.5–181°, identified with the previously described sample by comparison of infrared spectra.

C. From Tetracarboethoxyethylene.—To 20.0 ml of a tetrahydrofuran solution containing 25.6 mmol of *o*-tolylmagnesium chloride was added, dropwise and with stirring, over a 1-hr period, a solution of 8.30 g (26.2 mmol) of tetracarboethoxyethylene[16] in 20 ml of tetrahydrofuran. After the reddish brown reaction solution had been refluxed for 15 min, it was washed successively with saturated aqueous NH_4Cl, with water, and with aqueous NaCl, and then dried and concentrated to leave 10.9 g of the crude tetraester **11** as a viscous yellow oil. A 9.82-g portion of this crude ester **11** was treated with refluxing concentrated aqueous HCl for 18 hr and then 75 ml of acetic acid was added and refluxing was continued for 14 hr. The resulting mixture was concentrated under reduced pressure and then partitioned between water and ether. The ethereal layer was extracted with aqueous NaOH and this aqueous phase was acidified and extracted with ether. After this ether extract had been dried and concentrated, the crude residual diacid **5** (2.20 g of brown semisolid) was heated to 120° with 10 ml of acetic anhydride for 30 min and then distilled to separate 1.45 g (33% based on the starting tetraester) of the anhydride **13** as a viscous yellow liquid, bp 155–160° (0.5 mm). This sample was identified with the subsequently described sample of the anhydride **13** by comparison of infrared spectra.

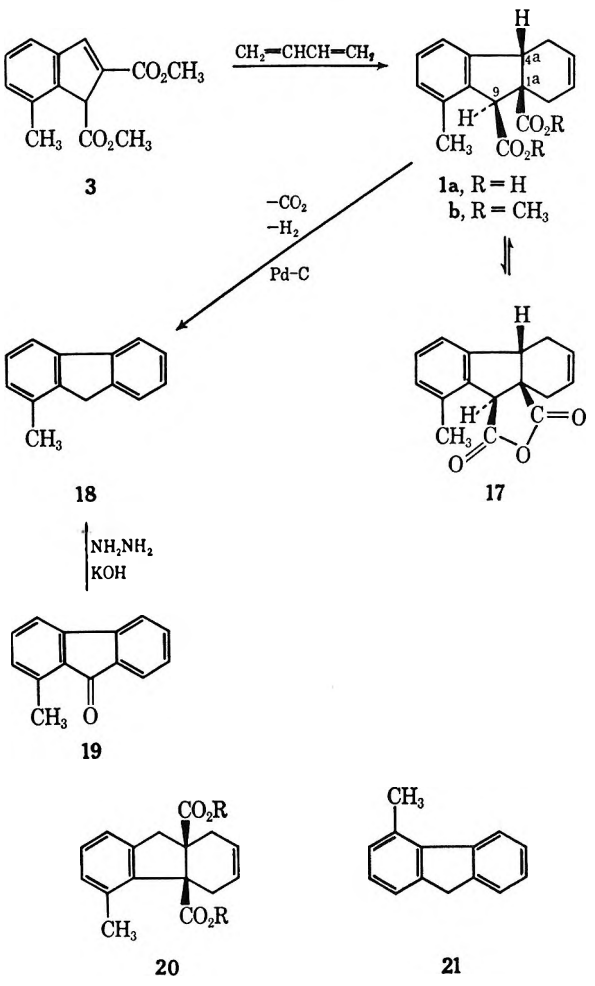
***o*-Tolylsuccinic Anhydride (13).**—A mixture of 208.2 g (1.0 mol) of the diacid **5** and 500 ml of acetic anhydride was refluxed for 1.5 hr and then distilled. The anhydride was collected as 160.5 g (84.3%) of a very viscous yellow liquid: bp 158–160° (0.5 mm) [lit.[4] bp 174–176° (5 mm)]; ir (liquid film), 1790 and 1860 cm^{-1} (C=O of five-membered cyclic anhydride). In one preparation, the anhydride **13** crystallized on standing as white prisms, mp 45.3–46.3°.

3-Carboxy-4-methyl-1-indanone (14a).—To a cold (ice bath) solution of 23.50 g (0.124 mol) of the anhydride **13** in 450 ml of methylene chloride was added, portionwise with stirring and cooling, 36.00 g (0.271 mol) of anhydrous aluminum chloride. After the addition was complete, the reaction mixture was stirred for 1 hr with cooling and then the ice bath was removed and the mixture was stirred for 12 hr at room temperature. The initially yellow reaction mixture turned red and finally brown in color. After the reaction complex had been decomposed by the addition of ice and hydrochloric acid, the organic layer was washed successively with water and aqueous NaCl and then dried and concentrated. The crude keto acid **5** remained as 21.50 g (91.5%) of brown prisms: mp 155–157° (lit.[4] mp 155–156.5°); ir (Nujol mull), 2600–3300, (carboxyl associated O–H), 1730 (C=O of an intramolecularly bonded carboxyl function), 1685 cm^{-1} (C=O of a hydrogen-bonded conjugated ketone in a five-membered ring); uv maxima, 249 mμ (ϵ 10,000) and 293 mμ (ϵ 2040).

3-Carbomethoxy-4-methyl-1-indanone (14b).—A solution of 21.0 g (0.111 mol) of the keto acid **14a** and 2.0 ml of concentrated sulfuric acid in 120 ml of methanol was refluxed for 20 hr and then cooled, diluted with aqueous $NaHCO_3$, and extracted with ether. The ethereal extract was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. The residual oil was distilled in a short-path still to separate 18.52 g (82.5%) of the keto ester **14b**, bp 117–122° (0.15 mm), which crystallized on cooling as white prisms: mp 50–52° [lit.[4] mp 53–54°, bp 140–150° (5 mm)]; ir (CCl_4), 1745 (ester C=O) and 1730 cm^{-1} (conjugated C=O in a five-membered ring); uv maxima, 249 mμ (ϵ 12,200) and 292 mμ (ϵ 2000); nmr (CCl_4), δ 3.55 (3 H singlet, O–CH_3), 2.26 (3 H singlet, aryl C–CH_3), 7.0–7.6 (3 H multiplet, aryl C–H), 4.07 (triplet, line separation 5.5 cps, Ar–CH–CO), and δ 2.67 (2 H multiplet, AB part of ABX pattern, –CH_2–CO); mass spectrum, molecular ion peak at *m/e* 204, abundant fragment peaks at *m/e* 145 (M − CO_2CH_3), 144, 115, 91, and 39.

2,3-Dicarbomethoxy-4-methyl-1-indanone (12).—A mineral oil dispersion containing 48.0 g (2 mol) of sodium hydride was washed free of mineral oil with pentane and then 700 ml of benzene and 360 g (4.0 mol) of dimethyl carbonate were added. This suspension was warmed to 60° and a solution of 115.4 g (0.565 mole) of the keto ester **14b** in 150 ml of benzene was added, dropwise and with stirring over a 2.5-hr period. The resulting suspension was heated to 60° with stirring for 2 hr

SCHEME III



(16) This material was purchased from the J. T. Baker Co.

and then cooled to room temperature and treated with 250 ml of acetic acid with concurrent cooling and stirring. The resulting mixture was poured onto crushed ice and the organic layer was separated. The aqueous phase was extracted with benzene and the combined benzene solutions were washed successively with aqueous $NaHCO_3$ and saturated, aqueous NaCl. After the organic solution had been dried and concentrated, the residual solid was washed with methanol to leave 115.2 g of the diester **12** as tan prisms, mp 94–97°. An additional 8.3 g (total yield 83.4%) crop, mp 92–96°, was separated from the mother liquors. A portion of this material was taken up in diisopropyl ether, decolorized with Norit, and cooled to deposit the keto diester **12** as white prisms: mp 92–94° (lit.[4] mp 96–97°); ir (CCl_4), 1745 (strong, ester C=O), 1730 (shoulder), 1715 (shoulder), 1660 (medium), 1620 (weak), and 1580 cm^{-1} (medium, enolic β-keto ester); nmr (CCl_4), δ 2.43 (3 H, partially resolved doublet, aryl CH_3–C), 7.3–7.9 (3 H multiplet, aryl C–H), 4.4–4.9 (1 H multiplet, Ar–CH–CO–), and 3.6–4.0 (7 H multiplet, CH_3–O and –CH–CO–). The shapes and relative intensities of the peaks in the regions δ 3.6–4.0 (shifted to δ 3.8–4.3) and 4.4–4.9 were altered when the sample was measured in deuteriochloroform suggesting that the solutions contain mixtures of *cis* and *trans* keto isomers as well as the enol tautomer. The highest peak in the mass spectrum is at *m/e* 230 (M − 32); abundant fragment peaks are found at *m/e* 145, 91, 44, 32, and 31.

An attempt to reduce 262.4 mg of the keto diester **12** with 11.0 mg of sodium borohydride in 35 ml of isopropyl alcohol at room temperature for 2.5 hr resulted in recovery of 244.2 mg (93%) of the crude starting material identified by its infrared absorption.

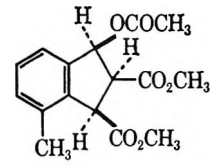
3-Acetoxy-1,2-dicarbomethoxy-7-methylindene (15).—A vigorously stirred solution of 85.7 g (0.328 mol) of the keto diester **12** and 200 g (1.96 mol) of acetic anhydride in 200 ml of benzene was treated with 3 drops of aqueous 70% perchloric acid and the resulting solution was stirred at 25° for 5 hr. The resulting solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. The residual brown oil was diluted with 400 ml of ether and then cooled and concentrated. The crystalline enol acetate **15** which separated was collected and washed with a benzene–hexane mixture (1:10 v/v) to leave 86.3 g (86.9%) of white prisms, mp 101.1–103°. Recrystallization from an ethyl acetate–hexane mixture afforded the pure enol acetate **15**: mp 102–103°; ir (CCl_4), 1785 (enol ester C=O), 1740 (ester C=O), 1720 (conjugated ester C=O), and 1625 cm^{-1} (conjugated C=C); nmr ($CDCl_3$), δ 7.0–7.4 (3 H multiplet, aryl CH), 4.67 (1 H singlet, benzylic CH), 3.79 (3 H singlet, OCH_3), 3.67 (3 H singlet, OCH_3), 2.38 and and 2.41 (two 3 H singlets, aryl CH_3 and $COCH_3$); uv maxima, 209 mμ (ε 17,600), 228 (13,200), 235 (shoulder, 10,800), and 290 (18,100).

Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30; mol wt, 304. Found: C, 63.16; H, 5.17; mol wt, 304 (mass spectrum).

3-Acetoxy-1,2-dicarbomethoxy-7-methylindan (16).—A solution of 20.0 g (65.8 mmoles) of the enol acetate **15** in 250 ml of acetic acid was hydrogenated at atmospheric pressure and 23.6° over the catalyst from 3.0 g of platinum oxide. After 40 min (hydrogen uptake 1920 ml or 1.2 equiv) the reaction was stopped and the mixture was filtered and concentrated under reduced pressure. The residual oil was crystallized from a benzene–hexane mixture to separate 13.61 g (67.7%) of one stereoisomer of the acetoxy diester **16** as fluffy white needles melting in the range 109–111°. Recrystallization separated the pure acetoxy diester **16**: mp 111.5–112°; ir (CCl_4), 1745 (shoulder) and 1738 cm^{-1} (ester C=O); uv maxima, 265 mμ (ε 306), 268 (shoulder, 288), 274 (260), and 293 (64); nmr ($CDCl_3$), δ 7.0–7.4 (3 H multiplet, aryl CH), 6.46 (1 H doublet, J = 6 cps, aryl >CH–O), 4.25 (1 H doublet, J = 8.5 cps, benzylic CH), 3.5–3.8 (7 H multiplet, two OCH_3 and CH–CO_2R), 2.29 and 2.00 (two 3 H singlets, aryl CH_3 and CO–CH_3).

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92; mol wt, 306. Found: C, 62.82; H, 5.83; mol wt, 306 (mass spectrum).

The oily material remaining in the mother liquors from this reaction appeared to be a mixture of the starting enol acetate and hydrogenolysis products. We were unsuccessful in isolating any additional pure material from the mixture. Both the nmr coupling constants (6 and 8.5 cps)[17] and the mode of preparation would suggest that the major product, the stereoisomer, mp 111.5–112°, possesses the stereochemistry illustrated in structure **16a**.



16a

1,2-Dicarbomethoxy-7-methylindene (3).—A solution of 9.8 g (33 mmol) of the acetoxy diester **16** and 1.0 g of *p*-toluenesulfonic acid in 500 ml of toluene was boiled for 3.5 hr during which time 250 ml of toluene was allowed to distil from the mixture. The resulting toluene solution was washed with water, dried, and concentrated under reduced pressure. The residual white solid was recrystallized from hexane to separate 7.8 g (98%) of indene **3** as colorless prisms: mp 78–80° (recrystallization raised the melting point to 79.9–81°); ir (CCl_4), 1745 (ester C=O), 1720 (conjugated ester C=O), and 1610 cm^{-1} (conjugated C=C); uv maxima, 230 mμ (ε 12,200), 237 (10,900), and 293 (16,300); nmr (CCl_4), δ 7.49 (1 H doublet, J = 1.5 cps, vinyl CH), 6.8–7.3 (3 H multiplet, aryl CH), 4.38 (1 H doublet, J = 1.5 cps, benzylic CH), 3.72 (3 H singlet, OCH_3), 3.54 (3 H singlet, OCH_3) and 2.33 (3 H singlet, aryl CH_3).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73; mol wt, 246. Found: C, 68.52; H, 5.89; mol wt, 246 (mass spectrum).

A solution of 247 mg (1.0 mmol) of the diester **3** and 59 mg (0.3 mmol) of *p*-toluenesulfonic acid in 20 ml of methanol was refluxed for 72 hr and then the crude neutral product (205 mg or 83% of white prisms, mp 60–78°) was recovered. The nmr spectrum (CCl_4) of this crude product corresponded to the nmr spectrum for the pure diester **3** (see above) except for the presence of an additional very weak peak at δ 4.92 which may be attributable to the signal from one of the methoxy functions in diester **4**. Comparison of these spectra with the spectra of known mixtures of analogous indene diesters[3] indicates that this crude product does not contain more than 5% of the diester **4**.

Diels–Alder Reaction with the Indene 3.—A mixture of 6.6 g (27 mmoles) of the diester **3**, 0.6 g of phenothiazine (as a radical inhibitor), 40 ml of cold (−70°) liquid 1,3-butadiene, and 50 ml of benzene was placed in an autoclave and heated to 180–190° for 18 hr. The mixture was cooled, an additional 40 ml of liquid butadiene was added, and the mixture was heated to 180–190° for an additional 36 hr. The resulting yellow solution was concentrated under reduced pressure and extracted repeatedly with portions of boiling methanol to remove the methanol-soluble product from the methanol-insoluble polymer. The methanol extracts were concentrated and the residue was treated with 100 ml of refluxing aqueous 10% NaOH for 14 hr. After the basic solution had been extracted with ether, it was acidified and the crude diacid **1a** which separated was collected. Recrystallization of the crude product from ether afforded 2.9 g (31%) of the **ether solvate of the diacid 1a** as colorless prisms: mp 75° dec; ir ($CHCl_3$), 2500–3300 (carboxyl OH) and 1715 cm^{-1} (carboxyl C=O); uv maxima, 266.5 mμ (ε 279), 270 (shoulder, 226) and 275 (199); nmr ($CDCl_3$), δ 12.60 (2 H singlet, COOH), 6.9–7.3 (3 H multiplet, aryl CH), 5.3–6.0 (2 H multiplet, vinyl CH), 4.2–4.5 (1 H multiplet, benzylic CH), 3.95 (1 H singlet, benzylic CH), 3.50 (4 H quadruplet, J = 7 cps, ethoxyl CH_2), 2.40 (3 H singlet, aryl CH_3), 1.6–3.0 (4 H multiplet, aliphatic CH), and 1.21 (6 H triplet, J = 7 cps, ethoxyl CH_3).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.27; H, 7.35.

A solution of this solvate in hexane, when heated, deposited the solvent free diacid **1a** as white needles: mp 214° dec; ir ($CHCl_3$), 2500–3200 (carboxyl OH) and 1710 cm^{-1} (carboxyl C=O); uv maxima, 266 mμ (ε 282), 270 (shoulder, 228) and 274.5 (205); nmr ($CDCl_3$), δ 12.60 (2 H singlet, COOH), 6.8–7.4 (3 H multiplet, aryl CH), 5.2–6.0 (2 H multiplet, vinyl CH), 4.1–4.5 (1 H multiplet, benzylic CH), 3.92 (1 H singlet, benzylic CH), 2.37 (3 H singlet, aryl CH_3) and 1.6–3.0 (4 H multiplet, aliphatic CH).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.31; H, 6.20.

Reaction of 982 mg (2.84 mmol) of the diacid etherate **1a** with excess ethereal diazomethane yielded 859 mg (100%) of the crude diester **1b** as white prisms, mp 84–87°. Recrystal-

(17) E. Lustig and E. P. Ragelis [*J. Org. Chem.*, **32**, 1398 (1967)] have reported values of 8.45 and 3.37 cps for the *cis* and *trans* vicinal coupling constants in 1-indanone.

lization from methanol afforded the pure diester **1b** as colorless prisms: mp 86–87°; ir (CCl_4), 1740 (ester C=O) and 1660 cm^{-1} (weak, C=C); uv maxima, 266 mμ (ε 274), 270 (shoulder, 223), and 274.5 (200); nmr (CCl_4), δ 6.7–7.2 (3 H multiplet, aryl CH), 5.1–5.9 (2 H multiplet, vinyl CH), 4.0–4.3 (1 H multiplet, benzylic CH), 3.79 (1 H singlet, benzylic CH), 3.63 (3 H singlet, OCH_3), 3.53 (3 H singlet, OCH_3), 2.28 (3 H singlet, aryl CH_3), and 1.6–2.9 (4 H multiplet, aliphatic CH); mass spectrum, molecular ion peak at *m/e* 300, abundant fragment peaks at *m/e* 181, 180, 166, and 165.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.86; H, 6.81.

A solution of 172 mg (0.51 mmol) of the diester **1b** and the sodium methoxide from 75 mg (3.3 mg-atom) of sodium in 3.0 ml of methanol-d_1 was refluxed for 3 days and poured into a mixture of deuterium oxide and acetic acid-d_1. The resulting mixture was concentrated under reduced pressure and an ether solution of the residue was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated to leave 159 mg (93%) of the crude partially deuterated diester **1b**, mp 76–82°. Recrystallization from methanol afforded 94 mg of the ester **1b**, mp 84–85°, which contained 16% d_0 species and 84% d_1 species. The nmr spectrum of this material corresponded to the spectrum previously described except that the singlet at δ 3.79 (benzylic CH) was markedly reduced in intensity.

A mixture of 1.064 g (3.08 mmol) of the etherate of the diacid **1a** and 632 mg of a 30% palladium-on-carbon catalyst was heated to 235° under a slow stream of nitrogen for 2.25 hr. The resulting mixture was extracted with boiling chloroform and the chloroform extract was filtered and concentrated. Recrystallization of the residual white solid from ethanol separated 243 mg (50.5%) of 1-methylfluorene (**18**) as white prisms, mp 83–84.5°; after sublimation at 80° (3 mm), the material melted at 85–87° (lit. mp 85°,[18a] 86°[18b]).[19] This material was identified with a subsequently described sample by a mixture melting point determination and by comparison of infrared and mass spectra.

To obtain an authentic sample of the fluorene **18**, a 300-mg (1.76 mmol) sample of the ketone **19**[20] was reduced with 1.5 ml of hydrazine hydrate and 0.60 g (11 mmol) of KOH in 20 ml of diethylene glycol for 3 hr at 175° and 0.5 hr at 250°. The crude neutral product (180 mg), isolated in the usual way, was recrystallized from ethanol to separate 120 mg of the fluorene **18**, mp 83.6–85.6°. After sublimation at 70° (0.2 mm), the product melted at 85–86°.

Preparation of the Anhydride 17.—The ether solvate of the diacid **1a** (1.448 g or 4.19 mmol) was distilled twice in a short-path still (0.2 mm and 180–190° bath) to yield 1.010 g (84%) of the anhydride **17** as a colorless liquid. The anhydride **17** crystallized on standing as white prisms: mp 99.6–101.6°; ir (CCl_4), 1790 and 1855 cm^{-1} (anhydride C=O in a five-membered ring); uv maxima (CH_3CN), 265 mμ (ε 307), 270 (shoulder, 246), and 274 (238); nmr ($CDCl_3$), δ 6.9–7.3 (3 H multiplet, aryl CH), 5.8–6.0 (2 H multiplet, vinyl CH), 4.29 (1 H singlet, benzylic CH), 3.84–4.1 (1 H multiplet, benzylic CH), 2.52 (3 H singlet, aryl CH_3), and 2.2–2.9 (4 H multiplet, aliphatic CH).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.70; H, 5.59.

A solution of 254 mg (1.0 mmol) of the anhydride **17** in 10 ml of methanol was refluxed for 3 hr and then concentrated under reduced pressure. The residual monomethyl ester(s) was esterified with excess ethereal diazomethane. The crude neutral product was recrystallized from methanol to separate 130 mg (43%) of the diester **1b**, mp 85–88°, identified with the previously described sample by a mixture melting point and comparison of infrared spectra. An additional 50 mg (17%) of the diester **1b**, mp 85–87°, was recovered from the mother liquor.

Registry No.—**1a**, 15448-20-1; ether solvate of **1a**, 15448-21-2; **1b**, 15448-22-3; **1b**, *C-9-d*$_1$, 15544-45-3; **3**, 15448-23-4; **10**, 15448-24-5; **15**, 15448-25-6; **16a**, 15448-29-0; **16**, 15448-26-7.

(18) (a) L. A. Pinck and G. E. Hilbert, *J. Amer. Chem. Soc.*, **68**, 751 (1946); (b) W. C. Lothrup and P. A. Goodwin, *ibid.*, **65**, 363 (1943).

(19) The other possible product would have been 4-methylfluorene (**21**) which is reported to melt at 71.5–72.5° [M. Orchin and E. O. Woolfolk, *ibid.*, **67**, 122 (1945)] and 70.4–71.2° [L. J. E. Hofer and W. C. Peebles, *Anal. Chem.*, **23**, 690 (1951)].

(20) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *J. Amer. Chem. Soc.*, **84**, 2614 (1962).

Perhydroindan Derivatives. X. The Diels–Alder Reaction with 6-Methoxyindene Derivatives[1a]

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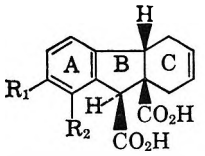
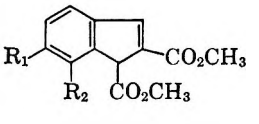
Both of the double-bond isomers of 1,2-dicarbomethoxy-6-methoxyindene (**4** and **17**) and 1,2-dicarbomethoxyindene (**19** and **20**) have been synthesized. In each case the less highly substituted double isomer **4** or **20** is the more stable. However, derivatives of each of these indenes react with 1,3-butadiene to give the Diels–Alder adduct derived from the more highly substituted double-bond isomer.

As noted in the accompanying paper,[2] we wished to synthesize the tetrahydrofluorene diacids **1** and **2** as



1, $R_1 = H$; $R_2 = CH_3$
2, $R_1 = OCH_3$; $R_2 = H$



3, $R_1 = H$; $R_2 = CH_3$
4, $R_1 = OCH_3$; $R_2 = H$

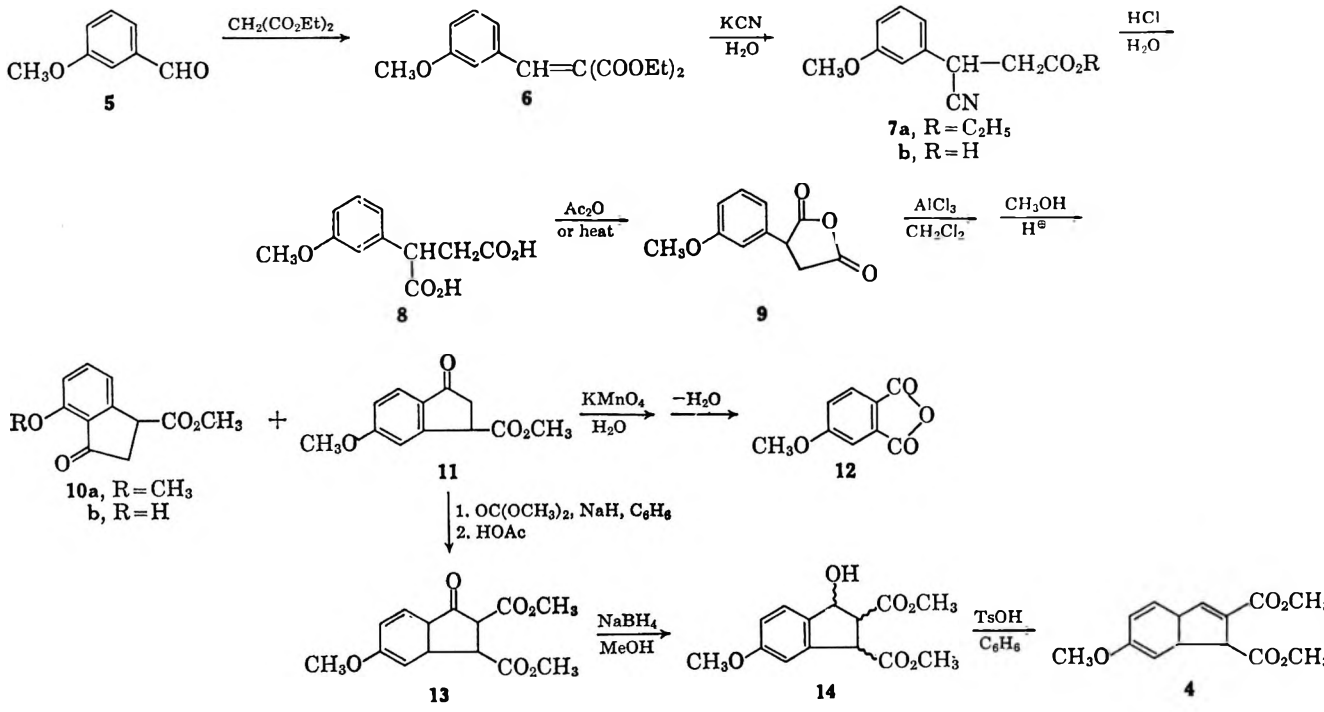
potential precursors for epiallogibberic acid and gibberellin derivatives in which the A ring is nonaromatic. It was our intention to use the indenes **3** and **4** as reactants with 1,3-butadiene to produce these acids **1** and **2**. The accompanying paper[2] describes the successful conversion of the indene **3** into the diacid **1**. In this manuscript, we describe the synthesis of the indene **4**. However, the reaction of this indene **4** with 1,3-butadiene did not yield the desired diacid **2**, but rather a structurally isomeric product.

The synthetic route (Scheme I) used for the indene derivative **4** followed the general pattern described[2] for the indene **3**. Differences were observed in the Friedel–Crafts cyclization of the anhydride **9** where the major product **11** was accompanied by lesser amounts (10–20%) of the alternative cyclization product **10**. The structure of the major product **11** was confirmed by oxidation to form the known phthalic acid derivative **12**. Unlike the result obtained in the previous study[2] with the 7-methylindanone derivative, the keto diester

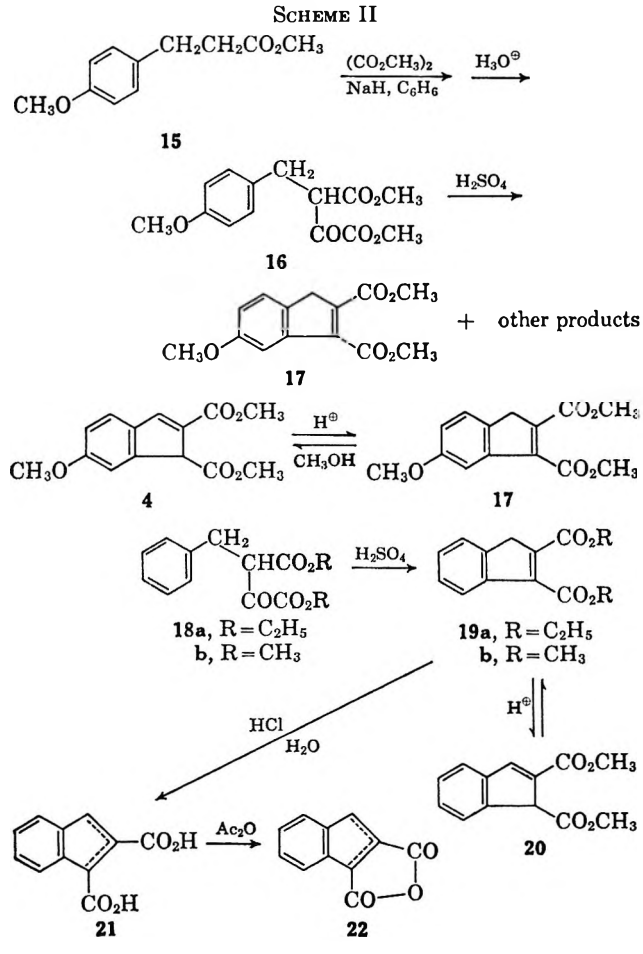
(1) (a) This research has been supported by grants from the National Science Foundation (Grant No. GP-5685) and the National Institutes of Health (Grant No. GM-08761); (b) National Institutes of Health Predoctoral Fellow, 1964–1967.

(2) H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, *J. Org. Chem.*, **33**, 957 (1968).

SCHEME I



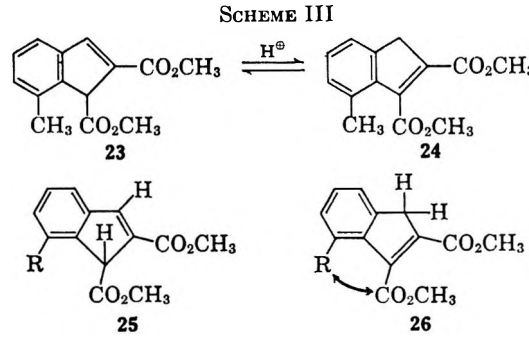
SCHEME II



13 could be successfully reduced to the alcohol **14** with sodium borohydride at low temperatures (−35°). Acid-catalyzed dehydration yielded the desired indene **4**.

Although nmr data established that the product from this reaction sequence (Scheme I) had the structure **4** rather than **17**, it was also pertinent to learn which isomer, **4** or **17**, was more stable. An authentic sample of the second double-bond isomer **17** was obtained in poor yield by the sulfuric acid catalyzed cyclization of the crude keto diester **16** (Scheme II). This synthesis was patterned after the cyclization[3] of the keto diester **18a** to form the unsaturated diester **19a**, a report which we confirmed by converting both keto diesters **18** into the unsaturated esters **19**. The acid-catalyzed equilibration of each of the pairs of dimethyl esters **4** and **17** and **19b** and **20** established that in both cases the less highly substituted isomers **4** and **20** were the more stable and constituted 85–95% of the equilibrated mixtures. This result corresponds to the previously reported finding[2] that the mixture obtained from treatment of the unsaturated diester **23** with acid contains at least 95% of the less highly substituted olefin **23** (Scheme III). The positions of these equilibria

SCHEME III



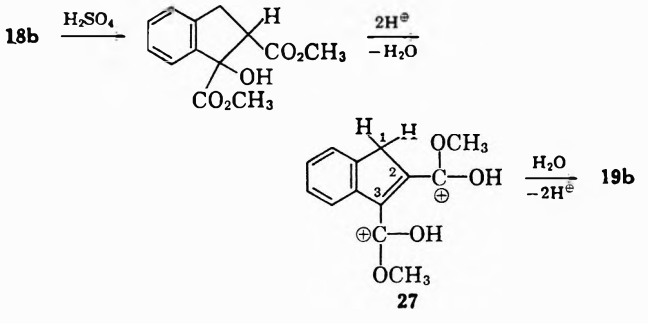
are understandable if one considers structures **25** and **26** for the two types of olefins. Only in the more highly substituted olefins **26** must one of the carbomethoxy groups be eclipsed (heavy arrow in **26**) with the *ortho* substituent R. This steric destabilization should be more important in the diester **24** where R = CH_3 (structure **26**) than in the cases **17** and **19b** where R = H

(3) (a) V. R. Skvarchenko, L. A. Chervoneva, and R. Ya. Levina, *J. Gen. Chem. USSR*, **30**, 52 (1960); (b) J. Bougault, *Compt. Rend.*, **159**, 745 (1914).

(structure **26**), an expectation which is in agreement with the positions of the three equilibria. Contrary to earlier reports,[3] we found that hydrolysis of diester **19a** yielded a mixture of diacids **21** in which the less highly substituted isomer predominated. Also, the anhydride **22** produced from this diacid **21** was a mixture of isomers which gave a mixture of 66% **20** and 34% **19b** when treated successively with methanol and with diazomethane.

Since each of these pairs of unsaturated esters is readily equilibrated by a methanolic solution of *p*-toluenesulfonic acid, it is of interest that only the *less stable* isomers **17** and **19** were isolated from reaction of the keto esters **16** and **18** with concentrated sulfuric acid. To demonstrate that this result should not be attributed simply to a different equilibrium position for the protonated derivatives of these diesters, a mixture of *ca.* 95% of **20** and *ca.* 5% **19b** was dissolved in concentrated sulfuric acid and then quenched in an ice–water mixture. The composition of the recovered mixture of esters **19b** and **20** was not altered significantly. Instead, we believe these cyclization results are better explained by assuming that the protonated olefinic diester (*e.g.*, **27**, Scheme IV) initially formed in the reaction mixture is not isomerized because there is no good base (*e.g.*, water, unprotonated ketone) present in the

SCHEME IV



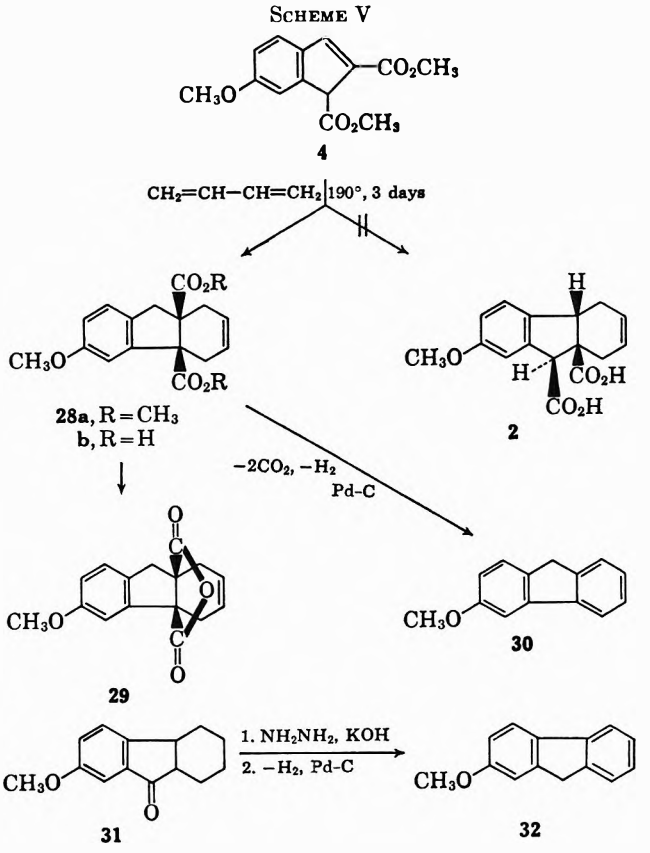
concentrated sulfuric acid to remove a proton from C-1,[4] a required step in the isomerization process. Presumably, the subsequent process of quenching the reaction mixture in an ice–water mixture does not provide time for the relatively slow abstraction of a proton from carbon[5] to compete with the rapid transfer of protons bound to oxygen.

Reaction of the more stable unsaturated ester **4** with 1,3-butadiene (Scheme V) required relatively vigorous conditions which lead to a substantial amount of diene polymerization accompanying the desired Diels–Alder reaction. From this reaction, we were successful in isolating only a single adduct **28** in yields of 40% or less. Both the nmr spectrum of the anhydride **29** derived from this adduct **28b** and decarboxylation and dehydrogenation of **28b** to 3-methoxyfluorene (**30**) rather than the isomer **32** established the structure of this adduct as **28** rather than the desired structure **2**. We must therefore conclude that under all of the various conditions where we studied this Diels–Alder reaction the isomerization **4** ⇌ **17** was more rapid than subse-

(4) For related examples, see (a) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1457 (1960); (b) C. G. Swain, and A. S. Rosenberg, *ibid.*, **83**, 2154 (1961).

(5) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

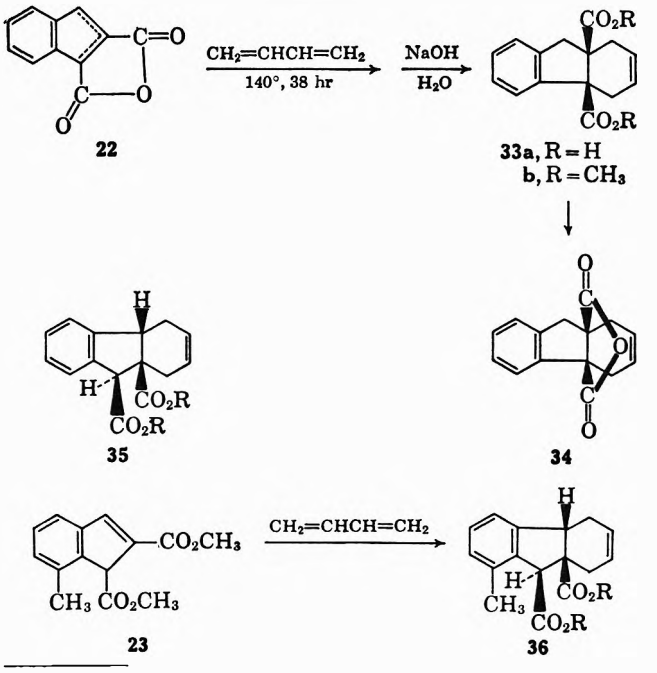
SCHEME V



quent Diels–Alder reaction and the less stable olefin **17** was evidently the more reactive dieneophile.

Earlier workers[3a] had reported that the product derived from treating the anhydride **22** with ethanol[6] underwent a Diels–Alder reaction with 2,3-dimethyl-1,3-butadiene to form an adduct **33** analogous to structure **28** (Scheme VI). However, they offered no evidence which would have distinguished between structures of the types **33** and **35** for their adduct. We there-

SCHEME VI



(6) Although the authors (ref 3a) described this material as an ethanol solvate of the anhydride **22**, we think it probable that they were working with one or more isomeric monoethyl esters.

fore examined this Diels–Alder reaction of 1,3-butadiene with the mixture of anhydrides **22** (mainly the less highly substituted olefin) and were able to isolate, after hydrolysis, only a single adduct **33a**. Examination of the nmr spectra of this adduct **33** and the related anhydride **34** verified the structure of the adduct as **33** and not **35**. Therefore, this reaction also appears to involve prior isomerization of the dienophile and preferential reaction of the less stable isomer with the diene to form the predominant, if not exclusive, adduct.

It is therefore apparent that the successful conversion of the 7-methylindene derivative **23** to the "expected" Diels–Alder adduct **36** is exceptional. Apparently in this case the *o*-methyl substituent in the dienophile **23** provides sufficient destabilization of the isomeric diester **24** (see structure **26** where R = CH_3), that reaction of the diene occurs primarily, if not exclusively, with the isomer **23**.

Experimental Section[7]

Ethyl β-(*m*-Methoxyphenyl)-β-cyanopropionate (7a).—*m*-Hydroxybenzaldehyde was methylated by the general procedure previously described[8] to form the methoxy aldehyde **5**, in 94.5% yield: bp 68–72° (0.6 mm); $n^{25}D$ 1.5527 [lit.[8] bp 88–90° (3 mm)]; uv maxima, 218 mμ (ε 21,500), 252 (9470), and 313 (2770). Following the general procedure described elsewhere,[9] this aldehyde **5** was converted into the arylidene malonate **6** in 95% yield as a pale yellow oil, bp 167–170° (0.6 mm) [lit.[13] bp 160° (0.003 mm)], which solidified on standing, mp 40–44°. Recrystallization from cyclohexane afforded the pure diester **6** as white prisms: mp 44–44.5°; ir (CCl_4), 1730 (ester C=O) and 1635 cm^{-1} (conjugated C=C); uv maxima, 213 mμ (ε 12,000), 234 (9120), and 280 (13,400); nmr (CCl_4), δ 7.48 (1 H singlet, vinyl CH), 6.6-7.3 (4 H multiplet, aryl CH), 4.18 (4 H quadruplet, J = 7 cps, $-CH_2O$), 3.68 (3 H singlet, CH_3O), 1.20 and 1.26 (6 H overlapping triplets, J = 7 cps for each, CH_3C).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.65; H, 6.59.

Reaction of 362 g (1.3 mol) of the arylidene malonate **6** with potassium cyanide, following a previously described procedure[11] except that the reaction mixture was not acidified, yielded 228 g (75.2%) of the cyano ester **7a** as a pale yellow oil: bp 164–166° (0.6 mm), $n^{21.5}D$ 1.5100; ir (CCl_4), 2240 (C≡N) and 1740 cm^{-1} (ester C=O); uv maxima, 222 mμ (ε 7230), 274 (2370), and 281 (2190); nmr (CCl_4), δ 6.4–7.4 (4 H multiplet, aryl CH), 3.9–4.4 (3 H multiplet, $-CH_2O$ and benzylic CH), 3.74 (3 H singlet, OCH_3), 2.78 (2 H, center of multiplet, $-CH_2CO_2R$), and 1.22 (3 H triplet, J = 7 cps, CH_3C).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.26; H, 6.49; N, 5.87.

The aqueous washings from this procedure[11] were found to contain the salt of a partially hydrolyzed product. Accordingly, the crude acidic product (**7b**, 58.5 g) recovered from the aqueous phase was hydrolyzed with aqueous HCl as subsequently described to yield 34.2 g (11.8%) of the succinic acid **8**, mp 175–179° dec.

α-(*m*-Methoxyphenyl)succinic Anhydride (9).—A mixture of 354 g (1.52 mol) of the cyano ester **7a**, 600 ml of concentrated aqueous HCl, and 3100 ml of water[12] was refluxed for 18 hr, cooled to 85°, treated with 500 ml of toluene, and then cooled to 5° with stirring.[13] The diacid **8**, collected on a filter and washed successively with cold water and with toluene, amounted to 280.5 g (82.5%) of white prisms: mp 177–178° dec; ir (KBr pellet), 1710 cm^{-1} (carboxyl C=O).

The combined toluene extracts from the hydrolysis of 3020 g (12.9 mol) of cyano ester **7a** were concentrated and a benzene solution of the residue (363 g of brown oil) was extracted with aqueous $NaHCO_3$ to separate, after appropriate manipulations, 269 g of crude acidic product as a pale yellow oil. A 255-g portion of this crude product was saponified with refluxing aqueous 10% NaOH to yield, after acidification and extraction of colored materials with benzene, an additional 204 g (7.1%) of the crude acid **8**, mp 170–175° dec.

A mixture of 203 g (0.90 mol) of the diacid **8** and 250 ml of acetic anhydride was heated to 90° with stirring until a solution was obtained. The resulting solution was concentrated under reduced pressure and the residual oil was crystallized from a benzene–cyclohexane mixture to separate 116 g of the anhydride **9** as white prisms, mp 65–67°. The material from the mother liquors was distilled [bp 185–195° (1 mm)] and then recrystallized to separate an additional 24 g (total yield 140 g or 75%) of the anhydride **9**: mp 65–67°; ir (CCl_4), 1870 and 1790 cm^{-1} (C=O of cyclic five-membered ring anhydride); uv maxima (CH_3CN), 218 mμ (ε 6950), 273 (2230), and 280 (2060); nmr ($CDCl_3$), δ 6.6–7.4 (4 H multiplet, aryl CH), 4.24 (1 H, center of multiplet, benzylic CH), 3.75 (3 H singlet, CH_3O), and 3.17 (2 H, center of multiplet, $-CH_2CO-$).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.00; H, 4.97.

A more convenient preparation of the anhydride **9** consisted of melting 224 g (1.00 mol) of the diacid **8** under a nitrogen atmosphere in a flask fitted with a 30-cm Vigreux column and heated with an oil bath held at 220–240°. After the acid had melted, the pressure in the system was reduced to 0.2 mm and the acid–anhydride mixture was allowed to reflux for 30 min. A small amount of distillate was collected in a cold trap during this reflux period. After the reflux period was complete, the Vigreux column was removed and the residue was distilled in a short-path still (0.2 mm and 240° bath) to separate 200 g (97%) of the crude anhydride as a viscous liquid which solidified on standing. The combined distillates from four runs were dissolved in 700 ml of methylene chloride and allowed to stand for 5 hr during which time 24 g (2.7%) of unchanged diacid **8** (mp 176–177° dec) separated and was removed by filtration. The filtrate was diluted with methylene chloride to a volume of 1.3 l. and then 1 l. of ether and 1 l. of petroleum ether (bp 30–60°) were added to precipitate 720 g (87.5%) of the pure anhydride **9** as white prisms, mp 66.5–68°. An additional 24 g (2.9%) of anhydride **9** (mp 65–67°) was obtained from the mother liquors. The combined fractions collected in the cold trap, the mother liquors, and unchanged starting material after conversion of 2650 g (11.8 moles) of diacid **8** into 2175 g (89%) of anhydride **9** was reworked to obtain an additional 101 g of anhydride **9** (mp 66–67.5°), total yield 2276 g (93.1%).

Friedel–Crafts Cyclization of the Anhydride 9.—To a solution of 300 g (1.46 mol) of the anhydride **9** in 2.0 l. of methylene chloride was added, portionwise and with stirring, 405 g (3.04 mol) of $AlCl_3$ while the temperature of the reaction mixture was kept at 12–15° by means of a cooling bath. After the addition was complete, the cooling bath was removed and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured, with stirring, into a mixture of ice and 400 ml of concentrated, aqueous HCl and the crude organic product (*ca.* 300 g) was collected and allowed to dry. This crude acid was esterified by reaction with 6.0 l. of refluxing methanol containing 10 ml of concentrated H_2SO_4 for 16 hr. The reaction mixture was concentrated and a solution of the residual solid in chloroform was washed successively with aqueous 10% NaOH, water,

(7) 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. Unless otherwise stated, the ultraviolet spectra were determined in 95% ethanol 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 (cps) or δ values (ppm) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a CEC, Model 21–130 or a Hitachi (Perkin–Elmer) mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates.

(8) R. N. Icke, C. E. Redemann, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 564.

(9) C. F. H. Allen and F. W. Spangler, ref 8, p 377.

(10) D. H. Hey and K. A. Nagdy, *J. Chem. Soc.*, 1894 (1953).

(11) C. F. H. Allen and H. B. Johnson, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 804.

(12) Attempts to accomplish this hydrolysis with concentrated aqueous HCl as had been done with the analogous phenyl compound[11] led to poor yields of impure material, presumably because of concurrent cleavage of the methoxyl function.

(13) The toluene layer dissolved both the partially hydrolyzed material and colored by-products formed during the acidic hydrolysis. If toluene was not added, the diacid **8** initially isolated was impure (mp 168–174°) and relatively difficult to purify by crystallization.

and aqueous NaCl and then dried and concentrated. Recrystallization of the resulting solid from a benzene–cyclohexane mixture separated 215 g (67%) of the keto ester **11** as white needles: mp 116–117°; ir (CCl_4), 1720 (indanone C=O) and 1750 cm^{-1} (ester C=O); uv maxima, 223 mμ (ε 15,700), 268 (15,600), 285 (shoulder, 11,700), and 293 (shoulder, 9800); nmr ($CDCl_3$), δ 7.81 (1 H doublet, J = 9 cps, aryl CH at C-7), 6.8–7.5 (2 H multiplet, aryl CH), 4.0–4.5 (1 H multiplet, benzylic CH), 3.95 (3 H singlet, OCH_3), 3.83 (3 H singlet, OCH_3), and 3.02 (2 H, center of multiplet, $-CH_2CO-$).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49; mol wt, 220. Found: C, 65.31; H, 5.71; mol wt, 220 (mass spectrum).

To prove the substitution pattern in the aromatic ring of the keto ester **11**, a mixture of 1.0 g (4.5 mmol) of the keto ester **11**, 5.0 g of $KMnO_4$, 0.2 g of Na_2CO_3, and 50 ml of water was refluxed until the color of the permanganate was discharged. The resulting mixture was cooled, acidified, and extracted with ether. After the ethereal extract had been dried and concentrated, the residual solid was distilled in a short-path still (0.01 mm and 130° bath) and the distillate was recrystallized from a benzene–cyclohexane mixture to separate 75 mg of **4-methoxyphthalic anhydride (12)**, mp 90–92°.[14] An authentic sample of this same anhydride **12** (identified by comparison of infrared spectra) was obtained by the comparable oxidation of 6-methoxy-1-indanone.

Concentration of the mother liquors remaining after crystallization of keto ester **11** afforded 22 g (7%) of a mixture[15] of the keto esters **11** and **10a**. A 4-g portion of this material was chromatographed on silicic acid to separate 1.25 g of keto ester **11** (in the early fractions eluted with hexane–ether mixtures) and 1.5 g of the keto ester **10a**, mp 93–96° (in the later fractions eluted with hexane–ether mixtures). Recrystallization from a benzene–cyclohexane mixture afforded 1.0 g of the pure **keto ester 10a** as white prisms: mp 95–96°; ir ($CHCl_3$), 1740 (ester C=O) and 1710 cm^{-1} (indanone C=O); uv maxima, 218 mμ (ε 25,800), 257 (10,400), and 312 (4800); nmr (CD_3COCD_3), δ 7.59 (1 H triplet, J = 8 cps, aryl CH at C-5), 7.17 (1 H doublet, J = 8 cps, aryl CH at C-4 or C-6), 6.96 (1 H doublet, J = 8 cps, aryl CH at C-4 or C-6), 4.1–4.5 (1 H multiplet, benzylic CH), 3.88 (3 H singlet, OCH_3), 3.72 (3 H singlet, OCH_3), 2.85 (2 H, center of multiplet, $-CH_2CO-$).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49; mol wt, 220. Found: C, 65.68; H, 5.56; mol wt, 220 (mass spectrum).

From a comparable Friedel–Crafts reaction, a small amount of the hydroxy keto ester **10b** was isolated from the base-soluble fraction. Recrystallization from a benzene–cyclohexane mixture afforded the pure **phenol 10b** as white needles: mp 88–89°; ir (CCl_4), 3330 (associated OH), 1750 (ester C=O), and 1690 cm^{-1} (indanone C=O lowered by intramolecular H bonding); uv maxima, 220 mμ (ε 22,800), 256 (10,300), and 315 (4140); nmr ($CDCl_3$), δ 9.25 (1 H singlet, OH), 6.8–7.8 (3 H multiplet, aryl CH), 4.0–4.6 (1 H multiplet, benzylic CH), 3.87 (3 H singlet, OCH_3), and 3.12 (2 H, center of multiplet, $-CH_2CO-$).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89; mol wt, 206. Found: C, 64.12; H, 5.00; mol wt, 206 (mass spectrum).

2,3-Dicarbomethoxy-5-methoxy-1-indanone (13).—To a vigorously stirred, warm (60°) suspension of 540 g (6.0 mol) of dimethyl carbonate, 65 g (2.7 mol) of sodium hydride [obtained by washing the dispersion in oil with petroleum ether (bp 30–60°)], 1 ml of methanol, and 100 ml of benzene was added a warm (*ca.* 70°) solution of 200 g (0.91 mol) of the keto ester **11** in 1000 ml benzene over a 100-min period. The rate of addition was adjusted such that the transient red color formed upon adding each drop of keto ester solution disappeared immediately and the reaction mixture remained a yellow-green color throughout the addition. After the addition was complete, the reaction mixture was maintained at 60° with stirring for 30 min and then cooled to 10° and acidified by the dropwise addition of 250 ml of acetic acid with stirring and external cooling. The reaction mixture was poured onto ice and the resulting mixture was acidified to pH 1 with aqueous HCl. After the organic layer had been separated, the aqueous phase was extracted with benzene and the combined organic layers were washed successively with water, aqueous $NaHCO_3$, and aqueous NaCl and then dried and concentrated. A solution of the residual brown oil (251 g) in 250 ml of methanol was cooled to −10° and the crystalline keto diester **13** which separated was collected and washed with 100 ml of cold (−50°) methanol and 300 ml of petroleum ether (bp 30–60°). The product **13** amounted to 228.5 g (90.5%) of light tan prisms, mp 60–64°. A sample, purified for analysis by crystallization from an ether–petroleum ether (bp 30–60°) mixture at −5°, melted at 58–60°. The variation in melting point of this product suggests that it probably a mixture of stereoisomers: ir (CCl_4), 1745 (ester C=O) and 1720 cm^{-1} (indanone C=O); uv maxima, 227 mμ (ε 13,100), 275 (15,100), 286 (14,500), and 296 (13,700); nmr ($CDCl_3$), δ 7.67 (1 H doublet, J = 8 cps, aryl CH at C-7), 6.8–7.3 (2 H multiplet, aryl CH at C-4 and C-6), 4.5–4.8 (1 H multiplet, benzylic CH), 4.0–4.3 (1 H multiplet, $COCHCO_2R$), 3.88 (3 H singlet, OCH_3), and 3.78 (3 H singlet, OCH_3).

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.33; H, 5.19.

1,2-Dicarbomethoxy-6-methoxyindene (4).—A cold (0°) solution of 100 mg (0.36 mmol) of the keto diester **13** and 14 mg (0.39 mmol) of sodium borohydride in 10 ml of methanol was stirred at 0° for 1 hr and then the reaction mixture was acidified, concentrated, and partitioned between ether and aqueous $NaHCO_3$. The organic layer was dried and concentrated to leave 91 mg of oil which solidified on standing. Chromatography on silicic acid separated 56 mg of solid fractions eluted with hexane–ether mixtures. Repeated recrystallization from ether–petroleum ether (bp 30–60°) mixtures at −5° separated one stereoisomer of the hydroxy diester **14** as colorless prisms: mp 72.5–74°; ir (CCl_4), 3580, 3475 (unassociated and associated OH), and 1740 cm^{-1} (ester C=O); uv maxima, 227 mμ (ε 8560), 279 (2760), and 286 (2490); nmr ($CDCl_3$), δ 7.22 (1 H doublet, J = 9 cps, aryl CH at C-6 or C-7), 6.5–7.0 (2 H multiplet, aryl CH), 4.8–5.3 (1 H multiplet, >CHO–), 4.0–4.4 (1 H multiplet, benzylic CH), 3.1–3.5 (1 H multiplet, $>CHCO_2R$), 3.71, 3.74, and 3.77 (9 H, three singlets, OCH_3).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.75; H, 5.70.

For preparative purposes, it was more efficient to dehydrate the crude alcohol **14** without purification. To a cold (−35°) solution of 49.5 g (1.3 mol) of sodium borohydride in 2.0 l. of methanol (neutralized with Na_2CO_3 before use) was added, dropwise with stirring and external cooling under a nitrogen atmosphere, a solution of 260 g (0.935 mol) of the keto diester **13** in 1.0 l. of methanol. After the addition was complete (*ca.* 30 min), the yellow reaction mixture was stirred at −35° for 2 hr and then neutralized by the dropwise addition of 130 ml of acetic acid. The solution was concentrated under reduced pressure and the residual yellow semisolid was partitioned between water and benzene. The benzene solution was dried, mixed with 2.5 g of *p*-toluenesulfonic acid, and then refluxed under a nitrogen atmosphere for 1 hr with continuous separation of water. The resulting benzene solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. A solution of the viscous yellow residue in a benzene–cyclohexane mixture deposited 198.9 g (81.3%) of the unsaturated diester **4** as pale yellow prisms, mp 97.5–99°. Recrystallization afforded an analytical sample as white needles: mp 97–98.5°; ir (CCl_4), 1740 (ester C=O) and 1720 cm^{-1} (conjugated ester C=O); uv maxima, 238 mμ (ε 10,600), 308 (14,700), and 318 (14,700); nmr ($CDCl_3$), δ 7.63 (1 H doublet, J = 2 cps, vinyl CH), 6.7–7.5 (3 H multiplet, aryl CH), 4.57 (1 H broad, benzylic CH), 3.78 (6 H singlet, OCH_3), and 3.67 (3 H singlet, OCH_3).

Anal. Calcd for $C_{14}H_{14}O_6$: C, 64.11; H, 5.38; mol wt, 262. Found: C, 64.11; H, 5.18; mol wt, 262 (mass spectrum).

Preparation of the Indenedicarboxylic Acid Derivatives 19–22.—Following a modification of previously described directions,[3] a mixture of 5.76 g (0.24 mol) of sodium hydride, 19.0 g (0.13 mol) of diethyl oxalate, 50 ml of benzene, and 0.6 ml of ethanol was treated with a solution of 22.1 g (0.12 mol) of ethyl hydrocinnamate in 50 ml of benzene. When the reaction was complete, the mixture was neutralized by adding 5 ml of acetic acid and the crude keto diester **18a** was separated as 39 g of pale yellow oil. This crude ester **18a** was added, dropwise and with stirring, to 300 ml of cold (0–5°), concentrated H_2SO_4. After the resulting solution had been stirred at 0–5° for 2 hr, it was poured onto ice and then extracted with ether. The ethereal solution was washed successively with water, aqueous $NaHCO_3$, and aqueous NaCl and then dried and concentrated to leave 24 g of the crude

(14) 4-Methoxyphthalic anhydride is reported to melt at 96°: R. Melby, R. Crawford, D. McGreer, and R. B. Sandin, *J. Amer. Chem. Soc.*, **78**, 3817 (1956). 3-Methoxyphthalic anhydride, the alternative possibility, is reported to melt at 159–160°: E. L. Schumann, M. G. Van Campen, and C. H. Tilford, *J. Org. Chem.*, **23**, 763 (1958).

(15) A thin layer chromatography plate coated with silicic acid and eluted with an ether–benzene mixture was employed for this analysis.

semisolid product. Recrystallization from a cyclohexane–petroleum ether (bp 30–60°) mixture afforded 16.05 g (51%) of the diester **19a** as pale yellow prisms: mp 75–77° (lit. mp 76–77°,[3a] 78°[3b]); ir (CCl_4), 1735 and 1715 cm^{-1} (coupled C=O vibrations of a diester); uv maxima, 229 mμ (ε 13,300), 236 (13,000), and 289 (15,300); nmr ($CDCl_3$), δ 7.2–7.7 (4 H multiplet, aryl CH), 4.44 and 4.29 (4 H, two overlapping quadruplets, each with J = 7 cps, ethoxy CH_2), 3.74 (2 H singlet, benzylic CH_2), and 1.41 and 1.33 (6 H, two overlapping triplets each with J = 7 cps, ethoxyl CH_3).

A mixture of 16.0 g (61 mmol) of the diester **19a** and 600 ml of aqueous 6 *M* HCl was heated under reflux for 4 hr and then mixed with ice, cooled, and filtered. The residual crude diacid **21** amounted to 15 g, mp 222–227° dec (lit. mp 215–217° dec,[3a] 215° dec[3b]). A portion of the material was recrystallized from aqueous ethanol to separate the diacid (presumably still a mixture **21**) as light tan needles, mp 236–238° dec. A suspension of 0.50 g of the crude diacid **21** (mp 222–227° dec) in 20 ml of ethyl acetate was esterified with excess ethereal diazomethane. The crude neutral product was isolated as 0.35 g of a yellow liquid which partially crystallized on standing. The crude product contained 90% of the diester **20** and 10% of the diester **19b** as determined by a subsequently described nmr analysis.

A suspension of 13 g (64 mmol) of this crude diacid **21** and 50 ml of acetic anhydride was heated to 110° with stirring for 1 hr. The resulting solution was cooled in an ice bath to separate 6.0 g of the crude anhydride **22** as orange needles, mp 150–165° dec. Recrystallization from benzene afforded the mixture of isomeric anhydrides **22** as 4.2 g (36%) of orange needles, mp 150–170° dec.[16] Subsequent recrystallization and sublimation did not alter the melting behavior of this mixture; the infrared (CCl_4) bands were at 1845 and 1775 cm^{-1} (anhydride C=O in a five-membered ring).

Anal. Calcd for $C_{11}H_6O_3$: C, 70.97; H, 3.25. Found: C, 71.27; H, 3.40.

A 0.30-g sample of this anhydride mixture **22** was dissolved in 10 ml of boiling methanol and then the solution was concentrated under reduced pressure. A solution of the residual crude monomethyl ester in ethyl acetate was esterified with excess ethereal diazomethane. The nmr analysis of the resulting mixture of dimethyl esters (235 mg, mp 48–57°) indicated the presence of 66% of the diester **20** and 34% of the diester **19b**.

A solution of 7.0 g (34 mmol) of the crude diacid mixture **21** and 0.5 ml of concentrated H_2SO_4 in 350 ml of methanol was refluxed for 16 hr under a nitrogen atmosphere and then concentrated under reduced pressure. An ether solution of the residue was washed successively with water, aqueous $NaHCO_3$, and aqueous NaCl and then dried and concentrated to leave 3.9 g of crude diester as an oil which crystallized on standing, mp 52–57°. Recrystallization from a cyclohexane–petroleum ether (bp 30–60°) mixture afforded 3.16 g of a mixture of diesters as white prisms, mp 50–59°, which contained (nmr analysis) 87% of the diester **20** and 13% of the diester **19b**. Several fractional recrystallizations of this material from cyclohexane separated 0.28 g of the diester **20** as white needles: mp 59–61°; ir (CCl_4), 1745 (unconjugated ester C=O) and 1725 cm^{-1} (conjugated ester C=O); uv maxima, 228 mμ (ε 15,700), 236 (15,600), and 288 (15,700); nmr ($CDCl_3$), δ 7.1–7.8 (5 H multiplet, vinyl and aryl CH), 4.58 (1 H partially resolved multiplet, benzylic CH), 3.77 (3 H singlet, OCH_3) and 3.63 (3 H singlet, OCH_3).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21; mol wt, 232. Found: C, 67.07; H, 5.21; mol wt, 232 (mass spectrum).

Following previously described procedures, a mixture of 2.88 g (0.12 mol) of sodium hydride, 7.7 g (0.065 mol) of dimethyl oxalate, 0.3 ml of methanol and 25 ml of benzene was treated with a solution of 9.85 g (0.060 mol) of methyl hydrocinnamate in 25 ml of benzene. After the reaction was complete, the crude mixture was neutralized with 2.5 ml of acetic acid and the crude organic keto diester **18b** was isolated as 18 g of yellow oil. This keto diester **18b** was added dropwise and with stirring, to 150 ml of cold (0–5°), concentrated H_2SO_4. After the resulting solution had been stirred for 2 hr at 0–5°, it was poured onto ice and extracted with ether. The organic layer was washed successively with water, aqueous $NaHCO_3$, and aqueous NaCl and then dried and concentrated. The residual crude diester **19b** (6.1 g, mp 69–76°) was recrystallized from cyclohexane to separate the pure diester **19b** as 4.68 g (34%) of white prisms: mp 81–83°; ir (CCl_4), 1740 and 1720 cm^{-1} (coupled C=O vibrations of a diester); uv maxima, 228 mμ (ε 14,500), 236 (14,200), and 289 (15,400); nmr ($CDCl_3$), δ 7.2–7.7 (4 H multiplet, aryl CH), 3.96 (3 H singlet, OCH_3), 3.82 (3 H singlet, OCH_3), and 3.71 (2 H singlet, benzylic CH_2).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21; mol wt, 232. Found: C, 67.55; H, 5.43; mol wt, 232 (mass spectrum).

A series of known mixtures of diesters **20** and **19b** were prepared to establish the validity of an nmr analytical scheme based upon the areas under peaks δ 4.58 (from **20**) and 3.96 (from **19b**). To determine the equilibrium concentrations of the two esters, solutions of each of the diesters in 5–15 ml of methanol containing 20–25 mg of *p*-toluenesulfonic acid were refluxed for 60 hr and then concentrated. A solution of each residue in chloroform was washed successively with aqueous $NaHCO_3$ and aqueous NaCl, and then dried, concentrated, and analyzed by measuring its nmr spectrum. From 100 mg of the diester **20**, the recovered diesters (83 mg) contained 83% of **20** and 17% of **19b**. From 250 mg of the diester **19b**, the recovered diesters (240 mg) contained 87% of **20** and 13% of **19b**. Thus the average equilibrium concentration in refluxing methanol is 85% of diester **20** and 15% of diester **19b**.

A 0.50-g sample of a mixture of diesters containing (nmr analysis) *ca.* 5% of diester **19b** and *ca.* 95% of diester **20** was dissolved in 5 ml of cold (5°), concentrated H_2SO_4. After the solution had been stirred for 1 hr at 5°, it was poured onto ice and the resulting mixture was extracted with chloroform. The chloroform solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. The residual oil (0.40 g), which crystallized on standing, contained (nmr analysis) *ca.* 95% of the diester **20** and *ca.* 5% of the diester **19b**.

1,2-Dicarbomethoxy-6-methoxy-1-indene (17).—Following previously described procedures, a mixture of 2.88 g (0.12 mol) of sodium hydride, 7.7 g (0.065 mol) of dimethyl oxalate, 0.2 ml of methanol, and 20 ml of benzene was treated with a solution of 11.6 g (0.060 mol) of methyl β-(*p*-methoxyphenyl)propionate (**15**) in 30 ml of benzene. The organic product (15 g or 89%) was a pale yellow oil. Although attempts to obtain analytically pure samples of the keto ester **16** were complicated by decarbonylation which accompanied distillation, a partially purified sample of the keto ester **16** was obtained as a pale yellow oil: $n^{27}D$ 1.5102, by distillation in a short-path still (0.1 mm and 150° bath); ir (CCl_4), 1760 (shoulder) and 1735 cm^{-1} (ester and ketone C=O); uv maxima, 226 mμ (ε 11,600), 277 (4480), and 283 (4140); nmr (CCl_4), δ 7.00 (2 H doublet, J = 9 cps, aryl CH), 6.66 (2 H doublet, J = 9 cps, aryl CH), 4.22 (1 H triplet, J = 7 cps, $COCHCO_2R$), 3.73 (3 H singlet, OCH_3), 3.67 (3 H singlet, OCH_3), 3.60 (3 H singlet, OCH_3), and 3.06 (2 H doublet, J = 7 cps, benzylic CH_2).

To 100 ml of cold (0–10°), concentrated sulfuric acid was added, dropwise and with stirring, 13 g (0.046 mol) of the crude keto diester **16**. The resulting solution was stirred for 2 hr at 5–10° and then poured onto ice and extracted repeatedly with chloroform. The organic extract was washed successively with aqueous NaOH and aqueous NaCl and then dried and concentrated. The residual pale yellow oil (1.7 g) contained[16] two components which could be detected under an ultraviolet lamp, the more rapidly eluted being the unsaturated ester **17**. Chromatography on silicic acid separated 75 mg of the crude diester **17** as a white solid, mp 105–110°, eluted in the early ether–hexane fractions and 480 mg of an unknown component (a pale yellow oil) eluted in the later hexane–ether fractions. The crude diester was recrystallized from cyclohexane to separate 40 mg of the pure diester **17** as white needles: mp 128–130°; ir ($CHCl_3$), 1735 and 1715 cm^{-1} (coupled C=O vibrations of a diester); uv maxima, 239 mμ (ε 11,500), 308 (13,600), and 318 (13,300); nmr ($CDCl_3$), δ 6.7–7.5 (3 H multiplet, aryl CH), 3.97 (3 H singlet, OCH_3), 3.83 (6 H singlet, two OCH_3), and 3.68 (2 H singlet, benzylic CH_2).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38; mol wt, 262. Found: C, 64.15; H, 5.58; mol wt, 262 (mass spectrum).

A solution of 34 mg of the diester **17** and 5 mg of *p*-toluenesulfonic acid in 5 ml of methanol was refluxed for 40 hr and then subjected to the usual isolation procedure. Recrystallization of the crude product from benzene afforded 10 mg of the diester **4**, mp 96–98°, identified with the previously described sample by a mixture melting point determination and comparison of infrared spectra.

(16) Previous investigators (ref 3a) had recrystallized their crude anhydride from ethanol and described the product, mp 184–185°, as the anhydride solvated with one molecule of ethanol (ref 6).

To examine the equilibration of the unsaturated esters **4** and **17**, a solution of 250 mg of the diester **4** and 100 mg of *p*-toluenesulfonic acid in 5 ml of methanol-d_1 was refluxed for 56 hr and then concentrated. A chloroform solution of the residual solid was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. Recrystallization of the residue from methanol gave 125 mg of the partially deuterated derivative of diester **4**, mp 97–98.5°. The nmr spectrum ($CDCl_3$) of this material corresponded to the spectrum described previously except that the doublet at δ 7.63 (vinyl CH) and the broad peak at 4.57 (benzylic CH) were of much diminished intensity. The mass spectrum of the material indicated the presence of 13% d_0 species, 54% d_1 species, and 33% d_2 species. In a similar experiment, a solution of 1.0 g of the diester **4** and 0.40 g of *p*-toluenesulfonic acid in 20 ml of methanol was refluxed for 48 hr and then subjected to the same isolation procedure. The pure recovered diester **4**, melting within the range 96–98°, amounted to 641 mg. The nmr spectrum of the crude solid (258 mg) recovered from the mother liquor indicated that less than 5% of the second unsaturated ester **17** was present as judged by the presence of only a very small nmr peak at δ 3.97 characteristic of one of the OCH_3 signals in the diester **17**. Accordingly, we conclude that less than 10% of the diester **17** is present in equilibrium with the diester **4**.

Reaction of the Unsaturated Anhydrides 22 with 1,3-Butadiene.—A solution of 3.55 g (1.88 mmol) of the anhydrides **22** (mixture of double-bond isomers as previously described), 0.50 g of diphenylsulfide (as an inhibitor), and 20 ml of liquid 1,3-butadiene in 50 ml of benzene was heated to 140° in an autoclave for 38 hr. The resulting mixture was concentrated under reduced pressure and a mixture of the residue with 75 ml of aqueous 10% NaOH was refluxed for 10 hr. The resulting aqueous solution was separated, washed with chloroform, acidified, and extracted with chloroform. The chloroform extract was washed successively with water and aqueous NaCl and then dried and concentrated to leave 2.18 g (45%) of the crude solid diacid **33a**. A small portion of this crude product was recrystallized from a methanol–cyclohexane mixture to separate the diacid **33a** as light tan needles, mp 148–152° dec. A 0.50-g portion of the crude diacid was distilled in a short-path still (0.1 mm and 190° bath) to separate the crude anhydride **34**. A cold (10°) cyclohexane solution of this crude product deposited 0.29 g of pure anhydride **34** as white prisms: mp 91–92.5°; ir (CCl_4), 1850 and 1790 (anhydride C=O in a five-membered ring); uv maxima (CH_3CN), 261 mμ (ϵ 903), 266 (1380), and 273 (1580); nmr ($CDCl_3$), δ 7.0–7.6 (4 H multiplet, aryl CH), 5.9–6.2 (2 H multiplet, vinyl CH), 3.71 and 3.19 (2 H, two doublets each with J = 17 cps, benzylic CH_2), and 2.0–3.2 (4 H multiplet, aliphatic CH).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; mol wt, 240. Found: C, 75.19; H, 5.09; mol wt, 240 (mass spectrum).

A solution of 0.50 of the crude diacid **33a** in 15 ml of ethyl acetate was esterified with excess ethereal diazomethane. The crude neutral product (0.30 g, mp 95–97°) was recrystallized from cyclohexane to separate the diester **33b** as light tan prisms: mp 95–97°; ir (CCl_4), 1745 cm^{-1} (ester C=O); uv maxima, 261 mμ (ϵ 805), 267 (1190), and 274 (1330); nmr ($CDCl_3$), δ 7.0–7.4 (4 H multiplet, aryl CH), 5.2–6.0 (2 H multiplet, vinyl CH), 3.73 (3 H singlet, OCH_3), 3.57 (3 H singlet, OCH_3), and 1.7–3.8 (6 H multiplet, aliphatic CH).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34; mol wt, 286. Found: C, 71.11; H, 6.38; mol wt, 286 (mass spectrum).

Reaction of the Unsaturated Diester 4 with 1,3-Butadiene.—A mixture of 300 g (1.14 mol) of 2,3-dicarbomethoxy-5-methoxy-1-indene (**4**), 900 ml of benzene, 900 ml of liquid 1,3-butadiene, and 15 g of diphenylsulfide (added as an inhibitor) was heated to 190° in an autoclave under a helium atmosphere (400 psi) for 20 hr. The reaction vessel was cooled, an additional 900 ml of liquid 1,3-butadiene was added, and the resulting mixture was heated to 190° for 44 hr. The resulting yellow reaction mixture was concentrated under reduced pressure to leave a viscous yellow oil (850 g) which was vigorously extracted with ten 500-ml portions of boiling methanol to separate the methanol-soluble product from the insoluble polymeric material. The combined warm (45°) methanol extracts were filtered through Celite and then concentrated under reduced pressure. The residual yellow-green semisolid (350 g) was triturated with 350 ml of ether, allowed to stand at 0° for 2 days, and then filtered to separate the product (ether insoluble) from the solution of the remaining polymeric material. The residue was washed with 250 ml of cold (−70°) ether to leave 128 g (35.4%) of the diester **28a** as white prisms, mp 125–126°, which contained[16] only a minor amount of the starting unsaturated ester **4**. Recrystallization from methanol separated 117 g (32.4%) of the pure diester **28a** as white prisms: mp 126–127°; ir (CCl_4), 1735 cm^{-1} (ester C=O); uv maxima, 218 mμ (shoulder, ϵ 10,000), 284 (3180), and 292 (shoulder, 2840); nmr ($CDCl_3$), δ 6.5–7.3 (3 H multiplet, aryl CH), 5.6 (2 H broad, vinyl CH), 2.0–3.9 (6 H multiplet, aliphatic CH), 3.53, 3.68, and 3.75 (three 3 H singlets, OCH_3). Except for different numbers of methoxyl peaks the nmr spectra of esters **33b** and **28a** resemble one another closely in the region δ 2.0–4.0.

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37; mol wt, 316. Found: C, 68.03; H, 6.25; mol wt, 316 (mass spectrum).

A mixture of 250 g (0.79 mol) of the diester **28a** and 190 g (4.75 mol) of NaOH in 1850 ml of methanol and 1700 ml of water was refluxed under a nitrogen atmosphere for 3 hr at which time 1.4 l. of methanol was allowed to distil from the mixture. The residual solution (bp 85°) was refluxed for an additional 20 hr and then concentrated under reduced pressure, diluted with water, and extracted with chloroform. The aqueous phase was filtered through Celite and then neutralized with aqueous HCl. The resulting solution was seeded with the diacid **28b** (to prevent the inital separation of the diacid as an oil) and then acidified to pH 1 by the dropwise addition of concentrated aqueous HCl. The mixture was cooled to 5° and the crude, crystalline diacid **28b** (232 g, mp 121–123° dec) was collected and washed with water. A 2.177-g sample of this crude diacid **28b** (contaminated with some sodium salt) was dissolved in methanol, acidified with aqueous HCl, and precipitated with added water to separate 2.08 g of the diacid **28b** as light tan prisms, mp 172–174° dec. A comparable sample of the diacid was crystallized from an ethyl acetate–petroleum ether (bp 30–60°) mixture to separate the diacid **28b** used for characterization as pale tan prisms: mp 165–167° dec; ir ($CHCl_3$), 1710 cm^{-1} (carboxyl C=O); uv maxima, 220 mμ (shoulder, ϵ 9430), 283 (3270), and 290 (2790).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.53; H, 5.56.

When a 1.00-g sample of the crude diacid **28b** was heated to 180–200° at 0.2-mm pressure, the corresponding anhydride **29** distilled as 676 mg (72%) of colorless liquid. A solution of this distillate in a benzene–cyclohexane mixture deposited 485 mg of the pure anhydride **29** as white prisms: mp 78–80°; ir (CCl_4), 1850 and 1785 cm^{-1} (anhydride C=O in a five-membered ring); uv maxima (CH_3CN), 285 mμ (ϵ 3340) and 292 mμ (ϵ 3130); nmr ($CDCl_3$), δ 6.7–7.3 (3 H, multiplet, aryl CH), 5.8–6.1 (2 H multiplet, vinyl CH), 3.74 (3 H singlet, OCH_3), 2.8–3.7 (2 H, a partially resolved AB pattern, benzylic CH_2), and 2.0–3.1 (4 H multiplet, aliphatic CH). Except for the methoxy absorption the nmr spectra of the anhydrides **29** and **34** are practically identical in the region δ 2.0–4.0.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.03; H, 5.24.

To verify the relationship of the diester **28a** and the anhydride **29**, 300 mg of the anhydride was saponified with aqueous 10% NaOH and then acidified to yield 307 mg of the diacid **28b**, mp 167–170° dec. Esterification of this diacid **28b** with ethereal diazomethane gave, after recrystallization from a cyclohexane–petroleum ether (bp 30–60°) mixture, 190 mg of the diester **28a**, mp 124–125°, identified with the previously described sample by a mixture melting point determination.

A mixture of 1.00 g of the crude diacid **28b** and 0.50 g of a 30% palladium-on-carbon catalyst was heated to 235° over a 45-min period under a stream of nitrogen and then held at 235–240° for an additional 2 hr. The resulting mixture was cooled, partially dissolved in boiling benzene, and filtered through Celite. After the filtrate had been concentrated under reduced pressure, the residual solid (0.5 g) was chromatographed on silicic acid. The fractions eluted with an ether–hexane mixture (1:20 v/v) contained 0.40 g of 3-methoxyfluorene (**30**), mp 76–79°. Recrystallization from methanol afforded 0.31 g of the fluorene **30** as white needles: mp 78–80° (an additional recrystallization from cyclohexane raised the melting point to 82–83°); uv maxima, 259 mμ (ϵ 15,800), 268 (14,700), 305 (10,200), and 312 (11,600); uv maxima ($CHCl_3$), 263 mμ (ϵ 14,600), 271 (14,200), 306 (10,300), and 313 (11,600) [lit.[17] uv maxima ($CHCl_3$), 262 mμ (ϵ 20,000), 270 (20,000), 306

(17) W. S. P. Neish, *J. Org. Chem.*, **16**, 694 (1951).

(13,000), and 312 (16,000)]; nmr ($CDCl_3$), δ 7.0–7.8 (6 H multiplet, aryl CH), 6.78 (1 H doublet of doublets, J = 2.5 and 8.5 cps, C-2 aryl CH), 3.77 (3 H singlet, OCH_3), and 3.69 (2 H singlet, benzylic CH_2); mass spectrum, molecular ion at m/e 196, abundant fragment peaks at m/e 181, 165, 153, and 152. The sample was identified with an authentic sample,[18] mp 76–78°,[19] by a mixture melting point determination and comparison of infrared spectra.

For comparison, a sample of 2-methoxyfluorene (**32**) was synthesized from the known[20] methoxyhexahydrofluorenone **31**. Wolff–Kisner reduction of 0.27 g of this ketone **31** with 0.6 g of KOH, 1.0 ml of aqueous 85% hydrazine, and 24 ml of diethylene glycol at 175–220° yielded 0.20 g of the crude hexahydrofluorene derivative which was mixed with 0.10 g of a 30% palladium-on-carbon catalyst and heated to 235° under a stream of nitrogen for 2.5 hr. The resulting mixture was extracted with chloroform and the resulting extract was filtered through Celite and concentrated under reduced pressure. The residual four-component mixture[21] (0.20 g, mp 95–99°) was chromatographed on silicic acid. The fractions (0.11 g, mp 97–101°, two components[21]) eluted with an ether–hexane (1:50 v/v) mixture were recrystallized from methanol to separate 30 mg of the pure 2-methoxyfluorene (**32**) as white needles: mp 107–108° (lit. mp 110–111°,[22a] 109°[22b,c]); uv maxima, 207 mμ (ε 35,500), 272 (22,100), 303 (6750), and 314 (6580); uv maxima ($CHCl_3$), 276 mμ (ε 19,400), 304 (7070), and 315 (6950) [lit.[23] uv maxima, 271 mμ (ε 22,000), 303 (6500), and 314 (6200); lit.[17] uv maxima ($CHCl_3$), 272 mμ (ε 20,000), 306 (6300), and 314 (6300)]; nmr ($CDCl_3$), δ 6.7–7.7 (7 H multiplet, aryl CH) and 3.74 (5 H singlet, OCH_3 and benzylic CH_2); mass spectrum, molecular ion at m/e 196, abundant fragment peaks at m/e 181, 153, and 152. The material was identified with a commercial sample[24] of the 2-methoxy isomer **32** by a mixture melting determination and comparison of infrared spectra. The spectra of the isomeric methoxyfluorenes **30** and **32** are distinctly different.

Registry No.—**4**, 15378-00-4; **6**, 6771-54-6; **7a**, 15378-01-5; **8**, 15378-02-6; **9**, 15378-03-7; **10a**, 15378-04-8; **10b**, 15378-05-9; **11**, 15378-06-0; **13**, 15378-07-1; **14**, 15378-08-2; **16**, 15378-09-3; **17**, 15378-10-6; **19b**, 15378-11-7; **20**, 15378-12-8; **21** (less highly substituted), 15378-13-9; **21** (more highly substituted), 15378-14-0; **22** (less highly substituted), 15378-15-1; **22** (more highly substituted), 5796-60-1; **28a**, 15412-43-8; **28b**, 15378-17-3; **29**, 15378-18-4; **33a**, 15378-19-5; **33b**, 15378-20-8; **34**, 15378-21-9.

(18) This sample was purchased from K & K Laboratories, Inc., Plainview, N. Y.

(19) The compound has been reported to melt at (a) 84–85° [N. Ishikawa and M. Okuzaki, *Yuki Gosei Kagaku Kyokai Shi*, **16**, 610 (1958); *Chem. Abstr.*, **53**, 3168 (1959)]; (b) 82–83° [W. S. P. Neish, *Rec. Trav. Chem.*, **69**, 207 (1950)]; and (c) 81–82° [W. D. Zabler and R. Huisgen, *Chem. Ber.*, **96**, 765 (1963)]. C. J. Collins and B. M. Benjamin [*J. Amer. Chem. Soc.*, **75**, 1644 (1953)] have reported the same compound to melt at 101–101.5°. This discrepancy may be attributable to the isolation of a second crystalline form of the 3-methoxyfluorene.

(20) W. G. Dauben and J. W. Collette [*ibid.*, **81**, 967 (1959)] report mp 99–100°. A sample, mp 98–99°, was prepared by Mr. T. M. Bare in our laboratories.

(21) A thin layer chromatography plate coated with silicic acid and eluted with a benzene–petroleum ether (bp 30–60°) mixture was employed for this analysis.

(22) (a) N. Ishikawa and M. Okazaki, *Yuki Gosei Kagaku Kyokai Shi*, **16**, 467 (1958); *Chem. Abstr.*, **52**, 18340 (1958). (b) G. W. Gray, J. B. Hartley, and A. Ibbutson, *J. Chem. Soc.*, 2686 (1955). (c) J. D. Dickinson and C. Eaborn, *ibid.*, 2337 (1959).

(23) E. Sawicki, *J. Org. Chem.*, **21**, 271 (1956).

(24) Purchased from the Aldrich Chemical Co., Inc., Milwaukee, Wis.

Solvents of Low Nucleophilicity. X. Inductive and Participation Effects in the Addition of Trifluoroacetic Acid to Cyclopropanes[1]

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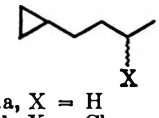
We have studied the carbonium ion formation which, formally, occurs in the ring-opening reactions of butylcyclopropane, 4-cyclopropyl-2-chlorobutane, and 4-cyclopropyl-2-butyl trifluoroacetate with trifluoroacetic acid. Cyclopropanes reacted approximately 300 times faster than comparable alkenes. Cyclopropane openings showed similar inductive effects but smaller effects of chlorine participation and (probably) hydrogen participation, compared with additions to unbranched alkenes and solvolyses of secondary tosylates.

Since quantitative information concerning the rates and products of electrophilic reactions of simple, substituted cyclopropanes is lacking, we have studied the reaction of trifluoroacetic acid with three substituted cyclopropanes carefully chosen to elucidate the role of hydrogen shifts and of inductive and participation effects in such reactions. The significance of the present study is that, by comparison with our previous studies, it provides the first comparison of carbonium ion formation *via* the following three different pathways: (1) cyclopropane opening, (2) additions to alkenes, and (3) tosylate solvolyses.

Increased interest in electrophilic ring-opening reactions of cyclopropanes has resulted from studies indicating the intermediacy of equilibrating edge- and/or end-protonated cyclopropane intermediates[2] and of the corresponding species derived from electrophilic attack of bromine[3] or acyl cations.[4] Although it is not yet known whether indications of unusual mechanisms will be confined to reactions of cyclopropane itself, the ring-opening reactions of substituted cyclopropanes take on new interest for comparison purposes. The presently reported study, however, has no direct connection with the question of unusual intermediates in reactions of cyclopropanes.

Description and Results

The compounds chosen for study were butylcyclopropane (**1a**), 4-cyclopropyl-2-chlorobutane (**1b**), and



1a, X = H
b, X = Cl
c, X = $OCOCF_3$
d, X = OH

(1) Supported in part by St. Louis University. Use of equipment furnished *via* National Science Foundation Grants GP2917 and GP20904 is gratefully acknowledged.

(2) R. L. Baird and A. A. Aboderin, *J. Amer. Chem. Soc.*, **86**, 252 (1964).

(3) N. C. Deno and D. N. Lincoln, *ibid.*, **86**, 252 (1964); **89**, 5357 (1966).

(4) H. Hart and R. L. Schlosberg, *ibid.*, **88**, 3347 (1966).

4-cyclopropyl-2-butyl trifluoroacetate (**1c**). Preparation of **1a** from hexene by the Simmons–Smith reaction posed no difficulty, but the comparable reaction with 5-chloro-1-hexene and 5-hexen-2-ol failed. Fortunately the modified procedure of Ginsig and Cross[5] gave excellent conversion of 5-hexen-2-ol into **1d**, from which **1b** and **1c** were prepared.

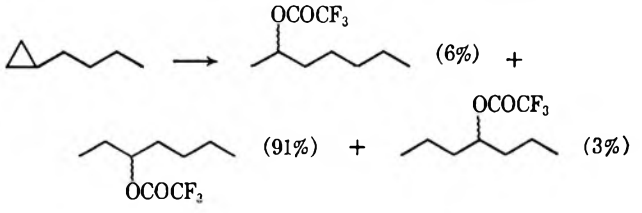
Butyl cyclopropane was found to react rapidly with trifluoroacetic acid, but fortunately at a rate ($t_{1/2}$ = 191 sec) just within the range measurable by conventional methods at 0°. By another fortunate circumstance the rates of cyclopropane ring openings were just sufficiently fast that the reactions could be followed by titration of the alkenes formed in the reactions, without interference due to addition of trifluoroacetic acid to the alkenes. As a third fortuitous circumstance, the cyclopropanes were *unreactive* toward the iodine monobromide reagent which quantitatively reacts with alkenes in the titrimetric analysis! Rates and percents of elimination, determined in the same experiment, are given in Table I.

TABLE I
RATES OF REACTION OF TRIFLUOROACETIC ACID WITH SUBSTITUTED CYCLOPROPANES AT 0° AND PERCENTAGES OF ELIMINATION

Compd	X	$k \times 10^6$, sec^{-1}	Elimination, %
1a	H	3260	39.2
1b	Cl	98.1	32.2
1c	$OCOCF_3$	10.2	27.7

The substitution products obtained by reaction of butylcyclopropane consisted of 3-heptyl trifluoroacetate, the expected product of Markovnikov ring opening, along with smaller amounts of products arising from hydride shift as given in Scheme I. 4-Cyclopropyl-2-

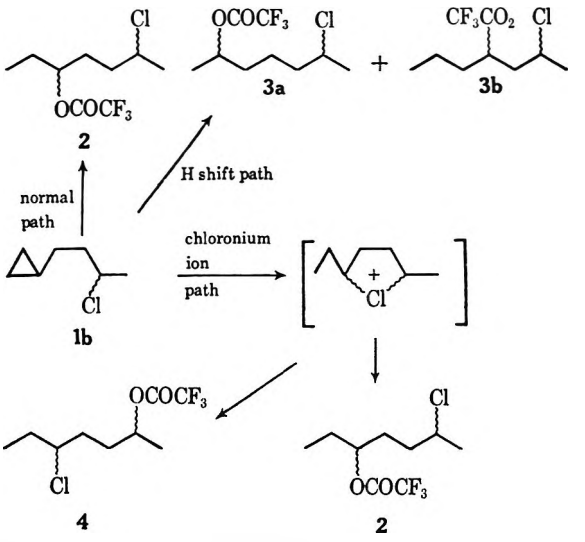
SCHEME I
ESTERS FORMED FROM BUTYLCYCLOPROPANE



chlorobutane was expected possibly to react in part *via* a path involving a 1,4-chlorine shift. Analogous chlorine shifts and/or other indications of chlorine participation have now been observed in the addition of trifluoroacetic acid to alkenes[6a] and alkynes[6b] and in the trifluoroacetolysis, formolysis, and acetolysis of secondary tosylates.[6c] The products which might be formed from 4-cyclopropyl-2-chlorobutane (**1b**) by "normal," "H shift," and "chloronium ion" paths are shown in Scheme II. The nmr spectrum of the isolated chloroheptyl trifluoroacetates obtained from **1b** showed a doublet at δ 1.51 (CH_3CHCl–) and a partially obscured doublet at 1.34 ($CH_3CHOCOCF_3$–) whose

(5) R. Ginsig and A. D. Cross, *J. Am. Chem. Soc.*, **87**, 4629 (1965).
(6) (a) P. E. Peterson, C. Casey, E. V. P. Tao, A. Agtarap, and G. Thompson, *ibid.*, **87**, 5163 (1965). (b) P. E. Peterson and J. E. Duddey, *ibid.*, **88**, 4990 (1966). (c) P. E. Peterson, R. J. Bopp, D. M. Chevli, E. L. Curran, D. E. Dillard, and R. J. Kamat, *ibid.*, **89**, 5902 (1967).

SCHEME II
REACTION PATHS OF 4-CYCLOPROPYL-2-CHLOROBUTANE

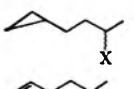
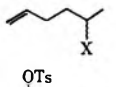
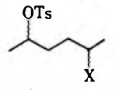


areas were indicative of the percentage ratio 84:14. The latter doublet could arise from **4**, the product of chlorine shift, or **3a**, the product of hydrogen shift. Since only 6% out of the 14% would be expected to arise from hydrogen shift, based on the result found for the reaction of butylcyclopropane, the nmr analysis was indicative of 8% 1,4-chlorine shift (16% chloronium ion formation, assuming equally probable formation of **4** and **2** from the chloronium ion). The assumption that the presence of chlorine does not affect the per cent of hydrogen shift is of course open to question. However, confirmation of the per cent of 1,4-chlorine shift was obtained by pyrolysis of the chlorotrifluoroacetates, followed by hydrogenation of the resulting unsaturated chlorides, to give 2-chloroheptane (from **2**, **3a**, and **3b**) and 3-chloroheptane (from **4**). Comparison of the nmr spectrum of the chloroheptane mixture with spectra of authentic mixtures indicated the presence of 11% 3-chloroheptane, in reasonable agreement with the earlier estimate.

Discussion

In Table II the cyclopropane ring-opening reactions which we studied are compared with other carbonium ion-forming reactions in the same solvent (trifluoroacetic acid). Formally, the tosylate and alkene reactants compared in Table II may yield the same carbonium ion, whereas the cyclopropanes give closely

TABLE II
COMPARISON OF TRIFLUOROACETOLYSIS OF CYCLOPROPANES, ALKENES, AND TOSYLATES

	H shift, %, X = H	Elimination, %, X = H	k_Δ/k_s, (Cl shift)	ρ_I
	6, 3	19.5, 19.5?	0.25	−3.50
	10[a]	24[a]	11[b]	−3.43
	22[c]	86[c]	65, 99[b]	−3.30[b]

[a] See ref 13. [b] See ref 6c. [c] See P. E. Peterson, *J. Amer. Chem. Soc.*, **82**, 5834 (1960).

comparable secondary ions which, however, differ in that an ethyl substituent is present in place of methyl. We assume that this structural difference is not the major factor which leads to the marked reaction trends to be discussed below. Subject to some additional ambiguities of interpretation (to be discussed) the first three reaction characteristics—per cent hydrogen shift, per cent elimination, and tendency for 1,4-chlorine participation—exhibit somewhat similar trends as the substrate varies in this sequence: cyclopropane, alkene, tosylate. All of the reactions exhibit similar and notably large inductive rate retardations of electron-attracting substituents as reflected in the Taft–Hammett ρ_I values.

The trends shown in Table II fit very well into a concept introduced in a recent paper from our laboratories concerning the nature of inductive and participation effects.[6c] Specifically a reaction type (*e.g.*, cyclopropane ring opening, as reported here) is postulated to exhibit a *characteristic participation tendency* which is reflected not only in the tendency for halogen participation (column 3, Table II) but also in the tendency for hyperconjugation of carbon and/or hydrogen in the carbonium ion transition state. According to our concept[6a] the increasing percentages of hydrogen shift shown in the first column of Table II reflect an increasing tendency for hydrogen hyperconjugation as secondary carbonium ions are formed from cyclopropanes, alkenes, and tosylates, respectively. The carbonium ion formed from butylcyclopropane can, of course, undergo a hydrogen shift in two directions (*cf.* Scheme I), and our discussion is based on the reasonable hypothesis that the two processes should be considered separately. Also it may be noted that the percentages of hydrogen shift have been determined only in the substitution product in each case.

The increasing percentages of elimination shown in the second column of data in Table II are likewise conveniently ascribed to increasing hydrogen hyperconjugation in the order shown. Again there is some question concerning the treatment of the cyclopropane data, since the intermediate cation may eliminate in two directions to give *cis*- or *trans*-2-heptene and *cis*- or *trans*-3-heptene. In the absence of an analysis for the four elimination products it seems most appropriate to assume that the observed 39% of elimination products is divided equally in the two directions. Direct comparison is then appropriate with the data for 1-hexene, which represents elimination in one direction (isomerization) in competition with substitution at the cationic carbon. The 86% elimination for 2-heptyl tosylate may be presumed to represent predominant elimination in one direction (to give *cis*- and *trans*-2-hexene) although the per cent elimination is so large as to make the direction a less important consideration.

Finally there is some question as to whether the ratio of rate constants for the reactions proceeding with 1,4-chlorine participation to those for normal solvolysis (k_Δ/k_s) should be judged from reaction rates, from the per cent halogen shift, or from the per cent of solvolysis with net retention of configuration (for tosylates). Regardless of the choice, however, the trend is that shown in Table II.

If increasing participation tendency with change of reactant is a reflection of increasing electron deficiency in the transition state, it would appear that an increasing magnitude of the respective ρ_I values would be found, reading down in the last column, Table II. It may be seen that no such trend is observed. In our paper dealing with the origin of inductive and participation effects[6c] we hypothesized that a chloroalkyl tosylate (considered as a typical example) shows substantial ground-state destabilization arising from dipole–dipole repulsion between the substituent and the reaction site. This ground-state interaction would decrease the absolute magnitude of ρ_I, since the latter quantity reflects only the additional interaction between the substituent and the reaction site upon going from the ground state to the transition state. Since alkenes are probably strongly hydrogen bonded in trifluoroacetic acid, leading to a larger than usual σ_I value for the double bond,[7] it is not unreasonable to postulate that moderate ground-state destabilization similarly affects the alkene reactions (Table II). Cyclopropanes would presumably show the least effect. According to this view, then, for the reaction in Table II, increasing positive charge in the transition state is found for reactions of cyclopropanes, alkenes, and tosylates, respectively, leading to increased participation, although concomitantly increasing ground-state destabilization in electronegatively substituted starting materials leads to relatively constant ρ_I values.

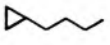
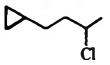
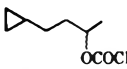
The argument outlined need not be regarded as more than a working hypothesis which originally was used to compare reactions of alkenes, alkynes, and tosylates, and which has now been extended to cyclopropane reactions. Some difficulties of this generalized theory of inductive and participation effects are, in fact, evident. Trends are not quantitatively parallel, for example. Furthermore ground-state effects would not appear to differ enough in alkenes and in cyclopropanes to account for the large difference in the chlorine participation tendency for reactions of these compounds. Certainly specific (and presently unpredictable) steric effects may be expected to be present in the reactions occurring by a halogen participation path. Despite these difficulties, the concept of participation tendency as a reaction parameter which may be determined experimentally, and which reaches a minimum in cyclopropane reactions (among those we have compared), provides a useful correlation of our results and a highly suggestive guide to further studies.

It is worth noting that cyclopropane ring openings have proved to be the *most suitable carbonium ion reactions for studies of inductive effects* in aliphatic, and presumably certain other systems, owing to their relative freedom from complications due to participation. Furthermore their relatively fast rates assure freedom from side reactions in many instances, including, as we have mentioned, freedom from interference due to additions to alkenes formed in the ring openings. A comparison of cyclopropane and alkene reactivities is made in Table III. Also listed there are values of k_H/k_X, the ratios of the rate constants for reaction of unsubstituted and substituted cyclopropanes, respectively, and other related quantities. Table III represents the first quantitative comparison of cyclopropane and alkene reactivities. In this con-

(7) For references to such hydrogen bonding, see R. C. Fahey and D.-J. Lee, *J. Amer. Chem. Soc.*, **80**, 2780 (1967).

TABLE III

REACTIVITY OF CYCLOPROPANES TOWARD TRIFLUOROACETIC ACID. COMPARISON WITH ALKENES. SUBSTITUENT EFFECTS

Cyclopropane	$k_{cyclopropane}$[a] / $k_{alkenes}$	k_H/k_X	Log (k_H/k_X) 3.5	σ_I
	332	1.0	0	0
	54	33.3	0.43	0.47[b]
	307	319	0.72	0.72[b]

[a] Calculated using data in ref 13. [b] For values, see ref 10a and b.

nection we note that LaLonde and Tobias have said, "That the acid-promoted addition of acetic acid to olefins is slower than the addition to cyclopropanes has been demonstrated."[8a]

In the present work the cyclopropane ring is seen to be approximately 300-fold more reactive than alkenes toward trifluoroacetic acid, the smaller ratio (54) for the chlorosubstituted compounds being attributable to halogen participation in the alkene reaction. The previously mentioned much greater reactivity of alkenes toward iodine bromide in carbon tetrachloride–acetic acid constitutes a striking reversal of the reactivity toward acids. A possible correlation with hard and soft acid–base behavior[9] is suggested, cyclopropanes representing the harder base which combines preferentially with hard (protonic) acids. Finally, it may be noted from the third and fourth columns in Table III that the three cyclopropane reactivities studied give a satisfactory Hammett–Taft correlation, using σ_I values presumably appropriate to trifluoroacetic acid.[10] The slight deviation from the line exhibited by the chloro substituent is approximately of the magnitude expected, based on the observed percentage of halogen participation (*cf.* Table II).

Experimental Section

Chemicals.—Butylcyclopropane[11] was obtained in 26% yield in our study by the Simmons–Smith reaction[12] of 1-hexene. Trifluoroacetic acid (Allied Chemical) was distilled through a 3-ft, helix-packed column, and the center cut retained.

4-Cyclopropyl-2-butanol.—5-Hexen-2-ol (36.8 g, 0.5 mole, from sodium borohydride reduction of commercial allyl acetone) was added over a period of 30 min to a stirred mixture of 93.6 g of zinc–copper couple, 500 ml of dry ether, 316 g (1.15 mole) of methylene iodide, and several crystals of iodine. As previously recommended,[5] the mixture was distilled to half of the original volume, made up to the original volume with dry ether, and heated at 85–90° for 6–7 hr in a high pressure vessel. The ether layer was decanted, and combined with two 50-ml ether washings of the couple. The ether layer was washed with ten 50-ml portions of saturated sodium bicarbonate (until the water layer did not contain a white precipitate of zinc salts). Washing (saturated sodium chloride), drying (magnesium sulfate), and spinning-band distillation of the ether layer gave 31.2 g (55%) of gas chromatographically pure (6-ft diethylene glycol succinate on firebrick) 4-cyclopropyl-2-butanol: bp 75° (20 mm); nmr multiplets, δ −0.17 to +0.92.

Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.62; H, 12.25.

4-Cyclopropyl-2-chlorobutane.—4-Cyclopropyl-2-butanol (30.0 g, 0.26 mole) was mixed with 20.8 g (0.26 mole) of dry pyridine, and 31.4 g (0.26 mole) of thionyl chloride was added over a period of 35 min. The mixture was heated to 80–90° for 7 hr. The resulting pyridine hydrochloride was dissolved in a minimum amount of water. Distillation of an ether extract gave 4.4 g (bp 73°, 50 mm) of pure material and other less pure fractions which were preparatively gas chromatographed (8-ft diethylene glycol adipate column) to give a total of 9.1 g (26%) of 4-cyclopropyl-2-chlorobutane with nmr multiplets at δ −0.12 to +0.83.

Anal. Calcd for $C_7H_{13}Cl$: C, 63.39; H, 9.91. Found: C, 63.55; H, 9.88.

4-Cyclopropyl-2-butyl Trifluoroacetate.—An ice-cold mixture of 4-cyclopropyl-2-butanol (9.29 g, 0.081 mole) in 35 ml of ether was added during 15 min to an ice-cold mixture of 25.6 g (0.12 mole) of trifluoroacetic anhydride in 50 ml of ether. After 6 min, isolation by extraction was begun (water, aqueous sodium bicarbonate, aqueous sodium chloride). The ether extract gave 11.4 g (67%) of gas chromatographically pure (6-ft diethylene glycol adipate) 4-cyclopropyl-2-butyl trifluoroacetate: bp 70° (29 mm); nmr multiplet, δ −0.19 to +0.88.

Anal. Calcd for $C_9H_{13}F_3O_2$: C, 51.43; H, 6.23. Found: C, 51.47; H, 6.23.

Kinetic Method.—Sufficient cyclopropane compound to make a 0.1 *M* solution was weighed in a 25-ml volumetric flask, brought to 0.00 ± 0.05°, and diluted to 25 ml with trifluoroacetic acid, 0.125 *M* in sodium trifluoroacetate, also at 0.00°. Aliquots (2 ml) were withdrawn at intervals and analyzed for alkene concentration by the iodine monobromide titrimetric method described previously.[13]

Products of Reaction of Butylcyclopropane with Trifluoroacetic Acid.—Butylcyclopropane (10.0 g) was cooled to 0.0° and diluted to 100 ml with trifluoroacetic acid, 0.125 *M* in sodium trifluoroacetate, also at 0°. After 97 min (86% reaction, measured by titration of an aliquot), the mixture was poured into 200 ml of ice cold water and 100 ml of ether. Extraction and distillation gave 2.37 g of alkene, bp 52–62° (61%, based on 39.2% "elimination," measured in a kinetic run), and 9.31 g (39%, based 60.8% "substitution") of trifluoroacetate esters, bp 72–78.5° (55 mm). The esters were analyzed on a 150-ft capillary Dow-Corning 550 silicone column (*cf.* Scheme I) by comparison with authentic 2-, 3-, and 4-heptyl trifluoroacetates.

Products of Reaction of 4-Cyclopropyl-2-chlorobutane.—The procedure was similar to that used in the reaction of butylcyclopropane except that 7.00 g of 4-cyclopropyl-2-chlorobutane was allowed to react in a volume of 100 ml for 12.3 hr (96.9% reaction, by titration). Distillation gave a chloroheptene fraction of 1.32 g (59% based on 32% elimination: bp 51–60°, (30 mm), nmr multiplet, δ 5.31–5.68) and an ester fraction of 5.72 g (62% based on 68% substitution).

The ester 4.16 g was pyrolyzed in a 20 × 2 cm glass column packed with glass helices. The ester (mixed chloroheptyl trifluoroacetates) was dropped into the tube, which was heated to 410° and through which dry nitrogen was passed, over a period of 5 min. The products were collected in a Dry Ice–acetone cold trap.[14] The product was diluted to twice its original volume

(8) (a) R. T. LaLonde and M. A. Tobias, [*J. Amer. Chem. Soc.*, **86**, 4068 (1964)] studied the cyclopropane ring opening of *exo*-7-methylbicyclo[4.1.0]-heptane and *exo*-6-methylbicyclo[3.1.0]hexane in glacial acetic acid, 0.09 *N* in sulfuric acid, at 47° for 36 and 24 hr, respectively. Their contention that their reaction products did not arise to an appreciable extent from addition of acetic acid to first-formed alkenes on the basis of the "slower addition of acetic acid to olefins" appears to deserve further comment.[8b] (b) P. E. Peterson and E. V. P. Tao, [*J. Org. Chem.*, **29**, 2322 (1967)] have shown that *branched* alkenes reach equilibrium with the corresponding tertiary acetates in 0.0145 *M* toluene–sulfonic acid hydrate in acetic acid at 35° in a few days. It seems certain, therefore, that the 1-ethylcyclohexene (22% of the 53% olefin yield) and 1-methylcycloheptene (13% of 53%) formed from *exo*-7-methylbicyclo[4.1.0]heptane *did react* in the experiment of LaLonde and Tobias, although the equilibrium yield of tertiary acetates may have been small. Although quantitative data are not yet available, it seems likely that branched alkenes will be found to react faster with acids (to give tertiary carbonium ions) than those cyclopropanes which can give only secondary carbonium ions, contrary to the assumptions of LaLonde and Tobias.

(9) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

(10) (a) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *ibid.*, **85**, 709 (1963). (b) P. E. Peterson and G. Allen, *J. Org. Chem.*, **27**, 2290 (1962).

(11) J. T. Grogson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *ibid.*, **20**, 275 (1955).

(12) R. D. Smith and H. E. Simmons, *Org. Syn.*, **41**, 73 (1962).

(13) P. E. Peterson and G. Allen, *J. Org. Chem.*, **27**, 1505 (1962).

(14) In a prior control experiment 5-chloro-2-hexyl trifluoroacetate was shown to undergo loss of trifluoroacetic acid without loss of hydrogen chloride under these conditions.

with ether, washed, dried, and hydrogenated over prereduced platinum oxide. Removal of ether (spinning-band column) and preparative gas chromatography (3 ft × 0.25 in., 20% diethylene glycol adipate column) gave 0.43 g of pure material having the retention time of 2- and 3-chloroheptane. Since these chloroheptanes were not separated on four different capillary columns, the mixture from pyrolysis and hydrogenation was analyzed by comparison of the nmr spectrum (neat) with spectra of quantitatively prepared mixtures of 2- and 3-chloroheptane. The spectrum was identical with that of a mixture prepared from 100 μl of 2-chloroheptane and 12 μl of 3-chloroheptane (corresponding to 10.7 mole % 3-chloroheptane). Assuming that our procedure did not result in selective product formation from the original mixture, or in chlorine migration, during pyrolysis (both assumptions seem to be reasonably good) the above-mentioned percentage is a measure of the chlorine shifted products in the cyclopropane ring-opening reaction.

Registry No.—1a, 930-57-4; 1b, 15451-38-4; 1c, 15451-39-5; 1d, 15451-40-8; trifluoroacetic acid, 76-05-1.

Solvents of Low Nucleophilicity. XI. Modified Aromatic σ Values in the Addition of Trifluoroacetic Acid to Phenylbutenes[1]

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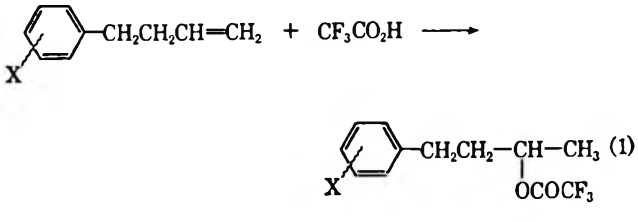
Rates of addition of trifluoroacetic acid to 4-phenyl-1-butenes substituted in the *meta* and *para* positions of the benzene ring were determined. Oxygen- and nitrogen-containing substituents were more electron attracting than expected from the σ^0 values of the substituents, owing to hydrogen bonding of the solvent to the substituents. The solvent modification of aliphatic and aromatic σ values is compared.

In connection with studies of enhanced inductive effects in trifluoroacetic acid attributable to hydrogen bonding between trifluoroacetic acid and oxygen- or nitrogen-containing groups,[2] we were prompted to examine the effect of such hydrogen bonding on aromatic substituent effects.

The reaction of substituted phenylbutenes with trifluoroacetic acid (eq 1) appeared to be ideally suited for such a study. The desirable absence of phenyl



participation in this system may be inferred from the studies of Heck and Winstein.[3] Also, the potential cationic carbon in the carbonium ion intermediate which may be envisioned for the reaction of eq 1 is just far enough from the phenyl group to prevent rearrangement to a more stable benzyl cation by hydrogen shift in the rate-determining step.[4] Finally the large effects of distant substituents upon reaction rates for addition of trifluoroacetic acid to alkenes suggests that rate effects should be large compared to experimental errors, despite the relative remoteness of the substituents in the phenylbutenes. Actually there are only a few studies of aromatic substituent effects in cases where there is no possible conjugation between the substituent and the reaction site, and the discovery of additional reactions suitable for such studies is of interest itself.

Results

The phenylbutenes were obtained as a gift (for a reference, see the Acknowledgment), or synthesized as described in the Experimental Section. The rates of reaction with trifluoroacetic acid, measured at 60.0°, are given in Table I. Also listed are

TABLE I

RATES OF ADDITION OF TRIFLUOROACETIC ACID TO 4-PHENYL-1-BUTENES AT 60.0°

Substituent	10^5k, sec^{-1}	Effective σ_I[a]
p-CH_3	408	0.063
m-CH_3	353	0.080
H	257	0.1[b]
p-OCH_3	218	0.112
p-Cl	93.5	0.168
m-OCH_3	87.4	0.181
p-Br	84.5	0.176
m-Cl	71.7	0.206
p-CO_2CH_3	31.2	0.259
p-$COCH_3$	18.0	0.300
p-CN	10.5	0.341

[a] Values of σ_I for the substituted phenyl groups, calculated according to eq 11 (*cf.* discussion section). [b] From ref 12.

"effective σ_I" values to be discussed later. It is interesting that the rate constants vary over a range of 40-fold (for *p*-methyl and *p*-cyano) despite the distance of seven carbons between the substituent and the reaction site (counting the cationic carbon as 1). A Hammett plot of the data, using σ^n values[5] is shown in Figure 1. The correlation line is drawn through the points for nonhydrogen-bonding substituents. The substantially increased electron-attracting effect of oxygen- and nitrogen-containing substituents, ascribable to hydrogen bonding of the solvent to the substituent, is immediately apparent.

Present Status of Solvent Modified σ Values.—Before proceeding to a closer examination of solvent-

(1) Supported in part by National Science Foundation Grant GP 2917.

(2) P. E. Peterson, C. Casey, E. V. P. Tao, A. Agtarap, and G. Thompson, *J. Amer. Chem. Soc.*, **87**, 5163 (1965).

(3) R. Heck and S. Winstein, *ibid.*, **79**, 3105 (1957).

(4) Similar direct formation of a phenylethyl-type bridged cation cannot be ruled out *a priori*.

(5) The origin and applicability of σ^n values, which differ slightly from the Hammett σ values, is reviewed in the next section.

modified σ values observed in our study, it is appropriate to review briefly the somewhat complex picture which has evolved from recent studies of substituent effect correlations. The original Hammett σ values, based on substituted benzoic acid ionization constants, are now known to include some discernible effects of direct interactions between resonance-donor substituents such as *p*-CH_3O and the reaction site. By scrupulously excluding cases which might involve such interactions and using several reaction series, Bekkum, Verkade, and Wepster[6] obtained normal "σ^n" values presumably applicable to nonconjugating reaction sites of the type considered in the present paper. Using remote reaction sites (in phenylacetic acid ionizations) Taft[7] derived a similar set of values, designated σ^0. Some success was achieved in making a separation of σ^0 values into an inductive (polar) effect, σ_I, and a resonance effect σ^0_R, according to eq 2 and 3 which

$$\sigma_p^0 = \sigma_I + \sigma_R^0 \quad (2)$$

$$\sigma_m^0 = \sigma_I + 0.5\sigma_R^0 \quad (3)$$

are applicable to *para* and *meta* substituents, respectively, in reactions where there is no direct resonance between the substituent and the reaction site. For other reaction series correlated by the original Hammett σ values, a similar set of simultaneous equations (4 and 5) could be solved to yield approximately the

$$\sigma_p = \sigma_I + \sigma_R \quad (4)$$

$$\sigma_m = \sigma_I + {}^1/_3\sigma_R \quad (5)$$

same σ_I values, which are applicable also to *aliphatic* reactivity, but solution for σ_R values gave variable results for different reactions, suggesting that the correlation with Hammett σ values was itself a somewhat rough approximation in that slightly varying resonance effects were ignored.

The σ_I values "extracted" from aromatic σ values were found to be linearly related to "aliphatic" σ^* values, according to eq 6. Accordingly, values ob-

$$\sigma_I = 0.45\sigma^* \quad (6)$$

tained from either origin may be used interchangeably, although in practice the user must select a source of σ_I values if slightly differing values are available from aromatic and aliphatic reactivity, respectively. Attempts to further improve eq 2 and 3 by allowing variability of the parameters gave only inconclusively better results,[8] suggesting that 2 and 3 are adequate at present.

Finally, unexpected, but voluminously documented, correlations of σ_I and σ_R^0 with *meta*-substituted and *para*-substituted fluorobenzene fluorine nmr frequencies were reported, the *meta* frequencies surprisingly yielding *aliphatic* inductive constants directly according to eq 7.[9]

$$\int_H^{m\text{-X}} = -7.10\,\sigma_I + 0.6 \text{ ppm} \quad (7)$$

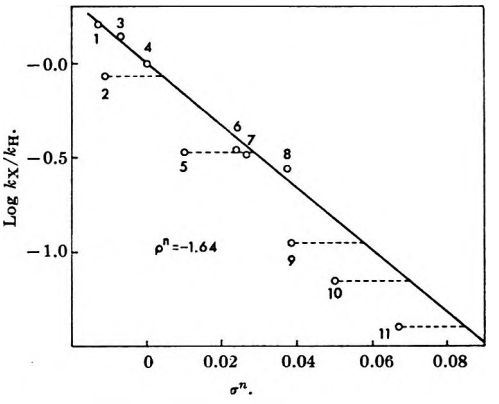


Figure 1.—Plot of log k_X/k_H *vs.* σ^n for Substituted Phenylbutenes. Identification: 1, *p*-CH_3; 2, *p*-CH_3O; 3, *m*-CH_3; 4, H; 5, *m*-CH_3O; 6, *p*-Cl; 7, *p*-Br; 8, *m*-Cl; 9, *p*-CO_2CH_3; 10, *p*-$COCH_3$; 11, *p*-CN.

Frequencies of fluorobenzenes substituted in the *para* position with a group which is electron releasing by resonance were found to be correlated with the resonance parameters σ_R^0, especially when the relatively small "inductive" contribution, $\int_H^{m\text{-X}}$, was subtracted (eq 8).[10] These relationships serve to de-

$$\int_H^{p\text{-X}} - \int_H^{m\text{-X}} = -29.5\,\sigma_R^0 \quad (8)$$

fine σ values in instances where reactivity data are not available. Furthermore they are subject to several discernible solvent effects, of which enhancements of σ_I and σ_R^0 values in trifluoroacetic acid are perhaps the most striking. But are the enhanced values applicable to *reactivity?* In the absence of experimental data, the authors[10] speculated that "the solvent effects on σ_R values obtained from eq 7 and 8 (this paper) may be taken to indicate the expected magnitudes of solvent effects on the reactivity effects of (hydrogen bonding) substituents, but the precise quantitative applicability of these substituent parameters is questionable."

Comparison of Nuclear Magnetic Resonance and Reactivity Data.—The rates of reaction of substituted phenylbutenes (Table I), along with early studies of substituted aliphatic alkenes, now provide a fairly comprehensive picture of the solvent modification of σ values as judged from reactivities in trifluoroacetic acid. In Table II values of $\Delta\sigma_I$ from nmr data for the

TABLE II

SOLVENT MODIFICATION OF σ VALUES

Substituent	σ^n	σ^0	$\Delta\sigma^n$ [a]	$\Delta\sigma^0$ [b]	$\Delta\sigma_I$ (nmr) [c]
p-CH_3O	−0.111	−0.12	0.185	0.166	0.26
m-CH_3O	0.10	0.13	0.155	0.165	0.26
p-CO_2CH_3	0.385	0.46	0.173	0.119	0.24
p-$COCH_3$	0.502	0.46	0.201	0.270	0.28
p-CN	0.67	0.69	0.175	0.187	0.26
Average			0.178	0.181	

[a] Based on deviations from the "least squares" line through points for nonhydrogen-bonding substituents, log $k_H/k_X = -1.64\sigma^n - 0.004$. [b] Based on deviations from the "least squares" line log $k_H/k_X = -1.58\sigma^0 - 0.010$. [c] From ref 9.

change from normal solvents to trifluoroacetic acid are compared with $\Delta\sigma^n$ and $\Delta\sigma^0$ values based on deviations

(6) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chem.*, **78**, 815 (1959).

(7) R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960), and references cited therein.

(8) S. Ehrenson, *Progr. Phys. Org. Chem.*, **2**, 195 (1964).

(9) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963).

(10) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *ibid.*, **85**, 3146 (1963).

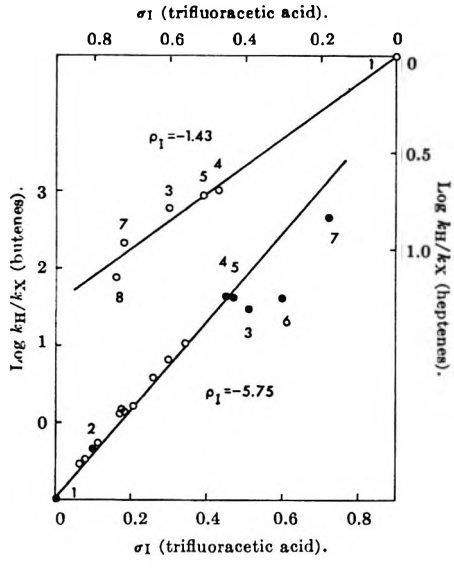
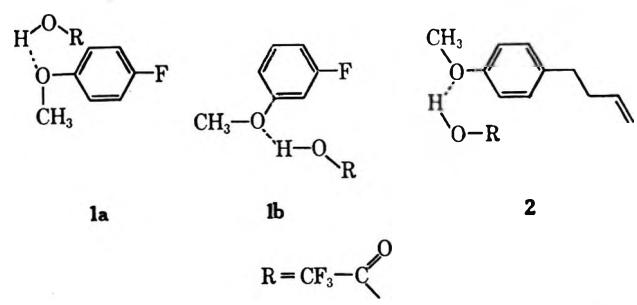


Figure 2.—Plot of log k_X/k_H *vs.* σ_I (trifluoroacetic acid) for the reaction of 4-substituted 1-butenes (lower plot) and 7-substituted 1-heptenes with trifluoroacetic acid. Note the reversed coordinate direction and changed scale in the heptene (upper) plot. Identification: 1, H; 2, C_6H_5; 3, OCH_3; 4, Br; 5, Cl; 6, $OCOCH_3$; 7, $OCOCF_3$; 8, C≡N. For the identification and description of our derived σ_I values for the substituted phenylbutenes (open circles, lower plot), see Table I and the discussion section.

from the correlation line of the Hammett plot of Figure 1 and the similar plot in which σ^0 values are used. In only one instance (p-CH_3O) does the available nmr data permit calculation of $\Delta\sigma_R^0$ from eq 8. Since the value of $\Delta\sigma_R^0$ thus derived is only 0.09, we may hopefully infer that the $\Delta\sigma_I$ values represent a large part of the solvent shift of σ_m^0 and σ_p^0 values derived from substituted fluorobenzene nmr data. This assumption certainly is subject to question, but some support is provided by the observation that $\Delta\sigma_I$ values from nmr data are larger than the over-all changes $\Delta\sigma$ based on phenylbutene reactivity. The nmr method seems to have overestimated the solvent shift of σ values, but it does reproduce the tendency for all $\Delta\sigma^n$ values to be essentially identical among the substituents studied. The somewhat different solvent shifts exhibited by $\Delta\sigma^0$ are attributable to the fact that our $\Delta\sigma$ values are only a few times larger than the expected errors in σ values. The largest discrepancy between σ^n and σ^0 values occurs for the p-CO_2R group (σ^n = 0.38, σ^0 = 0.46). The smaller σ^n value seems preferable in this instance because it seems likely that the carbethoxy group is less electron withdrawing than the p-$COCH_3$ group (σ^n = 0.50, σ^0 = 0.46), and also because it seems likely that the $\Delta\sigma$ values of these groups should be similar in magnitude, as found for $\Delta\sigma^n$ values.

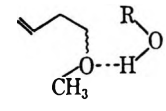
It is instructive to compare the hydrogen-bonded structures involved in the two types of measurement of substituent effect enhancement. This comparison is made below (structures **1a**, **1b**, and **2** for a typical substituent, OCH_3). Both **1a** and **1b** used for the nmr measurements, and **2**, used for the reactivity measurement, are comparable in structure in that an aromatic substituent is involved in each instance, although it could be argued that **1b** will contain an abnormally weak hydrogen bond, compared with **2**, as a consequence of the inductive effect of the *meta* fluorine. Such



1a **1b** **2**

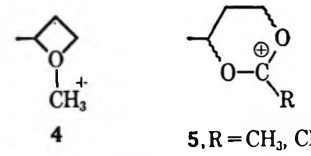
an effect would lead to smaller solvent modifications of σ values derived from nmr data, contrary to the observed trend. It is possible that the nmr data is influenced by differential hydrogen bonding to fluorine in fluorobenzene and substituted fluorobenzenes, an effect not present in phenylbutenes.[11] In conclusion, despite the similar structures of **1a**, **1b**, and **2**, nmr data seems to provide only a semiquantitative guide to solvent modifications of σ values, as originally anticipated.[10]

An even less favorable occasion for correlation arises in the comparison of **1b** with structures such as **3** (4-methoxy-1-butene) where the hydrogen-bonding ca-



3

pacity of the aromatic and aliphatic substituents might be expected possibly to be quite different. Nevertheless the previously discussed identification of *meta*-substituted fluorobenzene frequencies with *aliphatic* σ_I values (eq 6) seems to lead to a comparison of this type. A Hammett–Taft plot, in which σ_I values are used, offers a means of correlating the rates of reaction of 4-substituted 1-butenes, determined previously,[2] with those of phenylbutenes, reported in this paper. Since we have no other applicable values of σ_I available, we have nothing to lose from the inclusion of hydrogen-bonding substituents and enhanced σ_I values from nmr data in such a plot. We may, in any event, use non-hydrogen-bonding substituents and the corresponding solvent independent σ_I values from nmr data to establish the correlation line. Such a plot for 4-substituted 1-butene reactions is shown in Figure 2, with the correlation line passed through points for the nonhydrogen-bonding substituents chlorine and bromine. The incorporation of points for substituted phenylbutenes into the plot of Figure 2 is discussed in the next section. The hydrogen-bonding substituents for 4-substituted 1-butenes deviate from the line in a direction which could indicate that solvent augmented σ_I values have been over-estimated by the nmr method, or else that the rates of reaction of these substituents are faster than expected, owing perhaps to neighboring-group participation to give transition states of types **4** or **5**.

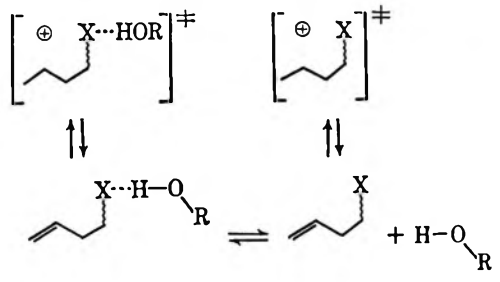


4 **5**, R = CH_3, CF_3

(11) For a study of the hydrogen-bonding properties of aliphatic fluoro compounds, see R. West, D. L. Powell, L. S. Whatley, M. K. T. Lee, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 84, 3321 (1962).

Still further complications in the solvent modification of σ_I values might arise from the possibility of concurrent reaction through nonhydrogen-bonded transition states (Scheme I). In this connection the

SCHEME I
REACTION THROUGH HYDROGEN-BONDED AND NONHYDROGEN-BONDED TRANSITION STATES



Hammett–Taft plot of rates of reaction of 7-substituted 1-heptenes is of some interest, since participation effects are probably negligible in the heptene reactions,[2] This plot, based on rate data published previously.[2] is also given in Figure 2. In this instance, the σ_I values based on nmr data account sufficiently well for the observed rates that postulation of a new set of aliphatic σ_I values based on aliphatic reactivity in trifluoroacetic acid seems unnecessary at present despite the insecure foundation of the nmr based values.

Attenuation of Substituent Effects. Role of the Aromatic Ring and of the Solvent.—Assuming that the Hammett equation and Hammett–Taft equation apply to the reactions of the phenylbutenes and the 4-substituted 1-butenes, respectively, it is possible to combine the two equations to give a single equation which represents both sets of reactivities, as shown previously.[12] The Hammett–Taft equation for the comparison of 4-phenyl-1-butene with 1-butene is given in eq 9 where the subscript Ph denotes 4-phenyl-1-bu-

$$\log (k_{Ph}/k_H) = \rho_I\sigma_{IPh} \quad (9)$$

tene and the subscript H denotes 1-butene. The Hammett equation for the comparison of *meta*- and *para*-substituted 4-phenyl-1-butenes with 4-phenyl-1-butene is shown in eq 10. The result of adding eq 9

$$\log (k_{Ph_x}/k_{Ph}) = \rho\sigma \quad (10)$$

and 10 is eq 11. An alternative form is given in eq 12.

$$\log (k_{Ph_x}/k_H) = \rho_I\sigma_{IPh} + \rho\sigma \quad (11)$$

$$\log (k_{Ph_x}/k_H) = \rho_I[\sigma_{IPh} + (\rho/\rho_I)\sigma] \quad (12)$$

In eq 10, 11, and 12, ρ and σ may be taken to be ρ^n and σ^n or ρ^0 and σ^0. The term in brackets (eq 12) is seen to be a substituent constant for substituted phenyl groups, applicable to aliphatic reactivity. In Figure 2 the points for substituted phenylbutenes (open circles) are those derived from eq 12, using σ^n values. The only reason for the inclusion of these points is to show the useful range of aliphatic σ values available from the inclusion of substituted phenyl groups as inductive substituents. No significance should be attached to the fit for these points since σ^n values for hydrogen-bonding substituents are defined as the values which give a fit in the Hammett plot (*i.e.*, they are our $\sigma^n + \Delta\sigma^n$ values). Phenylbutenes having nonhydrogen-bonding substituents fit the plot of Figure 2 to the extent that phenylbutene itself fits, and to the extent that the Hammett relationship is followed (Figure 1).

Applying the relationship $\sigma_p^0 = \sigma_I + \sigma_R^0$, eq 12 may be written as in eq 13 in which ρ and σ have been taken

$$\log (k_{Ph_x}/k_H) = \rho_I[\sigma_{IPh} + (\rho^0/\rho_I)\sigma_I + (\rho^0/\rho_I)\sigma_R^0] \quad (13)$$

to be ρ^0 and σ^0. We note that the term ρ^0/ρ_I represents the factor by which the inductive portion of the aromatic substituent effect is attenuated, compared with the effect when the same substituent is attached to C-4 of 1-butene. From Table II, footnote *b*, and Figure 2, the value of ρ^0/ρ_I is 1.58/5.75 = 0.274. This attenuation factor is of interest in connection with studies of tosylate solvolyses in trifluoroacetic acid, where attenuation factors have been shown to be solvent dependent, the least attenuation with increasing distance between the substituent and the reaction site being found in trifluoroacetic acid.[13] Previously a value of ρ/ρ_I of 0.147 has been found[14] for the ionization of phenylacetic acids in water compared with ionization of acetic acids. As in purely aliphatic reactions the reactions of trifluoroacetic acid with phenylbutenes are seen to be characterized by remarkably little attenuation of inductive effects with increased distance between the substituent and the reaction site.

Since *meta*-substituted benzenes contain three more carbon atoms between the substituent and the reaction site than the parent compounds, it is interesting to calculate the attenuation factor per carbon atom in the two cases cited above. The results are 0.274 = $(0.65)^3$ and 0.147 = $(0.528)^3$. These attenuation factors per carbon atom are very similar to the attenuation factors per methylene group (ϵ values) which characterize the addition of trifluoroacetic acid to ω-substituted 1-alkenes (ϵ 0.065) and the ionization constants of aliphatic acids in water (ϵ 0.41, 0.47, 0.49 and 0.39, for the substituents Cl, Br, I, and CN in acetic and propionic acids).[15] Clearly the benzene ring is not especially effective, compared to an aliphatic chain, in transmitting the inductive effect of *meta* substituents. The slower attenuation observed for the reaction of butenes in trifluoroacetic acid is expected, based on the previously published hypothesis[13] that the charge on a carbonium ion is delocalized to some extent by overlap with neighboring bonds (hyperconjugative interaction). According to this view, moving the substituent farther from the reaction site allows increased delocalization of the carbonium ion charge, so that in effect the carbonium ion charge follows the substituent down the chain as the substituent is placed farther from the reaction site. Since our hypothesis concerning the role of charge delocalization in aliphatic carbonium ions[13] is speculative, its continuing success in predicting trends in attenuation of substituent effects is of interest as added evidence for the hypothesis.

Implications of Variable σ Values for Aromatic Reactivity.—The solvent variability of aromatic σ^n or σ^0 values, demonstrated in our study, implies that σ and σ^+ values will show similar effects. So far the

(12) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 332 (1964).

(13) P. E. Peterson, R. J. Bopp, D. M. Chevli, E. L. Curran, D. E. Dillard, and R. J. Kamat, *J. Amer. Chem. Soc.*, **89**, 5902 (1967).

(14) *Cf.* ref 12. The value 0.147 is obtained from the values ρ = 0.56 and $\rho_I = \rho^*/0.45$ = 3.82.

(15) Calculated from data given by G. Kortum, W. Vogel, and K. Andrussow in "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworth and Co. Ltd., London, 1961.

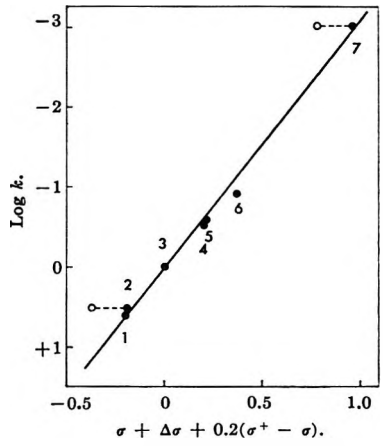


Figure 3.—Plot of log k_X/k_H for the ditritiation of 4′-substituted [4-^{3}H]biphenyls (from ref 17) *vs.* an expression using modified σ values (closed circles) and unmodified σ values (open circles). Identification: 1, CH_3; 2, OCH_3; 3, H; 4, Cl; 5, Br; 6, 3Cl; 7, NO_2.

implication based upon inspection of plots relating rates of aromatic substitution reactions to σ^+ reactivities[16] and also upon inspection of the nmr data of ref 9 and 10 is that acetic and formic acid will show much smaller, possibly negligible, substituent modifications arising from hydrogen bonding between the solvent and various substituents. However, in one reported instance of electrophilic aromatic substitution in trifluoroacetic acid (detritiation of 4′-substituted 4-tritiated biphenyls) solvent modified effects of nitro and methoxy substituents closely similar to those reported here for hydrogen-bonding substituents were found.[17] The origin of the effects was not completely clear, however. They were ascribed to " 'incipient protonation,' which may be hydrogen bonding."[18] It was of interest to determine whether correction terms, $\Delta\sigma$, having the approximate magnitude observed in our study, would lead to a linear free-energy relationship in the case of the detritiation data. Accordingly we corrected the σ values in the equation previously found[17] to correlate the rates of disilylation of 4′-X-4-trimethylsilylbiphenyls in *acetic* acid containing sulfuric acid, using as correction terms our $\Delta\sigma^n$ value for CH_3O and the estimated $\Delta\sigma$ value 0.18 for NO_2, to obtain the result shown in Figure 3. The reasonably good results suggest that $\Delta\sigma$ values of the type found in our study may be applicable also to σ^+ and σ reactivities. In view of possible complications arising from equilibria of the type shown in Scheme I, however, it would not be surprising if even special sets of σ constants will fail to give linear free-energy relationships for various types of reactions in trifluoroacetic acid. On the other hand, the use of modified σ constants is especially attractive for *remote* substituents, since complications arising from the equilibria of Scheme I should be absent (because substituents are assured of being hydrogen bonded in the transition state as well as in the ground state). It is precisely such cases which are of great interest in testing theoretical predictions of reactivity, as Dewar and Grisdale have pointed out.[19] Since reactions in trifluoroacetic acid seem especially well suited for such studies, owing to the large magnitude of ρ values so far encountered, and to the relatively high solubility of nonpolar and polar reactants, it may well be worthwhile to further define the nature of substituent effect modifications induced by trifluoroacetic acid.

(16) (a) L. M. Stock and H. C. Brown, *J. Amer. Chem. Soc.*, **84**, 1242 (1962). (b) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(17) R. Baker, R. W. Bott, C. Eaborn, and P. M. Greasley, *J. Chem. Soc.*, 627 (1964).

(18) For further documentation of the hydrogen bonding origin of effects in trifluoroacetic acid, see P. E. Peterson, *J. Org. Chem.*, **31**, 439 (1966).

Experimental Section

Synthetic Procedures.—All compounds prepared in our study exhibited the expected infrared and nmr spectra. Distillations were performed on spinning-band columns.

4-(*p*-Bromophenyl)-1-butene.—A published procedure was followed.[20] *p*-Bromobenzyl bromide (37 g, 0.15 mole) in 50 ml of anhydrous ether was added over a period of 1 hr to a stirred mixture of 3.6 g (0.15 g-atom) of magnesium turnings, 1.00 ml of ether, and a small crystal of iodine. After an additional 10 min, 15.3 g (0.2 mole) of allyl bromide in 50 ml of anhydrous ether was added during an interval of 10 min. After 0.5 hr the ether was replaced with benzene, and the mixture was refluxed 1 hr and poured into 250 ml of 2 *N* HCl. Distillation of an ether extract gave 9.9 g (32%) of 4-(*p*-bromophenyl)-1-butene, bp 65–67° (0.6 mm).

Anal. Calcd for $C_{10}H_{11}Br$: C, 56.89; H, 5.25. Found: C, 56.45; H, 5.37.

4-(*p*-Cyanophenyl)-1-butene.—Our procedure was based on one previously described.[21] 4-(*p*-Bromophenyl)-1-butene (21 g, 0.1 mole), cuprous cyanide (20.6 g, 0.115 mole), and dimethyl formamide (100 ml) were allowed to reflux for 6 hr. The brown mixture was poured into a solution of ferric chloride hydrate (40 g) and concentrated hydrochloric acid (10 ml) in water (50 ml) and heated at 60–70° for 20 min. The dark-colored layers were separated with some difficulty, and the hot aqueous layer was extracted with toluene. The organic extracts were washed (dilute hydrochloric acid, water, 10% sodium hydroxide), filtered, dried, and distilled to give 10.5 g (67%) of 4-(*p*-cyanophenyl)-1-butene, bp 101–105° (1.2 mm).

Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05. Found: C, 83.67; H, 7.26.

4-(*p*-Carboxyphenyl)-1-butene and 4-(*p*-Carbomethoxyphenyl)-1-butene.—4-(*p*-Cyanophenyl)-1-butene (4.71 g, 0.030 mole), was dissolved in 95% ethanol (20 ml). A solution of sodium hydroxide in aqueous ethanol (1:1, 10 ml) was added, and the solution was refluxed overnight. Most of the alcohol was then removed by distillation, and the ice-cooled residue was acidified with 10% hydrochloric acid solution. The white precipitate was separated by filtration, washed twice with water, and recrystallized from aqueous ethanol to give 4.65 g (90%) of 4-(*p*-carboxyphenyl)-1-butene, mp 120–121°.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.68; H, 6.75.

The ethereal solution of diazomethane, prepared from N,N′-dimethyl-N,N′-dinitrosoterephthalimide (70% in mineral oil, from Aldrich Chemical Co., Inc.) and potassium hydroxide (16.8 g) in water (50 ml) and ethoxy ethylene glycol (35 ml), was added to 4-(*p*-carboxylphenyl)-1-butene (prepared as above) until the solution retained a yellow color. After the solution was kept for 30 min at room temperature, ether was removed by distillation, and the ester was distilled to yield 4.0 g (93%), bp 89–93° (0.7 mm).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.73; H, 7.41.

4-(*p*-Acetylphenyl)-1-butene.—The procedure was that used previously to prepare 9-acetylphenanthrene.[22] Methylmagnesium iodide was prepared from magnesium turnings (2.88 g, 0.12 g-atom) and methyl iodide (17.04 g, 0.12 mole) in anhydrous ether (50 ml) under nitrogen atmosphere. Ether was then replaced with benzene. 4-(*p*-cyanophenyl)-1-butene (9.42 g, 0.12 mole) was added quickly to the above solution and stirred

(19) M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, **84**, 3548 (1962).

(20) (a) R. Wilkinson, *J. Chem. Soc.*, 3057 (1931). (b) P. Kozacik and E. E. Reid, *J. Amer. Chem. Soc.*, **60**, 2436 (1938).

(21) L. Friedman and H. Schechter, *J. Org. Chem.*, **26**, 2522 (1961).

(22) J. E. Callen, C. A. Dornfeld, and G. H. Coleman in "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., 1962, p 26.

under reflux for 3 hr. It was then cooled in an ice bath to 0°, 6 *N* hydrochloric acid (30 ml) was added with stirring and the mixture was refluxed for 6 to 8 hr.

After cooling the layers were separated, and the organic layer was washed with dilute sodium carbonate solution and water. The solvent was removed by distillation and the product was distilled under reduced pressure to yield 5.1 g (49%), bp 81–83° (0.45 mm).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 83.10; H, 7.87.

Rate Determinations.—The iodine monobromide titrimetric method used to follow the disappearance of alkenes has been described previously.[23] A quantitative hydrogenation procedure was used in the case of 4-(*m*-methoxyphenyl)-1-butene and 4-(*p*-methoxyphenyl)-1-butene, since the aromatic ring was brominated by the titrimetric reagent in these instances. Aliquots (2 or 3 ml) were withdrawn from the reacting solutions and injected through a serum cap into the reaction vessel of an atmospheric pressure hydrogenation apparatus, which contained 25 mg of 10% palladium on carbon (presaturated with hydrogen) and 5 ml of acetic acid to quench the reaction of trifluoroacetic acid with the alkene. The reaction vessel and the 10-ml hydrogen buret were jacketed and maintained at 25.0° by water circulated from a constant-temperature bath. Both a "course" (mercury) and "fine" (butyl tartrate) manometer were used to achieve volume readings of high precision. The rate constant for the reaction of 4-phenyl-1-butene with trifluoroacetic acid was measured both by the titrimetric method (10^5k = 25.7 sec^{-1}) and by hydrogenation (10^5k = 25.1 sec^{-1}).

(23) P. E. Peterson and G. Allen, *J. Org. Chem.*, **27**, 1505 (1962).

Registry No.—4-(*p*-Bromophenyl)-1-butene, 15451-32-8; 4-(*p*-cyanophenyl)-1-butene, 15451-33-9; 4-(*p*-carbomethoxyphenyl)-1-butene, 15451-34-0; 4-(*p*-carboxyphenyl)-1-butene, 15451-35-1; 4-(*p*-acetylphenyl)-1-butene, 15451-36-2; trifluoroacetic acid, 76-05-1.

Acknowledgment.—We wish to express our deep gratitude to Dr. Michael M. Martin, Department of Chemistry, University of Michigan, who contributed the samples of phenylbutenes having the substituents H, *m*-Cl, *p*-Cl, *m*-CH_3, *p*-CH_3, *m*-OCH_3, and *p*-OCH_3.[24]

(24) *Cf.* M. M. Martin and G. J. Gleicher, *J. Amer. Chem. Soc.* **86**, 233, 238 (1964).

Intermediates in Nucleophilic Aromatic Substitutions. III.[1] Meisenheimer Complexes of 1-Alkoxy-2,4-dinitronaphthalenes

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The rate constants for the formation and decomposition of the Meisenheimer complex (**1**) formed by the attack of methoxide ion on 1-methoxy-2,4-dinitronaphthalene (**4**) in methanolic solution have been determined at 8.10, 25.00, and 35.00°, allowing a determination of K, k_1, k_2, and energies and entropies of activation for the process. These data indicate **1** to be approximately 250 times more stable than the corresponding complex formed from 1-methoxy-2,4-dinitrobenzene but significantly less stable than the corresponding picryl complex. The rate of decomposition of crystalline **1** in methanol and in aqueous buffers has been examined over the pH range 4.97–10.85 at 25.00°; the decomposition is strongly catalyzed by acids. In addition to **1**, the stable crystalline Meisenheimer complexes (**2** and **3**) resulting from the attack of ethoxide ion on **4** and on 1-ethoxy-2,4-dinitronaphthalene (**5**) have been isolated; complex **2** was also prepared by reaction of methoxide ion with **5**. Infrared and proton magnetic resonance spectral studies establish complexes **1**–**3** to be 1,1-dialkoxy-2,4-dinitro-5,6-benzocyclohexadienylides.

Meisenheimer complexes are brightly colored adducts formed by the attack of a nucleophile at an electron-deficient position of an aromatic ring. The structures and stabilities of these complexes and their role in nucleophilic aromatic substitutions has received considerable attention in recent years.[3] Proton magnetic resonance (pmr) spectra of the 1-alkoxy-2,4,6-trinitrobenzene Meisenheimer complexes showed the two alkoxyl groups to be covalently linked to the same carbon atom.[4] In the preceding paper of this series,[5] we reported the isolation of complexes formed by the attack of alkoxide ions on 2,4-dinitroanisole and 2,4-dinitrophenetole and showed them to be 1,1-dialkoxy-2,4-dinitrocyclohexadienylides by pmr and infrared studies. The equilibrium constant for the formation of the potassium methoxide complex of 2,4-dinitroanisole in methanolic dioxane[5] was found to be several 1000-fold smaller than that for the ethoxyl complex of 2,4,6-trinitroanisole in ethanol.[6]

Dewar has calculated[7] that the formation of cyclohexadienyl intermediates from substituted benzenes requires a 10 kcal mol^{-1} loss inre sonance energy, whereas the resonance energy difference between naphthalene and the 1,1-disubstituted naphthalene intermediate is only 2 kcal mol^{-1}. One would expect, therefore, a smaller activation energy for nucleophilic substitution at a naphthalenoid than at a benzenoid carbon atom. This expectation has been verified by Elias and Parker[8] who found that the energy of activation for the nucleophilic substitutions of 1-chloro-2,4-dinitronaphthalene is approximately 3 kcal mol^{-1} less than that for 1-chloro-2,4-dinitrobenzene. Similarly, one would expect the formation of more stable Meisenheimer complexes with 1-substituted naphthalenes than with the corresponding benzene compounds. Although the formation of the methoxyl complex of 1-methoxyl-2,4-dinitronaphthalene in methanolic so-

(1) Part II: C. E. Griffin, E. J. Fendler, W. E. Byrne, and J. H. Fendler, *Tetrahedron Lett.*, 4473 (1967).

(2) NASA Postdoctoral Fellow, 1966–1967.

(3) For a recent review, see R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

(4) K. L. Servis, *J. Amer. Chem. Soc.*, **89**, 1508 (1967); M. R. Crampton and V. Gold, *J. Chem. Soc.*, 4293 (1964); *Sect. B*, 893 (1966).

(5) W. E. Byrne, E. J. Fendler, J. H. Fendler, and C. E. Griffin, *J. Org. Chem.*, **32**, 2506 (1967).

(6) J. B. Ainscough and E. F. Caldin, *J. Chem. Soc.*, 2528 (1956).

(7) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, p 177.

(8) D. H. Elias and R. E. Parker, *J. Chem. Soc.*, 2616 (1962).

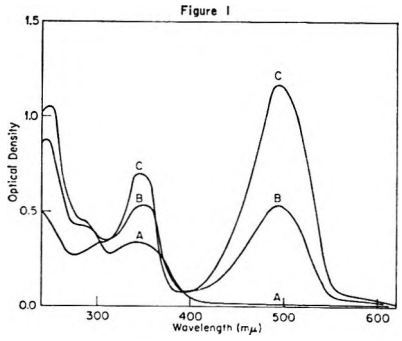
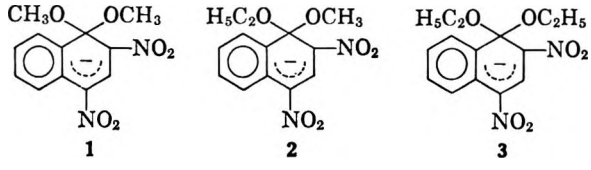


Figure 1.—Absorption spectra of 1-methoxyl-2,4-dinitronaphthalene (5.124×10^{-5} *M*) in methanolic sodium methoxide at 25.0° using a pair of 1.00-cm matched cells ([$NaOCH_3$]: A, 0; B, 0.00297 *M*; C, 0.0267 *M*).

lution[9] and the isolation of a solid from the same system[10,11] have been previously reported, no quantitative studies of this reaction have been undertaken. We wish to report the synthesis, isolation, and chemical and physical properties of the crystalline complexes **1–3**, and to present kinetic and thermodynamic data on the formation and decomposition of **1**.



Experimental Section

The solvents and reagents were prepared, purified, and standardized as previously described.[5] 1-Chloro-2,4-dinitronaphthalene (Eastman) and 1-methoxy-4-nitronaphthalene (Aldrich) were commercial products.

1-Methoxy-2,4-dinitronaphthalene (4) was prepared by the addition of 8.56 ml of 5.84 *M* (50 mmol) potassium methoxide in methanol to a warm solution of 10.10 g (40 mmol) of 1-chloro-2,4-dinitronaphthalene in 40 ml of benzene. The reaction mixture was refluxed with stirring for 3 hr, cooled, and extracted with 0.5 *M* sulfuric acid. The aqueous layer was reextracted with benzene, and the benzene was removed from the combined extracts by rotary evaporation. The light yellow crystals were recrystallized from absolute methanol, mp 97.5–98° (lit.[11] mp 98.5°). The same method was used to prepare **1-ethoxy-2,4-dinitronaphthalene (5)** using 2.42 *M* potassium ethoxide in ethanol. After recrystallization from absolute ethanol, **5** melted at 91.5–92° (lit. mp 92–93°,[10] 93°,[12a] and 90° [12b]).

The methoxy complex (1) of 1-methoxy-2,4-dinitronaphthalene was prepared by the addition of 0.73 ml (4.25 mmol) of 5.84 *M* potassium methoxide in methanol to a solution of 1.07 g (4.32 mmoles) of **4** in 1.5 ml of DMSO. After evaporation of some solvent with dry nitrogen, the bright red crystals were filtered under nitrogen, washed with benzene and anhydrous ether, and dried in a vacuum desiccator over P_2O_5, mp 90–92° dec.

Anal.[13] Calcd for $C_{12}H_{11}KN_2O_6 \cdot (CH_3)_2SO$: C, 42.2; H, 4.3; K, 9.8; N, 7.0; S, 8.2. Calcd for $C_{12}H_{11}KN_2O_6 \cdot 2(CH_3)_2SO$: C, 40.5; H, 4.9; K, 8.2; N, 5.9; S, 13.5. Found: C, 39.9; H, 4.6; K, 8.4; N, 6.3; S, 9.3 (the presence of DMSO in this sample was confirmed by pmr spectroscopy).

The same method was used to prepare the **ethoxyl complex (3) of 1-ethoxy-2,4-dinitronaphthalene** from 2.42 *M* potassium ethoxide in ethanol and **5** in DMSO; **3** melted at 215–218° dec.

Anal. Calcd for $C_{14}H_{15}KN_2O_6$: C, 48.4; H, 4.8; K, 11.3; N, 8.1. Found: C, 47.5; H, 4.75; K, 11.5; N, 7.8.

Complex **1** was also isolated with *ca.* 2 mol of benzene of crystallization by the same procedure with the exception that a solution of **4** in 1.5 ml of dry benzene was used; **1** melted at 189–191° dec. Drying the complex at less than 0.1 mm at 50–60° for 4 hr followed by a further 12-hr drying at 80–90° at the same pressure resulted in no detectable (pmr) loss of benzene.

The same general procedure was used to prepare **1** from a solution of 4.32 mmol of **4** in 1.0 ml of dioxane by the addition of 0.72 ml (4.25 mmol) of 5.95 *M* potassium methoxide in methanol; **the ethoxyl complex (2a) of 1-methoxy-2,4-dinitronaphthalene** was prepared from a solution of **4** in dioxane with an ethanolic solution of potassium ethoxide; **the methoxyl complex (2b) of 1-ethoxy-2,4-dinitronaphthalene** was prepared from a solution of **5** in dioxane with a methanolic solution of potassium methoxide; and **3** was prepared from a solution of **5** in dioxane with an ethanolic solution of potassium ethoxide. The observed melting points (with decomposition) follow: **1**, 185°; **2a**, 195°; **2b**, 210°; **3**, 205°.

Anal. Calcd for $C_{12}H_{11}KN_2O_6$ (**1**): C, 45.3; H, 3.5; K, 12.3; N, 8.8. Calcd for $C_{12}H_{11}KN_2O_6 \cdot C_4H_8O_2$: C, 47.3; H, 4.7; K, 9.6; N, 6.9. Found: C, 47.3; H, 4.8; K, 8.7; N, 7.0.

Anal. Calcd for $C_{13}H_{13}KN_2O_6$ (**2a**): C, 48.5; N, 3.9; K, 11.8; N, 8.4. Found: C, 47.5; H, 3.95; K, 11.7; N, 8.36.

Anal. Calcd for $C_{13}H_{13}KN_2O_6$ (**2b**): C, 48.5; H, 3.9; K, 11.8; N, 8.4. Found: C, 45.7; H, 4.0; K, 11.6; N, 7.9.

Anal. Calcd for $C_{14}H_{15}KN_2O_6$ (**3**): C, 48.4; H, 4.8; K, 11.3; N, 8.1. Found: C, 48.5; H, 4.5; K, 11.1; N, 8.2.

The presence of *ca.* 1 mol of dioxane of crystallization in this sample of **1** was indicated by its pmr spectrum.

The unsymmetrical complex **2**, mp 210° (with preliminary darkening), was also prepared by the addition of ethanolic potassium ethoxide to a solution of **4** in DMSO; some difficulty was encountered in the crystallization of this material and the addition of benzene to the reaction mixture was necessary. Although the infrared and pmr spectra of the product were essentially identical with those of **2a** and **b**, satisfactory elemental analyses were not obtained.

The visible and ultraviolet spectra of **1** and **4** were obtained on a Beckman DU-2 spectrophotometer; a pair of matched 10.0-mm cells with Teflon stoppers were used. The cell compartment was equipped with a set of Beckman dual thermospacers; the temperature was measured inside the cells and was maintained within ±0.02°. The pH of the buffer solutions used for the studies of the decomposition of **1** was measured at 25.0° by an Orion Model 801 digital pH meter (reproducibility ±0.002 pH). Infrared spectra were recorded on Perkin-Elmer Models 21 and 221 spectrophotometers; all spectra were recorded as Nujol mulls.

Pmr spectra (60 MHz) were obtained with a Varian Associates A-60 spectrometer at 25° (probe temperature maintained with a V6040 variable-temperature controller). Unless otherwise noted, all spectra were determined on solutions in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard; chemical shifts are given on the τ scale in parts per million relative to TMS (τ 10.00 ppm) and are accurate to ±0.03 ppm. Chemical-shift data were taken from spectra determined at a sweep width of 500 Hz; the reported coupling constants are the average of at least three determinations at 50-Hz sweep widths and are accurate to ±0.2 Hz. Frequency swept and 100-MHz double-resonance experiments were carried out with a Varian Associates HA-100 spectrometer.

Results

The absorption spectra of 5.12×10^{-5} *M* 1-methoxy-2,4-dinitronaphthalene (**4**) in methanol and in methanolic sodium methoxide are given in Figure 1 and Table I. On increasing the concentration of the methoxide ion, a new absorption band appears at 495 mμ which reaches its maximum at a sodium methoxide concentration of 5.3×10^{-2}*M* and remains constant up to 2.94 *M*. The constancy of the absorbance over a 50-fold increase in methoxide ion concentration indicates that the equilibrium **1** is complete at a methoxide ion

$$4 + OCH_3^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 1 \qquad (1)$$

(9) R. Foster, C. A. Fyfe, P. M. Emslie, and M. I. Foreman, *Tetrahedron*, **23**, 227 (1963).

(10) S. S. Gitis and A. I. Glaz, *J. Gen. Chem. USSR*, **33**, 888 (1963).

(11) D. S. Gilbert, Thesis, Leicester College of Technology, Leicester, England, 1963.

(12) (a) P. Hiermann, *J. Prakt. Chem.*, **44**, 243 (1891); (b) F. Ullmann and W. Bruck, *Ber.*, **41**, 3932 (1908).

(13) All analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

TABLE I

INTERACTION OF 1-METHOXY-2,4-DINITRONAPHTHALENE (5.124×10^{-5} *M*) WITH METHANOLIC SODIUM METHOXIDE

Temp, °C	[NaOCH₃], *M*	Optical density at 350 mμ[a]	Optical density at 495 mμ[a]	α	K,[b] l. mol⁻¹	$10^3 k_{obsd}$, sec⁻¹	k_1,[c] l. mol⁻¹ sec⁻¹	k_1,[d] l. mol⁻¹ sec⁻¹	$10^3 k_2$,[c] sec⁻¹	$10^3 k_2$,[d] sec⁻¹
8.10	0.000	0.310	0.000							
	0.000742	0.366	0.221	0.17	275	0.92	0.213		0.76	
	0.00148	0.449	0.376	0.29	280	1.10	0.217		0.79	
	0.00267	0.517	0.600	0.46	330	1.34	0.214	0.215	0.77	0.77
	0.327	0.542	1.308	1.00						
	1.635	0.583	1.310							
25.00	0.000	0.330	0.000							
	0.000742	0.384	0.173	0.13	204	4.33	0.82		3.7	
	0.00148	0.418	0.307	0.23	200	5.52	0.92		4.2	
	0.00222	0.475	0.426	0.32	214	5.98	0.88		4.0	
	0.00297	0.525	0.535	0.40	230	6.74	0.89	0.95	4.1	3.95
	0.00594	0.580	0.778	0.58	237					
	0.0148	0.665	1.043	0.78	245					
	0.0267	0.700	1.172	0.84	210					
	0.0534	0.720	1.326	1.00						
	0.327	0.745	1.328							
	1.635	0.735	1.328							
	2.943	0.800	1.310							
35.00	0.000	0.320	0.000							
	0.000742	0.367	0.138	0.104	160	11.8	1.82		10.5	
	0.00148	0.368	0.267	0.20	171	13.5	1.86		10.8	
	0.00222	0.444	0.365	0.28	174	14.7	1.83		10.7	
	0.00267	0.419	0.453	0.31	169	15.6	1.84	1.70	11.0	10.8
	0.00742	0.563	0.771	0.58	183					
	0.0148	0.635	0.970	0.73	181					
	0.327	0.750	1.328	1.00						
	1.635	0.820	1.328							

$E_1 = 13.8 \pm 0.8$ kcal mol⁻¹ $\quad \Delta S_1^{\ddagger} = -17 \pm 2$ eu[e,f]

$E_2 = 16.5 \pm 0.8$ kcal mol⁻¹ $\quad \Delta S_2^{\ddagger} = -18 \pm 2$ eu[e,g]

[a] Using a 1.00-cm cell. [b] Calculated by using eq 2. [c] Calculated by using eq 4. [d] Calculated by using eq 3. [e] Calculated at 25.00°. [f] Calculated by using the second-order rate constants, k_1. [g] Calculated by using the first-order rate constants, k_2.

concentration of 5.3×10^{-2} *M*. The fraction (α) of **4** converted into the complex **1** can therefore be evaluated at lower methoxide ion concentrations by dividing the optical densities at 495 mμ by 1.328 (see Table I). From the α values the equilibrium constant K can be readily calculated by using the expression given in eq 2

$$K = \frac{\alpha}{([\mathrm{NaOCH_3}] - \alpha[\mathbf{4}])(1 - \alpha)} \qquad (2)$$

(assuming that $[\mathrm{NaOCH_3}] \gg [\mathbf{4}]$). Plots of [**4**]/absorbance at 495 mμ *vs.* $1/[\mathrm{NaOCH_3}]$ gave good straight lines at all three temperatures indicating that the equilibrium in eq 1 prevails without any complications. Using the Benesi–Hildebrand equation,[14a] the following values for ϵ and K were obtained, respectively, at 8.10, 25.00 and 35.00°: 35,500, 185; 29,400, 175; and 23,700, 185. The equilibrium constants obtained by this method are in reasonable agreement with those calculated by the use of eq 2 (Table I). Owing to the very nature of the calculation and to the high extinction coefficients involved, this method inevitably leads to less accurate equilibrium constants than those presented in Table I. At the lower methoxide ion concentrations, the red color was not formed immediately and the attainment of the equilibrium could be followed by measuring the increase of absorbance at 495 mμ. Since the concentration of **4** was by some 100-fold smaller than that of the methoxide ion, a first-order relationship was observed. Such first-order plots for typical runs are given in Figure 2. Since the rate of equilibrium attainment is proportional to the distance from equilibrium, the observed first-order rate of attainment of the equilibrium, k_{obsd}, is expressed by eq 3 or 4. Using eq 3, plots of k_{obsd}

$$k_{obsd} = k_1[\mathrm{NaOCH_3}] + k_2 \qquad (3)$$

$$k_{obsd} = k_1([\mathrm{NaOCH_3}] + 1/K) \qquad (4)$$

against sodium methoxide concentration at 8.10, 25.00, and 35.00° gave good straight lines whose slope is k_1 and whose intercept is k_2. Equation 4 permits independent calculation of k_1 and k_2 by using k_{obsd} and the corresponding equilibrium constants (obtained from eq 2). The results of both sets of calculations are given in Table I. From the rate constants obtained from eq 3 we have calculated the equilibrium constants at 8.10, 25.00, and 35.00° to be 278, 240, and 167, respectively. The agreement between the two sets of rate and equilibrium constants is excellent. Using the two sets of k_1 and k_2 values at the three temperatures, linear Arrhenius plots were obtained from which the energies and entropies of activation have been calculated (Table I). Allowing an over-all ±7% error in the individual rate constants at the temperature interval used (26.90°), the statistical error in E is ±0.8 kcal mole⁻¹ and in ΔS is ± 2.0 eu.[15]

(14) (a) The Benesi–Hildebrand equation[14b] for the present case is 2a

$$\frac{[\mathbf{4}]}{A} = \frac{1}{\epsilon} + \frac{1}{K\epsilon[\mathrm{NaOCH_3}]} \qquad (2a)$$

where A is the absorbance and ϵ is the extinction coefficient for complex **1**. (b) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).

(15) L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, **1**, 1 (1963).

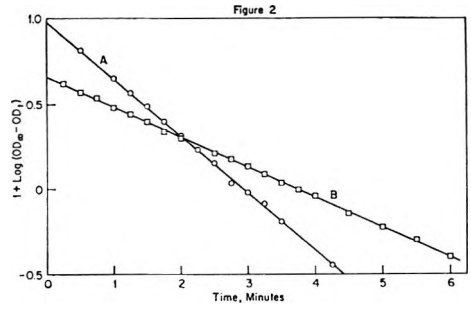


Figure 2.—Plot of 1 + log ($OD_\infty - OD_t$) against time for the attainment of equilibrium of 1 [4] = 5.12×10^{-6} *M*: A, [$NaOCH_3$] = 2.222×10^{-3} *M*, 35.00°; B, [$NaOCH_3$] = 2.93×10^{-3} *M*, 25.00°.

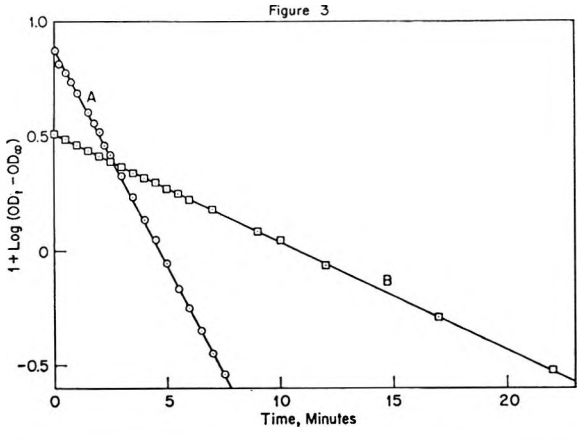


Figure 3.—Plot of 1 + log ($OD_t - OD_\infty$) against time for the decomposition of 1 in aqueous buffers at 25.00° (A, pH = 6.64; B, pH = 8.80).

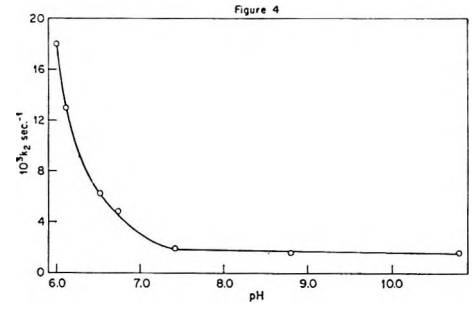


Figure 4.—pH–Rate profile for the decomposition of 1 at 25.00°.

The bright red crystalline Meisenheimer complexes of 1-alkoxy-2,4-dinitronaphthalenes are fairly stable in the solid state. They are soluble and reasonably stable in DMSO, DMF, dioxane, acetone, and acetonitrile, and in water, methanol, and ethanol but slowly decompose in these latter polar protic solvents.

The rates of decomposition of the solid 1 in methanol and in aqueous buffers at different pH values have been obtained by following the decrease in optical densities at 495 mμ in a thermostated cell compartment of a Beckman DU-2 spectrophotometer. Plots of typical runs are given in Figure 3, and the data are given in Table II. Figure 4 shows the pH–rate profile for the decomposition of 1. In methanol, 4 undergoes solvolytic exchange to yield the naphthol; the half-life of this "solvolysis" is, however, 1000 hr at 35°.[11] Similarly the decomposition of 1 at high pH ultimately gives the naphthol. The naphthol does not, however, absorb at 495 mμ; thus the observed rate constant corresponds to k_2.

TABLE II

DECOMPOSITION OF THE METHOXYL COMPLEX OF 1-METHOXYL-2,4-DINITRONAPHTHALENE IN METHANOL AND IN WATER AT 25.00°

pH[a]	$10^3 k_2$, sec^{-1}	$10^{-4} k_2^{H^+}$, $l.\ mol^{-1}\ sec^{-1}$ [b]
Abs MeOH	4.16	
5.97	18.0	1.52
6.11	13.0	1.46
6.21	11.0	1.48
6.52	6.40	1.53
6.64	4.98	1.43
7.42	1.97	
8.80[c]	1.76	
10.85[d]	1.76	

[a] 0.01 KH_2PO_4 buffer, except where stated otherwise. [b] $k_2^{H^+} = (k_2$ (measured) $- k_2°)/[H^+]$, where $k_2° = 1.76 \times 10^{-3}$ sec^{-1}. [c] 0.01 *M* $KHC_8H_4O_4$ buffer. [d] 0.01 *M* K_2HPO_4 buffer.

The infrared absorption data for the complexes and the parent ethers are given in Table III, and the pmr parameters for the same compounds are given in Table IV.

Discussion

The methoxyl Meisenheimer complex (1) of 1-methoxy-2,4-dinitronaphthalene forms very readily upon mixing a dilute solution (5×10^{-5} *M*) of the ether (4) with a 15-fold excess of sodium methoxide in methanol. The absorption maximum at 495 mμ is attributed to the formation of 1 since the absorption maximum of the isolated solid 1 in methanol occurs at this wavelength. The increased absorption relative to 4 at 350 mμ with increasing methoxide ion concentration is possibly due to the formation of another species, the formation of which is favored by high methoxide ion concentration (see Table I). A similar situation exists with the interaction between methoxide ion and 2,4-dinitroanisole.[5] However, the methoxyl complex of 2,4-dinitroanisole forms considerably less readily than its naphthalene analog (1). Indeed, at the methoxide ion concentrations used it was found necessary to use polar cosolvents to enhance the stability of the methoxyl-2,4-dinitroanisole complex.[5] The absorption maxima due to 4 plus a second complex have shifted to a longer wavelength in relation to the 2,4-dinitroanisole complex (from 316 to 350 mμ). Similar bathochromatic shifts were observed in the 2,4-dinitroanisole–6X complexes as the electron-withdrawing power of X was increased.[16] This observation is in accord with the fact that an additional phenyl ring in the naphthalene system increases the electronegativity of the C-1 carbon atom.

The stability of 1 is also evident from its equilibrium constant which is approximately 250 times greater than that for its benzene analog. The equilibrium constant for the formation of the methoxyl Meisenheimer complex of 2,4,6-trinitroanisole is 7700,[17] while that for 1 is 230 at 25.0°. The magnitude of the equilibrium constant for the formation of 1 facilitated calculation of the rate constants for the formation and decomposition of 1 at the three different temperatures (Table I). The validity of the assumptions used in

(16) R. J. Pollitt and B. C. Saunders, *J. Chem. Soc.*, 1132 (1964).
(17) V. Gold and C. H. Rochester, *ibid.*, 1687 (1964).

TABLE III

INFRARED SPECTRA[a] OF 1-METHOXY-2,4-DINITRONAPHTHALENE, 1-ETHOXY-2,4-DINITRONAPHTHALENE, AND THEIR MEISENHEIMER COMPLEXES

1-Methoxy-2,4-dinitronaphthalene (4)	1-Ethoxy-2,4-dinitronaphthalene (5)	Potassium methoxide complex of 1-methoxy-2,4-dinitronaphthalene (1)	Potassium ethoxide complex of 1-methoxy-2,4-dinitronaphthalene (2a)	Potassium methoxide complex of 1-ethoxy-2,4-dinitronaphthalene (2b)	Potassium ethoxide complex of 1-ethoxy-2,4-dinitronaphthalene (3)
1581 vs, sh	1583 vs, sh	1581 vs, sh	1581 vs, sh	1580 vs, sh	1580 vs, sh
1545 w	1545 w	1550 s, sh	1550 s, sh	1550 s, sh	1545 s, b
1525 m, sh	1526 m, sh				
1515 m, sh	1516 m, sh	1512 w	1512 w	1511 w	1510 w
1493 m, sh	1496 w	1493 m, sh	1493 m, sh	1494 m, sh	1503 s
		1451 w	1451 w	1451 w	1454 w
		1448 vw	1448 vw	1448 vw	1450 w
1415 s	1416 m	1411 s	1421 m	1419 m	1419 m
	1400 w				
1345 s	1335 s, b	1358 m	1358 m	1357 m	1360 s
		1325 m	1326 m	1326 m	1329 m
		1287 w			1297 w
1270 m	1262 s	1263 s	1263 s	1262 s	1265 s
1243 m	1230 w	1230 m	1230 m	1320 m	1230 m
1212 w	1220 w	1218 m	1210 m	1210 m	
	1200 vw				1190 m
1172 m	1155 m	1172 m			
		1122 s, b	1135 s, b	1135 s, b	1140 s, b
1100 s	1092 s	1090 m	1105 m, b	1105 m, b	1100 m, b
1048 w	1038 w	1058 m, b	1050 m, b	1049 m, b	1050 m
		1027 m			
1000 m	1015 s		1005 w	1005 w	1005 m
962 s	968 vw	957 w	956 w	956 w	959 m
		941 m	941 m		942 m
919 m	923 m	923 s	923 s	923 s	923 s
905 s	905 s				
		885 w			
	869 s	872 s			875 w
837 s	830 s	815 s	817 s	818 s	818 s, sh
805 s	793 s	796 m	792 m	791 m	790 m
789 m	789 m				
772 vs	773 s	770 s			
753 vs	760 s	762 m	762 s	761 s	762 s, sh
743 w		738 m	735 m	733 m	736 m
723 m	724 m	703 s	713 s	713 s	715 s
682 m	684 m	660 s	660 s, b	660 s, b	663 s

[a] Frequencies (cm^{-1}) and intensities of observed bands (vs = very strong, s = strong, m = medium, w = weak, vw = very weak s = shoulder on neighboring band, b = broad).

this treatment (see Results) is amply verified by the excellent agreement between the k_2 values calculated from the attainment of the equilibrium for 1 using K (Table I) and those determined directly at 25.00° (Table II).

The stability of 1 is further demonstrated by its observable rate of decomposition in water in the 5.97–10.85 pH region (Table II and Figure 4). The decomposition is catalyzed very strongly by acids. Decreasing the pH from 8.00 to 5.97 results in a tenfold increase in the decomposition rate. Similar decomposition studies on the 1,1-dialkoxypicrylic Meisenheimer complexes in aqueous buffer solutions have been reported.[18] The rate constant for the spontaneous decomposition of 1, $k_2°$, at 25.00° is six times greater than that for the methoxyl complex of 2,4,6-trinitroanisole. The second-order rate constant for the acid-catalyzed decomposition of the methoxyl 2,4,6-trinitroanisole complex at 25.00° is 1.2×10^4 l. mol^{-1} sec^{-1}. The corresponding value for the decomposition of 1 is 1.5×10^4 l. mol^{-1} sec^{-1} (Table II), indicating that the acid catalysis is more pronounced for the decomposition of 1 than for the picrylic complex.

The energies of activation for the formation and decomposition of 1 (Table I) are best illustrated by potential energy diagrams. For purposes of comparison, corresponding diagrams for the 2,4-dinitroanisole[19] and 2,4,6-trinitroanisole[19,20] complexes are also included (Figure 5).

It can be seen readily that the stabilities of these Meisenheimer complexes are in the order 2,4-dinitroanisole < 4 < 2,4,6-trinitroanisole. It was suggested that an activation energy of 12–18 kcal mol^{-1} (E_2 in Figure 5) is needed in order to isolate an adduct formed in a nucleophilic aromatic substitution reaction.[21] This requirement is clearly met even for the 2,4-dinitroanisole complex, whose isolation we reported previously.[5] The fact that the saddle of the potential energy diagram for the formation of 1 lies below that of the initial state (4) suggests that in symmetrical methoxyl exchange reactions between methoxide ion

(18) J. Murto and J. Vainionpää, *Suomen Kemistilehti*, **B39**, 133 (1966).

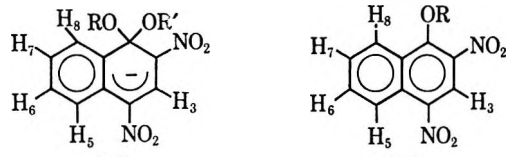
(19) J. H. Fendler, *J. Amer. Chem. Soc.*, **88**, 1237 (1966).

(20) J. Murto and E. Kohrakha, *Soumen Kemistilehti*, **B39**, 128 (1966).

(21) R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 294 (1960).

TABLE IV

PMR SPECTRA OF MEISENHEIMER COMPLEXES AND PARENT 2,4-DINITRONAPHTHYL ETHERS[a]



1–3 4, 5

Compd	Source[b]	R	R′	3	5	8	6,7	OCH_3	OCH_2	CCH_3	Solvent[c]	J_{56}	J_{57}	J_{68}	J_{78}
1	A	CH_3	CH_3	0.67	2.25	1.24	2.70	7.22			7.45	7.4	2.7	2.2	7.8
1	B	CH_3	CH_3	0.67	2.25	1.24	2.70	7.20			(2.6)				
											6.40	7.6	2.7	2.2	7.8
											(0.98)				
2a	A	CH_3	CH_2CH_3	0.77	2.23	1.25	2.73	7.29	7.09	9.04	None	7.5	2.7	2.3	7.9
2a	B	CH_3	CH_2CH_3	0.72	2.23	1.23	2.73	7.29	7.03	9.04	6.44	7.4	2.7	2.3	7.9
											(0.075)				
2b	B	CH_3	CH_2CH_3	0.75	2.22	1.23	2.70	7.24	7.09	9.02	6.44	7.4	2.7	2.3	7.9
											(0.03)				
3	A	CH_2CH_3	CH_2CH_3	0.79	2.23	1.27	2.72		7.17	9.04	7.44	7.4	2.7	2.5	7.8
											(0.59)				
3	B	CH_2CH_3	CH_2CH_3	0.77	2.23	1.27	2.73		7.15	9.04	6.44	7.4	2.7	2.4	7.9
Multiplicity				1	2 × 2	2 × 2	m	1	m	3	(0.13)				
4		CH_3		1.34	1.68		2.17	5.87							
5		CH_2CH_3		1.22	1.59		2.06		5.67	8.49					
Multiplicity				1	m		m	1	4	3					

[a] All spectra are recorded in DMSO-d_6 at 25°. Chemical shifts are given on the τ scale in parts per million relative to internal TMS; coupling constants are given in Hz. For details, see Experimental Section. [b] Solvent used in preparation: A = DMSO; B = dioxane. [c] Solvent of crystallization was as in source. Number of moles of solvent per mole of complex is indicated in parentheses; integrals for DMSO include solvent DMSO-d_6.

FIGURE 5

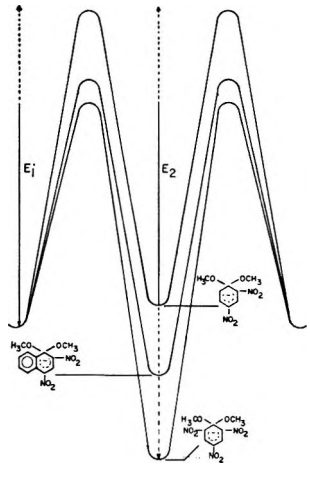


Figure 5.—Potential energy diagrams for the formation and decomposition of dialkoxy Meisenheimer complexes.

and **4**, the decomposition of **1** should be the rate-determining step. This is indeed the case, as has been verified by experimental data.[11] Similarly the rate-determining step for the methoxyl exchange reaction between methoxide ion and 2,4,6-trinitroanisole is the decomposition of the intermediate complex.[19]

The formation of complex **1** from **4** and methoxide ion results in an increase in the order of the system. This is reflected by the negative entropy of activation ($\Delta S_1^{\ddagger}$ in Table I). Using a rate constant of 4.0 l. mol^{-1} sec^{-1} [17] and an energy of activation of 13 kcal mol^{-1} [19] for the formation of the methoxyl 2,4,6-trinitroanisole complex, we calculate the entropy of activation for this reaction to be −14 eu. Similarly comparing values from the literature,[17,19] we obtain −11 eu for $\Delta S_2^{\ddagger}$ for the decomposition of the methyl picrate complex. However, it is difficult to compare $\Delta S_1^{\ddagger}$ with $\Delta S_2^{\ddagger}$ since their standard states are different. Nevertheless, their magnitude and direction are consistent within the series of compounds studied so far. Furthermore, it appears that the rates of symmetrical methoxyl exchange reactions, and hence the stabilities of the Meisenheimer complexes in this series, are dependent to a larger extent on the respective enthalpies rather than on the entropies of activation. This is in good agreement with the thermodynamic parameters of other nucleophilic aromatic substitutions.[22] Using electron affinities and bond and solvation energies, Miller calculated the energy levels of the initial, transition, and intermediate states of numerous nucleophilic aromatic substitutions.[22,23] From this data he estimated the energies and entropies of activation for these reactions and found that the calculated and experimentally obtained values agreed well and that the entropies of activation varied little in comparison with changes in the activation energies.[22]

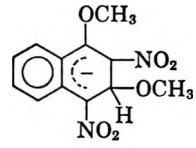
Furthermore, using this treatment Miller estimated the thermodynamic parameters for the formation and decomposition of **1** and found them to be in excellent agreement with the experimental values in Table I.[24]

We continue to use infrared and proton magnetic resonance spectroscopic techniques to confirm the postulated structures of intermediates **1–3**. The infrared spectra of charge transfer complexes closely resemble those of their parent ethers with the addition of the internal vibration frequencies of the added alkoxyl groups.[25] The presence of the additional ketal

(22) D. L. Hill, K. C. Ho, and J. Miller, *J. Chem. Soc., Sect. B*, 299 (1966).
(23) J. Miller, *J. Amer. Chem. Soc.*, **85**, 1628 (1963).
(24) J. Miller, private communication, 1967.
(25) (a) R. A. Friedel, *J. Phys. Chem.*, **62**, 1341 (1959); (b) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

bands[26] at 1126–1058 cm^{-1} (Table III) are consistent with the proposed covalent structure of the complexes. In our previous paper[5] we reported the isolation of complexes from the reaction of 2,4-dinitroanisole and potassium ethoxide and, separately, from 2,4-dinitrophenetole and potassium methoxide and showed them to be identical by infrared and pmr spectroscopy. We have now prepared the 1-methoxy-1-ethoxy-2,4-dinitronaphthalene complexes (2a and 2b) by these two routes and found their spectra (Tables III and IV) to be identical.

The pmr parameters observed for complexes 1–3 and the parent ethers 4 and 5 are given in Table IV; the spectra of a representative complex parent ether pair (3 and 5) are given in Figure 6. The spectra are completely in accord with the postulated structures (1,1 complexes) and eliminate alternate formulations, *i.e.*, those involving attack of alkoxide ion at positions other than C-1 of 4 or 5. For example, formation of the 3 complex (6) would require methoxyl



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nonequivalence and a marked upfield shift for H-3,[4] observations clearly inconsistent with the experimental observations. Only 1,1 complexes could account for the observation of alkoxyl equivalence for 1 and 3, single methoxyl and ethoxyl resonances for 2 and the five aromatic resonances for 1–3. The spectra of the various complexes prepared by different routes, *e.g.*, 1 from both DMSO and dioxane solutions and 2 from both 4 and 5, were identical within experimental error, with the exception of the peaks due to solvent of crystallization; satisfactory integrated intensities were obtained for all resonances. The only previous report of pmr data for naphthalene Meisenheimer complexes is that of Foster, *et al.*,[9] who have reported aromatic proton chemical shift data for complex 1 prepared by the *in situ* reaction of methoxide ion and 4. The chemical shifts reported for H-3 and H-5 are essentially identical with those observed in this study; Foster, *et al.*, did not, however, observe separation of the H-8 resonance from the H-6, H-7 multiplet.

The pmr criteria for the structure of Meisenheimer complexes have been summarized previously[4,5] and need not be reiterated here in detail. In addition to the structural support provided by the gross appearance of the spectra as cited above, alkoxyl and aromatic proton chemical shifts provide more detailed confirmation of structure. It has been shown that the transition from the sp^2 hybrid C-1 of the parent ethers to the sp^3 hybrid C-1 of the 1,1 complexes in the di- and trinitrobenzene series[3–5,9,27] results in an upfield shift for alkoxyl proton resonances: methoxyl complexes, $\Delta\delta$ 1.20 ppm; ethoxyl complexes, $\Delta\delta_{OCH_2}$ 1.21–1.33 ppm, $\Delta\delta_{C-CH_3}$ 0.33–0.37 ppm.[1] Closely comparable upfield alkoxyl shifts are observed for the complexes 1–3: $\Delta\delta_{OCH_3}$ 1.33–1.42 ppm, $\Delta\delta_{OCH_2}$ 1.36–1.50 ppm, $\Delta\delta_{C-CH_3}$ 0.53–0.55 ppm. As required by the postulated structures, the methoxyl reso-

(26) E. D. Bergmann and S. Pinchas, *Rec. Trav. Chim.*, **71**, 161 (1952).
(27) R. Foster and C. A. Fyfe, *Tetrahedron*, **21**, 3363 (1965).

Figure 6

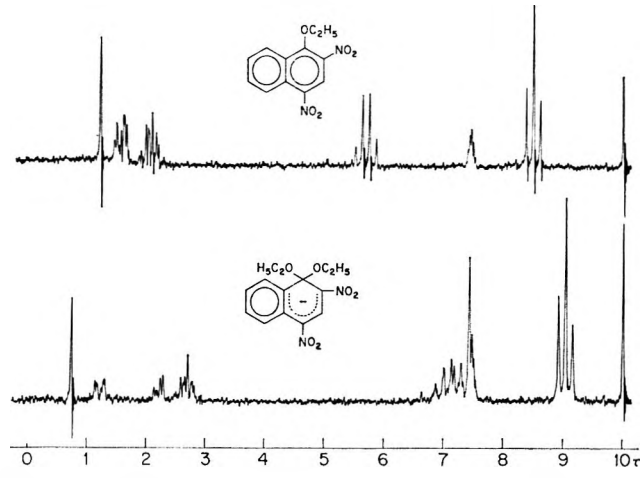


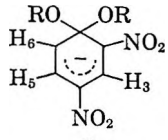
Figure 6.—Proton magnetic resonance spectra of 1-ethoxy-2-4-dinitronaphthalene (5) and its ethoxy complex (3a) in DMSO-d_6.

nances of 1 and 2 are singlets. However, the methylene resonance of the diethoxy complex 3 was considerably more complex than the expected quartet; a 50-Hz sweep width spectrum of this region showed thirteen resolved transitions downfield from the DMSO-d_5 resonance. The complexity of this multiplet is greater than would be expected if the two ethoxyl groups were in different magnetic environments as in 6 (two quartets would be anticipated) and is most probably due to methylene proton nonequivalence resulting from a restriction of rotation about the carbon–oxygen bonds of the ethoxyl groups. If such a nonequivalence were involved, the methylene resonance would comprise the AB portion of an ABX_3 system and a total of 16 transitions should be observable; a first-order analysis of this multiplet supported this postulation. The A portion of the resonance (two quartets with J_{AB} = 9.4 and J_{AX} = 7.5 Hz and τ_A 6.97 ppm) was cleanly resolved. Five transitions of the B portion were observed from which J_{BX} = 7.3 Hz could be obtained and, using the value of J_{AB} from the A portion, τ_B could be estimated as 7.17 ppm. This assignment was confirmed by a double-resonance experiment at 100 MHz; irradiation of the methyl triplet at τ 9.04 ppm resulted in collapse of the methylene resonance to an AB quartet (the most upfield transition of this quartet was partially obscured by the DMSO-d_5 peak.) A value of J_{AB} = 9.4 Hz was obtained from the decoupled spectrum. Kaplan and Roberts have reported a geminal coupling of −9.3 Hz for the methylene protons of diethyl acetal.[28] The methyl triplet of 3 showed no further splitting. A similar methylene nonequivalence was apparent in the spectra of the mixed complex 2, but could not be fully resolved because of overlap with the methoxyl singlet.

It has been shown previously that the aromatic protons of Meisenheimer complexes are relatively strongly shielded as compared with the corresponding protons of the parent ethers.[4,5,9,27] The magnitude of this upfield shift ($\Delta\delta$) has been shown to be positionally dependent for the 1,1 complexes (7) of 2,4-dinitrophenyl ethers,[5] reflecting relative charge densities at the various positions, *i.e.*, H-3, 0.04–0.07; H-5, 1.26–1.40; H-6, 2.50–2.57 ppm. The greater de-

(28) F. K. Kaplan and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 4666 (1961); P. R. Shafer, D. R. Davis, M. Vogel, K. Nagarajan, and J. D. Roberts, *Proc. Natl. Acad. Sci.*, **47**, 49 (1961).

shielding of H-6 would be expected since conventional canonical structures for the ions would place the maximum charge density at H-2, -4, and 6. An interpretation of aromatic proton chemical shifts in naphthalene complexes **1**–**3** is somewhat less straightforward. Among other factors, the interpretation is complicated by the fact that the four aromatic protons of the unsubstituted ring of the naphthalene complexes comprise an ABCD system,[29] while the previously examined complexes (**7**)[5] contain a more readily interpretable ABX system.



7

The aromatic proton resonances of 1-ethoxy-2,4-dinitronaphthalene (**5**) consist of a one-proton singlet (H-3) at τ 1.22 and two pseudo-symmetric two-proton multiplets centered at τ 1.59 and 2.06 ppm (Table IV and Figure 6). The chemical shift observed for H-3 is quite similar to those observed for the comparable resonances in other 2,4-dinitro-substituted naphthalenes.[30] The downfield (τ 1.59 ppm) multiplet is assigned to H-5 and H-8, while the upfield multiplet is assigned to H-6 and H-7. The symmetry of these multiplets indicates that the chemical shifts of the protons comprising the multiplets are almost identical, a conclusion confirmed by the observation that the structure of the multiplets was unchanged at 100 MHz. Similar ABCD spectra have been observed for indole and benzofuran[29b] and for 1-methyl-4-nitronaphthalene.[31] The low field assignment for H-5 and H-8 is based on the well-established deshielding effect of *peri* substituents in naphthalene systems;[30-32] the chemical shifts for all four protons are quite closely comparable with those reported for model structures.[30,32] The assignment was confirmed by a double resonance experiment at 100 MHz; irradiation of the upfield multiplet caused collapse of the 1.59-ppm multiplet to two partially resolved singlets at τ 1.53 and 1.60 ppm. Essentially identical spectra in terms of multiplicity structure were observed for the corresponding methyl ether **4** and for the ABCD system of 1-methoxy-4-nitronaphthalene. No separations of these resonances were achieved by solvent changes (DMSO-d_6 acetone, trifluoroacetic acid); the line separations and relative intensities of the transitions of the multiplets were essentially unaffected by these changes.[33]

The appearance of the aromatic resonances of the diethoxy complex **3** is markedly altered in terms of both multiplicity and chemical shifts from that of ether **5**. The H-3 resonance remains a singlet, but is shifted downfield ($\Delta\delta$ −0.45) to 0.77 ppm; H-8 also shows a downfield shift ($\Delta\delta$ −0.32) to 1.27 ppm. However, the H-5, H-6, and H-7 resonances show the expected upfield shifts: H-5, τ 2.23 ($\Delta\delta$ 0.64); H-6 and H-7, 2.73 ppm ($\Delta\delta$ 0.66). As cited previously, all three ring protons of the benzene complexes (**7**) show upfield shifts and of considerably larger magnitudes than the maxima observed for **3**; smaller shifts might be anticipated for **3** since the negative charge is delocalized over more atoms than in the case of **7**. These shifts indicate a significant decrease in electron density at the 3 and 8 positions of the complex relative to the parent ether with an increase in electron density at the 5, 6, and 7 positions. On the basis of canonical contributions, the increase at H-5 and H-7 is expected, although the similarity in increase for H-6 and H-7 and the actual decrease in electron density at H-3 and H-8 is not readily explicable. The deshielding at H-8 is probably due in part to the change in hybridization at C-1. In the starting ether, H-8 undergoes *peri* shielding as a result of the anisotropic effect of the C-1 ethoxyl group, whereas in the complex **3**, two ethoxyl groups are present at C-1 and it might be expected that the combined anisotropic effect of these two carbon–oxygen bonds might be sufficient to overcompensate for any shielding due to increased charge density at H-8. An examination of models of **3** and **5** indicates the changes in geometry at C-1 (vectors from center of carbon–oxygen bond to H-8) should produce an increase in anisotropic deshielding for H-8. Recently, HMO calculations of π-electron densities in **4** and the symmetrical complex **1** have been reported.[34] These calculations indicate that in the formation of **1** from **4** there is a slight increase in electron density in the unsubstituted ring, but that most of the accumulation of negative charge is in the nitro groups; pertinent to the observations above, however, is the conclusion that electron density should decrease to a marked extent in the substituted ring, *i.e.*, at H-3. In this regard, the experimentally observed $\Delta\delta$ values are in qualitative accord with the results of HMO calculations. Similar changes are observed in the aromatic resonances for complexes **1** and **2**.

As indicated above, the formation of the complex **3** from ether **5** results in an increase in the chemical-shift difference of H-5 and H-8 so that both resonances are the expected first-order multiplets (doublets of doublets); *i.e.*, H-5 is coupled to both H-6 and H-7. The following coupling constants are observed: J_{56} = 7.4, J_{57} = 2.7, J_{78} = 7.8, and J_{68} = 2.5 Hz. The magnitudes of these coupling constants are comparable with those observed in related naphthalene systems.[30a,35] The singlet structure of the H-3 resonance of **5** is unchanged in the complex; the same symmetry is observed for the H-6, H-7 multiplet in both the starting ether and the complex. The aromatic resonances of complexes **1** and **2** are essentially identical in character.

In order to establish that the 1,1 complexes (**1**–**3**) were the initially formed species in the reaction of alkoxide ions with **4** and **5** and not the result of rearrangement of some less stable species, as in the case of the picryl complexes,[3,4] the *in situ* generation of **1** was examined. Treatment of a 1 *M* solution of **4** in DMSO-d_6 with 1 equiv of potassium methoxide in methanol led to the immediate development of the

(29) (a) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964); (b) P. J. Black and M. L. Heffernan, *Australian J. Chem.*, **18**, 353 (1965).

(30) (a) P. R. Wells, *J. Chem. Soc.*, 1967 (1963); (b) F. Bell and K. R. Buck, *ibid., Sect. C*, 904 (1966).

(31) P. R. Wells and P. G. E. Alcorn, *Australian J. Chem.*, **16**, 1108 (1963).

(32) A. Zweig, J. E. Lancaster, and M. T. Neglia, *Tetrahedron*, **23**, 2577 (1967).

(33) The low-field portion of the AB signal for H-2 and H-3 of 1-methoxy-4-nitronaphthalene overlaps the H-5, H-8 signal; the chemical shift of this doublet does show a solvent dependence.

(34) P. Caveng, P. B. Fischer, E. Heilbronner, A. L. Miller, and H. Zollinger, *Helv. Chim. Acta*, **50**, 848 (1967).

(35) J.-C. Richer and C. Lamarre, *Can. J. Chem.*, **43**, 715 (1965).

spectrum of **1**. In a similar experiment, the potassium methoxide solution was added dropwise with the spectrum recorded after each addition of methoxide. The development of peaks ascribable to **1** and the disappearance of those due to **4** were observed; after the addition of 1 equiv of base, only the peaks due to the complex were observed. In neither experiment were peaks ascribable to any third species observed; the initial observations of the spectra of these solutions were made within 20 sec of the time of addition of methoxide ion. No changes were observed in the spectra of solutions of complexes **1–3** which had been allowed to stand at room temperature for extended periods of time. This solution behavior is one manifestation of the greater stability of these complexes as compared to those of the 2,4-dinitrophenyl ethers which undergo a relatively rapid rearrangement to the isomeric 1,2 complexes.[5,36] No exchange of ring protons with solvent deuterons (from DMSO-d_6) was observed for solutions of **1–3**, but, in the presence of excess base, exchange is rapid and complete. Addition of a large excess of potassium methoxide in methanol to a solution of **4** in DMSO-d_6 led to the immediate development of the spectrum of **1**, but the intensities of the aromatic resonances of **1** underwent a rapid decrease and after 3–5 min all of the aromatic protons appeared to have exchanged with a concomitant increase in the intensity of the DMSO-d_5 peak.

(36) E. J. Fendler, W. E. Byrne, J. H. Fendler, and C. E. Griffin, unpublished results.

Registry No.—**4**, 13772-69-5; **5**, 15352-94-0.

Acknowledgment.—We are indebted to Drs. S. Castellano and J. J. Burke for helpful discussions and to Dr. B. D. Martin for assistance in the determination of pmr spectra. This work was supported, in part, by the U. S. Atomic Energy Commission and instrumentation provided by a grant (FR 00292) from the National Institutes of Health was used.

Nucleophilic Addition–Elimination Reactions of 1,2-Di-*p*-toluenesulfonylethene[1]

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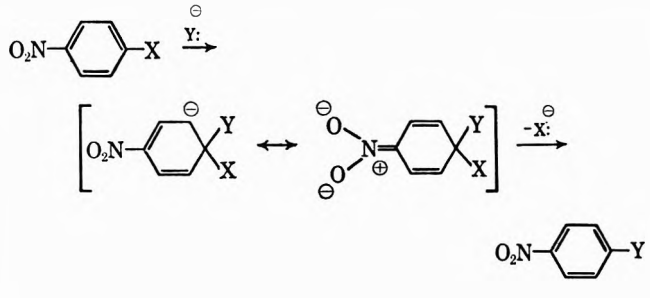
The addition–elimination reactions of *cis*- and *trans*-1,2-di-*p*-toluenesulfonylethene (**1** and **2** in text) with azide, methoxide, and thiophenoxide ions occur with a high degree of retention of configuration of the substrate. Trimethyl phosphite reacts with both **1** and **2** to yield dimethyl *trans*-2-*p*-toluenesulfonylethenephosphonate and methyl *p*-toluenesulfinate. With cyclohexylamine, the *trans*-addition–elimination product is obtained with both **1** and **2**. Ethylenimine gives an adduct with **1** and **2** plus the expected addition–elimination product. Phenylmagnesium bromide reacts with **1** to give *trans*-β-styryl *p*-tolyl sulfone. *cis*-1,2-Di-*p*-toluenesulfonylethene reacts with diazomethane to give 3(5)-*p*-toluenesulfonylpyrazole. Sodium azide reacts with **1** in dimethyl sulfoxide to give 4(5)-*p*-toluenesulfonyltriazole which has been shown to arise from the cyclization of *trans*-2-azidovinyl *p*-tolyl sulfone under basic conditions.

Although nucleophilic substitution reactions at aryl carbon atoms are generally difficult, they occur readily when electron-withdrawing groups are substituted *ortho* or *para* to the leaving group, owing to the stabilization of the transition state (or in some cases, an intermediate).[3]



Similarly, the replacement of vinylic halides is facilitated by electron-withdrawing groups β to the site of substitution. Addition–elimination reactions of this type have been reviewed by Patai and Rappaport,[4] and nucleophilic substitution reactions of β-halovinyl ketones,[5] β-chloroacrylonitrile,[6] β-halovinyl sulfones,[7] and β-halovinyl fluorides[8] are well documented in the literature. However, disulfonylethenes where the sulfone group is both the activating and leaving group have received scant attention. The only nucleophilic addition–elimination reactions so far reported are those of *cis*- and *trans*-1,2-dibenzenesulfonylethene, 1,2-di-*p*-nitrobenzenesulfonylethene, and 1-benzenesulfonyl-2-*p*-nitrobenzenesulfonylethene with cyclohexylamine and piperidine.[9] In order to extend the scope of these reactions *cis*- and *trans*-1,2-di-*p*-toluenesulfonylethene (**1** and **2**) were chosen for study.

Results and Discussion

Scheme I summarizes the reaction products without specifying stereochemistry. In the stereochemical studies the reactions of both **1** and **2** were carried out

(1) This paper was presented in part at the 153rd National Meeting of the American Chemical Society, April 1967, Miami, Beach, Fla.

(2) National Institutes of Health Predoctoral Fellow, 1966–1967.

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, p 452 ff.

(4) S. Patai and Z. Rappoport, "The Chemistry of Alkenes," Interscience Publishers, Inc., New York, N. Y., 1964, p 525 ff.

(5) A. E. Pohland and W. R. Benson, *Chem. Rev.*, **66**, 161 (1966).

(6) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1963).

(7) (a) L. Maioli and G. Modena, *Gazz. Chim. Ital.*, **89**, 854 (1959); (b) G. Modena and P. E. Todesco, *ibid.*, **89**, 866 (1959); (c) G. Modena, P. E. Todesco, and S. Tonti, *ibid.*, **89**, 878 (1959); (d) S. Ghersetti, G. Lugli, G. Melloni, G. Modena, P. E. Todesco, and P. Vivarelli, *J. Chem. Soc.*, 2227 (1965).

(8) J. D. Park and W. C. Frank, *J. Org. Chem.*, **32**, 1333 (1967); J. D. Park, J. R. Dick, and J. H. Adams, *ibid.*, **30**, 400 (1965).

(9) F. Montanari, *Gazz. Chim. Ital.*, **87**, 149 (1957).

TABLE I

REACTIONS OF NUCLEOPHILES WITH *cis*- AND *trans*-1,2-DI-*p*-TOLUENESULFONYLETHENE

cis- or *trans*-TsCH=CHTs + N: ⟶ TsCH=CHN + Ts^-

Sulfone	N	Solvent	Temp, °C	Time, hr	Yield, %	% *cis*	% *trans*	Other, %	Mp, °C	Lit. mp, °C
1	N_3^-	CH_3CN–H_2O	25	17.5	58	90	10		*cis*, 43–45	48–50[a]
2	N_3^-	CH_3CN–H_2O	25	17.5	39	0	60	18, 40	72–74	75–76[a]
1	C_6H_5SH–$(C_2H_5)_3N$	CH_3CN	25	20	69	90	10			
2	C_6H_5SH–$(C_2H_5)_3N$	CH_3CN	25	20	69	0	100		107–110	111–112[b]
1	$C_6H_{11}NH_2$	CH_3CN	25	26	88	0	100		130–132	131.5–132.5[b]
2	$C_6H_{11}NH_2$	CH_3CN	25	25	95	0	100			
1	CH_3O^-	CH_3CN	25	20	83	95	5		*cis*, 82–83	87[c]
2	CH_3O^-	CH_3CN	25	20	88	0	100		*trans*, 62–63	67[c]
1	$(CH_3O)_3P$	None	25	0.017	70	0	100		108–110	
2	$(CH_3O)_3P$	None	90	0.17	83	0	100		108–110	

[a] Reference 7b. [b] Reference 7c. [c] Reference 7a.

TABLE II

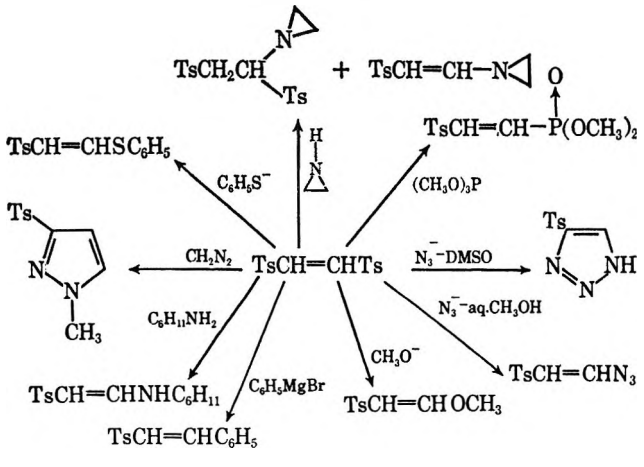
REACTIONS OF NUCLEOPHILES WITH 1 IN VARIOUS SOLVENTS

N	Solvent	Temp, °C	Time, hr	Yield, %	% *cis*	% *trans*	Other %	Mp, °C
N_3^-	CH_3OH–H_2O	25	43–72	29	40	60		*cis* to *trans* isomerism under reaction conditions
N_3^-	CH_3CN–H_2O	25	17.5	58	90	10		
N_3^-	DMSO	25	28	46			18, 45	156–158
C_6H_5SH–$(C_2H_5)_3N$	Ether	25	24	38	90	10		99–101 (lit.[a] 103–104)
C_6H_5SH–$(C_2H_5)_3N$	CH_3CN	25	20	69	80	20		
C_6H_5SH–$(C_2H_5)_3N$	CH_3OH	25	27	68	80	20		
C_6H_5SH–OCH_3^-	CH_3OH	25	18	37	75	25		
$C_6H_{11}NH_2$	CH_3OH	25	24	89	0	100		
$C_6H_{11}NH_2$	Ether	25	24	91	0	100		
$C_6H_{11}NH_2$	CH_3CN	25	26	88	0	100		
OCH_3^-	CH_3OH	25	20	59	100	0		
OCH_3^-	CH_3CN	25	20	83	95	5		*cis* to *trans* isomerism occurs with heating

[a] Reference 7b.

SCHEME I

SUMMARY OF REACTION PRODUCTS



with nucleophiles in acetonitrile at room temperature unless otherwise specified. Product isomer content was obtained from the nmr spectrum of the crude product to preclude postisomerization during the reaction work-up. Since the products contain both α and β vinyl protons, their coupling constants could be used as a basis for configurational assignments.[10] The stereochemistry of the products is summarized in Table I, and a summary of the *cis*/*trans* ratio of products in various solvents is presented in Table II. Nmr data are summarized in Table III.

TABLE III

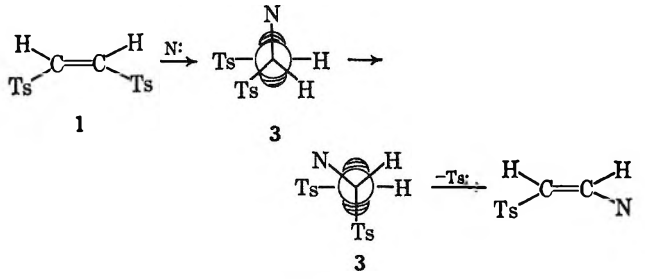
NMR DATA FOR $TsC\overset{\alpha}{H}=C\overset{\beta}{H}N$[a]

Isomer	N	Hβ, ppm	Hα, ppm	J, cps
cis (1)	N_3	6.9	5.75	8
trans (2)	N_3	*b*	6.1	13
cis (3)	OCH_3	6.4	5.5	6.5
trans (4)	OCH_3	*b*	5.75	12
cis (5)	SC_6H_5	*b*	6.25	10
trans (6)	SC_6H_5	*b*	6.00	14
trans (7)	NC_6H_{11} (H, O)	*b*	5.05	13
trans	$P(OCH_3)_2$	*b*	6.72	16

[a] All chemical shifts are reported in parts per million (ppm) relative to TMS. Spectra were taken in $CDCl_3$. [b] This proton is obscured by the aromatic signals.

The high degree of stereospecificity in the reactions of **1** and **2** with azide, thiophenoxide, and methoxide ions is best rationalized in terms of an attack by the nucleophile at the π orbital of the olefin to generate an intermediate in which the carbon atom adjacent to the carbon atom under attack is coplanar. Rotation of the tetrahedral carbon atom in this intermediate, **3**, occurs so as to experience the least eclipsing of large groups until the leaving group is in the plane of the developing p orbital of the product. Elimination of the leaving

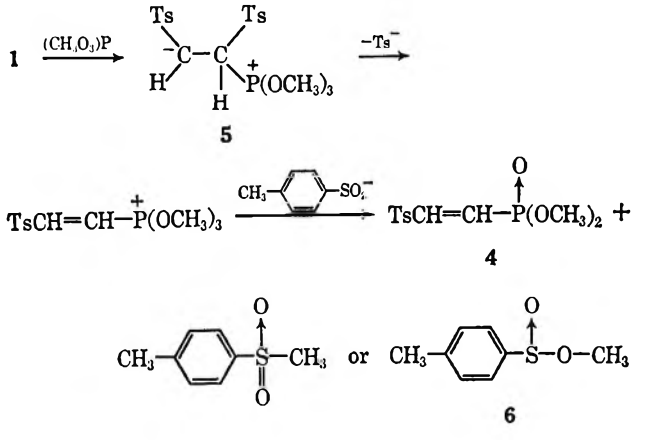
(10) L. M. Jackman, "Applications of N. M. R. Spectroscopy to Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, pp 85–87.



group of the intermediate will give a product with retention of configuration whereas rotation in the opposite direction will lead to the *trans* product.[11] Possibly, the methoxide ion is basic enough to convert **1** into *p*-toluenesulfonylacetylene which could then add methanol to give the *cis* product. The other nucleophiles used do not seem basic enough to give elimination then addition.

We have observed that, when **1** reacts with trimethyl phosphite at room temperature without solvent, heat is evolved within 1 min at which time **1** dissolved in the methyl phosphite. Within another minute dimethyl *trans*-2-*p*-toluenesulfonylethenephosphonate (**4**) crystallized. The isolation of the *trans*-phosphonate was surprising in view of the stereospecificity encountered in the previous reactions. In an effort to see if the *cis*-phosphonate was formed and was isomerized thermally, the reaction of **1** with trimethyl phosphite was carried out in an nmr tube in deuteriochloroform at −30°. However, no signals from the *cis* compound were detected and only the formation of the *trans* compound was evident. Possibly isomerization is occurring by reversible addition of methyl phosphite to the phosphonium intermediate. The primary step in this reaction is probably the formation of the betaine intermediate **5** which could form the product by one of two possible paths. Either it could eliminate a *p*-toluenesulfinate anion which could be alkylated as shown in Scheme II or the alkylation and elimination could take

SCHEME II



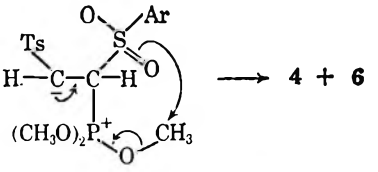
place in one concerted step as outlined in Scheme III. It can be seen that *p*-toluenesulfinate anion is an ambident ion and could undergo alkylation at either sulfur or oxygen to yield methyl *p*-tolyl sulfone or methyl *p*-toluenesulfinate. On the other hand, with a concerted mechanism one can envision a six-membered cyclic transition state leading only to O alkylation.

(11) S. I. Miller and P. K. Yonan [*J. Amer. Chem. Soc.*, **79**, 5931 (1957)] have discussed a similar mechanism.

Bissey and coworkers[12] have suggested a similar mechanism involving five- and seven-membered transition states for the reaction of certain vinylic halides with trialkyl phosphites, but their systems predict identical products by either mechanism. However, in all alkylations involving the *p*-toluenesulfinate anion with various alkylating agents, only S alkylation seems to have been observed and sulfones are isolated.[13]

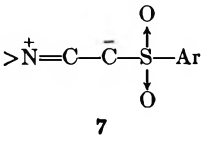
At first only methyl *p*-toluenesulfinate was isolated from the reaction of **1** with trimethyl phosphite which indicated that either the cyclic concerted mechanism of Scheme III was occurring or else the trimethyl phos-

SCHEME III



phonium group gives a high degree of O alkylation similar to the reaction of *p*-toluenesulfinic acid with diazomethane which gives methyl *p*-toluenesulfinate in quantitative yield. When methyl phosphite and **1** were allowed to react in methyl iodide, then a 20–30% yield of methyl *p*-tolyl sulfone could be detected. Careful examination of the original reaction revealed that 5% of the product was methyl *p*-tolyl sulfone. Therefore the mechanism in Scheme II is occurring since methyl iodide did not convert methyl *p*-toluenesulfinate into methyl *p*-tolyl sulfone. Thus there is as yet no evidence for Scheme III and the formation of methyl *p*-toluenesulfinate is best regarded as an alkylation of the *p*-toluenesulfinate anion by a hard alkylating agent which leads mainly to O alkylation. The methyl iodide was able to trap the anion and give the sulfone since it is a soft alkylating agent.

Compounds **1** and **2** react with cyclohexylamine to give only the *trans* product and this is in accord with the observations of others. Recently, Truce and Brady[14] have found that in the addition of amines to acetylenic sulfones, the *cis* product is formed at low temperatures and isomerizes to the *trans* isomer at room temperature. However, the addition of ethylenimine to acetylenic sulfones results in the formation of the *cis*-vinylamine. Vinylic displacements on 2-chlorovinyl aryl sulfones using ethylenimine as a nucleophile results in retention of the configuration about the double bond.[15] Truce has suggested that the spontaneous isomerization from *cis* to *trans* at room temperature is probably due to the immonium structure, **7**, and that



strain in the ethylenimine adducts prevents this structure from facilitating *cis* to *trans* isomerization.[14]

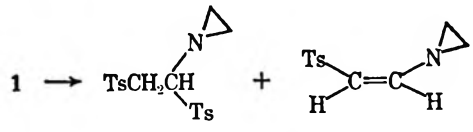
(12) J. E. Bissey, H. Goldwhite, and D. G. Rowsell, *J. Org. Chem.*, **32**, 1542 (1967).

(13) C. R. Noller, "Chemistry of Organic Compounds," W. B. Saunders Co., Philadelphia, Pa., 1965, p 312.

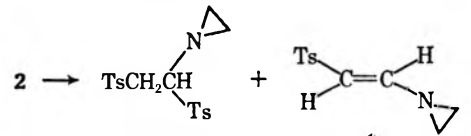
(14) W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).

(15) W. E. Truce, J. E. Parr, and M. L. Gorbarty, *Chem. Ind.* (London), 660 (1967).

We have carried out the reaction of ethylenimine with **1** and **2** and have observed the results shown below.

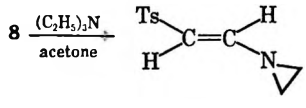


8 (35%) **9** (65%)



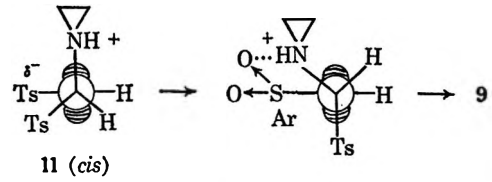
8 (>90%) **10** (<10%)

The formation of 1,2-di-*p*-toluenesulfonyl-1-ethyleniminoethane, **8**, represents the only case where an addition product has been isolated in our reactions. However, this is not an intermediate in the formation of *cis*-1-ethylenimino-2-(*p*-toluenesulfonyl)ethene, **9**, for it is stable to elimination under the reaction conditions and even when it is refluxed in triethylamine in acetone for 0.5 hr, less than 10% of it eliminates to give only *trans*-1-ethylenimino-2-(*p*-toluenesulfonyl)ethene, **10**.

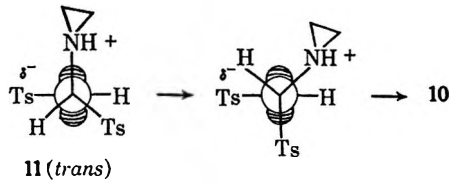


One rationalization for the formation of the adduct **8** is that the low basicity of the ethylenimine[16] renders its conjugate acid sufficiently acidic for protonation to become a favorable reaction. Thus the initial adduct of ethylenimine has two energetically favorable reaction pathways available to it, *i.e.*, intramolecular protonation and elimination.

Another interesting aspect of this reaction is that the protonated adduct is highly favored with the *trans* substrate, whereas elimination predominates with the *cis* substrate. In the initial intermediate **11** from the *trans* sulfone, rotation is necessary through a conformation having an eclipsed hydrogen atom and a sulfone group before elimination can occur. With the *cis* sulfone, the intermediate only has a hydrogen–hydrogen interaction barring rotation before elimination can occur. Therefore, elimination is favored in the reaction of ethylenimine with **1** and less of **8** is formed. In addition, rotation in the *cis* case to the conformation necessary for elimination would be favored by the electrostatic attraction between the sulfone and the ethylenimmonium



11 (*cis*)



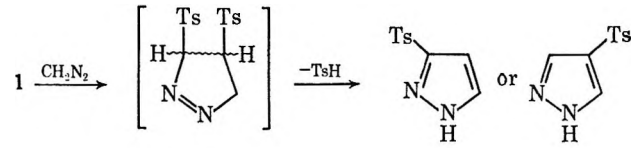
11 (*trans*)

group.[15] Rotation in the *trans* intermediate has to separate these charged centers.

The addition of Grignard reagents to α,β-unsaturated sulfones has been carried out by Kohler and coworkers who have found that the reaction proceeds slowly in moderately low yields.[17] We have added phenylmagnesium bromide to **1** and isolated a small amount of *trans*-β-styryl *p*-tolyl sulfone after chromatography over alumina. It is not known what degree of stereospecificity the reaction has since chromatography might have caused isomerization.

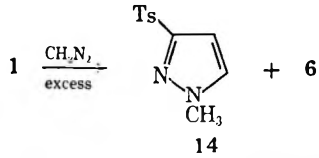
The addition of diazomethane to β-halo vinyl ketones results in the formation of pyrazoles.[6] It has been suggested that the reaction proceeds through the dipolar addition of diazomethane followed by the loss of hydrogen chloride to form the aromatic pyrazole.

In the reaction of diazomethane with **1** there is the possibility of the formation of two different pyrazoles, **12** and **13**, depending on the direction of loss of *p*-toluenesulfinic acid from the initial adduct.



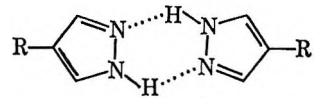
12 **13**

Pyrazole **12** can be isolated when excess diazomethane is removed immediately after the vigorous nitrogen evolution has ceased. This is consistent with the removal of the most acidic proton from the intermediate adduct. If **1** is allowed to stand overnight with excess diazomethane N-methyl-3(5)-*p*-toluenesulfonylpyrazole (**14**) is formed. The *p*-toluenesulfinic acid produced in the reaction proceeded to react with excess diazomethane to form methyl *p*-toluenesulfinate.



14

The structure of **12** was ascertained from its nmr spectrum. 4-Substituted pyrazoles show a singlet in the nmr spectrum for the annular protons which has been rationalized in terms of a hydrogen bonded dimer (**15**).[18] In the 3(5)-substituted pyrazoles, however,



15

the ring protons appear as an AB quartet with a splitting of about 2 cps. The nmr spectrum of **12** showed an AB quartet for the ring protons.

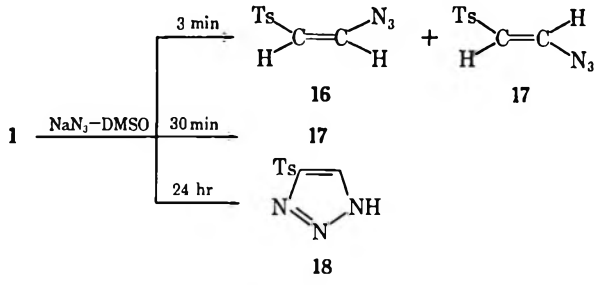
The reaction of sodium azide with **1** in methanol leads to the formation of **16** and **17**. The reaction time used was approximately 3 days, the yields were poor, and the separation of isomers was time consuming. When the reaction was carried out in dimethyl sulfoxide for 24 hr, a 50% yield of 4(5)-*p*-toluenesulfonyltriazole (**18**) was isolated. When the reaction time in dimethyl sulfoxide was shortened to 3 min, the

(16) P. A. Gembitskii, N. M. Loim, and D. S. Zhuk, *Russ. Chem. Rev.*, **35**, 105 (1966).

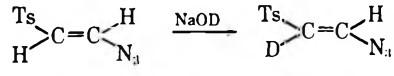
(17) E. P. Kohler and H. Potter, *J. Amer. Chem. Soc.*, **57**, 1316 (1935).

(18) J. K. Williams, *J. Org. Chem.*, **29**, 1377 (1964).

product composition was 85% *cis* and 15% *trans*, and at 30-min reaction time only the *trans* isomer in 43% yield was isolable. The preparation of the *trans*-vinyl azide in dimethyl sulfoxide is more convenient because the reaction time is shorter and no isomer separation is involved.



The isomerization of vinyl azide **17**, to triazole **18** has been discussed in a preliminary communication[19] and it was concluded that it is unique because the hydrogen atom α to the sulfone is acidic and produces under the reaction conditions, a carbanion which can cyclize without the loss of stabilization energy. To further substantiate this conclusion the acidity of the hydrogen atom α to the sulfone in **17** has been demonstrated by deuterium exchange. Thus, when the vinyl azide in deuteriochloroform is shaken with a sodium–deuterium oxide solution, there is a slow exchange of the proton α to the sulfone group. The reaction was 70% complete in 48 hr. The possibility that the exchange occurred through the addition of deuterium oxide followed by the elimination of HOD is not completely excluded. However, the exchange was closely monitored by nmr spectroscopy and no extraneous signals were detected.



4(5)-*p*-Toluenesulfonyltriazole was independently synthesized using *p*-toluenesulfonylacetylene and trimethylsilyl azide patterned after a method of triazole synthesis developed by Birkofer and Wegner.[20]

$$TsC{\equiv}CH + (CH_3)_3SiN_3 \longrightarrow \mathbf{18}$$

Experimental Section

All nmr spectra were run on a Varian A-60 or A-60A spectrometer using tetramethylsilane as an internal standard. Infrared spectra were obtained using a Beckman IR-5. All melting points were obtained on a Fischer-Johns melting point block and are uncorrected. Analyses of all new compounds were performed by Galbraith Laboratories, Knoxville, Tenn.

cis-**1,2-Di-*p*-toluenesulfonylethene** (1) was prepared according to the method of Snyder and Hallada[21] using *cis*-dichloroethylene instead of dibromoethylene in 45% over-all yield, mp 143–145° (lit.[21] mp 146–148°).

trans-**1,2-Di-*p*-toluenesulfonylethene** (2).—A mixture of 1.1 g of 1 and 1 ml of triethylamine in 100 ml of acetone was refluxed for 13 hr. The reaction mixture was cooled and 0.5 g of 2 was filtered, mp 225–228° (lit.[22] mp 228–229°).

Reaction of 1 and 2 with Sodium Azide in Aqueous Acetonitrile.—A solution of 2.0 g of 1 or 2 in 40 ml of acetonitrile and 16 g of sodium azide in 50 ml of water was stirred for 17.5 hr at room temperature. The reaction mixture was extracted with two 50-ml portions of ethyl acetate. The ethyl acetate extracts were washed twice with 100 ml of water and then dried over magnesium sulfate. The solvent was evaporated without using heat yielding a crude product which was weighed and the product isomer content determined by nmr. Yields are summarized in Table I, and nmr spectra are described in Table III.

Reaction of 1 with Sodium Azide in Aqueous Methanol.—A mixture of 6 g of 1 in 250 ml of methanol and 42 g of sodium azide in 150 ml of water was allowed to react at room temperature for 43 hr. Saturated sodium chloride was added to the reaction mixture and the product was extracted with ethyl acetate. The ethyl acetate extracts were dried and the solvent removed without heat yielding 1.5 g of crude product. Nmr analysis showed that 77% of this was composed of a 4:6 mixture of the *cis* and *trans* vinyl azides. Chromatography over alumina (Merck #71707) eluting with benzene and chloroform yielded 0.6 g of **17**, mp 72–74° (lit.[7b] mp 75–76°), and 0.3 g of **16**, mp 43–45° (lit.[7b] mp 48–50°). Nmr data are given in Table III. The *cis*-vinyl azide **16** isomerizes to the *trans*- (**17**) under the reaction conditions.

Reaction of Thiophenol with 1 and 2 in Various Solvents.—A mixture of 2.0 g of 1 or 2, 0.65 ml of thiophenol, and 0.82 g of triethylamine in 50 ml of acetonitrile was allowed to react at room temperature for *ca.* 20 hr. The reaction mixture was extracted with 150 ml of ethyl acetate and washed with 1 *N* NaOH. The ethyl acetate extracts were dried and the solvent removed without heat. The crude product was weighed and the product isomer content determined by nmr. The reactions of 1 in ether and methanol were carried out as described above for 24 and 27.5 hr, respectively. Tables I, II, and III give yields and nmr data.

Reaction of 1 and 2 with Sodium Methoxide.—A mixture of 1.0 g of 1 or 2 and 16.5 ml of a sodium methoxide solution (prepared from 0.4 g of sodium metal and 100 ml of methanol) in 50 ml of acetonitrile was allowed to react at room temperature for 20 hr. To the reaction mixture was added 50 ml of a saturated sodium chloride solution. The reaction mixture was then extracted with ethyl acetate, the extracts were dried and the solvent removed without heat (*cis* to *trans* isomerization occurs with heating). The reaction of 1 in methanol was carried out as described above. Tables I, II, and III give yields and nmr data.

Reaction of 1 with Trimethyl Phosphite.—A mixture of 1.0 g of 1 and 0.5 ml of trimethyl phosphite was allowed to react at room temperature for approximately 1 min at which time the reaction mixture became warm, liquefied, and resolidified. The solid was dissolved in ethyl ether and recrystallized yielding 0.6 g (70%) of white needles, mp 105–107°. After three recrystallizations the melting point was 108–110°.

Anal. Calcd for $C_{11}H_{16}O_5PS$: C, 45.51; H, 5.21. Found: C, 45.29; H, 5.32.

The reaction was repeated and an nmr spectrum of the crude reaction mixture revealed the presence of methyl *p*-toluenesulfinate and methyl *p*-tolyl sulfone in a ratio of 95:5. The presence of the small amount of sulfone was confirmed by glpc.

The reaction of 2 with trimethyl phosphite occurred after 0.7 g of 2 was combined with 0.35 ml of trimethyl phosphite. The reaction mixture was heated on a steam cone for 10 min until it liquefied. The reaction mixture was then cooled and purified as described above yielding 0.5 g of a white solid (83%), mp 105–108°. The compound had an identical nmr spectrum with the product derived from the reaction of 1 with trimethyl phosphite. The reaction was repeated using 0.2 g of 2 and 0.09 g of trimethyl phosphite. An nmr spectrum of the crude reaction mixture showed the formation of methyl *p*-toluenesulfinate and methyl *p*-tolyl sulfone in a ratio of 93:7.

Isolation of Methyl *p*-Toluenesulfinate from the Reaction of 1 with Trimethyl Phosphite.—The reaction of 1 with trimethyl phosphite was carried out as described above. The solvent was removed from the mother liquor of the first crystallization leaving 0.72 g of a yellow oil. The nmr spectrum showed that this was a 2:1 mixture of methyl *p*-toluenesulfinate and 4. Shaking the yellow oil with pentane caused the selective solution of the ester which had identical spectral properties with an authentic sample of methyl *p*-toluenesulfinate.

Methyl *p*-toluenesulfinate was prepared by the action of diazomethane on *p*-toluenesulfinic acid (prepared according to the method of Field and Grunwald[23] in 57% yield) in 62% yield

(19) J. S. Meek and J. S. Fowler, *J. Amer. Chem. Soc.*, **89**, 1967 (1967).
(20) L. Birkofer and P. Wegner, *Chem. Ber.*, **99**, 2512 (1966).
(21) H. R. Snyder and D. P. Hallada, *J. Amer. Chem. Soc.*, **74**, 5595 (1952).
(22) W. E. Truce and R. J. McManimie, *ibid.*, **75**, 1672 (1953).
(23) L. A. Field and F. A. Grunwald, *J. Org. Chem.*, **16**, 946 (1951).

as a colorless oil, bp 100–104° (2.5 mm) (lit.[24] bp 82–85° (0.1 mm)). The nmr spectrum ($CDCl_3$) showed signals at 2.39 (3 H singlet), 3.42 (3 H singlet), and 7.3 and 7.68 ppm (4 H aromatic quartet, J = 8 cps).

Reaction of 1 with Trimethyl Phosphite in Methyl Iodide.—To 0.5 g of 1 in 1 ml of methyl iodide was added 0.25 ml of methyl phosphite. The reaction mixture was allowed to stand at room temperature for 0.5 hr and then the excess methyl phosphite and methyl iodide were removed under reduced pressure. An nmr spectrum of the residual mixture showed that it contained methyl *p*-toluenesulfinate and methyl *p*-tolyl sulfone in a ratio of 2:1.

Reactions of 1 and 2 with Cyclohexylamine in Various Solvents.—To 1.0 g of 1 or 2 in 50 ml of acetonitrile was added 0.75 ml of cyclohexylamine. A precipitate formed immediately. After standing for 26 hr at room temperature the reaction was diluted with water and extracted with ethyl acetate. The ethyl acetate extracts were dried and evaporated. The product after crystallization from benzene–pentane had mp 131–132° (lit.[8c] mp 131.5–132.5°). The reaction of 1 with cyclohexylamine was similarly carried out in ether and methanol. Yields and nmr data are summarized in Tables I, II, and III.

Reaction of 1 with Ethylenimine in Ether.—To 1.0 g of 1 in 50 ml of ether was added with stirring at 0° 0.15 ml of ethylenimine in 3 ml of ether. The reaction mixture was worked up as described for the reactions in acetonitrile. After the ether was removed, the residue was dissolved in a small amount of ether and allowed to cool overnight. White crystals were filtered and had mp 106–108°. Since the melting point was depressed by further crystallizations (though the nmr spectrum did not change), the product was analyzed without further purification with satisfactory results. The nmr spectrum ($CDCl_3$) showed a doublet centered at 1.87 (4 H, ethylenimino protons), a singlet at 2.44 (6 H, tolyl methyl protons), an eight-line multiplet between 3.1 and 4.1 (3 H, α-sulfonyl protons), and an A_2B_2 aromatic quartet centered at 7.35 and 7.76 ppm, J = 8 cps (8 H).

Anal. Calcd for $C_{18}H_{21}NO_4S_2$: C, 57.02; H, 5.58; N, 3.69. Found: C, 56.93; H, 5.67; N, 3.58.

Reaction of *cis*-1,2-Di-*p*-toluenesulfonylethene with Ethylenimine.—To 1.0 g of 1 in 30 ml of acetonitrile at 0° was added with stirring 0.16 g of ethylenimine in 3 ml of acetonitrile. The reaction mixture was stirred for 4 min at 0° and 30 ml of water was added. The product was extracted with 100 ml of ether. The ether was dried and removed leaving 0.612 g of crude product which nmr analysis showed to be 65% *cis*-1-ethylenimino-2-(*p*-toluenesulfonyl)ethene and 35% 1,2-di-*p*-toluenesulfonyl-1-ethyleniminoethane.

Reaction of *trans*-1,2-Di-*p*-toluenesulfonylethene with Ethylenimine.—To 0.5 g of 2 in 15 ml of acetonitrile at 0° was added with stirring 0.08 ml of ethylenimine in 2 ml of acetonitrile. The reaction mixture was stirred for 4 min and 20 ml of water was added. Starting material 0.11 g was filtered, mp 222–227°. The ether was washed with water, dried, and removed without heat leaving 0.351 g of a white solid, mp 98–102°. The nmr spectrum of this solid showed that it was composed of at least 90% 1,2-di-*p*-toluenesulfonyl-1-ethyleniminoethane and less than 10% of 10. The nmr spectra of 9 and 10 were reported by Truce and were used for comparison.[15]

Reaction of 8 with Triethylamine in Acetone.—A solution of 0.065 g of 8 and 0.05 ml of triethylamine in 3 ml of acetone was refluxed for 0.5 hr. The solvent was removed using a stream of air and the residue analyzed by nmr. The nmr spectrum showed that less than 10% of the adduct had undergone elimination to 10 and that the remainder was unchanged starting material.

Reaction of Phenylmagnesium Bromide with 1.—A solution of phenylmagnesium bromide was prepared from 2.0 g of magnesium metal and 9 ml of bromobenzene in 40 ml of anhydrous ether. To 2.0 g of 1 in 100 ml of ether was added 6 ml of the above solution in 14 ml of ether. The solution was stirred at room temperature for 9 hr and then extracted with 100 ml of 10% sulfuric acid. The ether solution was treated with Norit, dried, and filtered. The ether was removed under reduced pressure without heat. The brown oil remaining was chromatographed and yielded 0.435 g of *trans*-β-styryl *p*-tolyl sulfone, mp 118–121° (lit.[17] mp 121°). The nmr spectrum ($CDCl_3$) showed signals at 2.38 (3 H singlet), 6.9 and 7.65 (2 H AB quartet, J = 15 cps), 7.84 and 7.3 (4 H quartet, J = 8 cps), and 7.38 ppm (5 H singlet).

(24) A. J. H. Houssa, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 1700 (1929).

3(5)-*p*-Toluenesulfonylpyrazole.—A solution of diazomethane, prepared from 3 g of N-nitrosomethylurea, in 400 ml of ether was dried for 1 hr over KOH pellets. This solution was then added to 1.1 g of 1. The solid dissolved slowly with nitrogen evolution, and after it had all gone into solution half of the volume of the ether and the excess diazomethane was removed using a stream of dry air. The remaining solution was cooled overnight. The remaining ether was removed and the oily residue was dissolved in ether–ethyl acetate and washed with 5% sodium carbonate solution. The organic layer was dried and the solvent removed. The remaining oil was chromatographed over a dry column of deactivated alumina (Merck #71707 which had been deactivated by adding 40 ml of water to 1 lb of alumina and heating under reduced pressure for 8 hr), and was eluted with pentane, benzene, and chloroform. The product (0.12 g) which was eluted with chloroform had mp 162.5–164.5° after recrystallization from ether–pentane. The infrared spectrum showed –NH absorption at 3370 cm^{-1}. The nmr spectrum ($CDCl_3$) showed signals at 2.36 (3 H singlet), 6.8 (1 H doublet, J = 2.5 cps), 8.05 (1 H doublet, J = 2.5 cps), and 7.85 and 7.25 ppm (4 H A_2B_2 aromatic quartet, J = 8 cps).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.03; H, 4.54; N, 12.61. Found: C, 53.93; H, 4.60; N, 12.51.

N-Methyl-3(5)-*p*-toluenesulfonylpyrazole.—A solution of diazomethane prepared as described above was added to 1.0 g of 1 which dissolved slowly with nitrogen evolution. The pale yellow color of the diazomethane remained after solution was complete and the reaction mixture was allowed to stand overnight at room temperature. The solvent was then removed with a stream of air and the residue dissolved in a small amount of ether and washed with a 5% sodium carbonate solution. The organic phase was dried and the solvent removed leaving an oily residue which was chromatographed as described above and yielded 0.11 g of methyl *p*-toluenesulfinate, and 0.4 g of the N-methylpyrazole. The analytical sample from ether–pentane had mp 73–74°. The infrared spectrum showed no –NH absorption. The nmr spectrum ($CDCl_3$) showed signals at 2.42 (3 H singlet), 4.02 (3 H singlet), 6.85 (1 H doublet, J = 2 cps), 7.5 (1 H doublet, J = 2 cps), and 7.3 and 7.85 ppm (4 H, A_2B_2 quartet, J = 8 cps).

Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86. Found: C, 55.77; H, 5.17; N, 11.86.

Reaction of 1 with Sodium Azide in DMSO.—To a solution of 2.0 g of compound 1 in 50 ml of DMSO was added 2.0 g of sodium azide; a brilliant yellow color appeared immediately. The reaction mixture was allowed to stand at room temperature for 28 hr and then poured onto ice and extracted with ethyl acetate. The ethyl acetate extracts were washed several times with water, dried and evaporated without heat to yield 0.6 g of a semicrystalline solid which after crystallization from water had mp 156–158°. There was no azide absorption in the infrared spectrum, and an –NH peak showed at 3.18 μ. The compound was soluble in 1 N NaOH and reprecipitated with acid. The nmr spectrum ($CDCl_3$) showed the presence of a *p*-toluenesulfonyl group and a signal at 8.5 ppm integrating for one proton relative to the *p*-toluenesulfonyl group.

Anal. Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.44; H, 3.95; N, 18.87.

Reaction of 1 with Sodium Azide in DMSO for 3 Min.—A solution of 4.44 g of sodium azide and 2.06 g of 1 in 30 ml of DMSO was allowed to stand at room temperature for 3 min, poured onto ice, and extracted with ether. The ether extracts were washed well with water, dried, and evaporated leaving 0.83 g of an oil which nmr analysis showed was composed of 85% of the *cis*-vinyl azide 16 and 15% of the *trans*-vinyl azide 17.

Reaction of Sodium Azide with 1 in DMSO for 30 Min.—To a solution of 14 g of 1 in 70 ml of DMSO was added 18 g of sodium azide. The reaction was stirred at room temperature for 30 min and then poured onto ice. The reaction was extracted twice with 50-ml portions of ether. The ether extracts were washed well with 1 N NaOH to remove any triazole 18 which might have formed and then with 1 l. of water in several portions. The ether was dried over anhydrous magnesium sulfate and then removed at reduced pressure without heat. The addition of ether to the residual oil and cooling caused the precipitation of *trans*-2-azidovinyl *p*-tolyl sulfone (4 g, 43%), mp 60–65° (lit.[7b] mp 75–76°). The nmr spectrum of this material showed that it was not contaminated with the *cis*-vinyl azide and did not show any other impurities.

Conversion of *trans*-2-Azidovinyl *p*-Tolyl Sulfone into 4(5)-*p*-Toluenesulfonyltriazole.—All isomerizations were carried out in

DMSO solution. The reaction mixtures were worked up by pouring them onto ice and extracting with ethyl acetate. The ethyl acetate extracts were washed several times with water and the solvent removed without heat. The composition of the crude products was determined by nmr and is described below.

Reaction of 17 with Sodium Azide and Sodium *p*-Toluenesulfinate.—A mixture of 0.66 g of **17**, 0.88 g of sodium azide, and 0.53 g of sodium *p*-toluenesulfinate dihydrate in 30 ml of DMSO was allowed to react at room temperature for 20.5 hr. The reaction was worked up as described above and yielded 0.39 g of a semicrystalline mass. The nmr spectrum showed that this was 57% triazole **18** and 43% starting vinyl azide.

Reaction of 17 with Sodium *p*-Toluenesulfinate.—A mixture of 0.5 g of **17** and 0.4 g of sodium *p*-toluenesulfinate dihydrate in 30 ml of DMSO was allowed to react at room temperature for 22.5 hr. The reaction was worked up and yielded 0.28 g of crude product which nmr analysis shows to be 62% triazole **18**, and 38% vinyl azide **17**. The addition of ether to the crude product caused the precipitation of a white solid, mp 147–151°, having an identical infrared spectrum with that of authentic **18**.

Reaction of 17 with Potassium *t*-Butylate in DMSO.—A mixture of 0.32 g of **17** and 0.3 g of potassium *t*-butylate in 30 ml of DMSO was allowed to react for 18 hr at room temperature. The reaction turned deep red-brown at its initiation and bubbled. Acidification, of the reaction mixture and work-up yielded 0.3 g of the product which the nmr spectrum shows to be 50% of triazole **18** contaminated with DMSO. Crystallization of the material from water yielded 0.13 g of a white solid, mp 151–155° (**18**, mp 156–158°).

Deuterium Exchange of *trans*-2-Azidovinyl *p*-Tolyl Sulfone.—To a solution of 0.155 g of **17** in 0.5 ml of deuteriochloroform was added 1 drop of 6.27% sodium deuteroxide solution. The reaction was monitored by nmr. After 35 min there was no apparent change in the spectrum. After 6.5 hr there was 29% exchange, after 22 hr 50% exchange, and after 48 hr 70% exchange of the proton α to the sulfonyl group.

Preparation of 4(5)-*p*-Toluenesulfonyltriazole.—A mixture of 0.2 g of *p*-toluenesulfonylacetylene[14] and 0.54 g of trimethylsilyl azide[25] was heated on a steam bath (80°) in a glass-stoppered test tube for 20 hr. After heating, 15 ml of water was added and the solution was boiled for 5 min and filtered. The triazole crystallized on cooling yielding 0.119 g (48%) of colorless needles, mp 156–158°, mmp 156–158° with **18**. Infrared and nmr spectra were identical with those of the compound prepared by the reaction of **1** with sodium azide in dimethyl sulfoxide for 28 hr.

Registry No.—**1**, 15645-75-7; **2**, 15717-50-7; **4**, 15717-49-4; **8**, 15717-51-8; **12**, 15717-52-9; **14**, 15645-76-8; **18**, 14631-74-4; **1**, 15645-78-0; **2**, 15645-79-1; **3**, 15717-53-0; **4**, 15645-80-4; **5**, 15717-54-1; **6**, 15717-55-2; **7**, 15717-56-3.

(25) L. Birkofer and A. Ritter, *Angew. Chem. Intern. Ed. Engl.*, **4**, 417 (1965).

Small-Ring Epoxides. I. The Synthesis and Reactions of a 4-Methylene-1-oxaspiro[2.2]pentane Derivative

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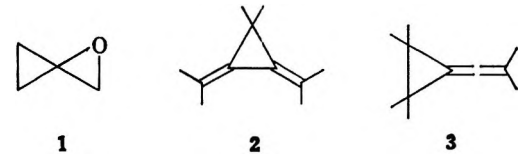
2,2,5,5-Tetramethyl-4-isopropylidene-1-oxaspiro[2.2]pentane (**4**) has been prepared by epoxidation of its dimethylenecyclopropane precursor **2**. Thermolysis of **4** gives the two ketones 2-isopropylidene-3,3,4,4-tetramethylcyclobutanone (**6**) and 2,5-dimethyl-4-isopropylidenehex-5-en-3-one (**7**). Solvolysis of **4** also generates **6** and **7** and, under mild conditions, a new alcohol, 2,5-dimethyl-4-isopropenyl-2,3-hexadien-5-ol (**13**), which is converted into **7** in acid. The mechanistic details of these thermal and solvolytic transformations are discussed in terms of related systems. The mass spectra of several of the compounds encountered in this work are interpreted.

The general subject of small-ring chemistry has received an increasingly large amount of attention in recent years. The advances achieved both in the synthetic and mechanistic aspects of this research area have been enormous and of considerable significance for other areas of organic chemistry. In connection with our interest in the effects of bond-angle strain on the properties and chemical reactivity of molecules, we have initiated a program designed to examine the oxygen analogs of various small-ring hydrocarbons. A comparison of the chemistry of these heterocycles with that of their parent carbocycles should provide further important information with regard to the chemical consequences of ring strain. The present paper is concerned with our initial studies on an interesting derivative of the oxaspiropentane skeleton (**1**).

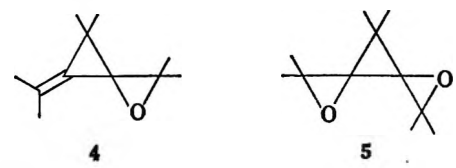
A convenient synthetic entry into this ring system is provided by our recent demonstration that alkenylidenecyclopropanes undergo smooth conversion into dimethylenecyclopropanes upon pyrolysis at reduced pressure in a flow system.[1] This reaction is illustrated by the synthesis of **2** from **3**. Precursor **3** is readily obtained from the base-catalyzed decomposition of 3-chloro-3-methyl-1-butyne[2] or, preferably,



1 **2** **3**

1-bromo-3-methyl-1,2-butadiene[3] in the presence of tetramethylethylene.

The buffered peracetic acid oxidation[4] of **2** proceeded nicely to give monoepoxide **4** in excellent yield along with a small quantity of diepoxide **5** when equivalent amounts of reactants were used.[5] The structure of **4** rests on its mode of synthesis and its spectroscopic properties, particularly the presence of six equivalent sharp singlets with the expected chemical



4 **5**

(1) J. K. Crandall and D. R. Paulson, *J. Amer. Chem. Soc.*, **88**, 4302 (1966).

(2) H. D. Hartzler, *ibid.*, **83**, 4990 (1961).

(3) S. R. Landor, A. N. Patel, P. F. Whiter, and P. M. Greaves, *J. Chem. Soc., Sect. C*, 1223 (1966).

(4) M. Korach, D. Nielson, and W. Rideout, *J. Amer. Chem. Soc.*, **82**, 4328 (1960).

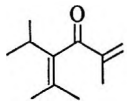
(5) The reactions of diepoxide **5** will be reported in a future publication.

shifts in the nmr spectrum. With a relatively simple synthesis of **4** in hand, a study of the chemistry of this interesting variant of system **1** was initiated.

Since the pyrolytic behavior of small-ring hydrocarbons has been a key feature in the study of their chemistry,[6] the first reaction of **4** to be examined in detail was its thermal isomerization. Compounds **6** and **7** were obtained as products upon flow pyrolysis at reduced pressure.

Compound **6** displays strong infrared bands of nearly equal intensity at 5.78 and 6.01 μ and ultraviolet absorption indicative of a conjugated chromophore (λ_{max}^{hexane} 244 mμ; ϵ 7750). Taken together these data suggest a conjugated cyclobutanone, probably constrained to a *cis* configuration.[7] The nmr spectrum shows two pairs of equivalent methyls on saturated carbon and two different methyl groups attached to olefinic carbon. A strong molecular-ion peak is observed in the mass spectrum of **6** at *m/e* 166. Compound **7** has a 5.93-μ carbonyl band and the appropriate group of absorptions for a disubstituted terminal olefin in its infrared spectrum, in addition to ultraviolet absorption indicative of a conjugated chromophore. The nmr spectrum suggests the presence of an isolated isopropyl group, a terminal methylene, and three methyls bonded to olefinic carbon. However illuminating, these data do not suffice to distinguish unequivocally between **7** and the alternate formulation illustrated by **8**.

A choice in favor of **7** was provided by lithium aluminum hydride reduction of the ketone to the corresponding alcohol. The compound obtained has spectral properties in general accord with **9** but not with structure **10**, the alcohol derived from **8**. In particular the nmr spectrum of **9** shows the methine proton on the hydroxyl-bearing carbon as a doublet at τ 5.99 with the large coupling constant of 9.5 cps. The isopropyl group appears as a pair of doublets spaced by 0.25 ppm because of its proximity to the neighboring asymmetric center which renders the two methyls magnetically nonequivalent.[8] It is interesting to note that, while **9** displays abnormally strong end absorption in the ultraviolet, a maximum is not apparent. This is consistent with severe steric distortion of the chromophoric system from planarity. Similar observations have been reported for other highly substituted 1,3-dienes.[9]



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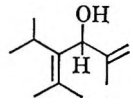


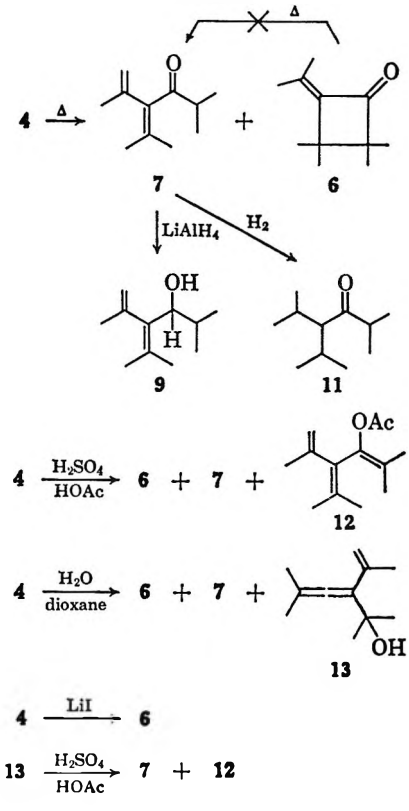
10

Catalytic hydrogenation of **7** produced the saturated ketone **11**. The nmr spectrum of this material shows complicated absorption for four protons in the methine region, a doublet centered at τ 8.99 for the methyls of the isopropyl group adjacent to the carbonyl, and two sets of doublets at τ 9.08 and 9.18 attributable to the magnetically nonequivalent[8] methyls of the two identical isopropyl groupings. A spectrum using benzene as solvent substantiated this interpretation since all six methyl signals were resolved under these conditions.

A control experiment established that **6** was not converted into **7** under the pyrolysis conditions. However, there was a marked dependence of the **6**–**7** product ratio ranging from 80:20 to 99:1 in various pyrolytic runs. When epoxide **4** was passed over Florisil at 200° in the pyrolysis unit, a 50% yield of **7** was obtained along with 5% of **6** and several other unidentified minor products.

Acid-catalyzed reactions in solution were also performed on **4** (Scheme I). Exposure to the protic medium provided by a sulfuric acid–acetic acid mixture produced **7** as the major material (76%) in the resulting mixture, the cyclobutanone **6** (12%), and a new compound (9%), identified as the enol acetate **12** on the basis of its spectral properties. Compound **12** shows strong bands in the infrared region at 5.70, 6.15, 8.3, and 11.1 μ while its nmr spectrum displays five separate methyls on olefin carbon atoms, an acetate methyl, and a disubstituted terminal methylene absorption. The enol acetate structure was confirmed by hydrolysis to ketone **7**. Cyclobutanone **6** was shown not to be converted into its acyclic isomer **7** in the sulfuric acid–acetic acid mixture.

SCHEME I



A very interesting and informative transformation occurred when **4** was exposed to the weakly protic medium provided by a 3% solution of water in dioxane for 24 hr at reflux temperature. This reaction was found to give 49% of **6**, 16% of **7**, and 35% of a new crystalline compound which is assigned structure **13**. The infrared spectrum of this material shows hydroxyl

(6) A recent review of the thermolysis of small-ring compounds is found in H. M. Frey, *Advan. Phys. Org. Chem.*, **4**, 147 (1966).

(7) Other 2-isopropylidenecyclobutanones show very similar spectral properties: see, for example, J. Conia and J. Sandrie, *Bull. Soc. Chim. France*, 744 (1963); G. B. Payne, *J. Org. Chem.*, **31**, 718 (1966); J. Gore, C. Djerassi, and J. Conia, *Bull. Soc. Chim. Fr.*, 950 (1967).

(8) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1962, p 75.

(9) W. F. Forbes, R. Shilton, and A. Balasubramanian, *J. Org. Chem.*, **29**, 3527 (1964); R. Criegee, U. Zirngibl, H. Furrer, D. Seebach, and G. Freund, *Chem. Ber.*, **97**, 2942 (1964).

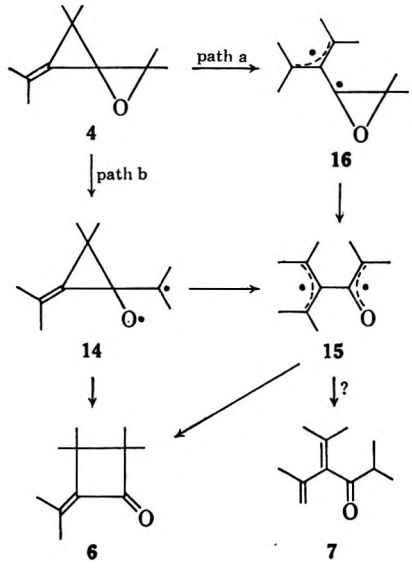
absorption, the terminal methylene bands, and a weak, but clearly perceptible allene peak at 5.15 μ. The ultraviolet spectrum (λ_{max}^{EtOH} 222 mμ, ϵ 13,600) is in reasonable accord with other examples of vinyl allenes.[10] The nmr spectrum has sharp singlets at τ 8.66 and 8.28 appropriate for methyls on a hydroxyl-bearing carbon and an olefinic center, respectively, an additional methyl on a double bond at 8.22 coupled weakly to the individual terminal methylene proton absorptions at 5.06 and 4.72, and a hydroxyl proton at 7.7. Finally, the mass spectrum displays a molecular-ion peak at *m/e* 166.

Hydrogenation of **13** in acidic methanol solution gave ketone **11** as the major product. This curious result is probably accountable by sequential acid-catalyzed rearrangement to the unsaturated ketone **7** and straightforward hydrogenation of the latter. In any event, subjecting **13** to sulfuric acid–acetic acid treatment gave ketone **7** as the only major product along with a small amount of enol acetate **12**.

Finally the effect of Lewis acids on **4** under aprotic conditions is typified by the reaction with anhydrous lithium iodide which yielded the cyclobutanone **6** as the major product. Ketone **7** was not among the trace amounts of other products formed.

Discussion.—The gas phase thermolysis of **4** to **6** is best described in terms of a homolytic bond-cleavage mechanism. Scheme II illustrates two pathways which

SCHEME II



adequately rationalize the observed conversion. Route a is initiated by bond breakage in the cyclopropane moiety whereas path b involves C–O homolysis of the epoxide ring. The initially formed diradical **14** in the latter sequence can conceivably rearrange directly to **6** in a concerted fashion or it might proceed *via* intermediate **15**. Comparison of the expected stabilities of **14** and **16**, however, strongly suggests that pathway a is the operative route to **6**. This conclusion is derived mainly from consideration of the relief of strain in the alternate bond-breaking steps. While a quantitative assessment of strain energies cannot be made for the complex system under discussion, qualitative considerations lead to the conclusion that reaction through the transition state leading to **16** should be preferred by a substantial margin. A crude estimate of the difference between the two modes of reaction can be obtained by comparison of the strain energies of ethylene oxide (13 kcal/mol)[11] and cyclopropane (27 kcal/mol).[12] The large differential between these values practically ensures a lower activation energy for the production of **16**, particularly since correction for other effects tends to increase the difference in energy between **14** and **16**. Thus, the extra strain imposed by the exocyclic methylene group[13] and the possibility of stabilizing resonance interaction of the developing radical centers of the transition state with the double bond[13,14] and the nonbonding orbitals on oxygen also favor **16**. The remaining details of path a are relatively straightforward. Rearrangement of the epoxy radical moiety of **16** to the α-keto radical **15** is in agreement with what is known about species of this nature.[15] Radical coupling of the latter interesting intermediate gives cyclobutanone **6** directly.

Unfortunately, the carbocyclic analog of **4** is not known, preventing a comparison of the two systems. Nonetheless a parallel transformation would be predicted for this species. The resemblance of the rearrangement of **4** to the thermal conversion of spiropentane into methylenecyclobutane is probably only a formal one since the latter reaction appears to be initiated by peripheral C–C bond cleavage[16] as opposed to the radial bond cleavage in **4**.

It should be noted that **15** can also serve as a reasonable precursor for the production of **7** by way of an intramolecular 1,5-hydrogen migration. However, the apparent capriciousness of the **6**/**7** ratio in the pyrolysis of **4** and the predominance of **7** in the reaction over Florisil lead to the *tentative* conclusion that **7** arises by a *heterolytic* process catalyzed by active surface sites in the pyrolysis chamber. Circumstantial evidence supporting this notion is found in the resistance of **6** to thermal conversion into **7**.

In contrast to the preferred explanation for the thermolysis of **4**, its transformations promoted by acids in solution are believed to be initiated by C–O bond breaking. The rearrangement of **4** to **6** is the only important reaction observed with lithium iodide in ether. In nucleophilic, protonic solvents, this is still a major process. The conversion is depicted in Scheme III as involving coordination of the electrophilic catalyst (H^+ or Li^+) with the oxygen atom, followed by bond heterolysis and preferential pinacolic migration of an allylic carbon atom. It is possible that bond breaking and bond making at the cationic center are concerted, but the migrating group is poorly situated for backside displacement in the ground-state geometry and the large distortion necessary to achieve the transition-state conformation would appear to argue against a one-step mechanism. Cation **17** could also yield the acyclic ketone **7** by transformation

(10) See, for example, E. R. H. Jones, H. H. Lee, and M. C. Whiting, *J. Chem. Soc.*, 341 (1960); F. T. Bond, *J. Org. Chem.*, **31**, 3057 (1966).

(11) R. A. Nelson and R. S. Jessup, *J. Res. Natl. Bur. Std.*, **48**, 206 (1952).

(12) R. B. Turner, P. Goebel, W. E. Doering, and J. F. Coburn, Jr., *Tetrahedron Lett.*, 997 (1965).

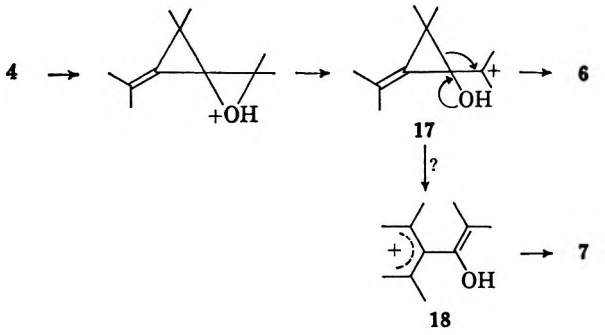
(13) J. P. Chesick, *J. Amer. Chem. Soc.*, **85**, 2720 (1963).

(14) W. E. Doering and J. C. Gilbert, *Tetrahedron Suppl.*, **7**, 397 (1966).

(15) T. J. Wallace and R. H. Gritter, *Tetrahedron*, **19**, 657 (1963).

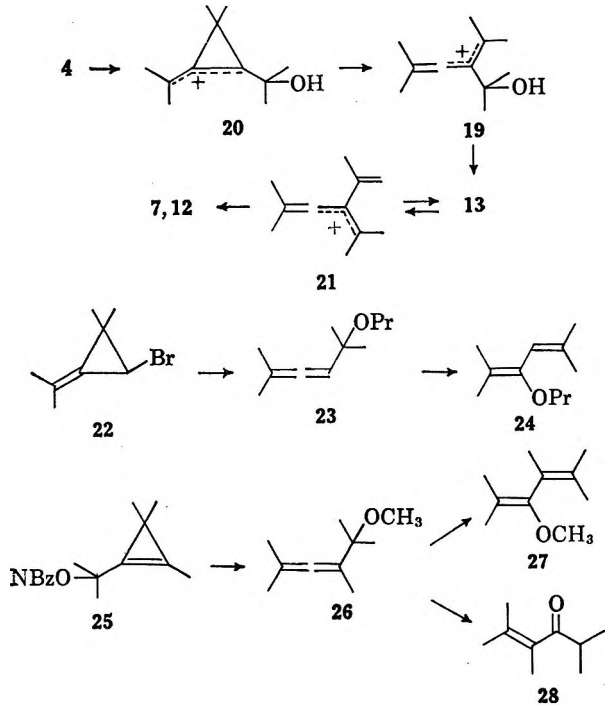
(16) A stimulating discussion of this point is included in ref 14.

SCHEME III



to **18** by a cyclopropylcarbinyl-type rearrangement[17] and subsequent deprotonation and tautomerization. The formation of enol acetate **12** is not particularly in accord with this mechanistic description, nor is the fact that acyclic ketone is not found in the lithium iodide experiment. This latter observation is somewhat difficult to reconcile with a common intermediate for **6** and **7**, since the cyclobutanone is found in all of the acid-catalyzed rearrangements, whereas **7** is observed only in the protonic solvent systems. In fact, the isolation of allene alcohol **13** from mild solvolysis conditions and demonstration that this material is converted into ketone **7** and enol acetate **12** in the sulfuric acid–acetic acid mixture provides strong positive evidence for a different mechanism. Thus, compound **13** is envisaged as arising from the alternate ring-opening possibility of protonated epoxide **4** which gives cation **19**, either directly or by way of **20** (*vide infra*), as shown in Scheme IV. Loss of a proton from

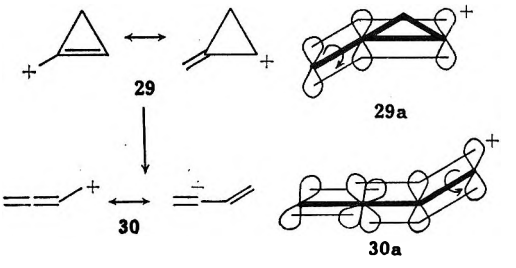
SCHEME IV



19 yields **13**. Reversible acid-catalyzed ionization of the hydroxy group of **13** then gives a related allenyl carbonium ion **21**, which serves as a precursor for **7** and **12**.

Supporting evidence for this interpretation can be gleaned from related work. Meinwald and coworkers[18] report that treating **22** with silver propionate gave allene **23** which rearranged further on attempted silicic acid chromatography to enol ester **24**. Closs and Böll[19] found that methanolysis of *p*-nitrobenzoate **25** produced the allene derivative **26** which was converted into enol ether **27** by acid and yielded ketone **28** upon hydrolysis. Thus, these two systems, which might reasonably be expected to generate an intermediate similar to **20**, show a striking behavioral parallel. Generation of allene products from the solvolysis of derivatives corresponding to the two resonance contributors of generalized cation **29** suggests (but, of course, does not require) the intermediacy of such a reactive species. The atomic orbital representation **29a** aids in visualizing the transformation to the allenyl carbonium ion **30**. This change can be pictured as involving a 90° rotation about the exocyclic C–C bond which necessarily attenuates the allylic conjugation indicated in **29**, but thereby allows overlap of the p orbital on the exocyclic carbon atom with the σ bond of the cyclopropyl ring. Electronic reorganization at this point generates the allene moiety of **30**. If this explanation is correct, it is notable that allene products are preferred kinetically from **30** although the enol derivatives appear to be more stable.

While the intervention of the common ion **29** provides the most economical explanation for the apparent similarity of the 1-cyclopropenylcarbinyl and 2-methylenecyclopropyl systems, there is no direct evidence (such as the isolation of skeletally intact products) which demands this intermediate. Consequently other mechanisms for the formation of **13** and its further reaction products deserve consideration. One of these is a single-step transformation of protonated **4** to cation **19**. An analogous mechanism is thought to obtain for the solvolysis of most cyclopropyl derivatives, which apparently give allyl cations as first intermediates.[20] Closs[19] has recommended con-



sideration of a bimolecular nucleophilic mechanism for the **25** to **26** conversion, but in the aqueous dioxane rearrangement of **4** the allene product **13** has lost a proton rather than combined with a nucleophile. In addition, nucleophilic attack at the heavily substituted tetrahedral carbons of **4**, **22**, and **25** is subject to question. Thus, although other rationalizations

(17) See (a) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 4390 (1959); (b) R. Breslow in "Molecular Rearrangements," Part 1, P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 259–280.

(18) J. Meinwald, J. W. Wheeler, A. A. Nimetz, and J. S. Liu, *J. Org. Chem.*, **30**, 1038 (1965).

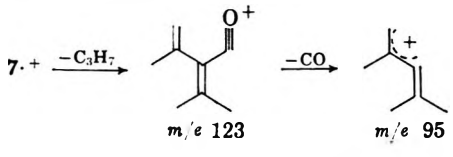
(19) Unpublished results cited in G. L. Closs, *Advan. Alicyclic Chem.*, **1**, 98 (1966).

(20) For a leading reference, see P. R. Schleyer, G. W. Van Dine, U. Schöllkopf, and J. Paust, *J. Amer. Chem. Soc.*, **88**, 2868 (1966).

are possible, the straightforward nature of the explanation utilizing intermediate **20** makes it more attractive at present. Direct evidence bearing on this point would, of course, be desirable.

Mass Spectra.—The mass spectral fragmentation of several of the key compounds obtained in this study deserve comment as examples of highly substituted molecules with a high concentration of functionality. In addition, the strained-ring compounds are of interest in determining whether correlations can be made between mass spectral and chemical behavior of such molecules.[21,22]

The mass spectrum of acyclic ketone **7** is relatively simple. In addition to a strong molecular ion, a small M − CH_3 peak, and the expected low-mass hydrocarbon fragments, there are only two important ions. The strong peaks at *m/e* 123 (M − C_3H_7) and 95 (M − C_3H_7CO) correspond to α cleavage at either side of the carbonyl group, but with the positive charge residing on the hydrocarbon fragment in the second case. Although direct fragmentation may lead to a portion of the *m/e* 95 ion, the observation of a metastable ion at *m/e* 73.5 demonstrates that at least some of *m/e* 95 arises by loss of carbon monoxide from the M − C_3H_7 ion. α cleavage of the unsaturated alkyl moiety (*m/e* 71) with retention of charge on the oxygen fragment amounts to 3% of the base peak at most.



An even simpler spectrum characterizes the saturated acyclic ketone **11**. Loss of the small isopropyl substituent by α cleavage gives an *m/e* 127 fragment (11%). Elimination of carbon monoxide from this ion yields an *m/e* 99 peak (19%) as substantiated by a metastable ion at *m/e* 77.3. The alternative α cleavage leads to a maximum of 6% abundance of an ion at *m/e* 71 (a portion of this peak may be derived from hydrocarbon fragments). The base peak appears at *m/e* 57 and is apparently a hydrocarbon fragment probably derived from loss of the neutral molecule propylene from the *m/e* 99 daughter ion. Perhaps the most suprising aspect of the mass spectrum of **11** is the almost complete absence of the expected fragment from a McLafferty rearrangement.[23] The 2% ion at *m/e* 128 is mainly attributable to isotopic contributions of the *m/e* 127 ion. Although there are six identical hydrogens appropriately situated for a McLafferty decomposition, apparently the rather severe nonbonded interactions present in **11** either retard this process by disfavoring the required conformations[24] or speed up

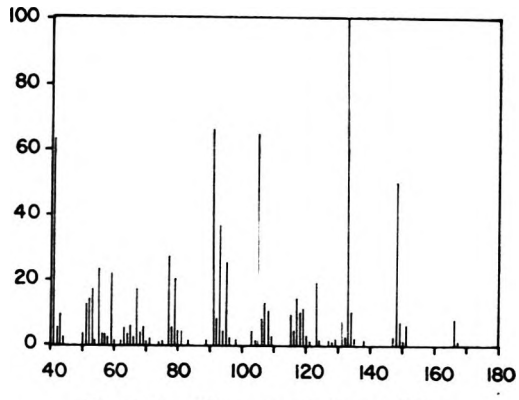
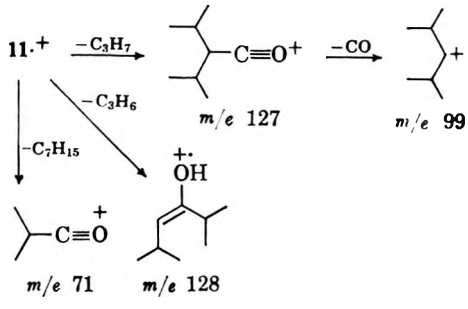
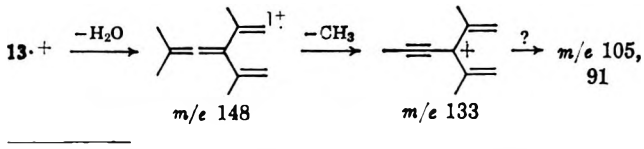


Figure 1.—The mass spectrum of **13**.

the relative rate of competing α fragmentation. A subsequent efficient decomposition of the McLafferty ion could account for its absence,[25] although such a process leading to important ions in the spectrum is difficult to rationalize.[26,27] Further information on the effects of steric hindrance on the McLafferty rearrangement would be useful in understanding the fragmentation of **11**.



The mass spectrum of allene alcohol **13** possesses some interesting features. Examination of Figure 1 reveals that the ion distribution is heavily weighted toward the higher mass fragments indicative that highly stabilized ions are being formed. The *m/e* 148 ion (50%) is a result of the expected loss of water. Elimination of a methyl radical from this species gives the base peak at *m/e* 133 (metastable at *m/e* 119.6). A possible interpretation of this process is illustrated below. The virtue of the indicated fragmentation is the production of an especially stable carbonium ion. This ion may well undergo substantial structural reorganization before further decomposition. Thus, the abundant fragments at *m/e* 105 and 91 are thought to derive from the *m/e* 133 ion by the loss of ethylene and propylene, respectively, perhaps in a process akin to the decomposition of aromatic molecules. In any event, the spectrum of **13** is both unusual and highly characteristic.



(21) Numerous workers have attempted to correlate photochemical reactions with mass spectral fragmentation: N. J. Turro, D. S. Weiss, W. F. Haddon, and F. W. McLafferty, *J. Amer. Chem. Soc.*, **89**, 3370 (1967); N. J. Turro, D. C. Neckers, P. A. Leermakers, D. Seldner, and P. D'Angelo, *ibid.*, **87**, 4097 (1964); A. L. Burlingame, C. Fenselau, W. J. Richter, W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *ibid.*, **89**, 3346 (1967); M. M. Bursey, L. R. Dusold, and A. Padwa, *ibid.*, 2649 (1967); F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

(22) P. Brown, J. Kossanyi, and C. Djerassi, *Tetrahedron Suppl.*, **8**, 241 (1966).

(23) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, pp 123–131.

(24) A documented summary of factors which are known to affect the McLafferty rearrangement is included in C. Djerassi and L. Tökés, *J. Amer. Chem. Soc.*, **88**, 536 (1967).

(25) For example, diisobutyl ketone (API mass spectrum 832) shows only a small peak (2%) corresponding to the loss of a molecule of propene, but an additional fragment (33%) at M − 84 indicates that the initial ion undergoes a second McLafferty rearrangement.

(26) Tautomerization of the McLafferty fragment followed by further decomposition might be considered, but recent evidence indicates that tautomeric processes are not in general important in mass spectrometry.[27]

(27) J. K. MacLeod, J. B. Thomson, and C. Djerassi, *Tetrahedron*, **23**, 2095 (1967).

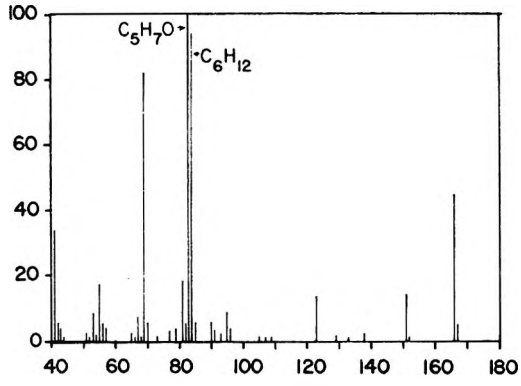


Figure 2.—The mass spectrum of 6.

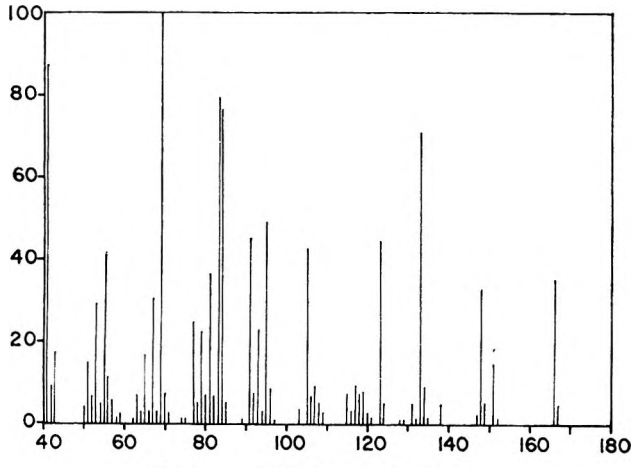
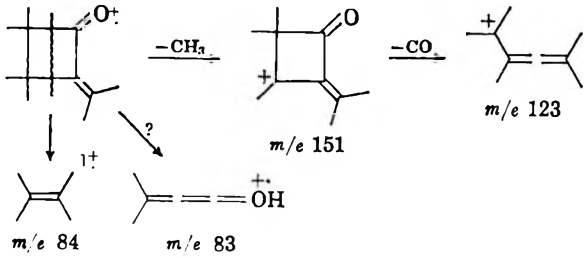


Figure 3.—The mass spectrum of 4.

Figure 2 displays the mass spectrum of cyclobutanone **6**. A molecular ion and an M − CH_3 peak are readily apparent. The fragment at *m/e* 123 probably arises by sequential loss of a methyl radical and carbon monoxide (or *vice versa*) from the molecular ion, perhaps as indicated to give an allenyl carbonium ion. The presence of an intense even-electron fragment at *m/e* 84 is striking. A metastable peak at 56.7 indicates that this ion decomposes further to *m/e* 69. Examination of the *m/e* 84 peak by high-resolution mass spectrometry indicated the constitution C_6H_{12} (*m/e* 84.0933) for the major contributor (93%) to this peak. This species is apparently the tetramethylethylene radical cation formed by fission of the cyclobutane ring in the manner observed for simple cyclobutanones.[28] Little of the ion in which the charge remains on the other fragment (*m/e* 82) is observed. Fragmentation in the alternate manner to give dimethylketene and tetramethylallene fragments is also not important. The *m/e* 83 base peak was also examined by high-resolution techniques and 97% of this peak

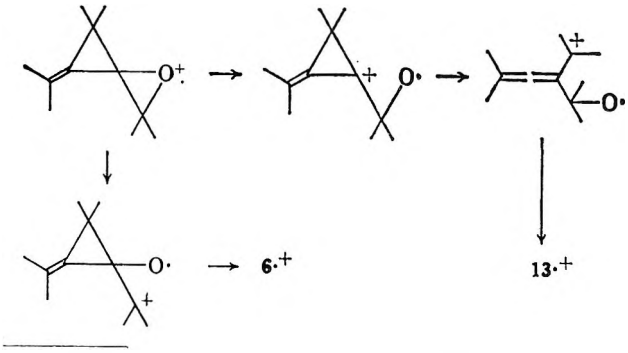


(28) H. Audier, J. M. Conia, M. Fétizon, and J. Goré, *Bull. Chim. Soc. Fr.*, 787 (1967).

was found to possess the empirical formula C_5H_7O (*m/e* = 83.0492). This amounts to the oxygen-containing moiety of the indicated ring fission *plus* a hydrogen atom, possibly to yield the indicated radical cation.

The spectrum of epoxide **4** (Figure 3) is rich in detail, possessing all of the peaks of both **6** and **13**. In fact, a reasonable facsimile of this spectrum can be generated by simply combining the spectra of **6** and **13** in an 8:7 ratio. While the synthetic spectrum thus produced is not an exact fit, the resemblance is nonetheless striking. Most of the peaks are of almost identical intensity with those of the experimental spectrum; there are no negative derivations that amount to as much as 10% of the base peak and positive variances appreciably larger than this are found only at *m/e* 69 and 95.

The significance of this comparison is by no means clear, but it is tempting to try to correlate the mass spectral behavior of **4** with its more normal chemistry. Thus, our tentative suggestion is that the molecular ion of the epoxide is undergoing rearrangement to the molecular ions of **6** and **13** and these isomeric species give rise to the observed spectrum. A relationship between pyrolytic behavior[29] and mass spectral fragmentation was originally sought, but the indication of *both* **6** and **13** tends to favor correlation with the acid-catalyzed chemistry. Similar explanations have been advanced previously to account for anomalous features of mass spectral fragmentations observed in other studies of epoxides.[22,30] One can argue that the epoxide molecular ion (indicated below with the charge localized on oxygen for convenience) is a reasonable model for a protonated epoxide and that mass spectral decomposition might parallel its solution chemistry. The suggested rearrangements indicated below are thus analogous to the carbonium-ion reactions of **4** discussed previously. (It should be noted, however, that the proposed production of the molecular ion of **13** does not have a complete parallel in the solution conversion of **4** into **13**, since an intramolecular hydrogen transfer is required. However, this structurally favorable process is viewed as occurring subsequent to the cationic skeletal rearrangement.) Further detailed study will be necessary to ascertain whether the notion of parallel mass spectral and solution carbonium-ion rearrangements of epoxides has any real merit and can be utilized in a predictive or correlative fashion.



(29) The inlet and source temperatures of the spectrometer were maintained such that thermal isomerization of **4** should not be important.

(30) S. Sasaki, Y. Itagaki, H. Moriyama, N. Nakanishi, E. Watanabe, and T. Aoyama, *Tetrahedron Lett.*, 623 (1966); Y. Ita gaki, T. Kurokawa, H. Moriyama, S. Sasaki, and Y. Watanabe, *Chem. Ind.* (London), 1654 (1965).

Experimental Section

General.—Infrared spectra were obtained with Perkin-Elmer Model 137 and 137G Infracord spectrophotometers. Unless otherwise specified these were taken in carbon tetrachloride solution. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian Associates A-60 spectrometer in carbon tetrachloride solution. Chemical-shift data are given as τ values. Mass spectra were obtained with an AEI MS-9 mass spectrometer at 70 eV. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Gas chromatography (glpc) was performed on Aerograph Model 600, Model 1200 (analytical, hydrogen flame detector), and A700 (preparative) chromatographs. The analytical column was 5 ft × 1/8 in. of 15% Carbowax 20M on 60/80 Chromosorb W; preparative columns were 10 ft × 3/8 in. of either 30% FFAP or 15% Carbowax 20M on 60/80 Chromosorb W. Percentage composition data were estimated by peak areas (uncorrected). Melting points were determined in sealed capillary tubes. Anhydrous magnesium sulfate was used for all drying operations. Microanalyses were performed by Midwest Microlabs, Inc.

1-(2-Methylpropenylidene)-2,2,3,3-tetramethylcyclopropane (3). A.—A mixture of 30 g of tetramethylethylene and 10 g of potassium *t*-butoxide was stirred under a nitrogen atmosphere for 10 min, after which 11.7 g of freshly distilled 1-bromo-3-methyl-1,2-butadiene was added over a 30-min period. The mixture was stirred at room temperature for 3 hr and 100 ml of pentane was added. The reaction mixture was suction filtered through a sintered-glass Buchner funnel containing Hyflow–Supercel filter aid. The pentane was distilled from the reaction mixture and the residue was eluted with hexane through a short column of Florisil. Removal of the hexane by flash evaporation gave 7.0 g (60%) of **3**. A recrystallized sample had mp 48–48.5° (lit.[2] mp 48.6–49.3°).

B.—Using the procedure of Hartzler,[2] yields of **3** on the order of 25–30% were obtained.

1,2-Bis(isopropylidene)-3,3-dimethylcyclopropane (2).—A 137-mg sample of **3** was pyrolyzed at 360° and 0.25 mm. The pyrolysis was carried out on a vacuum pyrolysis system consisting of a glass-helices packed Pyrex column, 10 mm × 130 mm, passing through an E. H. Sargent and Co. tube furnace. The sample was placed in a 5-ml flask attached at one end of the tube and a Dry Ice trap, 20 mm × 150 mm, was attached to the other end of the tube. Vacuum was applied at the trap and the pyrolysis product collected in the trap. The pyrolysis gave 131 mg (96%) of 1,2-bis(isopropylidene)-3,3-dimethylcyclopropane (**2**). The spectral properties of this product agree in detail with those reported by Bleiholder and Shechter.[31]

2,2,5,5-Tetramethyl-4-isopropylidene-1-oxaspiro[2.2]pentane (4).—To an ice-cold, mechanically stirred mixture of 2.01 g of **2** and 4.24 g of powdered, anhydrous sodium carbonate in 250 ml of methylene chloride was added dropwise 2.55 g of 40% peracetic acid which had been pretreated with a small amount of anhydrous sodium acetate. The mixture was stirred until the methylene chloride solution gave a negative starch–iodide test. The solid salts were removed by suction filtration and washed well with additional solvent. The solvent was removed from the filtrate by flash evaporation to give 2.13 g (96%) of product. Glpc analysis of the crude product showed 92% of **4** and 8% of **5**. Compound **4** has infrared bands at 5.65 (methylenecyclopropane),[32] 10.9 and 11.4 μ (epoxide). The nmr spectrum consists of equivalent sharp singlets at τ 8.86, 8.85, 8.62, 8.55, 8.26, and 8.21. Only end absorption was observed in the ultraviolet region (ϵ_{210} 13,000).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.62; H, 10.87.

Acid-Catalyzed Rearrangement of 4.—To a 200-mg sample of **4** dissolved in 75 ml of glacial acetic acid was added 30 drops of concentrated sulfuric acid and the mixture was stirred for 4 hr, poured into 200 ml of water, and extracted with six 25-ml portions of pentane. The pentane extracts were washed with two 25-ml portions of saturated sodium bicarbonate solution and dried. The solvent was removed by flash evaporation and the three products were isolated by preparative glpc as 76, 13, and 9% of the crude mixture.

The major material was 2,5-dimethyl-4-isopropylidenehex-5-en-3-one (**7**). The infrared spectrum of **7** displays bands at 3.22, 5.93, 6.15, and 11.1 μ. The nmr spectrum shows a six-proton doublet (J = 6.5 cps) at τ 9.00 ($CH(CH_3)_2$), a broad multiplet accounting for nine protons at 8.2 ($C{=}CCH_3$), a one-proton septet (J = 6.5 cps) centered at 7.24 ($CH(CH_3)_2$), and one-proton multiplets at 5.18 and 4.88 ($C{=}CH_2$). The ultraviolet spectrum (hexane) shows λ_{max} 239 mμ (ϵ 2000) and 211 (3600). The mass spectrum of **7** displays significant fragments at the following m/e values (percentage of the base peak given in parentheses): 166 (39), 151 (3), 123 (92), 95 (100), 71 (3), 67 (27), 55 (20), 43 (21), 41 (21).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.60; H, 10.93.

The second product is assigned as 2-isopropylidene-3,3,4,4-tetramethylcyclobutanone (**6**). This compound shows infrared bands at 5.78 and 6.01 μ. The nmr spectrum displays six-proton singlets at τ 9.01 and 8.79 ($C(CH_3)_2$) and three-proton singlets at 8.29 and 8.04 ($C{=}CCH_3$). The ultraviolet spectrum (hexane) shows λ_{max} 244 mμ (ϵ 7750).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.55; H, 10.98.

The third product is enol acetate **12**. The infrared spectrum shows peaks at 3.27, 5.70, 6.15, 8.3, and 11.1 μ. The nmr spectrum displays a six-proton singlet at τ 8.42 and a broad nine-proton band at 8.3 ($C{=}CCH_3$), a three-proton singlet at 8.04 (OAc), and one-proton multiplets at 5.40 and 5.09 ($C{=}CH_2$).

A small sample of enol acetate **12** was heated to 70° with 15 ml of glacial acetic acid, 5 ml of water, and 30 drops of concentrated sulfuric acid for 4 hr: the mixture was poured into water and extracted with several portions of pentane. After the combined extracts were dried, the solvent was removed to give a crude product containing **7** as the major component as established by glpc isolation and comparison with authentic material.

Control experiments with **6** and **7** demonstrated that these materials were not changed by the reaction conditions.

Reduction of 7.—A solution of 53 mg of ketone **7** in 10 ml of anhydrous ether was added to a stirred slurry of 50 mg of lithium aluminum hydride in 50 ml of ether. The reaction mixture was stirred for 30 min, 8 drops of water was added, and the mixture was stirred for 1 hr. The resulting mixture was suction filtered to remove the inorganic salts and the filtrate was dried. After removal of the solvent, a single product was isolated in almost quantitative yield. Alcohol **9** shows bands in its infrared spectrum at 2.86, 3.21, 6.04, 6.14, 9.88, and 11.2 μ. The nmr spectrum shows two three-proton doublets (J = 6.5 cps) centered at τ 9.25 and 9.00 (nonequivalent methyls of the isopropyl group), a broad six-proton signal at 8.31 and a broad three-proton signal at 8.16 ($C{=}CCH_3$), a one-proton peak at 7.8 (OH), a one-proton doublet (J = 9.5 cps) at 5.99 ($CHOH$), and one-proton multiplets at 5.44 and 4.99 ($C{=}CH_2$). The isopropyl hydrogen is obscured by the olefinic methyl resonances. The ultraviolet spectrum (hexane) shows no maximum, but strong end absorption is apparent: ϵ_{240} 275; ϵ_{220} 3590.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.65; H, 11.76.

Catalytic Hydrogenation of 7.—A solution of 100 mg of **7** in 25 ml of methanol was hydrogenated at atmospheric pressure using 30% palladium on charcoal as catalyst. After the uptake of 2 moles of hydrogen, the resulting mixture was filtered to remove the catalyst, the filtrate was poured into 100 ml of water, and extracted several times with 25-ml portions of pentane. The pentane extracts were combined and dried. After removal of the solvent, a single product was isolated in almost quantitative yield. Ketone **11** shows infrared bands at 5.85, 8.55, and 9.70 μ. The nmr spectrum displays a six-proton doublet (J = 6.5 cps) centered at τ 9.18, a six-proton doublet (J = 6.5 cps) centered at 9.06, a six-proton doublet (J = 6.9 cps) centered at 8.99, and a four-proton multiplet from 7.2 to 8.4. The nmr spectrum in benzene shows a six-proton doublet (J = 6.5 cps) centered at τ 9.18, a six-proton doublet (J = 6.5 cps) centered at 9.13, a six-proton doublet (J = 6.9 cps) centered at 9.02, and a four-proton multiplet from 7.3 to 8.2. The mass spectrum of **11** displays significant fragments at m/e (% base peak): 170 (3), 128 (2), 127 (11), 99 (20), 71 (7), 57 (100), 43 (41), 41 (12).

Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.77; H, 12.89.

Rearrangement of 4 in 3% Water–Dioxane.—A solution of 1.91 g of **4** in 100 ml of dioxane containing 3% water was refluxed for 24 hr and the resulting solution dried. Glpc analysis showed

(31) R. F. Bleiholder and H. Schechter, *J. Amer. Chem. Soc.*, **86**, 5032 (1964).

(32) W. Rahman and H. G. Kuivila, *J. Org. Chem.*, **31**, 772 (1966).

the formation of three products as 16, 49, and 35% of volatile reaction product. The products were isolated by preparative glpc.

The first product was identified as ketone **7** and the second product as ketone 6. The third component was a new compound whose structure is assigned as 2,5-dimethyl-4-isopropenyl-2,3-hexadien-5-ol (**13**), mp 35–36°. This material shows infrared absorption at 2.8, 5.15 (weak), 6.20, and 11.1 μ. The nmr spectrum displays a six-proton singlet at τ 8.66 ($C(CH_3)_2OH$), a six-proton singlet at 8.28 ($C{=}C{=}C(CH_3)_2$), a broad three-proton singlet at 8.22 ($C{=}CCH_3$), a one-proton signal at 7.7 (OH), and two one-proton multiplets at 5.05 and 4.72 ($C{=}CH_2$). The ultraviolet spectrum exhibits λ_{max}^{EtOH} 222 mμ (ϵ 13,600) and λ_{max}^{hexane} 218 mμ (ϵ 9000). The mass spectrum of **13** shows a parent ion at 166.1355 (calcd for $C_{11}H_{18}O$: 166.1358).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.35; H, 10.87.

Acid-Catalyzed Rearrangement of 13.—A small sample of allene **13** was stirred with 15 ml of glacial acetic acid containing 10 drops of concentrated sulfuric acid for 4 hr and the mixture was poured into water and extracted with several portions of pentane. After the combined extracts were dried, the solvent was removed to give a crude product containing **7** as the major component along with a small amount of enol acetate **12** as established by glpc isolation and comparison with authentic samples.

Rearrangement of 4 by Lithium Iodide.—A mixture of 26 mg of **4** and 0.5 g of anhydrous lithium iodide was heated to reflux in 30 ml of anhydrous ether for 56 hr. Glpc analysis indicated the formation of one major product (80%) which was collected by glpc and identified as ketone 6.

Pyrolysis of 4.—A 102-mg sample of **4** was pyrolyzed in the flow system at 400° and 0.25 mm. This gave an 80% yield of two products in an 80:20 ratio. Isolation by glpc and comparison with authentic samples demonstrated that these materials were ketones 6 and **7**, respectively. In other runs the amount of **7** in the mixture varied from a trace to 20%.

Pyrolysis of 4 over Florisil.—A sample of epoxide **4** was pyrolyzed over Florisil (which had been dried at 200° and 0.25 mm for 4 hr) at 200° in the flow system at 0.25 mm. Glpc analysis indicated formation of 50% of **7** and 5% of 6 which were collected by preparative glpc and compared with authentic samples.

Hydrogenation of 13 in Acidic Methanol.—A 100-mg sample of **13** was dissolved in 10 ml of reagent grade methanol to which 10 drops of concentrated sulfuric acid had been added. This solution was hydrogenated at atmospheric pressure using 30% palladium on charcoal as catalyst. After the uptake of 2 mol of hydrogen, the resulting mixture was filtered to remove the catalyst, the filtrate was poured into 25 ml of water, and extracted several times with 25-ml portions of pentane. The pentane extracts were combined, washed with 25 ml of saturated sodium bicarbonate, and dried. After removal of the solvent by flash evaporation, the major product was isolated by preparative glpc and found to be ketone **11**.

Registry No.—**3**, 13303-30-5; **4**, 15448-69-8; **6**, 4868-12-6; **7**, 15448-71-2; **9**, 15448-72-3; **11**, 15448-73-4; **12**, 15448-74-5; **13**, 15448-75-6.

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Solvent Shifts of Proton Resonances Induced by Benzene and Pyridine in Epoxides and Ethers. An Aid to Structure Elucidation

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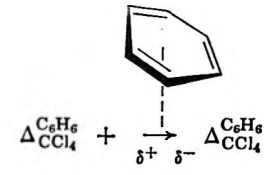
Received September 5, 1967

The solvent shifts of proton resonances induced by pyridine and benzene in some epoxides and ethers are reported. In the absence of severe steric effects or of effects due to additional functional groups, the benzene-induced shifts may be useful in differentiating an epoxide from a four-, five-, or six-membered cyclic ether. Different benzene-induced shifts are also observed for α- and β-methyl substituents in tetrahydrofuran derivatives. A preferred conformation for diisopropyl ether in which nonbonded interactions are minimal is also suggested by the solvent shifts. From a study of steric effects upon the shifts caused by the aromatic solvents in epoxyquinones, it is concluded that steric inhibition to the approach of bulk aromatic solvent to an epoxide proton flanked by a *t*-butyl group causes a deshielding contribution to the observed shift.

The solvent shifts of proton resonances induced by benzene relative to an "inert" solvent (solvent shift, $\Delta_{CCl_4}^{C_6H_6} = \delta_{CCl_4} - \delta_{C_6H_6}$ ppm) have proved to be of potential use in the elucidation of structural, stereochemical, and conformation problems; the empirical rules which have been deduced for ketones[1-6] may be cited as an example.

In general, it appears that benzene solvent molecules are transiently orientated by molecular or local solute dipoles, so that the benzene molecules solvate the positive end of the dipole while avoiding the negative end in a collision complex which may deviate from planarity due to steric factors (see the schematic representation **1**).[7]



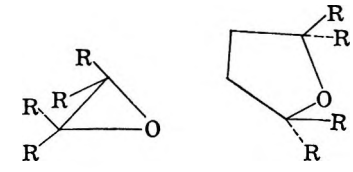
1

It appeared probable that useful correlations might be made for solvent shifts in epoxides and ethers and representative members of these classes have therefore been studied. In this paper the solvent shifts induced by both benzene ($\Delta_{CCl_4}^{C_6H_6}$) and pyridine ($\Delta_{CCl_4}^{C_5H_5N}$) are reported. The $\Delta_{CCl_4}^{C_6H_6}$ values are given first for the appropriate proton with each structure, followed by the

(1) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965).
(2) G. D. Connolly and R. McCrindle, *Chem. Ind.* (London), 379 (1965).
(3) P. Laszlo and D. H. Williams, *J. Amer. Chem. Soc.*, **88**, 2799 (1966).
(4) C. Timmons, *Chem. Comm.*, 576 (1965).
(5) J. Ronayne, M. V. Sargent, and D. H. Williams, *J. Amer. Chem. Soc.*, **88**, 5288 (1966).
(6) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 1651 (1965).
(7) J. Ronayne and D. H. Williams, *J. Chem. Soc., Sect. B*, 541 (1967).

corresponding $\Delta_{CCl_4}^{C_5H_5N}$ values in parentheses. All values refer to approximately 5% w/v solutions and normal probe temperature (37.5°). In those cases where the solvent shifts are approximate, the values could not be determined with the desired accuracy; *e.g.*, the resonances were very broad with poor signal to noise ratios.

Various types of cylic ethers (**2–10**) were studied and the values of $\Delta_{CCl_4}^{C_6H_6}$ seem to be quite useful in indicating both the ring size and location of alkyl substituents. Protons directly attached to the epoxide rings undergo a moderately large upfield shift (0.13–0.38 ppm) in benzene relative to carbon tetrachloride. This shift decreases with increasing ring size (compare **2, 6, 7, 10**). Such characteristic differences are to be anticipated since the α protons in a five- and six-membered cyclic ether lie nearer the negative end of the molecular dipole, *i.e.*, nearer the ether oxygen, than they do in trimethylene oxide which in turn has its α protons closer to the oxygen than those in ethylene oxide (contrast **11** and **12**, R = H). The type of association depicted in **1** will thus result in a relatively larger shielding of epoxide protons by benzene due to the anisotropy of the aromatic solvent and a gradual decrease in $\Delta_{CCl_4}^{C_6H_6}$ with increasing ring size.

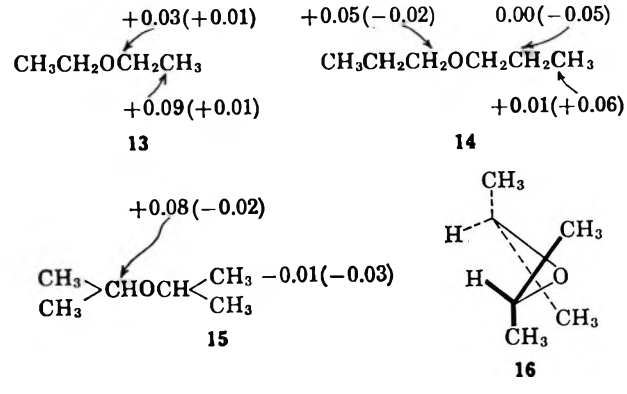


11 **12**

A similar generalization holds for α-alkyl substituents. The appropriate $\Delta_{CCl_4}^{C_6H_6}$ values for methylene or methyl protons directly attached to the epoxide rings in **3–5** are in the range +0.22 to +0.30 ppm, but in **8** the methyl resonance is shifted to slightly *lower* field in benzene. In the last case, the methyl group again lies nearer the negative end of the molecular dipole (contrast **11** and **12**, R = CH_3).

An additional consequence of the stereochemistry of association of benzene with five- and six-membered cyclic ethers is that, whereas α protons or α-alkyl substituents have small positive or negative $\Delta_{CCl_4}^{C_6H_6}$ values, β protons and β-alkyl substituents have larger positive values (see data for **7–10**). The differences in $\Delta_{CCl_4}^{C_6H_6}$ for α- and β-methyl groups are potentially the most useful since α and β protons are in any event differentiated by a large difference in chemical shift in any one solvent.

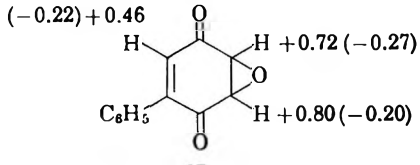
Three acyclic ethers (**13–15**) have also been examined. The most striking feature of these data is the small downfield shift of the methyl resonance of the diisopropyl ether (**15**) in benzene in contrast to the upfield shift of the α proton. In diisopropyl ether (**15**) the conformation (**16**) should be more highly populated than other possible conformations, because in **16** the nonbonded interactions are minimal. Hence the methyl groups would be expected on the average to spend more time near the negative end of the ether dipole (note the similarity between the positions and $\Delta_{CCl_4}^{C_6H_6}$ values of the methyl groups in 2,5-dimethyltetrahydrofuran (**6**) and **16**). The observed benzene solvent shifts support a preference for conformation **16** in diisopropyl ether.



13 **14** **15** **16**

(8) Quoted range of values covers shifts in both *cis* and *trans* isomers.
(9) Shifts the same within 0.01 ppm for both *cis* and *trans* isomers.

Solvent shifts induced by pyridine have also been correlated with structural features in some cases.[10-14] The $\Delta_{CCl_4}^{C_5H_5N}$ values are given in parentheses for the ethers discussed so far. The values for protons adjacent to the ether linkage (α position) are usually negative and if positive are very small ($\leq \pm 0.02$ ppm). Diagnostic differences for various ring sizes are not observed. However, the differences in $\Delta_{CCl_4}^{C_6H_6}$ and $\Delta_{CCl_4}^{C_5H_5N}$ values for α protons in the epoxides **3–5** are quite striking, the values being positive and negative, respectively. This trend (*vis.*, positive $\Delta_{CCl_4}^{C_6H_6}$ values *vs.* negative $\Delta_{CCl_4}^{C_5H_5N}$ values) for epoxide protons is greatly accentuated in some mono- and diepoxyquinones (**17–22** and **23–28**, respectively) which have been examined (the solvent shifts are summarized with the structural formulae as before).[15] The effect is strikingly illustrated, for example, by the occurrence of the epoxide proton resonances of **17** at lower field in pyridine by no less than 1 ppm relative to a benzene solution.



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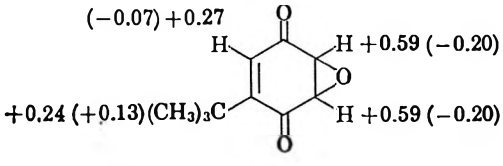

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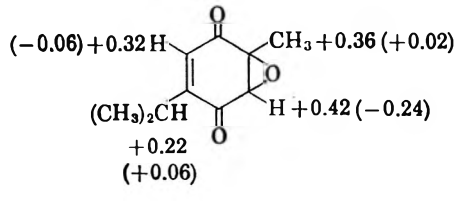

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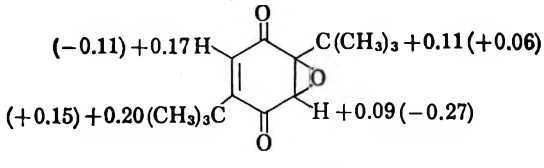

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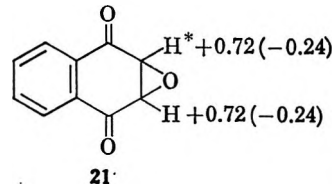

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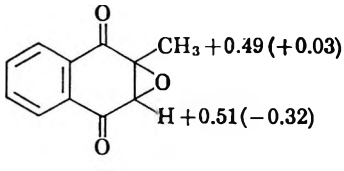

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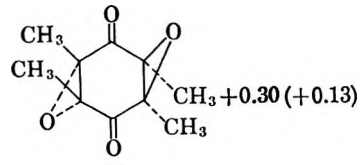

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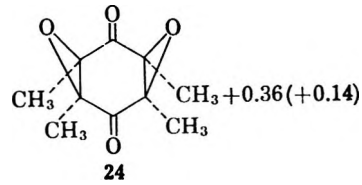

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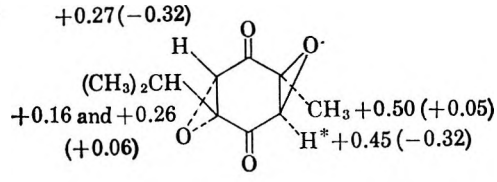

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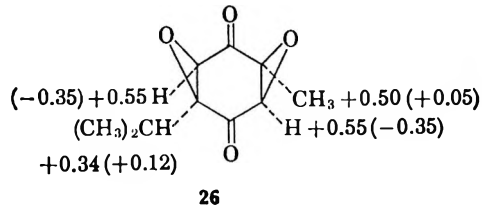

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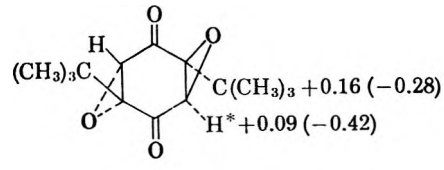

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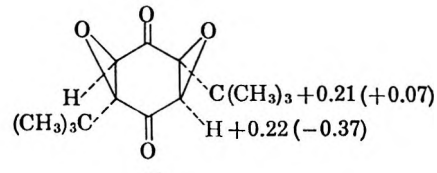


28

By the introduction onto the epoxide ring of substituents of moderate (methyl and isopropyl) and large (*t*-butyl) steric bulk, it has been possible to evaluate the effect of steric factors on the solvent shifts observed for epoxide protons. The relevant data are summarized in Table I for compounds of partial structure **29**.

The large upfield shifts of the epoxide protons in benzene solution when R is hydrogen are considerably reduced when R is methyl. A similar effect is seen on comparing the $\Delta_{CCl_4}^{C_6H_6}$ values for ethylene oxide (**2**), propylene epoxide (**3**), and 2-butene epoxide (**4**). A very large reduction in the upfield shift in benzene solution is observed when R is changed from hydrogen to a *t*-butyl group (Table I). These large changes in

(10) G. Slomp and F. Mackellar, *J. Amer. Chem. Soc.*, **82**, 999 (1960).
(11) R. M. Moriarty, *J. Org. Chem.*, **28**, 1296 (1963).
(12) F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).
(13) D. H. Williams, *Tetrahedron Lett.*, 2305 (1965).
(14) D. H. Williams and D. A. Wilson, *J. Chem. Soc., Sect. B*, 144 (1965).

(15) The solvent shifts for the mono- and diepoxyquinones refer to deuteriochloroform as reference solvent ($\Delta_{CDCl_3}^{C_6H_6}$ and $\Delta_{CDCl_3}^{C_5H_5N}$). The change of reference solvent was dictated by the solubility of the compounds, but, since the solvent shifts observed in the quinones are usually large (this is especially true for the differences induced by benzene and pyridine), the change does not adversely affect the conclusions.

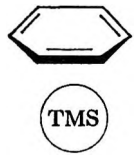
TABLE I

THE VARIATION OF SOLVENT SHIFTS OF EPOXIDE PROTONS (H*) WITH STERIC FACTORS

R	$\Delta^{C_6H_6}_{CDCl_3}$	$\Delta^{C_5H_5N}_{CDCl_3}$
H	+0.59 to +0.80	−0.20 to −0.27
CH_3	+0.34 to +0.55	−0.24 to −0.35
$(CH_3)_3C$	+0.09 to +0.22	−0.27 to −0.42

29

solvent shifts may *a priori* be associated largely with (i) steric inhibition of association of benzene at a polar site and (ii) steric inhibition to the approach of bulk solvent to the proton (H*) in question. The latter factor is independent of specific solute–solvent interaction, but must be considered since the exposed protons of a "spherical" solute (in this case the internal tetramethylsilane reference) are shifted upfield in benzene (relative to an external reference, even after a bulk susceptibility correction) because of the preferential orientation of disklike benzene molecules with respect to the "spherical" reference as indicated in **30**.[16] Therefore, a proton in the solute which is less exposed to the shielding effect associated with bulk benzene solvent than the protons of the reference will, in the absence of specific solvent–solute interactions, be deshielded relative to the internal reference. The factors considered under i and ii above should also be dominant in determining the pyridine-induced shifts. If steric inhibition of specific solvation is dominant in determining the differences in solvent shifts, then the shifts of H* in **29** should decrease in magnitude for *both* benzene and pyridine solution as R is changed from hydrogen to methyl to *t*-butyl. In contrast, if steric inhibition to the approach of bulk solvent is dominant, then both the $\Delta^{C_6H_6}_{CDCl_3}$ and $\Delta^{C_5H_5N}_{CDCl_3}$ values should become more negative as R is changed from hydrogen to methyl to *t*-butyl. In fact the $\Delta^{C_5H_5N}_{CDCl_3}$ values do become slightly larger (*i.e.*, more negative) as the bulk of R is increased, thus indicating the importance of steric inhibition to the approach of bulk solvent in these cases. This conclusion is supported by an examination of Dreiding models.



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It should also be possible to demonstrate the contribution to a solvent shift of steric inhibition to the approach of bulk solvent by means of variable temperature experiments. Such a contribution to the solvent shift will be temperature independent,[16] whereas that due to specific solute–solvent association will be temperature dependent (the shift increasing in magnitude at lower temperatures). Therefore **21**, **25**, and **27** were selected for a variable-temperature study in d_8-toluene solution (as benzene is unsuitable for variable-temperature work) and pyridine solution. Since one is here trying to demonstrate a mechanistic aspect of solvent shifts (rather than formulating an empirical correlation), it was thought desirable to choose the most truly "inert" solvent which is available as reference solvent (in place of CCl_4 or $CDCl_3$) and accordingly hexane was employed.[16] The epoxide **25** was relatively insoluble in hexane at normal probe temperatures and therefore the spectrum was obtained at 40, 60, and 80°. The chemical shift of the epoxide proton resonances were temperature independent within experimental error (±1 cps). The solvent shifts $\Delta^{C_7D_8}_{C_6H_{14}}$ and $\Delta^{C_5H_5N}_{C_6H_{14}}$ observed for the epoxide protons indicated by asterisks in the temperature range −40 to +100° (pyridine solutions) and −80 to +100° (d_8-toluene solutions) are summarized in Figure 1.

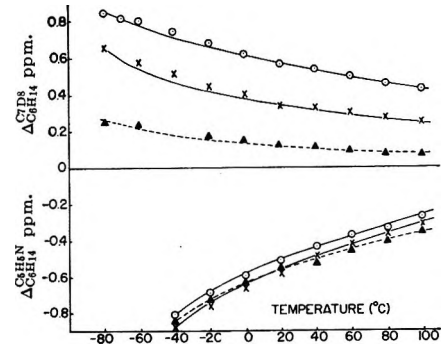

Figure 1.—Plot of solvent shift for epoxide protons in compounds **21** (○), **25** (×), and **27** (▲) against temperature.

Steric inhibition of complexing (*i.e.*, of specific solvent–solute interaction) will cause a decrease in the temperature dependence of that part of the solvent shift arising because of complexing. This temperature dependence of the solvent shift can be measured in terms of $\nu_{t_1} - \nu_0/\nu_{t_2} - \nu_0$ where ν_{t_1} and ν_{t_2} are the observed resonance frequencies of a proton at temperatures t_1 and t_2 in a complexing solvent and ν_0 is the resonance frequency of the proton in the absence of complexing.[17] If ν_0 for the epoxide protons of **21**, **25**, and **27** is taken as the chemical shift in hexane solution, then the calculated values of $\nu_{-80} - \nu_0/\nu_{+100} - \nu_0$ for solutions in d_8-toluene are 0.85/0.42, 0.65/0.23, and 0.26/0.07 (taken from Figure 1), *i.e.*, 2.0, 2.8, and 3.7, respectively. On the basis of this analysis, the greatest temperature dependence of the solvent shift is observed when the steric inhibition toward association of d_8-toluene at the polar sites is greatest. This situation is obviously impossible, and it must therefore be concluded that, in the absence of complexing, the epoxide protons of **25** and **27** would resonate at lower field in d_8-toluene solution than they do in hexane solution. This situation would arise if the epoxide protons of **25** and **27** are less accessible to shielding by bulk d_8-toluene solvent than the protons of the internal TMS reference. The same conclusion must also be reached from a consideration of the variable temperature study in pyridine solution (Figure 1). Although the solvent shift $\Delta^{C_5H_5N}_{C_6H_{14}}$ at 40° is greatest for the most sterically hindered epoxide proton of **27**, the temperature dependence of its resonance position (measured in terms of $\nu_{-40} - \nu_0/\nu_{+100}$

(16) A. D. Buckingham, T. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, **32**, 1227 (1960); see also J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., 1959, pp 424–426.

(17) For a theoretical discussion which relates the temperature dependent solvent shifts ($\Delta^{C_6H_6}_{CCl_4}$) to thermodynamic properties based upon an equilibrium between solute and solvent complexed solute, see ref 3.

$-\nu_0$ for pyridine and ν_0 taken from the hexane data) is least (2.9, 2.7, and 2.4 for **21**, **25**, and **27**, respectively). This observation may be interpreted in terms of a negative contribution to the solvent shift of the epoxide proton of **27** which is temperature independent. It is apparent that if the dotted lines of Figure 1 (curves for the di-*t*-butyl diepoxide) were extrapolated to high temperatures (approximating complex free solutions), they would approach each other at a resonance frequency for the epoxide proton *lower* than that observed for a hexane solution.

The stereochemistry assigned to the stereoisomeric pairs of diepoxides **23**–**24**, **25**–**26**, and **27**–**28** is only tentative[18] and unimportant for the present arguments. The assignments are based on the solvent-shift data and upon the conclusion that the less soluble higher melting isomer has the *trans* configuration.[18] In a *cis* diepoxide, the proton attached to one epoxide ring is further away from the negative end of the local dipole of the other epoxide ring relative to the situation in a *trans* diepoxide. Hence the compounds having the epoxide protons with the larger upfield solvent shifts in benzene are assigned the *cis* stereochemistry.

Experimental Section

Nmr Measurements.—The variable-temperature experiments were carried out using a Varian HA-100 nmr spectrometer with 2% w/v solutions. All other measurements were carried out on a Varian A-56/60 nmr spectrometer with 5% w/v solutions.

Epoxyquinones.—The epoxyquinones reported here were all synthesized by the direct oxidation of the corresponding quinone as reported in an earlier publication.[18]

Registry No.—Benzene, 71-43-2; pyridine, 110-86-1; **2**, 75-21-8; **3**, 15448-47-2; **4** (*cis*), 1758-33-4; **4** (*trans*), 15493-88-6; **5**, 15448-50-7; **6**, 503-30-0; **7**, 109-99-9; **8** (*cis*), 2144-41-4; **8** (*trans*), 15493-89-7; **9**, 13423-15-9; **10**, 142-68-7; **13**, 60-29-7; **14**, 111-43-3; **15**, 108-20-3; **17**, 10476-74-1; **18**, 10476-73-0; **19**, 10476-70-7; **20**, 10476-71-8; **21**, 15448-58-5; **22**, 15448-59-6; **23**, 15448-60-9; **24**, 10476-79-6; **25**, 10476-76-3; **26**, 10476-75-2; **27**, 10476-78-5; **28**, 10476-77-4; **29** (R = H), 15448-65-4; **29** (R = CH_3), 15448-66-5; **29** (R = $(CH_3)_3C$), 15448-67-6.

Acknowledgment.—Two of us (H. W. Moore and H. Raymond Shelden) are indebted to the National Science Foundation for partial support of this project from Grant GP. 5945.

(18) H. W. Moore, *J. Org. Chem.*, **32**, 1996 (1967).

Fluoroalkylamines

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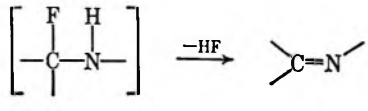
Received July 14, 1967

Lewis acids were used to activate fluorimines toward reactions with carbon nucleophiles. A wide variety of fluoroalkylamines was prepared and the chemistry of these very stable compounds was explored. A correlation between F^{19} nmr chemical shifts and the Hammett σ values is discussed.

Primary or secondary amines which contain fluorine atoms attached directly to their α-carbon atoms are known to be relatively unstable.[1] The base-catalyzed loss of the elements of hydrofluoric acid occurs readily (eq 1). The remarkable physical and chemical



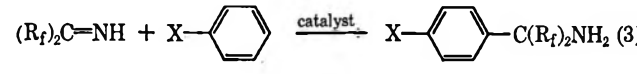
(1)

properties of the fluoro alcohols[2a] derived from fluoro ketones[2b,c] and carbon nucleophiles prompted a study of the fluoroalkylamines which might be derived from fluorimines[3] and carbon nucleophiles (eq 2). Fluoro

$$RH + (R_f)_2C{=}NH \longrightarrow RC(R_f)_2NH_2 \qquad (2)$$

ketones and fluorimines differ, however, in reactivity toward nucleophiles, the latter being less electrophilic. Only one case of a reaction of a fluorimine with a carbon nucleophile (the very electron-rich isobutylene) has been reported.[4] We have found that Lewis acids activate fluorimines so that they undergo many of the reactions shown by fluoro ketones. This method has proved to be an excellent route to a wide variety of fluoroalkylamines. Several fluoroalkylamines were also prepared by alternate, less general routes.

Preparation of Fluoroalkylamines.—α,α-Bis(fluoroalkyl)benzylamines were prepared from fluorimines[3] and aromatic hydrocarbons under vigorous Friedel–Crafts conditions (Table I). The reaction usually was carried out at elevated temperatures in a "Hastelloy"-lined autoclave at autogenous pressure (eq 3). Reac-



(3)

tivity closely paralleled normal electrophilic substitution, with electron-donating groups activating and electron-withdrawing groups deactivating the ring. Yields varied from high to low depending on the aromatic hydrocarbon. Disubstitution was observed with phenol and 2 equiv of hexafluoroisopropylidenimine[3] (HFAI), but the hexafluoroisopropylamino group was sufficiently ring deactivating to prevent disubstitution in unactivated aromatic hydrocarbons. *para,para'* disubstitution was observed when compounds containing two benzene rings separated by a heteroatom or carbon chain were employed. 3,5-Dimethyl-4-

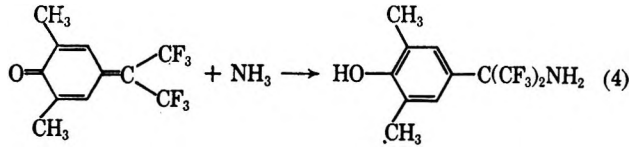
(1) F. S. Fawcett, C. W. Tullock, and D. D. Coffman [*J. Chem. Eng. Data*, **10**, 398 (1965)] describe the properties of N,N-bis(trifluoromethyl)amine; W. J. Middleton and C. G. Krespan [*J. Org. Chem.*, **30**, 1398 (1965)] describe the properties of heptafluoroisopropylamine.

(2) (a) W. J. Middleton and R. V. Lindsey, *J. Amer. Chem. Soc.*, **86**, 4948 (1964); (b) C. G. Krespan and W. J. Middleton, in "Reviews in Fluorine Chemistry," P. Tarrant, Ed., in press; (c) N. P. Gambaryan, E. M. Rokhlin, Yu. A. Zeifman, C. Ching-Yun, and I. L. Knunyants, *Angew. Chem.*, **78**, 1008 (1966).

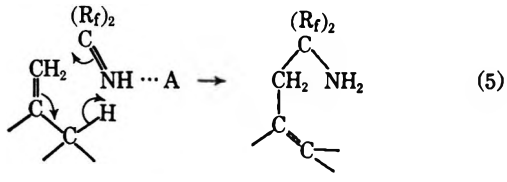
(3) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

(4) Y. V. Zeifman, N. P. Gambaryan, and I. L. Knunyants, *Izv. Akad. SSSR Ser. Khim.*, **1965** (8), 1472 (1965).

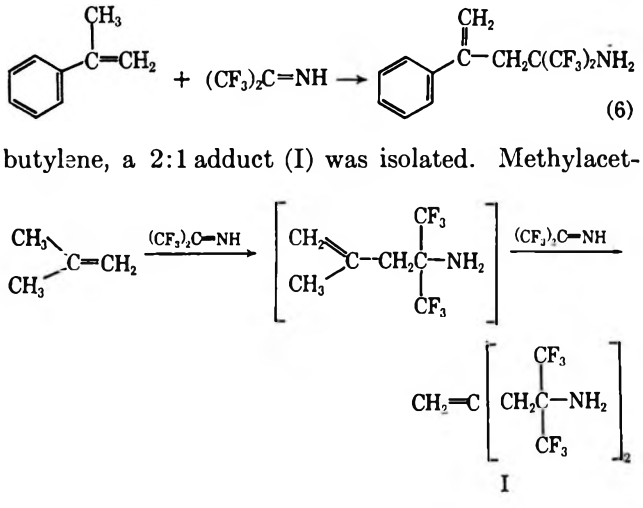
hydroxy-α,α-bis(trifluoromethyl)benzylamine was also prepared by a novel alternate route (eq 4).[5]



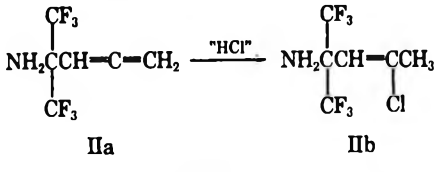
Terminal olefins which also contain a hydrogen atom in the 3 position react with fluorimines to form adducts in which the double bond migrates (Table III and eq 5). A six-centered mechanism may be involved.



Internal olefins were much less reactive, and under similar conditions no adducts could be isolated; this result is believed to be due to steric rather than electronic factors. The reaction with olefins occurs under milder conditions than with aromatics; thus, for molecules which contain both aromatic ring and a terminal double bond, the latter may react preferentially (eq 6). With the highly reactive olefin, isobutylene, a 2:1 adduct (I) was isolated. Methylacetylene condensed with HFAI (in the presence of BF_3), perhaps in a similar six-centered reaction, but the acid-sensitive product (allene IIa) could be isolated only in trace amounts. When $AlCl_3$ was used as catalyst, IIb was isolated instead of IIa.

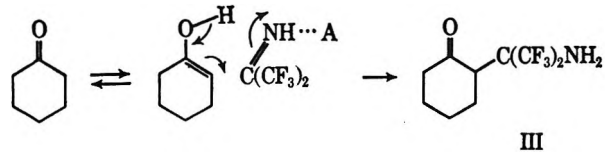


I



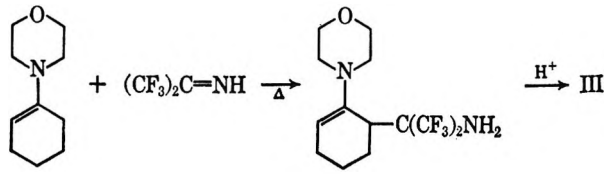
IIa IIb

Lewis acids also catalyze the reaction of fluorimines with active methylene compounds (Table II). These reactions may occur *via* the enol form of the carbonyl group. Ketamine III was prepared alternately by the reaction of HFAI with an enamine;

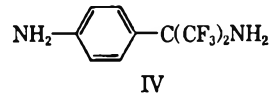


III

this uncatalyzed addition is an example of a reaction of fluorimines with exceptionally strong carbon nucleophiles. A similar sequence was observed with the morpholine enamine of cyclopentanone.



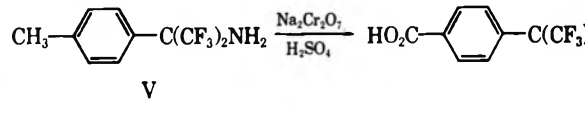
Properties and Chemistry.—One of the most striking properties of fluoroalkylamines in general is their stability. This property is particularly true for the benzylamines, which not only survive the vigorous Friedel–Crafts conditions used to prepare them, but are also stable at elevated temperatures in the presence of metals. Even the adduct (IV) of HFAI and aniline



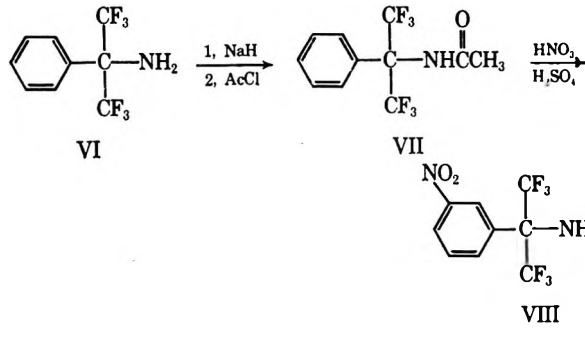
IV

shows no tendency to darken on storage, a property long associated with ordinary aromatic amines. The stability of IV is evidence of the inherent stability of the hexafluoroisopropylamino group and of its strong electron-withdrawing properties, which deactivate the ring.

Chromic acid oxidation of 4-methyl-α,α-bis(trifluoromethyl)benzylamine (V) left the amino group unaffected, while the methyl group was converted to a carboxyl group. Attempted acylation of bis(trifluoromethyl)benzylamine VI with refluxing acetyl chloride was unsuccessful; acetamide VI was prepared, however, *via* the sodium salt. Compound VII underwent ring nitration to give VIII with no hydrolysis



V



VI VII VIII

products. Hot 50% sulfuric acid was used to hydrolyze VIII to the corresponding free base IX. Ring bromination in the presence of iron gave *m*-bromo-α,α-bis(trifluoromethyl)benzylamine (X). In addi-

(5) We are indebted to Dr. W. A. Sheppard for a sample of the starting quinomethan; the preparation and other chemistry of this compound will be published shortly by Dr. Sheppard.

TABLE I.—REACTIONS OF FLUORIMINES WITH AROMATICS TO PREPARE α,α-DI(FLUOROALKYL)BENZYLAMINES

A. $X—C_6H_5 + R_fR'_fC{=}NH \longrightarrow p\text{-}X—C_6H_4C(R_f)(R'_f)NH_2$

X	R_f	R'_f	Method[a]	Catalyst	Temp, °C	Parent yield	Bp, °C (mm)	Mp, °C	Formula of product[f]
OH	CF_3	CF_3	A, 1, 21	$AlCl_3$		50			
			A, 1, 21	HF	150	73	80 (1.0)	70–73	$C_9H_7F_6NO$
			A, 1, 5	BF_3		40			
OCH_3	CF_3	CF_3	A, 2, 10	$AlCl_3$	150	56	65 (1.2)	53–53.5	$C_{10}H_9F_6NO$
NH_2	CF_3	CF_3	A, 1.7, 11	HF	150	4	81–85 (5–4.5)	69–70 (pentane–ether)	$C_9H_8F_6N_2$
H	CF_3	CF_3	A, 1, 6	$AlCl_3$	200	12[e]	95 (60)		$C_9H_7F_6N$
Cl	CF_3	CF_3	A, 1.6, 11	$AlCl_3$	225[f]	0.6	50 (1.25)		$C_9H_6ClF_6N$
F	CF_3	CF_3	B, 3, 14	$AlCl_3$	250	10	59 (10)		$C_9H_6F_7N$
$N(CH_3)_2$	CF_3	CF_3	A, 1.4, 10	$AlCl_3$	50	36		58.5–59.5 (pentane)	$C_{11}H_{12}F_6N_2$
Ph	CF_3	CF_3	A, 2, 11	$AlCl_3$	150	26	135 (2)	93–95	$C_{15}H_{11}F_6N$
CH_3	CF_3	CF_3	A, 1, 8	$AlCl_3$	150	41	125 (100)		$C_{10}H_9F_6N$
Br	CF_3	CF_3	B, 0.75, 6	$AlCl_3$	275	1	122 (10)	35–36	$C_9H_6BrF_6N$
CH_3	C_2F_5	C_2F_5	B, 0.25, 2	$AlCl_3$	175	8	30 (0.5)		$C_{12}H_9F_{10}N$
CH_3	CF_3	CF_2Cl	B, 0.6, 6	$AlCl_3$	150	28	79 (0.75)		$C_{10}H_9F_5ClN$

B. $RH + (CF_3)_2C{=}NH \longrightarrow R—C(CF_3)_2NH_2$

R		Method[a]	Catalyst	Temp, °C	Parent yield	Bp, °C (mm)	Mp, °C	Formula of product[f]
(3,5-Dimethyl-4-hydroxy)-phenyl-		A, 1, 25	HF	150	30	*h*	65–68	$C_{11}H_{11}F_6NO$
9-Anthracenyl		A,[d,i] 1, 6	$AlCl_3$	150	43		210	$C_{17}H_{11}F_6N$
$-C_6H_4-Y-C_6H_4-$[g]	Y- -O-	A, 2.4, 12.5	$AlCl_3$	150	37	124 (2)	50–52	$C_{18}H_{12}F_{12}N_2O$
	Y- -S-	B, 1.9, 11	$AlCl_3$	150	19	173–176 (3)		$C_{18}H_{12}F_{12}N_2S$
	Y- -NH-	B, 1, 15	$AlCl_3$	100	27	175 (7.5) short path	83–85	$C_{18}H_{13}F_{12}N_3$
	Y- $-CH_2CH_2-$	B, 2, 11	$AlCl_3$	150	15	145–146 (1–20)	116–117	$C_{20}H_{16}F_{12}N_2$
(1-Hydroxy-4-hexafluoroisopropylamino)phenyl		A, 1.2, 9	$AlCl_3$	200	36	*j*	82–84	$C_{12}H_8F_{12}N_2O$

[a] The following procedures were employed. (A) The reactants were heated in an autoclave for 8 hr. The autoclave was cooled and vented and the residue extracted with ether (filtered, dried, and distilled). (B) Same as A except sodium bicarbonate added before extraction (as solid or in aqueous wash) to neutralize acid. The first number after the method type is the weight ratio of imine to aromatic. The second number is the weight ratio of imine to catalyst. [b] Calibrated at 40, 20, 10, and 5% in $FCCl_3$ and extrapolated to infinite dilution. [c] Not calibrated; $FCCl_3$ as internal standard. [d] There was no visible decomposition of this benzylamine when heated in a sealed tube at 200° for 24 hr without metal or in the presence of Al, Cu, or soft iron; at 300° only minor decomposition was noted.

TABLE II.—REACTIONS OF HEXAFLUOROISOPROPYLIDENIMINE WITH ACTIVE METHYLENE COMPOUNDS

Substrate	Product	Method[a]	Catalyst	Temp, °C	Per cent yield	Bp, °C (mm)	Formula
Cyclohexanone	2-(Hexafluoroisopropylamino)cyclohexanone	A, 1.7, 34	$ZnCl_2$	125	45	84 (6)	$C_9H_{11}F_6NO$
$CH_2(CO_2CH_3)_2$	$(CO_2CH_3)_2CHC(CF_3)_2NH_2$[b]	B, 1.4, 7.3	$ZnCl_2$	100	13	56 (1.2)	$C_8H_9F_6NO_4$
$NCCH_2CO_2CH_3$	$(CO_2CH_3)(CN)CHC(CF_3)_2NH_2$[c]	B, 1.7, 6.5	$ZnCl_2$	100	45	57–59 (0.75)	$C_7H_6F_6N_2O_2$

[a] See Table I, footnote *a*. [b] Not calibrated: $FCCl_3$ as external standard. [b] Registry no.: 1558-89-9. [c] 15580-90-2.

Combustion analyses: Calcd, %	Combustion analyses: Found, %	H¹ nmr, τ	F¹⁹ nmr,[b] ppm	Other data
C, 41.70; H, 2.72	C, 41.70; H, 2.84	A_2B_2 centered at 2.68 (aromatic protons); broad singlets at 1.3 (OH) and 7.1 (NH_2) (acetone-d_6)	+75.15	Uv,[m] $\lambda_{max}^{ethanol}$ 278 (1030), 272 (1285), 225 (10,520); pk_a = 8.6
C, 43.96; H, 3.32 N, 5.13; F, 41.73	C, 43.84; H, 3.53 N, 4.85; F, 41.83	A_2B_2 at 2.8, 6.24 (OCH_3); 7.8 (NH_2) ($CDCl_3$)	+75.09	Gc, collected on silicone grease at 125°
C, 41.88; H, 3.13 N, 10.86; F, 44.00	C, 42.01; H, 2.98 N, 10.17; F, 44.01	A_2B_2 at 2.9; $2NH_2$ at 7.1 (neat)	+75.9[c] (neat)	Uv, $\lambda_{max}^{ethanol}$ 287 (1300), 247 (13,150); pk_a = 3.26, by uv in 55% water–45% dioxane
C, 44.46; H, 2.90 N, 5.76; F, 45.89	C, 44.75; H, 2.72 N, 5.54; F, 46.54	Aromatic protons at 2–3; NH_2 at 7.9 (neat)	+74.83	Uv, $\lambda_{max}^{ethanol}$ 266 (389), 260 (465), 254 (406), 250 (347)
C, 39.94; H, 2.18 N, 5.05; Cl, 12.77	C, 39.40; H, 2.63 N, 4.60; Cl, 12.99	A_2B_2 at 2.45; NH_2 at 7.85 (neat)	+74.5[c] (neat)	Other products found but not investigated
C, 41.39; H, 2.32 N, 5.37; F, 50.93	C, 41.98; H, 2.44 N, 15.48; F, 51.07	A_2B_2 at 2.47 (split further); NH_2 at 7.80 (neat)	+74.96 +111.3	Uv, $\lambda_{max}^{ethanol}$ 266 (271), 259 (269), 257.5 (292), 255 (251), 252.5 (248)
C, 46.15; H, 4.23 N, 9.81; F, 39.83	C, 46.95; H, 4.50 N, 9.45; F, 40.0	A_2B_2 at 2.9; $2CH_3$ at 7.16; NH_2 at 8.05	+75.15	Uv, $\lambda_{max}^{ethanol}$ 262 (21,000); pk_a = 2.26, by uv in 55% water–45% dioxane
C, 56.43; H, 3.48 N, 4.34; F, 35.72	C, 55.64; H, 3.48 H, 4.36; F, 36.49	Aromatic protons at 2.5; NH_2 at 8.0	+74.83	Uv, $\lambda_{max}^{ethanol}$ 252 (19,000)
C, 46.69; H, 3.53 N, 5.45; F, 44.33	C, 46.56; H, 3.61 N, 5.48; F, 44.10	A_2B_2 at 2.6, 7.83 (CH_3); 7.95 (NH_2) (neat)	+74.94	Uv, $\lambda_{max}^{ethanol}$ 268 (114), 265 (196), 259 (243), 252 (199); stability determination[d]
C, 33.56; H, 1.88 N, 4.35; Br, 24.81	C, 34.11; H, 2.08 N, 4.03; Br, 23.79	Broad singlet at 2.4; NH_2 at 7.83 ($CDCl_3$)	+74.96	Mass spectrum, parents at *m/e* 321, 323
C, 40.35; H, 2.54 N, 3.92; F, 53.19	C, 41.14; H, 2.83 N, 3.76; F, 53.44	A_2B_2 at 2.6; CH_3 at 7.63; NH_2 at 7.85	+77.31 ($2CF_3$) +116.7 ($2CF_3$)	
C, 43.88; H, 3.32 N, 5.13; Cl, 12.9	C, 44.60; H, 3.48 N, 4.97; Cl, 12.91	A_2B_2 at 2.6; CH_3 at 7.71; NH_2 at 7.9 (neat)	A_3B_2[k] at +71.07 (CF_3), +59.84 (CF_2Cl)	
See Experimental Section		$2CH_3$ at 7.7; aromatic protons at 2.55; NH_2, OH at 7.2 (acetone-d_6)	F¹⁹ nmr[c] +74.9 (acetone-d_6)	
C, 59.47; H, 3.23 N, 4.08; F, 33.21	C, 59.97; H, 3.35 N, 4.02; F, 32.60	Aromatic like 9-methylanthracene except more spread out at 2.2–3.8; NH_2 at 7.35 (DMSO-d_6)	+72.2 (DMSO-d_6)	Mass spectrum, parent at *m/e* 343
C, 43.21; H, 2.42 N, 5.60	C, 43.46; H, 2.48 N, 5.60	A_2B_2 at 2.6; NH_2 at 7.95	+74.9 (CCl_4)	Uv, $\lambda_{max}^{ethanol}$ 276 (1050), 268, (1350), 232 (15,050); mass spectrum, parent at *m/e* 500
C, 41.87; H, 2.35 N, 5.43; F, 44.27	C, 42.08; H, 2.58 N, 5.66; F, 44.27	A_2B_2 at 2.4; NH_2 at 7.85 ($CDCl_3$)	+74.5 ($CDCl_3$)	
C, 43.30; H, 2.62 N, 8.42; F, 45.7	C, 43.00; H, 2.60 N, 8.68; F, 44.88	A_2B_2 at 2.7; NH at 4.2; NH_2 at 8.0	+75.1 (CCl_4)	
C, 46.88; H, 3.15 N, 5.47; F, 44.50	C, 47.14; H, 3.26 N, 5.42; F, 44.68	A_2B_2 at 2.55 for aromatic protons; singlet at 7.04 (CH_2CH_2); NH_2 at 7.86 ($CDCl_3$)	+74.8 ($CDCl_3$)	Mass spectrum, parent at *m/e* 512
C, 33.97; H, 1.90 N, 6.61; F, 53.8	C, 34.15; H, 2.21 N, 6.38; F, 53.41	Aromatic protons at 2.0–3.3; $2NH_2$, OH at 8 ($CDCl_3$)	+74.4 +75.1 ($CDCl_3$)	

[e] Higher yields (25–50%) were obtained at 250° when an almost equimolar amount of $AlCl_3$ was employed (method B used). [f] Heated for 16 hr. [g] 2:1 adducts isolated, *para,para'* disubstituted. [h] Product isolated by short-path distillation at 0.3 mm. [i] Carbon disulfide used as solvent. [j] Vacuum sublimation at 0.05 mm employed in isolation of the product. [k] J = 12 cps. [l] Registry no., respectively: 14356-91-3; 14355-84-1; 14356-93-5; 15562-06-8; 14355-88-5; 14639-71-5; 14355-87-4; 14355-86-3; 14356-92-4; 14355-89-6; 14355-96-5; 14355-98-7; 14355-85-2; 14355-91-0; 14355-90-9; 14355-94-3; 14355-92-1; 14355-95-4; 14355-93-2. [m] In mμ (ε).

Combustion analyses: Calcd, %	Combustion analyses: Found, %	H¹ nmr, τ	F¹⁹ nmr,[b] ppm	Other data
See Experimental Section			Pair of quartets (J = 9) at +71, 74.5 (CCl_4)	$n^{25}D$ 1.4037; ir, 3400, 1620 cm^{-1} for $-NH_2$ and 1710 cm^{-1} for C=C; strong $-CF_3$ absorption
C, 32.33; H, 3.06 N, 4.72; F, 38.35	C, 33.13; H, 3.30 N, 5.34; F, 38.22	$2CH_3O-$ at 6.25; $-NH_2$ at 7.28; tertiary –H at 6.03 (neat)	Singlet at +74.4 (neat)	
C, 31.82; H, 2.67 N, 10.61	C, 32.83; H, 2.52 N, 10.71	NH_2 at 7.3; CH_2O at 6.11; >CH– at 5.70	A_2B, multiplet (J = 9) at +74 (CCl_4)	Mass spectrum, base peak at parent $-NH_3$; ir, 3425, 3367, 1631 cm^{-1} for NH_2, 2268 for C≡N, and 1765 for C=O

TABLE III

REACTIONS OF HEXAFLUOROISOPROPYLIDENIMINE WITH OLEFINS

Olefin	Product[a]	Method[a]	Catalyst	Temp, °C	Parent yield	Bp, °C (mm)	Formula	Combustion analyses—Calcd, %	Combustion analyses—Found, %	H¹ nmr, τ	F¹⁹ nmr,[b] cps	Other data
CH_2=$CHCH_3$	CH_2=$CHCH_2C(CF_3)_2NH_2$	A, 3, 3	$AlCl_3$	100	35	97–98	$C_6H_7NF_6$	C, 34.79; H, 3.41 N, 6.77; F, 55.04	C, 34.84; H, 3.11 N, 6.51; F, 55.41	AB_2 at 4.6; doublet (J = 7) at 7.27 (CH_2); singlet at 7.95 (NH_2) (neat)	+75.7 (neat)	Mass spectrum, parent at m/e 207
CH_3CH_2CH=CH_2	CH_3CH=$CHCH_2C(CF_3)_2NH_2$	A, 3, 17	$AlCl_3$	75[c]	19	114–118	$C_7H_9NF_6$	N, 6.34; F, 51.55	N, 5.82; F, 51.59	Multiplet (area 2) at 4.3; singlet (area 2) at 6.5; doublet (J = 6.5; area 2) at 7.38; doublet (J = 5; area 3) at 8.26 (neat)	+75.6 (neat)	Higher boiling product formed
1,7-Octadiene	$[NH_2C(CF_3)_2CH_2CH$=$CH-]_2$	B, 3.4, 11	$AlCl_3$	75[c]	29	98–107 (3–1.5)	$C_{14}H_{18}N_2F_{12}$	C, 38.18; H, 3.67 N, 6.37; F, 51.79	C, 38.76; H, 3.76 N, 6.09; F, 51.97	Vinyl-H at 4.39; isolated $-CH_2$ at 7.43; doublet (J = 7) at 7.80 $-CH_2CH-$; NH_2 at 8.25	+76.5 (CCl_4)	Preparative gc employed, mass spectrum, parent at m/e 440
$(CH_3)_2C$=CH_2	$(CF_3)_2-C(NH_2)-CH_2CCH_2-C(CF_3)_2$ (CH$_2$ bridge)	7, 14[d]	$AlCl_3$	100[d]	18	53 (1.2)	$C_{10}H_{10}F_{12}N_2$	C, 31.11; H, 2.62 N, 7.26; F, 59.07	C, 31.55; H, 2.52 N, 7.03; F, 59.01	Singlets at 4.75 ($=CH_2$), 7.30 ($2CH_2$), and 8.15 ($2NH_2$)	+78.9 (CCl_4)	$n^{25}D$ 1.3577
Styrene, α-methyl	$C_6H_5C-CH_2C(CF_3)_2NH_2$ (CH$_2$ bridge)	A, 1.3, 4	$ZnCl_2$	125[c]	12	68 (2–3)	$C_{12}H_{11}NF_6$	C, 50.89; H, 3.84 N, 4.95; F, 40.28	C, 51.03; H, 3.96 N, 4.41; F, 40.39	Aromatic $-H$ at 2.72; AB at 4.85 $=CH_2$ at 4.72; CH_2 at 6.92; NH_2 at 8.6	+75.7 (CCl_4)	$n^{25}D$ 1.4535

[a] See Table I, footnote *a*. [b] Not calibrated; $FCCl_3$ as internal standard. [c] 16 hr. [d] This experiment was carried out by Dr. D. C. England. A glass Carius tube containing the reactants was heated on a steam bath for 23 hr. The nonvolatile components (at room temperature) were mixed with 10% HCl and extracted with CH_2Cl_2 and the resulting extracts dried and distilled. [e] Registry no., respectively: 15580-86-6; 15580-87-7; 15580-88-8; 15717-35-8; 15581-05-2.

tion to X, an amine hydrobromide (XI) was also isolated from aprotic media but dissociated on storage. The ability of VI to form a hydrobromide suggests that fluoroalkylamines have at least moderate basic character and that their inertness to direct acylation may be due to steric as well as electronic causes.

F^{19} Nmr Studies.—Earlier workers[6] have found fluorine contact shifts to be a sensitive probe of charge distribution in the benzene ring. Table IV shows the

TABLE IV

F^{19} CHEMICAL SHIFTS OF $XC_6H_4C(CF_3)_2Y$ IN PARTS PER MILLION AT INFINITE DILUTION RELATIVE TO THE UNSUBSTITUTED COMPOUNDS

X \ Y	NH_2	OH[a]	F[b]
p-$N(CH_3)_2$	+0.32[c]	+0.35	+0.43
p-OH	+0.32		
p-OCH_3	+0.26		
p-F	+0.14	+0.23	+0.23
p-CH_3	+0.11	+0.09	+0.20
p-Br	+0.11	+0.12	+0.08
p-Ph	0.00		
p-CO_2H	−0.21		−0.17
m-Br	−0.12	+0.11	−0.07
m-NO_2	−0.07	+0.02	−0.07

[a] Reference 6a, in methanol containing 5% $CFCl_3$. [b] Reference 6a, in $CFCl_3$. [c] Values ±0.02 ppm, calibrated at 40, 20, 10, and 5% in $FCCl_3$ and extrapolated to infinite dilution.

change in $-CF_3$ absorption (Δ, ppm, from X = H at +74.83 ppm) with *para* substituent for the bis(trifluoromethyl)benzylamines compared with the corresponding values for bis(trifluoromethyl)benzyl alcohols and fluorides obtained by Sheppard.[6b] A normal correlation curve is found when values for the *para* substituents are plotted against σ_{R^0},[7] in agreement with Sheppard's findings. From the chemical shift of the ring fluorine atom in 4-fluorobis(trifluoromethyl)benzylamine (XIIa) (−1.72 ppm from fluorobenzene), it

XIIa, X = NH_2
b, X = OH

appears that the *p*-hexafluoroisopropylamino group is slightly less electron withdrawing than the *p*-hexa-

(6) (a) R. W. Taft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709, 3146 (1963). (b) W. A. Sheppard, *ibid.*, **87**, 2410 (1965), and references cited therein. We thank Dr. Sheppard for his assistance with this study.

(7) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *ibid.*, **81**, 5352 (1959).

fluoroisopropanol group (−2.00 ppm from fluorobenzene[6]); this effect probably reflects the difference in electronegativity between oxygen and nitrogen.

Experimental Section[8]

Reactions of Hexafluoroisopropylidenimine (HFAI) with Methylacetylene. A. With Boron Trifluoride Catalysis.—An 8-g sample of methylacetylene (0.2 mol), 0.5 g of hydroquinone, 2 g of boron trifluoride gas, and 34 g of hexafluoroisopropylidenimine[3] (0.2 mol) were heated at 150° for 16 hr. The recovered liquid (7 g) was mixed with 1 g of solid sodium bicarbonate and distilled through a spinning-band column. The material boiling at <58° (1 g) was 68% aminoallene IIa, as estimated by gas chromatographic analysis. A sample was collected by preparative gas chromatography (20% silicone grease column at 69°). The infrared spectrum showed a band at 1955 cm^{-1} for the allene absorption.

Anal. Calcd for $C_6H_5NF_6$: C, 35.13; H, 2.46; F, 55.59. Found: C, 35.50; H, 2.13; F, 56.68.

B. With Aluminum Chloride Catalysis.—When the above reaction was repeated using 3 g of $AlCl_3$ instead of BF_3, the allene was not isolated, but reacted further to give 1.6 g of an "HCl" addition compound, IIb, bp 67° (100 mm). This material showed no allene band in its infrared spectrum, but a >C=C< band at 1660 cm^{-1} instead. F^{19} nmr spectrum showed a singlet at +78.0 ppm from external $FCCl_3$. H^1 nmr spectrum showed vinyl H at τ 4.22 (area 1), $-CH_3$ at 7.48 (area 3), and NH_2 at 7.9 (area 2). The mass spectrum showed peaks at *m/e* 241, 243 (parent), at *m/e* 224, 226 (parent NH_3), and at *m/e* 206 (parent −Cl).

Anal. Calcd for $C_6H_6ClF_6N$: C, 29.83; H, 2.50; N, 5.80. Found: C, 30.29; H, 2.81; N, 5.18.

2-(Hexafluoroisopropylamino)cyclohexanone (III) *via* the Enamine Synthesis. A. Reaction of HFAI with 1-N-Morpholinocyclohexene.—A mixture of 20 g of the enamine[9] and 31 g of HFAI was placed into a 240-ml Hastelloy bomb tube and heated over a period of 6 hr to 150°. The temperature was held at 150° until all the gas was absorbed (4.5 hr). A dark amber liquid, $n^{25}D$ 1.4250, weighing 43 g, was recovered. Distillation of this liquid through a spinning-band column gave a 20-g fraction (50%), bp 110° (3.5 mm) to 104° (0.9 mm) and $n^{25}D$ 1.4479, which solidified on standing (mp 56–58.5°). A sample was recrystallized from pentane and had mp 61.4–63.3°. The infrared spectrum had bands at 3400, 3240, and 1615 cm^{-1} for $-NH_2$ absorption, a band at 1645 cm^{-1} for −C=C− stretch, a band at 3060 cm^{-1} for vinyl −C−H absorption, and a broad band at 1200 cm^{-1} for $-CF_3$ absorption. The F^{19} nmr spectrum clearly showed that the product was a mixture of double-bond isomers; it contained a singlet (19% of the area) at +73.5 ppm from $FCCl_3$ for the isomer with a tetrasubstituted double bond and a pair of quartets (81%) at +71.1 and +72.5 ppm (J = 8 cps) for the isomer with a trisubstituted double bond. The H^1 nmr spectrum supported the structural assignments, as the vinyl proton absorption at τ 4.45 corresponded to slightly less than one proton. Mass spectrometry showed the expected molecular ion peak at 332 and all the expected fragment peaks.

Anal. Calcd for $C_{13}H_{18}F_6N_2O$: C, 47.03; H, 5.47; N, 8.44; F, 34.34. Found: C, 47.32; H, 5.51; N, 8.33; F, 33.83.

B. Hydrolysis of the Enamine Adducts to III.—A suspension of 20 g of the enamine adducts in 150 ml of 3 *N* hydrochloric acid was placed in a stoppered flask and allowed to stand at room temperature for 24 hr. The yellow solution thus obtained was cooled in an ice bath and neutralized to pH 7–8 with solid sodium carbonate. A yellow oil formed. The mixture was extracted with ether, and the combined ether extracts were washed with water and dried over magnesium sulfate. The ether was removed under reduced pressure, and the residue distilled through a spinning-band column. The major product (7.7 g, 72% corrected yield) was the amino ketone III: bp 84° (6 mm), $n^{25}D$ 1.4037. Some (6.3 g) starting material was also recovered. The amino ketone had an infrared spectrum with bands at 3400, 3240, and 1620 cm^{-1}, indicating the $-NH_2$ group, and a strong >C=O absorption at 1710 cm^{-1} as well as strong $-CF_3$ absorption. The F^{19} nmr spectrum showed a pair of quartets at +71.0 and +74.7 ppm from $FCCl_3$ (J = 9 cps).

Anal. Calcd for $C_9H_{11}F_6NO$: C, 41.08; H, 4.22; N, 5.53; F, 43.30. Found: C, 41.17; H, 4.07; N, 5.81; F, 43.01.

2-(Hexafluoroisopropylamino)cyclopentanone *via* Enamine Synthesis. A. Reaction of HFAI with 1-N-Morpholinocyclopentane.—A 19-g sample of the enamine[9] and excess HFAI (40 g) were heated together at 150° for 8 hr in a 240-ml Hastelloy bomb tube. The adduct mixture (31.3 g, 87%), bp 80° (0.5 mm) and $n^{25}D$ 1.4372, was isolated. The infrared spectrum of the product had bands at 3370, 3290, and 1615 cm^{-1} for $-NH_2$ absorption, a −C=C− band at 1640 cm^{-1}, and a strong $-CF_3$ absorption. The F^{19} nmr spectrum showed the product to be a mixture of double-bond isomers. A singlet at +75.5 ppm from $FCCl_3$ (29% of the area) suggested the isomer with a tetrasubstituted double bond, while an eight-peak A_3B_3 pattern centered at +74.6 ppm suggested the isomer with a trisubstituted double bond.

Anal. Calcd for $C_{12}H_{16}N_2F_6O$: C, 45.28; H, 5.07; N, 8.80; F, 35.82. Found: C, 45.42; H, 5.12; N, 8.36; F, 36.13.

B. Hydrolysis.—The adduct mixture was hydrolyzed in 68% yield as described above for the C_6 analog. The amino ketone, 2-(hexafluoroisopropylamino)cyclopentanone, had $n^{25}D$ 1.3880 and bp 60–61° (55 mm). The F^{19} nmr spectrum contained a pair of quartets at 71.6 and +76.7 ppm from $FCCl_3$ (J = 9 cps).

Anal. Calcd for $C_8H_9NOF_6$: C, 38.56; H, 3.50; N, 5.62; F, 45.57. Found: C, 38.83; H, 3.74; N, 5.54; F, 45.57.

4-[1-Amino-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]benzoic Acid.—To a solution of 14 g (excess) of sodium dichromate dihydrate, 20 ml of concentrated sulfuric acid and 30 ml of water was added 8 g (0.031 mol) of 4-methyl-α,α-bis(trifluoromethyl)-benzylamine (III). The mixture was refluxed for 3 hr, stirred 17 hr at room temperature, and poured onto 40 g of ice. The white precipitate was collected on a filter and washed with water (12 g wet). The solid was dissolved in 5% aqueous sodium bicarbonate solution and extracted with ether to remove starting material. Reprecipitation with concentrated hydrochloric acid, washing with water, and drying at 40° under vacuum led to 2.7 g (30%) of the acid, mp 100–101°. The infrared spectrum showed bands at 3413 and 3300 cm^{-1} for NH_2, typical broad OH absorption and a carboxylic acid C=O bond at 1710 cm^{-1}. H^1 nmr spectrum (DMSO-d_6) showed a broad exchange peak at τ 3.4 (3 H) and a multiplet (4 H) at τ 1.8; in $CDCl_3$ the H^1 nmr spectrum was an A_2B_2 pattern (τ 1.9) and a broad peak at τ 4.3 (3 H). F^{19} nmr spectrum was a singlet at +76.42 ppm from internal $FCCl_3$ at infinite dilution. Ultraviolet bands were at λ_{max} 281 mμ (ϵ 1151), 273 (1220), 226 (12,600); the mass spectrum had a parent ion at 287 and required fragments.

Anal. Calcd for $C_{10}H_7F_6NO_2$: C, 41.82; H, 2.46; N, 4.88; F, 39.69; neut equiv, 287. Found: C, 42.45; H, 2.61; N, 5.26; F, 39.30; neut equiv, 280, 277.

N-[α,α-Bis(trifluoromethyl)benzyl]acetamide (VII).—A 12-g (0.05 mol) sample of benzylamine VI in 10 ml of glyme was added to 2.0 g of 54% sodium hydride–mineral oil in 60 ml of glyme and stirred at room temperature for 3 days. Then, 12 g of acetyl chloride was added at <10°. The mixture was refluxed for 3 days and decomposed with ice water. A white precipitate was collected, washed with water and pentane, and dried (12.6 g, 88%). A sample was recrystallized from ether–pentane and had mp 166–168°. F^{19} nmr spectrum showed a singlet at +67.6 ppm (external $FCCl_3$) in DMSO-d_6. The infrared spectrum showed secondary amide bands at 1690 and 1572 cm^{-1}. H^1 nmr spectrum (DMSO-d_6) showed aromatic −H at τ 2.52, $COCH_3$ at 7.80, and NH at 1.5. The ultraviolet spectrum showed λ_{max} 267 mμ (ϵ 279), 261 (345), 255 (280).

Anal. Calcd for $C_{11}H_9F_6NO$: C, 46.32; H, 3.18; N, 4.92. Found: C, 46.11; H, 3.26; N, 5.57.

N-[α,α-Bis(trifluoromethyl)-*m*-nitrobenzyl]acetamide (VIII).—To a 6.0-g sample of N-acetobenzylamine VII dissolved in 20 ml of concentrated sulfuric acid was added dropwise at 20–30° (ice bath) 5 ml of 90% nitric acid. After being stirred at room

(8) Boiling points and melting points are uncorrected. Nmr spectra were recorded on Varian Associates instruments (A-60, A-56-60, HR-60). Mass spectra were recorded on a CEC 21-103C instrument with a heated inlet at 150°. Ultraviolet spectra were taken in ethanol, and infrared spectra in CCl_4 unless otherwise specified. Fluorine nmr spectra are reported either at infinite dilution from $CFCl_3$ (also used as solvent) taken as 0 ppm (calibrated for quantitative discussion), or in dilute solution containing a trace of $CFCl_3$ or in dilute solution with neat $CFCl_3$ set externally at zero. To distinguish the second and third methods from the first, we shall refer to them as "not calibrated." Proton nmr spectra were measured in CCl_4 unless stated otherwise. Silicone grease columns at 50–250° were employed for gas chromatographic analysis.

(9) G. Stork, A. Brizzolara, H. Sandesman, J. Szuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

temperature for 1 hr, the reaction mixture was poured onto ice and extracted with ether. The ether extracts were washed with 5% sodium hydroxide solution and with water and were dried over magnesium sulfate. Evaporation gave 4.9 g (70%) of a white solid (VIII), mp 150–151°. The H^1 nmr spectrum (acetone-d_6) showed a multiplet at τ 1.6–2.5, NH absorption at 1.5, and $COCH_3$ at 7.88. F^{19} nmr spectrum showed a singlet at +69.4 ppm (external $FCCl_3$) in acetone-d_6. The ultraviolet showed λ_{max} 340 mμ (sh, ε 114), 257 mμ (ε 7970).

Anal. Calcd for $C_{11}H_8N_2O_3F_6$: C, 40.01; H, 2.44; N, 8.49; F, 34.53. Found: C, 40.89; H, 2.69; N, 8.71; F, 34.71.

m-Nitro-α,α-bis(trifluoromethyl)benzylamine.—A 1.0-g sample of N-acetate VIII was refluxed for 4 hr with 20 ml of 50% aqueous sulfuric acid. After being stirred at room temperature for 4 days, the mixture was poured onto ice and extracted with ether. The extract was washed with water and dried over magnesium sulfate; the ether was evaporated; and infrared analysis of the residue indicated that the hydrolysis was incomplete. This residue was combined with 2.0 g of additional N-acetate and 60 ml of 50% sulfuric acid and the mixture was refluxed for 24 hr and worked up as before. The infrared spectrum of the residue (1.93 g) showed little or no starting material present. Short-path distillation gave 0.8 g of amine IX, bp 128–131° (10 mm). H^1 nmr spectrum showed a multiplet (area 4) at τ 1.3–2.5 for aromatic –H and a singlet at 7.66 for NH_2. The infrared spectrum showed the characteristic NO_2 bands and no amide –CO. The mass spectrum showed the parent and expected fragmentation.

Anal. Calcd for $C_9H_6N_2O_2F_6$: C, 37.56; H, 2.10; N, 9.72; F, 39.56. Found: C, 37.54; H, 2.36; N, 9.72; F, 39.80.

m-Bromo-α,α-bis(trifluoromethyl)benzylamine (X) and Bis(trifluoromethyl)benzylamine Hydrobromide (XI).—A mixture of 24 g of α,α-bis(trifluoromethyl)benzylamine VI (0.1 mol) and 0.3 g of iron powder was heated at 100° with stirring while 16 g of liquid bromine (0.1 mol) was added in one portion. The reaction mixture was heated at 120° for 1.5 hr and at 100° for 17 hr. Crystals appeared on the thermometer. Filtration and washing with ether gave 4.6 g of a slightly orange solid which was purified by recrystallization from absolute ethanol–ether, mp 170–171°. The ultraviolet spectrum showed aromatic absorption at 266 mμ (ε 308), 260 (385), 253 (294), 250 (194). The infrared spectrum showed broad absorption suggestive of an amine hydrobromide. F^{19} nmr spectrum was a singlet at +72.2 ppm from $FCCl_3$. H^1 nmr showed a multiplet at τ 2.3 (5 H aromatic) and a singlet at τ 3.1 (3 H). The solid was, therefore, the hydrobromide XI of the starting amine.

Anal. Calcd for $C_9H_8BrF_6N$: C, 33.35; H, 2.50; F, 35.18; Br, 24.66. Found: C, 33.61; H, 2.82; F, 35.20; Br, 24.17.

The filtrate was taken up in ether, washed with 6 *N* HCl, 10% sodium bisulfite solution, brine, and water, and dried over magnesium sulfate. Infrared and gas chromatographic analyses showed mainly starting material; so the residue was recycled with 1.0 g of iron powder and 13 g of bromine. After the mixture was heated for 1 hr at 120° and 17 hr at 80° (no more crystals appeared), the above work-up was repeated. Distillation (spinning band) afforded 7.4 g (23% yield) of m-bromo-α,α-bis(trifluoromethyl)benzylamine (X), bp 56° (1 mm). The mass spectrum showed the parent ions and expected fragmentation. The ultraviolet spectrum was that of a disubstituted benzene with bands at 275 mμ (ε 380), 268 (480) and 262 (362). The F^{19} nmr spectrum showed a singlet at +74.70 ppm (calibrated in $FCCl_3$). The H^1 nmr spectrum showed a complex multiplet at τ 2.3 (total area 4, but *o*-H at τ 2.05 distinct) and an $-NH_2$ absorption at 7.98.

Anal. Calcd for $C_9H_6BrF_6N$: C, 33.56; H, 1.88; Br, 24.81; F, 35.38; N, 4.35. Found: C, 34.12; H, 2.17; Br, 24.63; F, 35.84; N, 4.12.

3,5-Dimethyl-4-hydroxy-α,α-bis(trifluoromethyl)benzylamine by the Quinomethan Route.—An 8.1-g (0.03 mol) sample of α,α-bis(trifluoromethyl)-2,6-dimethylquinomethan[5] was dissolved in 50 ml of anhydrous ether (orange color) and treated with ammonia gas for 1 hr at 25° and 0.5 hr at 35° (until color faded to light yellow). Excess ammonia and solvent were evaporated and the colorless solid residue was recrystallized from petroleum ether (40–60°) to give white cubes of 3,5-dimethyl-4-hydroxy-α,α-bis(trifluoromethyl)benzylamine (8.0 g, 93%), mp 62–63° (74–75° when the melt was allowed to solidify and then remelted).

Anal. Calcd for $C_{11}H_{11}F_6NO$: C, 46.00; H, 3.86; F, 39.69; N, 4.88. Found: C, 46.15; H, 3.95; F, 39.27; N, 4.72.

See Table I for spectral details.

Registry No.—IIa, 15580-91-3; IIb, 15580-92-4; cyclohexene trisubstituted enamine adduct, 15580-93-5; III, 15580-94-6; cyclopentene tetrasubstituted enamine adduct, 15580-95-7; cyclopentene trisubstituted enamine adduct, 15580-96-8; 2-(hexafluoroisopropylamino)cyclopentanone, 15580-97-9; 4-[1-amino-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]benzoic acid, 15580-98-0; VII, 15580-99-1; VIII, 15581-00-7; IX, 15581-01-8; X, 15581-02-9; XI, 15581-03-0; cyclohexene tetrasubstituted enamine adduct, 15581-06-3.

N,N-Difluoroalkylamines by Direct Fluorination of Alkylamines[1]

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Alkylamines were successfully fluorinated in bicarbonate-buffered aqueous solution to give N,N-difluoroalkylamines. In this way were synthesized N,N-difluorocyclohexylamine, N,N,N′,N′-tetrafluorohexamethylenediamine, N,N-difluoro-*n*-butylamine, N,N-difluorocyclopentylamine, and N,N-difluoro-*t*-butylamine. Attempts to convert N,N-dichloroalkylamines into N,N-difluoroalkylamines by metathetical reactions failed. An unusual method of oxidizing primary amines to nitriles was found. Chlorination of alkylamines to N,N-dichloramines followed by cesium fluoride dehydrochlorination gives the corresponding nitrile in high yield.

In 1961 Grakauskas[3] reported the elegant aqueous fluorination of urea to give N,N-difluorourea. Subsequently additional examples of aqueous fluorination were reported[3,4] which gave amide-type N,N-difluoro compounds. In our laboratories in 1959–1961 our goal was to synthesize N,N-difluoroalkylamines by direct fluorination of alkylamines. We succeeded by a procedure similar to that of Grakauskas but included an essential bicarbonate buffer. In this paper we report our successful and unsuccessful attempts to synthesize N,N-difluoroalkylamines.

The first N,N-difluoroalkylamine was synthesized by Frazer[5] who allowed both methyl and ethyl iodides to react with tetrafluorohydrazine in a light-initiated

(1) Abstracts, the Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 24–28, 1967, p 72.

(2) Department of Chemistry, San Diego State College, San Diego, Calif. 92115.

(3) V. Grakauskas, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 23M; also British Patent 960,126 (June 1964); *Chem. Abstr.*, **61**, 5523*b* (1964).

(4) R. E. Banks, R. N. Haszeldine, and J. P. Lalu, *Chem. Ind.* (London), 1803 (1964); *J. Chem. Soc. Sect. C*, 1514 (1966).

(5) J. W. Frazer, *J. Inorg. Nucl. Chem.*, **16**, 63 (1960).

gas phase reaction to give N,N-difluoromethyl- and difluoroethylamines.

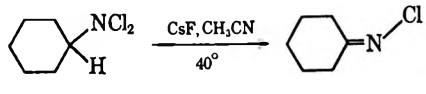
Petry and Freeman[6] synthesized difluoramines by reaction of tetrafluorohydrazine with azo compounds or with hexaphenylethane. Alkylation of carbonium ions with difluoramine (HNF_2) was reported by Graham and Freeman[7] to give N,N-difluoramines. Synthesis of bis(difluoramino) compounds by addition of tetrafluorohydrazine to unsaturated aliphatic and aromatic compounds has been reported by several authors.[8-14] Of the methods reported only the thermal addition of tetrafluorohydrazine to alkenes is really a useful method for preparing large quantities of difluoramino compounds. However, two difluoramino groups are introduced rather than just one. Further, the thermal addition reaction is *extremely hazardous;* tetrafluorohydrazine must be handled with great skill and caution. The method of synthesis which we report here is a direct fluorination of amines in which only one difluoramino group need be introduced and then only at the position of the original amino group. The reaction has the further advantage that it may be carried out safely on a convenient synthetic scale.

Results and Discussion

Our initial attempts to synthesize N,N-difluoroalkylamines were by metathetical reactions on N,N-dichloroalkylamines. Standard fluorinating agents were used such as cesium fluoride, potassium fluoride, silver(I) fluoride, antimony(III) fluoride, and sulfur tetrafluoride. In no case was an N,N-difluoroalkylamine obtained. However, some interesting results were obtained.

Reaction of silver(I) fluoride with N,N-dichloro-*t*-butylamine in refluxing acetonitrile gave isobutylene in greater than 80% yield. Reaction of sulfur tetrafluoride with N,N-dichloro-*t*-butylamine gave an hydrolytically unstable product which appeared to be *t*-butyliminosulfur difluoride on the basis of comparison of its infrared spectrum with infrared spectra of authentic iminosulfur difluorides. Cesium fluoride in refluxing acetonitrile very cleanly dehydrohalogenated amines with α hydrogens in over 90% yields.

$$CH_3CH_2CH_2CH_2NCl_2 \xrightarrow[40^\circ]{CsF,\ CH_3CN} CH_3CH_2CH_2C{\equiv}N$$

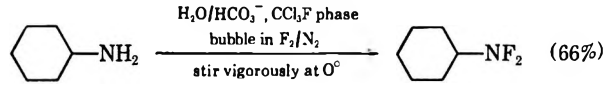


This finding provides a very unique and clean way of oxidizing amines under very mild conditions. The initial hypochlorite chlorination of amines to N,N-dichloramines is extremely mild and essentially a quantitative reaction when the procedure of Jackson, Smart, and Wright is followed.[15] The dehydrohalogenation occurs under such mild conditions that other functional groups in the molecule will be unaffected.

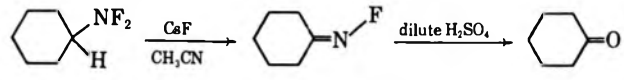
The discouraging results obtained in the attempted metathetical reactions prompted a change in the course of the investigation. The synthesis of N,N-dichloroamines for initial work was by aqueous chlorination in bicarbonate solution.[15] Although not expected

$$RNH_2 \xrightarrow[0^\circ]{HCO_3^-/H_2O,\ Cl_2} RNCl_2$$

to succeed, it was decided to fluorinate cyclohexylamine under the conditions used for forming N,N-dichloramines. In the first attempt about a 1% yield of a mixture of N,N-difluorocyclohexylamine and cyclohexanone was obtained from Dry Ice traps. The conditions of the reaction were modified to include an equal volume of inert trichlorofluoromethane as a second phase to extract product as fast as formed. Under these conditions N,N-difluorocyclohexylamine was obtained in 66%

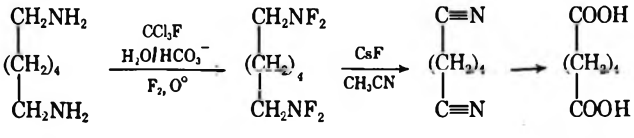


yield. The structure was proved by dehydrofluorination to N-fluorocyclohexylimine and then hydrolysis to cyclohexanone. The infrared and nmr spectral proper-



ties of N,N-difluorocyclohexylamine are given in Table I and are consistent with the structure assigned. Comparisons with the spectral properties of other N,N-difluoroalkylamines are made in Table I.

Aqueous fluorination of diamines can also be carried out. From hexamethylenediamine was obtained N,N,N′,N′-tetrafluorohexamethylenediamine in 25% yield. The infrared spectra and nmr spectra of the bisdifluoramine were consistent with the structure assigned. Chemical proof of structure was obtained by a stepwise conversion into adipic acid.



Using bicarbonate-buffered aqueous fluorination, cyclopentylamine, *n*-butylamine, and *t*-butylamine were converted into their corresponding N,N-difluoramines. The crude N,N-difluorocyclopentylamine contained mainly nitrocyclopentane and cyclopentanone as side-reaction products. The primary side-reaction products with N,N-difluoro-*n*-butylamine were butyronitrile and butyraldehyde. Side-reaction products predominated in the fluorination of *t*-butylamine and the yield of the corresponding difluoramine was low. Pertinent absorptions in the infrared and nmr spectra of the preceding difluoramines are summarized in Table I.

(6) R. C. Petry and J. P. Freeman, *J. Amer. Chem. Soc.*, **83**, 3912 (1961).
(7) W. H. Graham and J. P. Freeman, *ibid.*, **89**, 716 (1967).
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(12) T. E. Stevens and W. H. Graham, *J. Amer. Chem. Soc.*, **89**, 182 (1967).
(13) R. C. Petry, C. O. Parker, F. A. Johnson, and T. E. Stevens, *J. Org. Chem.*, **32**, 1534 (1967).
(14) R. C. Petry, C. O. Parker, F. A. Johnson, T. E. Stevens, and J. P. Freeman, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, O201.
(15) L. L. Jackson, G. N. R. Smart, and G. F. Wright, *J. Amer. Chem. Soc.*, **69**, 1539 (1947).

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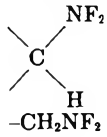
TABLE I
NMR AND INFRARED SPECTRAL DATA ON N,N-DIFLUOROALKYLAMINES

Difluoramine, RNF_2	Group	Nmr spectra: F^a	Nmr spectra: H^b	Ir spectra, absorptions, 10–12-μ region[c]
Cyclohexyl		Doublet, −2318 cps (J_{HF} = 25 cps)	Triplet, 202 cps (J_{HF} = 25 cps)	10.1 (w), 10.4 (s), 10.7 (w), 10.9 (w), 11.45 (w), 11.89 (vs), 12.12 (m)
Bishexamethylene	$-CH_2NF_2$	Triplet, −3122 cps (J_{HF} = 30 cps)	Triplet, 207 cps (J_{HF} = 30 cps)	10.4 (w), 10.6 (w), 11.20 (s), 12 00 (vs), broad shoulders at 12.20, 12.50
n-Butyl	$-CH_2NF_2$	Broad poorly resolved triplet, −3080 cps	Triplet, 198 cps (J_{HF} = 28 cps)	10.2 (w), 10.85 (s), 11.45 (m), 11.85 (s), 12.50 (w)
t-Butyl		Singlet, −1530 cps		9.6 (s), 10.5 (vs), 11.2 (vs)
Cyclopentyl				9.85 (m), 10.67 (m), 11.45 (s)

[a] F spectra at 56.4 Mc/sec relative to CCl_3F. [b] H spectra at 60.0 Mc/sec reported as positive values downfield from tetramethylsilane. [c] Wavelengths in μ. The N–F characteristic absorptions are in the 10–12-μ region.

The aqueous fluorination of amines was best achieved at a constant buffered pH near 7.5. No difluoramines were formed below pH 5.5 or above 9. Aromatic amines are insoluble in bicarbonate solution. At pH values low enough to bring aromatic amines into solution only azo-coupling products were obtained. The most probable fluorinating specie is hypofluorous acid formed initially from reaction of fluorine and water ($F_2 + H_2O$ = [HOF] +HF). No evidence is available to rule out hydrated molecular fluorine as an intermediate ($F_2 \cdot (H_2O)_x$). The presence of an equilibrium amount of free amine is probably important. A detailed study of the reaction of fluorine with water and with carefully buffered aqueous solutions seems highly desirable and will be carried out in the future.

Experimental Section

All melting points are corrected. Spectra were obtained with a Perkin-Elmer Model 21 and a Varian HR-56.4/60.0. Fluorine nmr spectra were recorded at 56.4 Mc/sec and are reported in cycles per second (cps) relative to the F absorption of trichlorofluoromethane. Proton nmr spectra were recorded at 60.0 Mc/sec and are reported in cycles per second (cps) relative to tetramethylsilane.

N,N-Difluorocyclohexylamine.—To an ice-cooled 2-l. flask equipped with a thermometer, Dry Ice condenser, high speed stirrer, and a gas sparger was added 1200 ml of water, 200 g (2.38 mol) of sodium bicarbonate, 70.0 g (0.707 mol) of cyclohexylamine, and 200 ml of trichlorofluoromethane. The mixture was stirred with great vigor to achieve intimate mixing (very important) until an internal temperature of less than 2° was observed. A fluorine–nitrogen stream (100 cc of F_2/min, 200 cc of N_2/min) was bubbled through the mixture for 5.5 hr. Nitrogen (200 cc/min) was bubbled through for 0.5 hr and 200 ml of CH_2Cl_2 was then added. The organic phase was separated and reduced in volume to 100 ml by distillation. The CH_2Cl_2 was washed successively with two 20-ml portions of cold concentrated H_2SO_4, three 100-ml portions of water, 100 ml of 5% HCO_3^- solution, and finally with 100 ml of water. After drying over $MgSO_4$, the CH_2Cl_2 solution was distilled under reduced pressure through a 25-cm Vigreaux column. N,N-difluorocyclohexylamine was collected over the boiling point range 69–81° (80–90 mm), $n^{25}D$ 1.4058.

Anal. Calcd for $C_6H_{11}NF_2$: C, 53.32; H, 8.20; N, 10.36. Found: C, 52.12; H, 8.26; N, 11.14.

The original aqueous phase was made basic with sodium hydroxide and extracted continuously with diethyl ether. From the ether extract was recovered 52 g of unreacted cyclohexylamine. The yield of N,N-difluorocyclohexylamine was 66% based on cyclohexylamine and 23% based on fluorine.

The sulfuric acid washes were neutralized with sodium hydroxide and extracted continuously with CH_2Cl_2. From the CH_2Cl_2 extract was obtained 1.0 g of cyclohexanone.

The structure of N,N-difluorocyclohexylamine was proved by treating 2.0 g with 10.0 g of cesium fluoride in 25 ml of dry CH_3CN at 40° for 48 hr. Solids were separated and the solution distilled. About 1.5 g of the product N-fluorocyclohexylimine was obtained by distillation under reduced pressure, bp ~60° (80 mm). The fluorine nmr spectrum at 56.4 Mc/sec had a single absorption at −935 cps from CCl_3F.

Anal. Calcd for $C_6H_{10}NF$: F, 12.7. Found: F, 12.3.

The sample of N-fluorocyclohexylimine was heated under reflux with 10 ml of 2 *M* H_2SO_4. Cyclohexanone was steam distilled and identified by its infrared spectrum and formation of a 2,4-dinitrophenylhydrazone, mp 160–161°.

N,N,N′,N′-Tetrafluorohexamethylenediamine.—A slurry prepared from 23.2 g (0.200 mol) of hexamethylene diamine, 66 g (0.80 mol) of sodium bicarbonate, 600 ml of water, and 200 ml of trichlorofluoromethane was fluorinated in a manner similar to that just described. Following a similar work-up 6.0 g (23% based on recovered starting material) of N,N,N′,N′-tetrafluorohexamethylenediamine was obtained, bp 70–75° (0.1 mm).

Anal. Calcd for $C_6H_{12}N_2F_4$: C, 38.29; H, 6.43; N, 14.89; F, 40.39. Found: C, 37.04; H, 6.58; N, 15.46; F, 39.6.

The structure of N,N,N′,N′-tetrafluorohexamethylenediamine was proved by a series of steps to convert it into dimethyl adipate. Purified 1,6-bis(difluoroamino)hexane (2.0 g) was heated in CH_3CN with 20 g of CsF under gentle reflux. Solid was filtered and solvent stripped off under reduced pressure to give a dark brown oil whose spectrum contained all the bands corresponding to adiponitrile plus extra bands from impurities. The impure adiponitrile was hydrolyzed with a solution containing 10 ml of 85% H_3PO, 4 ml of concentrated H_2SO_4 and 1 ml of water. After work-up 1.0 g of crude adipic acid, mp 149.3–150.8° (lit.[16] mp 153°) was obtained whose infrared spectrum was identical with that of authentic material. The adipic acid was converted by diazomethane into dimethyl adipate which had an identical gas chromatographic retention time and identical infrared spectrum with those of authentic dimethyl adipate.

Other N,N-Difluoroalkylamines.—The method for synthesis of N,N-difluorocyclohexylamine was used to synthesize the *n*-butyl, *t*-butyl, and cyclopentyl analogs. Structure of N,N-difluoro-*n*-butylamine was proved by dehydrofluorination to butyronitrile. Structure of N,N-difluorocyclopentylamine was proved by dehydrofluorination followed by hydrolysis to cyclopentanone. The structure of N,N-difluoro-*t*-butylamine was inferred from spectral data.

N,N-Dichlorocyclohexylamine.—The title compound was prepared by the method of Jackson, Smart, and Wright[16] with consistent yields of over 90%. The product was characterized by an intense absorption in its infrared spectrum at 14.45 μ.

N-Chlorocyclohexylimine.—A mixture of 10.0 g (0.0599 mol) of N,N-dichlorocyclohexylamine, 20.0 g (0.132 mol) of cesium fluoride and 100 ml of acetonitrile was stirred and heated at 45° for 48 hr. The reaction mixture was cooled to room temperature and filtered. The filtrate was subjected to sufficiently reduced pressure to distil off CH_3CN and the pressure was then reduced to 1 mm. N-Chlorocyclohexylimine distilled at 60° and amounted to 7.1 g (90%). On one occasion, rapid and violent decomposition occurred during distillation. Rudner[17] has previously reported that decomposition of N-chlorocyclohexylimine occurs at 90°.

(16) Handbook of Chemistry and Physics, 45th ed, The Chemical Rubber Co., Cleveland, Ohio, p C-358.

(17) B. Rudner, U. S. Patent 2,894,028 (1956).

Extreme caution must be exercised in distilling N-chlorocyclohexylimine.

The infrared spectrum of a film of N-chlorocyclohexylimine has absorption bands (μ) and relative intensities (absorbancies) as follows: 3.44 (vs), 5.78 (w), 6.20 (m), 6.91 (vs), 7.00 (s), 7.45 (m), 7.65 (m), 8.03 (m), 8.30 (m), 8.89 (m), 9.13 (w), 9.25 (w), 9.86 (w), 10.19 (s), 10.95 (w), 11.10 (w), 11.69 (m), 11.90 (w), 13.10 (m), and ~14.9 μ (s) cut-off of spectrum. Shoulders are not reported.

Oxidation of *n*-Butylamine to Butyronitrile.—The procedure of Jackson, Smart, and Wright[15] was used to synthesize N,N-dichlorobutylamine in greater than 90% yield. The dichloroamine was dehydrochlorinated and worked up in a manner similar to the procedure described for N-chlorocyclohexylimine. Butyronitrile was obtained in greater than 90% yield and identified by its infrared spectrum and by its identical gas chromatographic retention time with that of authentic butyronitrile.

Registry No.—N,N-Difluorocyclohexylamine, 14182-78-6; N-fluorocyclohexylimine, 15645-66-6; N,N,N′,N′-tetrafluorohexamethylenediamine, 15645-67-7; N,N-difluoro-*n*-butylamine, 10524-16-0; N,N-difluoro-*t*-butylamine, 646-55-9; N,N-difluorocyclopentylamine, 14182-80-0; N-chlorocyclohexylimine, 6681-70-5.

The Trichloromethylation Reaction. III. Reaction with Benzoic Anhydride and Participation by the Solvent 1,2-Dimethoxyethane[1]

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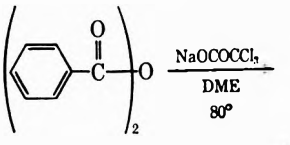
Received October 9, 1967

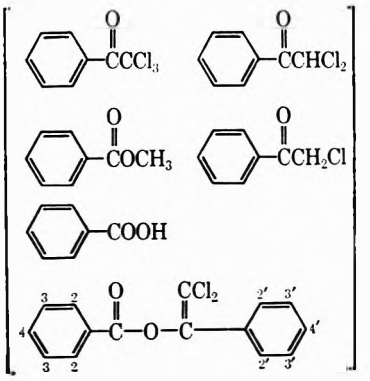
Reaction of sodium trichloroacetate with benzoic anhydride in dimethoxyethane (DME) solution yields $C_6H_5COOC(=CCl_2)C_6H_5$ (**1**, 79%), benzoic acid, some methyl benzoate, and minor amounts of α,α,α-trichloro-, α,α-dichloro-, and α-chloroacetophenone. A similar reaction with *p,p′*-dichlorobenzoic anhydride gives the corresponding *p,p′*-dichloro analog (**2**) of **1**, methyl *p*-chlorobenzoate, and the *p*-chloro analogs of the other minor components. The reaction of sodium trichloroacetate with α,α,α-trichloroacetophenone and *p,p′*-dichlorobenzoic anhydride in DME produces p-$ClC_6H_4COOC(=CCl_2)C_6H_5$ (**3**). The proposed mechanism for the formation of **1**, **2**, and **3** involves the abstraction of chlorine from α,α,α-trichloroacetophenone, initially produced by a normal trichloromethylation reaction, followed by a condensation of the enolate anion with the parent anhydride. The methyl benzoate originates from the DME solvent. Reaction of sodium trichloroacetate, α,α,α-trichloroacetophenone, and DME also gives methyl benzoate. Reaction of DME with various bases produces formaldehyde and ethylene. These results are accounted for by a mechanism involving the abstraction of a proton from the methyl group of DME and a resulting decomposition of the DME. The methoxide ion produced in the decomposition then attacks the trichloroacetophenone to give methyl benzoate.

Sodium trichloroacetate has been shown to be a useful reagent for the trichloromethylation of anhydrides.[2,3] The success of this reaction is greatly dependent upon the nature of the anhydride and the reactivity of the resulting product. High yields (70–90%) of trichloromethylation products are obtained in several instances, but in others the yields are moderate to very low. One factor which definitely affects the yield is the ease by which the primary trichloromethylation product reacts with sodium trichloroacetate to provide additional reaction products. In the case of succinic anhydride, the initially formed 5,5,5-trichlorolevulinic acid reacts further with the trichloromethyl anion to give dichloroprotoanemonin, apparently by α-proton abstraction followed by cyclization and elimination of hydrogen chloride.[4] The reaction of sodium trichloroacetate with benzoic anhydride, which was previously reported to give a 13% yield of α,α,α-trichloroacetophenone,[2] has now been found to be another case in which further reactions of the product occur. In this paper a detailed account of this reaction will be presented along with studies which have provided reasonable mechanisms to account for most of the observed products. An unusual participation by the solvent, dimethoxyethane, is included.

The reaction of sodium trichloroacetate with benzoic anhydride in dimethoxyethane (DME) solution results in a complex mixture of products (Scheme I). After

SCHEME I





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removal of the benzoic acid, the residue was separated by distillation into three fractions. The low boiling fraction was fairly pure methyl benzoate. The second fraction was a mixture of α,α,α-trichloro-, α,α-dichloro-, and α-chloroacetophenone in 1.4, 2.8, and 1.0% yield, respectively, as determined by vpc analysis. The

(1) Taken in part from the M. S. Thesis of R. E. Thomas, West Virginia University, Morgantown, W. Va., 1967, and the M. S. Thesis of D. E. Battin, Kanawha Valley Graduate Center of West Virginia University, Morgantown, W. Va., 1965. Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, and at the 42nd Annual Meeting of the West Virginia Academy of Science, Morgantown, West Virginia, April, 1967.

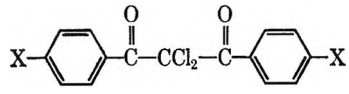
(2) A. Winston, J. P. M. Bederka, W. G. Isner, P. C. Juliano, and J. C. Sharp, *J. Org. Chem.*, **30**, 2784 (1965).

(3) A. Winston, J. C. Sharp, K. E. Atkins, and D. E. Battin, *ibid.*, **32**, 2166 (1967).

(4) A. Winston and J. C. Sharp, *J. Amer. Chem. Soc.*, **88**, 4196 (1966).

high boiling fraction was identified as the dichloromethylene compound 1, and was the major reaction product, obtained in 79% yield based on 2 moles of anhydride required per mole of compound 1.

The structural assignment of compound 1 is consistent with the elemental analysis, the carbonyl peak at 1750 cm^{-1} in the infrared spectrum, and the fact that on acidic hydrolysis both benzoic acid and dichloroacetophenone were obtained. The unsymmetrical structure 1, as opposed to the symmetrical structure A, is supported by the appearance of two aromatic multiplets in the nmr spectrum in the area ratio of 1:4 (Table I).



A, X=H
B, X=Cl

The downfield multiplet is assigned to the two H_2 protons *ortho* to the carbonyl group, while the upfield multiplet includes the eight other protons.

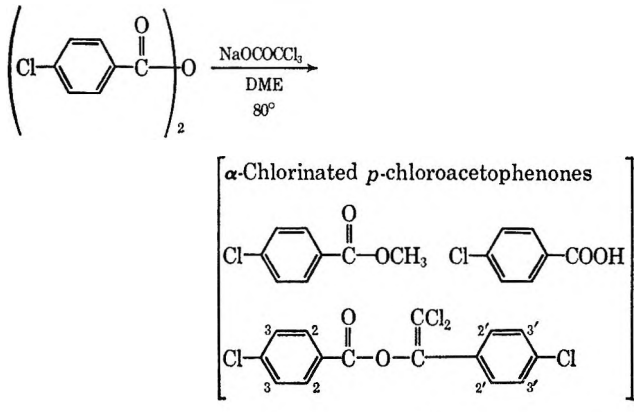
TABLE I
NMR AND INFRARED DATA

	Nmr[a]					
Compd	Proton assignment	Chemical shift, τ	Multiplicity	Area ratio	Coupling constants, cps	Infrared,[b] $\nu_{C=C}$, cm^{-1}
1	H_2	2.0	m	1		1750
	H_3,H_4,H_2' H_3',H_4'	2.6	m	4		
2	H_2	1.99	q[c]	1	$J_{2,3}$ = 8	1747
	H_3	2.56				
	H_2'	2.49	q[c]	3	$J_{2',3'}$ = 9	
	H_3'	2.76				
3	H_2	2.03	q[c]	2	$J_{2,3}$ = 8	1747
	H_3	2.66				
	H_2',H_3',H_4'	2.7	m	7		

[a] Carbon tetrachloride solution. [b] Neat. [c] The basic pattern is a quartet. Fine splitting due to AA', AB', and BB' coupling was observed, but was not analyzed in detail.

The *p,p'*-dichloro analog of 1 (compound 2) was prepared in 30% yield by the reaction of sodium trichloroacetate with *p,p'*-dichlorobenzoic anhydride in DME solution. Methyl *p*-chlorobenzoate, *p*-chlorobenzoic acid, and a small amount of a mixture of α-chlorinated *p*-chloroacetophenones were also obtained (Scheme II).

SCHEME II



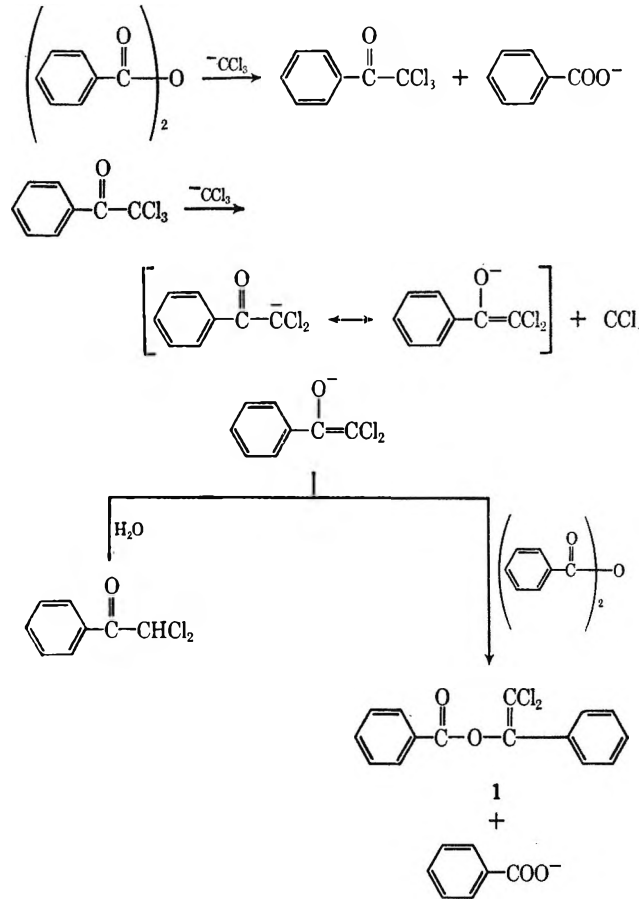
2

The presence of the two primary A_2B_2 quartets in the nmr spectrum of 2, Table I, clearly reveals the presence of the two nonequivalent *p*-chlorophenyl groups and completely rules out the alternate symmetrical structure B, which would possess only a single quartet. The downfield doublet at τ 1.99 is assigned to the H_2 protons, consistent with the usual downfield shift of aromatic protons *ortho* to a carbonyl substituent.

The study of the mechanism of the reaction of sodium trichloroacetate with benzoic anhydride involved two areas of investigation: (a) reactions leading to the dichloromethylene compounds 1 and 2 and (b) reactions leading to the rather surprising formation of methyl benzoate.

The mechanism shown in Scheme III accounts for the products indicated in Scheme I with the exception of methyl benzoate and α-chloroacetophenone. The first

SCHEME III



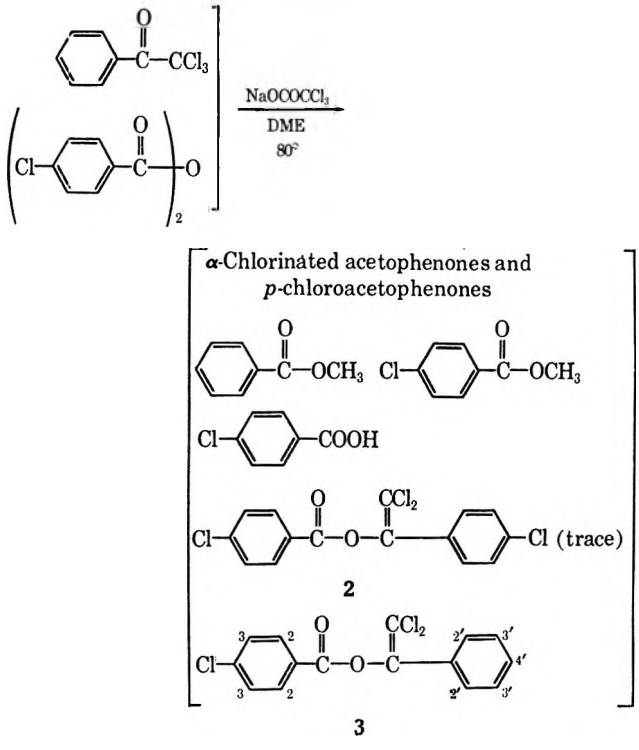
reaction of Scheme III shows the normal course of the trichloromethylation reaction of an anhydride. Abstraction of chlorine from the product, trichloroacetophenone, by the trichloromethyl anion would give rise to the enolate anion, which on condensation with unreacted benzoic anhydride would give 1, or on addition of water to the reaction mixture would give dichloroacetophenone. Chlorine abstraction is a typical reaction of the trichloromethyl ion and is known to lead to complex condensation products.[5]

In order to determine if 1 is indeed formed through a reaction involving both trichloroacetophenone and the anhydride, a mixed reaction was carried out between

(5) W. M. Wagner, H. Kloosterziel, and A. F. Bickel, *Rec. Trav. Chim.*, **81**, 933 (1962).

α,α,α-trichloroacetophenone, p,p'-dichlorobenzoic anhydride, and sodium trichloroacetate in DME solution (Scheme IV). Compound **3** was obtained in 25%

SCHEME IV



yield. A trace of **2**, but no **1**, was indicated by vpc. The position of the *p*-chloro substituent was established through the nmr spectrum (Table I), which exhibited the A_2B_2 pattern of a *para*-substituted phenyl ring with the A_2 protons *ortho* to a carbonyl substituent and the B_2 protons *ortho* to the chlorine. Confirmation of the structural assignment was obtained through acid methanolysis of **3**, which produced methyl *p*-chlorobenzoate and α,α-dichloroacetophenone.

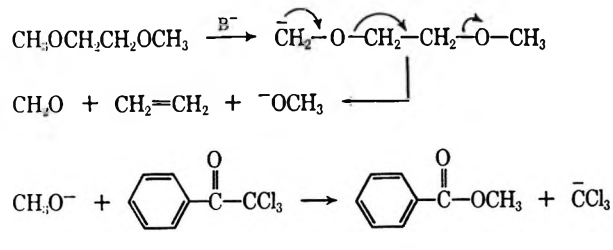
The isolation of **3** as the major product of this reaction is entirely consistent with the mechanism proposed in Scheme III, and confirms the proposal that formation of dichloromethylene compounds **1**, **2**, and **3**, requires the condensation of the trichloroacetophenone with the anhydride. A direct route, as proposed by Villieras and Normant[6] to explain the formation of similar dichloromethylene compounds from the reaction of trichloromethyl magnesium chloride with anhydrides, thus cannot apply to these sodium trichloroacetate reactions. The failure to detect **1** in the reaction shown in Scheme IV and the fact that from a reaction between sodium trichloroacetate and trichloroacetophenone in DME no **1** was obtained indicate that the condensation is not between the enolate anion and trichloroacetophenone. The origin of the α-chloroacetophenone (Scheme I) is still under investigation.

The origin of methyl benzoate produced in the reaction of sodium trichloroacetate with benzoic anhydride in DME must be through solvent participation. Not only is DME the only reasonable source of the methoxide ion, but, when other solvents such as dioxane or tetrahydrofuran were used, no methyl benzoate was observed. The reaction between sodium trichloroacetate, α,α,α-trichloroacetophenone, and DME also produces methyl benzoate, which suggests that the trichloromethyl anion reacts with DME to produce methoxide ion, which then reacts with trichloroacetophenone to form methyl benzoate by displacement of the trichloromethyl group. Other bases may be used to generate the methoxide ion from DME. Reaction of α,α,α-trichloroacetophenone with DME in the presence of either calcium hydride or phenyl(trichloromethyl)mercury provided small amounts of methyl benzoate.

In determining the mechanism by which the base reacts with DME to produce methoxide ion, two paths should be considered. Abstraction of a methyl proton, followed by decomposition of the DME anion, would produce formaldehyde, ethylene, and methoxide ion. On the other hand, abstraction of a methylene proton would lead to methyl vinyl ether and methoxide ion. In order to distinguish between these two possible paths, the volatile products of the reactions were analyzed. The gases evolved in the reaction between sodium trichloroacetate, α,α,α-trichloroacetophenone, and DME were condensed in a Dry Ice cold trap. Infrared analysis of the products collected revealed formaldehyde. Formaldehyde was also evolved on heating DME with sodium trichloroacetate, calcium hydride, or lithium aluminum hydride. The vapors from these reactions were also passed through a solution of bromine in carbon tetrachloride. On vpc analysis of the products isolated from the carbon tetrachloride, 1,2-dibromoethane was found, thus indicating ethylene as one of the products from the decomposition of DME. In the absence of base, refluxing DME still produced a trace of formaldehyde, but no ethylene could be found. Although methyl vinyl ether was sought in the cold trap as was the dibromide from the carbon tetrachloride solution, none was found.

The generation of methoxide ion, ethylene, and formaldehyde from DME by the action of base indicates that the mechanism of the reaction most likely proceeds through an initial abstraction of a proton from the methyl group by the base, followed, or accompanied, by a decomposition to give the observed products. The methoxide ion then attacks the trichloroacetophenone to give methyl benzoate (Scheme V). This decomposition of DME is an example of the "fragmentation reaction" recently reviewed by Grob and Schiess.[7]

SCHEME V



These results clearly reveal that DME is not nearly so inert as is generally thought, but under basic conditions is rather reactive, and this reactivity should be considered when DME is employed as a reaction medium.

Two reasons can now be provided to account for the low yields of trichloromethylation products occurring in

(6) J. Villieras and H. Normant, *Compt. Rend.*, **264**, 593 (1967).

(7) C. A. Grob and P. W. Schiess, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1 (1967).

certain cases. First, the trichloromethylation product may, through loss of chlorine or an active proton,[4] undergo condensation reactions which consume not only the trichloromethylation product itself, but the parent anhydride as well. Second, additional losses of the trichloromethylation products occur through reaction with methoxide ion from the DME solvent. It is significant that the yield of trichloromethylation product is quite high when the product happens to precipitate from the reaction mixture, and is thereby removed from the site of further reaction. The cyclic anhydrides, generally providing high yields, are of this class and precipitate during the reaction as the sodium salt of the trichloromethyl keto acids.[2,3]

The role of the solvent in determining product ratios is not fully understood. In tetrahydrofuran and dioxane the yields of α,α,α-trichloroacetophenone were markedly improved, increasing to 40 and 57%, respectively, while the yield of condensation product 1 decreased to about 40%. Apparently, in these solvents the relative rates of the various competing reactions do not favor the formation of the condensation product as they do in the case of DME.

The reaction of sodium trichloroacetate with DME suggests that the mechanism of dichlorocarbene insertion reactions may well proceed by way of an initial proton abstraction, followed by the successive addition of dichlorocarbene and a proton, as originally proposed in 1961 by Parham and Koncos.[8] Other proposed mechanisms include ylide intermediates,[8] direct insertion,[9] and hydride ion abstraction.[10] In the case of DME, if proton abstraction by base is rapidly followed by decomposition, dichlorocarbene addition would not be observed. In our work as well as that of Wagner, *et al.*,[5,11] no dichlorocarbene insertion products of DME have been found. In other cases, such as tetrahydrofuran,[10] where α insertion of dichlorocarbene readily occurs, fragmentation of the intermediate anion would not be expected.

Experimental Section

Melting points (determined on a Mel-Temp block) and boiling points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on the Perkin-Elmer 137 and Beckman IR-8 spectrophotometers. The nmr spectra were recorded on the Varian Associates, HA-60, high resolution spectrometer using TMS as the internal standard. Vapor phase chromatography was performed on a Perkin-Elmer 154 vapor fractometer with thermal conductivity detector without correction for molar response. The following columns, constructed from 0.25-in. copper tubing, were used: column A, 20% SE-30 on firebrick (60–80 mesh), 6 ft, 170°, with 30 psi of helium for methyl benzoate, methyl-*p*-chlorobenzoate, and α-chlorinated acetophenones and *p*-chloroacetophenones; column B, 2% SE-30 on Chromosorb W, 2 ft, 182°, with 10 psi of helium for **1**, **2**, and **3**; column C, 15% SF-96 on firebrick (60–80 mesh), 12 ft, 130°, with 21 psi of helium for 1,2-dibromoethane and methyl 1,2-dibromoethyl ether; column D, 5% diisodecylphthalate on Fluoropak 80 (20-80 mesh), 2 ft, 132°, with 13 psi helium for methyl benzoate. Compounds were identified by peak enhancement on admixture of the unknown mixture with authentic samples of the known compounds.

(8) W. E. Parham and R. Koncos, *J. Amer. Chem. Soc.*, **83**, 4034 (1961).
(9) E. K. Fields, *ibid.*, **84**, 1744 (1962).
(10) J. C. Anderson, D. G. Lindsay, and C. B. Reese, *J. Chem. Soc.*, 4874 (1964).
(11) W. M. Wagner, H. Kloosterziel, and S. Van der Ven, *Rec. Trav. Chim.*, **80**, 740 (1961); W. M. Wagner, H. Kloosterziel, and A. F. Bickel, *ibid.*, **81**, 925 (1962); W. M. Wagner, private communication.

Materials.—Dimethoxyethane (DME) and dioxane were stored over calcium hydride and distilled over calcium hydride before use. Tetrahydrofuran was treated with potassium hydroxide and distilled over calcium hydride. Sodium trichloroacetate was prepared from trichloroacetic acid and sodium hydride in ether, as described in an earlier communication.[3] *p,p'*-Dichlorobenzoic anhydride was prepared by the reaction of the acid chloride with pyridine.[12] Phenyl(trichloromethyl)mercury was prepared by the method of Logan.[13]

Reaction of Sodium Trichloroacetate with Benzoic Anhydride. A. DME Solvent.—A solution of 50 g (0.22 mol) of benzoic anhydride and 135 g (0.727 mol) of sodium trichloroacetate in 300 ml of DME was stirred at 85°. After 10 min a gelatinous solid separated. An additional 100 ml of DME was added and heating was continued for 2 hr. The reaction mixture was diluted with 500 ml of water and the solution was then extracted with ether. The ether solution was washed with two 150-ml portions of sodium bicarbonate solution and two 150-ml portions of water, dried over anhydrous magnesium sulfate, and evaporated to a small volume. Distillation gave 1.0 g (0.0073 mol, 3.3%) of methyl benzoate, bp 35–43° (2 mm), 2.2 g of a second fraction, bp 40–60° (0.3 mm), and 25.6 g (0.0873 mol, 79%) of **1**, a heavy oil, bp 140–165° (0.33 mm). The methyl benzoate was identified by comparison of the infrared spectrum with that of an authentic sample and by vpc. Vpc of the second fraction, using column A, showed that it was a mixture containing α-chloroacetophenone, α,α-dichloroacetophenone, and α,α,α-trichloroacetophenone in a molar ratio of 1.0:2.7:1.3, which is equivalent to 1.0, 2.8, and 1.4% yields, respectively. The third fraction, bp 140–165° (0.3 mm), was redistilled and analyzed.

Anal. Calcd for $C_{15}H_{10}Cl_2O_2$: C, 61.45; H, 3.44; Cl, 24.19. Found: C, 61.14; H, 3.39; Cl, 24.29.

B. Dioxane Solvent.—A mixture of 100 g (0.443 mol) of benzoic anhydride, 120 g (0.65 mol) of sodium trichloroacetate, and 1000 ml of dioxane was stirred at 110° for 5.5 days. The solution was cooled and filtered, and the bulk of the dioxane was removed by evaporation. The residue was dissolved in ether and washed twice with saturated sodium bicarbonate solution and twice with water. The solution was dried over anhydrous magnesium sulfate and evaporated. The residue was fractionally distilled to yield as a first fraction 63.5 g of an oil, bp 98.0–99.5° (3.2 mm). Vpc analysis of the oil, using column A, showed that it was a mixture of α,α,α-trichloroacetophenone and α,α-dichloroacetophenone in a 5.8:1.0 ratio, which is equivalent to a 57 and a 9% yield, respectively. A second fraction, 26 g (0.088 mol, 40%) of **1**, bp 150–164° (0.5 mm), was obtained.

C. Tetrahydrofuran Solvent.—A mixture of 40.0 g (0.18 mol) of benzoic anhydride, 100 g (0.54 mol) of sodium trichloroacetate, and 800 ml of tetrahydrofuran was stirred for 20 hr at 65° and then for 10 hr at room temperature. About 450 ml of tetrahydrofuran was removed by distillation. The residue was dissolved in ether and washed four times with a saturated solution of sodium bicarbonate and once with water. The solution was dried over anhydrous magnesium sulfate and evaporated. The residue was fractionally distilled to yield 4.0 g of 2-(dichloromethyl)tetrahydrofuran,[10] bp 54–56° (3.5 mm), bp 181° (1 atm), 19.4 g of an oil, bp 88° (0.6 mm), and 11.6 g (0.040 mol, 44%) of **1**, bp 165–168° (0.7 mm). Identification of 2-(dichloromethyl)tetrahydrofuran was made by spectral comparison with an authentic sample synthesized according to the method of Anderson.[10] Vpc of the oil, bp 88° (0.6 mm), using column A, showed that it was a mixture of α,α,α-trichloroacetophenone and α,α-dichloroacetophenone in 5:1 molar ratio, which is equivalent to 40 and 8% yields, respectively.

Acid Hydrolysis of Compound 1.—A solution of 1.0 g (0.0034 mol) of **1** in 25 ml of methanol was heated under reflux for 16 hr in the presence of a slow stream of anhydrous hydrogen chloride. The reaction mixture was taken up in ether and washed with dilute hydrochloric acid, 20% sodium hydroxide, and water. Evaporation of the ether gave 0.6 g of an oil, which was shown by its infrared spectrum to contain α,α-dichloroacetophenone. Acidification of the basic washings gave 0.3 g (0.002 mol) of benzoic acid, mp 121–122°.

The α,α-dichloroacetophenone fraction was dissolved in 25 ml of methanol. To the stirred solution was added 2 g of sodium

(12) C. F. H. Allen, C. J. Kibler, D. M. McLachlin, and C. V. Wilson in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 29.
(13) T. J. Logan, *J. Org. Chem.*, **28**, 1129 (1963).

borohydride over a 5-min period. Stirring was continued for an additional 15 min. The reaction mixture was diluted with 100 ml of water and extracted with ether. Evaporation of the ether gave 0.5 g of an oil, which on crystallization from hexane gave 0.3 g of 2,2-dichloro-1-phenylethanol, mp 53.0–53.5° (lit.[14] mp 54°).

Reaction of Sodium Trichloroacetate with *p,p'*-Dichlorobenzoic Anhydride in DME.—A mixture of 25 g (0.085 mol) of *p,p'*-dichlorobenzoic anhydride in 400 ml of DME was stirred at 85° for 2 hr in order to fully dissolve the anhydride. Sodium trichloroacetate, 60 g, was added and the mixture was stirred at 85° for 5 hr. After 2 and 4 hr, additional 15-g portions of sodium trichloroacetate were added for a total of 90 g (0.49 mol). About 150 ml of DME was removed by distillation. The residue was dissolved in ether and the ether solution was washed with sodium bicarbonate, sodium carbonate, and water and dried over magnesium sulfate. Evaporation of the ether followed by fractional distillation of the residue yielded 0.5 g of methyl *p*-chlorobenzoate, bp 80° (1.1 mm), mp 40–42° (lit.[15] mp 43°), 1.3 g of a second fraction of oil, bp 103–110° (0.5 mm), and 18.4 g of residue. The second fraction of oil was shown by vpc, using column A, to be a mixture of α,α,α-trichloro-*p*-chloroacetophenone and α,α-dichloro-*p*-chloroacetophenone in a molar ratio of 3.5:1, respectively. On standing for several weeks a brown solid crystallized from the dark residue. The solid was removed by filtration and sublimed to give 3.92 g (0.013 mol, 30%) of **2**. Recrystallization from petroleum ether (bp 65–67°) gave white crystals, mp 79.0–80.5°.

Anal. Calcd for $C_{15}H_8Cl_4O_2$: C, 49.76; H, 2.23; Cl, 39.18. Found: C, 49.56; H, 2.41; Cl, 39.27.

Methyl-*p*-chlorobenzoate was identified by comparison of the infrared and nmr spectra with those of an authentic sample and by vpc, using column A.

Reaction of Sodium Trichloroacetate with *p,p'*-Dichlorobenzoic Anhydride and α,α,α-Trichloroacetophenone in DME.—A mixture of 21 g (0.093 mol) of α,α,α-trichloroacetophenone, 15 g (0.051 mol) of *p,p'*-dichlorobenzoic anhydride, and 75 g (0.40 mol) of sodium trichloroacetate in 400 ml of dimethoxyethane was stirred at 85° for 2 hr. About 200 ml of DME was removed by distillation. The residue was dissolved in ether and the solution was washed with saturated sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and evaporated. The residue was fractionally distilled to give 8.1 g of a clear oil, bp 60–160° (1.0 mm), and 4.1 g (0.013 mol, 25%) of **3**, a heavy oil, bp 160–178° (0.7 mm). The first fraction was shown by vpc analysis, using column A, to be a mixture of methyl benzoate, methyl-*p*-chlorobenzoate, and various α-chlorinated acetophenones and *p*-chloroacetophenones. Acidification of the basic washings yielded 1.6 g (0.010 mol) of *p*-chlorobenzoic acid, mp 232–239° (lit.[16] mp 239–240°). On further purification by distillation, **3** crystallized. The solid was recrystallized twice from petroleum ether (bp 65–67°) to give fine white crystals, mp 49.0–49.5°.

Anal. Calcd for $C_{15}H_9Cl_3O_2$: C, 55.00; H, 2.77; Cl, 32.47. Found: C, 55.18; H, 2.84; Cl, 32.68.

The vpc retention time for **3** was midway between those of **1** and **2**. Vpc analyses of **3** before purification revealed a trace of **2**.

Acid Methanolysis of Compound 3.—A 1.25-g (0.0038 mol) portion of **3** was dissolved in 25 ml of methanol and heated under reflux for 19 hr in the presence of a slow stream of anhydrous hydrogen chloride. The solution was cooled and diluted with ether. The ether solution was washed with dilute hydrochloric acid, water, and sodium hydroxide solution. Acidification of the basic washings yielded 0.05 g of *p*-chlorobenzoic acid, mp 230–240° (lit.[16] mp 239–240°). The ether solution was dried over anhydrous magnesium sulfate and evaporated. Vpc of the residue, using column B, showed that the primary constituents of the mixture were α,α-dichloroacetophenone and methyl-*p*-chlorobenzoate.

Reaction of Sodium Trichloroacetate with α,α,α-Trichloroacetophenone in DME.—A mixture of 19.0 g (0.085 mol) of α,α,α-trichloroacetophenone, prepared by the reaction of sodium trichloroacetate with benzoic anhydride in dioxane, 40.0 g (0.216 mol) of sodium trichloroacetate, and 170 ml of DME was stirred at 85° for 20 min. Water was added and the mixture was extracted with ether. The ether solution was washed with sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and evaporated. The residue was fractionally distilled to yield 0.98 g (0.007 mol, 8.2%) of methyl benzoate, bp 70–73° (2.5 mm), and 7.0 g of a second fraction, bp 83–86° (0.6 mm). Vpc of the second fraction, using column A, revealed a mixture of α,α-dichloroacetophenone (31% yield) and α,α,α-trichloroacetophenone in a molar ratio of 3:1. Identification of methyl benzoate was based on comparison of its infrared spectrum with that of an authentic sample and by vpc using column A. Vpc, using column B, of the distillation residue revealed no trace of **1**.

In another experiment a mixture of 300 ml of DME and 23.5 g (0.104 mol) of α,α,α-trichloroacetophenone was stirred at 80° for 39 hr. Analysis of the reaction products by vpc failed to indicate the presence of any methyl benzoate or α,α-dichloroacetophenone. Only starting materials and a small amount of benzoic acid were obtained.

Reaction of Calcium Hydride with α,α,α-Trichloroacetophenone and DME.—A mixture of 20 g (0.088 mol) of α,α,α-trichloroacetophenone, 20 g (0.48 mol) of calcium hydride, and 450 ml of DME was stirred at 85° for 30 hr. The volatile vapors were swept into a Dry Ice trap. Infrared analysis of the contents of the trap revealed the presence of formaldehyde. The reaction mixture was evaporated and the residue was fractionally distilled to give 1.16 g (0.0085 mol, 9.7%) of methyl benzoate, bp 80–92° (5.0 mm), and 16.0 g (0.071 mol) of α,α,α-trichloroacetophenone, bp 83–87° (0.80 mm). The identification of the methyl benzoate fraction was confirmed by vpc using column A and by the infrared spectrum.

Reaction of Phenyl(trichloromethyl)mercury with α,α,α-Trichloroacetophenone and DME.—A mixture of 100 g (0.252 mol) of phenyl(trichloromethyl)mercury, 75 g (0.33 mol) of α,α,α-trichloroacetophenone, prepared by the reaction of sodium trichloroacetate with benzoic anhydride in dioxane, and 600 ml of dimethoxyethane was stirred at 85° for 3.5 hr. The solution was evaporated to a small volume. The residue was fractionally distilled to give 3.5 g of an oil, bp 40–85° (2.2 mm), and 2.8 g of an oil, bp 86–96° (2.2 mm). The first fraction was shown by vpc, using columns A and D, to be a mixture largely made up of trichloroacetophenone with smaller amounts of methyl benzoate and several unidentified compounds. The second fraction was shown by its infrared spectrum and by vpc, using column A, to be essentially trichloroacetophenone. The residue, 53 g, decomposed on standing and was not analyzed.

Analysis of the Volatile Gases Produced on Heating DME, A. With Sodium Trichloroacetate.—A solution of 25 g of sodium trichloroacetate in 500 ml DME was heated slowly with stirring to 85° over a 3-hr period. The solution was cooled and another 25-g portion of sodium trichloroacetate was added. The mixture was again heated slowly to 85° over a 5-hr period. The evolved vapors were bubbled through a solution of 10% bromine in carbon tetrachloride. Excess bromine was reduced by washing the carbon tetrachloride solution with a saturated solution of sodium sulfite. The carbon tetrachloride fraction was dried over anhydrous magnesium sulfate and evaporated. Vpc of the residue, using column C, showed that 1,2-dibromoethane was present.

In another reaction, the vapors were passed into a Dry Ice trap for 7 hr. The infrared spectrum of the trapped gases revealed the presence of carbon dioxide, DME, and formaldehyde. The spectrum also indicated the absence of methyl vinyl ether.

B. With Calcium Hydride.—A mixture of 1000 ml of DME and 20 g of calcium hydride was heated at 85° for 72 hr. The volatile gases were flushed out of the system with a stream of dry nitrogen. For the first 3 hr the volatile products were collected in a trap cooled in Dry Ice. Infrared analysis of the trapped contents revealed the presence of formaldehyde. During the remainder of the period the vapors were passed through a solution of bromine in carbon tetrachloride. Vpc of the products from the carbon tetrachloride solution revealed the presence of 1,2-dibromoethane.

C. With Lithium Aluminum Hydride.—A mixture of 600 ml of DME and 16 g of lithium aluminum hydride was heated at 85° for 60 hr. The volatile gases were flushed with a stream of dry nitrogen into a solution of 10% bromine in carbon tetrachloride. Vpc of the products from the carbon tetrachloride solution revealed the presence of 1,2-dibromoethane.

D. In the Absence of Added Bases.—Dimethoxyethane (350 ml) was heated under reflux for 53 hr. The volatile products

(14) T. Bergkvist, *Svensk Kem. Tidskr.*, **59**, 24 (1947); *Chem. Abstr.*, **41**, 5119 (1947).

(15) W. I. Jones, H. McCombie, and H. A. Scarborough, *J. Chem. Soc.*, **123**, 2688 (1923).

(16) P. A. S. Smith and B. Ashby, *J. Amer. Chem. Soc.*, **72**, 2503 (1950).

were swept with a stream of dry nitrogen into a trap cooled in Dry Ice. A sample of the volatile products was collected during the first 3 hr and another during the last 3 hr. In each case, the infrared spectrum of the trapped products indicated a trace of formaldehyde. In another reaction, 300 ml of DME was heated under reflux for 2.5 days. The vapors were passed through a 10% solution of bromine in carbon tetrachloride. Vpc of the products from the carbon tetrachloride failed to reveal any 1,2-dibromomethane.

Registry No.—**1**, 15649-35-1; **2**, 15649-36-2; **3**, 15649-37-3; benzoic anhydride, 93-97-0; 1,2-dimethoxyethane, 110-71-4; sodium trichloroacetate, 650-51-1.

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A Synthesis of Perfluoroalkyl Trifluorovinyl Ketones

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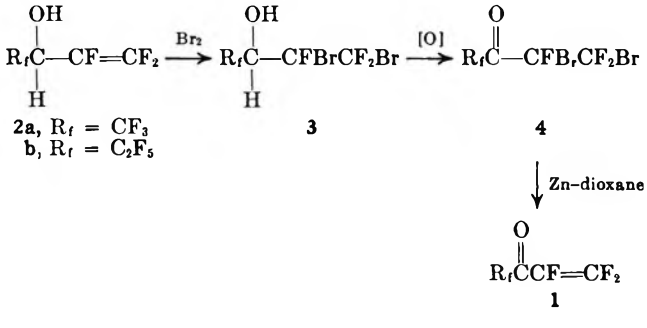
Trifluoromethyl trifluorovinyl ketone and pentafluoroethyl trifluorovinyl ketone have been prepared from corresponding alcohols by bromination to protect the double bond, oxidation, and debromination.

It was desired to prepare trifluoromethyl trifluorovinyl ketone (**1a**) to study its chemical reactivity. Consideration of the known reactions of derivatives of trifluoroacrylic acid[1] and of the effect to be expected from conjugation of the fluoroalkylcarbonyl group with the trifluorovinyl group led us to expect **1a** to be a very reactive compound. Thus, hexafluorocyclobutanone and hexafluoroacetone[2] have been shown to be extremely reactive and conjugation with the trifluorovinyl group[3] should increase this reactivity. The possibility did exist, however, that the functional groups would not conjugate for reasons similar to those which cause many substituted 1,3-butadienes to exist preferentially in the skew configuration.[4]

The synthetic route which led to **1a** is outlined in Scheme I. 1,1,1,3,4,4-Hexafluoro-3-buten-2-ol (**2a**),

SCHEME I



prepared by a route similar to that used for other perfluoroalkyl trifluorovinyl carbinols,[5] was brominated to form 3,4-dibromo-1,1,1,3,4,4-hexafluoro-2-butanol (**3a**), obtained as a mixture of diastereomeric forms. The secondary alcohol was oxidized with acid dichromate[6] to form 3,4-dibromo-1,1,1,3,4,4-hexafluoro-2-butanone (**4a**) in good yield. When the dibromo ketone was debrominated with zinc in boiling dioxane[7] under carefully controlled conditions, a mixture of ketone **1a** and solvent distilled which contained only small amounts of other components according to gas chromatographic analysis on several columns. Large scale chromatography was used to separate **1a**, a colorless, volatile liquid boiling near room temperature.

The unsaturated ketone was very sensitive to nucleophilic attack; it decomposed rapidly in protonic solvents with formation of fluoride ion. Purified samples were stable to storage at room temperature if sealed in ampoules with careful exclusion of moisture.

The observed reactivity of **1a** undoubtedly explains the failure of direct oxidation of **2a** to **1a** with a number of oxidizing agents. Even if **2a** is preferentially attacked by an oxidizing agent at the proton on carbon, the double bond of any **1a** formed is probably attacked immediately by the same reagent. Among oxidizing agents which destroyed **2a** without evidence of formation of **1a** were manganese dioxide, N-bromosuccinimide in acetone, and chromic acid in pyridine.

The structure of **1a** is confirmed by spectral data. The ultraviolet spectrum of **1a** shows that it is similar to methyl vinyl ketone. The peaks are λ_{max} 237 mμ (ϵ_{max} 6340), λ_{max} 316 mμ (ϵ_{max} 19), compared with λ_{max} 212 (ϵ 7100), λ_{max} 320 mμ (ϵ_{max} 27), for methyl vinyl ketone.[8] These data appear to indicate that the functional groups are coplanar. F^{19} nmr spectrum at 56.4 Mc showed four peaks centered at +703, +724, +1424, and +7028 cps from symmetrical difluorotetrachloroethane in the ratio of 1:3:1:1. Coupling constants were first order and of the expected magnitudes. The infrared spectrum showed strong bands at 5.6 and 5.9 μ for carbonyl and trifluorovinyl groups, but specific bands could not be assigned to each functional group.

The synthetic route was repeated starting from 1,1,2,4,4,5,5,5-octafluoro-1-penten-3-ol (**2b**) and pentafluoroethyl trifluorovinyl ketone (**1b**) was obtained. Compound **1b**, a colorless volatile liquid, bp 62°, was somewhat less reactive than **1a**, possibly owing to re-

(1) (a) J. D. Lazerte, D. A. Rausch, R. J. Koshar, J. D. Park, W. H. Pearlson, and J. R. Lacher, *J. Amer. Chem. Soc.*, **78**, 5639 (1956). (b) A. L. Henne and C. J. Fox, *ibid.*, **76**, 479 (1954).

(2) (a) D. C. England, *ibid.*, **83**, 2205 (1961). (b) H. E. Simmons and D. W. Wiley, *ibid.*, **82**, 2288 (1960).

(3) R. D. Chambers and R. H. Mobbs in "Advances in Fluorine Chemistry," Vol. 4, M. Stacey, J. C. Tatlow, and A. G. Sharpe, Ed., Butterworth, Inc., Washington, D. C., 1965, pp 50–112.

(4) A. A. Bothner-By and R. K. Harris, *J. Amer. Chem. Soc.*, **87**, 3445 (1965).

(5) P. Tarrant, P. Johncock, and J. Savory, *J. Org. Chem.*, **28**, 839 (1963).

(6) A. M. Lovelace, D. A. Rausch, W. Postelnek, "Aliphatic Fluorine Compounds," Reinhold Publishing Co., New York, N. Y., 1958, p 185.

(7) See ref 6, p 105.

(8) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1964, p 100.

duced solubility. Spectral data were very similar for the two compounds.

The relatively poor yields obtained in the debromination step of the synthesis of 1a and b coupled with the difficulty of studying their complex reactions prevented further characterization of the chemical reactivity of these interesting materials.

Experimental Section

1,1,1,3,4,4-Hexafluoro-3-buten-2-ol (2a).—A 1-l., four-necked flask fitted with a condenser protected by a drying tube, a thermometer, a dropping funnel, and a Truebore stirrer was dried in an oven at 140° overnight, assembled while hot, and allowed to cool. The flask was charged with 100 ml of tetrahydrofuran (freshly distilled from sodium hydride) and 13.6 g of magnesium. The stirred mixture was cooled to −30° and a solution of 90 g of trifluorovinyl bromide (distilled from calcium chloride) in 100 ml of freshly distilled tetrahydrofuran was added during 1 hr. A vigorous exothermic reaction occurred and the temperature reached −20° on several occasions. The mixture was stirred 1 hr and freshly distilled trifluoroacetaldehyde (25 ml of liquid at −80°) was distilled into the solution slowly. Maximum temperature during the reaction was −5°. After 1 hr, the mixture was warmed to room temperature and stored at about 5° for 64 hr. The solvent was removed under reduced pressure and the resulting dark, viscous residue treated with 250 ml of cold, concentrated sulfuric acid. The tarry residue was largely unaffected by sulfuric acid at 0° but was decomposed at 100°, at which temperature volatile products distilled. The three-layer mixture of products collected in a cold trap with the reaction flask at 100° under reduced pressure was distilled through a small column to give 27.8 g, about 25%, of 1,1,1,3,4,4-hexafluoro-3-buten-2-ol: bp 79–85°, $n^{25}D$ 1.3219–1.3297. When redistilled in a spinning-band still, the material distilled at 82° and had $n^{25}D$ 1.3164. A sample was purified for analysis by gas chromatography on a 16 ft × 0.75 in. silicone oil column at about 50°.

Anal. Calcd for $C_4F_6H_2O$: C, 26.68; H, 1.12; F, 63.31. Found: C, 26.66; H, 1.54; F, 61.54.

Infrared and nuclear magnetic resonance spectra agreed very well with the structure. The proton magnetic resonance was especially informative. The hydroxylic proton resonance was at −293 cps (60 Mc) from tetramethylsilane as an internal standard. Addition of trifluoroacetic acid caused this resonance to shift well downfield so that the resonance pattern of the other proton was revealed as a 32-line multiplet centered at −290 cps from tetramethylsilane. The protons do not split each other as shown by the single line for the OH; therefore, the 32 lines result from simple first-order splitting by each of the four chemical shifts of the six fluorine atoms, and the J values could be extracted simply. The fluorine resonance is very similar, with some of the splits too small to be measured.

3,4-Dibromo-1,1,1,3,4,4-hexafluoro-2-butanol.—In a 250-ml, round-bottomed flask, fitted with a magnetic stirrer and a condenser protected by a drying tube, were placed 79.8 g of trifluoromethyl trifluorovinyl carbinol and 71 g of bromine. The mixture was stirred and irradiated with an AH-3 lamp for 50 hr. The excess bromine was removed with a stream of nitrogen, and the product was distilled in a 9 in. × 0.25 in. Vigreux column. The fraction, bp 145–162°, was redistilled. There was obtained 120.9 g, or 89% of the theoretical amount, of material, bp 145–152°. A sample, bp 150°, $n^{25}D$ 1.148, was analyzed.

Anal. Calcd for $C_4H_2Br_2F_6O$: C, 14.13; H, 0.59; Br, 47.02, F, 33.54. Found: C, 14.33; H, 0.55; Br, 46.60; F, 33.37.

The infrared spectrum was consistent with the structure and the nuclear magnetic resonance spectrum, and gas chromatographic analysis of constant boiling fractions was consistent with the presence of two diastereoisomeric forms of the compound.

3,4-Dibromo-1,1,1,3,4,4-hexafluoro-2-butanone.—In a 500-ml, four-necked flask were placed 124 g of 3,4-dibromo-1,1,1,3,4,4-hexafluoro-2-butanol and 39 ml of concentrated sulfuric acid. A solution prepared from 111 g of sodium dichromate dihydrate, 155 ml of water, and 64.5 ml of concentrated sulfuric acid was placed in a dropping funnel connected to the flask. The material in the flask was heated to 65° and dropwise addition of the sodium dichromate solution was begun. The temperature rose to 95° and then fell. When it reached 80°, the mixture was heated on a steam bath and the speed of addition was increased to keep the temperature between 80 and 90°. The addition required 45 min. The mixture was heated under reflux (pot temperature, 92°) for 2 days. Concentrated sulfuric acid (150 ml), was added and the product was distilled under reduced pressure into a Dry Ice cooled receiver. The product (125 g) was added to 50 g of phosphorus pentoxide in the pot of a 9 in. × 0.25 in. Vigreux still, and the product was distilled. The product (114 g) which boiled at about 95–100°, was redistilled through a small spinning-band still to give 93.2 g (73.5% yield) of 3,4-dibromo-1,1,1,3,4,4-hexafluoro-2-butanone: bp 98.5–99.5°; $n^{25}D$ 1.3717.

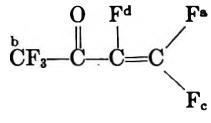
Anal. Calcd for $C_4Br_2F_6O$: C, 14.22; F, 33.74. Found: C, 14.56, 14.60; F, 33.54, 33.07.

Trifluoromethyl Trifluorovinyl Ketone.—A spinning-band still was fitted with a pot with a sidearm and dried by a stream of nitrogen. The pot was charged with 20 g of zinc dust and 50 ml of dioxane (freshly distilled from sodium). The solvent was heated to reflux and stirred and 10 g of 3,4-dibromo-1,1,3,4,4-hexafluoro-2-butanone was added dropwise. When the addition was begun, fractions were taken overhead. Gas chromatographic analysis of the distillate showed a new peak thought to be the desired ketone. Large scale gas chromatography allowed separation of a fraction identified by nmr spectroscopy as trifluoromethyl trifluorovinyl ketone.

Anal. Calcd for C_4F_6O: C, 26.98; F, 64.03. Found: C, 27.24; F, 63.28.

The infrared spectrum showed characteristic bands at 5.6 and 5.9 μ. The ultraviolet spectrum of the compound in octane showed λ_{max} 237 mμ (ϵ_{max} 6340) and λ_{max} 316 mμ (ϵ_{max} 19). This ultraviolet spectrum is comparable with that of methyl vinyl ketone, λ_{max} 212 mμ (ϵ_{max} 7100) and λ_{max} 320 mμ (ϵ_{max} 27).

The structure was confirmed by F^{19} nmr.



Resonance a is a pair of doublets centered at +703 cps from symmetrical tetrachlorodifluoroethane (CCl_2FCCl_2F), one doublet of which falls under resonance b. Resonance b is a pair of doublets centered at +724 cps. Resonance c is a widely split pair of peaks, each of which is a 14641 resulting from overlap of two 1,3,3,1's. It is centered at 1424 cps.

Resonance d is a widely split pair of peaks, each of which is a slightly overlapping pair of quadruplets. It is centered at 7028 cps.

Coupling constants were none for ab, 6 or 7 for ac, 34 or 35 for ad, 6 for bc, 14 for bd, and 110 cps for cd.

1,1,2,4,4,5,5,5-Octafluoro-1-penten-3-ol.—A 3-l., four-necked flask fitted with a stirrer, condenser, dropping funnel, and nitrogen inlet was dried in an oven, assembled hot, and cooled in a nitrogen stream. It was charged with 1 l. of tetrahydrofuran (distilled from sodium hydride) and 49 g of magnesium turnings. Trifluorovinyl bromide (360 g) (dried over calcium chloride) was added to the flask during 2 hr. The temperature of the reaction was kept at −20 to −30°. The mixture was stirred 2.5 hr at −25° and then 80 ml (measured at −80°) of pentafluoropropionaldehyde in 150 ml of dry tetrahydrofuran was added during 1 hr to the stirred mixture maintained at −20 to −10°. The mixture was warmed to room temperature and stirred overnight. Tetrahydrofuran (700 ml) was removed by distillation, and the residue was transferred to a 5-l. flask. Sulfuric acid (1 l.) was added and the flask was fitted with a distillation column. The tarry residue was alternately heated and cooled. Material began to distil when the flask reached 120° and continued to distil during a vigorous exothermic reaction. The product was taken up in ether, dried over magnesium sulfate, and filtered. The filtrate was stored over potassium fluoride pellets, again filtered, and distilled in a spinning-band still. Material boiling at 83–91°, 66.4 g., was identified as 1,1,2,4,4,5,5,5-octafluoro-1-penten-3-ol according to infrared and nmr analyses.

1,2-Dibromo-1,1,2,4,4,5,5,5-octafluoro-3-pentanol.—A mixture of 64 g of 1,1,2,4,4,5,5,5-octafluoro-1-penten-3-ol and 48 g of bromine was stirred for 1 hr to allow a slight exothermic reaction to subside and then it was irradiated with ultraviolet light for 18 hr. Distillation of the residue through a small column with a spinning band provided 86.9 g or 80% of the theoretical amount of 1,2-dibromo-1,1,2,4,4,5,5,5-octafluoro-3-

pentanol. A sample having bp 90–91° (97 mm) and $n^{25}D$ 1.3861 was analyzed.

Anal. Calcd for $C_5H_2Br_2F_8O$: Br, 40.00; F, 38.98. Found: Br, 40.46, 40.43, 40.68; F, 38.24.

Nmr examination of both of the products above indicated that they were alcohols (strong unsplit resonance with chemical shift moved by trifluoroacetic acid) containing another proton (complex splitting).

1,2-Dibromo-1,1,2,4,4,5,5,5-octafluoro-3-pentanone.—A 300-ml, four-necked flask fitted with a stirrer, thermometer, dropping funnel, and condenser was charged with 83.7 g of 1,2-dibromo-1,1,2,4,4,5,5,5-octafluoro-3-pentanol and 23 ml of concentrated sulfuric acid. A solution prepared from 65.5 g of sodium dichromate dihydrate, 92 ml of water, and 38 ml of concentrated sulfuric acid was added from a dropping funnel during 15 min. The mixture was stirred and heated on a steam bath for 24 hr. Concentrated sulfuric acid, 90 ml, was added and liquid products were evaporated with vacuum into a Dry Ice cooled receiver. Phosphorus pentoxide was added to the distillate, and it was vacuum-distilled into the receiver of a Vigreux column. Phosphorus pentoxide (15 g) was added and the mixture was distilled. There was obtained 66.3 g of 1,2-dibromo-1,1,2,4,4,5,5,5-octafluoro-3-pentanone, bp 112–116.5°. A sample, bp 116.5°, $n^{25}D$ 1.3587, was analyzed.

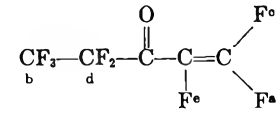
Anal. Calcd for $C_2Br_2F_8O$: Br, 41.20; F, 39.17. Found: Br, 40.33, 40.56; F, 38.08.

Pentafluoroethyl Trifluorovinyl Ketone.—The pot of a small spinning band still with a side arm closed by a serum stopper was charged with 30 ml of sodium-dried dioxane and 20 g of zinc dust. The mixture was stirred and heated and 5 ml of dioxane was distilled. The column was set to a slow take off and 4.8 g of 1,2-dibromo-1,1,2,4,4,5,5,5-octafluoro-3-pentanone was added from a syringe through the serum stopper in small portions. A vigorous reaction occurred and distillate boiling at 85–100°, about 20 ml in all, was collected. Gas chromatography indicated the presence of a new compound in the material, and a quantity of this material was collected by large scale gas chromatography on a 20 ft × 3/8 in. column of Dow Corning silicone 200 oil on 48–65 mesh firebrick. The pentafluoroethyl trifluorovinyl ketone had bp 62° and was pure.

Anal. Calcd for C_5F_8O: C, 26.33; F, 66.66. Found: C, 25.85; F, 66.62.

The ultraviolet spectrum was similar to that of the methyl compound having λ_{max} 242 mμ (ϵ_{max} 5500) and λ_{max} 318 mμ (ϵ_{max} 27). Infrared bands at 5.6 and 5.9 μ were characteristic.

The structure was confirmed by F^{19} nmr.



The resonance due to a, a pair of doublets, was centered at 680 cps from symmetrical tetrachlorodifluoroethane; that due to b, a doublet, was centered at 990 cps; that due to c, a pair of resonances, each of which was overlapping triplets, was centered at 1397 cps; that due to d, a pair of doublets, was centered at 3253 cps; the resonance due to e, a pattern of 21 lines formed by the overlapping of a pair of triplets split to quadruplets, was centered at 7029 cps. Coupling constants were 36 for ae, 12 for ac, 7 for be, 113 for ce, 8 for cd, and 22 cps for de.

Debromination of 22.5 g of dibromo ketone followed by gas chromatography of the product afforded 7.27 g, or 45% yield, of pentafluoroethyl trifluorovinyl ketone, about 98% pure according to gas chromatography. It had a boiling point of 62° with some decomposition.

Registry No.—**1a**, 15322-89-1; **1b**, 15322-70-0; **2a**, 15152-24-1; **2b**, 2070-67-9; **3a**, 15448-32-5; **3b**, 15448-33-6; **4a**, 15448-34-7; **4b**, 15448-35-8.

The Chemistry of Photodimers of Maleic and Fumaric Acid Derivatives. VI[1]

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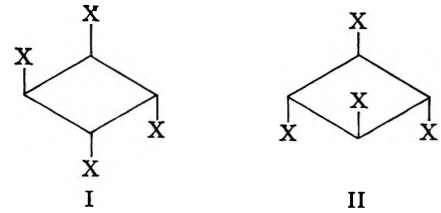
A number of 1,2,3,4-tetrasubstituted cyclobutanes have been prepared from *cis,trans,cis*- and *trans,trans,trans*-1,2,3,4-tetracarbomethoxycyclobutane. Two of these compounds, *cis,trans,cis*- and *trans,trans,trans*-1,2,3,4-tetraiodomethylcyclobutane, undergo an unexpected Grob-type cleavage with lithium aluminum hydride. A novel tricyclic system, namely, the bis anhydride of *trans,trans,trans*-1,2,3,4-cyclobutanetetracarboxylic acid, has also been prepared.

In earlier communications[1] it was reported that tetramethylenecyclobutane could be generated from a variety of substrates, including the 1,2,3,4-tetraiodomethyl- and tetrabromomethylcyclobutanes. At this time we wish to describe the synthesis of these precursors, as well as a variety of related compounds which are of interest in connection with independent studies of small ring systems.

The 1,2,3,4-tetrahydroxymethylcyclobutanes Ic and IIc were initially prepared by catalytic reduction of their respective methyl esters Ia and IIa at 250°.[5] Considerable isomerization and ring opening were encountered in the preparation of the *cis,trans,cis* isomer Ic under the rather drastic catalytic reduction conditions. Lithium aluminum hydride was subsequently found to provide homogeneous samples of Ic and IIc in high yields.



I II

a, X = CO_2CH_3 f, X = CH_2OTs
b, X = CO_2H g, X = CH_3
c, X = CH_2OH h, X = $COCH_3$
d, X = CH_2Br i, X = $COCHN_2$
e, X = CH_2I j, X = CH_2CO_2H

The tetraols Ic and IIc were converted into their respective tetrabromides Id and IId with phosphorus tribromide. The nmr spectrum of the *cis,trans,cis*-tetrabromide Id showed peaks at τ 6.35 (eight protons) and 7.25 (four protons). A similar spectrum was observed for the *trans,trans,trans* isomer IId (τ 6.44, eight protons

(1) For the last paper in this series, see G. W. Griffin and L. I. Peterson, *J. Amer. Chem. Soc.*, **85**, 2268 (1963).

(2) National Institutes of Health Fellow, 1960–1962.

(3) National Institutes of Health Fellow, 1959–1960.

(4) Author to whom inquiries regarding this paper should be addressed: Louisiana State University in New Orleans, New Orleans, La. 70122.

(5) G. W. Griffin, A. F. Vellturo, and K. Furukawa, *J. Amer. Chem. Soc.*, **83**, 2725 (1961).

and 7.79, one proton). The corresponding tetraiodides Ie and IIe[6] were prepared from their respective alcohols using red phosphorus and iodine.

p-Toluenesulfonyl chloride in pyridine converted the alcohols Ic and IIc into the tosylates If and IIf, respectively. The nmr spectrum of If exhibited signals at τ 5.95 (CH_2O, eight protons) and 7.55 (CH_3 and tertiary hydrogen, sixteen protons), in addition to the characteristic tosyl aromatic quartet centered at τ 2.40. The isomeric *trans,trans,trans* ester IIf showed signals at τ 6.10 (CH_2O), 7.56 (CH_3), 7.91 (tertiary cyclobutyl), and 2.40 (tosyl aromatic quartet).

It should be noted that the cyclobutyl proton signals of the compounds in the *trans,trans,trans* series appear at higher field than the corresponding protons in the *cis,-trans,cis* isomers.[7] This tendency has been observed in five such isomer pairs when the spectra are taken in carbon tetrachloride or deuteriochloroform. With few exceptions (*e.g.*, the tosylates) the melting points of the *trans,trans,trans* isomers are lower than those of the related centrosymmetric *cis,trans,cis* forms.

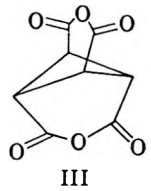
Two of the four possible isomeric 1,2,3,4-tetramethylcyclobutanes, the *cis,cis,cis* and *cis,cis,trans* forms, have been prepared by catalytic reduction of the *cis*- and *trans*-1,2,3,4-tetramethylcyclobutenes.[8] In connection with studies on the reduction of tetramethylenecyclobutane, it was of interest to synthesize the remaining isomers of 1,2,3,4-tetramethylcyclobutane, namely, Ig and IIg.

In our initial attempts to prepare the two unknown isomers of tetramethylcyclobutane, lithium aluminum hydride was allowed to react with the tetraiodides Ie and IIe. The desired tetramethylcyclobutane could not be detected upon attempted reduction of either iodide. The reduction products consisted entirely of terminally unsaturated hydrocarbons. In each instance a significant amount of 3,4-dimethyl-1,5-hexadiene was isolated. This diene was presumably formed by Grob-type cleavage[9] of the cyclobutane ring and nucleophilic attack by hydride ion on the iodomethyl groups. The numerous products formed in these reactions apparently arise from three competing processes, namely, Grob-type cleavage, E2 elimination, and nucleophilic substitution. Attempts to prepare the isomeric tetramethylcyclobutanes by lithium aluminum hydride reduction of the tetratosylates If and IIf were also unsuccessful.

trans,trans,trans-1,2,3,4-Tetraacetylcyclobutane (IIh) was prepared from the tetradiazo ketone (IIi) by the action of hydroiodic acid in chloroform. This convenient method for the conversion of acids into methyl ketones by way of the acid chloride and diazo ketone, originally reported by Wolfrom and Brown,[10] does not seem to have found widespread synthetic acceptance. The infrared spectrum of IIh shows the characteristic carbonyl frequency[11] at 1698 cm^{-1} and the nmr spectrum exhibits peaks at τ 6.68 and 7.95 in the expected ratio of 1:3. The gross structure of the "all-*trans*" tetraketone was confirmed by comparison of the tetramethyl ester of acid IIb formed by sodium hypobromite oxidation of IIh with an authentic sample of IIa. Some difficulty was encountered when an attempt was made to utilize the aforementioned diazo ketone technique for the preparation of *cis,trans,cis*-1,2,3,4-tetraacetylcyclobutane (Ih) from the tetradiazo ketone Ii. Alternate routes for the preparation of Ih involving the use of dimethyl cadmium and ethoxymagnesium diethylmalonate have also been tried without success.

A superior route to the extended acid IIj, which had been prepared and reported earlier,[12] has been developed and employs the tetrabromide IId as a precursor. Treatment of the bromide IId with potassium cyanide under reflux in ethanol provided the tetranitrile. The latter was subsequently hydrolyzed with base directly without isolation to the tetrabasic acid which was identical in all respects with that obtained earlier.

The bis anhydride III was prepared in 65% yield by treatment of *trans,trans,trans*-1,2,3,4-tetracarboxycyclobutane (IIb) with acetic anhydride. This is the last of three possible anhydrides of the 1,2,3,4-cyclobutanetetracarboxylic acids which remained to be synthesized. The *trans*-bis anhydride of *cis,trans,cis*-1,2,3,4-tetracarboxycyclobutane (Ib) and the *cis*-bis anhydride of the "all-*cis*" tetrabasic acid have been reported earlier.[5,13]



III

Experimental Section[14]

Preparation of *trans,trans,trans*-1,2,3,4-Tetrahydroxymethylcyclobutane (IIc). Method A. Catalytic Reduction.—To 100 ml of ethanol contained in a 250-ml steel bomb, was added 10 g (0.35 mole) of the "all-*trans*" tetraester IIa and 1.5 g of "copper chromite" catalyst.[15] Hydrogenation in a rocking autoclave at 250° required 8 hr. The initial pressure was 2000 psi, and this increased to 3200 psi during the course of the reaction. Removal of the catalyst by filtration and evaporation of the solvent under reduced pressure afforded the crude alcohol IIc in 98% yield. The tetrol, initially an oil, crystallized on standing.

The nmr spectrum of this compound, determined in deuterium oxide, exhibited signals at 68.7 and 170 cps (2:1) at higher field from water.

To 0.075 g (0.425 mmol) of the tetraol in 3 ml of pyridine was added 1 ml of benzoyl chloride. The resulting suspension was warmed at 80° for 2 min and then poured into 10 ml of water. The hydrolysis mixture was then extracted with ether and the combined organic phases dried over calcium sulfate. The volatile solvents were removed under reduced pressure and the residual oil was dissolved in ethanol. The ethanol solution upon cooling deposited 0.15 g (60%) of the tetrabenzoate of IIc: mp 87–88.5°; $\nu_{max}^{CCl_4}$ 3070, 3040, 2950, 2890, 1732 (s), 1450, 1312, 1272 (s), 1180, 1110, 1098, 1072, 1030, 710 (s) cm^{-1}.

(6) R. Criegee and H. Hover, *Chem. Ber.*, **93**, 2521 (1960).

(7) An exception is made for the isomeric tetrahydroxymethylcyclobutanes Ic and IIc where the reverse is true. In this case, intramolecular hydrogen bonding and/or solvent effects (D_2O) may be responsible for the apparent atypical behavior.

(8) R. Criegee and K. Noll, *Ann.*, **627**, 1 (1959).

(9) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955); C. Grob (Kekulé), "Symposium on Theoretical Organic Chemistry," Butterworth and Co. Ltd., London, 1959, p 114.

(10) M. L. Wolfrom and R. L. Brown, *J. Amer. Chem. Soc.*, **65**, 1516 (1943).

(11) L. J. Bellamy, *ibid.*, **65**, 132 (1943).

(12) G. W. Griffin, R. B. Hager, and D. F. Veber, *ibid.*, **84**, 1008 (1962).

(13) G. W. Griffin and D. F. Veber, *ibid.*, **82**, 6417 (1960).

(14) All melting points are uncorrected and were obtained using a stirred, Thomas–Hoover silicone oil bath. Infrared spectra were measured in a Perkin-Elmer Model 221 double-beam instrument and the proton magnetic resonance spectra were obtained using the Varian A-60 apparatus with tetramethylsilane as an internal standard. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(15) H. Adkins, E. Burgoyne, and H. Schneider, *J. Amer. Chem. Soc.*, **72**, 2626 (1950).

Anal. Calcd for $C_{36}H_{32}O_8$: C, 72.96; H, 5.44. Found: C, 73.12; H, 5.32.

The nmr spectrum determined in carbon tetrachloride shows absorption in the expected regions. Two doublets are present at τ 2.12 and 2.60, the characteristic region for aromatic protons. Peaks at τ 5.65 and 7.54 are consistent in area and position for that expected for $-CH_2O-$ and *t*-cyclobutyl hydrogens, respectively. The infrared spectrum determined in carbon tetrachloride shows a carbonyl band at 1732 (s) cm^{-1}.

Essentially the same procedure described above for the preparation of the *trans,trans,trans*-tetraol IIc was employed for the preparation of the *cis,trans,cis* isomer Ic.

Preparation of *cis,trans,cis*-1,2,3,4-Tetrahydroxymethylcyclobutane (Ic). Method B. Lithium Aluminum Hydride Reduction.—*cis,trans,cis*-1,2,3,4-Tetracarbomethoxycyclobutane (Ia) (12.0 g, 0.042 mol) dissolved in 320 ml of ether and 320 ml of benzene was reduced in the inverse manner by adding 4.0 g (0.11 mol) of lithium aluminum hydride. A superior procedure for accomplishing this consists of extracting the reducing agent into the stirred ether solution from a Soxhlet thimble with the hot solvent. After heating under reflux overnight, the reaction mixture was hydrolyzed with 40 ml of 50% aqueous methanol. The resulting mixture was filtered and the solid material subsequently extracted for 24 hr with methanol. After removal of the volatile solvents under vacuum the semicrystalline residue was dried over phosphorus pentoxide, (6.43 g, 87%). The nmr spectrum of Ic in D_2O exhibits resonance at 72.0 and 156 cps upfield from water in the expected 2:1 ratio.

The tetraol was characterized as its benzoate and after recrystallization from 1-butanol melted at 104–105°:[16] ν_{max}^{KBr} 3020, 2925, 1721 (s), 1312, 1268, 1179, 1118 (s), 1066, 1027, 955, 852, 830, 806 cm^{-1}.

The yields of the "all-*trans*" tetrabromomethyl derivative (IId), mp 54–55.5° (ethanol), were somewhat higher (10.2 g, 71%): ν_{max}^{KBr} 2961, 2937, 2922, 1435, 1317, 1252, 1232 (s), 1210 (s), 1100, 1075, 1060, 982, 900, 830, 818, 650 (s), 615 (s) cm^{-1}.

Anal. Calcd for $C_8H_{12}Br_4$: C, 22.45; H, 2.83; Br, 74.72. Found: C, 22.67; H, 3.16; Br, 74.45.

The nmr spectrum of the *cis,trans,cis* isomer (Id) determined in deuteriochloroform shows peaks at τ 6.35 and 7.25 (2:1) while that of the *trans,trans,trans* isomer (IId) exhibits signals at τ 6.44 and 7.79 (2:1).

Preparation of *trans,trans,trans*-1,2,3,4-Tetraiodomethylcyclobutane (IIe).—Molten *trans,trans,trans*-1,2,3,4-tetrahydroxymethylcyclobutane (10.0 g, 0.057 mol) was added with the aid of an infrared lamp to a mixture of iodine (63.3 g, 0.25 mol) and red phosphorus (5.15 g, 0.17 mol) which previously had been heated to 70° for 1 hr. The alcohol was added at such a rate that each drop reacted completely. The resulting solution was stirred at 120° for 5 hr. The reaction mixture was diluted with 50 ml of benzene and cooled to 0° and the excess phosphorus triiodide decomposed by adding ice water. The hydrolysis mixture was then extracted five times with 50-ml portions of benzene. The combined benzene extracts were washed with an aqueous solution of sodium sulfite to remove iodine and was dried over anhydrous calcium sulfate. The benzene was then removed under vacuum and the residual solid was recrystallized from cyclohexane to give colorless crystals of the tetraiodide (17.0 g, 48%, mp 102–102.5°): ν_{max}^{KBr} 2951, 2929, 1422, 1418, 1315, 1307, 1240, 1215, 1175 (s), 1085, 928, 800, 790, 610 cm^{-1}.

Anal. Calcd for $C_8H_{12}I_4$: C, 15.71; H, 1.32; I, 82.97. Found: C, 15.61; H, 1.50; I, 83.05.

Alternately, the *trans,trans,trans*-tetraiodide IIe may be prepared from the corresponding tetrabromide IId. *trans,trans,trans*-1,2,3,4-Tetrabromomethylcyclobutane (0.203 g, 4.7 mmol) and 0.31 g (20.5 mmol) of sodium iodide were dissolved in 50 ml of dry acetone and heated under reflux for 6 hr. The precipitated sodium bromide was separated by filtration and the solvent was removed under vacuum. Recrystallization of the residual material from cyclohexane gave 0.19 g (65%) of the tetraiodide (mp 102°) whose infrared spectrum was identical with that of the product obtained from the reaction of phosphorus triiodide with the *trans,trans,trans*-tetraalcohol IIc.

(16) It is noteworthy that an isomeric tetrabenzoate (mp 149–150°) tentatively assigned a cyclobutane structure was reported by Raphael. On the basis of its physical properties it is clear that, if this product is indeed a cyclobutane derivative, it does not possess the stereochemistry of Ic or IIc. See R. A. Raphael, *J. Chem. Soc.*, 401 (1952).

Preparation of *cis,trans,cis*-1,2,3,4-Tetraiodomethylcyclobutane (Ie).—Essentially the same procedure was employed as described earlier for the preparation of the *trans,trans,trans* isomer. The product obtained in 30% yield melted at 140° after recrystallization from cyclohexane: ν_{max}^{KBr} 2946, 2925, 1439, 1429, 1420, 1360, 1262, 1238, 1230, 1200 (s), 1185, 1175, 1140, 1115, 1035, 803, 669, 635 cm^{-1}.

Anal. Calcd for $C_8H_{12}I_4$: C, 15.71; H, 1.32; I, 82.97. Found: C, 15.71; H, 1.45; I, 83.25.

The *cis,trans,cis*-tetraiodide Ie was also prepared from the corresponding tetrabromide. *cis,trans,cis*-1,2,3,4-Tetrabromomethylcyclobutane (Id) was heated under reflux with sodium iodide in acetone. A 53% yield of the tetraiodide Ie (mp 139–140°) was obtained upon work-up in the manner described for the *trans,trans,trans* isomer prepared in this fashion. The iodide was shown to be identical with that obtained upon treatment of the *cis,trans,cis*-tetraol Ic with phosphorus triiodide by comparison of infrared spectra.

Preparation of the Tetratosylate (IIf) of *trans,trans,trans*-1,2,3,4-Tetrahydroxymethylcyclobutane.—*trans,trans,trans*-1,2,3,4-Tetrahydroxymethylcyclobutane (1.0 g, 6.25 mmol) was added in portions to a stirred solution of *p*-toluenesulfonyl chloride (4.8 g, 25.0 mmol) in 40 ml of dry pyridine. The temperature was maintained below 0° during the course of addition. After being stirred for 24 hr at 0°, the reaction mixture was poured into 90 ml of 10% hydrochloric acid solution at 0°. The oil which separated slowly solidified and was recrystallized from absolute ethanol to give 0.5 g (10%) of the colorless crystalline tetratosylate, mp 142–143°.

Anal. Calcd for $C_{36}H_{40}O_{12}S_4$: C, 54.53; H, 5.08. Found: C, 54.03; H, 4.98.

Preparation of the Tetratosylate (If) of *cis,trans,cis*-1,2,3,4-Tetrahydroxymethylcyclobutane.—Essentially the same procedure was employed which is described above for the preparation of the *trans,trans,trans* isomer IIf. The melting point of the *cis,trans,cis* tetratosylate If was 124.5–125° after recrystallization from absolute ethanol. Only a 10% yield of the product could be obtained.

Anal. Calcd for $C_{36}H_{40}O_{12}S_4$: C, 54.53; H, 5.08. Found: C, 54.02; H, 4.85.

The infrared spectra of If and IIf show absorption bands at 1357 and 1185 cm^{-1} characteristic of sulfonic acid esters.[17]

Conversion of *cis,trans,cis*-1,2,3,4-Tetratosylmethylcyclobutane (If) into *cis,trans,cis*-1,2,3,4-Tetraiodomethylcyclobutane (Ie).—*cis,trans,cis*-1,2,3,4-Tetratosylmethylcyclobutane (If) (1.00 g, 1.25 mmol) and sodium iodide (0.80 g, 5.33 mmol) were dissolved in 50 ml of dry acetone and heated at the reflux temperature for 6 hr. The precipitated sodium *p*-toluenesulfonic acid was collected by filtration and the volatile solvents were removed from the filtrate under vacuum. The residual white solid was recrystallized from cyclohexane to give 0.25 g (32%) of *cis,trans,cis*-1,2,3,4-tetraiodomethylcyclobutane, mp 139–140°. The infrared spectrum of this material was identical with that of the tetraiodide obtained from the reaction of *cis,trans,cis*-1,2,3,4-tetrahydroxymethylcyclobutane with phosphorus triiodide.

Conversion of *trans,trans,trans*-1,2,3,4-Tetratosylmethylcyclobutane (IIf) into *trans,trans,trans*-1,2,3,4-Tetraiodomethylcyclobutane (IIe).—The same reaction with sodium iodide as described above for the *cis,trans,cis* isomer was performed with *trans,trans,trans*-1,2,3,4-tetratosylmethylcyclobutane to give the corresponding *trans,trans,trans*-tetraiodide, mp 102–103° (48%). The identity of the product was again confirmed by direct comparison of the infrared spectrum with the previously obtained *trans,trans,trans*-tetraiodide.

Attempted Synthesis of *cis,trans,cis*- and *trans,trans,trans*-1,2,3,4-Tetramethylcyclobutanes (Ig and IIg).—In each instance 3.0 g (4.9 mmol) of the corresponding tetraiodide was placed in a Soxhlet thimble and extracted with the refluxing solvent into an ether solution (150 ml containing 0.5 g (0.013 mol) of lithium aluminum hydride). After the addition of the iodide was complete, the reaction mixture was cautiously decomposed with water and the ether layer was dried over anhydrous calcium sulfate. The ether was then removed by distillation. Gas chromatography of the higher boiling fractions using a Carbowax 20M column revealed that the mixture contained at least four components, none of which had the properties expected of the desired tetramethylcyclobutane. The infrared spectrum of

(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 364.

each component exhibited strong absorption in the 880–915 cm^{-1} region, characteristic of terminal olefinic groups. Only one of the major components was identified in each instance and this was shown to be 3,4-dimethyl-1,5-hexadiene by comparison of the infrared spectrum with that of the authentic diene.

Preparation of *trans,trans,trans*-1,2,3,4-Tetraacetylcyclobutane (IIh).—A solution of 15 g (0.049 mol) of the acid chloride of *trans,trans,trans*-1,2,3,4-tetracarboxycyclobutane (IIb)[12] in 300 ml of anhydrous ether was added over a period of 30 min to a solution of diazomethane prepared from 90 g of N-nitrosomethylurea.[18] The resulting mixture was stirred for 1 hr after addition was complete. The volatile solvents were then removed under reduced pressure to a volume of 250 ml and the solid tetradiazoketone IIi (16 g, 100%) collected on a filter. The infrared spectrum of this compound possesses bands at 2110 (s) and 1639 (m) cm^{-1} which are characteristic of diazoketones.[19]

The diazo ketone was suspended in 800 ml of chloroform in a separatory funnel and treated with 100 ml of 47% hydriodic acid in portions small enough that the evolution of nitrogen could be controlled. When the reaction had subsided, the funnel was shaken vigorously and the layers separated. The chloroform layer was washed first with 20 ml of water, then with sufficient saturated sodium thiosulfate solution to remove the liberated iodine, and finally with 20 ml of water. The organic phase was then dried over calcium sulfate, treated with Norit, and finally evaporated to dryness under reduced pressure. The residual solid was sublimed at 95° (0.8 mm) and the sublimate recrystallized twice from carbon tetrachloride to yield 5.9 g (75%) of *trans,trans,trans*-1,2,3,4-tetraacetylcyclobutane (IIh): mp 134–137°; ν_{max}^{KBr} 3400, 3006, 2943, 2920, 1698 (s), 1423, 1364, 1327, 1300, 1180 (s), 1068, 900, 600 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.10.

The nmr spectrum obtained in carbon tetrachloride had two singlet signals at τ 7.95 and 6.88 (3:1).

Hypobromite Oxidation of *trans,trans,trans*-1,2,3,4-Tetraacetylcyclobutane (IIh).—To a solution of sodium hypobromite, prepared by the addition of 0.30 ml (5.58 mmol) of bromine to 0.94 g (23.5 mmol) of sodium hydroxide in 13 ml of water at 5°, was added 100 mg (0.45 mmol) of *trans,trans,trans*-1,2,3,4-tetraacetylcyclobutane (IIh). After the resulting mixture had been stirred for 2 hr an additional 100 ml of water was added, and the bromoform removed by steam distillation. The residual solution was then cooled and acidified with hydrochloric acid. Evaporation of this acidic solution to dryness provided a solid residue which was transformed, by the action of diazomethane in ether, into *trans,trans,trans*-1,2,3,4-tetracarbomethoxycyclobutane (IIa) (61.3 mg, 48%).

Preparation of *trans,trans,trans*-1,2,3,4-Cyclobutanetetraacetic Acid (IIj) from the Tetrabromide IId.—To 60 ml of ethanol was added 48 g (0.112 mol) of the "*all-trans*" tetrabromide IId and 37 g (0.56 mol) of potassium cyanide. The resulting solution was heated under reflux for a period of 30 hr. The reaction mixture after first being cooled to 0° was filtered, and the material which collected on the filter was washed with two 100-ml portions of ethanol. The combined filtrates were then concentrated to approximately 75 ml and finally heated for 12 hr with 22.5 g (0.56 mole) of sodium hydroxide in 100 ml of ethanol. The reaction mixture was then cooled, diluted with 200 ml of water, and acidified to pH 2 with hydrochloric acid. After treatment with Norit, the volatile solvents were removed under reduced pressure. When the volume reached, approximately 50 ml 17.8 g (55%) of crystalline solid was deposited, which proved to be identical in all respects to a sample of *trans,trans,trans*-1,2,3,4-cyclobutanetetraacetic acid prepared earlier.[12]

Preparation and Structure Proof of the "Cage" Anhydride (III).—*trans,trans,trans*-1,2,3,4-Tetracarboxycyclobutane (28 g, 0.13 mol) and 900 ml of acetic anhydride were heated under reflux for 5 hr. The resulting solution was then distilled at atmospheric pressure to a residual volume of 200 ml which, upon cooling in an ice bath for several hours, deposited 15 g (63%) of crystalline "cage" anhydride III. Concentration of the mother liquor afforded an additional 3 g of anhydride. Recrystallization of III from acetic anhydride provided cubic crystals: mp >280° dec; ν_{max}^{KBr} 3060, 3050, 3030, 3020, 1820 (s), 1760 (s), 1262, 1220, 1195, 1110, 960, 810, 740 cm^{-1}.

Anal. Calcd for $C_8H_4O_6$: C, 48.99; H, 2.06. Found: C, 49.40; H, 2.32.

A small sample of III was allowed to stand in methanol. After 2 days the anhydride had dissolved and the excess methanol was removed under reduced pressure. Addition of diazomethane in ether to the residue afforded an ester identical in all respects with an authentic sample of *trans,trans,trans*-1,2,3,4-tetracarbomethoxycyclobutane (IIa).

Registry No.—Ic, 1128-49-0; Ic tetrabenzoate, 15377-84-1; Id, 15377-85-2; Ie, 15377-86-3; If, 4092-19-5; IIc, 15377-99-8; IIc tetrabenzoate, 15377-88-5; IId, 15377-89-6; IIe, 15523-33-8; IIf, 15523-34-9; IIh, 15377-90-9; III, 15377-91-0.

Acknowledgment.—The authors wish to express their gratitude for financial support of this study to the Army Research Office (Durham) and the Research Corporation. Two of us (R. B. H. and A. F. V.) are also indebted to the U. S. Public Health Service for financial support in the form of graduate research fellowships (G. F. 11,653 and G. F. 11,801). We also wish to acknowledge P. Petrellis for technical assistance.

(18) W. Bachman and W. Struve, *Org. Reactions*, **1**, 50 (1942).

(19) P. Yates and B. Shapiro with N. Yoda and J. Fugger, *J. Amer. Chem. Soc.*, **79**, 5756 (1957).

Evidence for the Formation of Two Tetrasubstituted Intermediates in the Alkaline Hydrolysis of Ethyl Thionbenzoate[1a]

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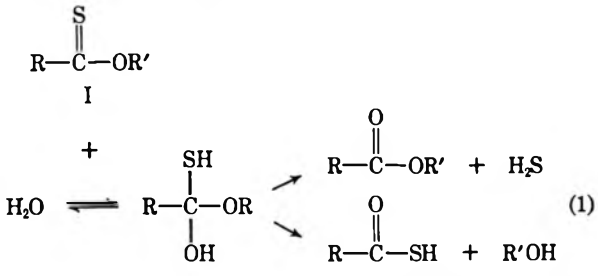
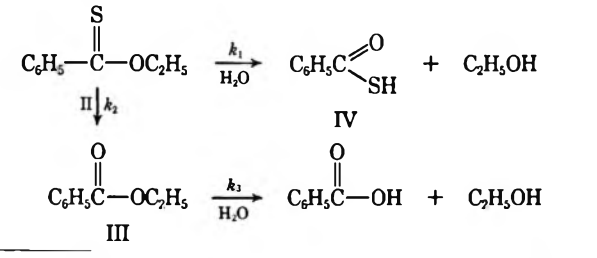
The effect of pH on the rate and the yield of ethyl benzoate and thiobenzoic acid in the hydrolysis of ethyl thionbenzoate in 50% aqueous dioxane has been studied. Over the pH range of 4–12 the product of hydrolysis is very largely ethyl benzoate arising from sulfur–oxygen exchange. Under more alkaline conditions the fraction of the reaction giving ethyl benzoate drops to 0.4 with thiobenzoic acid becoming the major product. The change in the course of the reaction with acidity may be accounted for by a pH-dependent equilibrium between at least two intermediates.

Tetrasubstituted[2] intermediates in the reaction of nucleophiles with carboxylic esters have generally been invoked to explain ^{18}O exchange,[3] spectral,[4] and kinetic data.[3,5] Thion esters,[6] I, constitute a particularly instructive system for the study of such intermediates since in aqueous medium the process which formally corresponds to oxygen exchange with carboxylic esters gives rise to sulfur–oxygen exchange and the formation of the corresponding oxo ester (eq 1).



(1)

Previously[6] it was found that ethyl thionbenzoate (II) in 40% aqueous acetone at 25.0° with 0.05 *M* sodium hydroxide gave 22% ethyl benzoate (III) resulting from sulfur–oxygen exchange and 78% hydrolysis to thionbenzoic acid (IV) and ethanol. Using hydrochloric acid as an hydrolysis catalysis at 125.0°, 85% of the reaction was found to proceed through sulfur–oxygen exchange. These studies have now been extended to provide more information on the effect of pH on the fraction of the reaction proceeding by each route.



Results and Discussion

Reaction Conditions.—The hydrolysis of ethyl thionbenzoate (II) was studied in 50% aqueous dioxane at an apparent pH of 1.5 to 15.3 and temperatures varying from 25.0 to 125.0°. The low pH region was obtained with 0.02 to 0.05 *M* *p*-toluenesulfonic acid while sodium hydroxide solutions, 0.002 to 0.5 *M*, were used in the alkaline region. Intermediate acidities, pH 4.5 to 10.8, were obtained with 2,6-lutidine–*p*-toluenesulfonic acid or diisopropylethylamine–*p*-toluenesulfonic acid buffers. The pH was measured with a glass electrode and calomel reference with 10^{-3} *M* hydrochloric acid in 50% aqueous dioxane being used to define a pH of three. Above a pH of 10.7 erratic pH measurements were obtained so an indicator overlap method[7] was employed to extend the pH values (see Experimental Section).

Kinetics.—The rate constants for the disappearance of ethyl thionbenzoate ($k_1 + k_2$) were obtained by a spectrophotometric analysis at 414 mμ or of extracted aliquots at 290 mμ. A typical run is given in Table I.

TABLE I

HYDROLYSIS OF 0.0107 *M* ETHYL THIONBENZOATE IN A DIISOPROPYLETHYLAMINE–*p*-TOLUENESULFONIC ACID BUFFER OF pH 10.7 IN 50% AQUEOUS DIOXANE AT 125.0° FOLLOWED BY ABSORBANCE AT 290 mμ

Time, 10^{-4} sec	Absorbance, mμ	$10^4(k_1 + k_2)$, sec^{-1}
0	0.995	
0.45	0.876	2.84
0.96	0.771	2.67
1.29	0.701	2.73
1.59	0.662	2.58
1.89	0.603	2.66
2.25	0.550	2.65
2.61	0.497	2.68
3.04	0.453	2.61
3.42	0.409	2.62
3.87	0.369	2.58
51.20	0.004	
	Least squares	2.60

Rate constants determined in 2,6-lutidine–*p*-toluenesulfonic acid buffers were found to be essentially independent of the buffer concentration employed (Table II), but measurements made in diisopropylethylamine–*p*-toluenesulfonic acid buffers had to be extrapolated to zero buffer concentration (Figure 1). Second-order rate constants observed in runs with added sodium hydroxide are summarized in Table III. The pseudo-

(1) (a) Research supported by the National Science Foundation; (b) Alfred P. Sloan Fellow.

(2) Intermediates in ester hydrolysis are often described as tetrahedral; however, the molecular asymmetry makes it unlikely that they actually conform to tetrahedral geometry.

(3) (a) D. Samuel and B. L. Silver in "Advances in Physical Organic Chemistry," Vol. 3, V. Gold, Ed., Academic Press Inc., New York, N. Y., 1965, p 123; (b) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (c) M. L. Bender and H. d'A. Heck, *J. Amer. Chem. Soc.*, **89**, 1211 (1967); (d) M. L. Bender and R. J. Thomas, *ibid.*, **83**, 4189 (1961); (e) M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *ibid.*, **83**, 4193 (1961).

(4) (a) M. L. Bender, *ibid.*, **75**, 5986 (1953); (b) Y. Hirshberg, D. Lavie, and E. D. Bergmann, *J. Chem. Soc.*, 1030 (1951).

(5) *E.g.*, (a) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, **87**, 4138 (1965); (b) S. L. Johnson, *ibid.*, **86**, 3819 (1964); (c) G. E. Lienhard and W. P. Jencks, *ibid.*, **87**, 3855 (1965); (d) L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 4117 (1964); (e) T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 4886 (1964).

(6) S. G. Smith and M. O'Leary, *J. Org. Chem.*, **28**, 2825 (1963).

(7) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y. 1940, p 252.

TABLE II

SUMMARY OF THE FIRST-ORDER RATE CONSTANTS FOR THE DISAPPEARANCE OF ETHYL THIONBENZOATE IN 50% AQUEOUS DIOXANE AT 125.0°

pH[a]	Added reagents: HOTs,[b] 10^2M	Added reagents: Amine, 10^2M	NaOH, 10^2M	Ethyl thionbenzoate, 10^3M	10^5k_{obsd}, sec^{-1}	10^5k_1, sec^{-1}	10^5k_2, sec^{-1}	$k_1/(k_1+k_2)$
1.45	4.96			1.1	1.52	0.16	1.36	0.10
1.95	1.93			1.2	0.842	0.11	0.831	0.13
4.5	8.18	8.69[c]		1.2	0.392	0	0.41	0
5.6	2.43	4.41[c]		0.92	0.40			
5.6	4.90	8.54[c]		1.02	0.419	0.003	0.416	0
5.6		[d]		0.97	0.375			
6.3	0.70	4.41[c]		0.97	0.404			
6.3	1.28	8.50[c]		1.11	0.427	0.003	0.424	0
6.3		[d]		1.40	0.375			
7.0	0.15	4.40[c]		1.23	0.406			
7.0	0.31	8.70[c]		0.88	0.427	0.046	0.381	0.11
7.0		[d]		1.09	0.375			
9.4	5.09	5.58[e]		1.04	0.493			
9.4	8.52	9.22[e]		1.05	0.523	0	0.606	0
9.4		[d]		1.05	0.456			
10.3	2.42	4.39[e]		1.11	1.11			
10.3	4.09	7.35[e]		1.05	1.35			
10.3	5.08	9.16[e]		1.09	1.55	0	1.62	0
10.3		[d]		1.08	0.680			
10.7	1.20	4.58[e]		1.03	1.94			
10.7	1.80	6.87[e]		1.08	2.29			
10.7	2.41	9.16[e]		1.07	2.60	0	2.86	0
10.7		[d]		1.08	1.29			
10.8[f]	0.81	4.59[e]		1.07	2.46	0	2.80	0
10.8[f]	1.22	6.87[e]		1.08	2.91			
10.8[f]	1.62	9.16[e]		1.02	3.30	0	3.48	0
10.8[f]		[d]		1.06	1.66	0	1.92	0
12.0[f]			0.175	0.087	738[h]	36.9[h]	743[h]	0.05
12.7[f]			0.35	0.130	1,030[h]	143[h]	847[h]	0.14
12.8[f]			0.55	0.125	1,900[h]	730[h]	1,100[h]	0.38
13.2[f]			1.12	0.128	5,600[h]	3,020[h]	2,600[h]	0.52
13.3[f]			1.55	0.75	4,600[h]	2,660[h]	2,000[h]	0.57
14.0[f]			3.06	0.99	12,500[h]	8,400[h]	3,400[h]	0.67
14.5[g]			10.5	1.27	33,000[h]	20,000[h]	12,000[h]	0.60
15.0[g]			31.7	1.20	70,000[h]	37,000[h]	31,000[h]	0.53
15.3[g]			50.0	1.05	72,000[h]	43,000[h]	28,000[h]	0.59

[a] Apparent pH determined at 25° in 50% aqueous dioxane with glass electrode–calomel reference electrode. [b] *p*-Toluenesulfonic acid. [c] 2,6-Lutidine. [d] Extrapolated to zero buffer concentration. [e] Diisopropylethylamine. [f] Determined with indicators. [g] Estimated from a plot of apparent pH *vs.* log (NaOH). [h] Rate constants in the presence of sodium hydroxide calculated from data at 25.0 and 50.1°.

TABLE III

SUMMARY OF SECOND-ORDER RATE CONSTANTS FOR THE DISAPPEARANCE OF ETHYL THIONBENZOATE, k_{obsd}, THE APPEARANCE OF ETHYL BENZOATE, k_2, AND THE APPEARANCE OF THIOBENZOIC ACID, k_1, IN THE PRESENCE OF SODIUM HYDROXIDE IN 50% AQUEOUS DIOXANE

pH[a]	Temp, °C	10^3[NaOH], M	Ethyl thionbenzoate, 10^3M	10^3k_{obsd}, M^{-1} sec^{-1}	10^3k_1, M^{-1} sec^{-1}	10^3k_2, M^{-1} sec^{-1}	$k_1/(k_1+k_2)$
12.0	50.0	0.175	0.0866	43.2	2.8	40.6	0.065
12.7	25.0	0.325	0.132	5.80	2.34	3.46	0.40
12.7	50.0	0.381	0.127	39.4	13.6	25.8	0.35
12.8	25.0	0.588	0.125	5.23	2.29	2.94	0.44
12.8	50.0	0.540	0.118	39.3	16.7	22.6	0.42
13.2	25.0	1.12	0.128	5.01	2.64	2.38	0.53
13.2	50.0	1.09	0.128	41.8	22.2	19.6	0.53
13.3	25.0	1.56	0.69	5.04	3.30	1.74	0.65
13.3	50.0	1.57	0.83	37.2	23.4	13.8	0.63
14.0	25.0	2.98	0.85	5.11	3.69	1.42	0.72
14.0	50.0	3.14	1.12	39.9	28.2	11.2	0.71
14.5[b]	25.0	10.5	1.27	4.29	2.92	1.37	0.68
15.0[b]	25.0	31.66	1.20	3.01	1.83	1.18	0.61
15.3[b]	25.0	50.4	1.07	1.96	1.26	0.70	0.64

[a] Apparent pH determined by indicator method. [b] Estimated from a plot of apparent pH *vs.* log (NaOH).

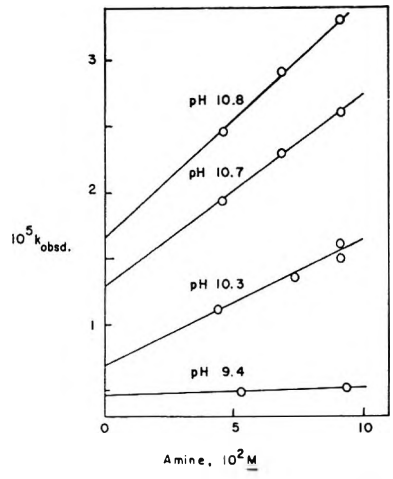


Figure 1.—Plot of first-order rate constants for the disappearance of ethyl thionbenzoate in 50% aqueous dioxane at 125.0° as a function of the concentration of diisopropylethylamine in amine–*p*-toluenesulfonic acid buffers.

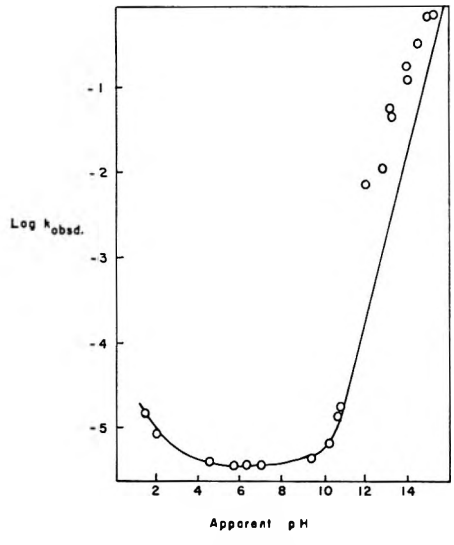


Figure 2.—Plot of log k_{obsd} for the disappearance of ethyl thionbenzoate in aqueous dioxane at 125.0° *vs.* pH.

first-order rate constant, k_{obsd}, for the acidic and buffered runs as well as the second-order rate constants divided by the initial base concentration obtained in the runs with added sodium hydroxide were all corrected, where necessary, to the same temperature of 125.0°, and extrapolated to zero buffer concentration are summarized in Table II and displayed in Figure 2.

The kinetic data are represented reasonably well by eq 3 from a pH of 1.5–10.8, the line in Figure 2 being calculated with the indicated parameters. Deviation of experimental data from eq 3 under more alkaline

$$k_{obsd} = 3.1 \times 10^{-4} a_{H^+} + 3.8 \times 10^{-6} + \frac{1.8 \times 10^{-16}}{a_{H^+}} \quad (3)$$

conditions is most likely due to the long extrapolation required to represent the data at a single temperature as well as inadequate control of ionic strength. It is clear, however, that uncatalyzed water hydrolysis is the predominate reaction in neutral solution with substantial acid catalysis below a pH of *ca.* 3. Direct hydroxide participation is apparent above a pH of *ca.* 10.

The presence of the oxygen exchanged product, ethyl benzoate, was detected in aliquots taken during the reaction by an analysis of the uv absorbance at both 230 and 290 mμ in runs containing sodium hydroxide and by glpc analysis under all other conditions. A sample run is illustrated in Table IV and Figure 3.

TABLE IV

HYDROLYSIS OF 0.0089 *M* ETHYL THIONBENZOATE IN THE PRESENCE OF 0.0158 *M* SODIUM HYDROXIDE IN 50% AQUEOUS DIOXANE AT 50.0° BY ABSORBANCE AT 230 AND AT 290 mμ

Time, 10^{-3} sec	Ethyl benzoate, 10^3 *M*	Ethyl thionbenzoate, 10^3 *M*	$10^2 k_1$, M^{-1} sec^{-1}	$10^2(k_1 + k_2)$, M^{-1} sec^{-1}
0	0.325	8.175		
0.265	0.646	7.050	1.42	3.87
0.538	0.849	6.219	1.35	3.64
0.838	1.030	5.336	1.31	3.79
1.125	1.115	4.758	1.33	3.68
1.410	1.223	4.179	1.30	3.75
1.696	1.314	3.738	1.34	3.73
1.990	1.323	3.338	1.32	3.73
2.292	1.360	3.002	1.34	3.71
2.601	1.399	2.718	1.38	3.66
2.913	1.375	2.455	1.36	3.65
		Av	1.38 ± 0.07	Least squares 3.72 ± 0.02

It has been shown previously that the rate constant, k_2, of eq 2 may be calculated from the concentration at any time of ethyl benzoate, [O], the thion ester, [S], the initial thion ester concentration, $[S]_0$, and k_3 by using eq 4.

$$k_2 = \frac{([O]/[S])(k + k_2 - k_3)}{-1 + ([S]^{(k_3 - k - k_2)/(k_1 + k_2)}/[S_0])} \quad (4)$$

The values of k_3 were obtained from separate experiments using ethyl benzoate as the substrate. These values are tabulated in Tables V and VI. It is of interest to note that under acidic, pH < 2, and alkaline, pH > 10, reaction conditions ethyl benzoate hydrolyses at a rate comparable with that of ethyl thionbenzoate. However, in the intermediate, neutral region the thion ester is much more reactive toward hydrolysis. At a pH of 7, for example, at 125°, ethyl thionbenzoate hydrolysis is faster than ethyl benzoate by a factor of *ca.* 10^3.

TABLE V

SUMMARY OF FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF ETHYL BENZOATE AT 125.0° IN 50% AQUEOUS DIOXANE

pH[a]	Added reagents: HOTs,[b] 10^2 *M*	Added reagents: Amine, 10^2 *M*	Ethyl benzoate, 10^3 *M*	$10^3 k_1$, sec^{-1}
1.45	4.70		0.90	4.16
1.95	1.93		1.21	1.53
4.5	8.44	8.74[c]	1.09	0.0487
5.6	4.82	8.94[c]	1.14	0.00328
6.3	1.27	8.50[c]	1.07	0.0021
7.0	0.27	8.53[c]	1.03	0.0031
9.4	8.41	9.12[d]	1.07	0.0280
10.3	5.05	9.16[d]	0.54	0.318
10.7	2.42	9.22[d]	1.18	0.680
10.8	0.80	4.62[d]	1.22	0.636
10.8	1.62	9.16[d]	1.32	0.835

[a] Apparent pH determined with a glass electrode–calomel reference electrode. [b] *p*-Toluenesulfonic acid. [c] 2,6-Lutidine. [d] Diisopropylethylamine.

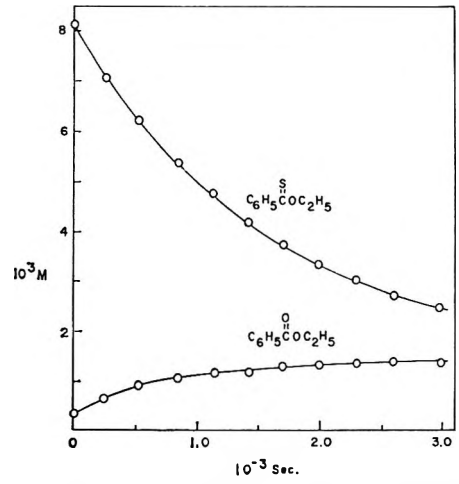


Figure 3.—Plot of concentration *vs.* time in the hydrolysis of 0.0089 *M* ethyl thionbenzoate in presence of 0.0158 *M* sodium hydroxide in 50% aqueous dioxane at 50.0°.

TABLE VI
SUMMARY OF SECOND-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF ETHYL BENZOATE IN THE PRESENCE OF SODIUM HYDROXIDE IN 50% AQUEOUS DIOXANE

pH[a]	Temp, °C	NaOH, 10^2 *M*	Ester, 10^2 *M*	10^2k_2, M^{-1} sec^{-1}
12.0	50.0	0.123	0.110	25.59
12.7	25.0	0.385	0.140	4.70
12.7	50.0	0.381	0.134	27.9
12.8	25.0	0.539	0.133	5.17
12.8	50.0	0.543	0.129	27.1
13.2	25.0	1.12	0.130	5.23
13.2	50.0	1.09	0.129	30.0
13.3	25.0	1.57	0.99	5.12
13.3	50.0	1.55	0.98	27.6
14.0	25.0	3.05	1.34	5.21
14.0	50.0	3.14	1.39	29.62
14.5[b]	25.0	10.70	1.33	5.14
15.0[b]	25.0	29.55	1.45	4.33
15.3[b]	25.0	51.7	0.91	3.09

[a] Apparent pH determined with indicators. [b] Estimated from a plot of apparent pH *vs.* log (NaOH).

From the summary of values of k_1 and k_2 given in Table II, it is apparent that the hydrolysis of ethyl thionbenzoate proceeds very predominately through ethyl benzoate from a pH of 4 to 11. Hydrolysis to thiobenzoic acid occurs to the extent of about 10% in 0.05 *M* toluenesulfonic acid solution. Under strongly alkaline conditions *ca.* 70% of the reaction results in formation of thiobenzoic acid (Table III) at 25°.

The dramatic change in the course of the reaction from essentially all sulfur–oxygen exchange to 68% of cleavage of the acyl–alkoxy bond with a change in pH from *ca.* 11 to 14 (Table III) is illustrated at the experimentally observed temperature of 25° in Figure 4. This change in initial products is not simply the result of a change to hydroxide as the attacking nucleophile since in the region from pH 9 to 12 the rate of hydrolysis increases by a factor of 10^3, reflecting the reactivity of hydroxide, yet the products do not change, only the sulfur–oxygen exchanged product, ethyl benzoate being observed. Apparently the acidity of the medium is more important than the nature of the nucleophile in determining the products. This is consistent with the formation of intermediates which are

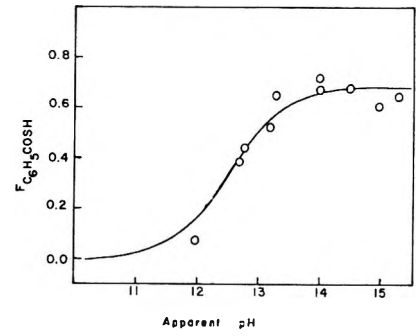
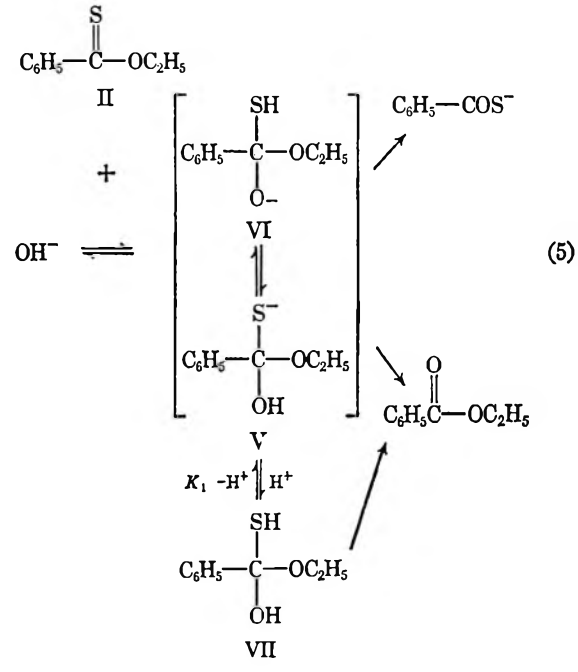


Figure 4.—Plot of fraction of thiobenzoic acid produced, $F_{C_6H_5COSH}$, *vs.* pH from the reaction of ethyl thionbenzoate in 50% aqueous dioxane containing various concentrations of sodium hydroxide. The line was calculated from eq 7 using a value of 10^{13} for k_4/K_5k_2.

in acid–base equilibrium or at least exchange protons at a rate competitive with product formation.

A reaction scheme which should be considered for the conditions where the reaction is first order in the concentration of sodium hydroxide is given in eq 5



where the mercaptide anion V, alkoxide anion VI, and the neutral adduct VII all contribute to formation of products. The alkoxide, VI, is included since the mercaptide anion V would not be expected to give much sulfur–oxygen exchange. In the absence of anion VI, this would result in the fraction of the reaction yielding thiobenzoic acid approaching unity with increasing pH rather than the observed value of 0.68, assuming rapid proton transfers. The relative amounts of VI and V should, to a first approximation, be independent of pH.

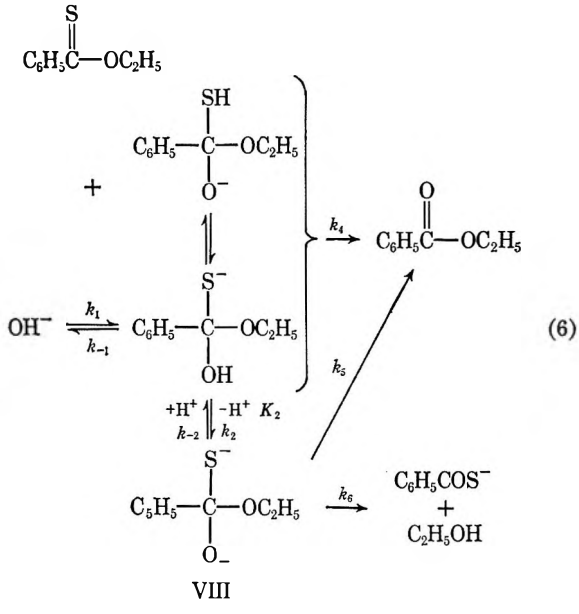
The value of the equilibrium constant, K_1, is not known but may be approximated by using Kreevoy's[8] correlation of the pK_a's of mercaptans with structure.[9] The σ^* value[9] for $C_6H_5CH(OH)-$ indicates that one hydroxyl group decreases the pK_a of benzyl mercaptan from 9.43 to 7.6. Assuming the σ^* value of a methoxyl

(8) M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, III, and L. T. Ditsch, *J. Amer. Chem. Soc.*, **82**, 4899 (1960).

(9) (a) R. W. Taft, Jr., *ibid.*, **74**, 2729 (1952); (b) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., 1956, Chapter 13.

group is the same as an ethoxyl group and group additivity gives an estimated pK_a in water of 5.8.

Even with a substantial medium effect[10] on the estimated pK_a for the solvent change from water to 50% aqueous dioxane (ΔpK_a of 1.9[10] for benzoic acid) the change in the course of the reaction with pH (Figure 4) occurs in a region (pH 12–14) where essentially all of the intermediate VII would have been converted into the corresponding pair of anions. This suggests that a much less acidic proton is responsible for the observed variation of product distribution with pH. Such a scheme is outlined in eq 6 in which the formation of the



dianion VIII is depicted as the source of thiobenzoic acid. The observed kinetics indicate that at high pH, for this scheme to be applicable, k_{-1} is small relative to $k_2(OH^-)$. The midpoint in the plot (Figure 4) corresponds to a pK_a of *ca.* 12.5 for formation of the dianion from the monoanion. On this base, the fraction of the reaction yielding thiobenzoic acid is given by eq 7. The

$$\text{Fraction } C_6H_5COS^- = \frac{k_6}{k_6 + k_5 + (k_4H^+/K_2)} = \frac{2.2}{3.2 + (k_4H^+/k_5K_2)} \quad (7)$$

limiting yield of thio acid at high base concentrations fixes the ratio of k_6/k_5 at 2.2. The line in Figure 4 describing the change in products with concentration of sodium hydroxide was calculated for a value of 10^{13} l./mol for k_4/k_5K_2. Using the estimated value for K_2 of 3×10^{-13} indicates that sulfide is lost from the dianion VIII three times faster than bisulfide and/or sulfide is lost from the monoanion.

Although it is possible to account for the over-all course of the reaction in alkaline solution with eq 6, it is possible that proton transfer is not fast relative to loss of sulfur or oxygen and equilibration of intermediates is not actually obtained. Bender[3d] has suggested such a mechanism to account for the effect of substituents on the hydrolysis and isotopic oxygen exchange of substituted methyl benzoates.

(10) J. H. Elliot and M. Kilpatrick, *J. Phys. Chem.*, **45**, 485 (1941).

Experimental Section

Ethyl thionbenzoate was prepared from the corresponding imino ester by the method of Renson and Bidaine.[11]

Other Materials.—Commercially available ethyl benzoate (Eastman) and diisopropylethylamine (Aldrich) were distilled before use. Eastman *p*-toluenesulfonic acid monohydrate (25 g) was dissolved in 500 ml of ether and then precipitated by slowly adding an equal volume of cyclohexane. The product was filtered and dried in a vacuum desiccator.

The 2,6-lutidine (Eastman) was treated with boron trifluoride[12] and distilled twice before use, bp 141–143° (lit.[12] bp 143.4°).

Ethyl phenylacetate (Matheson) (*ca.* 50 g) was dissolved in 100 ml of cyclohexane, washed with two 30-ml portions of 7% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, concentrated, and distilled under reduced pressure, bp 62–62.5° (0.7 mm) (lit.[13] bp 100.5° (10 mm)). Gas chromatographic analysis on a 3.5-ft 20% XF-1150 on Chromsorb W column at 120° showed a small peak amounting to 0.6% of the area of the main peak. Since ethyl phenylacetate was used as the internal standard for quantitative gas chromatography and the small peak appeared under the ethyl thionbenzoate peak, a small correction was necessary in the thion ester peak area.

Solvent.—Deionized water was distilled before use. Dioxane was purified as described by Fieser.[14] The solvent was prepared by mixing equal volumes of water and dioxane. Acid and base titers were stable under the reaction conditions to within ±1%. Spectrophotometric analysis of samples of solvent after subjection to the various reaction conditions showed no interfering absorbances.

The density of the solvent at the reaction temperatures was determined by measuring the volume of a known weight of solvent in a pycnometer which had a graduated neck and which had been calibrated with distilled water. The density data, Table VII, were used to correct concentrations for expansion of the solvent at reaction temperatures above 25.0°.

TABLE VII
SUMMARY OF THE DENSITY OF 50% AQUEOUS DIOXANE AT THE REACTION TEMPERATURES

Temp, °C	Density, g/ml
25.0	1.034
50.0	1.014
75.0	0.993
100.0	0.969
125.0	0.942

Measurement of Apparent pH.—All pH measurements were made at 25°. A solution of 0.001 *M* hydrochloric acid in 50% aqueous dioxane was defined as pH 3.0 and used to calibrate a glass electrode and calomel reference electrode for measurements of apparent pH of 1.45–10.7. The electrodes were equilibrated in 50% aqueous dioxane at least 24 hr before a measurement and were kept in the same solvent between measurements.

Owing to erratic electrode behavior, apparent pH values above 10.7 were determined by an indicator overlap method using thymol blue, clayton yellow, alizarin yellow R, and indigo carmine indicators.

Since no indicator was readily available with a pK_a large enough to allow measurement of the apparent pH of solutions with greater than 0.05 *M* sodium hydroxide, the pH was estimated from a plot of apparent pH for solutions of 0.00175 to 0.05 *M* sodium hydroxide *vs.* log (NaOH). Such a plot was linear with the intercept being equal to the pK_w, the negative log of the autoprotolysis constant, for 50% aqueous dioxane. The value obtained was 15.7 which agrees well with the value of 16.05 obtained by Baughman and Grunwald[15] using the potentiometric data of Harned and Fallon.[16]

(11) M. Renson and J. Bidaine, *Bull. Soc. Chim. Belges*, **70**, 519 (1961).
(12) H. C. Brown, S. Johnson, and H. Podall, *J. Amer. Chem. Soc.*, **76**, 5556 (1954).
(13) M. J. Timmermans, *J. Chim. Phys.*, **56**, 984 (1959).
(14) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Company, Boston, Mass., 1955, p 285.
(15) G. Baughman and E. Grunwald, *J. Amer. Chem. Soc.*, **80**, 3844 (1958).
(16) H. S. Harned and L. D. Fallon, *ibid.*, **61**, 2374 (1939).

Kinetic Procedure.—Solutions of *p*-toluenesulfonic acid were used at apparent pH of 1.45 and 1.95. For an apparent pH of 4.5 to 7.0, 2,6-lutidine–*p*-toluenesulfonic acid buffers were used and at apparent pH of 9.4 to 10.8, diisopropylethylamine–*p*-toluenesulfonic acid buffers were employed. The buffered solutions were prepared by diluting aliquots of stock solutions in 50% aqueous dioxane of the appropriate amine and of *p*-toluenesulfonic acid with solvent. Solutions of the desired buffer concentration and apparent pH were obtained by varying the aliquot volumes. Sodium hydroxide solutions were used at an apparent pH of 12.0 and above. Before use, the solutions were cooled in an ice bath and deoxygenated by bubbling nitrogen through them for 30 min.

Sealed ampoules were employed for reactions run at 100–125°. For reactions at 25.0 and 50.0° glass bottles, which were fitted with silicone rubber seals and screw caps in which a hole had been drilled to allow removal of aliquots with a syringe during the reaction, were used.

Rate constants for the disappearance of ethyl thiobenzoate in 50% aqueous dioxane were calculated from data obtained by measuring the absorbance of the reaction sample at 414 mμ on a Beckman DU spectrophotometer equipped with a photomultiplier. The disappearance of ethyl thionbenzoate was also followed spectrophotometrically at 290 mμ after extraction of reaction samples by the procedure described below. The rate of hydrolysis of ethyl benzoate in 50% aqueous dioxane was determined by extracting reaction samples as described below and analyzing the extracts spectrophotometrically at 230 mμ.

Extraction Procedure.—An 2.016-ml aliquot of the reaction solution was added to a separatory funnel containing 10 ml of cyclohexane and 10 ml of 7% aqueous sodium bicarbonate. When the reaction was carried out in the presence of *p*-toluenesulfonic acid or sodium hydroxide, the aqueous layer was extracted with two additional 5-ml portions of cyclohexane. When an amine buffer was present, the aqueous bicarbonate layer was extracted with one additional 5-ml portion of cyclohexane, the combined extracts were then washed with 10 ml of 5% aqueous hydrochloric acid and the aqueous acid layer extracted with an additional 5-ml portion of cyclohexane. In each case, the combined extracts, *ca.* 20 ml, were diluted to 25 ml for spectrophotometric analysis. Extraction of aliquots of solutions of known ethyl thionbenzoate and ethyl benzoate concentration showed that the recovered amounts of each ester were within ±3% of the original concentration.

Determination of Ethyl Benzoate and Ethyl Thionbenzoate Concentrations During the Reaction.—In order to calculate values of k_2 from eq 4, it is necessary to determine the concentrations of both ethyl benzoate and ethyl thionbenzoate. For runs in the presence of sodium hydroxide, these esters were extracted from the reaction mixture and the absorbance was measured at both 230 and 290 mμ using a Beckman DU spectrophotometer which allows the desired concentrations to be calculated.

For runs at an apparent pH of 1.45 to 10.8, the concentrations of ethyl benzoate and ethyl thionbenzoate were calculated from quantitative gas chromatographic data. Aliquots of the reaction mixture were extracted as described for spectrophotometric analysis except that a known amount of a solution of ethyl phenylacetate in cyclohexane was added to each separatory funnel. The cyclohexane extracts were concentrated at 90–95° to *ca.* 0.5 ml by distilling the solvent through a 6-in. Vigreaux column. Injections of 0.15–0.25 ml samples were made into a 3.5-ft 20% KF-1150 on Chromosorb W column at 120° using an Aerograph A-90 gas chromatograph. The order of appearance of the compounds was ethyl benzoate, ethyl phenylacetate, and ethyl thionbenzoate. Peak areas were measured with a disk chart integrator. The area of the ethyl thionbenzoate peak was corrected for the minor peak in the internal standard by subtracting 0.6% of the area of the ethyl phenylacetate peak.

The calibrations were done by extracting and chromatographing aliquots of solutions of ethyl benzoate and ethyl thionbenzoate of known concentration in 50% aqueous dioxane. Analysis of samples of a solution of known concentrations of ethyl benzoate, ethyl phenylacetate, and ethyl thionbenzoate in cyclohexane before and after treatment with the above extraction procedure indicated that there was no change in relative peak areas within ±2%.

Registry No.—II, 936-61-8; III, 93-89-0; IV, 98-91-9.

Reductive Cyclization of α,ω-Dihalides with Chromium(II) Complexes

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Various 3-substituted alkyl halides are readily reduced by ethylenediaminechromium(II) reagent in DMF solutions at room temperatures. γ-Dihalides and γ-halo tosylates are reductively cyclized in excellent yields to cyclopropanes. Protolytic reduction of the carbon–halogen bond is the most relevant competing reaction. The latter becomes significant when groups in the γ position of alkyl halides are hydroxy, acetoxy, phenoxy, amino, cyano, phthalimido, or triethylammonium. The role of chromous reagent in reductive cyclization is compared with the mechanism of protolytic reduction and the mechanism of reductive elimination of vicinally substituted alkyl halides. Similar free-radical and alkylchromium intermediates are involved in all of these reductive processes. Factors which determine the relative rates of cyclization and protonation of the metastable γ-substituted alkylchromium species are discussed. The effects of γ or β substituents in reductive cyclization or reductive elimination are compared and contrasted; leaving-group ability is considered to be an important attribute for γ substituents in cyclopropane formation. Evidence is presented for neighboring-group participation by a γ-iodine atom in the homolytic removal of the initial halogen by ligand transfer to Cr^{II}en. Stereochemical studies with *meso*- and *dl*-2,4-dibromopentanes show that there is no specificity in cyclopropane formation. Reductive cyclization of α,δ-dihalides and higher homologs with Cr^{II}en was not promising.

Reductive cyclization of α,ω-dihaloalkanes and derivatives is a useful method of preparing cycloalkanes. The stoichiometry of the process (half-reaction) is given by eq 1. Zinc,[1] magnesium,[2] and Grignard reagents[3] have been used as reducing agents. Recently, other novel methods for α,γ cyclization using allyl chloride and diborane[4] as well as azetidine and difluoramine[5] have been reported.

$$XCH_2(CH_2)_nCH_2Y + 2e \longrightarrow \begin{pmatrix} (CH_2)_n \\ | \\ CH_2{-}CH_2 \end{pmatrix} + X^- + Y^- \quad (1)$$

(1) R. Shortridge, R. Craig, K. Greenlee, J. Derfer, and C. Boord, *J. Amer. Chem. Soc.*, **70**, 946 (1948); **67**, 1863 (1945); (b) H. Haas, E. McBee, G. Hinds, and E. Glusenkamp, *Ind. Eng. Chem.*, **28**, 1178 (1936); M. Murray, *ibid.*, **66**, 812 (1944); J. Battleson, *ibid.*, **68**, 2153 (1946); V. Slabey, *ibid.*, **68**, 1335 (1946); H. Shechter, *Org. Syn.*, **44**, 30 (1964); P. Leriverend and J. Conia, *Bull. Soc. Chim. France*, 116 (1966).

(2) J. Grayson, K. Greenlee, J. Derfer, and C. Boord, *J. Org. Chem.*, **20**, 275 (1955); *J. Amer. Chem. Soc.*, **75**, 3344 (1953).

(3) N. Rabjohn and M. Cohen, *ibid.*, **74**, 6290 (1952); L. Slaugh, *ibid.*, **83**, 2734 (1961); M. Kharasch, M. Weiner, W. Nubenberg, A. Bhattacharya, T. Wang, and N. Yang, *ibid.*, **83**, 3232 (1961); M. Kharasch, J. Sallo, and W. Nudenberg, *J. Org. Chem.*, **18**, 575 (1953); **21**, 129 (1956); C. DePuy, G. Dappen, K. Eilers, and R. Klein, *ibid.*, **29**, 2813 (1964); W. Smith, *ibid.*, **23**, 509 (1958).

(4) N. Hawthorne, *J. Amer. Chem. Soc.*, **82**, 1886 (1960).

(5) C. Bumgardner, K. Martin, and J. Freeman, *ibid.*, **85**, 97 (1963).

Although some attempts have been made to carry our mechanistic studies with the metals, they inherently suffer from lack of solubility. Chromous salts are particularly effective and versatile reducing agents for organic halides.[6] They are readily accessible and solubility in many organic solvents makes them desirable for kinetic studies. The reduction potential of the Cr^{II}–Cr^{III} couple (0.44 V) can be enhanced significantly by complex formation.

The reactivity of organic halides toward Cr^{II} [7] decreases in the order iodide > bromide > chloride and the use of Cr^{II} as a reducing agent has been restricted to the more reactive systems. Recently, we found that the scope of these halide reductions can be increased considerably by use of ethylenediaminechromium(II) reagent,[8] which is simply prepared from Cr^{II} by addition of ethylenediamine. Both of these reagents react by similar mechanisms and differ mainly by the greater reactivity of the latter.

The reduction of the more reactive benzylic and allylic halides, α-halo ketones and analogous compounds by Cr^{II} commonly leads to replacement of halogen by hydrogen (type I, protolytic reduction, eq 2) or dimerization of the alkyl moiety (type II, coupling, eq 3).[9,10] Alkyl and aryl halides, which are too unreactive toward Cr^{II}, require Cr^{II}en for reduction (eq 2).[8]

$$CH_3CH_2CH_2CH_2Br + 2Cr^{II}en + H^+ \longrightarrow CH_3CH_2CH_2CH_3 + 2Cr^{III}en(Br^-) \quad \text{type I} \quad (2)$$

$$2PhCH_2Cl + 2Cr^{II} \longrightarrow (PhCH_2)_2 + 2Cr^{III}(Cl^-) \quad \text{type II} \quad (3)$$

A variety of alkyl halides substituted in the β position react with Cr^{II} and Cr^{II}en, particularly the latter, to afford high yields of alkenes (type III, reductive elimination, eq 4).[11,12] Vicinal dihalides, β-halohydrins, β-haloamines and their derivatives, as well as epoxides and episulfides, are reductively eliminated by these reagents.[13]

$$YCH_2CH_2Br + 2Cr^{II}en \longrightarrow CH_2{=}CH_2 + 2Cr^{III}en(Br^-,Y^-) \quad \text{type III} \quad (4)$$

All three classes of reduction by the Cr^{II} complexes given proceed *via* common intermediates. The reactions follow second-order kinetics, first order in each reactant. Since the activation processes and over-all reactions differ in stoichiometries, multistep sequences are involved. The general steps given by eq 5–9 have been proposed where R_Y denotes an alkyl moiety β substituted with Y. In this mechanism an alkylchromium cation II is common to all three reactions and products are determined by its mode of reaction (eq 7, 8, and 9).

$$R_Y{-}X + Cr^{II} \longrightarrow \underset{\text{I}}{R_Y\cdot} + Cr^{III}X \quad (5)$$

$$I + Cr^{II} \longrightarrow \underset{\text{II}}{R_YCr^{2+}} \quad (6)$$

$$II + H^+ \longrightarrow R_YH + Cr^{III} \quad \text{type I} \quad (7)$$

$$II + R_Y{-}X \longrightarrow (R_Y)_2 + Cr^{III}(X^-) \quad \text{type II} \quad (8)$$

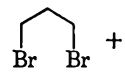
$$II \longrightarrow R + Cr^{III}(Y^-) \quad \text{type III} \quad (9)$$

In principle, processes 8 and 9 are analogous since a carbon–carbon bond in each is constituted from reaction of a carbon–chromium and a carbon–halogen bond (Y = halogen) by intermolecular and intramolecular processes, respectively. By extending this argument, it should be possible to cyclize a γ-substituted alkyl halide to cyclopropanes and higher homologs to larger cycloalkanes. In this report we wish to describe our studies directed toward exploring the mechanisms of such cyclizations.

Results and Discussion

Chromous perchlorate solutions were prepared from pure chromium by dissolution in 1 *M* aqueous perchloric acid.[14] All reactions were carried out in 90 vol % dimethylformamide (DMF)–water in the absence of air. Rubber serum capped flasks with solvent were flushed with nitrogen and an aliquot of Cr^{II} solution was added *via* a hypodermic syringe. Addition of a measured amount of ethylenediamine (en) to the clear blue chromous perchlorate solution generated Cr^{II}en[15] (purple) *in situ*. Organic halide was added finally and the homogeneous mixture was allowed to react at room temperature.

A series of trimethylene halides listed in Table I was treated with Cr^{II}en under these conditions. Trimethylene diiodide and dibromide reacted completely with Cr^{II}en within 10 min and afforded quantitative yields of



$$+ 2Cr^{II}en \longrightarrow \triangle + 2Cr^{III}en(Br^-) \quad (10)$$

cyclopropane. On the other hand, trimethylene dichloride as well as the iodochloride and bromochloride reacted with excess Cr^{II}en to afford to a mixture of cyclopropane and propane, quantitatively. The same mixture of hydrocarbons (Table I) was obtained irrespective of the trimethylene chlorohalide employed. The pro-

TABLE I

REDUCTIVE CYCLIZATION OF TRIMETHYLENE DIHALIDES WITH Cr^{II}en[a]

—$XCH_2CH_2CH_2Y$—		Concn,	Cr^{II},	en,	Conversion,	—Distribution—	
X	Y	*M*	*M*	*M*	%	Propane	Cyclopropane
I	I	0.013	0.09	0.18	94	<0.02	100
Br	Br	0.014	0.09	0.18	98	<0.05	100
I	Cl	0.018	0.09	0.18	94	18	82
I	Cl	0.018	0.09	1.8	100	<0.05	100
Br	Cl	0.019	0.09	0.18	98	19	81
Br	Cl	0.019	0.09	1.8	100	<0.05	100
Cl	Cl	0.013	0.09	0.18	100	14	86
						n-Butane	Methylcyclopropane
$XCH(CH_3)CH_2CH_2Y$							
Br	Br	0.016	0.09	0.18	100	6	94
Br	Br	0.016	0.09	11	100	4	96
Cl	Cl	0.024	0.09	0.18	...	24	76
Cl	Cl	0.024	0.09	11	95	1	99

[a] Substrate added (by syringe) to excess Cr^{II}en reagent in 10 vol % aqueous DMF at room temperature.

(6) J. Kochi, *Rec. Chem. Progr.*, **27**, 207 (1966).

(7) Cr^{II} is used to denote chromous ion in aqueous solutions of DMF and other solvents. Hexacoordination with solvent is indicated, but no attempt will be made to specify coordination unless necessary for the discussion.

(8) J. Kochi and P. Mocadlo, *J. Amer. Chem. Soc.*, **88**, 4094 (1966).

(9) J. Kochi and D. Davis, *ibid.*, **86**, 5264 (1964).

(10) J. Kochi and D. Buchanan, *ibid.*, **87**, 853 (1965).

(11) W. Kray and C. Castro, *ibid.*, **86**, 4603 (1964).

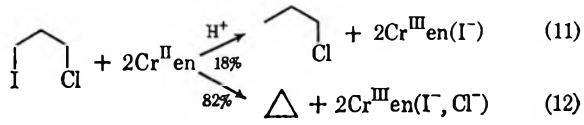
(12) D. Singleton and J. Kochi, *ibid.*, **89**, 6547 (1967).

(13) J. Kochi, D. Singleton, and L. Andrews, *Tetrahedron*, in press.

(14) H. Lux and G. Illman, *Ber.*, **91**, 2143 (1958).

(15) Cr^{II}en denotes the ethylenediaminechromium(II) reagent obtained by reacting Cr^{II} and ethylenediamine in a 1 to 2–3 *M* ratio. It consists largely of the bisethylenediaminechromium(II) complex. *Cf.* R. Peesok and J. Bjerrum, *Acta. Chem. Scand.*, **11**, 1418 (1957).

pane arose by the stepwise protolytic reduction of trimethylene iodochloride (0.73 mmol), since only cyclopropane (0.59 mmol, 81%) and *n*-propyl chloride (0.12 mmol, 16%) were formed when the reaction was quenched with oxygen after 5 min. Independently, it was shown that $Cr^{II}en$ reagent converted *n*-propyl chloride much more slowly than *n*-propyl iodide into propane.



(11)

(12)

The competition between reductive cyclization and protolytic reduction also occurred in 1,3-dihalobutanes as shown in Table I. In this system, protolytic reduction was relatively more important than it was in the corresponding trimethylene dihalide.

The rate of the reaction between trimethylene dihalides and $Cr^{II}en$ was first order each in $Cr^{II}en$ reagent and dihalide. The second-order rate constant for trimethylene dibromide and $Cr^{II}en$ at 0° in 10 vol % aqueous DMF was 0.36 l./mol sec.

In this regard, the kinetics of the cyclization were similar to protolytic reductions of organic monohalides (eq 2)[9,16] and reductive elimination of vicinal dihalides (eq 4).[11-13] Likewise, a multistep sequence and formation of metastable intermediate(s) are indicated for cyclization. Under similar experimental conditions the relative rates of reduction of *n*-butyl iodide, bromide, and chloride decreased in this order: 7×10^3, 5×10^2, 1, respectively.[16] In view of these large differences in rates of halogen transfer, we conclude that reaction between trimethylene iodochloride or bromochloride and $Cr^{II}en$ occurred initially at the iodine and bromine sites. Thus, the same intermediate was generated from trimethylene iodochloride, bromochloride, and dichloride. Partitioning of this intermediate to cyclopropane and *n*-propyl chloride must have occurred subsequent to transfer of the first halogen to $Cr^{II}en$.

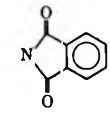
The formation of cyclopropane quantitatively from trimethylene diiodide and dibromide indicated that the analogous intermediates from these compounds generate only cyclopropane. The effect of various γ substituents on cyclopropane formation in a series of 3-substituted propyl halides is given in Table II.

Reductive Cyclization and Elimination *vs.* Protolytic Reduction.—In reductive elimination and cyclization of 2- and 3-substituted alkyl halides by $Cr^{II}en$, the principal competing reaction was protolytic reduction (eq 2). The latter proved to be a useful measure of the ease with which various substituents in the β and γ positions were removed. Factors which affect the loss of a β substituent and a γ substituent in the two series are not precisely the same. A γ-halogen substituent was not required since γ-tosyloxypropyl bromide and chloride also reacted with $Cr^{II}en$ to produce cyclopropane quantitatively. The analogous γ-hydroxy-, acetoxy-, and aminopropyl halides, on the other hand, gave no cyclopropane, but yielded only the product of protolytic reduction, *i.e.*, propyl alcohol, acetate, and amine, respectively.

(16) J. Powers, unpublished observations. The structure and chemistry of alkylchromium species will be presented later.

TABLE II

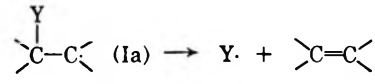
REDUCTION OF 3-HALOPROPYL DERIVATIVES WITH $Cr^{II}en$[a]

—$XCH_2CH_2CH_2Y$— X	Y	Concn, *M*	Conversion, % Propane	Cyclopropane	Product
Br	OH	0.015	<0.02	<1	Propyl alcohol
Br	OTs	0.010	<0.02	100	...
Br	OAc	0.015	<0.05	<0.1[b]	Propyl acetate
Br	CN	0.010	<0.05	<1	Butyronitrile
Br	$N^+(C_2H_5)_3$	0.010	<0.02	<1	Triethylpropylammonium
Br	NH_2	0.010	<0.05	<0.1	Propylamine
Br		0.016	<0.02	<0.1	N-Propylphthalimide
Br	OPh	0.30	<0.03	<0.1	Propyl phenyl ether
Cl	OH	0.022	<0.02	<0.1	Propyl alcohol
Cl	OTs	0.024	<0.05	95	...

[a] Substrate added to excess $Cr^{II}en$ reagent in 10 vol % aqueous DMF at room temperature. Cr^{II} (0.09 *M*) and ethylenediamine (0.18 *M*). [b] Quantitative yields of *n*-propyl acetate formed.

In 1,2 eliminations, β-hydroxy-, β-phenoxy-, β-acetoxy-, and β-aminoethyl bromides and chlorides afforded only ethylene and no protolytic reduction. Phthalimido and cyano substituents in neither β-ethyl nor γ-propyl halides were eliminated in reactions with $Cr^{II}en$, since N-ethyl- and N-propylphthalimides as well as propionitrile and butyronitrile were reduction products from the corresponding bromides and chlorides.

Mechanism of Cyclopropane Formation.—Reductive elimination of β-substituted alkyl halides with $Cr^{II}L$[17] had been postulated to proceed *via* a β-substituted alkyl radical I (eq 4, R_Y = β-Y-alkyl). Alkene is formed *via* three competing processes (eq 13, 14, and 15).[12] The β fragmentation (eq 13) is only important



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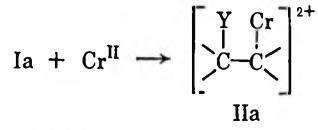
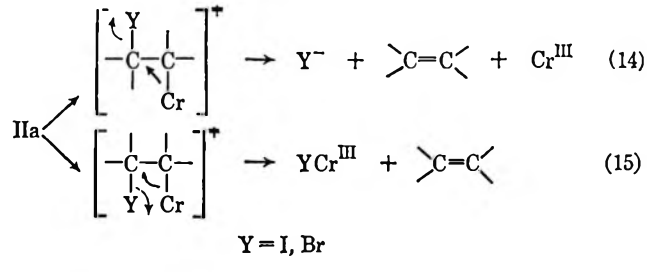




(14)

(15)

with β-bromo and iodo substituents and it can be obviated by use of excess $Cr^{II}L$ reagent. In the latter case, reaction between $Cr^{II}L$ and radical Ia is sufficiently fast such that subsequent elimination only occurs from the alkylchromium intermediate IIa.[16] The relative importance of routes 14 and 15 in elimination is largely dependent on the nature of Y. For tosyloxy, the displacement of tosylate ion (eq 14) was preferred, whereas no chloride ion was formed from β-chloroethyl-

(17) $Cr^{II}L$ is used generically to denote all chromous species, irrespective of ligands.

chromium ion and elimination generated only $ClCr^{III}$ (eq 15). A β-bromoalkylchromium intermediate produced alkene by both paths concurrently. Tosylate and to a certain extent bromide are favored leaving groups in nucleophilic displacements[18] and unimolecular solvolyses.[19] Other substituents such as chloride, acetate, hydroxide, or amide are poorer leaving groups. The distinction between these paths for fragmentation of II lies primarily in the ability of the leaving groups to depart as anions (eq 14). The alternative path requires synchronous bonding to chromium to facilitate departure (eq 15) of those β substituents which are poorer leaving groups. A transoid transition state has been postulated for the former and a cisoid one for the latter.[12] Acylamido, phthalimido, and cyano groups are sufficiently poor in both capacities so that protonolysis (eq 7) is more favorable than either route for elimination.

Kinetic studies support a similar mechanism for reduction of 3-substituted alkyl halides. The intermediate propyl radical III is formed by halogen transfer to Cr^{II}en (eq 16). In contrast to the behavior of β-

$$YCH_2CH_2CH_2Br + Cr^{II}en \longrightarrow YCH_2CH_2CH_2\cdot + Cr^{III}X \quad (16)$$

iodo- or β-bromoalkyl radicals, fragmentation of γ-iodo- or γ-bromopropyl radicals to cyclopropane does not appear to be a spontaneous process at these temperatures.[20] Reaction of III with Cr^{II} leads to a γ-substituted propylchromium intermediate IV similar to the β-substituted analogs II from 1,2-dihalides.

$$III \not\rightarrow \triangle + Y\cdot \quad (17)$$

$$III + Cr^{II}en \longrightarrow \underset{IV}{YCH_2CH_2CH_2Cren^{2+}} \quad (18)$$

Y = I, Br

The alkyl chromium intermediates II and IV show different abilities to undergo 1,2 and 1,3 eliminations, respectively. Thus, groups such as hydroxy, phenoxy, acetoxy, alkoxy, and amino which require coordination to chromium in 1,2 eliminations are not removed at all in 1,3 systems. Quantitative yields of cyclopropane are obtained from propylchromium derivatives IV only with γ substituents such as iodo, bromo, and tosyloxy, which are favored leaving groups in anionic displacements, and which can also depart unassisted from β-substituted analogs II (eq 14). Furthermore, in γ-chloropropylchromium, cyclization (eq 20) and protonolysis (eq 19) are so balanced that the former is only four times faster than the latter. However,

$$ClCH_2CH_2CH_2Cren^{2+} \xrightarrow{H^+} ClCH_2CH_2CH_3 + Cr^{III}en \quad (19)$$

$$ClCH_2CH_2CH_2Cren^{2+} \longrightarrow Cl^- + \triangle + Cr^{III}en \quad (20)$$

protonolysis of alkylchromium species in aqueous DMF is retarded by bases.[16] The competition between cyclization and protonolysis of γ-chloropropyl chromium can be altered to favor the former simply by use of excess en to act as a base. Thus, γ-chloropropyl iodide, bromide, and chloride react with Cr^{II}en in the presence of excess en (see Table I) to afford quantitative yields of cyclopropane.

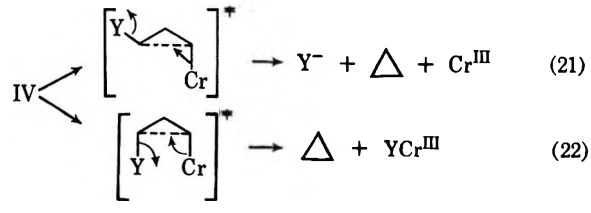
In Table III a variety of γ substituents are listed together with the mode of decomposition of the corresponding propylchromium derivative and L, the leaving group constant. The latter is obtained from the equation $\log (k_i/k_0) = \gamma L$, which correlates the rates of nucleophilic substitution of a series of alkyl derivatives.[18] A similar parameter can be obtained from solvolysis reactions. For comparison, values are also given in Table III for the formation of ethylene by reductive elimination of the lower homologs, 2-substituted ethyl halides, with the same Cr^{II}en reagent. We postulate that cyclopropanes are only formed from γ-substituted propylchromium intermediates IV by an internal displacement process (eq 21), which is similar

TABLE III

COMPETITION BETWEEN CYCLIZATION, ELIMINATION, AND PROTONOLYSIS IN REACTIONS OF γ- AND γ-SUBSTITUTED ALKYLCHROMIUM DERIVATIVES

Substituent Y		γ-Y-Propylchromium[a]	β-Y-Ethylchromium[b]	Leaving-group constant[c] L
p-Tosyloxy	(TsO)	Δ	=	0.63
Bromo	(Br)	Δ	=	0.00
Iodo	(I)	Δ	=	0.04
Chloro	(Cl)	Δ + H	=	−1.61
Trimethylammonium	[$(CH_3)_3N^+$]	H	=	−3.54
Acetoxy	(CH_3CO_2)	H	=	−4.68
Methoxy	(CH_3O)	H	=	<−6.54
Hydroxy	(HO)	H	=	*d*
Benzamido	(PhCONH)	H	H	*d*
Cyano	(NC)	H	H	*d*
Amino	(H_2N)	H	=	*d*

[a] Δ denotes cyclization, H denotes protonolysis. [b] = denotes elimination. [c] From ref 18. [d] Where L has not been determined, relative order is assumed.



to eq 14 in β eliminations. The alternative decomposition of IV by loss of YCr^{III} in a cyclic transition state (eq 22) similar to a *cis* elimination (eq 15) in 1,2 systems does not appear relevant (*vide infra*).

Anionic character is not highly developed in the transition state of the cyclization (eq 21), since the driving force for internal displacement of the γ substituent is not large. Only readily displaced groups such as iodide, bromide, and tosylate and to a certain extent chloride are ejected. Acetate, phenoxide, and trimethylamine, which are undistinguished as leaving groups go, are not displaced and the intermediate IV is preferentially protonated. Furthermore, Cr^{II}en undoubtedly reacts with 1,3-dihalobutanes (Table I) *via* transfer of the secondary rather than the primary

(18) E. Thornton, "Solvolysis Mechanisms," Ronald Press, Inc., New York, N. Y., 1964, p 163 ff.

(19) A Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 82.

(20) There are differing indications concerning the cyclization of γ-iodopropyl radicals to cyclopropane (*cf.* D. Blomstrom, K. Herbig, and H. Simmons, *J. Org. Chem.*, **30**, 959 (1965); L. Kaplan, *J. Amer. Chem. Soc.*, **89**, 1753, 4566 (1967)). In both cases, much elevated temperatures were employed compared to studies reported here.

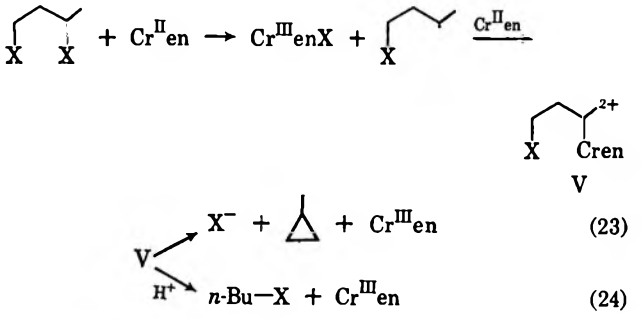
TABLE IV

RELATIVE RATES OF REDUCTION OF ORGANIC HALIDES WITH Cr^{II}en BY COMPETITION STUDIES[a]

Substrate A	Coreductant B	k_A/k_B	Relative rates A
$CH_3CH_2CH_2CH_2Br$	$BrCH_2CH_2CH_2Br$	0.015 ± 0.002	0.015
$(CH_3CH_2)_3N^+CH_2CH_2CH_2Br$	*b*	...	~0.3[c]
$CH_3CH_2CH_2CH_2I$	$ICH_2CH_2CH_2I$	0.017 ± 0.003	0.43
$ClCH_2CH_2CH_2Br$	$CH_3CH_2CH_2CH_2Br$	14 ± 2	0.22
$TsOCH_2CH_2CH_2Br$	$CH_3CH_2CH_2CH_2I$	1.1 ± 0.1	0.47
$ClCH_2CH_2CH_2I$	$CH_3CH_2CH_2CH_2I$	6 ± 0.5	2.7
$BrCH_2CH_2CH_2Br$	$BrCH_2CH_2Br$	0.065 ± 0.001	1.0
$ICH_2CH_2CH_2I$	$BrCH_2CH_2Br$	1.6 ± 0.2	25

[a] Cr^{II} added rapidly (by syringe) to solutions of excess halide mixture, ethylenediamine in DMF at room temperature. All solutions homogeneous and $Cr(ClO_4)_2$ was 0.0052 *M* and ethylenediamine was 0.020 *M*. For substrate concentrations see Table VI, Experimental Section. [b] Determined by following Cr^{II} disappearance. Second-order plot curved upward slightly; $k_2 = 7.7 \pm 1.6 \times 10^{-6}$ l./mole sec. In solutions of 20% aqueous DMF containing 1 *M* perchloric acid $Cr^{II}_0 = 0.037$ *M*, bromoammonium salt = 0.010 *M*. Under the same conditions trimethylene dibromide, $k_2 = 2.7 \times 10^{-4}$ l./mole sec. [c] Relative rate estimated from *b* by assuming the same relative reactivity for Cr^{II} and Cr^{II}en. Therefore, value is lower limit.

halogen, owing to the greater reactivity of the former. The attendant secondary alkylchromium intermediate V is less inclined to eject the γ-halide (eq 23) than the



primary analog IV and protonolysis (eq 24) is a more important competing process. This behavior is in accord with the stability of alkylchromium species, which generally increase in the order primary < secondary < tertiary.[8,16]

Grignard reagents substituted in the γ position even with such poorer leaving groups as alkoxides afford cyclopropanes in good yields.[2,3] These organomagnesium compounds undoubtedly evoke more carbanionic character, as does the recently reported electrochemical reduction of 3-substituted propyl halides.[21]

Participation in Halogen Transfer to Cr^{II}.—In addition to affecting products of reduction, γ substituents also alter the rate of loss of halogen to Cr^{II} (eq 5). The rates of disappearance of Cr^{II} and alkyl halide in these reductions are directly related to this step, since the subsequent association of radicals (eq 6) with another Cr^{II} is fast. The relative rates of reduction of various halides in Table IV with Cr^{II}en were measured by a competitive method since reactions were too rapid to follow by conventional techniques.

In Table V, the relative rates of reduction of γ-substituted propyl halides by Cr^{II}en are compared to the parent propyl halide. The corresponding data for relative rates of reductive elimination of a series of β-substituted ethyl bromides[13] are also included for comparison. We further conclude from the data presented in Table V that the γ-iodo substituent increases the rate of halogen transfer to Cr^{II}en. A similar effect is even more evident with a β-bromo substituent in 1,2 eliminations (column 4). The effect of a β-iodo

(21) M. Rifi, *J. Amer. Chem. Soc.*, **89**, 4442 (1967).

TABLE V

RELATIVE RATES OF REDUCTION OF γ-SUBSTITUTED PROPYL HALIDES BY Cr^{II}en[a]

		Relative rates[b]		
Substituent Y		γ-Y-Propyl iodide	γ-Y-Propyl bromide	β-Y-Ethyl bromide[c]
Methyl	(CH_3)	1	1	1
Chloro	(Cl)	7	20	100
p-Tosyloxy	(TsO)	...	30	60
Bromo	(Br)	(10)[d]	70, 35[e]	600, 300[e]
Iodo	(I)	60, 30[e]	(100)[f]	...

[a] In aqueous DMF solutions at room temperature. [b] Relative rates given only to one significant figure for emphasis. [c] See ref 13. [d] Estimate by interpolation. [e] Statistical correction of two applied. [f] Estimate by extrapolation. See text.

substituent could not be examined owing to instability of 1,2-diiodides.[22]

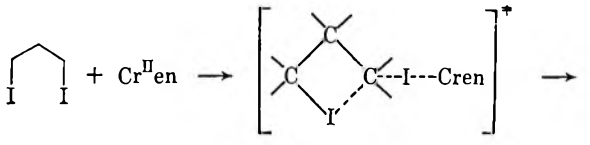
The effect of a γ-iodine in accelerating the rates of reductive cyclization of 1,3-dihalides merits further discussion. These rates can be compared by using the least reactive halogen, *i.e.*, a γ-chlorine, as a standard for comparison. Thus, as shown in Table V, in the series of propyl iodides a γ-iodine is four to five times more effective than a γ-chlorine. In a corresponding series of propyl bromides, the γ-bromine increases the rate of reduction less than twice as much as a γ-chlorine. The greater effectiveness of a γ-iodo substituent compared to a γ-bromine given by these *parallel* studies is certainly a lower estimate, since *n*-butyl iodide is approximately 30 times more reactive than *n*-butyl bromide toward Cr^{II}en (Table IV). As a result, substituent effects in the more reactive iodide series are transmitted less than they are in the bromide series,[23a] as shown further by the sevenfold acceleration by γ-chlorine in the iodide series and a 20-fold effect effect felt in the bromide series. Unfortunately, the study of 3-bromo-1-iodopropane is not meaningful owing to the ambiguity regarding which halogen is initially transferred to Cr^{II}en (*i.e.*, iodine transfer or iodine-assisted bromine transfer). We anticipate, however,

(22) F. Jensen and W. Coleman, *J. Org. Chem.*, **23**, 869 (1958); M. Cava and D. Napier, *J. Amer. Chem. Soc.*, **79**, 1701 (1957); T. Paterson and J. Robertson, *J. Chem. Soc.*, **125**, 526 (1924).

(23) (a) This also follows from Hammond's postulate (G. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955)). The compressed reactivity scale also applies to reactions of Cr^{II} and Cr^{II}en (see ref 13). (b) These rough estimates are obtained by a simple extrapolation and interpolation of the data presented in Table V. (c) We have no evidence which indicates that γ-iodopropyl radical, as the bridged cyc lic species has sufficient stability to be treated in its *subsequent* reactions separately from the open chain form. Evidence for bridged β-iodoalkyl radicals has been presented (P. Skell and R. Pavlis, *ibid.*, **86**, 2956 (1964)).

that a γ-iodine would assist *bromine transfer* to $Cr^{II}en$ by a factor of greater than 100 compared with a tenfold acceleration of *iodine transfer* by γ-bromine.[23b] These substituent effects would be even further magnified if Cr^{II} were used as the reductant rather than $Cr^{II}en$.[13]

We attribute the accelerating effect of a γ-iodo substituent on the rate of reduction to its neighboring-group participation during halogen transfer to Cr^{II}-en.[24] A transition state for this assistance is given in eq 25.[23c] A similar participation by iodine has been



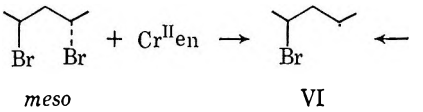
$$Cr^{III}Ien + ICH_2CH_2CH_2\cdot \quad (25)$$

proposed in the thermolysis of aroyl and acyl peroxides.[25a] In those cases, however, a five- rather than a four-membered transition state would be invoked.[25b]

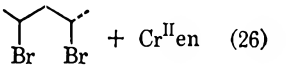
Neighboring-group participation by β-bromine in reduction of alkyl halides by Cr^{II} was shown both to affect the rate[12] strongly as well as the stereochemistry of elimination.[24] In the γ position the effect of bromine as shown in Table IV is marginal.[24b] Such studies with the propyl system show that effect of substituents in the γ position are highly attenuated relative to β substituents. Both rates of halogen transfer to Cr^{II} (eq 5) as well as decomposition of the alkylchromium intermediate (eq 22) which depend on such cyclic participation are damped markedly. We conclude that participation in reaction 25 or 15 derives driving force more from stabilization due to electron delocalization or coordination than to steric forces, because of its highly selective role in 1,2 processes. In 1,3 and higher processes only those groups which participate strongly seem to continue to exert their influence by such a mechanism.

Stereochemistry of 1,3-Reductive Cyclization.—Each isomer of the pair of 2,4-dibromopentanes was separately reduced by Cr^{II} under various conditions, shown in Table VI. Reducing agents were $Cr^{II}en$ in DMF and Cr^{II} in dimethyl sulfoxide (DMSO), which were conditions successfully employed to effect stereospecific *trans* elimination from *dl*- and *meso*-2,3-dibromobutanes.[24] These results show that under optimum conditions for stereospecificity in reductive eliminations, there is no specificity in the reductive cyclization of the homologous 2,4-dibromopentanes.

In vicinal elimination of alkyl dibromides, a 1,2-bromine bridged radical plays a key role in controlling the over-all stereochemistry of the elimination process.[24] The lack of stereospecificity in the reductive cyclization of the homologous 2,4-dibromopentanes indicates that the analogous 1,3-bromine bridged radical is unimportant (kinetically).[23c] This is also consistent with the lack of significant γ-bromine participation in the initial bromine transfer to Cr^{II} (eq 16, Y = Br; *cf.* Table V, column 3). Stereochemical integrity is, thus, lost with the formation of the 4-bromo-2-pentyl radical VI, by virtue of the absence of bridging



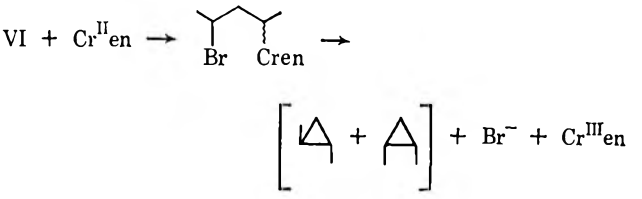
meso VI



(26)

dl

by a γ-bromine. The formation of various ratios of epimeric pairs of 2-bromo-3-pentylchromium derivatives in a subsequent step will be determined by the particular Cr^{II} species extant and the solvent. These isomers can lead to different relative amounts of *cis*- and *trans*-dimethylcyclopropanes reported in Table VI.



Reductive Cyclization of Higher Homologs.—Tetramethylene dibromide and diiodide reacted readily with $Cr^{II}en$ reagent. Only small amounts of cyclobutane were formed and protolytic reduction to *n*-butyl bromide and *n*-butyl iodide was the dominant route. The latter underwent further reduction to *n*-butane under the conditions of the experiment. Since protonolysis of the γ-iodobutylchromium intermediate is retarded

$$ICH_2CH_2CH_2CH_2I \xrightarrow[H^+]{Cr^{II}en} ICH_2CH_2CH_2CH_3 \xrightarrow[H^+]{Cr^{II}en} CH_3CH_2CH_2CH_3 \quad (27)$$

at lower acid concentrations, reduction of these dihalides was also examined at relatively high concentrations of ethylenediamine. Slightly larger amounts of

TABLE VI

REDUCTIVE CYCLIZATION OF *meso*- AND *dl*-2,4-DIBROMOPENTANE BY CHROMOUS REAGENTS[a]

2,4-Dibromopentane	Concn, *M*	Cr^{II}, *M*	en, *M*	Solvent	Dimethylcyclopropane[e] *trans*	*cis*
meso	0.0152	0.082	0.18	DMF[b]	51	49
meso	0.0154	0.083	11	DMF[c]	44	56
meso	0.0154	0.083	...	DMSO[d]	60	40
dl	0.0152	0.082	0.18	DMF[b]	50	50
dl	0.0154	0.083	11	DMF[c]	44	56
dl	0.0154	0.083	...	DMSO[d]	60	40

[a] Reactions run at room temperature. [b] 86 vol % DMF–water. [c] 22 vol % DMF–en. [d] 87 vol % DMSO–water. [e] Calculated assuming 1:1 calibration in glpc 15 ft Dowtherm A, *trans* (8.4 min), cis (12.9 min), *n*-pentane (8.2 min); *cf.* with dimethylcyclopropanes obtained from pyrazolines (R. Crawford and A. Mishra, *J. Amer. Chem. Soc.*, **87**, 3768 (1965)).

(24) (a) J. Kochi and D. Singleton, *J. Amer. Chem. Soc*, in press. (b) Neighboring-group participation alone, is not responsible for acceleration in the rate of reduction. The effect of substituents in the γ position is also, no doubt, a composite of polar and steric effects as shown by the faster reduction of γ-chloropropyl bromide and iodide compared to the corresponding butyl halide. We feel that the γ-iodo substituent exerts an effect larger than expected on the basis of comparison with γ-chloro and bromo substituents.

(25) (a) J. Leffler and J. West, *J. Org. Chem.*, **27**, 4191 (1962). See also *J. Amer. Chem. Soc.*, **80**, 5435 (1958); *J. Org. Chem.*, **26**, 733 (1961); **25**, 424 (1960); *cf.* R. Woolford and R. Gedye, *Can. J. Chem.*, **45**, 291 (1967). (b) There have also been some recent attempts to show halogen bridging from nonvicinal positions in free radicals (W. Trahanovsky and M. Doyle, *J. Org. Chem.*, **32**, 146 (1967); L. Montgomery and M. Matta, Abstracts, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, p 22K).

cyclobutane were formed, but still not in sufficient quantities to warrant further study.

Pentamethylene dibromide and diiodide also reacted with $Cr^{II}en$ readily, but no cyclopentane was formed. *n*-Amyl bromide and iodide were the major products, which reacted further with $Cr^{II}en$ reagent to afford *n*-pentane. In the same manner, hexamethylene dibromide and diiodide afforded only products of protolytic reduction with $Cr^{II}en$.

In the reduction of this series of polymethylene dibromides and diiodides, it is apparent that transfer of bromine or iodine to $Cr^{II}en$ produced the free radical I and ω-halopolymethylenechromium derivatives VII were generated in the usual manner. Cyclization of the latter (eq 29, $n > 1$) to cycloalkanes is not favored

$$XCH_2(CH_2)_nCH_2Cr^{2+} \xrightarrow{H^+} XCH_2(CH_2)_nCH_3 + Cr^{III} \quad (28)$$

$$XCH_2(CH_2)_nCH_2Cr^{2+} \rightarrow X^- + \begin{pmatrix}(CH_2)_n\\ CH_2{-}CH_2\end{pmatrix} + Cr^{III} \quad (29)$$

relative to protonolysis (eq 28). Barring specific effects, the probability for ring closure by internal displacements generally decreases with ring size. This is illustrated by the synthesis of methyl cyclopropyl ketone specifically from the base-catalyzed conversion of 5-chloropentanone-2.[26] Furthermore, the driving force for internal displacement of halide ion in VII is not as great as it is in organomagnesium or zinc reagents (*vide supra*). These factors, coupled with the greater proton availability in aqueous DMF solutions compared to aprotic media used in Grignard reactions, tilt the balance for competition between protonolysis (eq 28) and cyclization (eq 29) toward the former in the higher homologs.

Reduction of Trimethylene Oxide and Sulfide.—The reduction of trimethylene oxide by $Cr^{II}en$ occurred slowly at room temperature over several days. No cyclopropane or propane was liberated. *n*-Propyl alcohol was the only product found. Trimethylene sulfide reacted with $Cr^{II}en$ rapidly, but neither cyclopropane nor propane were found.

These compounds, like their lower homologs, epoxides and episulfides, probably react with $Cr^{II}en$ through the heteroatom.[13,24] The intermediate radicals generate alkylchromium compounds, which only yield products of protolytic reduction. They resemble intermediates from γ-hydroxy- and mercaptopropyl halides.

$$\square_A + Cr^{II}en \rightarrow Cr^{III}enACH_2CH_2CH_2\cdot \xrightarrow{Cr^{II}en}$$

$$Cr^{III}enACH_2CH_2CH_2Cren^{2+}$$

$$Cr^{III}enACH_2CH_2CH_2Cren^{2+} \xrightarrow{H^+} HACH_2CH_2CH_3 + Cr^{III}en$$

$$A = O, S$$

Experimental Section

Materials.—The following Eastman White Label chemicals had the physical constants listed and were used directly: 1-bromobutane, $n^{26}D$ 1.4370 (lit.[27] $n^{20}D$ 1.4398); 1-iodobutane, $n^{26}D$ 1.4970 (lit.[27] $n^{20}D$ 1.5001); 1,3-dibromopropane, $n^{24.8}D$ 1.5206 (lit.[28] $n^{20}D$ 1.5232); 1,3-dichloropropane, $n^{24.8}D$ 1.4461 (lit.[29] $n^{25}D$ 1.4362); 3-bromopropanol-1 was contaminated with approximately 12% trimethylene dibromide, $n^{24.8}D$ 1.4912 (lit.[30] $n^{20}D$ 1.4883); 3-bromopropyl phenyl ether, $n^{28}D$ 1.5441; 3-chloropropyl tosylate; trimethylene sulfide, $n^{28}D$ 1.5081.

Columbia supplied the following materials which were used without further purification: N-(3-bromopropyl)phthalimide, mp 79.5–80.0° (lit.[27] mp 72°); 3-bromopropylamine hydrobromide, mp 179–180° (lit.[31] 169–172°); 3-chloropropanol, $n^{24.8}D$ 1.4444 (lit.[27] $n^{20}D$ 1.4469); trimethylene oxide, $n^{24.8}D$ 1.3977 (lit.[27] $n^{25}D$ 1.3897) was contaminated with approximately 12% allyl chloride; 1-chloro-3-iodopropane, $n^{24.8}D$ 1.5451 (lit.[32] $n^{20}D$ 1.5472); 4-bromobutyronitrile, $n^{24.8}D$ 1.4747, was contaminated with approximately 7% trimethylene dibromide (lit.[33] $n^{20}D$ 1.4818); 1,3-dichloropropane, $n^{24.8}D$ 1.4417 (lit.[29] $n^{25}D$ 1.4362).

1,2-Dibromoethane, $n^{26}D$ 1.5353 (lit.[27] $n^{20}D$ 1.5389), and 1-bromo-3-chloropropane, $n^{24.8}D$ 1.4844 (lit.[27] $n^{20}D$ 1.4950), were from Dow and were used directly.

City Chemicals supplied 1,3-diiodopropane, $n^{24.8}D$ 1.6402 (lit.[27] $n^{20}D$ 1.6423), which was colorless and was used without further purification.

3-Bromopropyl tosylate was prepared from 3-bromopropanol-1 and tosyl chloride using Tipson's procedure:[34] bp 153–155° (0.05 mm); $n^{28}D$ 1.5345 lit.[34b] bp 130–140° (0.001 mm).

3-Bromopropyltriethylammonium bromide was prepared from trimethylene dibromide and triethylamine in ether.[21] It reacted rapidly with $Cr^{II}en$ and consumed 2.1 equiv/mol of salt (>96% assay).

meso- and *dl*-2,4-Dibromopentanes were prepared by Pritchard and Vollmer's procedure.[35] Complete separation of the cyclic sulfites was effected, but partial epimerization occurred during conversion to the dibromide: *meso* isomer, bp 50–51° (4 mm); $n^{27}D$ 1.5000; contained 88% *meso* by glpc; *dl* isomer, bp 47–48° (4.3 mm); $n^{32}D$ 1.4937; contained 93% *dl* isomer lit.[35] *meso*, $n^{20}D$ 1.5015 (95%); *dl*, $n^{20}D$ 1.4968 (98%).

Chromous perchlorate solutions were prepared as before[9] and were 0.5–0.9 *M* in strength.

Dimethylformamide (Du Pont; specified distillation range 0.6°) was used as received. Matheson Coleman and Bell ethylenediamine (98–100%) was used either neat or as a standard solution in dimethylformamide.

All operations involving chromous solutions were carried out under a helium atmosphere.

Experimental Procedure.—Solutions of the chromous–ethylenediamine reagent were prepared by addition (*via* syringe) of an aqueous chromous perchlorate solution to degassed solutions of ethylenediamine in dimethylformamide. The reagent solutions were prepared in 50- or 125-ml erlenmeyer flasks capped with rubber septa, which were secured with tightly wound rubber bands. About 0.5 mmol of as tandard solution of substrate was added by syringe to the stirred reagent. When the mixture had changed in color from royal blue to purple or red, an internal standard was added and the products were analyzed by gas chromatography. Gaseous products were sampled directly. Liquid products were analyzed by partitioning an aliquot between dilute perchloric acid and an organic solvent, followed by glpc examination of the organic layer.

The method was modified somewhat for the competition reactions, where a large (greater than tenfold) excess of organic halides was employed. A solution of the organic halides in DMF

(26) (a) G. Cannon, R. Ellis, and J. Leal, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 593. (b) The methylene hydrogens are as reactive as the α-methyl hydrogens in methyl ethyl ketone toward hydroxide in aqueous dioxane (J. Warkentin and O. Tees, *J. Amer. Chem. Soc.*, **88**, 5540 (1966)). The preferential cyclization to a three- rather than five-membered ring probably derives much from entropic factors. (c) It may be possible to cyclize reductively α′α-dihalo and α,α,α′α′-tetrahalo ketones to cyclopropanones and cyclopropenones with Cr^{II}, respectively (*cf.* R. Breslow, *et al.*, *ibid.*, **87**, 1326 (1965); R. Doerr and P. Skell, *ibid.*, **89**, 4684 (1967)).

(27) "Handbook of Chemistry and Physics," 45th ed, Chemical Rubber Co., Cleveland, Ohio, 1964–1965.

(28) C. P. Smyth and W. S. Walls, *J. Amer. Chem. Soc.*, **54**, 2266 (1932).

(29) S. S. Rossander and C. S. Marvel, *ibid.*, **50**, 1493 (1928).

(30) A. Karvonen, *Acad. Sci. Fennicae*, **5A**, 1 (1914); *Chem. Abstr.*, **14**, 2176 (1920).

(31) F. Schaefer, *J. Amer. Chem. Soc.*, **77**, 5929 (1955).

(32) W. E. Hanford and R. M. Joyce, Jr., U. S. Patent 2,440,800 (1942); *Chem. Abstr.*, **42**, 6373 (1948).

(33) L. Leclercq and A. Bruylants, *Bull. Soc. Chim. Belges*, **58**, 149 (1949).

(34) (a) J. Tipson, *J. Org. Chem.*, **9**, 239 (1944); (b) O. Hromatka, G. Stehlik, and F. Sauter, *Monatsh.*, **91**, 107 (1960).

(35) J. Pritchard and R. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).

TABLE VII

COMPETITIVE REDUCTION OF ORGANIC HALIDES WITH $Cr^{II}en$

Substrate (A)	M^b	Substrate (B)	M	Av k_A/k_B
$CH_3CH_2CH_2CH_2Br$	0.0135	$BrCH_2CH_2CH_2Br$	0.0135	0.014
	0.0541		0.0135	0.013
	0.135		0.0135	0.017
$CH_3CH_2CH_2CH_2I$	0.00982	$ICH_2CH_2CH_2I$	0.0123	0.014
	0.0393		0.0123	0.020
	0.0982		0.0123	0.018
$BrCH_2CH_2CH_2Br$	0.0135	$BrCH_2CH_2Br$	0.0186	0.065
	0.0405		0.0186	0.066
$ICH_2CH_2CH_2I$	0.0123	$BrCH_2CH_2Br$	0.0186	1.47
	0.0221		0.0186	1.81
$ClCH_2CH_2CH_2I$	0.0177	$CH_3CH_2CH_2CH_2I$	0.0491	6.3[c]
	0.0089		0.0491	7.4[c]
	0.0089		0.0786	5.4[c]
$ClCH_2CH_2CH_2Br$	0.0185	$CH_3CH_2CH_2CH_2Br$	0.0676	13.9[c]
	0.0093		0.0676	16.4[c]
	0.0093		0.108	13.2[c]
$BrCH_2CH_2CH_2OTs$	0.00332	$CH_3CH_2CH_2CH_2I$	0.0098	1.2
	0.00133		0.0196	1.1
	0.00067		0.0491	0.98

[a] Chromous solution added rapidly by syringe to solution of halides and ethylenediamine in DMF at room temperature. [b] $[Cr(ClO_4)_2]$ 0.00518 M, ethylenediamine 0.0202 M. [c] Correction factor of 1.21 included to account for competitive reduction.

was degassed, then the requisite amount of ethylenediamine was added to the rapidly stirred mixture, followed *immediately* by the chromous solution. Various ratios of reactants were employed and relative rates determined in the usual manner. Typical data are included in Table VII.

Gas Chromatographic Data.—Ethylene, propylene, and cyclopropane were measured on a 15-ft Dowtherm A column against *n*-butane as marker (standard). A 6-ft QFI column was used to measure *n*-propyl chloride *vs.* isopropyl chloride marker.

The gases were examined using a Case-constructed instrument having a thermal conductivity detector; liquids, in solution, were measured on a Varian Aerograph A-200 equipped with flame-ionization detectors.

Registry No.—Ethylenediaminechromium(II), 15525-39-0.

Acknowledgment.—We wish to thank the National Science Foundation for a generous grant which supported this study and Mr. John Powers for the preparation of *meso*- and *dl*-2,4-pentanediols.

Structure of Diene–Phosphonous Dihalide Addition Products and of Derived Phospholenes and Phospholene Oxides[1]

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It has been shown that the cycloadducts of methylphosphonous dichloride and butadiene, isoprene, 3,4-dimethylbutadiene, or piperylene give rise to 3-phospholene oxides on hydrolysis and 3-phospholenes on reduction with magnesium. The cycloadduct from butadiene was also shown to contain the 3-phospholene ring. The 3-phospholene oxides may be caused to rearrange to 2-phospholene oxides either thermally or by refluxing aqueous base. Acid treatment was effective only for rearranging the 3-methyl derivative. The 3,4-dimethyl derivative resisted rearrangement conditions. Phenylphosphonous dibromide (synthesized by a new method from phenylphosphinic acid and phosphorus tribromide) also gave an adduct with isoprene shown by nmr studies to contain the 3-phospholene ring, which was preserved in the oxide and phospholene. However, the isoprene–phenylphosphonous dichloride adduct contained the 2-phospholene ring; the derived oxide and phospholene were also the 2 isomers. Independent syntheses of the isomeric 1-phenyl-3-methylphospholene oxides confirmed the assignments. The adduct from piperylene and phenylphosphonous dibromide also gave on hydrolysis the 3-phospholene oxide, while that from phenylphosphonous dichloride gave the 2 isomer.

The cycloaddition of conjugated dienes and phosphonous dihalides was first reported by McCormack in 1953.[2,3] The halophosphorane adducts and derived products were assumed to contain the 3-phospholene ring. It was not until 1963 that it became evident that the double bond in products derived from the adducts could appear in the 2,3 position. This behavior was first encountered among adducts from the related reaction of dienes and phosphorus trihalides,[4,5] where it was found that the trichloride gave 2-phospholene derivatives while the tribromide gave the 3 isomer. It was later stated that adducts of phenylphosphonous dichloride with isoprene or butadiene gave on hydrolysis the 2-phospholene oxides rather than the

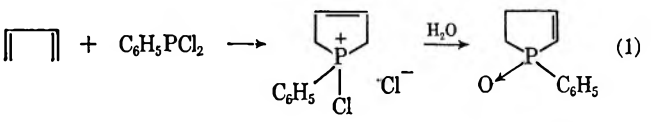
(1) Supported by Public Health Service Research Grant CA-05507 from the National Cancer Institute.

(2) W. B. McCormack, U. S. Patents 2,663,736 and 2,663,737 (Dec 22, 1953).

(3) The literature on this reaction has been reviewed recently: L. D. Quin, "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press Inc., New York, N. Y., 1967, Chapter 3.

(4) U. Hasserodt, K. Hunger, and F. Korte, *Tetrahedron*, **19**, 1563 (1963).

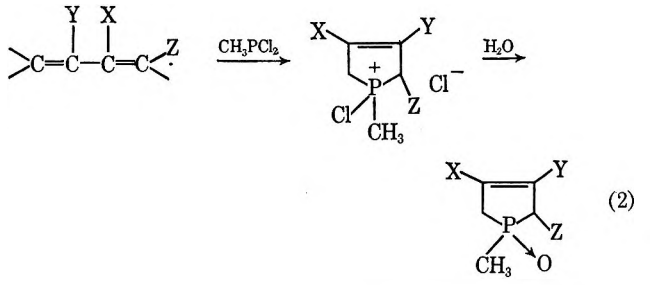
(5) B. A. Arbuzov, A. O. Vizel, Y. Y. Sametov, and K. M. Ivanovskaya, *Dokl. Akad. Nauk SSSR*, **159**, 582 (1964).



(1)

expected 3 isomers[6] (eq 1), and proton magnetic resonance (pmr) spectral studies[7] supported this contention. This observation has placed considerable doubt[3] on the exact structure of many compounds arising from phosphonous dichloride–diene adducts. We have resolved some of the uncertainty by studying the phospholenes and their oxides resulting from reduction and hydrolysis, respectively, of adducts derived from an alkyl (methyl[8a]) and an aryl (phenyl[8b]) phosphonous dichloride. The study has revealed that the structure of the adduct, and therefore also of derived products, is controlled by the nature of the substituent on the phosphonous dichloride, a methyl substituent leading to 3-phospholene derivatives and phenyl to 2-phospholenes. For the latter substituent, we shall show that replacing chlorine by bromine in the phosphonous dihalide leads to the 3-phospholene system, in parallel to the behavior of the phosphorus trihalides.[4,5] The specificity of the various reactions is remarkably high.

P-Methylphospholene Oxides.—A group of four new P-methyl oxides (**1a–d**) was prepared by addition to cold water of the adducts of methylphosphonous dichloride with dienes (eq 2). The oxides were hygro-



(2)

1a, X = Y = Z = H
b, X = Z = H; Y = CH_3
c, X = Y = CH_3; Z = H
d, X = Y = H; Z = CH_3

scopic and difficult to obtain in pure form. For analysis, they were converted to the dibromides, although in two cases (those of **1b** and **c**) instability was encountered. Pmr spectra[9,10] (Table I) of these compounds provide convincing evidence for the assignment of the double bond to the 3,4 position. Compound **1a** had a simple spectrum reflecting the symmetry of the molecule, and consisted of doublets (due to coupling with P^{31}) for the methyl protons at δ 1.60 (J = 13 cps), methylene protons at 2.43 (J = 11 cps), and vinyl protons at 5.87 (J = 28 cps). The spectrum of compound **1b** was quite similar; the two sets of methylene

(6) K. Hunger, U. Hasserodt, and F. Korte, *Tetrahedron*, **20**, 1593 (1964).

(7) H. Weitkamp and F. Korte, *Z. Anal. Chem.*, **204**, 245 (1964).

(8) Preliminary communications: (a) L. D. Quin, J. A. Peters, C. E. Griffin, and M. Gordon, *Tetrahedron Letters*, 3689 (1964); (b) L. D. Quin and T. P. Barket, *Chem. Commun.*, 914 (1967).

(9) The pmr spectral properties of the 3-phospholene ring as incorporated in phosphinic derivatives have been described by others.[7] Very large coupling constants for the vinyl protons β to phosphorus (J_{PCCH}) are characteristic of the system. The values exceed J_{PCH}. A valuable and extensive discussion of the pmr spectra of organophosphorus compounds, including some of those described in this paper, may be found in the Ph.D. dissertation of M. Gordon, University of Pittsburgh, Pittsburgh, Pa., 1965.

(10) B. A. Arbuzov, Y. Y. Sametov, A. O. Vizel, and T. B. Zykova, *Dokl. Akad. Nauk SSSR*, **159**, 1062 (1964).

TABLE I

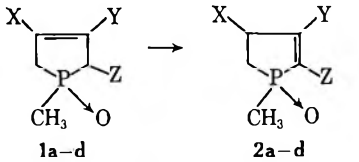
SPECTRAL PROPERTIES OF P-METHYLPHOSPHOLENES AND OXIDES[a]

Compd	γ_{C-C}^{neat}, cm^{-1}	δ (J, cps)[b] P–CH_3	=CH	CH_2	C–CH_3
		A. 3-Phospholene Oxides[c]			
1a	1620	1.60 (13.0)	5.87 (28.0)	2.43 (11.0)	
1b	1655	1.61 (13.0)	5.48 (29.0)	2.23–2.72[d]	1.79[e]
1c	*f*	1.56 (13.5)[g]		2.47[h]	1.68[e]
		B. 2-Phospholene Oxides[i]			
2a	1585	1.93 (13.5)	6.1–7.8[j]	2.2–3.3[j]	
2b	1615	1.87 (13.5)	6.29 (25.7)	2.1–3.2[j]	2.29[e]
2d	1634	1.82 (13.0)	6.77 (40.0)[k]	1.6–3.1[j]	2.20 (11.0)[l]
		C. 3-Phospholenes[i]			
3a	1626	0.82 (3.5)	5.80 (7.0)	1.7–2.95[m]	
3b	1658	0.87 (3.5)	5.38 (5.5)	2.0–2.9[m]	1.78[e]
3c	*f*	0.82 (3.5)		1.9–2.95[m]	1.65[e]
		D. Benzyl Bromide Salts of 3-Phospholenes[n]			
4a[c]		2.98 (15.0)	6.43 (28.5)	3.92 (10)	
4b[o]		2.37 (14.5)	5.38 (30)	3.24 (10)	1.72[e]
4c[o]		2.38 (14.5)		3.22 (10)	1.60[e]

[a] The spectra of the 2-methyl derivatives **1d** and **3d**, which exist in *cis* and *trans* forms, have been described elsewhere.[11] [b] Doublets from coupling with P^{31}. [c] Pmr run in $CDCl_3$ solution with external standard. [d] Broad, partly resolved doublet; peak separation, 11 cps. [e] Singlet. [f] Not observed. [g] Downfield peak overlapped by C—CH_3 signal. [h] Unsymmetrical, broad doublet; peak separation, 11 cps. [i] Pmr run neat with external TMS. [j] Complex multiplet. [k] Each peak shows additional small splitting. [l] Each peak additionally split 1.7 cps, presumably by vinyl proton. [m] AB multiplet of ABX system. [n] Benzyl CH_2 signals: **4a**, 5.24 (16.7); **4b**, 4.58 (17.2); **4c**, 4.58 (17). [o] Pmr run in $CDCl_3$ with internal standard.

protons, although in slightly different environments because of the 3-methyl substituent, nevertheless were indistinguishable and appeared as a doublet with broad peaks. Compound **1c** showed no vinyl proton signals; compound **1d**, obtained as a separable mixture of *cis* and *trans* isomers,[11] showed two vinyl protons. The latter observation could also indicate the double bond to be in the 4,5 position. However, it will be seen shortly that such a 2-phospholene oxide bearing no substituents on the double bond had a characteristic complicated spectrum not observed for this sample. It is of interest that the protons within the methylene groups of oxides **1a**, **1b**, and **1c** fail to show nonequivalence due to disposition of one proton *cis* to P–CH_3 and the other *cis* to P → O. The protons are equivalent also in the benzyl bromide salts of the corresponding phospholenes (*vide infra*). It will be noted later in this paper, however, that the phospholenes *do* possess nonequivalent protons.

Hunger, *et al.*,[6] found that thermal treatment or exposure to refluxing aqueous base caused rearrangement of the double bond in certain 1-hydroxy-3-phospholene oxides to the 2,3 position, and we have made a similar observation for the 1-methyl-3-phospholene oxides. The observation is of synthetic value as the 2-phospholene oxides so obtained are not available at present by any other method. Refluxing aqueous acid



1a–d **2a–d**

was also used for the first time for such a rearrangement; it was effective for rearranging only one of the

(11) L. D. Quin, J. P. Gratz, and R. E. Montgomery, *Tetrahedron Letters*, 2187 (1965).

TABLE II

REARRANGEMENTS OF 1-METHYL-3-PHOSPHOLENE OXIDES

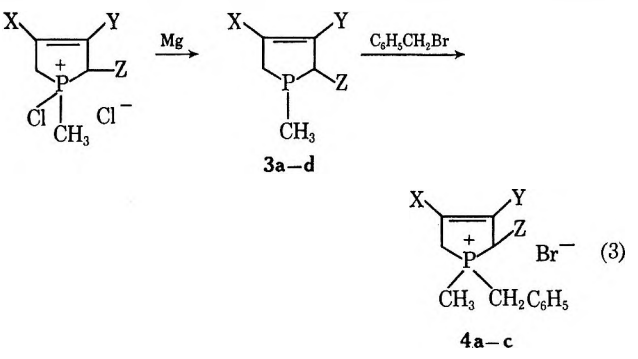
Oxide used	Composition[a] of recovered oxide: Thermal[b]	Base[c]	Acid[d]
1a	1:1 (12 or 20 hr)	2:3 (24 or 48 hr)	e
1b	1:1 (6.5 or 12 hr)	1:2 (27 hr)	1:9 (96 hr)
1c	9:1[f] (13.5 hr)	9:1[f] (46 hr)	9:1[f] (52 hr)
1d	1:9 (53 hr)	>99% 2d (23 hr)	e

[a] Ratio of 1 to 2 as determined by gc. [b] Reflux of neat liquid. [c] Reflux in 3 *N* sodium hydroxide. [d] Reflux in 3 *N* hydrochloric acid. [e] No detectable rearrangement. [f] The amount of 2c was calculated from two peaks on the chromatogram presumed to be *cis* and *trans* forms.

oxides (**1b**). From the results summarized in Table II, one arrives at the following conclusions. (1) The 3 isomer is stabilized to all rearranging conditions by the presence of two methyl substituents on the double bond (**1c**), as has been noted for some other phospholene derivatives.[6] (2) Acid treatment effects extensive rearrangement if the starting 3-phospholene bears one methyl substituent on the double bond (**1b**), but causes little or no rearrangement if the double bond is unsubstituted (**1a**, **d**). This is suggestive of a carbonium ion mechanism for the rearrangement; the former case would involve creation of a tertiary ion by electrophilic attack of a proton on the double bond, followed by proton loss, whereas in the latter case a less stable secondary ion would have to be created. (3) A particular preference for the 2 isomer appears if the double bond moves from an unsubstituted to a substituted situation, as seen by the greater tendency of **1d** to rearrange to **2d** than of **1a** to rearrange to **2a**.

Each of the 2-phospholene oxides **2a**, **b**, and **d** was isolated by distillation in pure form. No attempt was made to isolate **2c**, which was formed in only small amount. The infrared and pmr spectra (Table I) showed distinct differences from those of the 3-phospholene oxides. In the infrared, a difference directly associated with the position of the double bond was noted for two isomer pairs (**1a**–**2a**, **1b**–**2b**). The C=C stretching vibration occurred at lower frequency and significantly greater intensity for the 2 isomers. Both effects have been noted for other phospholene derivatives[7], and the appearance of the band at lower frequency (by 24 cm^{-1}) for a vinylphosphonate than for an allylphosphonate has also been observed.[12] The frequency difference was not observed for **1d**–**2d**, presumably because of a counter effect in the creation of the trisubstituted double bond in **2d** from a disubstituted one in **1d**. The pmr spectra were in accord with the assigned structures. For **2a**, the vinyl proton signals were a complex multiplet spread over the range δ 6.3–7.8. Another 2-phospholene oxide derivative (1-hydroxy) bearing no substituents on the double bond has been found to exhibit a similar complex spectrum, which has been analyzed in terms of cross-ring coupling.[7] The methylene region (δ 2.1–3.2) of **2a** also was considerably more complex than that of the symmetrical 3 isomer since there are two methylenes experiencing different shielding in **2a**. Oxide **2b** had its vinyl signal as a doublet (J_{PCH} = 25.7 cps) at δ 6.29, each peak of which showed slight additional splitting. The more downfield position of the vinyl proton relative to **1b** is in keeping with its location α or β to phosphorus, respectively. As additional proof of structure, the C-methyl substituent was indicated to be on the double bond from its singlet at δ 2.29. Finally, compound **2d** had a single vinyl proton (doublet at δ 6.77, J_{PCCH} = 40 cps with further splitting) and a methyl group on the double bond. Its signal at δ 2.20 was split by phosphorus (J_{PCCH} = 11.0 cps) and by the vinyl proton (1.7 cps). Comparison of δ for the vinyl proton in **2b** and **2d** reveals the proton of the latter (β) to be more deshielded (about 0.5 ppm) than the former (α). The situation is thus similar to that in α,β-carbonyl compounds, where it is well known that a β proton is more deshielded than an α proton. The same relation is evident in the 2- and 3-methyl derivatives of 1-phenyl-2-phospholene oxide (**7a** and **7b**, Table III).

P-Methylphospholenes.—With the magnesium–tetrahydrofuran system described previously,[13] the 3-phospholenes **3a**–**d** were prepared (eq 3) from the



(3)

corresponding adducts. Only **3b**[13] and **d**[11] have been previously reported. The new phospholenes were analyzed as the benzyl bromide salts.

The pmr spectra (Table I) of the phosphines were predictably different from those of the corresponding oxides, since trivalent phosphorus generally produces a much smaller chemical shift and coupling constant than does tetracovalent phosphorus as in phosphoryl or phosphonium compounds.[14] For example, in **3a**, the P–CH_3 doublet appears at δ 0.82 with J = 3.5 cps, and the vinyl protons appear at 5.80 (J = 7.0 cps). In contrast to the oxides and benzyl bromide salts corresponding to these phospholenes, the protons within the methylene groups of **3a**, **b**, and **c** are nonequivalent, and lead to ABX spectra (where X is P^{31}). The same is true of P-phenylphospholenes (*vide infra*). A separate study of this phenomenon is being made in collaboration with Dr. C. E. Griffin, University of Pittsburgh, and will be reported later. Phospholene **3d** shows another property of interest; it exists as *cis* and *trans* isomers owing to the configurational stability of trivalent phosphorus. The separation and properties of these isomers have been reported elsewhere.[11]

The pmr spectra (Table I) of the phospholenes confirm the assignment of the double bond to the 3 position. Phospholene **3c** has no vinyl protons and is necessarily the 3 isomer; the characteristic ABX pattern for its methylene protons is reproduced in the spectra of **3a** and **b**, which could not be the case if each methylene group were differently shielded as in the 2 isomer.

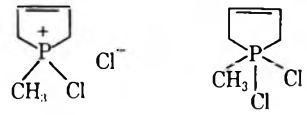
(12) R. G. Gillis, J. F. Horwood, and G. L. White, *J. Amer. Chem. Soc.*, **80**, 2999 (1958).

(13) L. D. Quin and D. A. Mathewes, *J. Org. Chem.*, **29**, 836 (1964).

(14) J. B. Hendrickson, M. L. Maddox, J. J. Sims, and H. D. Kaesz, *Tetrahedron*, **20**, 449 (1964).

Furthermore, the benzyl bromide salts show each ring methylene group to be equivalent, giving a sharp doublet due to P^{31} coupling.

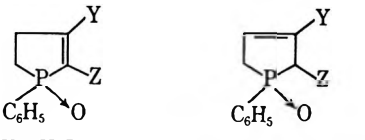
P-Methyl Cycloadducts.—The adducts are highly reactive to water and are not readily characterized directly. We have, however, succeeded in obtaining the pmr spectrum of the butadiene–methylphosphonous dichloride adduct in deuteriochloroform. The spectrum is entirely consistent with the symmetrical 3-phospholene ring system; the spectrum consists only of three doublets, P–CH_3 at δ 3.87 (J = 14 cps), the two methylenes at δ 4.47 (J = 8 cps), and vinyl H at δ 6.82 (J = 36 cps). The large downfield shifts resemble those of the benzyl bromide salt (see Table I), and suggest that, at least in solution, phosphorus is ionic (**5**) in these adducts rather than covalent (**6**).



5 **6**

Support for this assignment has come from the P^{31} spectrum of the deuteriochloroform solution; a signal at −112 ppm from 85% phosphoric acid was obtained. This value is in line with those reported for tri(*n*-butyl)dichlorophosphorane (−106 ppm in acetonitrile, −104 ppm in nitrobenzene), which has been established to be ionic.[15] Were phosphorus pentacovalent, a signal at much higher field would have been observed.

P-Phenylphospholene Oxides.—The appearance of the double bond in the 3 position of the oxides from hydrolysis to methylphosphonous dichloride adducts was in opposition to results[6] with P-phenyl compounds, where adduct hydrolysis had apparently given the 2-phospholene oxides. However, this observation has now been confirmed with the preparation of two oxides, **7a** and **b**, from the adducts with piperylene and isoprene, respectively. Oxide **7a** was obtained by addi-



7a, Y = H; Z = CH_3 **8a**, Y = H; Z = CH_3
b, Y = CH_3; Z = H **b**, Y = CH_3; Z = H

tion of the adduct to water, and was recovered by chloroform extraction after basification of the mixture. It was readily seen to have the 2-phospholene system by its pmr spectrum (Table III). The methyl group was located on the double bond (δ 1.79); it was coupled with phosphorus (J = 11.5 cps) and lacked the additional coupling to be expected if there were a methine proton as in the 3 isomer **8a**. This coupling has been observed in 1,2-dimethyl-3-phospholene oxide (**1d**).[11] Furthermore, there were two distinct methylene signals. Oxide **7b** was obtained from the procedure of McCormack[16] which is said to provide the 3 isomer. The product was predominantly the 2-phospholene oxide; gas chromatography revealed the presence of only about 4.5% of the 3 isomer (**8b**, *vide infra*) in the extracted oxide. The pmr spectrum (Table III) of

(15) G. A. Wiley and W. R. Stine, *Tetrahedron Letters*, 2321 (1967).
(16) W. B. McCormack, *Org. Syn.*, **43**, 73 (1963).

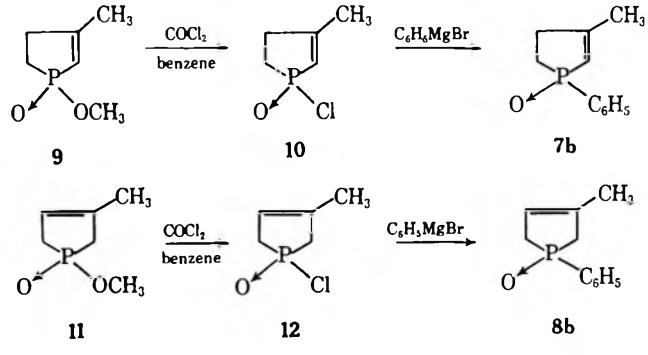
TABLE III
PMR SPECTRA OF P-PHENYLPHOSPHOLENES AND OXIDES

	δ (J,[a] cps)		
	=CH	CH_2	C–CH_3
2-Phospholene oxides[b]			
7a	6.67 (41)[c]	1.8–3.1[d]	1.79 (11.5)[e]
7b	5.97 (25.5)[f]	1.8–3.1[d]	2.08[g]
3-Phospholene oxides[b]			
8a[h]	5.38–6.45	2.3–3.4[i]	0.62–1.6
8b	5.62 (31.5)	2.4–2.9[j]	1.83[g]
Phospholenes[k]			
14	5.40 (8.0)	1.95–3.15[k]	1.70[g]
17	5.68 (42)[c]	1.5–2.8[d]	1.80[l,m]
Benzyl Bromide Salts[b,n]			
15[o]	5.43 (31.5)	3.0–4.3[d]	1.73[g]
18[p]	6.60 (28.7)	2.1–3.5[d]	2.0[g]

[a] Doublets from coupling with P^{31}. [b] $CDCl_3$ solution with internal standard. [c] Each peak shows small additional coupling. [d] Complex multiplet. [e] Each peak split 2 cps, presumably by vinyl proton. [f] Lit.[7] 5.83 (25.8). [g] Singlet. [h] Mixture of *cis* and *trans* forms giving superimposed spectra. [i] Includes methine proton. [j] Unsymmetrical doublet with broad peaks of 11 cps separation. [k] Neat with internal standard. [l] AB multiplet of ABX system. [m] Doublet from coupling with vinyl proton of 2 cps. [n] Benzyl CH_2 signals: **15**, 4.89 (16.0); **18**, 4.68 (15.7). [o] 49 mg in 0.3 ml of $CDCl_3$. [p] 110 mg in 0.3 ml of $CDCl_3$.

the product after distillation resembled that already reported for **7b** by Weitkamp and Korte,[7] although traces of **8b** were evident in our spectrum as in the gas chromatogram. That this product indeed had structure **7b** was proved by preparing authentic specimens of the isomeric pair of 2- and 3-phospholene oxides. It is well established[6,7] that the cycloadduct from isoprene and phosphorus trichloride on alcoholysis gives a 2-phospholene derivative (*e.g.*, **9**) whereas the phosphorus tribromide adduct leads to a 3-phospholene derivative (*e.g.*, **11**). These derivatives from methanolysis were subjected to the reaction sequence shown in Scheme I previously employed in the synthesis of P-alkyl phospholene oxide.[6] Oxide **7b**, a low

SCHEME I



9 **10** **7b**
11 **12** **8b**

melting solid, was identical in physical and spectral properties with the oxide obtained by hydrolysis of the isoprene–phenylphosphonous dichloride adduct. Oxide **8b**, a liquid, was quite different from **7b** in its spectral properties. In the infrared, **8b** had a weak C=C stretching band at 1646 cm^{-1}; **7b** would be expected to have this band at lower frequency, and indeed a strong band was present at 1612 cm^{-1} (possibly associated with a phenyl absorption). The pmr spectrum of **8b** contained the vinyl doublet at higher field (δ 5.62) and with a larger coupling constant (31.5 cps) than for **7b** (δ 5.97, J_{PCH} = 25.5 cps). Furthermore,

the two methylenes of **7b**, being differently shielded, gave a complex multiplet (δ 1.8–3.1) rather than a doublet as in **8b**.

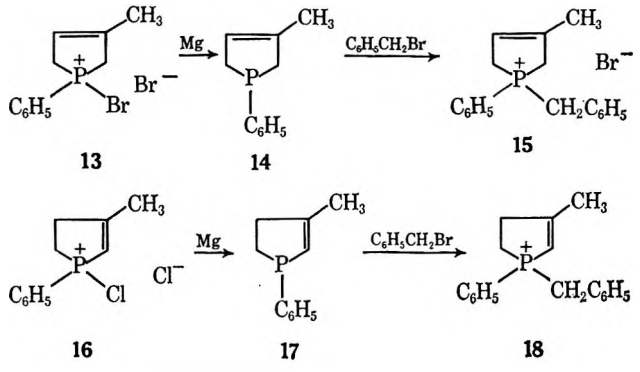
We have furthermore found that cycloadducts from phenylphosphonous **dibromide** provide the 3-phospholene oxides on hydrolysis, a result analogous to the use of phosphorus tribromide *vs.* phosphorus trichloride. Thus, the isoprene–phenylphosphonous dibromide adduct yielded oxide **8b** on hydrolysis, with only about 0.5% of isomer **7b**, and the piperylene adduct gave the new oxide **8a**[17,18] as a mixture of *cis* and *trans* isomers. This isomerism, which will be the subject of further study, was evident from the presence of two C–CH_3 signals, each a four-line pattern from coupling with P^{31} and the methine proton at C_2. Although arylphosphonous dibromides have been used previously in cycloadditions,[3] it has been assumed that the oxide from hydrolysis is the same as that from hydrolysis of arylphosphonous dichloride adducts.

A brief study of the rearrangement of oxides **7b** and **8b** was made. No change took place with either oxide when separately exposed overnight to 3 *N* sodium hydroxide or to 3 *N* hydrochloric acid at room temperature. However, reflux of either mixture containing **8b** caused extensive rearrangement to the 2-phospholene derivative **7b**. The efficacy of acid for the rearrangement of the related 1,3-dimethyl-3-phospholene oxide (**1b**) has already been noted. The mixtures starting with the pure 2-phospholene oxide (**7b**) showed a small amount of **8b** to be formed, suggesting that the rearrangements are reversible.

The formation of the 2-phospholene oxide system from phenylphosphonous dichloride adducts is not entirely general; it has been established elsewhere[6] that the adduct with 2,3-dimethylbutadiene gives mainly the 3-oxide.

P-Phenylphospholenes.—The position of the double bond in the phospholenes from magnesium reduction of the adducts has been found to be the same as in the phospholene oxides from hydrolysis. Thus, the isoprene–phenylphosphonous **dibromide** adduct gave a 45% yield of 1-phenyl-3-methyl-3-phospholene (**14**), as determined by its pmr spectrum and that of its benzyl bromide salt (**15**). Both spectra (Table III) resembled those of the corresponding P-methyl derivatives, the former showing the ABX multiplet. Also on oxidation **14** gave the 3-phospholene oxide **8b**. The isoprene–phenylphosphonous **dichloride** adduct had previously[13] been reduced in this laboratory, and the product assigned structure **14**. This product is in fact the 2-phospholene isomer (**17**) (Scheme II). On oxidation it is converted into 2-phospholene oxide **7b**. Furthermore, its pmr spectrum differed considerably from that of **14** (Table III). Most notable was the extraordinary size of the P^{31}–vinyl H coupling (J_{PCH} = 42 cps). Phosphorus in trialkyl phosphines normally has a small geminal coupling constant (*e.g.*, 3.5 cps for P–CH_3 in **3a–c**) when attached to sp^3 carbons. Few data are available for an attachment to sp^2 carbon; trivinylphosphine is, however, reported[19] to have a somewhat larger than normal value (11.74 cps) for coupling to the α carbon.

SCHEME II



The adduct from 2,3-dimethylbutadiene and phenylphosphonous dichloride had already been demonstrated[13] by pmr spectroscopy to be reduced to 1-phenyl-3,4-dimethyl-3-phospholene. This is consistent with hydrolysis to the 3-phospholene oxide.[6] As for the phosphorus trichloride adducts, the presence of two methyl groups tends to stabilize the double bond in the 3 position. Similar stability in 1,3,4-trimethylphospholene oxide (**1c**) to various rearranging conditions has already been noted.

P-Phenyl Cycloadducts.—In their discussion of the formation of 2-phospholene derivatives from cycloadducts of phosphorus trichloride, Hunger, *et al.*,[6] assumed that the cycloadduct itself possessed the 3-phospholene ring and that rearrangement occurred during subsequent reactions. It is mentioned in their paper, without data, that the adducts do have spectra supporting this structure. This explanation did not seem satisfactory to us for the phenylphosphonous dichloride adducts; hydrolysis to the oxide or magnesium reduction in dry THF represent quite dissimilar reactions; yet the product of each is almost entirely the 2 isomer. As an alternative explanation, the phosphonous dichloride **adduct** could be a 2-phospholene derivative, while the dibromide adduct could be the 3 isomer. From a study of the pmr spectra of the adducts with isoprene, we have concluded that this is indeed the case. The spectra (in deuteriochloroform) are distinctly different in the vinyl proton region. The dichloride adduct **16** has a doublet (J = 32.2 cps) at δ 7.0, while the dibromide adduct **13** had a doublet of larger J (37.5 cps) at considerably higher field (δ 5.80). The same difference may be noted in the benzyl bromide salts of the isomeric phospholenes; the salt of the 2 isomer **18** has the signal at δ 6.60 (J_{PCH} = 30 cps), and that of the 3 isomer **15** is at δ 5.43 (J_{PCCH} = 31.5 cps). Confirmation of a structural difference for the adducts may be obtained from examination of the methylene signals. The dibromide adduct has a symmetrical 4 H signal, though broad and unresolved, at δ 4.15; the dichloride has a complex multiplet (δ 3.1–3.9) for two differently shielded methylenes.

The P^{31} spectra of the adducts in deuteriochloroform solution support their description as phosphonium, rather than pentacovalent, derivatives. Adduct **13** has its signal at −89 ppm from 85% H_3PO_4, while that of **16** is at −99 ppm. Such downfield positions speak against the presence of neutral, pentacovalent phosphorus.

(17) This structure has previously been given to the oxide from the phenylphosphonous dichloride–piperylene adduct.[2,18] This oxide is now known to have structure **7a**, and **8a** is reported here for the first time.

(18) B. A. Arbuzov, L. A. Shapshinskaya, and V. M. Erokhina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2074 (1962).

(19) W. A. Anderson, R. Freeman, and C. A. Reilly, *J. Chem. Phys.*, **39**, 1518 (1963).

Conclusions

It has been conclusively shown that the position of the double bond in diene–phosphonous dihalide adducts is controlled by structural features of both participants in the reaction. Methylphosphonous dichloride with butadiene and some of its methyl derivatives provides the 3-phospholene system. However, the replacement of methyl by phenyl on phosphorus generally leads to the 2-phospholene ring. An exception, which constitutes an example of product control by the diene, occurs with 2,3-dimethylbutadiene, where the stabilizing effect of two methyls on a double bond in the 3 position determines the orientation. On replacement of chlorine by bromine in the phenyl system, the 3-phospholene ring results. The specificity of these cycloadditions is quite high, and it has been shown that the double bond once located in the adducts holds its position during subsequent conversions into other derivatives. The range of substituents on phosphorus so far studied is not sufficient to define the factors controlling the orientation of the double bond, and predictions of product structure from other phosphonous dihalides would seem to be difficult to make with confidence at this time. Since nothing is presently known about the mechanism of the cycloaddition, it remains unknown if the proton migration, which must occur to give 2-phospholene derivatives, takes place before or after ring closure. The most attractive possibility is that the cycloaddition proceeds in a normal manner and initially results in the 3-phospholene derivative; it is followed by an allylic shift made possible by activation of the α position by positive phosphorus. An explanation might then be at hand for the fact that the rearrangement has so far been observed only when phosphorus bears particularly electronegative substituents (*e.g.*, phenyl and chlorine, rather than phenyl and bromine or methyl and chlorine) since the electron attracting power of phosphorus on the α carbon will be enhanced by such substituents.

Experimental Section[20,21]

Methylphosphonous Dichloride–Diene Adducts.—Preparations were based on the following proportions: 1 mol of diene, 400 ml of hexane, and 1.2 g of cupric stearate polymerization inhibitor, to which mixture was added 1 mol of phosphonous dichloride. Wide-mouth, screw-cap bottles, sealed with wax, were convenient reaction vessels, even for the butadiene. The adducts began to separate as nicely crystalline solids generally after a day or two at room temperature, but the mixtures were not processed until the adducts were needed. Generally the mixtures stood for several weeks or even months. They were filtered and the adducts washed with pentane in a drybox.

Preparation of 1-Methyl-3-phospholene Oxides and Their Dibromides.—About 10–20 g of the adduct was treated slow with 10–20 ml of water, with ice bath cooling. While cold, the mixture was neutralized with concentrated sodium hydroxide, filtered to remove precipitated sodium chloride, and extracted with chloroform. The extract was dried with magnesium sulfate and then distilled. Yields of oxides from adducts varied from 60 to 80%. Boiling points obtained were 59° (0.16 mm), **1a** (low-melting solid); 82–83° (0.5 mm), **1b**; 58–64° (0.17–0.25 mm), **1d** (isomer mixture[11]). Compound **1c** was purified by sublimation at 100° (5 mm). The compounds were hygroscopic and it was difficult to obtain melting points or analytical data for them. Oxides **1a–c** were converted into the 3,4-dibromides by addition of a chloroform solution containing 1 mol of bromine to a chilled chloroform solution of the oxide. Consumption of the bromine was rapid. After 1 hr, the mixture was washed with dilute sodium thiosulfate solution, dried with magnesium sulfate, and stripped of solvent. The residual solids were somewhat unstable toward hot solvents in recrystallization attempts; they were crystallized by Dry Ice chilling of solutions prepared at room temperature in ether (for **1b** and c) or toluene–pentane (for **1a**). Oxide **1d** was separated into *cis* and *trans* isomers as described elsewhere.[11] Spectral data for **1a–c** are given in Table I; analytical data for the dibromides appear in Table IV.

Preparation of 1-Methyl-3-phospholenes and Their Benzyl Bromide Salts.—A slurry of 0.2 mol of the adduct in 400 ml of THF was treated slowly with 0.22 g-atom of activated magnesium in a flame-dried, nitrogen-flushed apparatus. The reaction was generally mildly exothermic, but was allowed to proceed with no temperature control. The reaction was completed by an 8–10 hr reflux period. If the reaction failed to start, the mixture was heated to reflux and held there for 10–12 hr. (On a few occasions, the reaction could not be initiated; an explanation for this behavior is lacking at present.) The mixture was then treated slowly with about 30 ml of concentrated hydrochloric acid; after residual magnesium had dissolved, the mixture was stripped of THF. The residue was taken up in water, made basic with 0.5 *N* sodium hydroxide solution, and steam distilled. The product layer was separated and dried with Drierite prior to distillation. Yields and boiling points were 73%, 114–115° (**3a**); 46%, 138–139.5° (lit.[18] 135–136°) (**3b**); 79%, 160–161° (**3c**); 54%, 130–134° (isomer mixture) (**3d**)[11]. Spectral data are in Table I. Benzyl bromide salts were prepared in ether solution at room temperature, and recrystallized from methanol–ethyl acetate. Analytical data for the salts are given in Table IV; spectroscopic data are in Table I.

Rearrangement of 1-Methyl-3-phospholene Oxide (1a). Thermal.—The oxide (38.8 g) under nitrogen was refluxed by heating in an air bath at 280°. After 12 hr, gas chromatography (gc) was performed with a 1 m by 8 mm column of 15% Dow-Corning silicone oil 710 on 60–80 mesh Chromosorb W at 150°. (These conditions were used in all gc described subsequently for 1-methylphospholene oxides; in general, the ratio of retention times for the 3 isomer to the 2 isomer was about 1:1.5.) Peaks of equal size for unchanged **1a** and for the 2-oxide **2a** were observed. There was no change in the ratio after another 8 hr. Distillation with a 1-ft column of glass helices gave a 5-ml sample containing 94% **1a** and 6% **2a**; fractionation with a spinning-band column then provided pure **2a** (see Table I and IV).

With Base.—A mixture of 1 g of **1a** and 6 ml of 3 *N* sodium hydroxide was refluxed for 24 hr. A portion of the mixture was neutralized and extracted with chloroform. Gc revealed the ratio **1a**:**2a** to be 2:3. The original mixture after an additional 48 hr showed no change in this ratio.

With Acid.—A mixture of 1 g of **1a** and 6 ml of 3 *N* hydrochloric acid was refluxed for 24 hr. After neutralization and extraction into chloroform, the product was shown by gc to contain only a trace of **2a**.

Rearrangement of 1,3-Dimethyl-3-phospholene Oxide (1b). Thermal.—A 8-g sample of **1b** was refluxed in an air bath at 300° for 6.5 hr. The ratio of **1b** to the 2-oxide **2b** was found by gc to be 1:1. The ratio was unchanged after an additional 6 hr.

With Base.—A sample of 1.8 g of **1b** was refluxed for 27 hr with 10 ml of 3 *N* sodium hydroxide. The mixture was neutralized and extracted with chloroform. Gc showed the ratio of **1b** to **2b** to be about 1:2.

With Acid.—The product after 43-hr reflux of 15 ml of 3 *N* hydrochloric acid and 2.5 g of **1b** was found by gc to contain 84% of **2b**. A 33.4-g sample of **1b** was then refluxed for 96 hr in 500 ml of 3 *N* hydrochloric acid. Gc revealed the product to contain 90% **2b**. The mixture was neutralized with solid sodium hydroxide and concentrated *in vacuo* until precipitation of sodium chloride commenced. The mixture was filtered and the filtrate extracted with chloroform. After drying over magnesium sul-

(20) All operations involving trivalent phosphorus compounds were conducted in a nitrogen atmosphere. Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride. Phenylphosphonous dichloride was obtained from Eastman; a procedure for methylphosphonous dichloride[21] synthesis has been published. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were taken on a Mel-Temp apparatus and are corrected; boiling points are uncorrected. Infrared spectra were run on Perkin-Elmer 137 and 237 spectrophotometers. Proton nmr were run on a Varian A-60 spectrometer; P^{31} nmr were obtained on a Varian V-4300 B nmr spectrometer at 19.3 Mc. P^{31} chemical shifts are expressed in parts per million from 85% H_3PO_4 and were obtained by tube interchange with P_4O_6 as secondary standard.

(21) J. A. Pianfetti and L. D. Quin, *J. Amer. Chem. Soc.*, **84**, 851 (1962).

TABLE IV

PHYSICAL AND ANALYTICAL DATA FOR PHOSPHOLENE DERIVATIVES

Compd	Bp, °C (mm)	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Phosphorus, % Calcd	Phosphorus, % Found
1a dibromide[a]		145.5–146	$C_5H_9Br_2OP$	21.76	21.93	3.29	3.62		
1b dibromide[b]		103–103.5	$C_6H_{11}Br_2OP$	24.85	24.82	3.82	3.82		
1c dibromide		98–100[c] dec	$C_7H_{13}Br_2OP$	27.66	27.50	4.31	4.80	10.19	10.30
2a	72 (0.08)		C_5H_9OP	51.72	51.70	7.81	7.91	26.68	26.78
2b	81 (0.14)		$C_6H_{11}OP$	55.38	55.53	8.52	8.50	23.80	23.90
2d	67–68.5 (0.18–0.20)		$C_6H_{11}OP$	55.38	55.71	8.52	8.63	23.80	23.63
4a		185–186.5	$C_{12}H_{16}BrP$	53.15	53.31	5.95	6.01	11.42	11.64
4c		185.5–187.5	$C_{14}H_{20}BrP$	56.20	56.14	6.74	6.65	10.35	10.46
7a	131–133 (0.32)[d]		$C_{11}H_{13}OP$	68.74	68.99	6.82	6.87	16.12	16.14
8a	124–132 (0.16)[e]		$C_{11}H_{13}OP$	68.74	68.98	6.82	6.96	16.12	16.36
8b	133–134 (0.24)		$C_{11}H_{13}OP$	68.74	68.55	6.82	6.72	16.12	16.28
15		178–180	$C_{18}H_{20}BrP$	62.26	62.08	5.80	5.87	8.92	9.13
18		184–185	$C_{18}H_{20}BrP$	62.26	62.33	5.80	5.86	8.92	9.09

[a] Calcd for Br: 57.92. Found, 57.68. [b] Calcd for Br: 55.12. Found, 55.07. [c] Approximate only owing to decomposition. [d] The reaction leading to **7a** has been performed elsewhere but claimed to give **8a**. Boiling point values have been reported: 160–180° (1 mm),[2] 158–159° (3.5 mm).[18] [e] A mixture of *cis* and *trans* isomers.

fate, the filtrate was distilled; there was obtained 25.7 g (77%) of mixed oxides. Distillation with a spinning-band column gave 13.7 g of pure **2b** (see Tables I and IV).

Rearrangement of 1,3,4-Trimethyl-3-phospholene Oxide (1c). Thermal.—A 2.3-g sample of **1c** was refluxed in an air bath at 300° for 6 hr. Gc showed the mixture to contain about 80% unchanged **1c** and about 5% each of two other compounds of slightly longer retention time. Refluxing for an additional 7.5 hr caused no change in the composition.

With Base. A similar product composition resulted from refluxing 0.6 g of **1c** with 5 ml of 3 *N* sodium hydroxide.

With Acid. A 0.6-g sample of **1c** was not detectably affected by refluxing with 5 ml of 3 *N* hydrochloric acid for 18 hr. After another 52 hr, the product contained about 10% each of the two new compounds. No isolations were attempted.

Rearrangement of 1,2-Dimethyl-3-phospholene Oxide (1d). Thermal.—A 25-g sample of **1d** (*cis* and *trans*[11]) was refluxed in an air bath at 265° for 53 hr. The 2-oxide (**2d**) comprised 90% of the gas chromatographable product. The mixture was distilled through a 1-ft column of glass helices; there was obtained 6 g of **2d** (Tables I and IV) whose purity was indicated by gc to be about 99%.

With Base.—The volatile product from refluxing 0.6 g of **1d** with 5 ml of 3 *N* sodium hydroxide for 23 hr was shown to be exclusively **2d**.

With Acid.—A mixture of 0.6 g of **1d** was refluxed for 18 hr with 5 ml of 3 *N* hydrochloric acid. Gc showed that no rearrangement to **2d** had occurred. After an additional 52 hr, only a trace of **2d** was detected.

Synthesis of Phosphorus Trihalide–Isoprene Adducts.—To a widemouth bottle was added 1 g of copper stearate and 38.3 g (0.562 mol) of isoprene, and then 58.5 g (0.426 mol) of phosphorus trichloride. The bottle was tightly sealed and put aside for 1 month. The mixture had become solid and reaction was presumed complete. The phosphorus tribromide–isoprene adduct was prepared similarly. The adducts were used directly in alcoholysis reactions.

Synthesis of 1-Methoxy-3-methyl-2-phospholene Oxide (9).—To 400 ml of methylene chloride was added 85 g (0.426 mol) of phosphorus trichloride–isoprene adduct. The mixture was held at −10° while 37 ml of methanol (dried over sodium sulfate) was slowly added. The solution was then allowed to come to room temperature. It was flushed with nitrogen for 1 hr, cooled to 0°, and then neutralized with saturated sodium bicarbonate solution to pH 7 (Hydrion paper). The methylene chloride layer was separated and the aqueous layer extracted with methylene chloride. The organic layers were combined and the solvent removed. The residue was distilled; after a forerun at 40° (0.6 mm), the product was received at 83–90° (0.6 mm). This fraction was redistilled with a spinning-band column to give 11.3 g of **9**,[7] bp 79° (0.4 mm), in 18.5% yield. Its pmr spectrum ($CDCl_3$, internal standard) contained a vinyl proton doublet (J = 24.0) at δ 6.3 (lit.[7] for ethyl ester, J = 23.75 cps).

Synthesis of 1-Methoxy-3-methyl-3-phospholene Oxide (11).—The procedure for the synthesis of **9** was followed, and employed 200 ml of methylene chloride, 199.5 g (0.351 mol) of phosphorus tribromide–isoprene adduct, and 40 ml of methanol. On distillation, the product was received at 69–72° (0.23 mm). This was redistilled with a spinning-band column to give 15.9 g (33.6% yield) of **11**, bp 65° (0.75 mm) (lit.[22] bp 117–119° (10 mm)). Its pmr spectrum ($CDCl_3$, internal standard) contained a vinyl proton doublet (J_{PCCH} = 35.5 cps) at δ 5.87 (lit.[10] J = 36.5 cps).

Synthesis of 1-Chloro-3-methyl-2-phospholene Oxide (10).—A solution of 9.27 g (0.0715 mol) of 1-methoxy-3-methyl-2-phospholene oxide (**9**) in an equal volume of carbon tetrachloride was placed in an ice bath and treated with 77.5 ml of a 12% solution of phosgene (0.078 mol) in benzene. After standing overnight, phosgene and solvents were removed by vacuum distillation. Continued distillation gave 5.53 g of **10** at 100° (0.3 mm), 51.2% yield. A boiling point of 91° (0.07 mm) has been reported[6] previously.

Synthesis of 1-Chloro-3-methyl-3-phospholene Oxide (12).—The procedure was similar to that used for the synthesis of **10**, and employed 9.57 g (0.073 mol) of 1-methoxy-3-methyl-3-phospholene oxide (**11**) and 0.10 mol of phosgene (100 ml of 12% solution). Distillation gave 4.74 g (43% yield) of **12**, bp 77° (0.5 mm). Analysis was not attempted.

Synthesis of 1-Phenyl-3-methyl-2-phospholene Oxide (7b) from 1-Chloro-3-methyl-2-phospholene Oxide (10).—Phenylmagnesium bromide solution (from 4.5 ml (0.044 mol) of bromobenzene and 1.08 g (0.044 g-atom) of magnesium) in 50 ml of dry THF at 5–10° was treated with 5.53 g (0.0366 mol) of 1-chloro-3-methyl-2-phospholene oxide (**10**) dissolved in a few milliliters of THF. Immediately after the addition was complete, excess Grignard reagent was decomposed by adding 20 ml of ice water, followed by 100 ml of 6 *N* hydrochloric acid. After drying over sodium sulfate, the extract was distilled to give 1.45 g (22.4% yield) of a low-melting solid product having bp 150° (15 mm); bp 173–174° (0.7 mm) has been reported in a different synthesis.[16] Spectral properties are reported in Table III.

Synthesis of 1-Phenyl-3-methyl-3-phospholene Oxide (8b) from 1-Chloro-3-methyl-3-phospholene Oxide (12).—The Grignard reagent from 3.6 ml (0.035 mol) of bromobenzene and 0.89 g (0.037 g-atom) of magnesium in 20 ml of dry THF was added to a chilled mixture of 4.74 g (0.0314 mol) of 1-chloro-3-methyl-3-phospholene oxide (**12**) in THF. As soon as addition was complete, there were added a few small pieces of ice and then 100 ml of 6 *N* hydrochloric acid. The mixture was then extracted with five 30-ml portions of chloroform and the extract dried over sodium sulfate. The solvent was stripped off, and the residue was distilled with a spinning-band column. There was obtained 3.24 g (53.5% yield) of liquid product, bp 136° (2.0 mm). This is the first authenticated synthesis of this compound. Spectral and analytical data are given in Tables III and IV, respectively.

Synthesis of 1-Phenyl-3-methyl-2-phospholene Oxide (7b) by Adduct Hydrolysis.—The procedure of McCormack[15] was followed. To 1 l. of ice water was added 38.6 g (0.156 mol) of phenylphosphonous dichloride–isoprene adduct which had been washed with petroleum ether (30–60°). A 10-ml aliquot of the

(22) A. O. Vizel, M. A. Zvereva, K. M. Ivanovskaya, I. A. Studentsova, V. G. Dunaev, and M. G. Berim, *Dokl. Akad. Nauk SSSR*, **160**, 826 (1965).

solution was titrated and the required amount of concentrated sodium hydroxide was added to neutralize 90% of the acid in the bulk of the solution. It was then brought to pH 7 (Hydrion paper) with solid sodium bicarbonate. The chloroform was stripped off and the residue distilled to provide 16.4 g of **7b** at 149° (0.26 mm). A modified procedure was also used. To the solution of 200 ml of ice water and 75 g of sodium bicarbonate was added 38.6 g (0.156 mol) of adduct. After the hydrolysis was complete the pH was found to be about 7. The solution was saturated with salt and extracted with a large quantity of chloroform. The extract was dried and the chloroform was stripped off. Gc indicated the crude product to contain 4.5% of isomer **8b**. The residue was distilled giving 18.7 g of **7b** at 149° (0.26 mm). These preparations of **7b** were identical in spectral properties with **7b** from the Grignard reaction of **10**. The compound is a solid for which mp 60–65° has been reported.[16]

Synthesis of Phenylphosphonous Dibromide.—A new method for the preparation of phenylphosphonous dibromide was em-

$$C_6H_5\overset{H}{P}(O)OH + PBr_3 \longrightarrow C_6H_5PBr_2$$

ployed. The reaction is similar to that described by Frank for phenylphosphonous dichloride synthesis.[23] The new method compares favorably in its simplicity with other methods. To 160 ml of phosphorus tribromide (1.6 mol) was added in portions 99 g (0.696 mol) of Eastman practical-grade phenylphosphinic acid. The addition required no external cooling. A viscous oil formed on the surface as the reaction proceeded. After 24 hr with occasional agitation, the lower liquid layer was separated and distilled with a Vigreux column (8 in.) under reduced pressure. Excess phosphorus tribromide was recovered at 50° (11 mm) and phenylphosphonous dibromide (143 g, 76.7%) then distilled at 121–123° (11 mm) (lit.[24] 124–126° (11 mm)). The P^{31} chemical shift was -151.8 ± 0.5 ppm.[25] (This new method has also been successfully used to synthesize *m*-bromophenylphosphonous dibromide from *m*-bromophenylphosphinic acid;[26] a yield of 38.2% was obtained using 2.3 g of phosphinic acid: bp 164° (11 mm); P^{31} signal at -147 ± 0.5 ppm).

Synthesis of 1-Phenyl-3-methyl-3-phospholene Oxide (8b) by Adduct Hydrolysis.—To 300 ml of ice water was added 18.46 g (0.055 mol) of phenylphosphonous dibromide–isoprene adduct. The mixture was neutralized with solid sodium bicarbonate to a pH of 7. This solution was extracted with 250 ml of chloroform and the extract dried over sodium sulfate. The solvent was stripped off and the residue distilled to give 3.74 g of **8b** at 136° (0.26 mm). The product was identical with that from the Grignard route on **12**.

Rearrangement of 1-Phenyl-3-methyl-3-phospholene Oxide (8b). By Acid.—A mixture of 1 g of **8b** and 25 ml of 3 *N* hydrochloric acid was allowed to stand overnight at room temperature. An aliquot was neutralized with sodium bicarbonate, and a benzene extract was gas chromatographed (5-ft SE-30 column, 4:1 on Chromosorb W, 275°). Only **8b** was detected. A similar extract after 29 hr of reflux contained **8b** and **7b** in the approximate ratio 1:10.

By Base.—A mixture of 1 g of **8b** and 25 ml of 3 *N* sodium hydroxide was allowed to stand overnight at room temperature. A benzene extract contained only **8b** by gc. After 48 hr of reflux, an extract contained both **8b** and **7b**, in the ratio 1:3.5.

Rearrangement of 1-Phenyl-3-methyl-2-phospholene Oxide (7b).—Both acid and base treatments at reflux were performed as for the 3-phospholene oxide isomer (**8b**). After 29 hr in acid, a mixture of **7b** and **8b** (about 10:1) was formed. After 48 hr in base, the mixture contained **7b** and **8b** in the ratio 5.5:1.

Preparation of 1-Phenyl-2-methyl-2-phospholene Oxide (7a).—The adduct from 3 months' standing of a mixture of 12.2 g (0.179 mol) of *trans*-piperylene, 39.7 g of phenylphosphonous dichloride, and 0.5 g of cupric stearate, after washing with pentane, was added in portions to 200 ml of ice-cold water. The mixture was neutralized with sodium bicarbonate, and the product extracted with chloroform. After drying over sodium sulfate, the solution was stripped of solvent and the residue distilled. Oxide **7a** (9.34 g, 27% yield on piperylene used) was received at 131–133° (0.32 mm). Spectral properties are given in Table III; analyses are in Table IV.

Preparation of 1-Phenyl-2-methyl-3-phospholene Oxide (8a).—The adduct from 15.5 g (0.228 mol) of *trans*-piperylene, 58 g (0.217 mol) of phenylphosphonous dibromide, and 0.5 g of cupric stearate was treated in the manner used for preparation of oxide **7a**. The product (30.7 g, 88% yield on phenylphosphonous dibromide) had bp 124–132° (0.16 mm). The wide boiling point is probably due to the presence of *cis* and *trans* isomers, which were evident on the pmr spectrum (Table III). The isomers have not yet been separated. Analyses are in Table IV.

Synthesis and Characterization of 1-Phenyl-3-methyl-3-phospholene (14).—To 200 ml of THF (sodium dried) and 52.1 g (0.155 mol) of phenylphosphonous dibromide–isoprene adduct was added slowly with vigorous stirring 5.4 g (0.2 g-atom) of freshly cleaned magnesium. The mixture was refluxed for 5 hr and then neutralized with excess saturated sodium bicarbonate solution. The resulting emulsion was continuously extracted with benzene for 24 hr. The benzene was removed and the residue distilled to give 12.3 g (45.1% yield) of **14** at 125° (13 mm). Spectral data appear in Table III. A sample (in benzene) was converted into the benzyl bromide salt, which was recrystallized from methanol–ethyl acetate (spectral data, Table III; analytical data, Table IV.)

Another sample was converted into the oxide. To 30 ml of 10% hydrogen peroxide solution was added a few milliliters of 1-phenyl-3-methyl-3-phospholene. After 24 hr, excess peroxide was decomposed with a small amount of reduced Adams catalyst. Water was stripped off and the residue distilled. Infrared spectroscopy and gc of the product confirmed it to be primarily 1-phenyl-3-methyl-3-phospholene oxide (**8b**) with a few per cent of 1-phenyl-3-methyl-2-phospholene oxide (**7b**).

Characterization of 1-Phenyl-3-methyl-2-phospholene (17).—This compound was available from a previous[13] reduction of the isoprene–phenylphosphonous dichloride adduct. Spectral properties are now reported in Table III. A sample was converted to the benzyl bromide salt; data are provided in Tables III and IV. Another sample on hydrogen peroxide oxidation was seen by infrared and gc studies to be converted into oxide **7b**.

Registry No.—**1a**, 930-38-1; **1b**, 15450-79-0; **1c**, 15450-80-3; **2a**, 872-45-7; **2b**, 15450-68-7; **2c**, 15450-82-5; **3a**, 872-37-7; **3b**, 15450-84-7; **3c**, 14410-05-0; **4a**, 1130-42-3; **4b**, 15450-87-0; **4c**, 14409-96-2; **7a**, 15450, 89-2; **7b**, 707-61-9; **8a**, 15450-91-6; **8b**, 7564-51-4; **14**, 15450-93-8; **15**, 15450-94-9; **17**, 1445-83-6; **18**, 15450-96-1.

Acknowledgments.—We are grateful to Mr. Stephen W. Dale of this department for obtaining the P^{31} nmr spectra and to Dr. C. E. Griffin, University of Pittsburgh, for the preparation and discussion of some of the pmr spectra in the early phases of the work. T. P. B. was supported by a National Science Foundation Traineeship.

(23) A. Frank, *J. Org. Chem.*, **26**, 850 (1961).

(24) W. Kuchen and W. Grünewald, *Angew. Chem.*, **75**, 576 (1963).

(25) K. Moedritzer, L. Maier, and L. C. D. Groenweghe [*J. Chem. Eng. Data*, **7**, 307 (1962)] reported −152 ppm.

(26) L. D. Quin and J. S. Humphrey, Jr., *J. Amer. Chem. Soc.*, **83**, 4124 (1961).

Rearrangements in Five-Membered Rings of Restricted Mobility[1]

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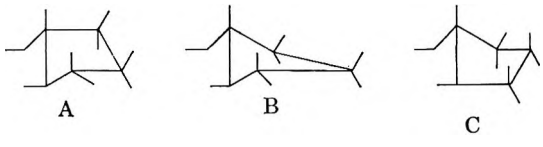
Base-catalyzed rearrangements of 16α-mesyloxy-17α-hydroxy steroid derivatives bearing a 17β-acetyl group in which the ketone is protected as the ethylene ketal proceed exclusively with ring contraction to four-membered D-ring derivatives. When the 17β substituent is an alkyl group, a competing rearrangement to 16-ketones occurs, presumably through intramolecular sulfonyl group transfer. The relative rates of these rearrangements seem to be influenced by electronic factors. *cis*-Bicyclo[3.3.0]octane derivatives bearing analogous functions also undergo ring contraction but to a lesser extent. Conformational reasoning is used to explain the rearrangement results.

In contrast to six-membered rings in which the relationship between reactivity and conformation has been extensively studied, the application of conformational reasoning to five-membered rings has played a minor role due to the mobility of cyclopentanes. This mobility can be reduced by fusion to a rigid system, providing an opportunity for the correlation of properties with specific conformations. Such studies would be appropriate in the five-membered D ring of steroids, due to the available information on their conformation. According to Brutcher, *et al.*,[2] the D ring can adopt three conformations (A, B, or C), depending on sub-

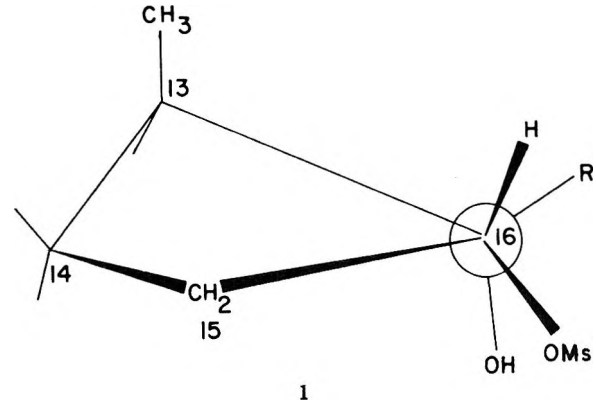


stituents present on the ring. Although these conformations do not allow complete *anti* coplanar relationship of ring bonds and bond attached to the ring, certain derivatives might adopt a conformation in which the four-center coplanar transition state, preferred in some ionic rearrangements, could be more easily attained.

A great number of rearrangements involving ring D are known,[3] but their outcome is usually determined by stereochemical considerations involving groups adjacent to ring D rather than by the conformation of the ring D itself.

The object of the present work was the investigation of base-catalyzed pinacol-type rearrangements of tertiary–secondary vicinal *cis*-diol monosulfonates located on five-membered rings of steroids or bicyclic systems. When such rearrangements occur in six-membered rings, they are known to result in ring contraction if the migrating bond in the ring and the leaving group adopt an *anti* coplanar conformation. In order to perform an analogous ring contraction of a five-membered to a four-membered ring, the necessary functions had to be placed in a way compelling the ring to adopt a conformation in which the bonds involved would be nearest to coplanarity. The appreciable angle strain involved in such a ring contraction also had to be taken into consideration; thus the occurrence of an alternative transformation could not be excluded *a priori*.

Steroidal D rings bearing a 17β side chain and 17α-hydroxy-16α-mesyloxy functions were considered conformationally appropriate for performing such rearrangements. Envelope C is considered to be the conformation of lowest energy for 17β-substituted D rings.[2] The 1,3-interaction between the 17α-hydroxyl and the 14α-hydrogen which might be expected to destabilize envelope C in favor of the half-chair B is counteracted by the presence of the 16α-mesyloxy grouping; examination of Dreiding models[4] shows that in conformation C the 1,3 interaction between the C-14 hydrogen and the C-16 group is weaker than in conformation B. The chances for a ring contraction in a base-promoted rearrangement were thus enhanced because in the envelope C the 13,17 bond and the leaving group are nearest to coplanarity[5,6] as seen in the Newman projection of the D ring, viewed from C-16 toward C-17 (1).



1

Our studies were first conducted on a system bearing a 17β-acetyl side chain, in which the ketone was protected as the ethylene ketal in order to prevent the possibility of D-homoannulation occurring under basic conditions, because of the presence of the 17α-hydroxyl group. Thus 5α-pregn-16-en-3β-ol-20-one 3-acetate (I)[7] was converted into the corresponding ethylene ketal II and then hydroxylated with osmium tetroxide in pyridine, affording selectively the 16α,17α-diol derivative III. Treatment of III with methanesulfonyl chloride in pyridine yielded the mesylate IV, which, on exposure to potassium *t*-butoxide in *t*-butyl

(1) For preliminary reports regarding part of the present work, see (a) E. Ghera, *Tetrahedron Letters*, 4181 (1965), and (b) E. Ghera, *ibid.*, 17 (1966).

(2) (a) F. V. Brutcher, Jr., and W. Bauer, *J. Amer. Chem. Soc.*, **84**, 2236 (1962); (b) F. V. Brutcher, Jr., and E. J. Leopold, *ibid.*, **88**, 3156 (1966).

(3) For a review, see N. L. Wendler in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1099.

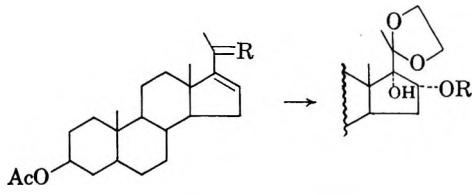
(4) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(5) The deviation from coplanarity of the involved bonds, as measured with the help of Dreiding models, is approximately 30 ± 5° for conformation C, 46 ± 5° for conformation B, and 64 ± 5° for conformation A. See ref 6 for measurements which allow the deduction of similar angles.

(6) A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, **86**, 1221 (1964).

(7) P. Crabbé, M. Perez, and G. Vera, *Can. J. Chem.*, **41**, 156 (1963).

alcohol solution, was converted into a mixture of crystalline products. Separation by column chroma-



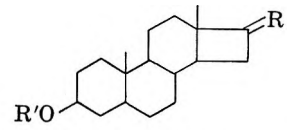
I, R = O
II, R = $(OCH_3)_2$

III, R = H
IV, R = Ms

tography showed that this mixture consisted exclusively of two isomers, which have been formulated as the C-16 epimeric 3β-hydroxy-5α-21-methyl-21,21-ethylenedioxy-D-norpregnan-20-ones V and VI on the basis of both spectroscopic and degradative evidence. Both epimers exhibited a carbonyl band at 5.83 μ in their infrared spectra, the rather low wavelength absorption band for a ketone vicinal to a cyclobutane ring being due to the adjacent ethylenedioxy group.[8] The nmr spectrum of the major epimer (V), on which most of the identification work has been done, contained a double doublet corresponding to one proton at 3.16 ppm, which is attributed to the 16α-hydrogen split by the two C-15 protons. The signal of the ethylenedioxy grouping appeared as a singlet due to the magnetically equivalent environment of the four protons and the C-18 methyl protons resonated at 0.87 ppm. In the 16α epimer VI the C-18 methyl protons were deshielded, the signal being shifted to 1.26 ppm. This difference in the chemical shift of C-18 protons (23–24 cps), which has been found subsequently to be constant for other pairs of 20-keto-D-nor 16-epimers, is somewhat greater than the constant difference of 17 cps reported[9] for C-17 epimeric pregnane derivatives and is probably due to a change in the geometry of the angular methyl group relative to the C-20 ketone. In both 16α and 16β epimers the C-18 methyl protons appear shifted relatively downfield by comparison with analogous normal pregnane derivatives.[9] The assignment of configuration at C-16 has been confirmed by the Cotton effect in the ORD which is positive for the major isomer V and negative for VI.[10]

The composition of the mixture of the two epimers formed under the equilibrating conditions of the rearrangement could be determined by measurement of the optical rotation of the mixture, since the rotations of the pure epimers were known, and was found to be *ca.* 71% of V and 29% of VI. Treatment of either epimer with base under equilibrating conditions resulted in the formation of the same epimeric mixture as obtained from conversion of mesylate IV, thus proving that the carbonyl group was adjacent to the epimerizable center.

Unequivocal proof for the assigned structures was provided by chemical degradation. The removal of the ethylene ketal grouping, as a first step toward the intended degradation, could not be achieved with either epimer, even by prolonged heating with acid. The stability of the ketal grouping may be attributed to the difficulty of formation of an intermediate cation located α to a ketone. An analogous case of a stable α-keto ethylene ketal in a steroid side chain has been previously recorded,[8] although explained differently. Reduction of V by means of sodium borohydride in methanol afforded the diols VII (epimeric mixture) in which the ketal grouping could be easily cleaved under standard acidic conditions yielding the ketol derivatives VIII. Further reduction with lithium aluminum hydride afforded the triols IX which on cleavage with sodium periodate furnished an air-sensitive aldehyde X characterized by its infrared and nmr spectra. Acetylation of the C-3 hydroxyl group followed by oxidation using the Jones procedure[11] afforded the D-nor-16β-carboxylic acid, XI, identical with an authentic sample.[12]



V, R = $\overset{\text{H}}{\diagdown}\!\!\diagup\!\!\underset{}{\text{COC}(\text{OCH}_2)_2\text{CH}_3}$; R′ = H

VI, R = $\overset{\text{COC}(\text{OCH}_2)_2\text{CH}_3}{\diagdown}\!\!\diagup\!\!\underset{}{\text{H}}$; R′ = H

VII, R = $\overset{\text{H}}{\diagdown}\!\!\diagup\!\!\underset{}{\text{CH(OH)C}(\text{OCH}_2)_2\text{CH}_3}$; R′ = H

VIII, R = $\overset{\text{H}}{\diagdown}\!\!\diagup\!\!\underset{}{\text{CH(OH)COCH}_3}$; R′ = H

IX, R = $\overset{\text{H}}{\diagdown}\!\!\diagup\!\!\underset{}{\text{CH(OH)CH(OH)CH}_3}$; R′ = H

X, R = $\overset{\text{H}}{\diagdown}\!\!\diagup\!\!\underset{}{\text{CHO}}$; R′ = H

XI, R = $\overset{\text{H}}{\diagdown}\!\!\diagup\!\!\underset{}{\text{COOH}}$; R′ = Ac

The generality of this ring contraction in steroid derivatives bearing the same substituents in ring D has been demonstrated by performing the rearrangement on an additional system with an aromatic ring A. The mesylate XVI was prepared starting from 3-acetoxy-19-norpregna-1,3,5(10),16-tetraen-20-one, XII (see Experimental Section), and rearranged under similar conditions to a mixture of epimers from which the major 16β-D-nor epimer XXIV has been isolated in a 52% yield. The relative magnitude of the two C-18 signals in the nmr spectrum showed that the ratio of epimers is similar to that found in the previously described rearrangement.

Thus the course of the base-catalyzed rearrangement in the systems described proceeds exclusively with ring contraction and provides a convenient method for the synthesis of various D-nor steroids.[13] Other products, which could have resulted by alternative 1,2 migration of the 17β side chain or by base-promoted elimination, have not been detected.

Our attention was next turned to the investigation of the influence which an electron-donating 17β-alkyl side chain might exercise on the ring-contracting

(8) For a similar effect associated with the vicinity of an ethylenedioxy grouping, see, *e.g.*, S. Bernstein, M. Heller, and W. S. Allen, *J. Org. Chem.*, **26**, 1333 (1961).

(9) M. B. Rubin and E. C. Blossey, *ibid.*, **29**, 1932 (1964).

(10) See G. Muller, C. Huinh, and J. Mathieu, *Bull. Soc. Chim. Fr.*, 296 (1962), for circular dichroism measurements of D-norpregnenolones.

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

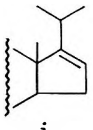
(12) J. Meinwald, G. G. Curtis, and P. G. Gasman, *J. Amer. Chem. Soc.*, **84**, 116 (1962). A sample of XI was obtained by the courtesy of Dr. H. Reimann of the Shering Corp.

(13) The only other method is the photolysis of diazo ketones which leads to D-nor-16-carboxylic acids. For literature data, see ref 1a.

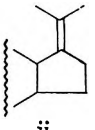
rearrangement. In rigid six-membered systems, where no ambiguity exists concerning the coplanarity of migrating and departing groups, the outcome of analogous ionic rearrangements depends only on the geometry of the molecule.[14] In the specific case of a five-membered ring in which this coplanarity is not completely achieved and the ring contraction is associated with appreciable angle strain, a change in electronic properties of the substituent could provide a reason for a different reaction course. The steric influence of a different 17β substituent (even if pseudoequatorial) on the conformation of the D ring could be of some importance also. A 17β-*t*-butyl substituent would be sterically most similar to the side chain bearing the C-20 ethylene ketal group, although it involves some new interactions due to the six additional hydrogen atoms attached to the carbon atoms vicinal to C-20. However, attempts to condense *t*-butyllithium with androsterone, considered a possible route to the desired 17-*t*-butyl derivative, were unsuccessful, probably because of steric hindrance. Therefore, two other 16α-17α-dihydroxy derivatives, the first bearing a 17β-ethyl side chain (XVIII) and the second a 17β-isobutyl side chain (XXXI), were synthesized and their mesylates submitted to rearrangement conditions.

The synthesis of such steroidal systems presents difficulties and may be considered of intrinsic interest. One route would involve the preparation of Δ^{16}-17-alkyl derivatives which could be used for further hydroxylation of the 16,17 double bond. Thus the reduction of a C-20 ketone to a methylene group in common Δ^{16}-17-acetyl systems could provide intermediates with an ethyl side chain. However, the Wolff–Kishner reduction of α,β-unsaturated C-20 ketones is known to yield $\Delta^{17(20)}$ products,[15] whereas attempted preparation of Δ^{16}-20-thioketals, for the purpose of further reductive cleavage, was vitiated by 1,4 addition of ethanedithiol.[16]

Other possible intermediates, 17α-alkyl-17β-hydroxy derivatives, obtained by Grignard addition to 17-ketones, are usually rearranged on acid dehydration with migration of the angular C-18 methyl group or, in certain conditions, a 17,20 double bond can be formed. Only the simplest, Δ^{16}-17 methyl analog could be obtained by the pyrolysis of the corresponding 17β-acetate.[17] The use of 16α,17α-dihydroxy-20-keto derivatives as starting compounds for the reduction of the carbonyl group or alkylation at C-20 proved impractical in our hands because of the ease by which these compounds undergo D-homoannulation. The preparation of 20-methyl-5,16-pregnadien-3β-ol (partial structure i),

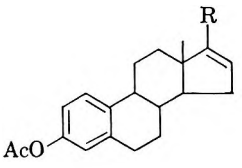


i

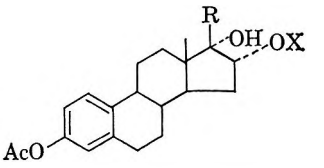


ii

which could serve for further hydroxylation, has been previously reported.[18] Repetition of the synthesis afforded a compound whose properties agreed with those reported but which exhibited no C-16 vinyl proton in the nmr spectrum. Since two methyl singlets appear at 1.59 and 1.72 ppm, it is suggested that the double bond is actually in the 17,20 position (partial structure ii).

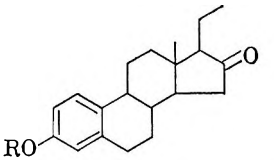


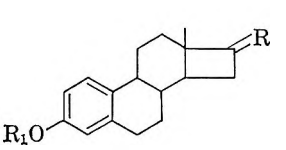
XII, R = $COCH_3$
XIII, R = $C(OCH_2)_2CH_3$
XIV, R = C≡CH



XV, R = $C(OCH_2)_2CH_3$; X = H
XVI, R = $C(OCH_2)_2CH_3$; X = Ms
XVII, R = C≡CH; X = H
XVIII, R = CH_2CH_3; X = H
XIX, R = CH_2CH_3; X = Ms
XX, R = CH_2CH_3; X = Ac
XXI, R = CH_2CH_3; X = Ts

The unreactivity of acetylenic bonds toward osmium tetroxide was exploited in the synthesis of the first system XVIII. Dehydration of 17α-ethinylestradiol 3-acetate with phosphorous oxychloride in pyridine afforded the enyne XIV in fair yield. Hydroxylation of the latter with osmium tetroxide in pyridine resulted in the exclusive formation of the 16α,17α-diol XVII as proven by nmr spectroscopic data. Catalytic hydrogenation afforded the 17β-ethyl derivative XVIII which was converted into the mesylate XIX. Treatment with potassium *t*-butoxide under conditions similar to those employed previously resulted in the conversion of XIX into a mixture of C-16 epimeric D-nor derivatives, separated as their acetates, XXV and XXVI, and an additional isomer, which was identified as 3-hydroxy-17β-ethyl-estra-1,3,5(10)trien-16-one (XXII). The percentage composition of the mixture was established by vpc analysis of the corresponding acetate mixture as 52% of 16β epimer (XXV), 20% of 16α epimer (XXVI), and 28% of XXIII.





XXII, R = H

XXIII, R = Ac

XXIV, R_1 = H; R_2 = $COC(OCH_2)_2CH_3$ / H

XXV, R_1 = Ac; R_2 = $COCH_2CH_3$ / H

XXVI, R_1 = Ac; R_2 = H / $COCH_2CH_3$

XXVII, R_1 = H; R_2 = OH / H

XXVIII, R_1 = H; R_2 = O

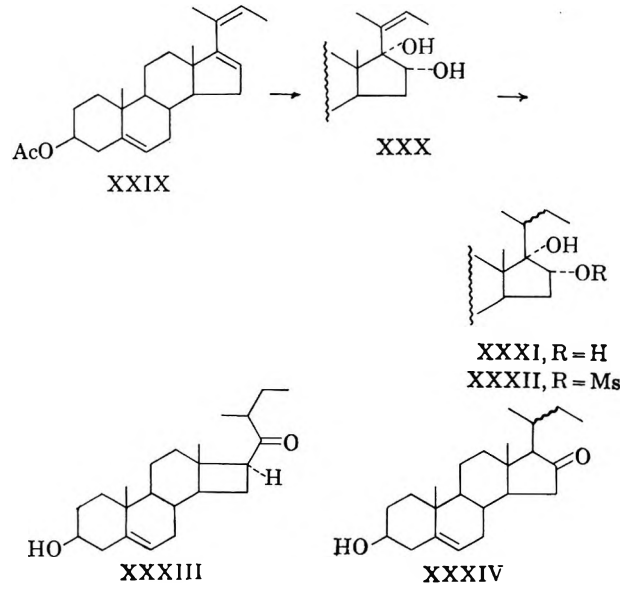
The stereochemical assignments for the C-16 epimers were made on the basis of the C-18 methyl signal in the nmr spectrum observed at 0.87 ppm in XXV and 1.27 ppm in XXVI and were confirmed by the signs of the Cotton effects of the ORD curves. The conversion of each epimer by base treatment into a mixture of both proved here too that the epimeric center is vicinal to the

(14) See ref 3, p 1084, for a review with references on this subject.
(15) R. Fischer, G. Lardelli, and O. Jeger, *Helv. Chim. Acta*, **33**, 1335 (1950).
(16) E. Ghera, unpublished results. See also J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **73**, 1528 (1951).
(17) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *ibid.*, **86**, 269 (1964).
(18) J. P. Dusza and W. Bergmann, *J. Org. Chem.*, **25**, 79 (1960).

carbonyl group. The degradative evidence was obtained by submitting a mixture of XXV and XXVI to Baeyer–Villiger oxidation followed by hydrolysis of the derived esters to a mixture of C-16 epimeric D-norestradiols XXVII. Oxidation by the Jones procedure[11] afforded D-norestrone XXVIII, the structure of which was established by the characteristic infrared carbonyl absorption band and by mass spectral evidence.

The third isomer obtained from the rearrangement exhibited in the infrared spectrum the absorption band of a five-membered cyclic ketone and, therefore, might have been expected to be a 16-substituted 17-ketone formed by the 1,2 migration of the side chain. Such a migration would be expected to compete with ring contraction in the case of ambiguous coplanarity conditions or due to sufficient mobility of the cyclopentane ring. However, this assumption was disproved by the negative Cotton effect of the ORD curve which was incompatible with the proposed structure but characteristic of 14α-17β-alkyl 16-ketones.[17] Moreover, treatment with sodium in deuteriomethanol resulted in exchange of three hydrogen atoms in ring D, as found by mass spectroscopic evidence: the M − 28 peak, representing the loss of C-6 and C-7,[19] remained unchanged after labeling whereas the intense M − 84 and M − 85 fragments, due to the loss of ring D in the original compound,[17] are shifted in the labeled compound to M − 87 and M − 88, showing that the exchange occurred only in ring D. These results substantiated the unexpected formation of the 16-ketone XXII and the latter assignment was confirmed by an independent synthesis of XXII using a Serini reaction which consists in the treatment of a 1,2-diol monoacetate with zinc.[20] This reaction, which has been utilized mainly for the conversion of 17-hydroxy-20-acetoxy steroidal derivatives to inverted 20-ketones, was found recently of synthetic use also in other systems.[21] Heating the triol diacetate XX with zinc followed by equilibration with base yielded a product identical in all respects with the ketone XXII.

The formation of a 16-ketone occurred to an even greater extent when a branched 17β-isobutyl-substituted system (XXXII) was submitted to base-catalyzed rearrangement. The synthetic route for the preparation of XXXII started from 3β-acetoxy-pregna-5,16-dien-20-one, which in a Wittig reaction with ethylidenetriphenylphosphorane yielded a single triene XXIX, to which the *trans* configuration may be assigned because *cis*-oriented methyl groups would imply a less favorable arrangement in the transition state.[22] The reaction of triene XXIX with osmium tetroxide (1.1 equiv) at low temperature resulted in the formation of XXX in good yield by selective hydroxylation of the 16,17 double bond from the α side, while the trisubstituted double bonds of the side chain and of ring B remained untouched. In agreement with the assigned structure the nmr spectrum showed a singlet at 1.67 ppm due to the C-21 methyl attached to a double bond. The upfield shift of the C-18 methyl signal (0.62 ppm) is explained by the restricted rotation of the side chain around the 17,20 bond, which forces the angular methyl group into the shielding cone of the 20,22 double bond. Catalytic hydrogenation of XXX affected only the side chain, yielding XXXI (C-20 epimers). Exposure of the corresponding epimeric 16-mesylates XXXII to potassium *t*-butoxide under the usual conditions resulted in formation of a mixture of isomers which exhibited in the infrared spectrum the 5.78-μ band due to the 16-ketones XXXIV (C-20 epimeric mixture) and the 5.88-μ band, characteristic for C-20 ketones in C-16 D-nor epimers. The percentage composition of the mixture of products obtained from the rearrangement showed a substantial increase in formation of 16-ketones (52%) at the expense of ring-contracted C-16 epimers (48%), compared with the 17β-ethyl-substituted series. These products were separated by extensive column chromatography and the assigned structures have been confirmed by characteristic spectroscopic data, analogous to those obtained in the previous series. The structure of the 16-ketones XXXIV was supported by their negative Cotton effects in the ORD and by introduction of three deuterium atoms in ring D by deuterium exchange.



XXIX XXX XXXI, R = H XXXII, R = Ms XXXIII XXXIV

An explanation of this latter rearrangement to 16-ketones by the participation of the neighboring 17α-*cis*-hydroxyl grouping was hardly acceptable in view of the basic conditions of the reaction. Moreover, the mesylate XIX was found stable and unreactive when exposed to different solvolytic conditions and the formation of oxides or ketones was not observed. However, ketones can be formed as a result of base-promoted reactions of epoxides[23] and therefore the behavior of a 17β-alkyl-substituted 16α,17α-oxido derivative in the basic conditions of the rearrangement was investigated. An appropriate derivative has been prepared by pyrolysis of 17α-methyl-17β-acetoxyandrostane which is known to yield a mixture of *endo*- and *exo*-cyclic olefins.[17] After treatment of the latter with *m*-chloroperbenzoic acid, the pure 16α,17α-oxide XXXV was separated and exposed to potassium *t*-butoxide in *t*-butyl alcohol but proved completely stable in these conditions.

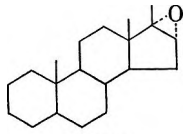
(19) C. Djerassi, J. M. Wilson, H. Budzikiewicz, and J. W. Chamberlin, *J. Amer. Chem. Soc.*, **84**, 4544 (1962).

(20) For references on Serini reactions, see E. Ghera, M. Gibson, and F. Sondheimer, *ibid.*, **84**, 2953 (1962).

(21) E. Ghera and F. Sondheimer, *Tetrahedron Lett.*, 3887 (1964).

(22) See, *e.g.*, J. P. Dusza, *J. Org. Chem.*, **25**, 93 (1960), for a similar formation of one isomer.

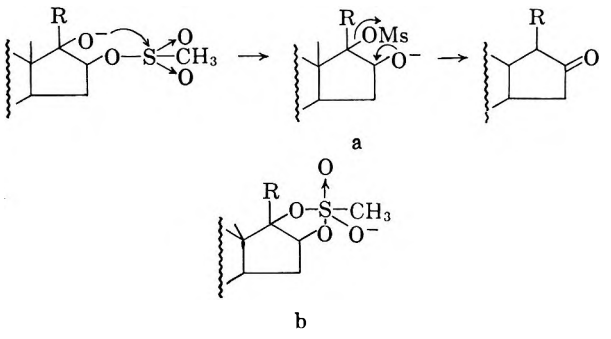
(23) J. K. Crandall and Luan-Ho Chang, *J. Org. Chem.*, **32**, 435 (1967).



XXXV

In view of these results, the possibility that the C-16 ketone originates from S–O bond cleavage in the mesylate has been taken into consideration. The base-catalyzed rearrangement would then proceed by intramolecular nucleophilic attack of the C-17 hydroxyl anion on the sulfur atom and cleavage of the S–O bond followed by a 1,2-hydrogen shift as shown in Scheme I (a); the pathway by which the transfer takes place could involve the formation of an intermediate cyclic "orthosulfonate" ion (b). Such a hypothesis seemed questionable in view of the well-documented behavior of similar *cis*-diol monosulfonates in six-membered ring systems[24] where base-catalyzed rearrangements occur by C–O bond cleavage in sulfonates; it should be noted, however, that the formation of a small amount

SCHEME I



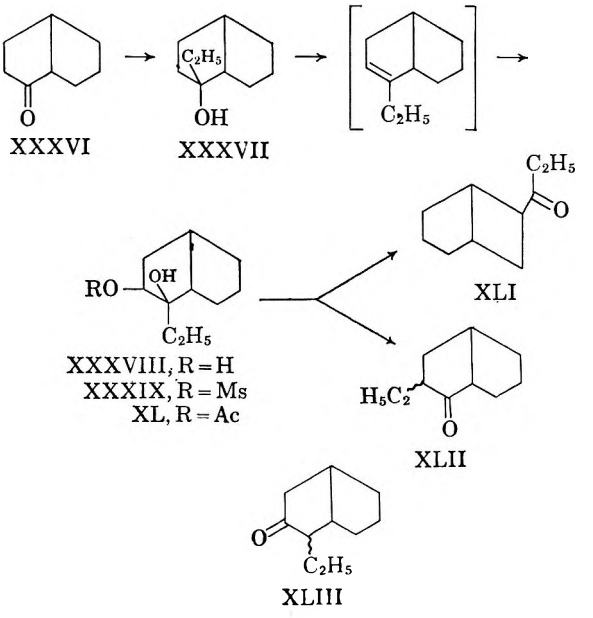
of a ketone which may have resulted by the cleavage of the S–O bond in a similar rearrangement has been observed in one instance.[25] The base-induced cleavage of the sulfur–oxygen bond has been reported to occur in "isolated" secondary sulfonate groups of carbohydrates[26] and in other systems where the displacement of the sulfonate ion by the attack of the nucleophile on carbon is sterically hindered.[27] A base-catalyzed, intramolecular sulfonyl group transfer has been reported recently in a carbohydrate system.[28]

Indirect evidence for the hypothesis of internal attack was obtained by submitting to identical rearrangement conditions the tosylate XXI instead of the mesylate XIX; the tosylate sulfur atom could be expected to be less susceptible to nucleophilic attack, due to resonance interaction with the aromatic system.[29] The composition of the mixture of products obtained from XXI, as determined by vpc analysis after acetylation, consisted from 96% D-nor epimers (XXV and XXVI) and only 4% XXIII, providing support for these considerations.

In summary, base-catalyzed reactions of the systems studied involve two competing reactions, ring contraction and rearrangement to 16-ketones. It would appear that the relative rates are influenced by electronic factors, the rate of the ring contraction being retarded by electron-donating C-17 substituents.

Finally, we investigated the behavior in analogous reactions of a *cis*-fused bicyclic derivative, *exo*-2-hydroxy-3-mesyloxy-*endo*-2-ethylbicyclo[3.3.0]octane (XXXIX) (Scheme II). Our purpose was to examine the scope of these rearrangements and their relationship to preferred conformations by using a five-membered ring of a fused system simpler than a steroid and of different strain and conformational properties.

SCHEME II



The mesylate XXXIX was prepared starting from the bicyclooctan-2-one XXXVI through the Grignard adduct XXXVII which yielded on dehydration the olefin with a trisubstituted double bond, as confirmed by the presence of a vinyl proton at 5.2 ppm in the nmr spectrum. The hydroxylation of the double bond with osmium tetroxide afforded, by attack from the less hindered side, a single, *exo*-diol XXXVIII (*vide infra*) which was converted into the corresponding mesylate.

Information on the preferred conformation of *cis*-bicyclo[3.3.0]octanes is hardly available. However, from examination of Dreiding models,[4] it seems reasonable to predict that the rings will adopt two envelope conformations in which the C-3 and C-7 atoms, respectively, will be out of the plane formed by four other atoms; in one of the envelopes the tip will be below the plane, whereas in the other it will be above, as shown in **2a**, the proposed conformation for *cis*-bicyclo[3.3.0]-octane. In this way the number of eclipsed bonds would be reduced, the 1,3 interactions between the C-2 and C-8 methylene groups and between the C-4 and C-6 groups being relieved through staggered arrangements.

(24) *Inter alia*, see N. L. Wendler, R. F. Hirschmann, H. L. Slates, and R. W. Walker, *J. Amer. Chem. Soc.*, **77**, 1632 (1955); R. B. Bates, G. Buchi, T. Matsura, and R. R. Schaffer, *ibid.*, **82**, 2327 (1960); Y. Mazur and M. Nussim, *ibid.*, **83**, 3911 (1961); N. L. Wendler, *Tetrahedron*, **11**, 213 (1960).

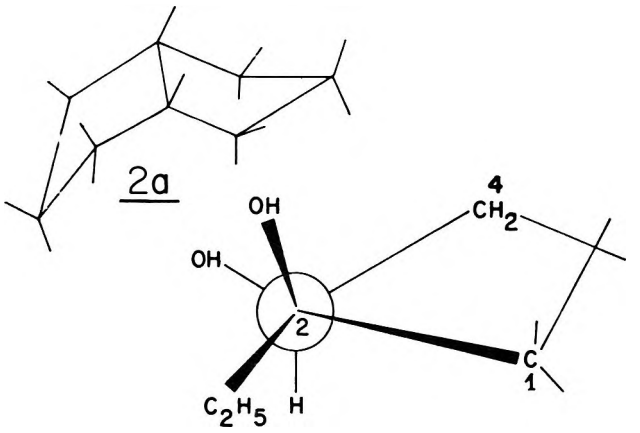
(25) N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

(26) S. P. Tipson, *Advan. Carbohydrate Chem.*, **8**, 207 (1953).

(27) *Inter alia*, see W. Huckel and H. Pietrzok, *Ann.*, **543**, 232 (1940); G. Stork, E. E. Van Tamelen, L. Y. Friedman, and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **75**, 384 (1953); A. C. Cope and T. Y. Shen, *ibid.*, **78**, 5912 (1956).

(28) J. S. Brimacombe and L. C. N. Tucker, *Chem. Commun.*, 903 (1966).

(29) See, *e.g.*, E. T. Kaiser and D. H. Eargle, Jr., *J. Amer. Chem. Soc.*, **85**, 1821 (1965).



2b

Evidence for conformational preference in the substituted ring of the diol XXXVIII and mesylate XXXIX was provided by their respective nmr spectra. The C-3 *endo* proton of the diol, treated as the X portion of an ABX system, shows a triplet (J = 8.5 cps) with some broadening of the center line, whereas in the corresponding mesylate the same proton appears as a double doublet (J = 9 cps, J' = 7.5 cps). In spite of limitations imposed on the use of the Karplus relationship for the deduction of dihedral angles in strained five-membered rings containing electronegative substituents, it seems safe to assume that the two large J values exclude the possibility of bisection of the C-4 methylene group by the vicinal C-3 proton.[30] The substituted ring should thus adopt an envelope conformation with C-3 below the plane of the four other carbon atoms. The dihedral angle between the vicinal *cis*-hydroxyl groups in XXXVIII can be approximated as *ca.* 40° by the determination of the shift of OH stretching frequency in the infrared spectrum due to hydrogen bonding, using the modified Kuhn relationship.[2a] Thus the deviation from coplanarity of the migrating and departing groups would be of 20 ± 5° and the substituted ring of diol XXXVIII viewed from C-2 would appear as shown in **2b**.

The base-catalyzed rearrangement of XXXIX resulted in the formation of 2-propionylbicyclo[3.2.0]-heptane (XLI, 23%) and of the epimeric 3-ethylbicyclooctan-2-ones (XLII, 77%, about 1:1 epimeric ratio). The structure of propionylbicyclo[3.2.0]heptane followed from the characteristic mass spectral fragmentation (M − 29 and M − 57), absence of unsaturation, infrared carbonyl absorption at 5.86 μ, and the nmr spectrum of the corresponding semicarbazone which showed that the methylene group of the side chain is vicinal to the C=N bond (quartet at 2.22 ppm). As only one isomer has been detected by vpc with capillary column, it is formulated as *exo* substituted. The epimeric 3-ethyl-*cis*-bicyclooctan-2-ones have been identified by spectroscopic data and by independent synthesis from XXXVI and ethyl iodide. In the latter case the same ratio of epimers (about 1:1) has been obtained, showing their similar stability at equilibrium.[31] The presence of *cis*-2-ethyl-bicyclooctan-3-one XLIII, which could have been formed as described above in steroid rearrangements, has been ruled out by the preparation of the latter from the diol XXXVIII (by acid dehydration) and from acetate XL (by a Serini reaction). The epimeric composition of XLIII as obtained by the first method (84% *exo*- and 16% *endo*-ethyl epimer) agreed with the expected greater stability of *exo*-2-substituted bicyclooctan-3-ones, while the results of the Serini reaction (96% *exo* epimer), which was expected to proceed with inversion at C-2,[20] were in agreement with the *exo*-diol assignment for XXXVIII. Base treatment of the Serini product gave the same mixture of epimers as after acid dehydration.

The above observations show that ring contraction occurs also in the *cis*-bicyclo[3.3.0]octane system, though to a lesser extent than in the D ring of steroids. The difference in results between the two systems might be attributed to a greater mobility of the five-membered ring in the bicyclic system. Hence the 1,2 migration of the ethyl group, proceeding at a greater relative rate, can occur preferentially in the latter system in spite of the seemingly favorable conformational conditions for ring contraction. For the same reason the sulfonyl group transfer, which explains the formation of 16-ketones in the previously described rearrangements, does not take place in the bicyclic systems.

Experimental Section[32]

3β-Acetoxy-20-ethylenedioxy-5α-pregn-16-ene (II).—A mixture of 750 mg of 3β-acetoxy-5α-pregn-16-en-20-one (I),[7] 100 ml of benzene, 7 ml of ethylene glycol, and 100 mg of *p*-toluenesulfonic acid was refluxed for 18 hr with stirring and azeotropic elimination of water with the help of a Dean–Stark separator. The solution was cooled, washed with aqueous sodium bicarbonate and water, dried, and the solvent was evaporated after addition of 1 drop of pyridine. Crystallization from methanol and 1 drop of pyridine yielded the ethylene ketal II (650 mg), mp 108–116°. The analytical sample melted at 120–122° (from methanol), $[\alpha]_D$ −4°.

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.32; H, 9.40.

3β-Acetoxy-20-ethylenedioxy-5α-pregnane-16α,17α-diol (III).—To a solution of II (1.1 g) in 12 ml of purified dry pyridine was added osmium tetroxide (1.2 g) in pyridine (16 ml) and the mixture stirred for 2.5 hr. A solution of 2 g of sodium bisulfite in 30 ml of water and 7 ml of pyridine was then added and vigorous stirring continued for 5 min. After addition of water the product was isolated with chloroform by work-up in the usual manner. Chromatography using hexane and 20% chloroform afforded 840 mg of crystals, mp 192–196°, homogeneous on tlc. The analytical sample, after two crystallizations from hexane and chloroform, melted at 202–204°: $[\alpha]_D$ −6°; infrared bands at 2.84, 5.79, 7.98, 9.69, and 10.50 μ; nmr signals at 0.82 (C-19), 0.32, (C-18), 1.35 (C-21), 2.01 (acetate), 3.9 ppm br (ethylene ketal).

Anal. Calcd $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.92; H, 9.10.

3β-Acetoxy-16α-methanesulfonyloxy-20-ethylenedioxy-5α-pregnan-17α-ol (IV).—To the ice-cooled solution of III (650 mg) in pyridine (3 ml) was added methanesulfonyl chloride (0.4 ml) and the solution was set aside at room temperature for 14 hr. Addition of ice water, extraction with chloroform, and work-up

(30) See, for instance, ref 6 or P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964), for data on J in resembling strained systems and for references.

(31) See, *e.g.*, R. Granger, P. Nau, and J. Nau, *Bull. Soc. Chim. Fr.*, 1811 (1959), and preceding papers on the relative stability of 2- and 3-substituted *cis*-bicyclo[3.3.0]octanes.

(32) Melting points are uncorrected and were determined on a Kofler block. Optical rotations were measured in chloroform (*ca.* 1% solution) unless indicated otherwise. Nmr spectra were run on a Varian A-60 spectrometer in deuteriochloroform, with tetramethylsilane as internal standard. Signals are given in parts per million. Infrared spectra were determined in chloroform solution, unless indicated otherwise. The phrase "work up in the usual manner" means that the organic layer is washed with diluted (5%) hydrochloric acid, aqueous sodium bicarbonate solution, and water, dried over anhydrous sodium sulfate, and the solvent evaporated. Florisil 60/100 mesh was used for column chromatography, unless indicated otherwise.

in the usual manner afforded the crude methanesulfonate which crystallized on trituration with pentane. Chromatography on silica BDH (elution with benzene and 10% chloroform) yielded 610 mg of purified IV, mp 190–193°. The analytical sample (from hexane–chloroform) melted at 193–194°: $[\alpha]_D$ −51°; infrared bands at 5.78, 7.48, 7.94, and 8.50 μ; nmr signals at 3.02 (methanesulfonate) and 4.06 ppm br (ketal).

Anal. Calcd for $C_{26}H_{42}O_8S$: C, 60.68; H, 8.23. Found: C, 60.45; H, 8.05.

16β,- (V) and 16α,3β-Hydroxy-21-methyl-21-ethylenedioxy-5α D-norpregnan-20-ones (VI).—A solution of purified methanesulfonate IV (630 mg) in *t*-butyl alcohol (120 ml) was added under nitrogen to a solution of *t*-potassium butoxide prepared from 200 mg of potassium and 20 ml of *t*-butyl alcohol. After 6 hr stirring under nitrogen at 70° the solution was neutralized with acetic acid, diluted with water, and extracted several times with chloroform. The combined organic layers were washed with sodium chloride solution, dried, and evaporated under reduced pressure to yield 440 mg of crystalline material homogeneous on tlc (benzene–10% methanol or cyclohexane–30% ethyl acetate as developer), mol wt 376 (mass spectroscopy). Crystallization with methanol–10% water afforded a first crop (186 mg) of the 16-β epimer V, mp 164–169°. The mother liquor was chromatographed on neutral alumina (activity II) starting with hexane and proceeding to hexane and 10–15% chloroform. Elution provided first a small amount of the 16α epimer VI (mp 134–138°) followed by a mixture of V and VI while the later fractions yielded an additional amount of 80 mg of the 16-β epimer V. Recrystallization from methanol gave an analytical sample of V: mp 170–171°; $[\alpha]_D$ +73°; λ_{max}^{EtOH} 310 mμ (ε 63); infrared bands at 5.83 and 9.68 mμ; nmr signals at 0.83 (C-19), 0.87 (C-18), 1.38 (C-21 methyl), 4.0 (ethylene ketal), and 3.16 ppm (H-16, double doublet, J = 9 cps, J' = 6 cps); ORD in methanol (c 0.123), $[\phi]_{350}$ +4900°, $[\phi]_{337}$ +8700°, $[\phi]_{317}$ 0°, $[\phi]_{292}$ −8400°.

Anal. Calcd for $C_{23}H_{36}O_4$; C, 73.36; H, 9.64; Found: C, 73.05; H, 9.82.

The first eluted minor epimer VI (23 mg) was crystallized from hexane and chloroform: mp 139–141°; $[\alpha]_D$ +10°. In the infrared spectrum there were observed only fine structure differences from the spectrum of epimer V; nmr signals appear at 1.26 (C-18 protons) and 3.21 ppm (H-16); ORD in methanol (c 0.117), $[\phi]_{350}$ −1700°, $[\phi]_{333}$ −4100°, $[\phi]_{316}$ 0°, $[\phi]_{285}$ +6800°.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.12; H, 9.44.

Optical rotation of the epimeric mixture obtained from rearrangement (after chromatographic elimination of grease and impurities) $[\alpha]_D$ +55° (value used for the calculation of the ratio of epimers in the mixture).

Base-Catalyzed Equilibrations of D-Nor Epimers V and VI.—To a 1% methanolic solution of each epimeric ketone was added a 5% solution of potassium methoxide in methanol and the two resulting solutions were kept for 24 hr under nitrogen. Dilution with water and extraction with chloroform gave, in both cases, a mixture of the two 16-epimers, exhibiting in the nmr spectrum the 0.87 and 1.26 signals of C-18 protons of about the same relative magnitude as in the mixture obtained directly from rearrangement of IV.

Conversion of 16β-D-Nor Epimer V into 3β-Acetoxy-5α-D-norandrostane-16β-carboxylic Acid XI.—To 90 mg of V in 6 ml of methanol was added 40 mg of sodium borohydride and the mixture was stirred for 3 hr at room temperature. Isolation with chloroform yielded a crystalline mixture of diols VII (75 mg, no carbonyl absorption in infrared). The crude material was dissolved in methanol (8 ml) containing 1.5 ml of diluted sulfuric acid (8% v/v). After 3 hr reflux the solution was cooled, diluted with water, and extracted with chloroform. The extract was washed with sodium bicarbonate and sodium chloride solutions, dried, and concentrated *in vacuo* affording 60 mg of crystalline ketodiols VIII; mol wt 334 (mass spectrum); carbonyl absorption in the infrared spectrum at 5.85 μ. The crude product was dissolved in dry tetrahydrofuran (5 ml) and added to a suspension of lithium aluminum hydride (40 mg) in 5 ml of dry ether. After stirring for 2 hr at room temperature the excess reagent was decomposed with a solution of sodium sulfate in water and the mixture dried with anhydrous sodium sulfate. Filtration and hot chloroform washings afforded, after evaporation of the solvent from filtrate, 52 mg of isomeric, crystalline triols IX, the infrared spectrum of which showed strong OH at 2.96 μ and was devoid of carbonyl absorption. To the solution of triols IX (52 mg) in acetone (3 ml) was added 100 mg of sodium periodate in 2.5 ml of water and the mixture stirred for 5 hr. Dilution with water, extraction with chloroform, and evaporation of solvent without excessive heating afforded the unstable aldehyde X characterized by the nmr signal at 9.77 and infrared bands at 3.68 and 5.83 μ, mol wt 292 (mass spectrum). The crude aldehyde was acetylated and the obtained crude 3-acetate was oxidized by the Jones procedure,[11] with ice cooling. Extraction with chloroform afforded 20 mg of the D-nor acid XI, which crystallized by trituration with hexane. Sublimation (125°, 0.2 mm) afforded the pure acid, mp 237–239°, identical by tlc, mixture melting point, and infrared comparison with an authentic sample.[12]

3-Acetoxy-20-ethylenedioxy-19-norpregna-1,3,5(10),16-tetraene (XIII).—To a solution of 3-acetoxy-19-norpregna-1,3,5(10),-16-tetraen-20-one (XII, 300 mg)[33] in benzene (45 ml) and ethylene glycol (3.5 ml) was added *p*-toluenesulfonic acid (30 mg) and the solution refluxed for 8 hr, water being removed with the help of a Dean–Stark tube. The work-up (as described for ethylene ketal II) afforded a residue which was reacetylated overnight in the usual manner; extraction with chloroform containing traces of pyridine and purification by chromatography (elution with hexane and 20% chloroform) afforded 210 mg of XIII, mp 94–99°. The analytical sample (from methanol) melted at 103–104°, $[\alpha]_D$ +58°.

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.52; H, 8.10.

3-Acetoxy-20-ethylenedioxy-19-norpregna-1,3,5(10)-triene-16α,17α-diol (XV).—To a solution of 550 mg of XIII in pyridine (6 ml) was added osmium tetroxide (500 mg) in 12 ml of pyridine and the mixture stirred for 3 hr. A solution of sodium bisulfite (1 g) in water (15 ml) was then added and the mixture stirred for additional 7 min. Extraction with chloroform and work-up in the usual manner yielded a solid residue which was chromatographed. Elution with hexane and 40% chloroform yielded 410 mg of XV, mp 204–209°. The analytical sample (from hexane and chloroform) melted at 210–212°: $[\alpha]_D$ +62°; infrared bands at 2.85, 5.75, 9.60, and 10.55 μ; nmr signals at 0.87 (C-18), 1.41 (C-21), 2.26 (acetate), and 4.01 ppm br (ethylene ketal).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.32; H, 7.80.

The corresponding **16-methanesulfonate XVI** was prepared by the method described for methanesulfonate IV. The analytical sample (from hexane and chloroform) melted at 202–203°: $[\alpha]_D$ +12°; infrared bands at 5.75, 7.48, 8.20, and 8.52 μ.

Anal. Calcd for $C_{25}H_{34}O_6S$: C, 60.73; H, 6.93. Found: C, 60.42; H, 6.72.

16β-3-Hydroxy-21-methyl-21-ethylenedioxy-19-nor-D-norpregna-1,3,5(10)-trien-20-one (XXIV).—The methanesulfonate XVI (215 mg) in *t*-butyl alcohol (100 ml) was reacted with *t*-potassium butoxide (from 80 mg of potassium and 10 ml of *t*-butyl alcohol), using the same conditions and work-up as described for the rearrangement of methanesulfonate IV. The obtained residue (164 mg) showed one spot on tlc and mol wt 356 (mass spectrum). Chromatography and crystallization of the fractions eluted with chloroform–hexane (1:1) afforded 78 mg of the 16-β epimer, XXIV, mp 184–189° (from chloroform and hexane, 52% yield); recrystallization raised the melting point to 193–194°; $[\alpha]_D$ +114°; carbonyl band in the infrared spectrum at 5.83 μ; nmr signals at 0.90 (C-18), 1.42 (C-21 methyl), 3.26 (H-16, double doublet, J = 9 cps, J' = 6 cps), 4.03 ppm s (ketal).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.43; H, 8.14.

The fractions which were eluted first and the mother liquor from crystallizations of the 16β epimer contained a mixture of the latter and of the 16α epimer which was not separated in pure state but identified by the 1.29-ppm (C-18) signal in the nmr spectrum.

3-Acetoxy-17-ethinylestra-1,3,5(10),16-tetraene (XIV).—A solution of 2.4 g of ethinylestradiol 3-acetate in 20 ml of dry pyridine and 1.3 ml of freshly distilled phosphorous oxychloride was stirred at 120° for 2 hr, cooled, and poured on 100 g of ice and 25 ml of hydrochloric acid. Extraction with ether containing 20% chloroform followed by washings of the organic layer with aqueous bicarbonate solution and water yielded, after drying and evaporation of the solvent, a residue (1.64 g) homogeneous on tlc, mp 104–109° (from methanol). Filtration

(33) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin, and J. Romo, *J. Amer. Chem. Soc.*, **73**, 1523 (1951).

through silica and recrystallization afforded the analytical sample: mp 115–116°; $[\alpha]_D$ +48°; infrared bands at 3.02, 4.77, 5.72, 8.30 μ.

Anal. Calcd for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.26, H, 7.53.

3-Acetoxy-17β-ethinylestra-1,3,5(10)-triene-16α,17α-diol (XVII).—To a solution of the crude enyne XIV (1.63 g) in 80 ml of pyridine was added osmium tetroxide (1.5 g) and the mixture kept in dark at room temperature for 48 hr. A solution of 1.3 g of sodium metabisulfite in 210 ml of water and 150 ml of pyridine was then added and stirring continued for 1 hr. Addition of water and extraction with chloroform in the usual manner yielded a residue which was chromatographed. Elution with hexane and 40% chloroform yielded 1.02 g of XVII: mp 182–187°; the analytical sample melted at 186–188° (from hexane and ether); $[\alpha]_D$ +45°; infrared bands at 2.90, 3.01, 5.71, and 8.30 μ; nmr signals at 0.92 (C-18) 2.55 (acetylene proton), and 4.49 ppm br (C-16).

Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.36; H, 7.32.

3-Acetoxy-17β-ethylestra-1,3,5(10)-triene-16α,17α-diol (XVIII).—A solution of 525 mg of XVII in 15 ml of ethyl acetate was stirred in hydrogen over 2% palladium on calcium carbonate. After absorption of 1.9 molar equiv (63 ml), the hydrogenation was stopped and the catalyst filtered. The residue was chromatographically purified (elution with 30% chloroform and hexane), yielding 480 mg of XVIII, mp 106–109°. The analytical sample melted at 112–113° (from ether and pentane): $[\alpha]_D$ +22°; nmr signals at 0.75 (C-18) and 0.98 ppm t (side-chain methyl).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.53; H, 8.35.

The corresponding diacetate XX was prepared by acetylation of XVIII and purified by chromatography (hexane and 15% chloroform as eluent): mp 140–141° (from hexane); $[\alpha]_D$ −19°.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.75; H, 7.88.

3-Acetoxy-17β-ethyl-16α-methanesulfonyloxyestra-1,3,5(10)-trien-17α-ol (XIX).—To a cooled solution of 500 mg of XVIII in 4 ml of pyridine was added a mixture of 0.5 ml of methanesulfonyl chloride and 0.5 ml of pyridine and the reaction mixture kept overnight at 10°. Addition of ice and isolation with chloroform in the usual manner yielded the crude XIX (540 mg) homogeneous on tlc, mp 169–176°. Recrystallization (ether and hexane) raised the melting point to 177–179°: $[\alpha]_D$ +9°; infrared bands at 5.71, 8.30, 7.32, and 8.50 μ; nmr signals at 0.78 (C-18), 1.03 t (side chain methyl), 3.02 (methanesulfonate), 4.95 ppm t (H-16, J = 6 cps).

Anal. Calcd for $C_{23}H_{32}O_6S$: C, 63.29; H, 7.39. Found: C, 63.65; H, 7.42.

Base-Catalyzed Rearrangement of Methanesulfonate XIX. Isolation of 3-Hydroxy-17β-ethylestra-1,3,5(10)trien-16-one (XXII) and of Epimeric 16β-XXV and 16α-XXVI-3-Acetoxy-21-methyl-19-nor-D-norpregna-1,3,5(10)trien-20-ones.—A solution of methanesulfonate XIX (1 g) in 650 ml of *t*-butyl alcohol was added to a solution of *t*-potassium butoxide (from 800 mg of potassium and 80 ml of *t*-butyl alcohol) and the reaction mixture stirred under nitrogen at 65° for 14 hr. Work-up (as described for the rearrangement of methanesulfonate IV) yielded 710 mg of residue homogeneous on tlc, mol wt 298 (mass spectroscopy). The infrared spectrum showed two carbonyl bands at 5.79 and 5.88 μ, the latter being of greater intensity. The 16-ketone XXII (70 mg) was separated by heating the residue with benzene and filtration of the formed crystals; it exhibited in the infrared spectrum (KBr) the 5.79-μ carbonyl band; mp 282–284°; $[\alpha]_D$ (pyr) −76°; ORD in tetrahydrofuran (c 0.085), $[\phi]_{350}$ −2980°, $[\phi]_{324}$ −10,170°, $[\phi]_{305}$ 0°, $[\phi]_{280}$ +11,330°.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.32; H, 8.57.

Because of its low solubility, the 16-ketone XXII was acetylated for vpc (*vide infra*) and nmr analysis (angular methyl at 0.73) and the purity of the noncrystalline acetate XXIII was checked by reconversion to XXII.

The remainder of the material from rearrangement (640 mg) was chromatographed and all fractions eluted first (hexane and 20–30% chloroform) which showed in the infrared spectrum only the 5.88-μ carbonyl band were combined, acetylated, and the acetate mixture chromatographed again. The fractions eluted first (70 mg, hexane and 60% benzene) showed in the nmr spectrum the presence of the angular methyl at 1.27 and consisted of the 16α epimer XXVI, which could not be obtained crystalline: $[\alpha]_D$ +46°; ORD in methanol (c 0.087), $[\phi]_{350}$ 0°, $[\phi]_{307}$ −4500°, $[\phi]_{291}$ 0°, $[\phi]_{265}$ +8800°.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.28. Found: C, 77.52; H, 8.24.

The corresponding semicarbazone formed readily and had mp 205–207°.

Anal. Calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.18; H, 7.81; N, 10.22.

The following chromatographic fractions yielded 180 mg of 16β epimer XXV, mp 106–112° (from pentane and traces of chloroform). The analytical sample (from methanol) melted at 114–115°: $[\alpha]_D$ +145°; nmr bands at 0.87 (C-18), 1.06 t (C-21 methyl), 2.27 (acetate); the H-16 proton was superimposed on benzilic protons at about 3 ppm; ORD in methanol (c 0.089), $[\phi]_{350}$ +4600°, $[\phi]_{306}$ +11,050°, $[\phi]_{286}$ 0°, $[\phi]_{265}$ −9800°.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.28. Found: C, 77.45; H, 8.16.

In a separate experiment the mixture of products, as obtained from the rearrangement of XIX, was acetylated and submitted to vpc analysis (1% XE-60 on 100–120 mesh Gaschrom Q, 5 ft × 1.8 in. column), showing the composition: XXVI (20%, relative retention time 1), XXV (52%, retention time 1.3), and XXIII (28%, retention time 1.66).

The separate equilibration of ketones XXV and XXVI, as described for the epimers V and VI, yielded in both cases epimeric mixtures of the same composition, as determined by the relative magnitude of the C-18 angular methyl signals in the nmr spectrum.

Preparation and Rearrangement of *p*-Toluenesulfonate XXI.—To a solution of XVIII (110 mg) in pyridine (2 ml) was added *p*-toluenesulfonyl chloride (150 mg) and the solution kept at room temperature overnight. Addition of water, extraction with chloroform, and work-up in the usual manner yielded 120 mg of residue which was chromatographed on silica. Elution with hexane and 10% chloroform afforded 65 mg of XXI: mp 146–148°; analytical sample (from ether and pentane) melted at 149–150°; $[\alpha]_D$ +16°.

Anal. Calcd for $C_{29}H_{36}O_6S$: C, 67.95; H, 7.08. Found: C, 67.87; H, 6.85.

The treatment of XXI with base in conditions analogous to those used on methanesulfonate XIX yielded a residue homogeneous on tlc, which exhibited in the infrared spectrum the 5.88-μ carbonyl band and a shoulder at 5.79 μ. Acetylation followed by vpc analysis in conditions identical with those used on the rearrangement products obtained from XIX showed that the mixture consisted exclusively from XXVI (25%), XXV (71%), and XXIII (4%).

Conversion of D-Nor Epimers XXV and XXVI to D-Norestrone.—To a solution containing a mixture of the D-nor epimers XXV and XXVI (100 mg) in 0.8 ml of chloroform was added 180 mg of perbenzoic acid in 3 ml of chloroform and the mixture set aside at 10° for 4 weeks. The solution was diluted with chloroform, washed with aqueous sodium bicarbonate solution, and then with water. The organic layer was dried, concentrated, and the residue dissolved in a 1% methanolic potassium hydroxide solution and heated to reflux during 10 min. After cooling the solution was diluted with water and extracted with chloroform. The residue showed on tlc the presence of a polar product which was separated chromatographically (on elution with hexane and 40% chloroform) from some unoxidized material and identified as the epimeric mixture of D-norestradiols XXVII (52 mg, mp 205–220°): mol wt 258 (mass spectrum); hydroxyl bands at 2.79 and 2.92 μ (KBr) in the infrared spectrum. Oxidation of XXVII (45 mg) in a 3 ml of acetone by the Jones procedure at ice bath temperature, followed by chromatography of the obtained product (hexane and 20% chloroform), afforded D-norestrone XXVIII (23 mg). The analytical sample melted at 263–265°: $[\alpha]_D$ (pyr) +81°; carbonyl band in the infrared spectrum at 5.64 μ; mass spectrum, m/e 256 (molecular ion), 228, 214, 199, 186.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.45; H, 7.92.

Deuteration of Ketone XXII.—The ketone XXII (12 mg) was dissolved in deuteriomethanol (5 ml) containing 20% heavy water and 40 mg of sodium. After heating to reflux for 12 hr under nitrogen, the solution was concentrated *in vacuo* and heavy water was added. Extraction with chloroform gave 8 mg of 17,15,15-d_3-XXII, mp 266–272°, showing mass spectral peaks at 301 (M^+), m/e 286, 273, 214, and 213 as compared with 298

(M^+), *m/e* 283, 270, 214, and 213 in the parent, nonlabeled ketone.

Synthesis of Authentic 16-Ketone XXII.—The diacetate XX (55 mg) was thoroughly mixed with 1 g of zinc powder and the mixture was heated in a glass tube under nitrogen at 160° for 35 min. After cooling, warm chloroform was added and the zinc was removed by filtration. The residue obtained by evaporation of the solvent (38 mg) was dissolved in a 1% methanolic potassium hydroxide solution and left overnight at room temperature. Dilution with water and extraction with chloroform yielded a residue which showed on tlc two spots, one corresponding in R_f value to that of XXII and a second, more polar spot, due probably to the triol formed by hydrolysis of the unreacted diacetate XX. Chromatographic separation (elution with 25–30% chloroform and hexane) yielded 12 mg of the less polar compound which after crystallization (benzene) was found identical with the 16-ketone XXII by mixture melting point and infrared spectrum comparison.

3β-Acetoxy-20-ethylidenepregna-5,16-diene (XXIX).—A 1.37 *N* ethereal solution of butyllithium (19.8 ml, 27 mmol), was added to 12.48 g (30 mmol) of ethyltriphenylphosphonium iodide[34] in 120 ml of dry ether with swirling, under nitrogen. After 2 hr stirring a solution of 3β-acetoxypregna-5,16-dien-20-one (2.13 g, 6 mmol) in 100 ml of ether was added and the mixture was stirred for an additional 4 hr and then allowed to stand overnight. The ether was distilled off and at the same time dry tetrahydrofuran was added and the mixture refluxed for 4 hr. Water was then added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water until neutral, dried, and the solvent evaporated. The residue was acetylated overnight and the obtained material was chromatographed, affording 190 mg of triene XXIX (elution with 10–15% chloroform and hexane) followed by unreacted starting material (940 mg). The triene was recrystallized by dissolution in a small amount of chloroform and addition of methanol: mp 129–131°; $[\alpha]_D$ −66°; λ_{max}^{isooct} 242 mμ (ε 13,800); nmr peaks at 0.97 (C-19), 1.07 (C-18), 1.57 d (*J* = 7 cps, C-23), 1.74 (C-21), 2.04 (acetate), 5.30–5.88 ppm br (three vinyl protons).

Anal. Calcd for $C_{25}H_{36}O_2$: C, 81.47; H, 9.85. Found: C, 81.40; H, 9.72.

3β-Acetoxy-20-ethylidenepregn-5-ene-16α,17α-diol (XXX).—To a stirred solution of the triene **XXIX** (200 mg) in 11 ml of pyridine, kept at −20° with the help of a Dry Ice–acetone bath, was added dropwise a solution of osmium tetroxide (154 mg, 1.1 equiv) in dry tetrahydrofuran (6 ml). After 1 hr the temperature was raised to −10° and after 1 additional hour the cooling was discontinued. After 3 hr from the starting of the reaction a solution of 1.7 g of sodium metabisulfite in 20 ml of pyridine and 28 ml of water was added and the mixture stirred for 1 hr at room temperature. Addition of water and extraction with chloroform in the usual manner yielded 165 mg of product homogeneous on tlc, mp 171–178°. The analytical sample (from chloroform and hexane) melted at 182–184°: $[\alpha]_D$ −102°; nmr bands at 0.62 (C-18), 0.97 (C-19), 1.69 (C-21, partly overlapping the C-23 doublet), 2.03 (acetate), 5.40 br (H-6), and 5.62 ppm br (H-22).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.32; H, 9.45.

3β-Acetoxy-20-ethylpregn-5-ene-16α,17α-diol (XXXI, C-20 Epimers).—Purified diene (170 mg) in dioxane was added to prereduced platinum oxide in the same solvent and stirred under hydrogen. After the fast absorption of 1 equiv of hydrogen the catalyst was filtered and evaporation of filtrate yielded 154 mg of the C-20 epimeric 16α,17α-diols XXXI, mp 146–165°, showing a single spot on tlc and nmr signals at 0.79 (C-18), 1.02 (C-19), 2.02 (acetate), 5.40 ppm br (H-6).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97. Found: C, 74.34; H, 9.80.

The corresponding mixture of **C-20 epimeric 16-methanesulfonates XXXII** was prepared in 80% yield as described for methanesulfonate XIX and melted between 190 and 202°: nmr signals at 0.83 (C-18), 1.04 (C-19), and 3.08 ppm (methanesulfonate).

Anal. Calcd for $C_{26}H_{42}O_6S$: C, 64.71; H, 8.77. Found: C, 64.95; H, 8.60.

3β-Hydroxy-21-methyl-21-ethyl-16β-D-norpregn-5-en-20-one (XXXIII) and C-20 Epimeric Mixture of 3β-Hydroxy-20-ethylpregn-5-en-16-ones (XXXIV).—Treatment of methanesulfonate XXXII (540 mg) with base during 7 hr at 70° using the reagents and work-up as described for methanesulfonate XIX yielded 360 mg of residue which exhibited a single spot on tlc, mol wt 334 (mass spectrum), and showed two carbonyl bands, at 5.78 and 5.88, in the infrared spectrum. Complete chromatographic separation of all obtained isomers was precluded by their almost identical polarity. However, careful chromatography on 30 g of Florisil, using hexane and 20–30% chloroform, provided at first fractions containing the two C-16 substituted D-nor epimers which exhibited only the 5.88-μ carbonyl band in the infrared spectrum (115 mg). Two crystallizations from methanol and 10% water afforded the pure 16β epimer XXXIII: mp 131–132°; $[\alpha]_D$ +49°; nmr signals at 0.90 (C-18), 1.02 (C-19), 3.05 br (H-16), 5.40 ppm br (H-6); ORD in methanol (*c* 0.095), $[\phi]_{350}$ +1100°; $[\phi]_{315}$ +9059°, $[\phi]_{298}$ 0°, $[\phi]_{276}$ −12,600°.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.00; H, 10.36.

The mother liquor from crystallizations of XXXIII contained the corresponding 16α epimer (C-18 protons at 1.29 in the nmr spectrum and negative Cotton effect in ORD) which could not be obtained completely free from the major 16β epimer. Continued elution provided after some intermediate fractions a mixture of 20α- and 20β-ethyl 16-ketones XXXIV, which crystallized on trituration with pentane, melted in the range 79–96°, and exhibited the 5.78-μ carbonyl band in the infrared region. The mass spectrum showed the following fragmentation: *m/e* 344 (M^+), 326, 315, 311, 273, 259, and 213. ORD in methanol (*c* 0.092) showed $[\phi]_{370}$ −1150°, $[\phi]_{320}$ −10,300°, $[\phi]_{303}$ 0°, $[\phi]_{278}$ +10,700°.

Anal. Calcd for $C_{23}O_2H_{36}$: C, 80.18; H, 10.53. Found: C, 80.40; H, 10.62.

Deuteration of XXXIV (as described for XXII, with reflux for 1 hr) afforded 17,15,15-d_3-XXXIV, which showed the following peaks in mass spectrum: *m/e* 347 (M^+), 329, 318, 314, 276, 262, and 213.

The crude mixture obtained from rearrangement consisted from *ca.* 48% D-nor epimers and 52% 16-ketones XXXIV, as found by repeated chromatographic separation and by comparative infrared analysis: weighed amounts of D-nor epimers and of XXXIV were mixed and the sizes of the two carbonyl bands in the resulting mixture were compared with the relative sizes of the corresponding bands in the crude mixture of isomers.

Solvolytic Experiments with Methanesulfonate XIV.—The methanesulfonate XIV (100 mg) was submitted to the following reactions: reflux during 24 hr in 5 ml of glacial acetic acid containing 0.2 g of potassium acetate, reflux for 24 hr in *t*-butyl alcohol, stirring in 10 ml of *t*-butyl alcohol containing 2 ml of formic acid and 1 ml of water at 50° for 24 hr. The starting material was recovered unchanged from all these reactions. Prolonged boiling (48 hr) in glacial acetic acid (10 ml) in the presence of acetic anhydride (1 ml) resulted in the formation of a new unsaturated product (tetramitromethane test) due probably to the migration of the C-18 angular methyl and formation of a 13,14 double bond (no vinyl proton in nmr). The absence of a new carbonyl or oxide function in this product was proven by infrared and nmr spectroscopy.

Preparation and Treatment with Base of 17β-Methyl-16α,17α-oxido-5α-androstane (XXXV).—The pyrolysis of 17α-methyl-17β-acetoxy-5α-androstane[17] yielded a mixture of two olefins, the Δ^{16}-17-methyl derivative being the major component (70–80%, according to the magnitude of the vinyl proton shift at 5.26 in the nmr spectrum). This mixture (80 mg) was dissolved in 4 ml of chloroform and *m*-chloroperbenzoic acid (80 mg) was added. After being allowed to stand for 16 hr at room temperature the reaction mixture was diluted with chloroform, washed with sodium bicarbonate solution and water, dried, and evaporated. The residue (70 mg) was twice crystallized from methanol yielding the oxide XXXV (32 mg): mp 153–155°; $[\alpha]_D$ +25°; nmr signals at 0.74 and 0.78 (angular methyls), 1.35 s (C-17 methyl), and 3.18 ppm (H-16, $W_{1/2}$ = 2.5 cps).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.42; H, 11.23.

After being kept in the usual basic conditions (as described for the rearrangement of methanesulfonates) during 24 hr at 70°, the starting material was recovered unchanged (tlc, infrared, melting point).

***cis,exo*-1-Ethylbicyclo[3.3.0]octan-*endo*-1-ol (XXXVII).**—A solution of *cis*-bicyclo[3.3.0]octan-2-one[35] (XXXVI, 6.2 g) in 30 ml of dry ether was added to the reagent prepared from 2.4 g

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(35) A. C. Cope and W. R. Schmitz, *J. Amer. Chem. Soc.*, **72**, 3056 (1950).

of Mg, 15.6 g of ethyl iodide, and 150 ml of ether. The mixture was stirred overnight at room temperature, then treated with ice and diluted hydrochloric acid and extracted with ether. After removal of the solvent the residue was purified by distillation, yielding 4.8 g of the carbinol: bp 72–73° (5 mm); n_D 1.492.

Anal. Calcd for $C_{10}H_{18}O$: C, 86.88; H, 13.12. Found: C, 86.53; H, 13.20.

cis,endo-**2-Ethylbicyclo[3.3.0]octane-*exo,exo*-2,3-diol (XXXVIII).**—Crude XXXVII (2.8 g) was refluxed in benzene (80 ml) and *p*-toluenesulfonic acid (200 mg) for 3 hr. The solution was then cooled, washed with aqueous sodium bicarbonate and water, dried, and concentrated to 30 ml at normal pressure. The nmr spectrum of this solution exhibited the presence of a vinyl proton (5.2 br). Osmium tetroxide (5 g) in ether (40 ml) was added to the above benzene solution of the olefin and the mixture was allowed to stand in the dark for 48 hr. Chloroform (60 ml) was then added and hydrogen sulfide passed through the mixture for 5 min using external cooling with cold water. After 2 hr the formed precipitate was removed by filtration, the filtrate evaporated, and the residue chromatographed. Elution with hexane and chloroform (1:1) yielded 1.2 g of XXXVIII: mp 82–83° (from pentane–ether); nmr signals at 0.98 t (methyl) and 3.78 ppm t (C-3, J = 8.5 cps); infrared bands (CCl_4), 3640 (free OH) and 3576 cm^{-1} (bonded OH); $\Delta\nu$ 64 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.35; H, 10.54.

The corresponding **3-acetate (XL)** had mp 73–74° (from pentane, at cold).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.70; H, 9.45.

The corresponding **3-methanesulfonate (XXXIX)** was prepared in the usual way (6 hr, room temperature): mp 74–75° (from ether and pentane); nmr signals at 1.02 t (methyl) and 4.65 ppm dd (J = 8.5 cps, J' = 7.5 cps).

Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.22; H, 8.12. Found: C, 53.06; H, 8.16.

Base-Catalyzed Rearrangement of Methanesulfonate XXXIX.—A solution of XXXIX (330 mg) in 15 ml of ether was added to a solution of *t*-potassium butoxide (containing 80 mg of potassium) in 5 ml of *t*-butyl alcohol and the mixture stirred for 1.5 hr at 35° under nitrogen. Addition of water was followed by extraction with ether and removal of the solvent on a water bath at normal pressure with the help of a Vigreux column. The residue showed one homogeneous spot on tlc, the conversion being most probably near to quantitative. A vpc analysis using a 70-m glass capillary column coated with a ureide[36] showed the presence of three products: ***cis,exo*-2-propionylbicyclo[3.2.0]heptane XLI** (23%, relative retention time 100) and the epimeric ***cis*-3-ethylbicyclo[3.3.0]octan-2-ones XLII** (*endo* and *exo*, 77%, retention times 106 and 107.5, in about 1:1 ratio). The liquid bicycloheptane XLI was separated by chromatography of the residue on alumina Woelm activity I (elution with pentane and 1% ether) and showed a carbonyl band in the infrared spectrum at 5.86 μ, negative tetranitromethane test and mass spectral peaks at m/e 152 (M^+), 123, 95, and 85.

The corresponding semicarbazone had mp 172–173° (from methanol) and exhibited nmr signals at 1.06 t (methyl) and 2.23 ppm qu (methylene group vicinal to methyl).

Anal. Calcd for $C_{11}H_{19}ON_3$: C, 63.13; H, 9.15; N, 20.08. Found: C, 62.90; H, 8.96; N, 20.15.

The epimers XLII were eluted next and showed in the infrared spectrum a carbonyl band at 5.78 μ and in the mass spectrum m/e 152 (M^+) and 124; these peaks were shifted after deuteration (by the usual method described previously for the deuteration of 16-ketone XXXIV) to m/e 154 and 126.

(36) B. Feibush and E. Gil-Av, *J. Gas Chromatog.*, **5**, 257 (1967).

Preparation of Authentic *cis*-3-Ethylbicyclooctan-2-ones XLII.—To a solution of *t*-potassium butoxide (from 30 mg of potassium) in *t*-butyl alcohol was added bicyclooctan-2-one (XXXVI, 160 mg) in 5 ml of dry ether followed by ethyl iodide (140 mg) in 5 ml of ether and the mixture stirred under nitrogen for 7 hr at 70°. Addition of water and extraction with pentane yielded a mixture which contained, except unreacted starting material, the two epimers XLII in the same ratio as obtained from rearrangement (identification by vpc analysis[36] with injection of a mixed sample and mass spectrum).

Preparation of Epimeric *cis*-2-Ethylbicyclooctan-3-ones XLIII. A. By Acid Dehydration of XXXVIII.—The diol XXXVIII (30 mg) was dissolved in 3 ml of ethyl alcohol containing 0.2 ml of sulfuric acid and the solution was boiled under reflux for 1.5 hr. Isolation with ether yielded, after evaporation of the solvent at normal pressure, a material which showed one spot on tlc and a carbonyl band in the infrared spectrum at 5.77 μ; vpc analysis showed two peaks, corresponding to the *exo*-substituted epimer XLIII, 84%, retention time 112 (relative to previously described isomers) and the *endo* epimer XLIII (16%, retention time 128): mass spectral peaks, m/e 152 (M^+) and 124.

B. **From the Acetate XL by a Serini Reaction.**—To the acetate XL (40 mg) dissolved in 1.5 ml of toluene was added 500 mg of zinc and the mixture boiled under reflux, with stirring, during 14 hr. The zinc was removed by filtration and washed with ether and the filtrate washed with water, dried, and evaporated under normal pressure on a water bath. Vpc analysis in the previously mentioned conditions showed that the product contained mostly the *exo* epimer (96%) and only traces (4%) of the *endo* epimer. The semicarbazone of *exo* XLIII had mp 178–179° (from methanol).

Anal. Calcd for $C_{11}H_{19}ON_3$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.20; H, 9.32; N, 20.35.

Treatment of the Serini product with 1 *N* methanolic potassium hydroxide at room temperature (16 hr under nitrogen) increased the relative amount of the *endo* epimer to 16% (by vpc analysis).

Registry No.—II, 4787-61-5; III, 4787-62-6; IV, 4787-63-7; V, 4787-64-8; VI, 4787-65-9; XI, 4787-66-0; XIII, 4787-67-1; XIV, 14030-45-6; XV, 4787-68-2; XVI, 4787-69-3; XVII, 15261-27-5; XVIII, 14030-46-7; XIX, 14030-47-8; XX, 15476-25-2; XXI, 15493-83-1; XXII, 14038-18-7; 17,15,15-d_3-XXII, 15476-26-3; XXIV, 4787-70-6; XXV, 15476-19-4; XXVI, 14188-71-7; XXVI semicarbazone, 15493-85-3; XXVIII, 14038-17-6; XXIX, 15471-65-5; XXX, 14038-19-8; XXXI-20-α, 14188-73-9; XXXI-20-β, 15493-87-5; XXXII-20-α, 15493-67-1; XXXII-20-β, 15493-68-2; XXXIII, 14038-21-2; XXXIV-20-α, 15476-09-2; XXXIV-20-β, 15622-66-9; XXXV, 15493-70-6; XXXVII 15493-71-7; XXXVIII, 15476-10-5; XXXIX, 15476-18-2; XL, 15476-11-6; XLI, 15476-12-7; XLI semicarbazone, 15493-72-8; XLII (*endo*), 15476-13-8; XLII (*exo*), 15476-14-9; XLIII (*endo*), 15476-15-0; XLIII (*exo*), 15476-16-1; XLIII (*exo*) semicarbazone, 15476-17-2.

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Thalictrum Alkaloids. VIII.[1-3] The Isolation, Structural Elucidation, and Synthesis of Dehydrothalicarpine

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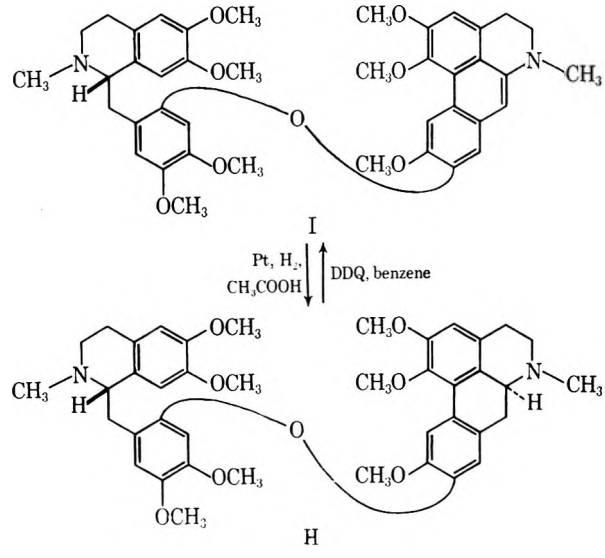
Evidence is presented for assignment of structure and configuration I to dehydrothalicarpine, a new dehydroaporphine alkaloid isolated from the roots of *Thalictrum dasycarpum* Fisch. and Lall. Elementary analysis of the alkaloid and its dimethiodide and spectral data supported a $C_{41}H_{46}N_2O_8$ molecular formula. Sodium–liquid ammonia cleavage yielded 6′-hydroxylaudanosine (III) and 2,10-dimethoxydehydroaporphine (IV). The 2,10-dimethoxydibenzo[*de,g*]quinolin-7-one (VII) and 1,2,10-trimethoxydibenzo[*de,g*]quinolin-7-one (VIII) structures were proposed for two minor products isolated from the sodium–liquid ammonia reaction mixture. Catalytic hydrogenation of dehydrothalicarpine (I) gave thalicarpine (II). A formal total synthesis was achieved by a route which involved oxidation of thalicarpine with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to dehydrothalicarpine.

The genus *Thalictrum* has served as a uniquely profuse source of new and novel benzylisoquinoline and aporphine alkaloids. Thus, *Thalictrum* species have yielded, *inter alia*, the first benzylisoquinoline alkaloid with a C-5 oxygenated substituent,[4] the first dimeric benzylisoquinoline–aporphine alkaloid,[1b,c,5] the first bisbenzylisoquinoline with a C-5 oxygenated substituent,[6] and the first bisbenzylisoquinoline with a diphenyl ether terminus at C-5, which was also the first unsymmetrical bisbenzylisoquinoline recognized to contain a twenty-membered ring.[1a] We report herewith the isolation, structural elucidation, and synthesis of dehydrothalicarpine (I), the first naturally occurring dehydroaporphine alkaloid.[2,7]

In an earlier communication,[5] we reported the extraction of an alkaloid mixture from the roots of *Thalictrum dasycarpum* Fisch. and Lall from Wisconsin. Furthermore, the fractionation of the nonquaternary nonphenolic alkaloid fraction by chromatography on Florisil was described in detail, as was the procedure for isolation of thalicarpine (II) from the appropriate chromatographic fraction. The present report describes the isolation of thalidasine,[1a] argemonine, and dehydrothalicarpine (I) (mp 186–187°, $[\alpha]^{29}D$ +55°) from other chromatographic fractions of the nonquaternary nonphenolic alkaloid fraction.

The molecular formula $C_{41}H_{46}N_2O_8$ was assigned for dehydrothalicarpine on the basis of elemental analysis



of the alkaloid and its dimethiodide derivative. Analysis showed the presence of seven O-methyl groups. The nmr spectrum showed signals for six N-methyl protons, twenty-one O-methyl protons, eleven aliphatic protons, and eight aromatic protons. The signal for one N-methyl group appeared at an unusually low field (τ 7.01). The ultraviolet absorption spectrum showed maxima at 265 mμ (ϵ 49,940) and 331 mμ (ϵ 13,400), indicative of a more highly conjugated chromophore than that of thalicarpine. The latter structural feature was indicated also by the more intense absorption at 6.20 μ in the infrared spectrum of dehydrothalicarpine.

The most useful reaction in structural studies of dimeric alkaloids which possess diphenyl ether moieties has been cleavage by the action of metallic sodium in liquid ammonia.[8] Sodium–liquid ammonia cleavage of dehydrothalicarpine yielded a complex mixture of products. However, by a combination of thick layer and column chromatographic procedures, a phenolic base (III) and three nonphenolic bases (IV, VII and VIII) were isolated from the reaction mixture.[9]

The phenolic cleavage product was readily characterized as 6′-hydroxylaudanosine (III) by direct comparison of its hydroiodide salt with a sample obtained

(1) (a) Part VII: S. M. Kupchan, T.-H. Yang, G. S. Vasilikiotis, M. H. Barnes, and M. L. King, *J. Amer. Chem. Soc.*, **89**, 3075 (1967). (b) Part VI: M. Tomita, H. Furukawa, S.-T. Lu, and S. M. Kupchan, *Chem. Pharm. Bull.* (Tokyo), **15**, 959 (1967). (c) Part V: M. Tomita, H. Furukawa, S.-T. Lu, and S. M. Kupchan, *Tetrahedron Letters*, 4309 (1965).

(2) This work was presented, in part, at the Symposium on Selected Recent Advances in Natural Products Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April, 1965, Abstracts, p 31P. The name dehydrothalicarpine is adopted for the alkaloid earlier called thalictrucarpine.

(3) This investigation was supported by Public Health Service Research Grant HE-02952 from the National Heart Institute. T.-H. Yang thanks the National Council on Science Development, Republic of China, for partial financial support.

(4) (a) E. Fujita and T. Tomimatsu, *J. Pharm. Soc. Japan*, **79**, 1082 (1959); (b) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).

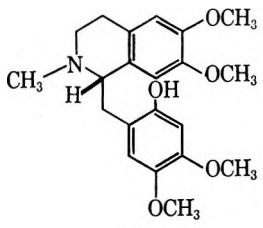
(5) S. M. Kupchan, K. K. Chakravarti, and N. Yokoyama, *J. Pharm. Sci*, **52**, 985 (1963).

(6) (a) J. Padilla and J. Herran, *Tetrahedron*, **18**, 527 (1962); (b) M. Shamma, B. S. Dudock, M. P. Cava, K. V. Rao, D. R. Dalton, D. C. DeJongh, and S. R. Shrader, *Chem. Commun.*, 7, (1966).

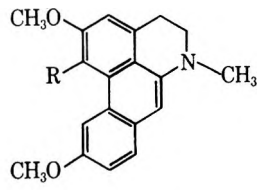
(7) H. B. Dutschewska and N. M. Mollov [*Chem. Ind.* (London), 770 (1966)] have reported their independent isolation and structural elucidation of dehydrothalicarpine from *Thalictrum minus ssp. elatum*. Direct comparison with our alkaloid of a sample of dehydrothalicarpine kindly provided by Dr. Mollov demonstrated the identity of the respective materials.

(8) M. Tomita, *Progr. Chem. Org. Nat. Prod.*, **9**, 175 (1952).

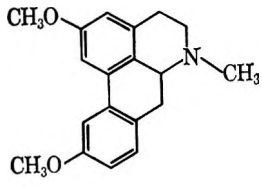
(9) It is noteworthy that no *d*-2,10-dimethoxyaporphine was detectable among the products obtained by sodium–liquid ammonia cleavage of dehydrothalicarpine, in contrast to the results reported in ref 7. The difference may be attributable to a difference in experimental procedures.



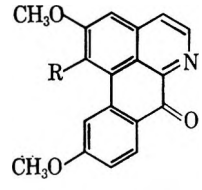
III



IV, R = H
V, R = OCH_3



VI



VII, R = H
VIII, R = OCH_3

earlier by sodium–liquid ammonia cleavage of thalicarpine.[1b,c,10]

The major nonphenolic base IV was characterized as 2,10-dimethoxydehydroaporphine on the basis of elemental analysis and characteristic and intense ultraviolet absorption.[11] The structural assignment was confirmed by catalytic reduction of IV to *dl*-2,10-dimethoxyaporphine, characterized by spectral and chromatographic comparison with a sample of *d*-2,10-dimethoxyaporphine (VI) obtained from thalicarpine.[1b,c,10]

The second nonphenolic base VII was assigned the empirical formula $C_{18}H_{13}NO_3$ on the basis of elemental analysis, and the low hydrogen content indicated a highly unsaturated structure. The infrared spectrum showed a band at 6.02 μ, indicative of the presence of a conjugated ketone. The ultraviolet spectrum resembled those of liriodenine[12] and related dibenzo[*de*,*g*]quinolin-7-one derivatives.[13a] The nmr spectrum showed the presence of two methoxy groups and seven aromatic protons and the absence of N-methyl and aliphatic protons, and hence strongly supported structure VII. Similarly, the 1,2,10-trimethoxydibenzo[*de*,*g*]quinolin-7-one structure (VIII) was suggested for the third nonphenolic (red) base on the basis of elemental analysis and infrared, ultraviolet, and nmr spectral characteristics. In view of the ease of oxidation of aporphines to liriodenine-type derivatives,[13] it appears likely that compounds VII and VIII were formed during the work-up of the sodium–liquid ammonia cleavage reaction, by oxidation of the presumed dehydroaporphine precursors, IV and V.

The foregoing evidence led to the postulation that the alkaloid should be formulated as a dehydrothalicarpine. This postulation was confirmed by catalytic reduction of dehydrothalicarpine to yield thalicarpine. Assignment of the double bond to the 6a,7 position of the aporphine moiety was made on the basis of the intensity of the ultraviolet absorption and the characteristic downfield shifts observed in the nmr spectrum for the C-11 proton and N-methyl signals of the dehydroaporphine system. The signal for the C-11 proton in dehydrothalicarpine occurs at τ 0.75. It has been noted earlier that exceptionally low τ values are found for protons in the 11 position of aporphines if position 1 is substituted by a methoxyl group.[14] The lowfield shift was attributed to deshielding by the neighboring ring as well as anisotropy effects of the C–O single bond, as the hydrogen is held very close to the opposite oxygen atom. The deshielding has been shown to be increased in 6a,7-dehydroaporphines, with resultant shifts of the C-11 proton resonance to still lower fields.[15] The downfield shift of the signal for an N-methyl group adjacent to the 6a,7 double bond of a dehydroaporphine has been noted earlier.[16]

Oxidation of thalicarpine with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and separation of the reaction mixture by partition chromatography[17] gave dehydrothalicarpine (47% yield). In view of the earlier synthesis of thalicarpine by condensation of L-6′-bromolaudanosine and L-N-methyllaurotetanine,[1b,c] the combined achievements constitute a direct formal total synthesis of dehydrothalicarpine.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Values of $[\alpha]D$ have been approximated to the nearest degree. Ultraviolet spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Infrared spectra were determined on Beckman Models IR-5A and -9 recording spectrophotometers. Nmr spectra were determined on a Varian A-60A spectrometer in deuteriochloroform solution with tetramethylsilane as the internal standard. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Paper chromatography was conducted by the descending technique on Whatman No. 4 paper. The paper was prewetted with McIlvain buffer of pH 5.4, and alkaloids were detected by spraying with a chloroform solution of bromophenol blue. The mobile phase consisted of petroleum ether (bp 65–68°)–butyl acetate–*n*-butyl alcohol (60:40:17 by volume).

Isolation of Dehydrothalicarpine (I).—The chromatographic separation on Florisil of the nonquaternary nonphenolic alkaloid fraction from *T. dasycarpum* roots has been described earlier.[5] The fractions eluted by 30 and 60% chloroform–benzene yielded thalicarpine. The fractions eluted with chloroform, 20% acetone–chloroform, and the initial fractions eluted with acetone were found to contain the same three principal components (R_f 0.20, 0.54, and 0.88, upon paper chromatography), and were combined. This alkaloid mixture (37 g) was rechromatographed on Florisil (1 kg) and eluted successively with benzene, 10 and 50% chloroform–benzene, chloroform, acetone, and finally, methanol. The fractions eluted with chloroform, enriched in the component of R_f 0.54, were combined in ethanol and treated with oxalic acid to yield, after recrystallization from ethanol, thalidasine oxalate[1a] (0.800 g), mp 160–162° and $[\alpha]^{26}D$ −53° (*c* 0.55, methanol).

Anal. Calcd for $C_{39}H_{44}N_2O_7 \cdot C_2H_2O_4 \cdot 2.5\ H_2O$: C, 62.50; H, 6.53; N, 3.56. Found: C, 62.46; H, 6.21; N, 3.19.

The mother liquor alkaloids after separation of thalicarpine and thalidasine oxalate were pooled with the remaining alkaloid fractions from both chromatographic separations on Florisil. The alkaloid mixture (25 g, shown by paper chromatography to contain two major components, of R_f 0.20 and 0.88) was chromatographed on alumina (400 g, Woelm "neutral" alumina, deactivated by intimate admixture with 12.5 ml of 10% acetic acid solution). The column was developed by successive elution

(10) S. M. Kupchan and N. Yokoyama, *J. Amer. Chem. Soc.*, **86**, 2177 (1964).

(11) *Cf.*, *e.g.*, M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Lett.*, 2937 (1966).

(12) M. A. Buchanan and E. E. Dickey, *J. Org. Chem.*, **25**, 1389 (1960).

(13) (a) M. Tomita, T.-H. Yang, H. Furukawa, and H.-M. Yang, *J. Pharm. Soc. Japan*, **82**, 1574 (1962); (b) T.-H. Yang, *ibid.*, **82**, 798 (1962).

(14) W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *J. Chem. Soc.*, 4778 (1964).

(15) N. M. Mollov and H. B. Dutschewska, *Compt. Rend. Acad. Bulgare Sci.*, **19**, 495 (1966).

(16) N. M. Mollov and H. B. Dutschewska, *Tetrahedron Lett.*, 853 (1966).

(17) K. S. Brown, Jr., and S. M. Kupchan, *J. Chromatog.*, **9**, 71 (1962).

with methylene chloride, 5, 10, 20, 30, and 40% chloroform–methylene chloride, and 50% methanol–chloroform. The first methylene chloride eluate (1.5 l.) was evaporated to dryness and the oily residue (15 g) was treated with warm acetone and filtered to remove insoluble fatty substances. The acetone-soluble alkaloids (13 g) were rechromatographed on deactivated alumina (400 g) with methylene chloride. The third, fourth, and fifth 500-ml eluates showed similar paper chromatographic patterns and were combined and evaporated to dryness. The alkaloidal residue (7.5 g) was crystallized from acetone and recrystallized several times from ethyl acetate to yield dehydrothalicarpine (1.02 g), mp 182–183°. Recrystallization from methanol gave crystals with mp 186–187°; $[\alpha]^{29}D$ +55° (c 0.44, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 3.55, 3.62, 6.20, 6.83, 8.00, 8.90 μ; λ_{max}^{EtOH} 265 mμ (ε 49,940), 331 (13,400); nmr signals at τ 7.58, 7.01 (6 H, two NCH_3), 6.74, 6.44, 6.22, 6.05, 5.99, 5.92 (21 H, seven OCH_3), and 3.77, 3.63, 3.48, 3.31, 3.18, 3.01, and 0.75 (8 H, aromatic *H*).

Anal. Calcd for $C_{41}H_{46}N_2O_8$: C, 70.87; H, 6.67; N, 4.03; 7(OCH_3), 31.27. Found: C, 70.59; H, 6.65; N, 4.11; OCH_3, 31.47.

The dimethiodide was prepared by refluxing a solution of dehydrothalicarpine (0.056 g) in methanol (1.5 ml) and methyl iodide (1.5 ml) for 6 hr. Evaporation of the solvents and crystallization of the residue from methanol gave dehydrothalicarpine dimethiodide (67 mg), mp 167–171°.

Anal. Calcd for $C_{41}H_{46}N_2O_8 \cdot 2CH_3I \cdot H_2O$: C, 51.81; H, 5.46; N, 2.81; I, 25.47. Found: C, 51.75; H, 5.36; N, 2.82; I, 25.66.

The chloroform–methylene chloride and chloroform–methanol eluates were combined and evaporated to dryness. The residue was rechromatographed on alumina (G., E. Merck, 40 g)–Celite (10 g) with 50% ethyl acetate–petroleum ether. The first and second 125-ml eluates were combined and evaporated to dryness, and the semisolid residue (6.74 g) was crystallized from ethyl acetate to yield thalicarpine (1.08 g). Fractional crystallization of the mother liquor alkaloids from ethyl acetate–ether gave colorless crystals (0.37 g), mp 156–157° and $[\alpha]^{26}D$ −200° (c 0.98, MeOH). The resemblance of the physical and spectroscopic properties of the alkaloid to those reported for argemonine[18] led to direct comparison and demonstration of identity (by mixture melting point determination, mixed tlpc and infrared and nmr spectral studies) with an authentic sample of argemonine.

Sodium–Liquid Ammonia Cleavage of Dehydrothalicarpine (I).—A three-necked, 1-l. flask equipped with a mechanical stirrer, a dropping funnel with a nitrogen gas inlet, and a nitrogen gas outlet on a dewar-type condenser was placed in an acetone–Dry Ice bath (bath temperature, −76°). Metallic sodium (1.7 g) was added in small portions with vigorous stirring until the blue color persisted for more than 15 min. Dehydrothalicarpine (0.96 g) was dissolved in 25 ml of dried toluene and placed in the dropping funnel. The reaction was carried out, under a nitrogen atmosphere, by adding small portions of the toluene solution and metallic sodium to the reaction vessel alternately so that the blue color of the reaction mixture was maintained. The reaction was stopped 30 min after all the toluene solution had been added to the mixture; the mixture maintained its blue color. About 0.9 g of metallic sodium had been consumed in the reaction. The reaction mixture was allowed to stand overnight in a hood to evaporate the ammonia. The residual toluene solution was washed with water (50 ml) and transferred with ether to a separatory funnel. The aqueous layer was extracted successively with ether (850 ml) until the extract gave a negative test to Dragendorff's reagent. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness, to yield 830 mg of light brown oil (fraction A). The alkaline aqueous extract was treated with ammonium chloride (20 g) and extracted with chloroform (200 ml). The chloroform extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness, to leave 62 mg of residue (fraction B).

Fraction A (830 mg) was subjected to thick layer chromatography on silica gel $HF_{254+366}$ (14 plates, 20 × 20 cm, 1-mm thick) with 10% methanol–chloroform. The band of highest mobility gave (upon elution with 25% methanol–chloroform) a green residue (493 mg). This material was subjected to thick layer chromatography on alumina G (five plates, 20 × 20 cm, 0.5 mm thick) with 1% methanol–chloroform, to yield fractions C (higher R_f, green 180 mg) and D (lower R_f, yellow, 44 mg). The band of second-highest mobility in the silica gel $HF_{254+366}$ separation gave fraction E (red, 19 mg) and the band of third highest mobility gave fraction F (168 mg).

2,10-Dimethoxydehydroaporphine (IV).—Fraction C (180 mg) was chromatographed on Woelm neutral alumina (10 g) in chloroform. The first chloroform eluate (200 ml) yielded a green residue (90 mg). This was dissolved in a small volume of ethanol–ether and treated with 10% hydrogen chloride in methanol to complete precipitation. The precipitate (65 mg) was collected, washed with ether, and recrystallized from ethanol–1-propanol to yield 2,10-dimethoxydehydroaporphine hydrochloride as microneedles, mp 127–131°.

Anal. Calcd for $C_{19}H_{19}NO_2 \cdot HCl \cdot {}^1/_3C_3H_7OH$: C, 68.41; H, 6.72. Found: C, 68.69; H, 6.87.

The free base, liberated from the hydrochloride salt by treatment with ammonium hydroxide, resisted attempts at crystallization: λ_{max}^{MeOH} 245 mμ (ε 40,640), 259 (sh), (34,640), 293 (15,140), 324 (6360), 386 (1430). Upon addition of acid, the maxima shifted to 240, 253, 261, 285, 303, and 314 mμ.

Further elution of the alumina column with chloroform yielded a yellow residue (13 mg, fraction G), which showed a tlc pattern resembling that of fraction D.

In a subsequent experiment, direct chromatography of fraction A (800 mg) on Woelm neutral alumina (200 g) in chloroform gave a first eluate (275 mg) which was converted directly into IV hydrochloride (161 mg), mp 127–131°.

Catalytic Reduction of 2,10-Dimethoxydehydroaporphine (IV). *dl*-2,10-Dimethoxyaporphine (VI).—A suspension of platinum oxide (21 mg) in glacial acetic acid (3 ml) was saturated with hydrogen and 2,10-dimethoxydehydroaporphine hydrochloride (21.3 mg) in acetic acid (1 ml) was added. The mixture was subjected to catalytic hydrogenation at 26° and atmospheric pressure. The reaction was stopped after 17 hr (hydrogen consumption, 1.44 ml) and the mixture was filtered. The catalyst was washed with a small amount of water. The filtrate was combined with the washing and evaporated to dryness under reduced pressure to yield a yellowish oil. The reaction product was dissolved in dilute hydrochloric acid solution and washed with ether. The acidic layer was made alkaline with 2% sodium hydroxide and extracted with ether. The ethereal extract was dried over anhydrous sodium carbonate and evaporated to dryness, to leave a yellowish oil (12.8 mg). The oily residue was dissolved in a small amount of dilute hydrochloric acid and filtered. Potassium iodide (100 mg) was added with stirring to the acidic solution to complete precipitation. The precipitate was collected, washed with a small amount of water and dried in a vacuum desiccator. The dried precipitate was crystallized from methanol to yield plates (8.7 mg, hydroiodide salt), mp 226–228° dec and $[\alpha]^{27}D$ ±0° (*c* 0.06, methanol).

Anal. Calcd for $C_{19}H_{21}NO_2 \cdot HI$: C, 53.91; H, 5.24. Found: C, 54.06; H, 5.06.

The ultraviolet absorption spectrum of the sample was identical with that of the hydroiodide of authentic *d*-2,10-dimethoxyaporphine obtained from sodium–liquid ammonia cleavage product of thalicarpine.[10] Liberation of the free base was effected by treatment of the hydroiodide salt in water with ammonium hydroxide and extraction with ether. Evaporation of the ether solution left a slightly yellowish residue. The infrared spectrum in chloroform and the mobility upon thin layer chromatography were identical with those of the authentic *d*-2,10-dimethoxyaporphine.

2,10-Dimethoxydibenzo[*de*,*g*]quinolin-7-one (VII).—Fractions D and G were combined (57 mg) and chromatographed on Woelm neutral alumina (5 g) in chloroform. Elution with chloroform (100 ml) gave a yellow residue (25 mg) which was crystallized first from chloroform–ether, and, then from acetone, to give yellow needles (VII, 13 mg): mp 218–220°; λ_{max}^{MeOH} 236 mμ (ε 25,470), 266 (24,500), 273 (sh) (22,330), 284 (18,830), 312 (6500), 345 (10,330) and 376 (9000); λ_{max}^{Nujol} 6.02 μ (conjugated ketone); nmr signals at τ 6.04 (6 H, two OCH_3) and 1.55–3.12 (7 H, aromatic *H*).

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50. Found: C, 74.07; H, 4.65.

In a subsequent qualitative experiment, tlc analysis indicated that oxidation of crude 2,10-dimethoxydehydroaporphine (IV) with activated manganese dioxide in chloroform solution yielded a two mixture enriched in VII.

(18) M. J. Martell, Jr., T. O. Soine, and L. B. Kier, *J. Amer. Chem. Soc.*, **85**, 1022 (1963), and earlier papers in the series. We thank Professor T. O. Soine cordially for an authentic sample of argemonine.

1,2,10-Trimethoxydibenzo[*de*,*g*]quinolin-7-one (VIII).—Fraction E (19 mg) was subjected to thick layer chromatography on silica gel $H_{2.4}$ (one plate, 20 × 20 cm, 0.5 mm thick) with 10% ethanol–chloroform. The principal band was transferred to a column and washed with chloroform. The chloroform eluate yielded a red solid residue (11 mg) which was recrystallized from acetone–ethanol to yield red microneedles (VIII, 5 mg): mp 256–258°; λ_{max}^{MeOH} 234 mμ (ε 33,330), 246.5 (41,050), 322 (7420), 470 (5830); λ_{max}^{KBr} 5.99 μ (conjugated ketone); nmr signals at τ 6.27 (3 H, OCH_3), 5.97 (6 H, two OCH_3), 1.75–2.82 (6 H, aromatic *H*).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71. Found: C, 70.95; H, 4.76.

6′-Hydroxylaudanosine (III).—Fraction F (312 mg) was dissolved in 10% acetic acid (5 ml) and the solution was filtered. The filtrate was treated with aqueous potassium iodide to complete precipitation. The precipitate was collected, washed with water, and recrystallized from ethanol to yield needles (118 mg), mp 184–186°. The melting point was not depressed by admixture with an authentic sample of 6′-hydroxylaudanosine hydroiodide, and the ultraviolet and infrared (Nujol) spectra and tlc mobility were identical with those of the authentic sample.[10]

Fraction B, shown by tlc to contain III as a major component, yielded 25 mg of III hydriodide.

Catalytic Reduction of Dehydrothalicarpine (I).—A suspension of platinum oxide (50 mg) in glacial acetic acid (15 ml) was saturated with hydrogen, and dehydrothalicarpine (50 mg) in acetic acid (2 ml) was added. The mixture was subjected to catalytic hydrogenation at 26° and atmospheric pressure. The reaction was terminated after 18 hr (hydrogen consumption, 10.0 ml) and the mixture was filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in 2.5% hydrochloric acid (10 ml). The solution was made alkaline with dilute ammonium hydroxide and extracted with chloroform. The chloroform was dried over anhydrous sodium sulfate and evaporated to dryness (residue, 41 mg). The residue was dissolved in the upper phase of the system Skellysolve B–ethylene chloride–methanol–water (10:2:2:0.16) and chromatographed on a column of Celite 545 impregnated with chlorophenol red and lower phase of the solvent system.[17] The fractions containing thalicarpine (tlc) were combined and crystallized from ether to yield thalicarpine (II, 17 mg), mp 156–158°, $[\alpha]^{29}D$ +133° (*c* 0.31, methanol). The melting point was not depressed by admixture with an authentic sample of thalicarpine, and the infrared spectrum and mixed tlc were identical with those of the authentic sample.

Oxidation of Thalicarpine (II) with DDQ.—To a stirred solution of thalicarpine (II, 1.00 g) in benzene (65 ml) was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (320 mg) in benzene (10 ml), and the solution was heated in an oil bath at 62° for 5 hr. A black powdery solid (855 mg) was separated by filtration, and the benzene solution was extracted with 2.5% hydrochloric acid. The solution was made alkaline with 10% ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure to dryness (residue, 502 mg). The residue was subjected to partition chromatography as described for thalicarpine above, and two bands were separated. The first band eluted corresponded to dehydrothalicarpine (364 mg) and the second to thalicarpine (26 mg). Crystallization of the first band from acetone yielded dehydrothalicarpine (338 mg), mp 180–183°, characterized by mixture melting point determination, mixed tlc, and ir, uv, and nmr spectral comparison with the authentic sample. The black solid (855 mg) separated from the original reaction mixture was shaken for 3 hr with 2.5% sodium hydroxide solution (25 ml) and benzene (100 ml). The benzene layer was filtered through a bed of anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The residue (460 mg) was subjected to partition chromatography, as described above, to yield 23 mg of dehydrothalicarpine, mp 180–183°, and 206 mg of thalicarpine, mp 150–155°. The yield of dehydrothalicarpine, based on unrecovered starting material, was 47%.

Registry No.—I, 7224-94-4; I dimethiodide, 15569-53-6; IV, 15562-38-6; IV hydrochloride, 15562-39-7; (±)-VI hydroiodide, 15562-40-0; thalidasine oxalate, 11040-48-5; VII, 15562-41-1; VIII, 15562-42-2.

The Alkaloids of *Tabernaemontana riedelii* and *T. rigida*

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The alkaloids of two Amazonian species of *Tabernaemontana* have been studied; each species yielded indole alkaloids of only one structural type. Thus, *T. riedelii* contained the new alkaloids (+)-8-oxominovincine and (+)-minovincine, as well as a mixture of (±)- and (+)-vincadifformine. *T. rigida* contained (±)-vincamine, (+)-vincamine, (+)-apovincamine, and a substance believed to be a mixture of (±)- and (−)-14-epivincamine.

The genus *Tabernaemontana* of the family Apocynaceae has been the subject of continued controversy with regard to problems of botanical classification. Even recent authorites such as Markgraf[3] and Woodson[4] have disagreed on the question of whether a considerable number of *Tabernaemontana* species should be retained within the genus or should be reclassified as members of related genera. At the present time, we are engaged in a broad study of the alkaloids of the genus *Tabernaemontana*, in the expectation that the results will have chemotaxonomic value in a future reclassification of the genus.

Indole alkaloids have been isolated and identified from a number of *Tabernaemontana* species.[5] These include *Tabernaemontana australis*,[6] *T. psychotrifolia*,[6] *T. oppositifolia*,[6] *T. alba*,[7] *T. pachysiphon*,[8] *T. pandacaqui*,[9] *T. mucronata*,[10] *T. laurifolia*,[11] *T. heyneana*,[12]

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(3) F. Markgraf, *Notizbl.* **14**, No. 121, 151 (1938).

(4) R. E. Woodson, Jr., "North American Flora: Asclepiadales-Apocynaceae," Vol. 29, Part II, 1938, p 103.

(5) The related genera *Voacanga*, *Ervatamia*, *Gabunia*, and *Conopharyngia* are not included in this listing.

(6) M. Gorman, N. Neuss, N. J. Cone, and J. A. Deyrup, *J. Amer. Chem. Soc.*, **82**, 1142 (1960).

(7) O. Collera, F. Walls, A. Sandoval, F. García, J. Herrán, and M. C. Perezamador, *Bol. Inst. Quim. Univ. Nacl. Auton. Mex.*, **14**, 3 (1962).

(8) J. Thomas and G. A. Starmer, *J. Pharm. Pharmacol.*, **15**, 487 (1963).

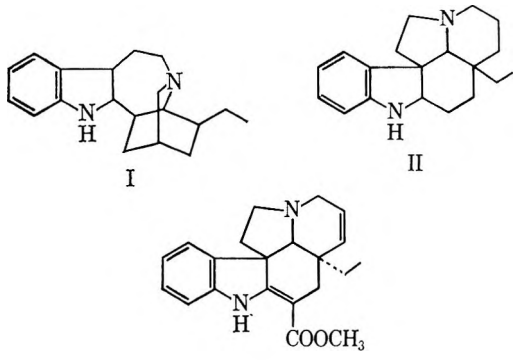
(9) G. Aguilar-Santos, A. C. Santos, and L. M. Joson, *J. Philippine Pharm. Assoc.*, **50**, 321, 333 (1964).

(10) A. C. Santos, G. Aguilar-Santos, and L. L. Tibayan, *An. Real Acad. Farm.*, **31**, 3 (1965).

(11) M. P. Cava, S. K. Mowdood, and J. L. Beal, *Chem. Ind.* (London), 2064 (1965).

(12) T. R. Govindachari, B. S. Joshi, A. K. Saksena, S. S. Sathe, and N. Viswanathan, *Chem. Commun.*, **97** (1966).

and *T. rupicola*,[13] as well as the ambiguous species *Peschiera affinis* (*T. affinis*).[14,15] Almost all of these alkaloids have the ibogamine-type skeleton (I); a few[13] are derived from this skeleton by rearrangement.[16] It seems significant that the large and important group of alkaloids having the aspidospermine-type skeleton (II) has been represented up to this time among *Tabernaemontana* alkaloids only by tabersonine (III).[7]

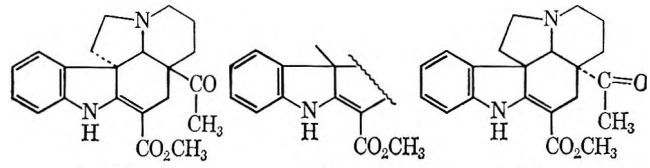


I II III

We now report the isolation and identification of a number of alkaloids, none of which have the ibogamine skeleton I, from the Amazonian species *Tabernaemontana riedelii* and *T. rigida*.

The Alkaloids of *T. riedelii*.—Since *T. riedelii* is a small shrub, the entire above-ground portion of the plant was examined without separation of the plant parts. Isolation of the crude tertiary base mixture was followed by chromatographic purification to give a mixture consisting mainly of three components; the latter were separated by partitioning between benzene and aqueous acid solutions of increasing acidity. One major constituent and two minor ones were thus obtained.

The amorphous major alkaloid of *T. riedelii* was assigned the structure of (+)-minovincine (IV) on the basis of the following evidence. Its ultraviolet spectrum shows maxima at 300 and 330 mμ, suggesting the presence of the chromophore V, present in a number of dihydroindole alkaloids.[17] Its nmr spectrum shows, in addition to four aromatic protons and a hydrogen-bonded NH at low field, a methyl singlet at δ 3.71 and at 1.82; the latter may be assigned to a carbomethoxy methyl and a C-acetyl methyl, respectively. Its infrared spectrum in chloroform solution shows carbonyls at 1670 and 1700 cm^{-1}, attributable to a hydrogen-bond ester group and an unconjugated ketone, respectively. Finally, direct comparison of the infrared spectrum of IV with the published spectrum of (−)-minovincine (VI)[18] show the two to be essentially identical.

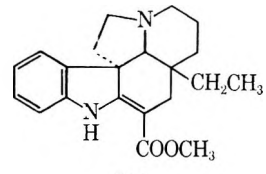


IV V VI

The mass spectrum of (+)-minovincine (IV) confirmed its molecular weight, and showed additional significant peaks at 309, 214, 138 (base peak), and 43. The breakdown pattern leading to the 138 and 214 fragments is quite typical for the aspidospermine-type skeleton.[19]

(+)-Minovincine (IV) has not been previously described, although it is the major alkaloid of *T. riedelii*. In contrast, the previously reported (−)-minovincine (VI) occurs only as a minor alkaloid in *Vinca minor* L.[18]

The first of the two minor bases of *T. riedelii* is, like minovincine, amorphous though homogeneous by thin layer chromatography. Its ultraviolet spectrum is similar to that of (+)-minovincine, suggesting the presence of the same chromophore V. Its infrared spectrum indicates the absence of a ketonic carbonyl, although the remainder of the spectrum in the 1600–1700-cm^{-1} region is quite similar to that of (+)-minovincine. It seemed very likely, therefore, that this base might be the desoxo analog of (+)-minovincine, namely, (+)-vincadifformine (VII). Support for this structure was obtained by mass spectrometry, which confirms the molecular weight (338); details of the spectrum are the same as those previously recorded for vincadifformine.[19]



VII

The amorphous (−)-vincadifformine, $[\alpha]D$ −540°, has been isolated from *Vinca minor* L.,[18] whereas the crystalline (±)-vincadifformine, mp 124–125°, has been isolated from *Vinca difformis* Pourr.[20] Since the rotation of our amorphous base is only +185°, it must be a mixture of (+)-vincadifformine (VII) and (±)-vincadifformine. Vincadifformine occurs also in *Rhazya stricta* as a mixture of the (+) and (±) forms.[21]

The second of the minor bases of *T. riedelii* forms colorless crystals: mp 257.5–259.5°; $[\alpha]D$ +268°. Its ultraviolet spectrum shows maxima at 298 and 330 mμ, suggesting the presence of chromophore V. Its infrared spectrum in potassium bromide is quite similar to that of (+)-minovincine, but it exhibits a carbonyl band at 1620 cm^{-1} in addition to the two minovincine carbonyls. The position of this third carbonyl band, together with the very weakly basic nature of the compound, suggested the structure of (+)-8-oxominovincine (VIII). Elemental analysis supported the compo-

(13) C. Niemann and J. W. Kessel, *J. Org. Chem.*, **31**, 2265 (1966).

(14) J. A. Weisbach, R. F. Raffauf, O. Ribeiro, E. Macko, and B. Douglas, *J. Pharm. Sci.*, **52**, 350 (1963).

(15) M. P. Cava, S. K. Talapatra, J. A. Weisbach, D. Douglas, R. F. Raffauf, and O. Ribeiro, *Chem. Ind.* (London), 1193 (1964).

(16) *Peschiera affinis* is a significant exception to this rule, since only alkaloids derived from the sarpagine-type skeleton have been isolated from it.[14,15] This fact lends chemotaxonomic support to its classification outside of the genus *Tabernaemontana*.

(17) K. Aghoramurthy and R. Robinson, *Tetrahedron*, **1**, 172 (1957); G. F. Smith and J. T. Wrobel, *J. Chem. Soc.*, 739 (1960); K. Bernauer, W. Arnold, C. Weissmann, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **43**, 717 (1960); J. Lévy, J. LeMen, and M. M. Janot, *Bull. Soc. Chim. Fr.*, 979 (1960).

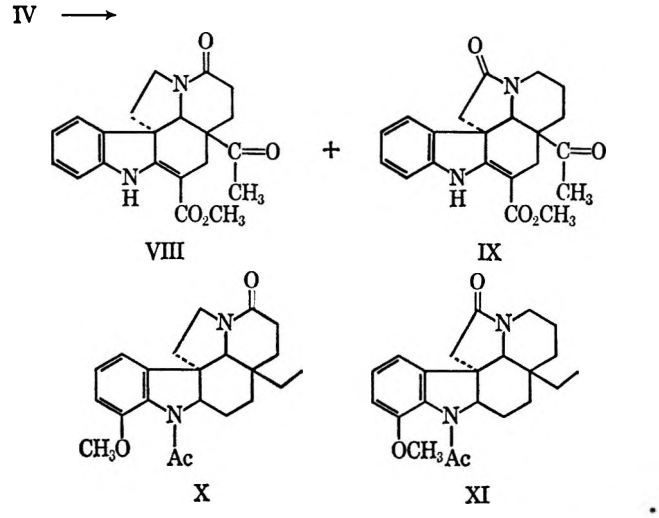
(18) M. Plat, J. LeMen, M. M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. Chim. Fr.*, 2237 (1962).

(19) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I (Alkaloids), Holden-Day, Inc., San Francisco, Calif., 1964, p 98 ff.

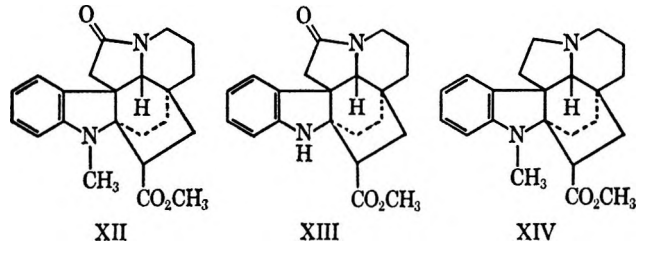
(20) J. Gosset, J. LeMen, and M. M. Janot, *Ann. Pharm. Fr.*, **20**, 448 (1962); C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, J. LeMen, and M. M. Janot, *Tetrahedron Lett.*, 235 (1962).

(21) G. F. Smith and M. A. Wahid, *J. Chem. Soc.*, 4002 (1963).

sition $C_{21}H_{22}N_2O_4$; the corresponding molecular weight (366) was confirmed by mass spectrometry.[22] Final proof of the structure of VIII was obtained by a study of the controlled permanganate oxidation of (+)-minovincine, which afforded two weakly basic lactams. The first product was the crystalline δ-lactam, (+)-8-oxominovincine (VIII), identical in all respects with the compound isolated from *T. riedelii*. The second product was the amorphous γ-lactam, 10-oxominovincine (IX). The lactam carbonyl frequencies of VIII and IX in chloroform solution are 1630 and 1670 cm^{-1}, respectively, as expected on the basis of the different sizes of the lactam rings. These values are in good accord with the corresponding reported values of 1625 and 1680 cm^{-1} for the lactam functions of compounds X and XI, respectively.[23]



(+)-8-Oxominovincine (VIII) is the first example of a naturally occurring aspidospermine-type alkaloid which contains a δ-lactam function. On the other hand, pleiocarpinilam (XII) and kopsinilam (XIII) are examples of related naturally occurring γ-lactam alkaloids.[24] It is of interest to note that an attempt to effect the air oxidation of pleiocarpine (XIV) to γ-lactam XII (or its δ-lactam isomer) was unsuccessful.[24] Consequently, the possibility that 8-oxominovincine may be an artifact arising from minovincine by air oxidation seems quite unlikely.



(+)-Vincadifformine, (+)-minovincine, and (+)-8-oxominovincine all have the same absolute configuration, namely, that shown in structures VII, IV, and VIII, respectively. This assignment follows from the known stereochemistry of (−)-vincadifformine and (−)-minovincine.[25]

The Alkaloids of *T. rigida*.—*Tabernaemontana rigida* Miers has a curious history of repeated botanical reclassification which is worthy of brief review in the light of the unexpected alkaloid type which it contains. The plant was first classified as *Tabernaemontana macrophylla* in 1860 by Miers,[26] who was unfortunately unaware of the earlier use of this name to describe a different species.[27] In 1878, Miers reassigned the plant to another genus, calling it *Phrissocarpus rigidus*.[28] Many years later, Markgraf assigned it to still a different genus, calling it *Anacampta rigida*.[29] Most recently, R. E. Woodson transferred it back to the genus *Tabernaemontana*, calling it *T. rigida* Miers.[30]

Since *T. rigida* is a tree of medium height (up to 5 m), only the rather thick bark was chosen for phytochemical examination. Conventional work-up of the bark for tertiary bases yielded a chloroform solution from which a considerable quantity of white powdery material separated on concentration. The solid fraction and the amorphous chloroform residue were investigated separately as fraction A and fraction B, respectively.

Fraction A was purified readily by crystallization from chloroform–methanol to give substance A_1, mp 227–228°, $[\alpha]D$ +4°. Elemental analysis indicated that A_1 had the empirical composition $C_{21}H_{26}N_2O_3$; its infrared spectrum indicated the presence of a carbonyl function (1757 cm^{-1}, in Nujol), and its ultraviolet spectrum showed maxima (226 and 279 mμ) consistent with the presence of an unsubstituted indole chromophore. The above data suggested that A_1 might be vincamine in the form of a mixture of (±)-vincamine and (+)-vincamine (XV), since the reported rotation of the latter is $[\alpha]D$ +41°.[31] Repeated crystallization of A_1 from tetrahydrofuran–methanol provided an efficient separation of the material into (±)-vincamine, mp 235–236°, and (+)-vincamine (XV), mp 232–233°, $[\alpha]D$ +40°; the infrared spectra of the two forms were identical (even in potassium bromide), and the identity of the (+)-vincamine was proven by direct comparison with an authentic sample.[32]

(+)-Vincamine (XV) has been isolated previously only from various species of *Vinca*, *i.e.*, *Vinca minor L.*,[33]

(22) The mass spectrum of VIII differs considerably from that of IV owing to the presence of the 8-oxo function. Although details of the spectrum are not given here, the major peaks are recorded in the Experimental Section.

(23) R. H. F. Manske, "The Alkaloids," Vol. VIII, Academic Press Inc., New York, N. Y., 1965, p 361.

(24) C. Kump and H. Schmid, *Helv. Chim. Acta*, **45**, 1090 (1962).

(25) W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann, and H. Schmid, *Helv. Chim. Acta*, **48**, 443 (1965).

(26) J. Mueller, *Fl. Bras.*, **6** [1], 75 (1860).

(27) J. L. M. Poiret in *Encyclopédie Meth. Bot.*, Suppl. V [1], 276 (1817).

(28) J. Miers in *Apocyn. S. Amer.*, 72 (1878).

(29) F. Markgraf, *Notizbl.*, **14**, 146 (1938).

(30) We are grateful to Dr. W. Rodriguez (Instituto da Pesquisas da Amazonia) for this information. The latest reclassification of this plant does not appear to have been published, presumably owing to the untimely death of Dr. Woodson.

(31) J. Trojánek, O. Štrouf, J. Holubek, and Z. Čekan, *Tetrahedron Lett.*, 702 (1961).

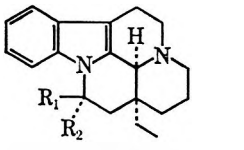
(32) We are indebted to Dr. I. Kompiš, Institute of Chemistry, Slovak Academy of Sciences, Bratislava, for a generous sample of (+)-vincamine.

(33) E. Schlittler and A. Furlenmeier, *Helv. Chim. Acta*, **36**, 2017 (1953); M. Pailer and L. Belohlav, *Monatsh.*, **85**, 1055 (1954); F. E. King, J. H. Gilks, and M. W. Partridge, *J. Chem. Soc.*, 4206 (1955); K. Szasz, L. Szporny, E. Bittner, I. Gyenes, E. Havel, and E. Mago, *Magy. Kém. Foly.*, **64**, 296 (1958); J. Trojánek, J. Hoffmannová, O. Štrouf, and Z. Čekan, *Collect. Czech. Chem. Commun.*, **24**, 526 (1959); J. Trojánek, K. Kavková, O. Štrouf, and Z. Čekan, *ibid.*, **26**, 867 (1961); J. Trojánek, O. Štrouf, K. Kavková, and Z. Čekan, *ibid.*, **27**, 2801 (1962); Z. Čekan, J. Trojánek, O. Štrouf, and K. Kavková, *Pharm. Acta Helv.*, **35**, 96 (1960); O. Bauerová, J. Mokry, I. Kompiš, S. Bauer, and J. Tomko, *Chem. Zvesti*, **15**, 523 (1961); J. Trojánek, O. Štrouf, K. Kavková, and Z. Čekan, *Chem. Ind.* (London), 790 (1961).

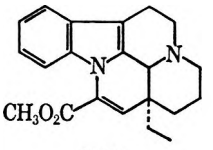
V. major L.,[34] *V. difformis* Pourr.,[35] and *V. erecta* R. and L.[36] (±)-Vincamine has not been encountered previously in nature.

Fraction B of the crude alkaloid mixture was partially resolved chromatographically. In addition to a further amount of (±)- and (+)-vincamine mixture, a fair yield of (+)-apovincamine (XVI) was isolated. The (+)-apovincamine was optically pure, indicating that it is probably not an artifact formed during the isolation process by the action of acid on vincamine.

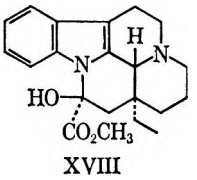
Further work-up of fraction B yielded small amounts of two additional bases, designated here as TR-1 and TR-2. Base TR-1, mp 186–187°, is isomeric with vincamine and is weakly levorotatory, $[\alpha]_D$ −5°. Its mass spectrum is virtually identical with that of vincamine,[19] suggesting that it is a diastereomer of the latter alkaloid. (−)-14-Epivincamine (XVII), $[\alpha]_D$ −36.4°, has been described as melting at 181–185° and as having a mass spectrum nearly identical with that of vincamine.[37] It is quite likely, therefore, that base TR-1 is a mixture of (−)-14-epivincamine (XVII) and (±)-14-epivincamine. Base TR-2, mp 209–211°, is also isomeric with vincamine but weakly dextrorotatory, $[\alpha]_D$ +1.8°; its infrared spectrum is distinctly different from that of vincamine in the fingerprint region. Like base TR-1, base TR-2 shows a mass spectrum which is virtually identical with that of vincamine. Base TR-2 would appear, therefore, to be a stereoisomer of vincamine (or possibly 14-epivincamine) in which the D–E ring juncture is *trans* rather than *cis;* 8-epivincamine (XVIII, as a mixture of + and ± forms) is the biogenetically most probable structure for this substance. Unfortunately, the chemical degradation of bases TR-1 and TR-2 could not be studied due to lack of material.



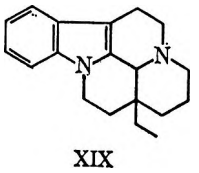
XV, R_1 = OH; R_2 = CO_2CH_3
XVII, R_1 = CO_2CH_3; R_2 = OH



XVI



XVIII



XIX

The apparently exclusive production of alkaloids having the eburnamine-type skeleton (XIX) by *T. rigida* is quite interesting from the chemotaxonomic point of view, since no alkaloids of this structural type have been found in any species of *Tabernaemontana* previously examined. Perhaps the earlier botanical classification of *T. rigida* as *Anacampta rigida*[29] should be reconsidered, and a phytochemical study of other *Anacampta* species should be undertaken in order to determine whether they also produce alkaloids of the vincamine type.

(34) N. R. Farnsworth, F. J. Draus, R. W. Sager, and J. A. Bianculli, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 589 (1960).

(35) M. M. Janot, J. LeMen, and Ch. Fan, *Ann. Pharm. Fr.*, **15**, 513 (1957).

(36) P. Ch. Yuldasev, *Izv. Akad. Nauk SSSR*, 188 (1953); S. Yu. Yunusov, P. Ch. Yuldasev, and N. V. Plechanova, *Dokl. Akad. Nauk Uzb. SSR*, **7**, 13 (1956); S. Yu. Yunusov and P. Ch. Yuldasev, *Zh. Obshch. Khim.*, **27**, 2015 (1957).

(37) J. Mokry and I. Kompiš, *Tetrahedron Lett.*, 1917 (1963).

Experimental Section[38]

Tabernaemontana riedelii. **Plant Material and Crude Tertiary Bases.**—The leaves and twigs of *T. riedelii* were collected by Mr. Luis Coelho in the vicinity of Manaus, Brazil, in February 1965. The dried and ground plant material (10 kg) was extracted exhaustively with 95% ethanol for several days. The concentrated alcoholic extract was extracted with ethyl acetate and the ethyl acetate solution was subsequently shaken with 10% aqueous sulfuric acid to remove tertiary bases. The aqueous acid solution was washed with benzene, and was then made alkaline with ammonia and extracted with chloroform to give, after solvent evaporation, 33.7 g of crude tertiary bases.

Separation and Characterization of the Tertiary Bases.—A major aliquot (26.7 g) of the crude tertiary bases was dissolved in chloroform (200 ml) and mixed with alumina (130 g), and the mixture was dried (*in vacuo*) and then mixed thoroughly with fresh alumina (390 g). The resulting powder was then eluted exhaustively in succession with (a) benzene, (b) chloroform, (c) chloroform–methanol 97:3, and (d) methanol; the weights of nonvolatile eluted bases were (a) 16.0 g, (b) 3.0 g, (c) 1.4 g, and (d) 2.0 g, respectively. The work described in this paper was carried out exclusively with the major benzene fraction; preliminary attempts to resolve the components of the more polar fractions were unrewarding.

The major portion (15.0 g) of the bases eluted by benzene was dissolved in benzene (100 ml) and the solution was extracted successively with aqueous acid of increasing acidity (see Table I). In each case the bases were liberated from the aqueous acid by ammonia and extracted with methylene chloride.

TABLE I

Acid used	Fraction	Wt, g
pH 4 phosphate–citrate buffer	F-1	1.76
pH 2.6 phosphate–citrate buffer	F-2	0.306
1 *N* hydrochloric acid	F-3	12.01
(Not extracted by 1 *N* HCl)	F-4	0.810

Fraction F-1 was not identified. Most of the material was lost during attempted chromatography on alumina, since the material was not recovered from the column even by polar solvents; it may have consisted of hydroxylic oxidation products formed during work-up.

Fraction F-2 was crude (+)-*vincadifformine* (VII). An aliquot (100 mg) of this fraction was purified by extraction with hot chloroform, the insoluble residue being discarded. The resulting amorphous (+)-vincadifformine (31 mg) was homogeneous by tlc (neutral alumina, 1:1 chloroform–benzene). The following physical data were recorded: $[\alpha]^{26}D$ +185° (*c* 1.0, ethanol); λ_{max} mμ (log ε) 220 (4.20), 297 (3.80), and 330 (3.86); $\nu_{max}^{CHCl_3}$ 3490, 1670, 1610, and 720 cm^{-1}. The mass spectrum shows a molecular ion peak at 338, and a base peak at 124.

Fraction F-3 was homogeneous by tlc (neutral alumina, 1:1 chloroform–benzene), and consisted entirely of (+)-minovincine (IV). The following physical data were recorded: $[\alpha]^{26}D$ +340 (*c* 1.0, ethanol); λ_{max} mμ (log ε) 228 (4.08), 300 (3.99), and 330 (4.17); γ_{max} 3400, 2800, 1700, 1670, 1600, and 742 cm^{-1}; $\nu_{max}^{CHCl_3}$ 3390, 2800, 1690, 1670, and 1600 cm^{-1}; δ 8.78 (NH, singlet), 7.30–6.67 (aromatic multiplet, 4 H), 3.71 (singlet, $-COOCH_3$, 3 H), 1.82 (singlet, $-COCH_3$, 3 H). The mass spectrum shows important peaks at 352 (M^+), 309, 214, 138, and 43.

Fraction F-4 crystallized slowly from a concentrated benzene solution to give 300 mg of (+)-8-oxominovincine (VIII), mp 252–253°; recrystallization from methanol gave fine colorless needles of pure VIII, mp 257.5–259.5°.

Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.73; H, 6.47; N, 7.55.

(38) Melting points are uncorrected. Analyses were carried out by Midwest Microlab Inc., Indianapolis, Ind. Mass spectra were determined using an Atlas CH-4 mass spectrometer. Unless otherwise specified, infrared spectra were determined in potassium bromide disks, ultraviolet spectra in 95% ethanol solution, and nmr spectra in deuteriochloroform solution. Column chromatography was carried out using Woelm neutral alumina, activity grade II, unless otherwise stated.

The following physical data were recorded: $[\alpha]^{26}D$ +268° (*c* 0.1, ethanol); λ_{max} mμ (log ε) 229 (4.30), 298 (4.32), and 330 (4.48); γ_{max} 3160, 1680, 1660, 1620, 1580; $\nu_{max}^{CHCl_3}$ 3390, 1670, 1630, 1580 cm^{-1}; nmr, δ 8.88 (NH, singlet, 7.34–6.73 (aromatic multiplet, 4 H), 3.75 (singlet, $-COOCH_3$, 3 H), 1.93 (singlet, $-COCH_3$, 3 H). The mass spectrum shows important peaks at 366 (M^+), 335, 308, 307, 214 (base peak), 154, 110, and 43.

Oxidation of (+)-Minovincine (IV) with Potassium Permanganate.—Into a solution of 250 mg of (+)-minovincine (IV) in 25 ml of acetone (reagent grade) cooled to 20°, was added all at once 250 mg of potassium permanganate. The mixture was stirred for 3 hr, an additional 100 mg of potassium permanganate was added, and the mixture was stirred for a further 2 hr at 20°. The excess of potassium permanganate was then removed by addition of ethanol until the purple color disappeared. The manganese dioxide was filtered off and the solvent evaporated *in vacuo;* the residue, after redissolving in benzene, was extracted with aqueous hydrochloric acid to recover unchanged starting material. (The reaction was not carried out until the starting material had completely reacted as the formation of degradation products was faster than the disappearance of the starting material.)

The aqueous acid solution was neutralized with aqueous ammonia and extracted with methylene chloride to give 122.2 mg of unchanged starting material. The benzene solution was dried over potassium carbonate and evaporated *in vacuo*, yielding 90 mg of a residue which showed two spots by tlc (neutral alumina, $CHCl_3$). Both compounds were separated by preparative tlc on a neutral alumina plate using chloroform as the developing solvent.

The alumina containing the less polar product was extracted with chloroform to give, after crystallization from methanol, fine needles of lactam VIII, mp 253–255° (5 mg), $[\alpha]^{26}D$ +269.0 (*c* 0.1, ethanol).

The infrared spectrum of this material ($CHCl_3$ solution) was identical with that of naturally occurring lactam VIII.

The alumina containing the more polar product was worked up by the same procedure as described above for lactam VIII. The resulting lactam IX (30 mg) was amorphous; infrared bands were at $\nu_{max}^{CHCl_3}$ 3480 (-NH), 1720 ($-COOCH_3$), 1695 ($-COCH_3$) 1670 (γ lactam), 1625, and 730 cm^{-1}.

Tabernaemontana rigida. **Plant Material and Crude Tertiary Bases.**—The bark of *T. rigida* was collected by Mr. Luis Coelho in the vicinity of Manaus, Brazil, in February 1965. The dried and ground bark (23 kg) was extracted exhaustively with 95% ethanol for several days. The concentrated alcoholic extract was extracted with ethyl acetate, and the ethyl acetate solution was subsequently shaken with 5% aqueous sulfuric acid to remove tertiary bases. The aqueous acid solution was washed with benzene, and was then made alkaline with ammonia and extracted with chloroform. Concentration of the chloroform extract to a small volume caused the separation of a gray powder (20.0 g), which was removed by filtration and designated as fraction A. Evaporation of the filtrate yielded fraction B as a gum (67.5 g).

Separation and Characterization of the Tertiary Bases. Examination of Fraction A.—Crystallization of fraction A from chloroform–methanol (1:1) yielded substance A_1 (12.85 g), mp 227–228°, which was homogeneous by tlc (alumina, $CHCl_3$–CH_3OH, 1:1). A small sample was recrystallized for analysis.

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.93; N, 7.90. Found: C, 71.18; H, 7.39; N, 7.90.

The following physical data were recorded: $[\alpha]^{26}D$ +4° (*c* 1.0, pyridine); λ_{max} mμ (log ε) 226 (4.13) and 279 (3.59); ν_{max} 1730 and 742 cm^{-1}.

Substance A_1 (12.0 g) was subjected to fractional crystallization from tetrahydrofuran–methanol (3:1), when it was separated into pure (±)-vincamine (9.0 g), mp 235–236°, and pure (+)-vincamine (XV, 1.8 g), mp 232–233°, $[\alpha]D$ +40° (*c* 1.0, pyridine). The (+)-vincamine obtained was identical (infrared spectrum, mixture melting point) with authentic material.[32]

Examination of Fraction B.—Fraction B was dissolved in warm 8% aqueous tartaric acid (1200 ml). The cooled brown solution was filtered through glass wool and extracted with five 500-ml portions of ether to remove neutral material (3.00 g). Basification of the aqueous acid solution with ammonia followed by extraction with five 500-ml portions of ether removed the major portion of the alkaloids, designated as fraction B_1 (33.8 g). Further extraction of the ammoniacal solution with chloroform (1000 ml) removed the remaining bases, designated as fraction B_2 (15.4 g). An extensive effort to resolve fraction B_2 by a combination of buffer separation and alumina chromatography failed; it will not be referred to further in this discussion.

Fraction B_1 was chromatographed on alumina (grade III, 860 g). A total of 71 fractions was obtained, which were recombined into six fractions on the basis of tlc similarities (see Table II).

TABLE II

Fraction	Eluent	Wt, g
B_{2a}	Benzene	9.5
B_{2b}	Benzene	3.0
B_{2c}	Benzene–Et_2O (2:1)	1.5
B_{2d}	Benzene–Et_2O (1:1)	3.0
B_{2e}	Chloroform	8.0
B_{2f}	Methanol	2.7

Fraction B_{2a} yielded, by direct crystallization from acetone, (+)-apovincamine (1.0 g), mp 158–159°; an additional amount of the same compound (0.50 g) was obtained from the mother liquors by rechromatography: $[\alpha]^{26}D$ +118° (*c* 2.11, chloroform). The following constants have been recorded for (+)-apovincamine:[39] mp 159–161°; $[\alpha]^{26}D$ +121° (chloroform). The ultraviolet spectrum and the infrared spectrum (chloroform solution) of the (+)-apovincamine isolated as described above were identical with those of (±)-apovincamine prepared from (±)-vincamine by acid dehydration.[31]

Fractions B_{2b} and B_{2c} yielded only a further quantity (3.10 g) of the crystalline mixture of (+)- and (±)-vincamine: mp 227–228°; $[\alpha]^{26}D$ +4°.

Fraction B_{2e} was rechromatographed on alumina, the column being eluted with benzene, 1:1 benzene–chloroform, and chloroform. The material eluted by benzene–chloroform was crystallized from acetone and petroleum ether to yield a small amount of crystalline material, designated as TR-2. Recrystallization from ethanol–methylenechloride yielded the pure base (0.015 g): mp 209–211°; $[\alpha]^{26}D$ +1.8° (*c* 1.45, pyridine); λ_{max} mμ (log ε) 225 (4.69) and 278 (4.14).

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.05; H, 7.51; N, 7.35.

Concentration of the mother liquors from TR-2 afforded crystals (0.070 g) of base TR-1: mp 186–187°; $[\alpha]^{26}D$ −5° (*c* 2.69, pyridine); λ_{max} mμ (log ε) 226 (3.58) and 277 (3.03).

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.82; H, 7.51; N, 7.46.

Registry No.—(+)-IV, 15622-69-2; (+)-VII, 15539-10-3; (+)-VIII, 15539-11-4; IX, 11040-85-0; (+)-XV, 15539-08-9; (±)-XV, 2122-39-6; (±)-vincadifformine, 11040-87-2.

(39) O. Clauser, K. Gesztes, and K. Szasz, *Tetrahedron Lett.*, 1147 (1962).

A Synthetic Approach to Some Steroidal Alkaloids

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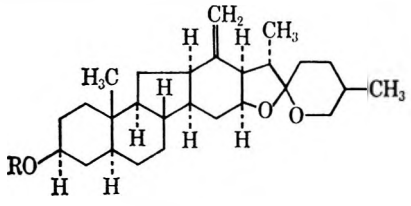
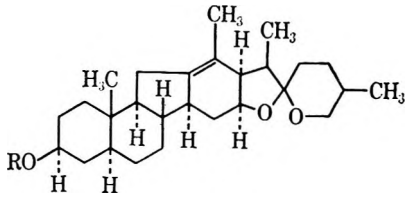
In an effort to prepare model compounds for the synthesis of cevine and veratramine, various reactions of C-nor-D-homosapogenins have been examined. The 3β-tetrahydropyranyl ether of $\Delta^{17a(18)}$-22a,5α-C-nor-D-homospirostene gave the 17aα,18 glycol with osmium tetroxide. Attempted oxidation to the hydroxy aldehyde gave only the 17α,18-nor ketone. Treatment of the $\Delta^{17a(18)}$ olefin with per acid gave a mixture of the 17aα,18- and 17aβ,18 oxides, which afforded the 18-aldehyde in low yield on rearrangement with acid. Conversion of this aldehyde into the 18-amine, *via* the oxime, and the attempted rearrangement of this amine to a pentacyclic cevine precursor are discussed. In an approach to veratramine, the aromatization of the D ring of $\Delta^{13(17a)}$-22a,5α-C-nor-D-homospirostan-3β-ol was attempted. These experiments gave either the 3-ketone or an aromatized ψ-sapogenin. The stereochemistry and spectral properties of these compounds are discussed.

The C-nor-D-homo steroids derived from hecogenin (**1a**, **2a**)[3,4] appear to be readily available and attractive starting materials for the partial synthesis of alkaloids of the cevine, jervine, and veratramine groups since the spiro ketal side chain with oxygen atoms attached at C-22 and C-26 would seem to permit a relatively simple approach to the E and F rings of a cevine model or the E ring of veratramine.

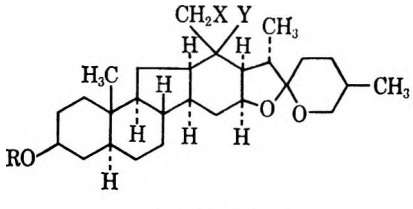


1a, R = H
b, R = C_5H_9O



2a, R = H
b, R = C_5H_9O

The initial goal in the proposed synthesis of the cevine nucleus was the conversion of exocyclic olefin **1** into a compound bearing a nitrogen atom at C-18 (**3a**). It was then planned that advantage could be taken of the "masked" carbonyl group at C-22 to form a pentacyclic Schiff base which could, hopefully, be converted into a deoxygenated cevine alkaloid derivative.



3a, X = NH_2; Y = H
b, X = OH; Y = OH; R = C_5H_9O
c, X = NH_2; Y = OH; R = C_5H_9O

Although the preparation of **1a** by the method developed by the Merck group[3a] proceeded well on a small scale, considerable difficulty was encountered in carrying out this preparation on larger quantities. Consequently, this procedure was modified by first forming the tetrahydropyranyl ether of hecogenin and reducing this to the rockogenin (12β-ol) derivative with lithium–liquid ammonia or sodium–1-propanol.[5] Conversion of rockogenin 3-tetrahydropyranyl ether into the methanesulfonate and reaction with potassium *t*-butoxide to give a mixture of **1b** and **2b** proceeded smoothly. The structure of **1b** was proven by conversion into the 3 acetate, which was identical with material prepared *via* the published procedure,[3a] whereas that of **2b** was confirmed by analysis and the similarity of the nmr spectrum to that reported for **2a**.[3b]

Attempted hydroboration of **1b** with either diborane generated *in situ*[6] or by externally generated diborane[7] gave complex mixtures of products. Although the successful hydroboration of a sapogenin has been reported,[8] repeated attempts to effect the hydroboration of this olefin gave only products in which the spiro ketal side chain has apparently been reduced.

Oxidation of **1b** with osmium tetroxide gave the 17aα,-18-diol. The stereochemistry at C-17a in this compound was tentatively assigned on the basis of a study of models of **1b**, and following the completion of our work, was confirmed by Coxon, *et al.*[9] Although analytical data (see Experimental Section) indicated that chromic acid–pyridine oxidation of this glycol gave the corresponding hydroxy aldehyde, which was then converted through the oxime into a compound which appeared to be an amino alcohol (**3c**), it was subsequently found that osmium tetroxide–hydrogen peroxide oxidation[10] of **1b** gave the same "hydroxy aldehyde." Since periodate

(1) Abstracted from the Ph.D. Dissertations of D. M. Alabran (1965) and A. C. Ruggles (1966), Clemson University, Clemson, S.C., presented in part at the Southeastern Regional Meeting of the American Chemical Society, Louisville, Ky., Oct 1966.

(2) NASA Fellow, 1965–1966.

(3) (a) R. Hirschmann, C. S. Snoddy, C. F. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4013 (1954); (b) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk [*Tetrahedron Lett.*, 119 (1965)] have recently revised the structure of tetrasubstituted olefin (**2a**).

(4) W. F. Johns [*J. Org. Chem.*, **29**, 2545 (1964)] and Y. Shimizu [*Tetrahedron*, **19**, 1027 (1963)] have also explored this synthetic route to the C-nor-D-homo steroidal alkaloids.

(5) J. W. Huffman, D. M. Alabran, T. W. Bethea, and A. C. Ruggles, *J. Org. Chem.* **29**, 2963 (1964). W. F. Johns[4] has accomplished much the same results through the use of rockogenin-3-pivalate. The Merck procedure suffers from first, the nonstereospecific lithium aluminum hydride reduction of hecogenin, and second, the partial formation of a 3β,12β-disuccinate in addition to the 3β ester.

(6) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **78**, 5695 (1956).

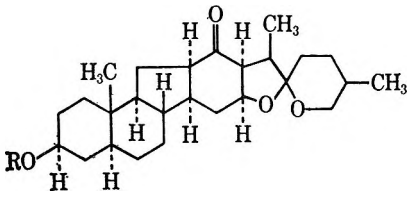
(7) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6428 (1959).

(8) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964).

(9) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **21**, 2489 (1965).

(10) R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963).

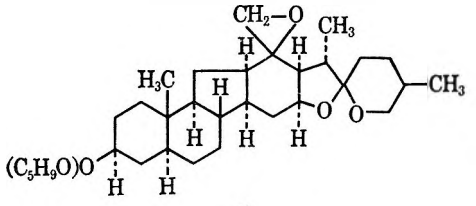
oxidation of **3b** also gave this compound, and reduction with sodium borohydride did not regenerate the diol but gave one of the stereoisomeric 17a alcohols, it is apparent that the "hydroxy aldehyde" is in fact the 18-nor ketone **4a**. Conversion of **4a** into the corresponding



4a, R = C_5H_9O
b, R = C_2H_3O

3β acetate **4b** gave material identical with that prepared by the Merck group.[3a,11] Attempted conversion of **3b** into the 18-methanesulfonate or tosylate also failed, giving only intractable material.

Since the route *via* the 17a,18 glycol did not appear promising, an attempt was made to obtain compounds similar to **3** through the 17a,18 oxides (**5**). Peracid



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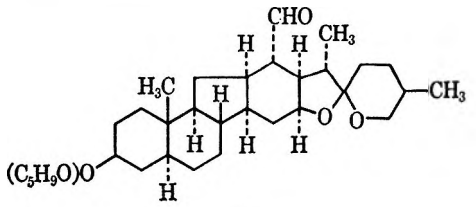
oxidation of **1a** (as the acetate) has been reported to give a mixture of two epoxides in a ratio of *ca.* 3:1.[3a] Although reaction of **1b** with *m*-chloroperbenzoic acid gave a solid of the correct formula and having a sharp melting point, it was subsequently found that this material was actually a mixture of two compounds (see Experimental Section). Attempted separation by chromatography failed, and when a larger quantity of alumina was employed, one stereoisomer was recovered, while the other was converted into a structural isomer. This compound showed a carbonyl peak at 5.79 μ and the absorption at 3.70 μ associated with an aldehyde. On the basis of these data, it was assumed that rearrangement of one of the epoxides had occurred to give the 18α-aldehyde (**6**) whereas the other was unaffected by chromatography. The stereochemistry at C-17a in **6** is assigned by analogy to that suggested for the corresponding 3-acetate by Coxon, *et al.*[9]



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On the basis of the relative amounts of the products from these experiments it was assumed that the major epoxide, that which was recovered unchanged, was the 17aβ oxide, while the isomer which was converted into the aldehyde was the 17aα isomer.[12] While this work was in progress a detailed account of the reactions of various compounds in this series appeared,[9] and this assumption was confirmed, not only on the basis of the course of the rearrangement, but on the position of the chemical shift of the C-18 protons, both of the recovered β epoxide and the α isomer, observed in the mixture.[9] The 18-aldehyde could be obtained preparatively by treating the original mixture of epoxides with aqueous perchloric acid which converts the α oxide into the aldehyde and the β isomer presumably to the allylic $\Delta^{13(17a)}$-18 alcohol,[9] which was not isolated.

Though the total amount of aldehyde which could be prepared by this route was small, owing principally to the unfavorable product ratio in the per acid oxidation of **1b**, sufficient material was obtained to investigate the conversion of **6** into the 18-amino compound. Although the oxime of **6** was obtained readily, this compound was apparently a mixture of *syn* and *anti* isomers which resisted purification. Reduction of the oxime with lithium aluminum hydride gave a noncrystalline material, assumed to be the 18-amine (**3a**, R = C_5H_9O) on the basis of its spectral properties. It is assumed that the aminomethyl group is α in this compound and that no isomerization occurred during the preparation of the oxime and reduction to the amine. A number of attempts to isomerize this material to the corresponding pentacyclic Schiff base gave either recovered starting material or the products of gross decomposition.

In view of the above difficulties encountered in isomerizing **3a** to a pentacyclic cevine precursor, and the unfavorable ratio of products obtained in the oxidation of the exocyclic olefin, this particular approach to the cevine alkaloids was abandoned.

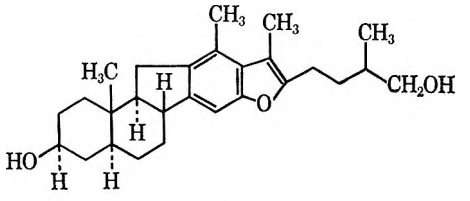
The somewhat less structurally complex steroid alkaloids of the jervine and veratramine group also contain a C-nor-D-homo steroid skeleton. It would appear that a rather simple dehydrogenation sequence based on the $\Delta^{13(17a)}$ olefin **2** could lead to a 22-oxo compound, which could in turn be converted into veratrine. Oxidation of **2a**, prepared by the Bamford–Stevens reaction of hecogenin tosylhydrazone,[3,4] with 2,3-dichloro-5,6-dicyanobenzoquinone or *o*-chloranil gave only the 3 ketone derived from **2a**. This compound could also be obtained by the chromic acid oxidation of **2a**. When the $\Delta^{13(17a)}$-3-tetrahydropyranyl ether (**2b**) was subjected to oxidation by either of the above quinones, only starting material was recovered. However, dehydrogenation of **2a** with selenium dioxide in acetic acid[13] followed by basic hydrolysis gave a compound $C_{27}H_{38}O_3$ in reasonable yield. The infrared spectrum of this material showed hydroxyl and aromatic absorption and the ultraviolet spectrum was that of a complex aromatic system. This compound formed a diacetate, the nmr spectrum of which showed three three-proton singlets (plus the acetate methyls) at δ 0.97, 2.30, and 2.52, and a single aromatic proton at δ 6.92. The rather characteristic resonances associated with the hydrogens adjacent to the spiro ketal oxygens (C_{16},C_{26}) were replaced by a multiplet at δ 3.96 and there were a considerable number of protons centered about 2.67, with a corresponding decrease in size of the high-field envelope. On the basis of

(11) The authors wish to thank Dr. Ralph F. Hirschmann of Merck Sharp and Dohme for a sample of 3β-acetoxy-17a-keto-22a-5α-C-nor-D-homo-18-norspirostene.

(12) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Aust. J. Chem.*, **18**, 759 (1965).

(13) W. M. Hoehn and C. R. Dorn, *J. Org. Chem.*, **30**, 316 (1965).

these data, it seemed probable that these compounds were C-nor-D-homo-5α-furostan-12,14,16,20(22)-tetraene-3β,26-diol (7) and its diacetate.[14] Since compound



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7 and its derivatives did not appear to be particularly attractive materials for a synthesis of veratramine, this approach to these alkaloids was also abandoned.[15]

The stereochemical assignments for the compounds in the C-nor-D-homo steroid series are largely due to the work of Coxon, *et al.*[9,12] These workers, as well as the Merck group,[3a] have attempted to explain the reactions of these compounds in terms of a ring-D boat conformation.[16] It has, however, been recently noted that ring D of jervine and its derivatives may exist in a distorted chair rather than a boat,[17] and a similar course of reasoning may be applicable to the C-nor-D homosapogenin. Coxon, *et al.*, have examined the rotatory dispersion curve of the 18-nor ketone (**4a**), which shows a negative Cotton effect, as expected for a compound with all substituents on the D ring in the β orientation.[12] The moderate amplitude of this Cotton effect ($a = -29$) is as consistent with a flattened chair conformation for ring D as for the boat form.[18] The lack of adequate model compounds for **4** make any definite conclusions regarding the conformation of this compound hazardous, however, the amplitude of the Cotton effect is well within the normal range for cyclohexanones and may tend to indicate that ring D is not a boat in this compound.

In an effort to prepare a simpler 18-nor-C-nor-D-homo ketone, the tetrahydropyranyl ether of 3α-hydroxypregnan-12-one[5] was reduced with sodium–1-propanol to the 12β alcohol. The stereochemistry of this compound was proven by conversion into the known 3α,12β-pregnanediol.[5] Conversion of this compound into the 12β-methanesulfonate, followed by treatment with potassium–*t*-butoxide[3a] gave material which, though nonpolar, did not show the absorption in the infrared around 6 and 11.2 μ associated with a terminal olefin. Tlc of this nonpolar material indicated that it was a mixture of two quite similar compounds, presumably the $\Delta^{13(17a)}$ olefin and an isomer. All attempts to separate these compounds or characterize them more fully failed.

(14) Following the completion of this work, W. F. Johns and L. Laos [*J. Org. Chem.*, **30**, 4220 (1965)] reported the preparation of this compound by an alternate route and studied its reactions in some detail.

(15) It seems probable that the driving force to form the ψ-sapogenin system is far greater than that to simply open the spiro ketal, forming an acyclic hydroxy ketone. Virtually the only success in utilizing the masked carbonyl of a sapogenin for the synthesis of steroid alkaloid is the synthesis of solasodine from diosgenin reported by F. C. Uhle [*ibid.*, **27**, 656 (1962)].

(16) From a study of Dreiding models the *cis* fused C and E rings of these compounds hold the D ring in a rigid boat rather than a twist conformation with a variety of pseudo-rotational forms.

(17) T. Masumune, N. Sato, K. Kobayashi, I. Yamazaki, and Y. Mori, *Tetrahedron*, **23**, 1591 (1967).

(18) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, pp 88–89, and references cited therein.

Additional insight into the conformation of ring D in these compounds may be obtained from the nmr spectra of the compounds in this series. In particular, the chemical shifts of the C-18 methyl protons in the two stereiosiomeric 17a-hydroxy-22a,5α-C-nor-D-homospirostan-3β-ols are of interest.[9,12] In both the C-18 methyl protons appear at δ 1.15. If the D ring were in either a boat or an undistorted chair conformation it would be expected that the chemical shifts for the protons in the isomer with the axial or "flagpole" methyl group would show a downfield shift. Since there is no difference in chemical shift, it seems probable that the D ring in these compounds also exists as a flattened chair. Although the reactions of all these compounds are most conveniently interpreted in terms of a boat form D ring, a study of models with this ring as a flattened chair indicates that this conformation will also give the reaction products observed by Coxon, *et al.*[9,12]

The nmr spectra of the compounds prepared in the course of this work are unexceptional and are summarized in Table I. It should be noted that the use of the

TABLE I

CHEMICAL SHIFTS OF SELECTED PROTONS IN THE C-NOR-D-HOMOSAPOGENINS[a]

Compd	C-18 protons	C-19 methyl	C-21 methyl (doublet)
1b	4.78 (m)[b]	0.80	1.09 (J = 7)
2b	1.70	0.80	1.18 (J = 7)
17aα,18-Diol	3.68 (m)	0.81	1.03 (J = 7)
4a		0.80	1.19 (J = 8)
5 (α oxide)	2.76 (d, J = 1)	0.77	0.98 (J = 7)
5 (β oxide)	2.42 (d, J = 1)	0.77	0.98 (J = 7)
3a (R = C_5H_9O)	2.08 (d, J = 3)	0.78	0.82 (J = 7)

[a] All spectra were run in deuteriochloroform using tetramethylsilane as internal standard. Signals are given in parts per million relative to this standard (δ). [b] Partially obscured by the signal from the 2 proton of the tetrahydropyran ring.

3-tetrahydropyranyl group as a blocking group complicates the nmr spectra to the point where it is very difficult to assign rigorously the peaks in the δ 3–5 region. The 2 proton in the tetrahydropyran ring appears as a multiplet centered about δ 5.7 and the protons at the 5 position of the tetrahydropyran and C-3, C-16, and C-26 of the sapogenin appear as an envelope from δ 3.2 to 4.2.

Experimental Section[19]

Rockogenin 3-Tetrahydropyranyl Ether 12-Methanesulfonate.—To a stirred solution of 1.0 g of the 3-tetrahydropyranyl ether of rockogenin[5] in 12 ml of dry pyridine was added 0.7 ml of methansulfonyl chloride. The resulting red solution was allowed to stand at room temperature 24 hr, poured slowly into ice water, and the light brown precipitate collected. Recrystallization from acetone gave 0.75 g (70%) of white crystals, mp 132–134° dec.

Anal. Calcd for $C_{33}H_{54}O_7S$: C, 66.63; H, 9.15. Found: C, 66.57; H, 9.16.

$\Delta^{17a(18)}$-22a,5α-C-Nor-D-homospirostene 3β-Tetrahydropyranyl Ether (1b).—To a stirred solution of potassium *t*-butoxide (from 0.34 g of potassium in 31 ml of *t*-butyl alcohol) was added 1.0 g

(19) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were run as potassium bromide pellets, using a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Nuclear magnetic resonance spectra were run in deuteriochloroform solution using a Varian A-60 spectrometer. Specific rotations were determined in chloroform, employing a Rudolph Model 70 polarimeter. Optical rotatory dispersion data were obtained using a JASCO Model ORD/UV-5 spectropolarimeter. Analyses were performed by Galbraith Laboratories, Knowville, Tenn.

of the above methanesulfonate. The solution was heated at reflux under nitrogen for 18 hr, during which time five additional ml of *t*-butyl alcohol were added. The reaction mixture was cooled, diluted with 2 ml of water, 7.5 ml of tetrahydrofuran, and 15 ml of methanol and heated under reflux for 2 hr more. The solvents were removed at reduced pressure; water was added and the precipitated solid collected and washed free of base, leaving a white solid, mp 142–149°. Recrystallization from acetone gave 83% of the exocyclic olefin: mp 186–187°, $[\alpha]^{27}D$ −63° (*c* 1.05).

Anal. Calcd for $C_{32}H_{50}O_4$: C, 77.06; H, 10.10. Found: C, 77.03; H, 10.23.

There was also obtained from the mother liquors a small quantity of a second compound, mp 161–164°, which did not show the infrared absorption at 11.2 μ typical of exocyclic olefins. The combined mother liquors from several runs gave a larger quantity of this material, the $\Delta^{13(17)}$ isomer **2b**, which crystallized from acetone as small needles: mp 184–186°; $[\alpha]^{27}D$ −58 (*c* 0.601).

Anal. Calcd for $C_{32}H_{50}O_4$; C, 77.06; H, 10.10. Found: C, 77.34; H, 10.27.

Treatment of the 3-tetrahydropyranyl ether of the exocyclic olefin with acetic acid gave the 3 acetate,[3a] mp and mmp 221–225°.

3-Tetrahydropyranyl Ether of 3β,17aα,18-Trihydroxy-22a,5α-C-nor-D-homospirostane (3b).—To a solution of 1.0 g of the exocyclic olefin **1b** in 27 ml of dry pyridine was added 1.0 g of osmium tetroxide. The brown solution was maintained at room temperature and stirred constantly. After 36 hr, 30 ml of water, 2.0 g of sodium bisulfite, and 12 ml of pyridine were added and the stirring was continued for 2 hr. The reaction mixture was extracted with chloroform. The chloroform extracts were washed with water and dried and the solvent removed *in vacuo* leaving a black oil. This oil was dissolved in 200 ml of ethanol, 3.4 g of sodium sulfite and 77 ml of water were added, and the mixture was heated under reflux. After 2 hr, 3 ml of 30% sodium hydroxide was added, and heating continued 2 hr. The mixture was evaporated to dryness, the residue dissolved in ether, washed with water, dried, and the solvent removed at the water pump. The resulting yellow oil was dissolved in hot acetone, water was added to turbidity, and following cooling, there was obtained 92% of glycol, mp 158–160°.

Anal. Calcd for $C_{32}H_{52}O_6$: C, 72.14; H, 9.84. Found: C, 72.24; H, 9.60.

3-Tetrahydropyranyl Ether of 3β-Hydroxy-17a-keto-22a,5α-C-nor-D-homo-18-norspirostane. A.—To 100 ml of slowly stirred pyridine was added 10 g of chromic oxide, followed by 0.5 g of glycol **3b**, and the mixture stirred at room temperature for 16 hr. Water was added, the mixture extracted with ether, the ether layer washed with several portions of water and dried, and the solvent removed at reduced pressure. The residue was recrystallized from acetone and water to give 81% yield of white solid, mp 186–188°, which showed carbonyl absorption at 5.84 μ.

Anal. Calcd for $C_{31}H_{45}O_5$: C, 74.36; H, 9.66. Found:[20] C, 74.01; H, 9.84.

B.—To a solution of 0.725 g of the 17a,18 glycol **3b** in 52 ml of ethanol was added 0.336 g of periodic acid dihydrate in 3 ml of water, and ethanol was added until the solution became homogeneous. The reaction mixture was allowed to stand overnight at room temperature, the solvent removed *in vacuo* at room temperature and the residue taken up in ether. The ethereal solution was washed with 5% sodium bicarbonate and water and dried, and the solvent removed at aspirator pressure to leave a white solid. Recrystallization from acetone and water gave material identical with that obtained in part A.

C.—To solution of 0.1 g of exocyclic olefin **1b** in 199 ml of *t*-butyl alcohol and 25 ml of 30% hydrogen peroxide was added 3 ml of 0.02 *M* osmium tetroxide in *t*-butyl alcohol.[10] The reaction mixture was stirred at room temperature for 48 hr and concentrated at reduced pressure and the residue dissolved in ether. The ethereal solution was washed with water and 5% sodium bicarbonate and dried and the solvent removed at reduced pressure. Recrystallization from acetone and water gave 0.075 g (74%) of nor ketone, mp and mmp 186–188°.

3β-Acetoxy-17a-keto-22a,5α-C-nor-D-homo-18-norspirostane 4b.—A solution of 0.045 g of the 3-tetrahydropyranyl ether 17a-ketone **4a** in 5 ml of acetic acid was heated at reflux for 24 hr, the solvent removed at reduced pressure and the residue dissolved in methylene chloride. After washing with 5% aqueous sodium bicarbonate and water, the solution was dried and the solvent removed leaving a yellow glass. Recrystallization from acetone–water gave 0.030 (67%) of white crystals, mp 220–222°. A sample of this compound supplied by Dr. R. F. Hirschmann of Merck Sharp and Dohme had mp 229–230°. The infrared spectra of the two samples were identical and a mixture melting point was 227–230°. The difference in melting point is apparently due to differences in crystal structure. The Merck sample exists as small needles, while that prepared in this laboratory is thin plates. The ORD curve (methanol) of this compound shows the following values: $[\alpha]_{500}$ −34°, $[\alpha]_{301}$ −480 and $[\alpha]_{268}$ +840. Coxon, *et al.*, reported $[\alpha]_{298}$ −645 and $[\alpha]_{263}$ +20.

3-Tetrahydropyranyl Ether of 3β,17aξ-Dihydroxy-22a,5α-C-nor-D-homo-18-norspirostane.—To a solution of 0.05 g of the nor ketone **4a** in the minimum amount of methanol was added 0.1 g of sodium borohydride and the mixture heated at reflux for 1 hr. The reaction mixture was diluted with water, acidified with concentrated hydrochloric acid, and extracted with methylene chloride. The organic layer was washed with water and dried and the solvent removed *in vacuo* to give 0.04 g (80%) of solid material. Recrystallization from acetone gave the alcohol, mp 216–218°.

Anal. Calcd for $C_{31}H_{50}O_5$: C, 74.06, H, 10.02. Found: C, 73.81; H, 9.94.

3-Tetrahydropyranyl Ether of 3β-Hydroxy-17a-oximino-22a,-5α-C-nor-D-homo-18-norspirostane.—To a solution of 0.2 g of the 18-nor ketone **4a** in 2 ml of 10% sodium hydroxide, 2 ml of water, and sufficient ethanol to make the solution homogeneous was added 0.5 g of hydroxylamine hydrochloride. The reaction mixture was heated at reflux for 3 hr, concentrated at reduced pressure and diluted with water. The oxime separated as an oil which resisted purification and was used as isolated for the next step.

3-Tetrahydropyranyl Ether of 3β-Hydroxy-17ξ-amino-22a,5α-C-nor-D-homo-18-norspirostane.—To a solution of 0.5 g of the oxime in 20 ml of dry ether–tetrahydrofuran (1:1) was added 1.0 g of lithium aluminum hydride and the mixture stirred at room temperature for 1 hr. The excess lithium aluminum hydride was decomposed with water, the layers separated, the ethereal solution dried, and the solvent removed at reduced pressure to give 0.5 g of brown oil. The oil was taken up in chloroform and chromatographed on neutral alumina. Elution with methanol gave 0.35 g (70%) of white solid, mp 149–151°, after recrystallization from methanol.

Anal. Calcd for $C_{31}H_{51}NO_4 \cdot CH_3OH$: C, 72.27; H, 10.05; N, 2.63. Found: C, 72.15; H, 10.00; N, 2.90.

Per Acid Oxidation of $\Delta^{17a(18)}$-22a,5α-C-Nor-D-homospirostene 3-Tetrahydropyranyl Ether.—To a solution of 0.25 g of the olefin **1b** in the minimum amount of chloroform was added dropwise a solution of 0.11 g of *m*-chloroperbenzoic acid also in the minimum amount of chloroform. The reaction mixture was stirred at room temperature for 45 min and then 1.0 g of sodium sulfite in 9 ml of water was added with vigorous stirring. The reaction mixture was diluted with chloroform, washed with successive portions of water and 5% sodium bicarbonate and dried and the solvent removed leaving a colorless solid. Recrystallization from acetone gave 0.13 g (52%) of white solid, mp 176–177°.

Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.59; H, 9.68.

Although this material was sharp melting and appeared homogeneous, tlc (silica gel G) showed that it actually consisted of two compounds. When 2.20 g of this material was dissolved in 1:1 hexane–benzene and chromatographed on 200 g of Merck acid-washed alumina, elution with the hexane–benzene mixture gave first a trace of unoxidized olefin, then 1.5 g of homogeneous (tlc) 17aβ,18 epoxide **5**, mp 182–183°, after recrystallization from acetone.

Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.53; H, 9.91.

Elution with benzene gave 0.5 g of 17aα-formyl-22a,5α-C-nor-D-homospirostane 3-tetrahydropyranyl ether **6**, mp 158–159°, after recrystallization from hexane.

Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.78. Found: C, 74.40; H, 9.98.

When a smaller ratio of alumina to compound was employed, the mixture of α and β epoxides was recovered unchanged and the

(20) Satisfactory analytical data could not be obtained for this compound. The original analysis gave C, 72.45; H, 9.43 (calcd for $C_{32}H_{50}O_6$: C, 72.64; H, 9.64). These data led to the incorrect conclusion that this material was the 17a-formyl-17a-hydroxy compound.

use of either BioRad neutral alumina or basic Merck alumina gave results similar to that observed with the acid-washed absorbent.

The acid-catalyzed rearrangement of the mixed 17aα and 17β 18 epoxides was accomplished by treating a solution of 1 g of mixed epoxides in 60 ml of methylene chloride and 120 ml of acetone with 1 ml of 1.5 *M* aqueous perchloric acid. The solution was allowed to stand at 20° for 10 min, water was added, and the product was extracted into methylene chloride and dried over magnesium sulfate. Evaporation of the solvent gave an oil which was taken up in benzene and chromatographed on Merck alumina. Elution with benzene and recrystallization from hexane gave 0.15 g of aldehyde **6**, mp 158–159°, identical with that obtained above from chromatography of the mixed epoxides.

18-Oximino-22a,5α,17β-C-nor-D-homospirostane 3β-Tetrahydropyranyl Ether.—A solution of 0.20 g of the 18-aldehyde **6**, 0.40 g of hydroxylamine hydrochloride, and 0.80 g of sodium acetate in 80 ml of methanol was heated at reflux for 16 hr. The solution was cooled, 80 ml of water added, and the solid product collected. Recrystallization from methanol gave 0.21 g of white solid, mp 155–165°. Repeated recrystallization from a variety of solvents failed to give sharp melting material and tlc showed two components, presumably the *syn* and *anti* oxime, having rather similar R_f values. The infrared spectrum showed absorption at 3.05 and 6.20 μ and the absence of a carbonyl band.

18-Amino-22a,5α,17β-C-nor-D-homospirostane 3β-Tetrahydropyranyl Ether 3c.—To a suspension of 0.10 g of the oxime in 30 ml of ether was added 0.075 g of lithium aluminum hydride and the reaction mixture stirred at room temperature overnight. The excess hydride was destroyed by the dropwise addition of water. The precipitated salts were filtered off, and the ethereal solution was dried and the solvent removed at reduced pressure leaving 0.018 g of oil. Although this material was essentially homogeneous by tlc it could not be induced to crystallize. The infrared spectrum showed absorption at 3.10 and weak absorption in the 6.1–6.3-μ region indicative of a primary amine.

Attempted Rearrangement of 22a,5α,17β-C-nor-D-homospirostan-18-amino-3β-tetrahydropyranyl Ether (3c). A.—A solution of 0.010 g of the 18-amine was heated in ether containing 1 drop of perchloric acid for 10 min. Evaporation of the solvent gave an oil which was shown to be starting material. This procedure was repeated using the reaction times of 30 min, 2 hr, and overnight. Starting material was obtained in each reaction.

B.—To a solution of 0.01 g of 18-amine **3c** in 1 ml of methylene chloride was added 1 drop of boron trifluoride etherate. The solution was allowed to stand overnight. The solution was neutralized with sodium hydroxide solution and the methylene chloride fraction separated and dried over magnesium sulfate. Evaporation of the solvent gave an intractable black gum.

C.—A solution of 0.050 g of 18-amine **3c** in 6 ml of acetic acid and 1 drop of perchloric acid was heated on a steam bath for 2 hr. The solution was cooled and neutralized with aqueous sodium hydroxide. The solution was extracted with ether and evaporation of the ether yielded a yellow glass. The infrared spectrum of the glass showed a carbonyl peak at 5.76 and bands at 8.04, 11.11 and 11.57 μ indicating that the spiro ketal was intact and the tetrahydropyranyl ether had been replaced by an acetate group.

Attempted Aromatizations of 3β-Hydroxy-$\Delta^{17(17a)}$-22a,5α-C-nor-D-homospirostene (2a). A.—A solution of 0.47 g of the olefin **2a** and 0.25 g of *p*-chloranil in 2 ml of *p*-xylene was heated at reflux for 20 hr. After cooling the mixture was diluted with hexane and chromatographed on an alumina column. Elution with various solvents gave a yellow oil which could not be crystallized.

B.—A solution of 0.47 g of the olefin **2a** and 0.23 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 2 ml of xylene was heated at reflux for 20 hr. The reaction mixture was cooled, extracted with hexane and evaporated to dryness leaving a yellow solid. The product, $\Delta^{13(17a)}$-22a,5α-C-nor-D-homospirostene-3-one, was crystallized from acetone giving 0.15 g (32%) of pale yellow crystals, mp 205–210°, raised to 208–210° upon further recrystallization. The infrared spectrum of the product showed carbonyl absorption at 5.86 μ.

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77. Found: C, 78.36; H, 9.86.

C.—When the reaction was repeated using *o*-chloranil, the same product was obtained in low yield.

$\Delta^{13(17a)}$-22a,5α-C-Nor-D-homospirosten-3-on.—A solution of 0.2 g of hydroxyolefin **2a** in 2.0 ml of acetone was treated dropwise with Kiliani's reagent until a slight permanent orange color was obtained. The solution was allowed to stand for 5 min at room temperature, several drops of water were added and the solution was filtered. The filtrate was treated with 0.1 ml of 1 *N* sodium hydroxide and 8 ml of water, the solid mass collected and recrystallized from acetone to give 0.12 g (60%) of ketone, mp 208–210°. The infrared spectrum was identical with the spectrum of both attempted aromatization products and the mixture melting point was 208–210°.

C-Nor-D-homo-5α-furostan-12,14,16,20(22)-tetraene-3β,26-diol.—To a solution of 1.0 g of endocyclic olefin in 20 ml of 90% acetic acid at 90°, 1.8 g of selenium dioxide was added. The dark solution was stirred and heated at 100–110° for 4 hr. The solution was then cooled to 80° and 1.3 g of finely powdered zinc was added. The mixture was heated to 90°, stirred for 4 hr, and filtered while hot, and the cake washed with 40 ml of hot acetic acid. The acetic acid was removed *in vacuo*. The residue was dissolved in 50 ml of 1 *N* methanolic potassium hydroxide solution and refluxed for 2 hr. Water was added and the red oil obtained was taken up in methylene chloride. Evaporation of the solvent gave 0.5 g of crystals of **7** which were collected and recrystallized from methanol, mp 192–195°. The analytical sample, mp 198–200°, was crystallized from methylene chloride. Johns[14] reports mp 202–203°.

Anal. Calcd for $C_{27}H_{38}O_2$: C, 78.98; H, 9.33. Found: C, 78.98; H, 9.51.

Chromatography of 1.49 g of the residue remaining from the crystallization of the furostantetraene on 60 g of Merck acid-washed alumina, deactivated with 5 ml of water, gave 0.49 g of unoxidized olefin **2a**, eluted with benzene. Elution with methylene chloride gave an additional 0.49 g of tetraene, mp 193–196°.

Since the tetraene was quite insoluble in common solvents, 0.08 g was heated for 20 hr on the steam bath in 5 ml of acetic anhydride and 5 ml of pyridine. The reaction mixture was poured into water and extracted with methylene chloride; the extracts were washed with water and dilute hydrochloric acid. Drying and removing the solvent gave an off-white solid, which on recrystallization from aqueous methanol gave the 3β,26 diacetate, mp 132–133° (lit.[14] mp 139–140°).

Anal. Calcd for $C_{31}H_{42}O_5$: C, 75.27; H, 8.56. Found: C, 75.45; H, 8.67.

The nmr spectrum of this compound showed the following peaks in addition to the saturated aliphatic envelope: δ 0.97 (s, C-19 methyl), 1.02 (d, J = 6, C-27 methyl), 2.04 (s, acetate methyls), 2.30 (s, C-18 methyl), 2.51 (s, C-21 methyl), multiplet centered about 2.67 (benzylic protons at C-8, C-11, and C-22), 3.96 (C-26, X_2 portion of an AX_2 pattern), 4.72 (C-3, CH–O, broad multiplet), and 6.92 (broadened s, C-14). The ultraviolet spectrum (CH_3OH) showed λ_{max} 256 mμ (log ε 4.25), 263 (4.24), 284 (3.84), 291 (3.81), 296 (3.83).

Tetrahydropyranyl Ether of 3α-Hyroxy-5β-pregnan-12-one.—To a suspension of 2.0 g of 3α-hydroxy-5β-pregnan-12-one[5] in 20 ml of dihydropyran was added 5 drops of phosphorus oxychloride with vigorous shaking after each drop. The reaction mixture was allowed to stand at 25–30° for 2 hr, 8 ml of 5% potassium hydroxide in methanol was added, and the mixture was poured into 40 ml of 25% aqueous methanol. The product was collected and after washing with 25% aqueous methanol was recrystallized from methanol to give 1 g (41%) of the tetrahydropyranyl ether as white crystals, mp 175–177°.

Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51. Found: C, 77.74; H, 10.56.

3-Tetrahydropyranyl Ether of 5β-Pregnane-3α,12β-diol.—To a solution of 1 g of the 3α-tetrahydropyranyl ether in 130 ml of *n*-propyl alcohol was added 10 g of sodium. The solution was heated at reflux for 1 hr, diluted with water, acidified with dilute hydrochloric acid, and extracted with methylene chloride. Upon evaporation of the methylene chloride a dark brown solid was obtained. Recrystallization from acetone gave 0.47 g (47%) of a white solid, mp 167–168°.

Anal. Calcd for $C_{26}H_{44}O_3$: C, 77.18; H, 10.96. Found: C, 77.43; H, 10.93.

5β-Pregnane-3α,12β-diol.—A solution of 0.4 g of tetrahydropyranyl ether from the sodium–alcohol reduction was heated at reflux in 5 ml of acetic acid for 24 hr, then evaporated to dryness *in vacuo*. The residue was dissolved in ether, washed with saturated sodium carbonate solution, dried, and the solvent removed leaving a colorless oil. Hydrolysis of the product by

heating in 5 ml of 1 *N* potassium hydroxide in methanol for 3 hr gave 0.22 g (53%) of 5β-pregnane-3α,12β-diol,[5] mp and mmp 165–168°.

3-Tetrahydropyranyl Ether of 3α-Hydroxy-12β-methanesulfonoxy-5β-pregnane.—To a chilled (0°) solution of 0.10 g of the 3-tetrahydropyranyl ether of the pregnan-12β-ol in 2 ml of pyridine was added slowly a chilled solution of 0.20 ml of methanesulfonyl chloride in 2 ml of pyridine. The reaction mixture was allowed to warm slowly to room temperature, and then to stand at room temperature for 18 hr. The pale brown solution was poured into ice water, then extracted with two portions of methylene chloride. The extracts were combined and washed with successive portions of water, dilute hydrochloric acid, and water. After drying the solvent was removed *in vacuo* with gentle warming to yield 0.11 g of pale yellow glass. This material is very unstable, both thermally and in solution, and decomposed on attempted purification. When 0.10 g was treated with potassium *t*-butoxide (from 0.10 g of potassium) in 10 ml of *t*-butyl alcohol, in the manner described for the rearrangement of the rockogenin derivative (see above), there was obtained 0.030 g of pale yellow, nonpolar (eluted with hexane–benzene 2:1 from alumina) material. Tlc (silica gel G) showed that this material was a mixture of two compounds in approximately equal amounts, and with very similar R_f values. The infrared spectrum did not show the peaks at 6.1 and 11.2 μ associated with a $\Delta^{17a,18}$ olefin.

Registry No.—**1b**, 15539-07-8; **2a** (3-one) (mp 208–210°), 15538-94-0; **2b**, 15538-95-1; **3a**, 15538-96-2; **3b**, 15538-97-3; **4a**, 15538-98-4; **4b**, 15538-99-5; **5** (17aα-oxide), 15622-67-0; **5** (17aβ-oxide), 15539-00-1; **6**, 15656-71-0; **7**, 4653-71-8; **7** diacetate, 4866-48-2; 3-tetrahydropyranyl ether of 3β,17aξ-dihydroxy-22a,5α-D-nor-D-homo-18-norspirostane, 15539-03-4; 3-tetrahydropyranyl ether of 3β-hydroxy-17aξ-amino-22a,5α-C-nor-D-homo-18-norspirostane, 15539-04-5; 3-tetrahydropyranyl ether of 3α-hydroxy-5β-pregnan-12-one, 15539-05-6; 3-tetrahydropyranyl ether of 5β-pregnane-3α,12β-diol, 15539-06-7; rockogenin-3-tetrahydropyranyl ether 12-methanesulfonate, 11040-86-1.

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The Thermal Decomposition of Tri-*sec*-butyl Phosphate[1]

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Organic phosphorus compounds containing *sec*-butyl groups are of practical importance in the solvent extraction technology of uranium.[2] No information has apparently been published as to their thermal stabilities; it therefore seemed of interest to compare the thermal stability of a secondary isomer with that of its normal counterpart.

The faster thermal dealkylation rate of tri-*sec*-butyl phosphate (TsBP) in comparison with tri-*n*-butyl phosphate (TBP) was qualitatively observed in earlier work.[3] Substantially faster thermal decomposition rates have been reported by Emerson, Craig, and Potts[4] for sulfoxides having both primary and secondary alkyl groups than for those containing only primary groups. A comparison of gaseous products from pyrolysis of the partial esters di-*sec*-butyl phosphoric acid (HDsBP) and di-*n*-butyl phosphoric acid (HDBP) has been made by Hanneman and Porter.[5] Our work, reported here, compares the thermal decomposition rates of, and isomeric olefin yields from, TsBP with those of TBP.[6,7]

The composition of butenes produced when TsBP was isothermally decomposed until no more gas evolved is shown in Table I. The reaction was run in the temperature range 180–241°. Very little variation in composition was found: butene-1 comprised 14–17% of the mixture, *trans*-butene-2, 44–48%, and *cis*-butene-2, 38–40%. Only 0.1% isobutylene was formed.

TABLE I

COMPOSITION OF BUTENES FROM COMPLETE PYROLYSIS OF TRI-*sec*-BUTYL PHOSPHATE (TsBP) AT VARIOUS TEMPERATURES

Temp, ±1°	Time, hr	Yield, %	Isomeric abundance, % Butene-1	Iso-butylene	*trans*-Butene-2	*cis*-Butene-2
180	6.8	96	13.8	...	48.0	38.2
200	1.4	88	15.6	...	45.2	39.2
212	0.6	90	17.3	...	44.5	37.8
241	0.05	90	15.1	0.1	44.3	40.5

Under similar conditions TBP yielded 54–55% butene-1, 25–26% *trans*-butene-2, 19–20% *cis*-butene-2, and 0.4% isobutylene.[7] Reaction time was considerably shortened at higher temperatures. At 180° nearly 7 hr were required for complete decomposition (cessation of gas evolution) but at 241° only 2–3 min were required. At this latter temperature, by comparison, TBP took about 2.5 hr to decompose completely.[7]

The composition of the butenes varied greatly from beginning to end of the pyrolysis (Table II). When only 2.5% of the TsBP had decomposed, half of the gas formed was butene-1 and the remainder was distributed between *cis*- and *trans*-butene-2. As the percentage of pyrolytically formed acid in the reaction mixture increased, the amount of butene-1 formed decreased. The last 10% of gas evolved contained only 8.6% butene-1. The latter stage in the pyrolysis was also the only one in which isobutylene was produced (0.2%).

The rates of formation of HDsBP by thermal action on TsBP at several temperatures are shown in Table III. At comparable temperatures the rates are over

(1) Research sponsored by the U. S. Atomic Energy Commission under contract with the Union Carbide Corp.

(2) (a) W. H. Baldwin and C. E. Higgins, Oak Ridge National Laboratory Chemistry Division Quarterly Progress Report for Period Ending March 31, 1951, ORNL-1053, 1951, p 83–88; also ORNL-1338, July 24, 1952 (declassified March 11, 1957). (b) T. V. Healy and J. Kennedy, *J. Inorg. Nucl. Chem.*, **10**, 128 (1959). (c) T. H. Siddall, III, *J. Amer. Chem. Soc.*, **81**, 4176 (1959). (d) C. A. Blake, Jr., A. T. Gresky, J. M. Schmitt, and R. G. Mansfield, Oak Ridge National Laboratory, ORNL-3374, Jan 8, 1963; *Chem. Abstr.*, **58**, 8597 (1963). (e) L. L. Burger, *Nucl. Sci. Eng.*, **16**, 428 (1963).

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(5) W. W. Hanneman and R. S. Porter, *ibid.*, **29**, 2996 (1964).

(6) C. E. Higgins and W. H. Baldwin, *ibid.*, **26**, 846 (1961).

(7) C. E. Higgins and W. H. Baldwin, *ibid.*, **30**, 3173 (1965).

TABLE II

BUTENE COMPOSITION AT VARIOUS STAGES OF TsBP DECOMPOSITION

Decomposn range,[a] %	Temp, ±1°	Heating time, hr	Butene composition			
			Butene-1	Isobutylene	*trans*-Butene-2	*cis*-Butene-2
0–2.5	184	2.4	49.1	...	31.5	19.4
0–4	200	0.7	45.8	...	32.9	21.3
0–6	200	0.9	40.1	...	35.4	24.5
0–10	200	1.1	32.3	...	38.9	28.8
0–17	200	1.3	24.9	...	42.6	32.5
0–29	200	1.5	19.3	...	45.8	34.8
0–66	190	3.7	18.0	...	45.7	36.2
0–100[b]	200	1.4	15.6	...	45.2	39.2
65–82	200	~0.01	8.6	...	48.5	42.4
90–100	208	~0.001	8.6	0.2	50.0	41.2

[a] Percentage of total butyl groups. [b] Table I (at 100% decomposition 88% of the butyl groups were recovered as butene isomers).

TABLE III

SPECIFIC REACTION RATES FOR THERMALLY INDUCED FORMATION OF HDsBP FROM TsBP

Temp, °C	180	190	200	212
$k \times 10^5$ sec^{-1}	0.84	1.8	4.1	12

100 times faster than those for the production of HDBP from TBP.[6] The values found apply only in the early stage of decomposition. Beyond 6–8 mol % HDsBP, acid-catalyzed decomposition became increasingly evident.

Pot residues at various stages of TsBP decomposition were analyzed as previously described[3] to see if any rearrangements had occurred in the residual alkyls. TsBP was heated at 190–200° until 13, 68, and 82% of the butyl groups had been eliminated. No rearrangement was detected in the remaining alkyls; the *sec*-butyl groups had not isomerized.

The alkyl groups from the TsBP and its pot residues decomposed to lighter fragments during the HBr dealkylation to a greater extent than the more thermally stable TBP. Where 99.7% pure *n*-butyl bromide was obtained from TBP,[3] 97–98% *sec*-butyl bromide was obtained from TsBP. The butyl bromide product from the 82% decomposed TsBP was only 94% pure. Most (4%) of the remainder appeared to be ethyl bromide.

Experimental Section

Materials.—TsBP was prepared by the reaction of purified *sec*-butyl alcohol and phosphorus oxychloride in the presence of pyridine.[8,9] The product was distilled at 94–97° at 2 mm: d^{25}_4 0.9652; n^{25}D 1.4175; MR 69.45 (calcd 69.74).

The purity of the *sec*-butyl alcohol used was checked by gas chromatography using a 1-m column of dinonyl phthalate (3 g/10 g of Celite 545, 30–50 mesh) at 110° and a carrier gas flow rate of 50 ml of helium/min. The *sec*-butyl alcohol was 99.6% pure. No butyl groups other than *sec*-butyl were found in the TsBP by the HBr dealkylation method and gas chromatography of the dealkylation products.[3] The TsBP was washed with dilute alkali and water and dried *in vacuo* before use.

Pyrolysis.—Rate measurements were made on 0.5–1-g samples (2–4 mmol, dry, acid free, degassed) of TsBP in the temperature range 180–241° (temperatures are corrected). The equipment was the same as described in earlier work.[7] The bath, preheated to the desired temperature, was raised about the reaction vessel to the same height on all runs. A mercury-filled gas buret and leveling bulb were used for the volume measurements. Rates were obtained by observing the amount of gas (butene isomers) produced as a function of time at a given temperature; values of $\ln [a/(a - x)]$ were plotted against heating time. In the expression $\ln [a/(a - x)]$, a is the initial concentration of TsBP ($a = 1$) and x, the mole fraction converted into HDsBP, was obtained assuming the HDsBP concentration to be equivalent to olefin production in the early stage of decomposition.

A larger sample (6 g, 23 mmol) of TsBP was decomposed 82% at 200° for the purpose of checking the pot residue for possible alkyl isomerization. Dealkylation with 48% HBr was done as before.[3]

Butene yields from the complete degradation of TsBP until no more gas evolved were high (88–96%). Yields were based on the olefin volume produced, converted into STP, compared with the theoretical volume possible.

Analysis.—Composition of the butenes resulting from pyrolysis of TsBP was detected gas chromatographically. Composition as a function of heating time was determined using a 13-ft column of *o*-nitrophenetole at ambient temperature as previously described.[10] Homogeneous samples of gases resulting from complete decomposition were analyzed using an ice-cooled, 24-ft column of propylene carbonate[11] (4 g/10 g of Celite 545, 30–50 mesh) at a helium flow rate of 40 ml/min. This column ensured detection of any isobutylene which might be formed during pyrolysis.

Butyl bromide composition after dealkylation of TsBP, both from starting material and after partial decomposition (13, 68, and 82%), was determined as before[3] using the method of Harris and McFadden.[12]

Registry No.—Tri-*sec*-butyl phosphate, 2528-45-2.

(8) C. R. Noller and G. R. Dutton, *J. Amer. Chem. Soc.*, **55**, 424 (1933); "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, 1943, p 109.

(9) We are indebted to Thomas W. Cole, Jr., for the preparation of this compound.

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Reaction of Alkyl Vinyl Ethers with Methyl α-D-Glucopyranoside[1]

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Methyl α-D-glucopyranoside was brought into reaction with a series of alkyl vinyl ethers in equimolar quantities, under acid catalysis, and the acetals obtained were analyzed by methylation techniques. After long reaction times the chloroethyl, cyclohexyl, ethyl, and isopropyl vinyl ethers had both C-4 and C-6 hydroxyls blocked by acetal formation. Methyl 4,6-*O*-ethylidene-α-D-glucopyranoside was isolated as the sole product formed, with ethyl and isopropyl vinyl ethers. At short reaction times, formation of methyl 6-*O*-(1-alkoxyethyl)-α-D-glucopyranoside was also observed with ethyl, isopropyl, and methyl vinyl ethers. 6-*O*-(1-Methoxyethyl) and 6-*O*-(1-ethoxyethyl) derivatives could be isolated as major products under defined reaction conditions. Evidence is furnished that the alkyl vinyl ethers react preferentially at the C-6 primary hydroxyl which may be followed by a further reaction of the acetal with an available hydroxyl group at C-4 in the same molecule to form the 4,6-*O*-ethylidene derivative.

Vinyl ethers react with hydroxyl groups under acid catalysis to form mixed acetals.[2-4] Acetals formed in this manner have been used in carbohydrate chemistry to serve as blocking groups, easily removable by dilute acid.[5,6] The cyclic vinyl ether 2,3-dihydropyran has been most widely used in reactions of this type. The formation of stereoisomers on the acetal carbon has been shown to occur;[7] however, this does not interfere with the use of the formed acetal as a blocking group, which is subsequently removed. Vinyl thioethers have been demonstrated to be suitable protective agents for hydroxyl groups; the hydroxyl group could be regenerated with silver ion under neutral conditions.[8] It has been observed[9] that the *O*-(1-methoxyethyl) group can be more readily removed than the *O*-tetrahydropyran-2-yl group.

Starch acetals of various degrees of substitution have been prepared in this laboratory[10] and also by other workers.[11] Before studying the distribution of substituents in starch derivatives of a low degree of substitution (preferably 1.0) it was deemed necessary to determine whether vinyl ethers undergo preferential reaction with any hydroxyl group of a simple monomer model, for example, methyl α-D-glucopyranoside. It is also of interest in synthetic carbohydrate chemistry to examine the possibility of using vinyl ethers for any selective or preferential reaction. With this objective, the reaction of several alkyl vinyl ethers with methyl α-D-glucopyranoside has been studied.

The reaction of equimolar proportions of a vinyl ether with methyl α-D-glucopyranoside in *N*,*N*-dimethylformamide solutions was performed, under catalysis by *p*-toluenesulfonic acid, over a period of days (Table I). The use of chloroethyl, cyclohexyl, ethyl, and isopropyl vinyl ethers was first investigated. The products obtained were then fully methylated and the acetal was later removed by a mild acid hydrolysis. Identification of the resulting methyl ethers of methyl α-D-glucopyranoside or D-glucose indicated the location of the acetal attachment.

TABLE I

REACTION OF METHYL α-D-GLUCOPYRANOSIDE WITH 1 MOLAR EQUIV OF VARIOUS VINYL ETHERS

			Methylated D-glucose	
Vinyl ether	Reacn time[a]	Acetal yield, %	Me Glycoside, yield, %	Identity[b]
Chloroethyl	4 days	54	90	2,3-Di-*O*-methyl
Cyclohexyl	7 days	65	90	2,3-Di-*O*-methyl
Ethyl	7 days	67	95	2,3-Di-*O*-methyl
Isopropyl	30 min	23	95	2,3-Di-*O*-methyl (~90%) 2,3,4-Tri-*O*-methyl (~10%)
	7 days[c]	60	60	2,3-Di-*O*-methyl[c]

[a] Ambient temperature (25 ± 3°); *p*-toluenesulfonic acid catalyst. [b] By paper chromatography (solvents A and B) in comparison with authentic specimens. [c] See Experimental Section.

Methylation and hydrolysis of the reaction product of isopropyl vinyl ether with methyl α-D-glucopyranoside gave a crystalline methyl di-*O*-methyl-α-D-glucopyranoside, not susceptible to oxidation by sodium periodate, the physical properties of which were in good agreement with those of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside. Hydrolysis gave a syrupy di-*O*-methyl-D-glucose having chromatographic and electrophoretic values identical with those of an authentic specimen of 2,3-di-*O*-methyl-D-glucose. Formation of the crystalline *N*-phenylglycosylamine derivative characterized the sugar as 2,3-di-*O*-methyl-D-glucose.

Chromatographic evidence indicated that methylation and hydrolysis of the reaction products of chloroethyl, cyclohexyl, and ethyl vinyl ethers with methyl α-D-glucopyranoside all gave 2,3-di-*O*-methyl-D-glucose as the only final product of this procedure (Table I). This shows that both C-4 and C-6 hydroxyls of methyl α-D-glucopyranoside had been blocked to methylation by acetal formation. The acetal product formed in each of the long-term reactions with isopropyl and ethyl vinyl ethers was purified from traces of methyl α-D-glucopyranoside by

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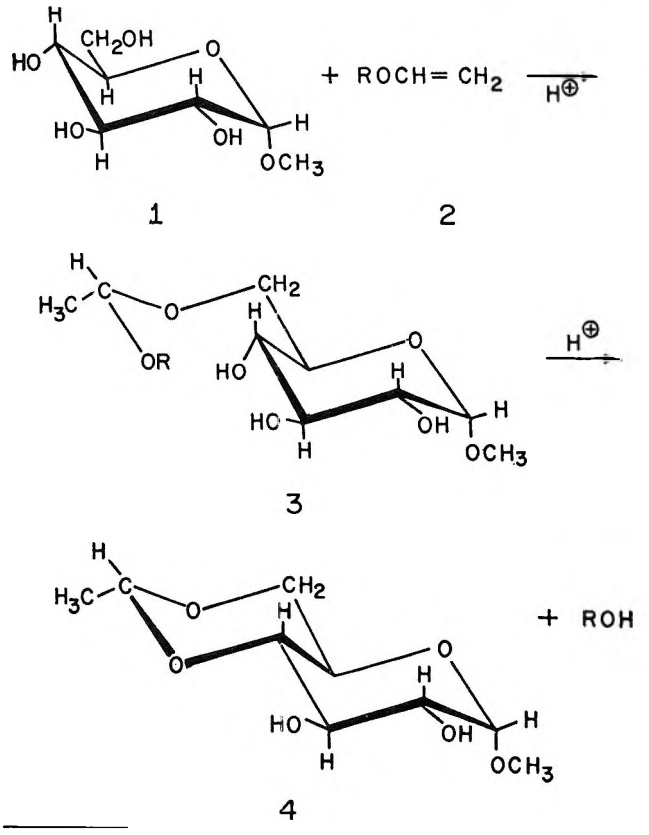
preparative thin layer chromatography and isolated. The sole product obtained was the crystalline methyl 4,6-*O*-ethylidene-α-D-glucopyranoside which also confirms the methylation results. When the reaction time of isopropyl vinyl ether with methyl α-D-glucopyranoside was reduced from several days to 30 min, a methylation assay showed 2,3-di-*O*-methyl-D-glucose as the main product with some tri-*O*-methyl-D-glucose tentatively identified as 2,3,4-tri-*O*-methyl-D-glucose (Table I).

Treatment of methyl α-D-glucopyranoside in about 3 *M* excess with methyl vinyl ether in the presence of boron trifluoride etherate gave a homogeneous (by thin layer chromatography), amorphous compound, in a good yield (70–75% of the crude reaction product), which has been identified as methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside on the basis of the following facts. This product could be partially converted into the known methyl 4,6-*O*-ethylidene-α-D-glucopyranoside; methylation and subsequent hydrolysis afforded 2,3,4-tri-*O*-methyl-D-glucose identified through its crystalline anilide; this material was chromatographically identical with a compound obtained from methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside by its reaction with methyl vinyl ether followed by deacetylation. Similar treatment of methyl α-D-glucopyranoside with ethyl vinyl ether in the presence of boron trifluoride etherate furnished a chromatographically homogeneous, noncrystalline product (yield ~80% of the crude product) which could likewise be identified as methyl 6-*O*-(1-ethoxyethyl)-α-D-glucopyranoside. This shows that the glycosidic group, a monocyclic acetal, does not exhibit to any significant extent the complex reactions described[12] for simple, acyclic acetals with vinyl ethers. Using again the same reaction conditions but replacing the boron trifluoride with *p*-toluenesulfonic acid, methyl 4,6-*O*-ethylidene-α-D-glucopyranoside was formed as a major product instead of methyl 6-*O*-(1-ethoxyethyl)-α-D-glucopyranoside. Reaction of equimolar proportions of methyl vinyl ether with methyl α-D-glucopyranoside, in the presence of *p*-toluenesulfonic acid for a 1- or 2-hr reaction period furnished methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside in approximately equal amounts, although, as noted before (Table I), the latter was formed as a major product when isopropyl vinyl ether was utilized under nearly the same conditions.



These results show that alkyl vinyl ethers (2) react preferentially as the C-6 hydroxyl of methyl α-D-glucopyranoside (1) followed by a subsequent reaction with the available C-4 hydroxyl group to form methyl 4,6-*O*-ethylidene-α-D-glucopyranoside (4). The 6-*O*-monosubstituted acetal (3) could, however, be trapped partially (*p*-toluenesulfonic acid catalysis) or almost completely (boron trifluoride etherate catalysis), depending on the reaction conditions.

Experimental Section[13]

Reaction of Methyl α-D-Glucopyranoside with 1 Molar Equiv of Several Vinyl Ethers.—A typical reaction was carried out in the following manner. Methyl α-D-glucopyranoside (15 g) was dispersed in dry *N*,*N*-dimethylformamide (30 ml) over Drierite (2 g). The vinyl ether (1 molar equiv) was added, followed by a catalytic amount of *p*-toluenesulfonic acid (80 mg). The reaction mixture was stirred for the desired reaction period (Table I) at ambient temperatures. Drierite and unreacted methyl α-D-glucopyranoside were removed by filtration; sodium hydrogen carbonate (100 mg) and water (2.0 ml) were added to the filtrate, which was concentrated to a syrup. The syrup was shaken with diethyl ether and filtered. The filtrate was concentrated to a syrup. The yields of the acetals obtained from various vinyl ethers are shown in Table I.

Methylation of the Reaction Product.—The above syrup (15 g) was dissolved in methyl iodide (100 ml) and silver oxide (25 g) was added. The mixture was shaken overnight at room temperature (or alternatively refluxed), filtered, and concentrated. The methylation procedure was repeated (4–5 times) until the infrared spectrum of the syrup showed the hydroxyl peak to be negligible. A portion of the above methylated syrup was hydrolyzed with 2 *N* sulfuric acid for 4 hr under reflux. Paper chromatographic examination (solvent A or B) of the neutralized (barium carbonate) hydrolyzate indicated the sugars resulting from the reactions with the various vinyl ethers (Table I).

Identification of 2,3-Di-*O*-methyl-D-glucose Following Methylation and Hydrolysis of the Reaction Product of Isopropyl Vinyl Ether with 1 Molar Equiv of Methyl α-D-Glucopyranoside.—The methylated acetal reaction product (3.0 g) from isopropyl vinyl ether was prepared as described above (7 days reaction time). Hydrolysis of this product with methanolic hydrogen chloride for 2 hr at reflux, followed by concentration and redistillation with

(12) R. I. Hoaglin and D. H. Hirsch, *J. Amer. Chem. Soc.*, **71**, 3468 (1949); R. I. Hoaglin and S. F. Clark, U. S. Patent 2,564,760 (1951); *Chem. Abstr.*, **46**, 2566 (1952).

(13) Paper chromatography was carried out on Whatman No. 1 filter paper in solvent systems 1-butanol–ethanol–water (4:1:5, v/v, solvent A), 1-butanone–1% ammonium hydroxide (10:1, v/v, solvent B) with indication by *p*-anisidine hydrochloride solution [L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.*, 1702 (1950)] or with silver nitrate and alkali [W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950)]. Solutions were concentrated under reduced pressure. Melting points were determined in a Thomas–Hoover capillary melting point apparatus. Infrared spectra were recorded with a Perkin-Elmer Infracord infrared spectrometer. Thin layer chromatography was ascending and was effected on 0.25–1.25 mm layers of silica gel G (E. Merck, Darmstadt, Germany) activated at 110°, using the solvent systems benzene–ethanol–water–10 *N* ammonium hydroxide (200:47:15:1, v/v, solvent D), methanol–ether (1:6, solvent D), and chloroform–acetone (1:1, v/v, solvent E) with indication by iodine vapor (preparative) or sulfuric acid. Microanalytical determinations were made by W. N. Bond. Acknowledgment is made to the experimental assistance of G. G. Parekh.

additional methanol, gave a crystalline glycoside (yield 1.85 g, 60%), mp 75–78°. Pure material was obtained on two recrystallizations from ethyl acetate (mp 82–83°, $[\alpha]^{22}D$ +150° (*c* 1.0, water) (lit.[14] mp 83–85°, $[\alpha]D$ +150° (water)) for 2,3-di-*O*-methyl α-D-glucopyranoside. The substance consumed no periodate during 24 hr at 35°.

Hydrolysis of the above methyl glycoside with 1 *N* sulfuric acid for 2 hr at reflux, followed by neutralization with barium carbonate, filtration, and concentration, afforded a di-*O*-methyl-D-glucose syrup: $[\alpha]^{20}D$ +58° (*c* 1.0 in water); R_G 0.6 (solvent A) and 0.4 (solvent B) identical with those of an authentic specimen[15] of 2,3-di-*O*-methyl-D-glucose. Electrophoresis in borate buffer at pH 10 for 5 hr at 600 V showed M_G 0.12 as did the authentic specimen, lit.[16] M_G 0.12. The crystalline anilide was prepared, mp 133° (lit.[17] mp 134°).

Acetal Isolation. A. From Isopropyl Vinyl Ether Reaction Products.—The reaction product (1.5 g) from isopropyl vinyl ether was isolated as described before and was subjected to preparative thin layer chromatography by two ascents with solvent C and extraction with methanol. The resultant syrup was crystallized from diethyl ether and the product was identified as methyl 4,6-*O*-ethylidene-α-D-glucopyranoside: yield 0.9 g (60%); mp 75°; $[\alpha]^{20}D$ +111.5° (*c* 0.5, methanol), lit.[18] mp 75–76°.

Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.27. Found: C, 49.34; H, 7.63.

Hydrolysis of the acetal reaction product (151 mg) with 2 *N* hydrochloric acid and distillation of the hydrolyzate into a solution of 2,4-dinitrophenylhydrazine in dilute hydrochloric acid[10] gave 1 molar equiv (93%) of acetaldehyde 2,4-dinitrophenylhydrazone.

B. From Ethyl Vinyl Ether.—The reaction product from ethyl vinyl ether was treated as described above and the product was identified as methyl 4,6-*O*-ethylidene-α-D-glucopyranoside in the same manner.

Reaction of Methyl α-D-Glucopyranoside with Methyl Vinyl Ether Using Boron Fluoride as Catalyst.—Methyl α-D-glucopyranoside (50 g, 0.25 mol) was dissolved in anhydrous dimethyl sulfoxide (100 ml) to which boron trifluoride etherate (4 drops) was added followed by the addition of methyl vinyl ether (5 ml, ~0.06 mol). The mixture was stirred magnetically in a closed flask for 2 hr at 35–40° (bath temperature). The catalyst was neutralized with an excess of powdered anhydrous sodium carbonate (stirred for 4 hr at room temperature). The mixture was filtered, the residue was washed with dimethyl sulfoxide, and the combined filtrates were concentrated to a syrup. This syrup was mixed thoroughly with chloroform whereupon unreacted methyl α-D-glucopyranoside (42 g) separated. The remaining methyl α-D-glucopyranoside and dimethyl sulfoxide were removed by repeating the concentration and addition of chloroform. The syrup (5.1 g) obtained from the chloroform solution, still containing traces of methyl α-D-glucopyranoside, consisted of one major and two minor components as shown by thin layer chromatography (solvents D and E). The major component (3.7 g, ~75% of the crude reaction product) was isolated by preparative thin layer chromatography (solvent D). In one experiment, further purification by thin layer chromatography (solvent E) was necessary. This solid material, methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside, did not crystallize, $[\alpha]^{20}D$ +46° (*c* 1.0, chloroform); 1 molar equiv of acetaldehyde formed on acid hydrolysis.

Anal. Calcd for $C_{10}H_{20}O_7$: C, 47.61; H, 7.93. Found: C, 48.03; H, 7.78.

A portion (100 mg) of the above compound was dissolved in chloroform (20 ml) to which *p*-toluenesulfonic acid (2.5 mg) was added. The solution became turbid after 2 min. After 15 min, the precipitate formed was filtered, washed with chloroform, and identified as methyl α-D-glucopyranoside (60 mg). The acid was neutralized with sodium carbonate after the total reaction period of 30 min and filtered. The filtrate showed only one spot by thin layer chromatography (solvents D and E) which had identical mobility with that of methyl 4,6-*O*-ethylidene-α-D-glucopyranoside. The chloroform solution was evaporated to dryness and the residue was crystallized from carbon tetrachloride and light petroleum ether (mp 74–76°, undepressed on admixture with a specimen of methyl 4,6-*O*-ethylidene-α-D-glucopyranoside, prepared by a known method,[19] which had mp 74–76°).

Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.27. Found: C, 48.84; H, 7.19.

This reaction was also performed in the presence of Drierite, using *N*,*N*-dimethylformamide and methylene chloride as solvents, and was found to follow the same course as described above.

Another portion (0.3 g) of the above amorphous compound, $[\alpha]^{20}D$ +46° ($CHCl_3$), was methylated with methyl iodide and silver oxide in the same way as described before. The completely methylated product (0.6 g) was hydrolyzed by refluxing with 1 *N* sulfuric acid for 10 hr, neutralized (barium carbonate), filtered, and evaporated to a syrup which showed one main spot with a very faint spot of slow moving component by paper chromatography (solvent A). These components were separated by paper chromatography and the main fraction (97 mg) was found to constitute about 97% of the mixture. The minor component (~2 mg) was not further investigated. A portion (50 mg) of the major component and distilled aniline (40 mg) were dissolved in ethanol (10 ml) and the solution was boiled under reflux for 4 hr. After evaporation of the aniline, the residue was left in the cold overnight for crystallization and the product was recrystallized from ether–petroleum ether (bp 30–60°): yield 48 mg; mp 143–145°, undepressed on admixture with an authentic specimen[20] of 2,3,4-tri-*O*-methyl-*N*-phenyl-D-glucopyranosylamine; $[\alpha]^{20}D$ −101° (*c* 1.0, ethanol, lit.[21] −103°).

Reaction of Methyl α-D-Glucopyranoside with 1 Molar Equiv of Methyl Vinyl Ether.—Methyl α-D-glucopyranoside (5 g) was dissolved in dry *N*,*N*-dimethylformamide (50 ml) to which *p*-toluenesulfonic acid (100 mg) and methyl vinyl ether (1.5 g) were added. The mixture was stirred for 1 hr at room temperature. The acid was neutralized with sodium carbonate, filtered, washed with *N*,*N*-dimethylformamide, and the combined filtrates were concentrated to a syrup. Unreacted methyl α-D-glucopyranoside was removed by mixing the syrup with chloroform, as mentioned in the previous case. The remaining portion was composed of two components in an approximate ratio 1:1, as shown by thin layer chromatography (solvent D), and these were chromatographically identical with methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside, respectively. The same results were obtained using a 2-hr reaction time and on variation of the quantity of *p*-toluenesulfonic acid.

Reaction of Methyl α-D-Glucopyranoside (Excess) with Ethyl Vinyl Ether. A. Boron Trifluoride as Catalyst.—Methyl α-D-glucopyranoside (25 g, 0.12 mole) was dissolved in anhydrous dimethyl sulfoxide (50 ml) to which were added successively boron trifluoride etherate (2 drops) and ethyl vinyl ether (2.3 g, 0.03 mol). The mixture was stirred for 2 hr at 35–40° and then anhydrous sodium carbonate (excess) was added, the mixture was stirred for another 4 hr, filtered, and washed with dimethyl sulfoxide. After removal of unreacted methyl α-D-glucopyranoside and dimethyl sulfoxide in the same manner as described in the case of the methyl vinyl ether reaction, the syrupy reaction product (2.4 g) afforded only one homogeneous solid material (1.9 g, ~80% crude reaction product) by preparative thin layer chromatography (solvent D). Trace amounts of another fast-moving component were present in the original mixture and were not investigated. The main reaction product, methyl 6-*O*-(1-ethoxyethyl)-α-D-glucopyranoside, failed to crystallize: $[\alpha]^{20}D$ +38° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_7$: C, 49.62; H, 8.27. Found: C, 49.11; H, 8.25.

The above compound (100 mg) was dissolved in methylene chloride or chloroform (20 ml) to which *p*-toluenesulfonic acid (2.5 mg) was added. The reaction was followed by thin layer chromatography (solvent D) and after 30 min at room temperature there was no starting material present. The products were methyl α-D-glucopyranoside (major) and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside.

(14) F. Smith and R. Montgomery, "The Chemistry of Plant Gums and Mucilages," Reinhold Publishing Corp., New York, N. Y., 1959, p 532.

(15) Obtained through the courtesy of Dr. D. Rees of the University of Edinburgh.

(16) Reference 14, p 129.

(17) E. Schlüchterer and M. Stacey, *J. Chem. Soc.*, 776 (1945).

(18) J. Honeyman and J. W. W. Morgan, *ibid.*, 3660 (1955).

(19) H. Appel, W. N. Haworth, E. G. Cox, and F. J. Llewellyn, *ibid.*, 793 (1938).

(20) Obtained from the collection of the late F. Smith through the courtesy of S. Kirkwood, University of Minnesota, St. Paul.

(21) J. D. Geerdes, B. A. Lewis, and F. Smith, *J. Amer. Chem. Soc.*, **79**, 4209 (1957).

B. *p*-Toluenesulfonic Acid as Catalyst.—To a magnetically stirred solution of methyl α-D-glucopyranoside (2.5 g, 0.12 mol) in anhydrous dimethyl sulfoxide (50 ml) was added *p*-toluenesulfonic acid (500 mg) followed by the addition of ethyl vinyl ether (2.3 g, 0.03 mol). Stirring was continued for 2 hr at 35–40°, sodium carbonate was added, and the mixture was agitated for 4 hr at room temperature. The reaction mixture was processed as described above. The major product was identical with methyl 4,6-*O*-ethylidene-α-D-glucopyranoside and the minor component was methyl α-D-glucopyranoside, as shown by thin layer chromatography (solvents D and E).

Preparation of the Methyl 6-*O*-(1-Alkoxyethyl)-α-D-glucopyranoside from Methyl 2,3,4-Tri-*O*-acetyl-α-D-glucopyranoside.—Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (0.7 g), prepared by a known method,[22] was dissolved in diethyl ether (20 ml) to which *p*-toluenesulfonic acid (10 mg) and methyl vinyl ether (0.5 ml) were added. The reaction appeared to be complete after the mixture had been shaken for 10 min, as indicated by thin layer chromatography (solvents D and E), and was stopped after 15 min by neutralizing the acid with sodium carbonate. The reaction mixture was filtered, and the salts were washed with ether. The combined filtrates were decolorized with carbon and concentrated to a syrup (0.790 g) with no hydroxyl group (ir spectroscopy) which was homogeneous by thin layer chromatography (solvents D and E) but resisted crystallization.

(22) B. Helferich, H. Bredereck, and A. Schneidmüller, *Ann.*, **458**, 111 (1927).

Anal. Calcd for $C_{16}H_{26}O_{10}$: C, 50.79; H, 6.87. Found: C, 50.62; H, 6.82.

A portion (0.350 g) of the above syrup was dissolved in absolute methanol (10 ml) to which was added 0.5 *N* sodium methoxide solution (1.5 ml). The mixture was shaken occasionally for 45 min at room temperature. After being treated with Amberlite IR-120 (H^+), the methanolic solution was concentrated to a syrup, which was found to contain trace amounts of methyl α-D-glucopyranoside by thin layer chromatography (solvents D and E). The syrup was shaken with chloroform and filtered and the filtrate was evaporated to dryness. The resultant solid compound was chromatographically identical with methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside obtained directly from methyl α-D-glucopyranoside, as described before, and on treatment with *p*-toluenesulfonic acid in chloroform this material was converted into methyl α-D-glucopyranoside (major) and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside as shown by thin layer chromatography (solvent D).

Similarly, a compound was prepared from methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside, by reaction with ethyl vinyl ether followed by deacetylation, and was found to be chromatographically (thin layer chromatography, solvents D and E) identical with the mono-*O*-(1-ethoxyethyl) derivative obtained from methyl α-D-glucopyranoside by boron trifluoride catalysis.

Registry No.—**1**, 97-30-3; **3** (R = Me) ($C_{10}H_{20}O_7$), 15717-31-4; **3** (R = Et) ($C_{11}H_{22}O_2$), 15649-43-1; **4**, 13225-11-1.

Purine Nucleosides. XIX. The Synthesis of Certain 8-Chloropurine Nucleosides and Related Derivatives[1]

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A new and improved procedure for the preparation of 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine (II) has been accomplished using bromine water. The first displacement of bromine with chlorine on a purine nucleoside was successfully achieved with phosphorus oxychloride to furnish 2-amino-6,8-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (III) which, with subsequent deblocking, yielded 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI). Nucleophilic displacement of the chloro groups on VI was demonstrated to occur preferentially at position 6 to afford several 8-chloro-2,6-disubstituted purine nucleosides. Nucleophilic displacement of both chloro groups was accomplished with thiourea to yield 2-amino-9-(β-D-ribofuranosyl)purine-6,8-dithione (VIII) and the completely deblocked 2,6,8-trichloro-9-(β-D-ribofuranosyl)purine (IX) was prepared for the first time *via* diazotization of VI.

The direct bromination of various purine nucleosides to afford the corresponding 8-bromopurine nucleosides has been recently reported[3–6] and was prompted primarily by the direct bromination studies of certain nucleic acids[7–9] (RNA and DNA). However, the first direct chlorination of a nucleic acid, soluble ribonucleic acid from yeast, with N-chlorosuccinimide has only recently been reported.[9] It was postulated[10] that 8-chloroguanosine was present as an intermediate prior to subsequent degradation. This is similar to other reports[11,12] which have previously described the degradation of guanine and guanosine when left in contact with an excess of brominating agent for an extended period of time. The present study describes the synthesis and chemical reactivity of several new and interesting 8-chloro-2,6-disubstituted purine nucleosides starting with readily available 2′,3′,5′-tri-*O*-acetylguanosine (I).

We have now developed a new and improved preparation of 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine in 90% yield from commercially available 2′,3′,5′-tri-*O*-acetylguanosine (I) using saturated bromine water. The crystalline nucleoside (II) prepared in this investigation was found to be identical in every respect with II prepared previously[5] (64%) by the direct bromination of I, using a mixture of glacial acetic acid, sodium acetate, and bromine. The anomeric configuration of all nucleosides reported herein is definitely established as β since the starting material in all cases was guanosine.

(1) This work supported by Research Contract No. PH-43-65-1041 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) 3M Co., St. Paul, Minn.

(3) R. L. Long, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, **32**, 2751 (1967).

(4) R. L. Long, R. K. Robins, and L. B. Townsend, "Synthetic Procedures in Nucleic Acid Chemistry," Interscience Publishers, Inc., New York, N. Y., in press.

(5) R. E. Holmes and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1242 (1964).

(6) M. Ikehara, S. Uesugi, and M. Kaneko, *Chem. Commun.*, 17 (1967).

(7) K. W. Brammer, *Biochim. Biophys. Acta*, **72**, 217 (1963).

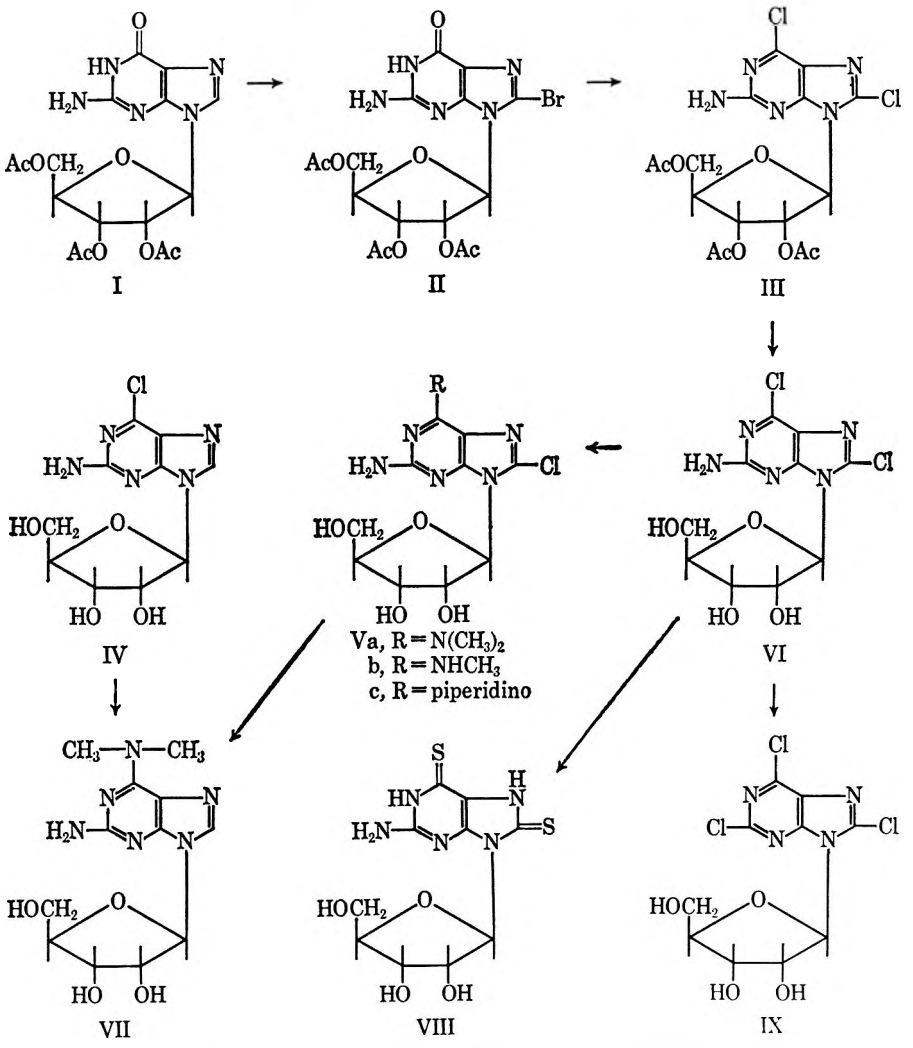
(8) J. Duval and J. P. Ebel, *Bull. Soc. Chim. Biol.*, **47**, 787 (1965).

(9) D. Londes, J. Duval, G. Aubel-Sadron, and J. P. Ebel, *ibid.*, **49**, 739 (1967).

(10) J. Duval and J. P. Ebel, *Compt. Rend.*, **263D**, 1773 (1966).

(11) E. Fischer and L. Reese, *Ann. Chem.*, **221**, 342 (1883).

(12) R. Shapiro and S. C. Agarval, *Biochem. Biophys. Res. Commun.*, **24**, 401 (1966).



Chlorination of II with phosphorus oxychloride in the presence of N,N-diethylaniline hydrochloride furnished what was at first assumed to be 2-amino-8-bromo-6-chloro-9-(2′,3′,5′,-tri-*O*-acetyl-β-D-ribofuranosyl)purine. However, it was soon discovered that the bromine had been replaced in position 8 to provide 2-amino-6,8-dichloro-9-(2′,-3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (III). This structural assignment was based on elemental analysis, including chlorine, and to our knowledge is the first report of a direct displacement of bromine by chlorine on a purine nucleoside.[13] Complete deacetylation without concomitant nucleophilic displacement of either chloro group was accomplished using methanolic ammonia at 5° to yield 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI). The ready availability of VI suggested a study on the relative reactivity of the chloro groups in an effort to determine if they could be replaced with any degree of selectivity. Treatment of III with anhydrous dimethylamine and sodium bicarbonate in anhydrous ethanol at reflux temperature furnished a 58% yield of crystalline nucleoside which was assigned the structure 2-amino-8-chloro-6-dimethylamino-9-(β-D-ribofuranosyl)purine (Va) on the basis of the following data. That monosubstitution had occurred was apparent from a visual inspection of a pmr spectrum of the product in dimethyl sulfoxide-d_6 which displayed a sharp singlet (six protons) at δ 3.4. This singlet was attributed to the presence of only one dimethylamino group and this was further substantiated by elemental analysis. This left only the determination of the actual site at which nucleophilic displacement had occurred. Catalytic removal of the remaining chloro group from Va was accomplished smoothly with palladium on powdered charcoal to furnish a product with a melting point 203–205°. That dechlorination had occurred was evident by the appearance of a sharp singlet in the pmr spectrum (dimethyl sulfoxide-d_6) at δ 8.0 which could be attributed only to an aromatic proton at either C-6 or C-8. The mixture melting point with a sample of 2-amino-6-dimethylamino-9-(β-D-ribofuranosyl)-purine (VII) which was obtained[14] from 2-amino-6-chloro-9-(β-D-ribofuranosyl)purine (IV)[15] showed no depression. It was subsequently demonstrated that the nucleoside prepared from IV and from Va possessed identical ultraviolet absorption and pmr spectra. Therefore, nucleophilic displacement had occurred preferentially at position 6 to afford 2-amino-8-chloro-6-dimethylamino-9-(β-D-ribofuranosyl)purine (Va). Similar treatment of VI with anhydrous methylamine and piperidine yielded 2-amino-8-chloro-6-methyl-

(13) A similar displacement of bromine by chlorine has been reported to occur with 4,5-dibromo-3-pyridazone: R. N. Castle and K. Kaji, *Tetrahedron Lett.*, 393 (1962).

(14) J. F. Gerster, J. W. Jones, and R. K. Robins [*J. Org. Chem.*, **28**, 945 (1963)] also report the preparation of VII from 2-amino-6-iodo-9-(β-D-ribofuranosyl)purine.

(15) An improved preparation of IV has been developed and was utilized in this investigation: J. F. Gerster, A. F. Lewis, and R. K. Robins, "Synthetic Procedures in Nucleic Acid Chemistry," Interscience Publishers, Inc., New York, N. Y., in press.

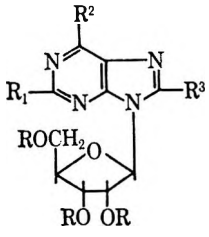
amino-9-(β-D-ribofuranosyl)purine (Vb) and 2-amino-8-chloro-6-(1-piperidyl)-9-(β-D-ribofuranosyl)purine (Vc), respectively.

That displacement of both chloro groups from VI could be achieved was demonstrated by the successful preparation of 2-amino-9-(β-D-ribofuranosyl)-6,8-dithione (VIII). Treatment of VI with aqueous thiourea in the presence of a catalytic amount of formic acid furnished a 64% yield of chromatographically pure VIII. The pmr spectrum of VIII in dimethyl sulfoxide-d_6 revealed the presence of broad singlets at δ 12.9 (one proton) and 12.1 (one proton) which were assigned to –NH protons at N-1 and N-7. This indicated that VIII exists in the thione form rather than the thiol form, at least in dimethyl sulfoxide-d_6. Additional corroboration for elimination of the thiol form was provided by the absence of an infrared absorption band at 2550–2600 cm^{-1} usually attributed[16,17] to –SH stretching. There was observed an absorption band in the infrared spectrum (KBr) in the 1550–1600-cm^{-1} area which was assigned[16,18] partially to —C=S stretching and partially to —C=N— stretching as part of a —N—C=S system.

The preparation of 2,6,8-trichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine[19] has been reported using the acid-catalyzed fusion procedure.[20] However, several attempts to obtain 2,6,8-trichloro-9-(β-D-ribofuranosyl)purine (IX) by deacetylation have been unsuccessful[21] because of the concomitant nucleophilic displacement of at least one of the chloro groups. We have now prepared IX for the first time by utilization of a procedure developed in our laboratory[22] for the preparation of 2,6-dichloro-9-(β-D-ribofuranosyl)purine.[23] Diazotization of VI with concentrated hydrochloric acid and sodium nitrite below −5° furnished 2,6,8-trichloro-9-(β-D-riboruranosyl)purine (IX). The ultraviolet absorption spectra of IX was very similar to the data reported[24] for other 9-substituted 2,6,8-trichloropurines. The ready availability of 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (IX) from guanosine provides an excellent starting material for the preparation of unusual 2-aminopurine nucleosides containing substituents at positions 6 and 8.

The ultraviolet absorption spectral data for all purine nucleosides prepared in this study are listed in Table I.

TABLE I
ULTRAVIOLET ABSORPTION OF CERTAIN PURINE NUCLEOSIDES[a]



Compd	R	R_1	R_2	R_3	pH	λ_{max}	ϵ_{max}
II	–C–CH₃ ‖ O	NH_2	OH	Br	1	262	16,600
					11	271	14,300
III	–C–CH₃ ‖ O	NH_2	Cl	Cl	1	310	8,300
						253	8,300
					11	310	8,800
						253	8,800
VI	H	NH_2	Cl	Cl	1	310	8,400
						252	9,900
					11	310	8,700
						251	10,000
Vc	H	NH_2	NC_5H_{10}	Cl	1	310[b]	11,900
						295	12,700
						263	14,400
					11	296[b]	16,900
						289	18,100
						235	18,500
Vb	H	NH_2	$NHCH_3$	Cl	1	308[b]	6,720
						292	11,200
						260	13,400
					11	280	14,300
						265[b]	11,900
						227[b]	14,900
Va	H	NH_2	$N(CH_3)_2$	Cl	1	297	11,700
						262	14,500
					11	285	16,200
						269[b]	13,100
						232	18,300
VIII	H	NH_2	–SH	–SH	1	372	31,500
						361[b]	21,000
						295[b]	9,260
						273	19,500
					11	346	20,900
						264	20,700
IX	H	Cl	Cl	Cl	1	285[b]	10,700
						279	11,700
						253	5,700
					11	285[b]	10,300
						279	11,400
						253	5,330
VII	H	NH_2	$–N(CH_3)_2$	H	1	298[b]	11,800
						291	12,000
						256	13,200
					11	282	17,600
						265	11,420
						229	21,600

[a] Beckman DK-2 spectrophotometer. [b] Inflection or shoulder.

Experimental Section[25]

2-Amino-8-bromo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-purin-6-one (II).—2′,3′,5′-Tri-*O*-acetylguanosine (I) (40 g) was slowly added with stirring to 1 l. of water to form a thick slurry. This slurry was stirred vigorously at room temperature while saturated bromine water was slowly added. The addition of bromine water was made in approximately 50-ml aliquots and at such a rate that the yellow color of the reaction mixture disappeared between each addition. The total time for complete addition was approximately 20 min at which time the color of the reaction mixture remained a pale yellow. This reaction mixture was allowed to stir for an additional 20 min at room temperature and the solid collected by filtration and immediately recrystallized from a mixture of acetone–water to yield 44 g (90%) of chromatographically pure 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine (II), mp 220–221°.

Anal. Calcd for $C_{16}H_{18}BrN_5O_8$: C, 39.40; H, 3.72; N, 14.33. Found: C, 39.32; H, 3.88; N, 14.11.

2-Amino-6,8-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (III).—Compound II (25 g) was added to 150 ml of phosphorus oxychloride containing 26 g of N,N-diethylaniline hydrochloride (anhydrous). This mixture was heated at reflux temperature for 6 min and the excess phosphorus oxychloride was

(16) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed, 1967, p 100.

(17) D. Harrison and J. T. Ralph, *J. Chem. Soc., Sect. B*, 14 (1967).

(18) J. R. Dyer, "Application of Absorption Spectroscopy of Organic Compounds," Prentice Hall Inc., Englewood Cliffs, N. J. (1965), p 38.

(19) J. Davoll, B. A. Lowy, *J. Amer. Chem. Soc.*, **74**, 1563 (1952); T. Sato, T. Shimadachi, and R. Ishido, *Nippon Kagaku Zasshi*, **81**, 1440 (1960).

(20) R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 311 (1967), and references cited therein.

(21) Unpublished observations from this laboratory.

(22) J. F. Gerster and R. K. Robins, *J. Org. Chem.*, **31**, 3258 (1966).

(23) Preparation of this nucleoside by deacetylation of 2,6-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine has been unsuccessful since a concomitant nucleophilic displacement of chlorine from position six occurs: H. J. Schaeffer and H. J. Thomas, *J. Amer. Chem. Soc.*, **80**, 3738 (1958).

(24) E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, **28**, 1662 (1963).

(25) Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. All pmr spectra were obtained on a Varian A-60 nmr spectrometer and values are recorded in δ units with TMS as an internal standard. Infrared spectra were obtained on a Beckman IR-5A spectrometer with pressed KBr pellets.

then removed *in vacuo* on a steam bath. The residue was poured onto 500 ml of crushed ice with vigorous stirring and additional ice was added as needed to keep the temperature of the solution below 0°. The solution was extracted with three 150-ml portions of methylene chloride and the combined extracts were washed with water until the washings were neutral to pH paper, then dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the resulting dark syrup was dissolved in 50 ml of ethanol. This solution was allowed to stand at 5° until a solid separated from solution and was collected by filtration. For analysis the solid was recrystallized from ethanol to yield 12.5 g (52%) of III, mp 138–140° and $[\alpha]^{22}D$ −3.85° (c 1, ethanol).

Anal. Calcd for $C_{16}H_{17}Cl_2N_5O_7$: C, 41.60; H, 3.72; N, 15.30; Cl, 15.35. Found: C, 41.53; H, 3.70; N, 15.33; Cl, 15.16.

2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI).—2-Amino-6,8-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-purine (III) (5 g) was dissolved in methanolic ammonia (previously saturated at −10°) and allowed to stand at 5° for 5 hr. The solution was evaporated to dryness *in vacuo* and the temperature of the water bath was maintained below 20°. The resulting solid was triturated with 10 ml of water and the solid collected by filtration to yield 3.7 g of crude product. Recrystallization from ethanol yielded 3.4 g of pure VI, mp 196° dec.

Anal. Calcd for $C_{10}H_{11}Cl_2N_5O_4$: C, 35.80; H, 3.30; N, 20.80. Found: C, 35.50; H, 3.78; N, 20.20.

2-Amino-8-chloro-6-dimethylamino-9-(β-D-ribofuranosyl)purine (Va).—To 50 ml of ethanol was added 1 g of 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI). Anhydrous dimethylamine (1 ml) and 1 g of sodium bicarbonate was added and the mixture heated at reflux temperature for 1 hr. The solid sodium bicarbonate was removed by filtration and the ethanol removed *in vacuo*. Additional ethanol (50 ml) was added to the residue and the solution was again evaporated to dryness *in vacuo;* this process was repeated several times to remove all traces of dimethylamine. The residual oil was triturated with diethyl ether and the resulting solid recrystallized from toluene to yield 600 mg (58%) of analytically pure product, mp 193–194°. The product was dried for 1 hr at 110° at approximately 0.1 mm over P_2O_5 for analysis.

Anal. Calcd for $C_{12}H_{17}ClN_6O_4$: C, 41.80; H, 4.97; N, 24.37. Found: C, 41.98; H, 5.10; N, 24.15.

2-Amino-8-chloro-6-methylamino-9-(β-D-ribofuranosyl)purine (Vb).—2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI) (1 g) was dissolved in 50 ml of ethanol and to this solution was added a mixture of 1 g of sodium bicarbonate and 1 ml of anhydrous methylamine. The reaction mixture was heated at reflux temperature for 1 hr, the sodium bicarbonate removed by filtration, and the filtrate evaporated to dryness *in vacuo*. The resulting crude solid was recrystallized from a mixture of acetone–ligroin (110–115°) to yield pure crystals (540 mg, 56%), mp 198–199° dec.

Anal. Calcd for $C_{11}H_{15}ClN_6O_4$: C, 40.00; H, 4.57; N, 25.40. Found: C, 40.01; H, 4.80; N, 25.18.

2-Amino-8-chloro-6-(1-piperidyl)-9-(β-D-ribofuranosyl)purine (Vc).—2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI) (1 g) was added to a solution of 0.6 ml of piperidine in 50 ml of ethanol. There was then added 1 g of sodium bicarbonate and the reaction mixture refluxed for 1 hr. The solid was collected by filtration and discarded and the filtrate evaporated to dryness *in vacuo*. The residue was then triturated with 10 ml of diethyl ether. The resulting solid was collected by filtration and recrystallized from toluene to yield 0.6 g (37%) of crystals melting at 193–194°. The product was dried at 110° for 1 hr at approximately 0.1 mm for analysis.

Anal. Calcd for $C_{15}H_{21}ClN_6O_4$: C, 47.10; H, 5.76; N, 21.80. Found: C, 47.04; H, 5.54; N, 21.69.

2-Amino-9-(β-D-ribofuranosyl)purine-6,8-dithione (VIII).—2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI) (1 g) was dissolved in 15 ml of water containing 1 g of thiourea. One drop of 25% formic acid was added and the solution heated at 80–85° for 1 hr while the reaction mixture was maintained at approximately pH 5 with concentrated ammonium hydroxide. The solution was a clear, bright yellow when the reaction was complete. The solution was evaporated to a syrup *in vacuo* and triturated with diethyl ether (50 ml). The resulting solid was recrystallized from methanol with a minimum amount of water. The solution was allowed to stand for 10–14 days and as the oil dissolved the product slowly crystallized from solution. There was obtained a yield of 625 mg (64%) of yellow product, mp 215–216° dec. This product was dried at 100° for 1 hr at approximately 0.1 mm over P_2O_5 for analysis, $[\alpha]^{25}D$ −48.48° (*c* 1.0, 0.0844 *N* NaOH).

Anal. Calcd for $C_{10}H_{13}N_5O_4S_2$: C, 35.35; H, 4.16; N, 20.60. Found: C, 35.35; H, 4.18; N, 20.10.

2,6,8-Trichloro-9-(β-D-ribofuranosyl)purine (IX).—2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI) (1 g) was added to 10 ml of concentrated hydrochloric acid which had been previously cooled to −10°. Sodium nitrite (415 mg) in 2 ml of water was added dropwise while maintaining the temperature between −5 and −10°. The resulting solution was allowed to stir at −5° for 20 min and then neutralized with concentrated ammonium hydroxide below −10°. The solution was then extracted with three 20-ml portions of cold methylene chloride. The combined methylene chloride extracts were washed once with water and dried over anhydrous magnesium sulfate. The methylene chloride was removed *in vacuo* and the remaining residue crystallized from acetone to yield 260 mg (24.6%) of pure product melting at 168°.

Anal. Calcd for $C_{10}H_9Cl_3N_4O_4$: C, 33.80; H, 2.53; N, 15.75. Found: C, 34.00; H, 2.65; H, 15.48.

2-Amino-6-dimethylamino-9-(β-D-ribofuranosyl)purine (VII).

Method 1.—2-Amino-8-chloro-6-dimethylamino-9-(β-D-ribofuranosyl)purine (Va) (1 g) was dissolved in 95% ethanol and 500 mg of 5% palladium on powdered charcoal was added. The mixture was hydrogenated at 45 psi in a hydrogen atmosphere at room temperature for 6 hr. The mixture was then filtered through a Celite pad and the filtrate evaporated to dryness *in vacuo*. Recrystallization of the residue from a mixture of acetone–methanol furnished 550 mg of the hydrochloride salt of VII, mp 199–200° dec. This salt was dissolved in 60 ml of water and 3.5 g of Dowex 3 was added to the aqueous solution. This mixture was allowed to stir at room temperature for 5 hr, the resin removed by filtration, and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from a mixture of acetone–methanol to afford a product which melted at 203–205°.

Method 2.—2-Amino-6-chloro-9-(β-D-ribofuranosyl)purine (IV) (1 g) was dissolved in 50 ml of anhydrous ethanol. Anhydrous dimethylamine (1 ml) was added and the solution heated at reflux temperature on the steam bath for 1 hr. The solution was taken to dryness *in vacuo* and additional ethanol added and again taken to dryness *in vacuo;* this process was repeated several times to remove the excess dimethylamine. The resulting oil was triturated with a 1:1 solution of acetone–diethyl ether. The residual oil solidified on standing and was recrystallized from a mixture of acetone–methanol two times to yield (0.55 g, 53%) a crystalline product melting at 203–204°. The product from method 1 and method 2 showed no depression in mixture melting point and possessed identical uv and pmr spectra.

R_f values of VII (prepared by method 1) were 0.66 in 5% aqueous NH_4Cl and 0.88 in EtOH–H_2O (7:3, v/v). R_f values of VII (prepared by method 2) were 0.67 in 5% aqueous NH_4Cl and 0.85 in EtOH–H_2O (7:3, v/v). Whatman No. 1 chromatography paper and descending technique were used.

Registry No.—II, 15717-45-0; III, 15717-46-1; Va, 15717-47-2; Vb, 15645-46-2; Vc, 15717-48-3; VI, 15645-47-3; VII, 15717-43-8; VIII, 15834-80-7; IX, 15717-44-9.

Reaction of Carbohydrates with Methylsulfonyl Chloride in *N,N*-Dimethylformamide. Preparation of Some Methyl 6-Chloro-6-deoxyglycosides[1]

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Reaction of hexopyranosides with methylsulfonyl chloride in *N,N*-dimethylformamide causes selective replacement of the primary hydroxyl groups by chlorine. The resulting 6-chloro-6-deoxyhexopyranosides are reduced to 6-deoxyhexopyranosides by lithium aluminum hydride in tetrahydrofuran. These reactions provide an improvement over current syntheses of 6-chloro-6-deoxyhexopyranosides and 6-deoxyhexopyranosides in the yield and number of steps involved.

Selective reactions of hydroxyl groups have led to useful intermediates in carbohydrate chemistry. In the case of carbohydrates containing primary hydroxyl groups, reaction with triphenylmethyl chloride in pyridine to form trityl ethers has been widely used because of the high yield and selectivity of the reaction and the ease of subsequent regeneration of the hydroxyl group with acid.[4] Recent studies[5,6] in our laboratories have been concerned with selective methylsulfonylation of methyl hexopyranosides in anhydrous pyridine and in mixtures of pyridine and triethylamine and of pyridine and *N,N*-dimethylformamide (DMF); these variations in solvent do not alter significantly the selectivity of the mesylation reaction. The present paper describes the results obtained when some methyl hexopyranosides were treated with methylsulfonyl chloride in DMF.

Initially we used the conditions described by Chalk, *et al.*,[6] that is, 2 equiv of methylsulfonyl chloride was added slowly to a solution of methyl α-D-glucopyranoside (1) in DMF at −20 to −40°. Thin layer chromatograms of the reaction mixture after 16 hr showed the presence of a product with mobility the same as that of methyl 6-chloro-6-deoxy-α-D-glucopyranoside (2) but different from that of methyl 6-*O*-mesyl-α-D-glucopyranoside (3), fast moving materials which gave a positive test for ester with ferric hydroxamate,[7] and a large amount of compound 1. The fast moving materials were identified as *O*-formate esters of compounds 1 and 2 from consideration of their nmr spectra and the nature of the deesterification products. These esters, which partially decomposed during silica gel chromatography or on storage at room temperature, were generally deesterified with sodium methoxide prior to column chromatography. We avoided the use of ketones as eluents during this work as we found that the use of methyl ethyl ketone as eluent in column chromatography on Brinkmann silica gel leads to acetal formation between the ketone and unchanged 1.

Fractionation of the deesterified reaction mixture on silica gel with ethyl acetate–ethanol–water (45:5:3) as the eluent gave chromatographically pure 2 in 64% yield, which crystallized on removal of the solvent. Recrystallization from 1-propanol gave material having melting point and specific rotation identical with those reported by Helferich, *et al.*[8] Elemental analysis values agreed with those expected for $C_7H_{13}O_5Cl$ and the absence of sulfur was shown. The nmr spectrum in D_2O showed the presence of 10 protons and the absence of an *O*-mesyl group; the infrared spectrum showed a strong band at 13.3 μ (>CCl) but no bands at 7.3 and 8.5 μ (*O*-mesyl).[9] Edington[10] reported the formation of formate esters in quantitative yield during tosylation of bis-2-hydroxyethyl terephthalate in DMF for 15 min at −5°, whereas at 65° for 4 hr or 100° for 15 min bis-2-chloroethyl terephthalate was obtained in 94% yield. We therefore tried raising the reaction temperature in our experiments; at 30° little change in the yield of compound 2 was observed but at 100° the yield was almost quantitative (Table I).

TABLE I

YIELDS OF METHYL 6-CHLORO-6-DEOXY-D-GLYCOPYRANOSIDES

Starting glycoside	Mesyl chloride, equiv	Temp, °C	Isolated yield of 6-chloro-6-deoxy product, %
Methyl α-D-glucopyranoside	2	−25	64
	2	30	59
	2	65	97
Methyl β-D-glucopyranoside	2	−25	42
	2	65	38
	10	−25	40
	10	65	91
Methyl α-D-mannopyranoside	10	65	86

Hess and Pfleger[11] reported the replacement of a primary tosyloxy group by chlorine during the tosylation of starch in pyridine above 30°. Similarly, bis-2-toluene-*p*-sulfonyloxyethyl terephthalate was converted into bis-2-chloroethyl terephthalate by treatment with pyridine and *p*-tolylsulfonyl chloride at 65°.[10] When methyl 6-*O*-mesyl-α-D-glucopyranoside (3) was treated with methylsulfonyl chloride and DMF at −25°, conditions which led to the conversion of 1 into 2 in 64% yield, unchanged 3 was recovered quantitatively demonstrating that 3 is not an intermediate in the conversion of 1 into 2.

Albright and coworkers[12] have used *p*-tolylsulfonyl chloride in DMF with testosterone to give testosterone

(1) Presented before the Division of Cellulose, Wood, and Fiber Chemistry at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

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(3) To whom all correspondence should be addressed.

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O-formate in 79% yield. These workers proposed a mechanism based on nucleophilic attack by alcohol R_3C^*OH on the iminium salt $(Me_2N^+{=}CHOSO_2C_6H_4Me)Cl^-$, derived from *p*-tolylsulfonyl chloride and DMF, to give an intermediate $Me_2N^+{=}CHOC^*R_3$ which is hydrolyzed to an *O*-formate. Edington[10] proposed the same mechanism to explain the production of bis-2-formyloxyethyl terephthalate. Attack by chloride ion on the above intermediate was postulated[12] to explain the formation in high yield of *p*-nitrobenzyl chloride from *p*-nitrobenzyl alcohol and of picryl chloride from picric acid. This mechanism appears to us to be the most likely explanation of the formation of bis-2-chloroethyl terephthalate from the corresponding alcohol in DMF–tosyl chloride, of the introduction of chlorine at the C-21 position of the 11α-acetoxy and 19-acetoxy derivatives of 17α, 21-dihydroxy-4-pregnene-3,20-dione[13] by DMF–tosyl chloride, and of our observations with glycosides.

As conductivity[14] and nmr[15] studies have shown that the concentration of the iminium salt is low, the rate of formation of this salt may be the rate-determining step. We attempted without success to improve the yield of compound **2** by reaction of the glycoside **1** with methylsulfonyl chloride in DMF in the presence of 1 equiv of lithium chloride (based on the amount of glucoside) at −25°. While deionizing the product of this reaction on a column of Rexyn 300 mixed bed resin we observed that unchanged **1** emerged before the product **2**. Following this observation we have developed a separation procedure[16] for mixtures of **1**, **2**, and methyl 6-deoxy-α-D-glucopyranoside (and for the β anomers) using anion-exchange resin with 75% aqueous 1-propanol as eluent. Mattisson and Samuelson have described a similar procedure.[17]

When methyl β-D-glucopyranoside was treated with 2 equiv of methylsulfonyl chloride in DMF at −25 or at 65°, methyl 6-chloro-6-deoxy-β-D-glucopyranoside (**4**)[18] was obtained in about 40% yield (Table I). Using 10 equiv of methylsulfonyl chloride at −25° the yield of **4** was again moderate, but at 65° the yield improved to 91%.

Treatment of methyl α-D-mannopyranoside with 10 equiv of methylsulfonyl chloride in DMF at 65° gave crystalline methyl 6-chloro-6-deoxy-α-D-mannopyranoside, known previously[19] only as a syrup, in 86% yield.

The use of methylsulfonyl chloride in DMF provides a selective method for the replacement of a primary hydroxyl group by chlorine; only trace amounts of compounds in which secondary hydroxyl groups had been substituted were encountered, and in the case of methyl α-D-xylopyranoside 99% of unchanged glycoside was recovered from the reaction. We have used the method successfully with other carbohydrate materials including disaccharides, cyclodextrins, and nucleosides; we will report these results later. The use of other compounds containing both sulfur and halogen, *e.g.*, *p*-tolylsulfonyl chloride,[12] sulfuryl chloride,[20] thionyl chloride,[21] or sulfur monochloride,[22] in place of methylsulfonyl chloride led to inferior yields of the chloro sugars. We have successfully employed N,N-dimethylacetamide in place of DMF.

Attempts to prepare methyl 6-deoxy-6-fluoro-α-D-glucopyranoside by this procedure using methylsulfonyl fluoride have so far been unsuccessful; the use of methanesulfonic anhydride in the hope of preparing 6-*O*-methylsulfonates led to the formation of *O*-formates.

Methyl 6-chloro-6-deoxyhexopyranosides can be reduced to the corresponding 6-deoxy sugars by lithium aluminum hydride in boiling tetrahydrofuran. For example, **2** is reduced to methyl 6-deoxy-α-D-glucopyranoside[23] in 87% yield; together with the methylsulfonyl chloride–DMF reaction this reduction provides a convenient preparation for 6-deoxyglycosides, superior to current methods[24,25] in both yield and number of steps involved.

Having achieved selective reaction at the primary hydroxyl group, in order for the chlorine atom that was introduced to be considered a good blocking substituent, it was necessary to regenerate the hydroxyl group in high yield. A convenient method is to regenerate the primary hydroxyl group from **2** via the 6-*O*-benzoate ester[26] by benzoate exchange[27] in DMF.

The chlorodeoxy- and deoxyglycosides described in this paper have been examined as substrates or inhibitors of glycosidases.[28]

Experimental Section[29]

General Procedure.—Methylsulfonyl chloride (2 or 10 equiv based on the amount of glycoside) was added dropwise to a stirred solution of the glycoside in anhydrous DMF (0.1 g/ml) maintained at the desired reaction temperature. After 16 hr at this temperature the mixture was concentrated to a syrup which was then dissolved in methanol and treated with sodium methoxide to destroy *O*-formate esters. The solution was concentrated and the product was chromatographed on silica gel. Elution with solvent 2 gave the methyl 6-chloro-6-deoxyglycoside and elution with ethyl acetate–methanol (9:1) gave unchanged methyl glycoside. The course of the fractionation was followed by tlc using solvents 1 or 2. The methyl 6-chloro-6-deoxyglycosides crystallized on removal of the solvent.

In some experiments with methyl α- and β-D-glucopyranosides the effect of the presence of dry lithium chloride (0.25 g/g of glycoside) in the reaction mixture was examined.

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(29) Solutions were concentrated under reduced pressure. Melting points were determined with a Thomas–Hoover capillary melting point apparatus and optical rotations were measured using an ETL-NPL automatic polarimeter. Nmr spectra were recorded on a Varian Model A-60 spectrometer. Ascending thin layer chromatography (tlc) was performed on silica gel GF_{254}; solvent 1 refers to benzene–chloroform–isopropyl alcohol (3:3:1) and solvent 2 is composed of ethyl acetate–ethanol–water (45:5:3). For the detection of spots, the chromatoplates were sprayed successively with a 1% solution of α-naphthol in ethanol and with 10% sulfuric acid and were then heated. Silica gel column chromatography was performed on Brinkmann silica gel (0.05–0.20 mm) using 100 g of silica gel for 1 g of sugar mixture. The microanalyses were performed by Mr. C. DiPietro and the nmr spectra by Mr. F. H. Bissett.

Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside.[8]—Treatment of methyl α-D-glucopyranoside (1.2 g) in DMF with methylsulfonyl chloride (1.06 ml, 2 equiv) at −25, 30, or 65°, as described above, gave methyl 6-chloro-6-deoxy-α-D-glucopyranoside with mp 113–114° and $[\alpha]^{30}D$ +139° (*c* 2.4, water) after recrystallization from 1-propanol. Constants previously reported[8] are mp 110–112° and $[\alpha]D$ +139.7° (*c* 2.5, water).

Anal. Calcd for $C_7H_{13}O_5Cl$: C, 39.52; H, 6.16; Cl, 16.69. Found: C, 39.23; H, 6.15; Cl, 16.82.

The yields of crystalline product under various reaction conditions are shown in Table I.

Methyl 6-Chloro-6-deoxy-β-D-glucopyranoside.[18]—Treatment of methyl β-D-glucopyranoside (1.2 g) in DMF with methylsulfonyl chloride (2 or 10 equiv) at −25 or 65° gave methyl 6-chloro-6-deoxy-β-D-glucopyranoside with mp 157–159° and $[\alpha]^{30}D$ −49° (*c* 1.0, water) after recrystallization from 1-propanol, in good agreement with values of mp 156–157°, $[\alpha]D$ −48.7° (*c* 2.5, water) previously reported.[18]

Anal. Calcd for $C_7H_{13}O_5Cl$: C, 39.52; H, 6.16; Cl, 16.69. Found: C, 39.34; H, 6.15; Cl, 16.72.

The yields of crystalline product under various reaction conditions are shown in Table I.

Methyl 6-Chloro-6-deoxy-α-D-mannopyranoside.[19]—Methyl α-D-mannopyranoside (1.2 g) was treated in DMF at 65° for 16 hr with methylsulfonyl chloride (10 equiv) and the reaction mixture was worked up to yield methyl 6-chloro-6-deoxy-α-D-mannopyranoside (1.124 g, 86% yield) with mp 75° and $[\alpha]^{30}D$ +60° (*c* 1.0, water) after recrystallization from 1-propanol. Jennings and Jones[19] report $[\alpha]D$ +59° (*c* 1.0, water).

Anal. Calcd for $C_7H_{13}O_5Cl$: C, 39.52; H, 6.16; Cl, 16.69. Found: C, 39.60; H, 6.18; Cl, 16.84.

The crystalline methyl 6-chloro-6-deoxy-α-D-mannopyranoside (0.5 g) was dissolved in 1 *N* sodium hydroxide (5 ml), kept for 10 hr at 30°, then deionized and concentrated to give methyl 3,6-anhydro-α-D-mannopyranoside (0.37 g, 93% yield) with mp 129° and $[\alpha]^{30}D$ +96° (*c* 3.0, water) after recrystallization from ethanol–benzene in good agreement with values reported previously.[30]

Anal. Calcd for $C_7H_{12}O_5$: C, 47.73; H, 6.82. Found: C, 47.86; H, 6.87.

Reaction with Methyl α-D-Xylopyranoside.—When methyl α-D-xylopyranoside (1.02 g) was treated in DMF at 65° for 16 hr with methylsulfonyl chloride (10 equiv), unchanged starting material (1.01 g, 99%) was recovered.

Methyl 6-Deoxy-α-D-glucopyranoside.[8,23]—Methyl 6-chloro-6-deoxy-α-D-glucopyranoside (200 mg) was treated for 16 hr with lithium aluminum hydride (100 mg) in boiling tetrahydrofuran (15 ml). Excess lithium aluminum hydride was decomposed by the cautious addition of ethyl acetate and the mixture was filtered. The filtrate was concentrated to dryness and the residue deionized with Amberlite MB-3 to give methyl 6-deoxy-α-D-glucopyranoside (145 mg, 87% yield) with mp 99° and $[\alpha]^{30}D$ +158° (*c* 1.0, water) after recrystallization from ethyl acetate.

Anal. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.87. Found: C, 47.06; H, 7.80.

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Methyl 6-Deoxy-β-D-glucopyranoside.—Methyl 6-chloro-6-deoxy-β-D-glucopyranoside (1.0 g) was treated for 24 hr with lithium aluminum hydride (500 mg) in boiling tetrahydrofuran (50 ml). After 24 hr additional lithium aluminum hydride (500 mg) was added and the reaction was continued for a further 24 hr. Excess lithium aluminum hydride was decomposed by cautious addition of moist tetrahydrofuran to the cooled mixture. Insoluble material was removed by filtration and the filtrate was concentrated to dryness. The product was worked up by silica gel chromatography to give methyl 6-deoxy-β-D-glucopyranoside (800 mg, 96% yield) with mp 130–131° and $[\alpha]^{30}D$ −42° (*c* 2.0, water) after recrystallization from ethyl acetate.

Anal. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.87. Found: C, 47.13; H, 7.88.

Methyl 6-Deoxy-α-D-mannopyranoside.[25]—Methyl 6-chloro-6-deoxy-α-D-mannopyranoside (625 mg) was reduced with lithium aluminum hydride in boiling tetrahydrofuran, as described for the preparation of methyl 6-deoxy-β-D-glucopyranoside, to provide syrupy methyl 6-deoxy-α-D-mannopyranoside (435 mg, 83% yield) with $[\alpha]^{30}D$ +61° (*c* 1.0, water) in agreement with the value reported previously.[25]

Anal. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.87. Found: C, 47.09; H, 7.84.

Methyl 6-deoxy-α-D-mannopyranoside (360 mg) was treated for 16 hr in pyridine (5 ml) with benzoyl chloride (1 ml) and worked up in the usual manner[25] to give methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-mannopyranoside (890 mg, 90% yield) with mp 133° and $[\alpha]^{30}D$ −176° (*c* 0.7 chloroform) after recrystallization from methanol in agreement with values reported previously.[25]

Methyl 6-*O*-Benzoyl-α-D-glucopyranoside.[26]—Methyl 6-chloro-6-deoxy-α-D-glucopyranoside (343 mg) was treated for 16 hr with sodium benzoate (1 g) in boiling DMF (30 ml); then the mixture was concentrated to dryness. The residue was dissolved in water and the solution was passed through a column of Amberlite IR-120 (H^+ form). The effluent was extracted with ether to remove benzoic acid and the aqueous solution was concentrated to a chromatographically pure syrup which gave crystalline methyl 6-*O*-benzoyl-α-D-glucopyranoside (357 mg, 74% yield) with mp 131° and $[\alpha]D$ +108° (*c* 1.2, water) after recrystallization from ethanol, identical with an authentic sample.[26]

Anal. Calcd for $C_{14}H_{18}O_7$: C, 53.85; H, 5.77. Found: C, 53.81; H, 5.75.

Registry No.—Methylsulfonyl chloride, 124-63-0; *N*,*N*-dimethylformamide, 68-12-2; methyl 6-chloro-6-deoxy-α-D-glucopyranoside, 4144-87-0; methyl 6-chloro-6-deoxy-β-D-glucopyranoside, 4990-84-5; methyl 6-chloro-6-deoxy-α-D-mannopyranoxide, 4990-80-1; methyl 3,6-anhydro-α-D-mannopyranoside, 15814-56-9; methyl 6-deoxy-α-D-glucopyranoside, 5155-43-1; methyl 6-deoxy-β-D-glucopyranoside, 6340-52-9; methyl 6-deoxy-α-D-mannopyranoside, 15814-59-2; methyl 6-*O*-benzyl-α-D-glucopyranoside, 4338-28-7.

The Reaction of Benzil with Methylsulfinyl Carbanion. The Phenoxide Ion Generation of Methylsulfinyl Carbanion in Low Concentration

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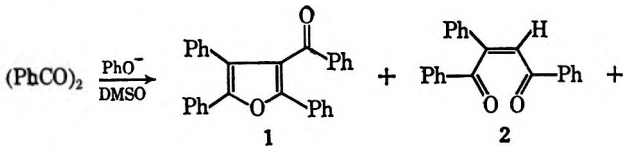
Phenoxide ion is shown to effect a reaction between benzil and dimethyl sulfoxide to yield 3-benzoyl-2,4,5-triphenylfuran (1), *cis*-α,β-dibenzoylstyrene (2), benzoic acid, and benzilic acid. A method for the generation of methylsulfinyl carbanion in very low concentration is presented. The structure proof of previously unreported 1 is described.

While certain alkoxide ions are reported to transform benzil to the corresponding benzilic ester,[1] phenoxide ion, due to its low reactivity, has been shown to be incapable of effecting the transformation in aqueous ethanol[2] and benzene.[1] In view of the many recent reports[3] of enhanced anion reactivity in polar aprotic solvents such as dimethyl sulfoxide (DMSO), it was felt that a new attempt to cause phenoxide ion to react with benzil was in order. This report describes the results obtained from the attempted reaction plus the characterization and structure determination of the reaction products.

No reaction was observed between benzil and phenoxide ion in DMSO at room temperature. On heating the solution to 100° for 48 hr, reaction occurred and the products isolated were 3-benzoyl-2,4,5-triphenylfuran (1), *cis*-α,β-dibenzoylstyrene (2), benzoic acid, and benzilic acid.



$PhCO_2H + Ph_2C(OH)CO_2H$

The possibility of some phenyl benzilate formation with subsequent hydrolysis to benzilic acid by water, an assumed by-product in the reaction(s) leading to 1 and 2, cannot be ruled out. The benzilic acid probably arises, however, from the reaction of benzil with this water by phenoxide ion catalysis.

Whereas details of the reaction mechanism are as yet incomplete, certain observations can be made at this time. It is believed, for example, that the reactive nucleophile in the system is methylsulfinyl carbanion (3) which is generated by proton exchange between solvent and the weakly basic phenoxide ion (eq 1). The con-

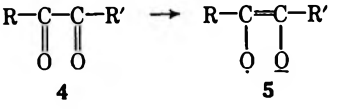
$$PhO^- + CH_3S(O)CH_3 \rightleftharpoons PhOH + CH_3S(O)CH_2:^- \quad (1)$$

3

clusion is supported by the fact that, when methylsulfinyl carbanion is generated in the usual manner[4] and then added to a stirred solution of benzil in DMSO, the same reaction products are obtained. However, the latter reaction is less satisfactory owing to lower yields of isolable products and greater yields of oils and tars. This reaction also establishes that benzilic acid formation is not limited to phenyl benzilate hydrolysis in the original reaction. To demonstrate the necessity of phenoxide ion in effecting the transformation, benzil was heated in DMSO at 100° for 48 hr, and only starting material was recovered.

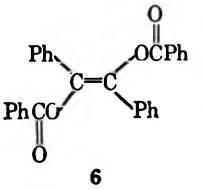
The observation that the reaction using phenoxide ion is essentially complete only after heating at 100° for two days indicates that the concentration of methylsulfinyl carbanion in the reaction is very low. This conclusion is supported by the fact that the reaction between benzil and prepared methylsulfinyl carbanion occurs rapidly at 20° and is noticeably exothermic. Phenoxide ion will possibly find general applicability as a reagent for generating methylsulfinyl carbanion in reactions where a low concentration of this nucleophile is necessary or desirable. However, such applications will necessarily be limited to situations where phenoxide ion competes ineffectively with the anion as a nucleophile and where higher temperatures are permissable.

Russell and coworkers have investigated extensively the reduction of the various types of diketones by anions in DMSO–*t*-butyl alcohol solution and have detected the formation of the corresponding semidiones (5) in appreciable concentrations.[5] Benzil (4, R = R′ = Ph) is reported to form the corresponding semidione when treated with benzoin in basic solu-



tion.[5a,6] Whether this reduction is occurring in the reaction under investigation or to what extent is not known.

Another unusual cleavage reaction of benzil in DMSO was recently observed in this laboratory.[7] In this instance, cyanide ion was shown to catalyze the isomerization of benzil to *trans*-α,β-stilbenediol dibenzoate (6); the same reactants in alcoholic solvent are



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(5) (a) G. A. Russell, E. T. Strom, E. R. Talaty, and S. A. Weiner, *ibid.*, **88**, 1998 (1966); (b) E. T. Strom, G. A. Russell, and J. H. Schoeb, *ibid.*, **88**, 2004 (1966), and references to earlier reports cited therein.
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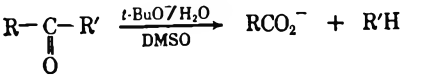
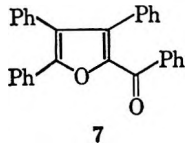
reported to yield benzaldehyde and the corresponding benzoate ester.[8]

A general method for cleaving nonenolizable ketones is reported to occur under mild conditions in aprotic solvents containing *t*-butoxide ion and water.[9]



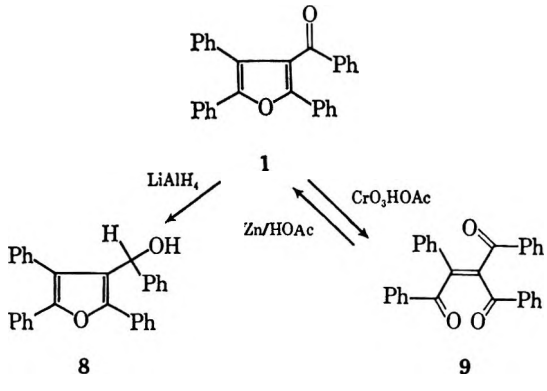
While 2-benzoyl-3,4,5-triphenylfuran (7) is known,[10]



7

its isomer, 1, is previously unreported. Compound 1 was characterized according to Scheme I.

SCHEME I



Functional group assignment was made in each case from the infrared spectrum. Data from nmr spectra confirmed the single carbonyl character of 1 in that: (a) the integrated proton ratio revealed deshielding of only two *ortho* hydrogens by the carbonyl anisotropic effect[11] and (b) only two hydrogens were gained in the reduction of 1 to 3-(α-hydroxybenzyl)-2,4,5-triphenylfuran (8) Oxidation of 1 to 2-benzoyl-1,3,4-triphenyl-2-butene-1,4-dione (9) is characteristic of 2,5-diphenylfurans.[12] Also, the reduction of 9 to 1 is characteristic of 2-butene-1,4-diones.[13]

Finally, 1 was prepared by independent synthesis from ω-desylacetophenone (10) according to Scheme II.

Although enolate ions are more susceptible to O-acylation than to C-acylation, where enolate ion is present in excess and time is allowed for product equilibration, the stable anion of the C-acylated product will predominate.[14] In the above reaction this stable anion can only be 13. When the anions of ω-desylacetophenone (11 and 12) were reacted with benzoyl chloride in 1,2-dimethoxyethane, using a reactant ratio of 2:1, respectively, 2-benzoyl-1,3,4-triphenylbutane-1,4-dione (14) was isolated in 58% yield. It is interesting to note that acylation of 1,4-diketones, *via* the enolate ions, leads to intermediate products that should be subject to facile intramolecular isomerization in addition to regular intermolecular isomerization.[14] For example, O-benzoylation of 11, the more stable enolate ion,[15] should give 15, the isomerization of which is easily illustrated (Scheme III).

On heating 14 with hydrochloric acid in ethanol, 1 was obtained in near quantitative yield. The reaction is characteristic of enolizable 1,4-diketones.[16]

Attempts to prepare 13 by treating the anion of dibenzoylmethane with desyl chloride in DMSO at elevated temperatures were unsuccessful presumably owing to the inertness of the anion. In each case dibenzoylmethane was recovered.

Other reaction products are well known. Mixture melting points and infrared spectra were used for characterization in each case.

Experimental Section[17]

Starting Materials.—Benzil, mp 94–95°, was obtained commerically and was used without further purification. Sodium phenoxide, prepared by the method of Kornblum and Lurie,[18] was dried overnight at 110° (1 mm) prior to use. ω-Desylacetophenone was prepared by the method of Smith.[19] Dimethyl sulfoxide was dried over molecular sieve (4A) and distilled from calcium hydride (1 mm.).[4] Other materials were of reagent grade and were used without further purification.

Benzil and Phenoxide Ion in Dimethyl Sulfoxide.—Benzil (2.10 g, 0.01 mol) and sodium phenoxide (1.16 g, 0.01 mol) were added to 135 ml of anhydrous dimethyl sulfoxide and heated in a closed system, under an atmosphere of nitrogen, at 100° for 48 hr. The dark brown reaction mixture was poured onto cracked ice, acidified, and extracted with ether. The etheral solution was extracted with sodium bicarbonate solution followed by a 5% solution of sodium hydroxide. The ether layer was washed with water, dried over calcium chloride, and evaporated. The solid residue, on trituration with ethanol, afforded 0.32 g of 3-benzoyl-2,4,5-triphenylfuran (1), mp 170–173°. Recrystallization from ethanol resulted in pale yellow crystals (very light and fluffy), mp 175–176°. The infrared spectrum showed a band at 6.05 μ (carbonyl) and a characteristic absorption at 11.15 μ which was used for the qualitative identification of 1 in reaction mixtures. The nmr spectrum exhibited multiplets at δ 7.5–7.8 and 6.9–7.4 in a ratio of 2:18.

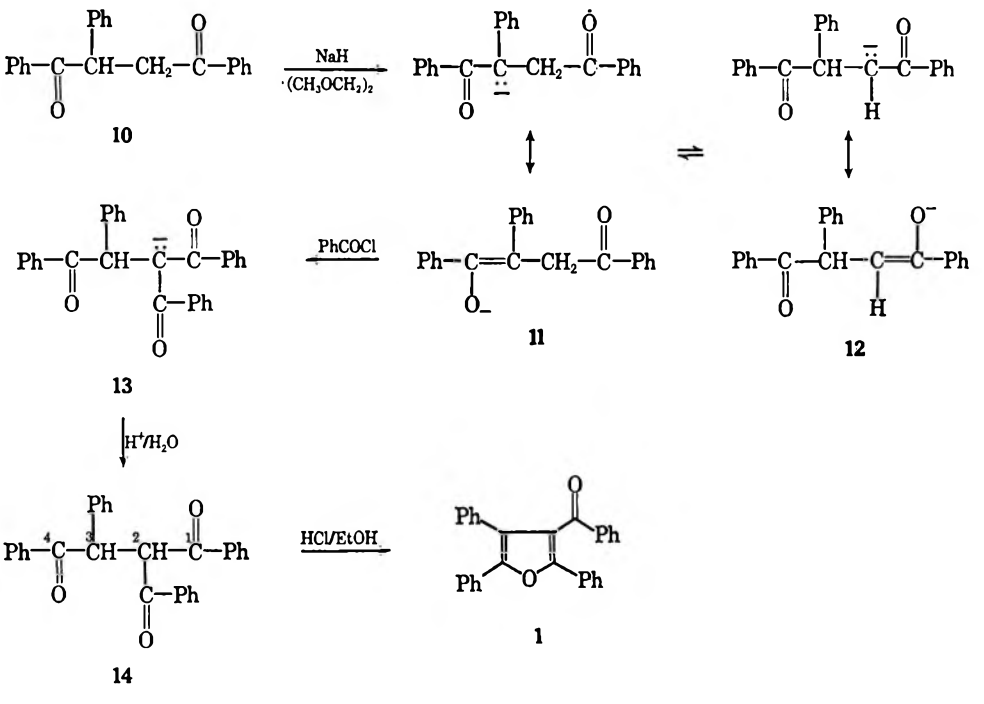
Anal. Calcd for $C_{29}H_{20}O_2$: C, 87.00; H, 5.00; mol wt, 400. Found: C, 86.94; H, 5.11; mol wt, 385.

The mother liquor from the ethanol trituration was evaporated, dissolved in 10 ml of benzene, and placed on a column containing 70 g of alumina (Alcoa, F-20). The column was developed with 600 ml of petroleum ether (bp 30–60°). Elution with petroleum ether–ethyl ether (90:10) resulted in an additional 0.13 g of 1 followed by 0.10 g of an oil which, on recrystallization from ethanol, yielded benzil, mp 93–94°. An unidentified oil, 0.18 g, was eluted with petroleum ether–ethyl ether (80:20 and 70:30). Elution with petroleum ether–ethyl ether (50:50) resulted in the isolation of 0.24 g of *cis*-α,β-dibenzoylstyrene (2), mp 128–129° (from ethanol), lit.[20] mp 129°. Mixture melting point and infrared spectra were used for identification.

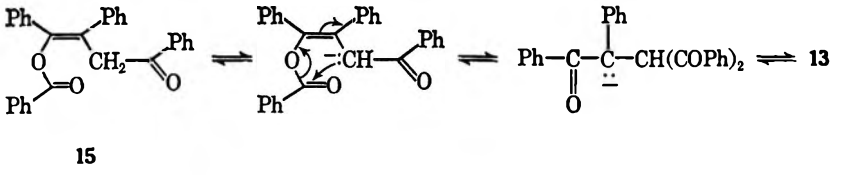
Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.62; H, 5.13. Found: C, 84.56; H, 5.30.

(8) H. Kwart and M. Baevsky, *J. Amer. Chem. Soc.*, **80**, 580 (1958).
(9) P. G. Gassman, J. T. Lumb, and F. V. Zalar, *ibid.*, **89**, 946 (1967).
(10) P. Yates and G. H. Stout, *ibid.*, **76**, 5110 (1954).
(11) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p 123.
(12) C.-K. Dien and R. E. Lutz, *J. Org. Chem.*, **22**, 1355 (1957).
(13) R. C. Elderfield and T. N. Dodd, Jr., in "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p 131, and references cited therein.
(14) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).
(15) The phenyl group has been shown to exert a stabilizing influence in determining the direction of enolization.[14]
(16) Reference 13, p 127.
(17) Melting points are uncorrected. Elemental analyses and molecular weight determinations were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined using the Nujol mull technique. The nmr spectra were determined in deuterated chloroform at 100 Mc using tetramethylsilane as an internal standard.
(18) N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959).
(19) A. Smith, *J. Chem. Soc.*, **57**, 643 (1890).
(20) F. R. Japp and F. Klingeman, *ibid.*, **57**, 673 (1890).

SCHEME II



SCHEME III



Finally, elution of the column with methanol produced a trace of red-brown oil that was not further characterized.

The sodium bicarbonate extract of the reaction mixture was acidified and extracted with ether. The ether layer was washed with water, dried with calcium chloride, and evaporated. Sublimation of the residue yeilded 0.39 g of benzoic acid, mp 119–121°, and a residue (0.30 g) of benzilic acid, mp 145–147° (from hexane–chloroform). Mixture melting point with an authentic sample in each case showed no depression.

From a reaction between phenoxide ion and benzil in DMSO at 90° for 24 hr, very low yields of products were obtained while large quantities of starting material were recovered.

From an experiment in which a solution of benzil in DMSO was heated for 48 hr at 100° in the absence of phenoxide ion, starting material was recovered in quantitative yield.

Benzil and Methylsulfinyl Carbanion in Dimethyl Sulfoxide.—Methylsulfinyl carbanion was generated by treating 0.45 g (0.01 mol) of sodium hydride, 56% by weight in mineral oil, with 60 ml of anhydrous dimethyl sulfoxide using the method of Corey and Chaykovsky.[4] The resulting solution was transferred, under nitrogen, to a dropping funnel *via* a connecting tube and added dropwise to a stirred solution of benzil (2.10 g, 0.01 mol) in 50 ml of dimethyl sulfoxide. The temperature was maintained at 20° throughout the addition (30 min). After stirring for an additional 1 hr, the solution was added to cracked ice, acidified, and extracted with ether. The ether layer was extracted with sodium bicarbonate solution and with 5% sodium hydroxide solution, washed with water, dried over calcium chloride, and evaporated. The oily residue failed to produce a solid on trituration with ethanol. The residue was then dissolved in 10 ml of benzene and placed on a column containing 80 g of alumina (Alcoa, F-20). The column was developed with 600 ml of petroleum ether (bp 30–60°). Elution with petroleum ether–ethyl ether (90:10) yielded 0.14 g of 3-benzoyl-2,4,5-triphenylfuran (1), mp 175–176° (from ethanol). Mixture melting point and infrared spectra showed the compound to be identical with the corresponding compound in the previous reaction. Elution with petroleum ether–ethyl ether (80:20 and 70:30) resulted in 0.16 g of an unidentified oil. Elution with petroleum ether ethyl ether (50:50) resulted in the isolation of 0.24 g of *cis*-α,β dibenzoylstyrene (2), mp 128–129° (from ethanol); the sample was identical (mixture melting point and infrared spectra) with the corresponding material in the previous reaction. Elution with methanol produced 0.35 g of an unidentified red oil.

The sodium bicarbonate extract of the reaction mixture was acidified and extracted with ether. The ether layer was washed with water, dried over calcium chloride, and evaporated. The solid residue, on sublimation, yielded 0.34 g of benzoic acid, mp 119–121° (from water) and 0.52 g of benzilic acid, mp 145–147° (from hexane–chloroform). A mixture melting point with an authentic sample in each case showed no depression.

3-(α-Hydroxybenzyl)-2,4,5-triphenylfuran (8).—A solution of 1 (0.26 g, 0.00066 mol) in 50 ml of ether was added dropwise to 0.25 g (0.006 mol) of lithium aluminum hydride in 150 ml of ether under an atmosphere of dry nitrogen. The reaction mixture was refluxed for 6 hr. Excess lithium aluminum hydride was destroyed with an ethereal solution of ethanol. Aqueous acid was added and the layers were separated. The ether layer was washed with water, dried over magnesium sulfate, and evaporated to yield 0.26 g (100%) of 8, mp 131–132° (from petroleum ether, bp 30–60°). The infrared spectrum showed weak hydroxyl absorption at 2.85 μ. The nmr spectrum revealed a 20 H multiplet at δ 6.8–7.8 (aromatic), a 1 H singlet at 5.94 (hydroxyl), and a 1 H singlet at 1.96 (methinyl).

Anal. Calcd for $C_{29}H_{22}O_2$: C, 86.57; H, 5.47. Found: C, 87.10; H, 5.67.

2-Benzoyl-1,3,4-triphenyl-2-butene-1,4-dione (9).—A solution of 1 (1.26 g, 0.0032 mol) and 0.63 g (0.0063 mol) of chromium trioxide in 200 ml of glacial acetic acid was heated at 80° for 40 min. The reaction mixture was added to ice and extracted with ether. The ether layer was washed with water and extracted with 5% sodium hydroxide solution until the extracts were alkaline. The ethereal solution was then washed with water, dried over calcium chloride, and evaporated. The pale yellow residue was triturated with hexane to yield 1.01 g (84% yield) of 9, mp 130–131° (from ethyl ether). The infrared

spectrum showed absorption at 6.05 μ (carbonyl) and the nmr spectrum exhibited only aromatic proton absorption, a 6 H multiplet at δ 7.8–8.1 and a 14 H muliplet at 7.0–7.5.

Anal. Calcd for $C_{29}H_{20}O_3$: C, 83.65; H, 4.81; mol wt, 416. Found: C, 83.39; H, 4.81; mol wt, 420, 415.

Reduction of 2-Benzoyl-1,3,5-triphenyl-2-butene-1,4-dione (9).—A sample of 9 (0.43 g, 0.001 mol) and 0.41 g (0.006 mol) of zinc powder were refluxed in 50 ml of glacial acetic acid for 1 hr. The reaction mixture was added to water and extracted with ether. Acetic acid was removed by extraction with 5% sodium hydroxide solution until the extracts were alkaline. The ethereal solution was washed with water, dried over calcium chloride, and evaporated to yield a residue (0.34 g, 85% yield), mp 168–172°. On recrystallization from ethanol, pale yellow crystals (mp 175–176°) were obtained that were identified as 1 from mixture melting point and spectral data.

2-Benzoyl-1,3,4-triphenylbutane-1,4-dione (14).—Sodium hydride (1.2 g, 0.028 mol), 56% by weight in mineral oil, was washed three times with small quantities of petroleum to remove the mineral oil, and added, under nitrogen, to a flask containing 150 ml of anhydrous 1,2-dimethoxyethane. ω-Desylacetophenone[19] (8.0 g, 0.026 mol) was added and the system was heated at 55° until the evolution of hydrogen gas had ceased (45 min). Vigorous evolution of gas occurred only near the end of the reaction. Benzoyl chloride, 1.75 g (0.01 mol), in 25 ml of 1,2-dimethoxyethane, was added dropwise to the dark-red solution. The reaction mixture was heated for 30 min and poured onto cracked ice. After acidification, the reaction mixture was extracted with ether. The ether solution was extracted with 5% sodium hydroxide solution until the extracts produced no more solid on acidification. The alkaline extracts were combined, acidified, and extracted with ether. The ethereal solution was washed with water, dried over calcium chloride, and evaporated to yield 3.07 g (58% yield) of **14**, mp 164.5–165° (from ethyl ether). The infrared spectrum showed carbonyl absorption at 5.95 and 6.05 μ. The nmr spectrum revealed 1 H (methinyl) doublets centered at δ 6.33 and 5.73 ($J \cong 5.1$ cps) and a 20 H (aromatic) multiplet at 6.8–8.0.

Anal. Calcd for $C_{29}H_{22}O_3$: C, 83.25; H, 5.26. Found: C, 83.22; H, 5.21.

The ether solution remaining after alkaline extraction was washed with water, dried over calcium chloride, and evaporated. Recrystallization of the residue gave 3.95 g (99% recovery) of ω-desylacetophenone, mp 124–126° (lit.[19] mp 126°).

Dehydration of 2-Benzoyl-1,3,4-triphenylbutane-1,4-dione (14).—A sample of **14** (1.0 g, 0.0024 mol) and 6.0 ml of concentrated hydrochloric acid were refluxed in 200 ml of ethanol for 2.5 hr. After evaporation of solvent, the residue was triturated with ethanol to yield 0.83 g (87% yield) of pale yellow solid, mp 175–176° (from ethanol). On admixture with **1**, no depression was observed in the melting point. The infrared spectra of the two samples were identical.

Registry No.—**1**, 15440-99-0; **2**, 13249-75-7; **3**, 13810-16-7; **4** (R = R′ = Ph), 134-81-6; **8**, 15441-02-8; **9**, 15441-03-9; **14**, 15441-04-0; phenoxide ion, 3229-70-7.

Acknowledgments.—We are grateful to Dr. M. R. Willcott of the University of Houston for obtaining the nmr spectra. We also acknowledge the assistance of Mr. James Doty and Mr. Tommy Wilbanks who prepared some of the starting materials.

Directive Effects in the Chlorination of Benzyl Chloromethyl Sulfides[1]

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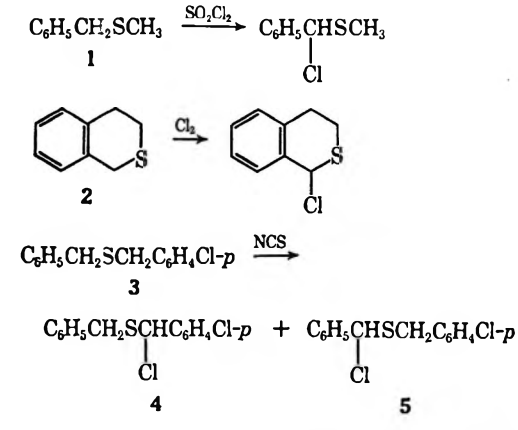
Received September 18, 1967

A series of benzyl chloromethyl sulfides has been prepared and treated sequentially with sulfuryl chloride and *m*-chloroperbenzoic acid. Separation and analysis of the resulting chloro sulfone mixtures have established the much greater directing influence of a chlorine atom when compared with a substituted phenyl group, except when the aromatic ring carries a *p*-nitro substituent.

When a sulfide possessing at least one hydrogen at an α-carbon atom is treated with 1 equiv of chlorine,[4] sulfuryl chloride,[5,6] or N-chlorosuccinimide (NCS)[1,7] in an inert solvent, α-chloro sulfides are produced. Addition of larger amounts of chlorinating agent generally results in more extensive halogenation.[6a,8] A major portion of the interest associated with this reaction derives from the unresolved nature of the detailed mechanism involved in the α-chlorination process.[5,6,9]

Only a limited number of isolated reports have appeared concerning directive effects in the chlorination of sulfides. Thus, chlorination of benzyl alkyl sulfides such as **1**[10] and **2**[11] has been shown to lead only to α-chlorobenzyl sulfides. Chlorinated isomers **4** and **5** are formed in the ratio of 1.6:1 when benzyl *p*-chloro-



benzyl sulfide (**3**) is treated with an equimolar quantity of N-chlorosuccinimide in carbon tetrachloride solu-

(1) α-Halo Sulfones. Paper IX. For previous paper in this series, see L. A. Paquette and J. C. Phillips, *Tetrahedron Lett.*, 4645 (1967). The authors wish to express their appreciation to the National Science Foundation for funds used in partial support of this Research Fellow, 1965–1967.

(2) Alfred P. Sloan Foundation Research Fellow, 1965–1967.

(3) Undergraduate research participant, 1965–1966.

(4) H. Böhme, H. Fischer, and R. Frank, *Ann.*, **563**, 54 (1949), and pertinent references cited therein.

(5) (a) F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955); (b) F. G. Bordwell, G. D. Cooper, and H. Morita, *ibid.*, **79**, 376 (1957).

(6) (a) W. E. Truce, G. H. Birum, and E. T. McBee, *ibid.*, **74**, 3594 (1952); (b) L. A. Paquette, *ibid.*, **86**, 4085 (1964).

(7) (a) D. L. Tuleen and T. B. Stephens, *Chem. Ind.* (London), 1555 (1966); (b) D. L. Tuleen and V. C. Marcum, *J. Org. Chem.*, **32**, 204 (1967).

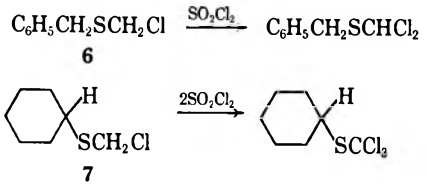
(8) (a) L. A. Paquette, *J. Amer. Chem. Soc.*, **86**, 4089 (1964); (b) L. A. Paquette and L. S. Wittenbrook, *ibid.*, **89**, 4483 (1967); (c) L. A. Paquette, L. S. Wittenbrook, and V. V. Kane, *ibid.*, **89**, 4487 (1967); (d) L. S. Wittenbrook, unpublished observations.

(9) C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962, p 59.

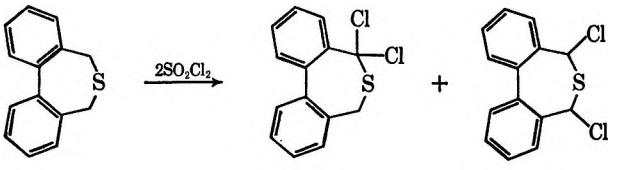
(10) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **73**, 5187 (1951).

(11) H. Böhme, L. Tils, and B. Unterbalt, *Chem. Ber.*, **97**, 179 (1964).

tion.[7b] Polychlorination of dimethyl sulfide results in all the hydrogens of one carbon atom being replaced by chlorine before the second methyl group is attacked.[6a] The same substitution behavior is displayed by chlorosulfides 6[8c] and 7.[8d] Whereas reaction of dibenzyl



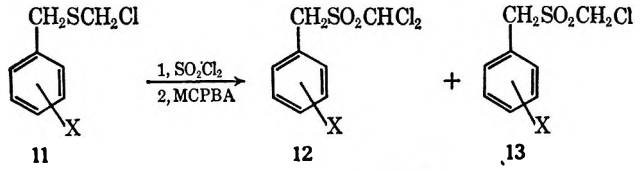
sulfide with 2 equiv of sulfuryl chloride produces the α,α-dichloro sulfide as the only product,[8a] it has been observed that 2,7-dihydro-3,4-5,6-dibenzothiepin (8) interestingly affords a mixture of 9 and 10 in a



ratio of 3.6:1 (based upon the isolation of pure dichloro sulfones) under the same conditions;[8a] in the latter case, it has been proposed that the strong inductive effect of the α-chloro substituent in the intermediate α-chloro sulfide is offset by steric factors operative in the transition state for α,α-dichlorination leading to substitution in the opposite direction. The present study describes directive effects operative in the sulfuryl chloride chlorination of a group of selected benzyl chloromethyl sulfides in which structural modifications have been introduced to provide additional insight into the requirements of such competitive proton abstraction processes and the mechanism of halogenation.

Results and Discussion

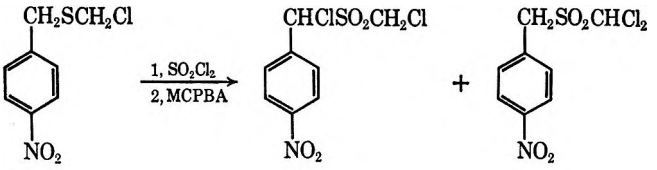
The sequential reaction of chloromethyl *p*-fluorobenzyl sulfide (11a) with 1 equiv of sulfuryl chloride and excess *m*-chloroperbenzoic acid (MCPBA) in chloroform solution afforded a mixture consisting of 12a (80%) and 13a (20%). Chlorination of chloro-



a, X = *p*-F; b, X = *p*-Cl; c, X = *m*-CF_3

methyl *p*-chlorobenzyl sulfide (11b) and chloromethyl *m*-trifluoromethylbenzyl sulfide (11c) under similar conditions produced dichloro sulfones 12b and 12c, respectively, as the only dichlorinated products. No evidence of halogenation at the benzylic methylene group was detected upon close examination of the nmr spectra of the crude reaction mixtures before and after oxidation. The mono- and dichloro sulfones were identified by elemental analysis and by their nmr and mass spectra. The chemical shifts of the various α-sulfonyl proton absorptions which are collected in Table I are seen to be unexceptional for these six compounds when the shielding constant for chlorine is taken into consideration. The electron-impact-induced fragmentations of 12b and 12c were found to result predominantly in direct cleavage of the benzylic C–S bond to give the corresponding tropylium cations. Thus, the mass spectrum of 12b displayed a base peak at *m/e* ($C_7H_6Cl^+$) and that of 12c a base peak at *m/e* 159 ($C_8H_6F_3^+$). No other peaks of greater than 15% relative intensity were observed.[12]

In contrast to the above results, when chloromethyl *p*-nitrobenzyl sulfide (14) was treated with 1 molar equiv of sulfuryl chloride and the crude mixture of dichloro sulfides was oxidized directly with MCPBA, the isomeric dichloro sulfones 15 and 16 were formed in



a ratio of 3:2. The nmr spectra of 15 and 16 (Table I) are closely related to those of compounds with similar structures. With particular regard to the spectrum of 15, it should be noted that the protons of the methylene

TABLE I

CHEMICAL SHIFTS OF BENZYLIC AND NONBENZYLIC α-SULFONYL PROTON(S) IN SELECTED α-CHLORINATED SULFONES[a]

Compd	δ, ppm Benzylic	δ, ppm Nonbenzylic
Dibenzyl sulfone	4.10	
$C_6H_5CH_2SO_2CHClC_6H_5$	4.44	(5.42)
13a	4.41	4.26
13b	4.37	4.21
13c	4.46	4.27
p-$NO_2C_6H_4CH_2SO_2CH_2Cl$	4.53	4.32
$C_6H_5CH_2SO_2CHCl_2$	4.56	6.04
12a	4.51	6.03
12b	4.53	6.06
12c	4.58	6.10
16	4.71	6.22
15	6.13	4.51, 5.10[b]
18		5.12
17	4.88	
$C_6H_5CH_2SO_2CCl_3$	4.77	

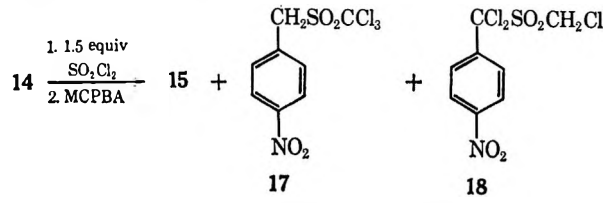
[a] Spectra were determined on *ca.* 15% solutions in $CDCl_3$; values are reported relative to internal tetramethylsilane and refer to singlets unless otherwise indicated. [b] AB pattern, J_{AB} = 13 Hz.

group appear as an AB pair of doublets. The nonequivalency of these protons, presumably caused by the spatial proximity of the asymmetric benzylic carbon atom, has been observed with a limited number of sulfones.[13] In further confirmation of the structural assignments, the mass spectrum of 16 was found to exhibit a base peak at *m/e* 136 $(C_7H_6NO_2)^+$ as expected from the analogous fragmentation of chloromethyl *p*-nitrobenzyl sulfone. The mass spectrum of 15 is clearly seen to be that of an α-chloro-*p*-nitrobenzyl sulfone because of the base peak at *m/e* 170 ($C_7H_5ClNO_2^+$).

(12) The favored fragmentation of sulfones to give R^+ and RSO_2^+ has been recognized previously: R. T. Aplin and K. Bailey, *J. Chem. Soc., Sect. B*, 513 (1967), and appropriate references cited therein.

(13) J. J. Looker, *J. Org. Chem.*, **31**, 2973 (1966); see also ref 7b.

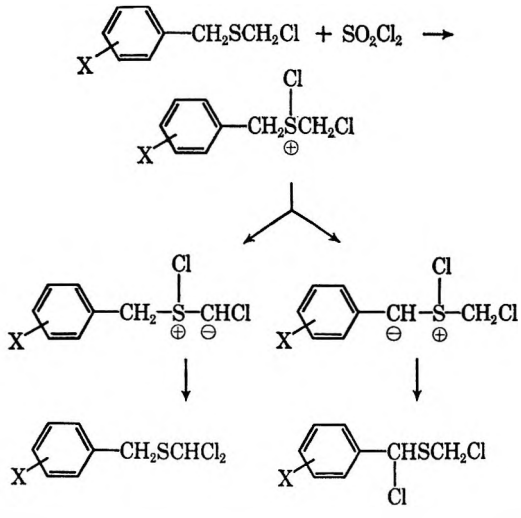
Chlorination of **14** with an excess (1.5 molar equiv) of sulfuryl chloride led after oxidation to a mixture of **15** (54%) and the isomeric trichloro sulfones **17** (38%) and **18** (8%). Assignment of structure to **17**



17 18

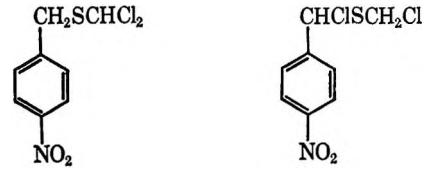
and **18** again rests on their nmr and mass spectra. Whereas **17** produces a base peak at *m/e* 136 ($C_7H_6NO_2^+$) upon electron impact, trichloro sulfone **18** is seen to undergo extensive fragmentation (base peak *m/e* 43).

The data presented here definitively establish the much greater directing influence of a chlorine atom when compared with a substituted phenyl group, except when the aromatic ring carries a *p*-nitro substituent. Even in this case, however, a more or less equitable situation obtains (ratio 1.5:1). Although the observed directive effects are inconsistent with the suggestion of Price and Oae[9] that the chlorination of sulfides by sulfuryl chloride may proceed by means of an intermediate radical stabilized by octet expansion of the adjacent sulfur atom, they do agree with the intervention of an ionic mechanism. Subsequent to S-chloro-



sulfonium salt formation, the more acidic α hydrogen is subject to abstraction and the resulting ylide is transformed to the observed α-chloro sulfide. On this basis, the nature of the products would be expected to be controlled by the relative acidities of the α protons which, in turn, reflect the relative basicities of the substituents (chlorine and substituted phenyl in the present instance) in the transition state. The present work emphasizes the powerful effect of the α-chloro substituent in this regard; only when the phenyl substituent bears a *p*-nitro substituent can it compete somewhat effectively with this halogen.

In conclusion, a further comment relevant to the results obtained when **14** was treated with excess sulfuryl chloride is in order. Comparison of the direction of initial chlorination in this run (ratio of **15** and **18** to **17** = 1.6:1) with the data when only 1 equiv of chlorinating agent was employed (ratio of **15** to **16** = 1.5:1) indicates that the same directional effect (within experimental error) is operative in both cases as, of course, it should be. Interestingly, however, dichloro sulfide **19** is converted into its S-chlorosulfonium chloride at a more rapid rate than is dichloro sulfide **20**, as indicated by the total conversion of **19**



19 20

to *p*-nitrobenzyl trichloromethyl sulfide (isolated as its sulfone). Furthermore, the total absence of trichloro sulfones in the run performed with 1 equiv of sulfuryl chloride points to the fact that the reactivity of the various chloro sulfides toward the chlorinating agent is **14** >> **19** > **20**. Since relative rates of chloro sulfonium salt formation very likely represent a quantitative assay of the relative basicities of benzylic sulfides toward the chloronium donor,[7b] the preceding evidence indicates that the same order holds for the basicities of the chloro sulfides in question.

Experimental Section[14]

General Procedure for the Preparation of Mercaptans.—A solution of 9.45 g (0.05 mol) of *p*-fluorobenzyl bromide and 4.57 g (0.06 mol) of thiourea in 40 ml of 70% aqueous ethanol was refluxed with stirring for 2 hr and cooled. At this point a small aliquot was isolated and the thiuronium bromide was recrystallized from ethanol to purity, mp 144–145°.

Anal. Calcd for $C_8H_{10}BrFN_2S$: C, 36.23; H, 3.80; N, 10.57. Found: C, 36.19; H, 3.96; N, 10.83.

The remainder of the cold solution was added slowly to a saturated aqueous solution of 16.8 g (0.2 mol) of sodium bicarbonate. The precipitated carbonate salt was separated by filtration and the filtrate was neutralized with hydrochloric acid. After the majority of the carbonate salt had been steam distilled, the neutralized filtrate was added and the steam distillation continued. The liberated mercaptan was extracted with ether; the ether solution was dried and evaporated and the residue was distilled to give 6.32 g (89%) of *p*-fluorobenzyl mercaptan, bp 69° (6 mm).

Anal. Calcd for C_7H_7FS: C, 59.12; H, 4.96; S, 22.55. Found: C, 59.78; H, 4.88; S, 22.59.

From *m*-trifluoromethylbenzyl chloride (Pierce Chemical Co.) there was prepared the thiuronium chloride, mp 194.5–195.5° (from ethanol) and the mercaptan, bp 55° (2.1–2.2 mm), $n^{24}D$ 1.4890. The latter substance was isolated in 72% yield.

Anal. Calcd for $C_9H_{10}ClF_3N_2S$: C, 39.93; H, 3.72; N, 10.35. Found: C, 39.94; H, 3.80; N, 10.45.

Anal. Calcd for $C_8H_7F_3S$: C, 49.99; H, 3.67; S, 16.68. Found: C, 50.30; H, 3.65; S, 16.94.

General Procedure for the Preparation of Benzyl Chloromethyl Sulfides.—Treatment of a solution of 47.6 g (0.30 mol) of *p*-chlorobenzylmercaptan (Wateree Chemical Co.) in 100 ml of dichloromethane with 9.0 g (0.30 mol) of paraformaldehyde and anhydrous hydrogen chloride at −20° under the prescribed conditions gave 43.7 g (70.5%) of **11b**, bp 118–119° (0.4 mm).

Oxidation of a small portion of this material with *m*-chloroperbenzoic acid in chloroform solution[7] gave **13b**, mp 155° (from cyclohexane).

Anal. Calcd for $C_8H_8Cl_2O_2S$: C, 40.18; H, 3.37. Found: C, 40.29; H, 3.48.

(14) Melting points are corrected and boiling points are uncorrected. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were determined with a Perkin-Elmer Model 237 spectrometer fitted with sodium chloride prisms. The nmr spectra were recorded with a Varian A-60 spectrometer. The mass spectra were measured with an AEI MS-9 mass spectrometer at an ionizing energy of 70 eV.

From *p*-fluorobenzyl mercaptan there was prepared the corresponding chloromethyl sulfide **11a** in 76.5% yield, bp 67° (0.3 mm). The sulfide was likewise characterized as its sulfone **13a**, mp 132° (from cyclohexane).

Anal. Calcd for $C_8H_8ClFO_2S$: C, 43.15; H, 3.62; S, 14.40. Found: C, 43.33; H, 3.69; S, 14.42.

From *m*-trifluoromethylbenzyl mercaptan there was prepared the corresponding chloromethyl sulfide **11c** in 79% yield, bp 67° (0.2 mm). The sulfide was oxidized to its sulfone (**13c**), mp 90° (from cyclohexane), for purposes of characterization.

Anal. Calcd for $C_9H_8ClF_3O_2S$: C, 39.60; H, 2.97; Cl, 31.04. Found: C, 39.64; H, 2.96; Cl, 13.00.

From *p*-nitrobenzyl mercaptan[15] there was prepared the corresponding chloromethyl sulfide **14**, mp 50–51° (from CCl_4), in 70% yield. Oxidation of **14** gave the related sulfone as colorless needles from chloroform–cyclohexane, mp 149.5–150.5°.

Anal. Calcd for $C_8H_8ClNO_4S$; C, 38.48; H, 3.23; Cl, 14.20. Found: C, 38.28; H, 3.16; Cl, 14.02.

General Procedure for the Chlorination and Oxidation of the Benzyl Chloromethyl Sulfides.—Under a nitrogen atmosphere, a solution of 1.0 g (7.3 mmol) of sulfuryl chloride in 10 ml of carbon tetrachloride was added dropwise to a stirred solution of 1.6 g (7.3 mmol) of chloromethyl *p*-nitrobenzyl sulfide (**14**) in 15 ml of the same solvent at 23°. After addition of the sulfuryl chloride had been completed, the solution was refluxed for 2.5 hr and cooled, and the solvent was removed under reduced pressure. The residue was immediately oxidized with 3.1 g (18.2 mmoles) of *m*-chloroperbenzoic acid in cold chloroform. The usual work-up[8] gave a pale yellow oil, the nmr spectrum of which was recorded. Careful chromatography of the oil on 80 g of silica gel [elution with benzene-chloroform (4:1)] afforded **15** and **16** in a ratio of 3:2 (total weight, 1.5 g).

The first compound to be eluted (**15**) was obtained as colorless needles from chloroform–cyclohexane, mp 106.5–107.5°.

Anal. Calcd for $C_8H_7Cl_2NO_4S$: C, 33.82; H, 2.48; Cl, 24.96. Found: C, 33.75; H, 2.37; Cl, 24.83.

The minor component (**16**) was obtained as colorless needles from chloroform-hexane, mp 121–122°.

Anal. Calcd for $C_8H_7Cl_2NO_4S$: C, 33.82; H, 2.48; Cl, 24.96. Found: C, 34.02; H, 2.68; Cl, 24.89.

When **14** (4.34 g, 20 mmol) was treated with 4.05 g (30 mmol) of sulfuryl chloride as above, there was isolated by chromatography on silica gel (in the order of elution) 2.35 g of **17**, mp 162–163° (from chloroform–hexane).

Anal. Calcd for $C_8H_6Cl_3NO_4S$: C, 30.16; H, 1.90; Cl, 33.38. Found: C, 30.23; H, 1.96; Cl, 33.34.

Further elution[16] with benzene–cyclohexane (4:1) gave 250 mg of **18**, mp 110–111° (from chloroform–cyclohexane).

Anal. Calcd for $C_8H_6Cl_3NO_4S$: C, 30.16; H, 1.90; Cl, 33.38. Found: C, 30.38; H, 2.01; Cl, 33.61.

The final compound to be eluted, mp 106.5–107.5°, was found to be **15**, the substance which was eluted first in the previous experiment. Further elution of the column with solvents of increasing polarity gave no additional material.

In similar fashion, reaction of 11.4 g (0.06 mol) of **11a** with 8.8 g (0.065 mol) of sulfuryl chloride afforded a mixture of two sulfones. Chromatography of a weighed aliquot of the total crude product indicated the mixture to be composed of 23% **13a**, mp 132°, and 77% **12a**, mp 62° (from cyclohexane).

Anal. Calcd for $C_8H_7Cl_2FO_2S$: C, 37.54; H, 2.89; S, 12.61. Found: C, 37.37; H, 2.74; S, 12.47.

In like fashion, **11b** afforded a mixture consisting of **13b**, mp 155°, and **12b**, mp 90.5° (from cyclohexane), in a ratio of 4:1.

Anal. Calcd for $C_8H_7Cl_3O_2S$: C, 35.12; H, 2.58; S, 11.72. Found: C, 34.75; H, 2.64; S, 11.71.

When **11c** was treated with sulfuryl chloride and *m*-chloroperbenzoic acid in the above manner, there was isolated upon careful chromatography the chloro sulfones **13c**, mp 90°, and **12c**, mp 70.5° (from cyclohexane), in a ratio of 2:1.

Anal. Calcd for $C_9H_7Cl_2F_3O_2S$: C, 35.19; H, 2.30; Cl, 23.09. Found: C, 35.16; H, 2.32; Cl, 22.96.

In all cases, the ratio of isolated product were found to compare favorably with the integrated intensity ratios of the various proton absorptions in the nmr spectra of the crude oxidation mixtures.

Registry No.—**11a**, 15894-24-3; **11b**, 15894-25-4; **11c**, 15894-26-5; **12a**, 15894-27-6; **12b**, 15894-28-7; **12c**, 15894-29-8; **13a**, 15963-74-3; **13b**, 15893-98-8; **13c**, 15893-96-6; **14** sulfone, 15893-97-7; **15**, 15893-99-9; **16**, 15894-00-5; **17**, 15894-01-6; **18**, 15894-02-7; *p*-fluorobenzyl thiuronium bromide, 15894-03-8; *p*-fluorobenzyl mercaptan, 15894-04-9; *m*-fluorobenzyl thiuronium chloride, 15894-05-0; *m*-fluorobenzyl mercaptan, 15894-06-1; dibenzyl sulfone, 620-32-6; $C_6H_5CH_2SO_2CHCl$-C_6H_5, 6668-15-1; *p*-$NO_2C_6H_4CH_2SO_2CH_2Cl$, 15893-97-7; $C_6H_5CH_2SO_2CHCl_2$, 10038-09-2; $C_6H_5CH_2SO_2CCl_3$, 15894-11-8.

(15) W. S. Hoffman and E. E. Reid, *J. Amer. Chem. Soc.*, **45**, 1833 (1923); W. J. Horn, *ibid.*, **43**, 2603 (1921).

(16) Clean separation of **17** and **18** was not always achieved. However, fractional recrystallization of the mixed fractions readily yielded pure **17** and **18**.

The Reaction of Aryl Chloroformates with Dimethylformamide. A Facile *in Situ* Synthesis of α-Chlorocresols

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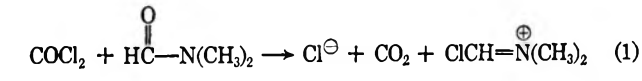
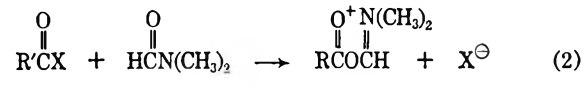
Aryl chloroformates react with dimethylformamide to liberate carbon dioxide and form aryloxy-substituted immonium salts. These in turn react with methanol to generate dimethylformamide, the corresponding phenol, and methyl chloride. An α-chlorotolyl chloroformate yields the α-chlorocresol which reacts with nucleophiles to give good yields of α-substituted cresols.

The reactions of acid halides with amides has been reviewed.[1] Most of these have involved inorganic chlorides (thionyl chloride, phosphorus oxychloride, phosgene) which characteristically yield halogen-substituted immonium salts[2] (eq 1). Some work has been



(1)

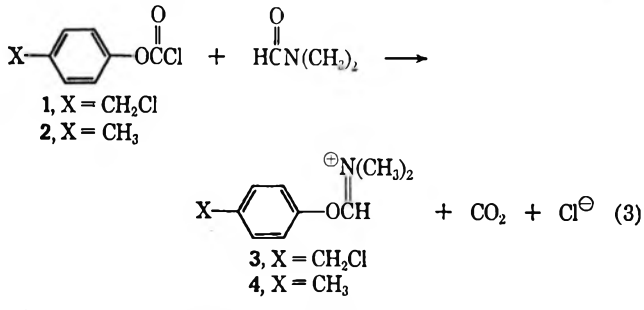
published on the reaction of organic acid halides with amides[1,2] wherein salts have been isolated and the composition designated as shown; however, there is



(2)

little information on the reaction of chloroformates with amides.[1] Bredereck[3,4] postulates an intermediate analogous to the product in eq 2 in the formation of tris(formylamino)methane from ethyl chloroformate and formamide and also in the amide-catalyzed rearrangement of alkyl cholorformates to alkyl chlorides. Hall[2] also attributes the conductivity of ethyl chloroformate solutions in dimethylformamide to this species.

We present here results of an investigation of the previously unreported reaction of aryl chloroformates with dimethylformamide. Using α-chloro-*p*-tolyl chloroformate (**1**) and *p*-tolyl chloroformate (**2**) the reaction presented in eq 3 occurs. Salts **3** and **4** react

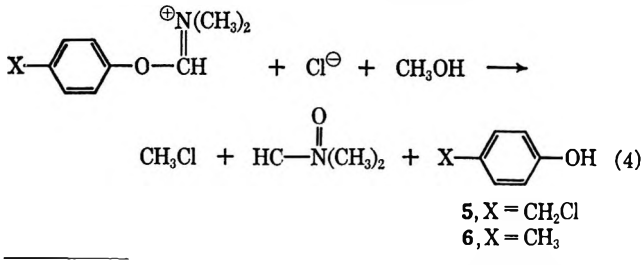


1, X = CH_2Cl
2, X = CH_3

(3)

3, X = CH_2Cl
4, X = CH_3

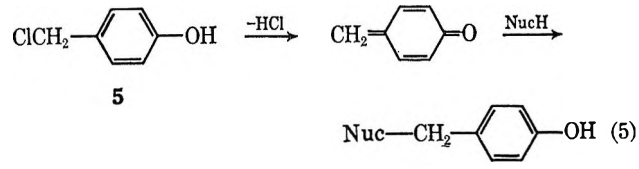
with 1 mol of methanol, giving dimethylformamide and methyl chloride (eq 4). The corresponding phenol,



(4)

5, X = CH_2Cl
6, X = CH_3

α-chloro-*p*-cresol (**5**) or *p*-cresol (**6**), is also found in essentially quantitative yield. Product **5** may then be treated with any of a number of nucleophiles to give good yields of α-substituted cresols, perhaps by way of an intermediate quinone methide[5] (eq 5).



5

(5)

α-Chloro-*p*-tolyl Chloroformate (1).—On mixing **1** with excess dimethylformamide there is a vigorous reaction and *ca.* 1 mol of carbon dioxide is liberated. A hygroscopic salt precipitates from solution (at 1–2 *M* concentration) for which elemental analyses are in agreement with **3**. The infrared spectrum shows a strong band at 1710 cm^{-1} (C=N⊕)[6] and a strong band appears at 1280 cm^{-1} (aryl–oxygen stretching). Nmr studies are confirmatory. After a short reaction time the spectrum of an equimolar mixture of **1** and dimethylformamide shows less than 5% of either starting material. The dimethylformamide portion of the spectrum shows a shift in the aldehydic proton from 8.05 to 10.50 whereas the methyl protons (originally at 2.83 and 2.94) appear at 3.37 and 3.66 ppm. Those at higher field are split (*ca.* 1.5 Hz) probably owing to *trans* coupling with the aldehydic proton although the reciprocal splitting was not resolvable. These data compare with spectra of the salt from dimethylformamide and phosgene presented by Martin and Martin.[7] With respect to the portion of the spectrum derivable from **1**, the benzylic protons are unchanged at 4.70, whereas the A_2B_2 aromatic pattern (7.26 and 7.52 ppm, J = 9 Hz) has collapsed to a single peak at 7.58 ppm. The downfield shifts (relative to starting materials) and also the increased nonequivalence of the N-methyl groups are all in accord with changes expected with **3**.

When a solution of **3** is treated with incremental amounts of methanol, the spectrum diminishes and after 1 mol has been added it is replaced by an entirely new one. This contains peaks representing 1 mol of methyl chloride (3.03 ppm), 1 mol of free dimethylformamide and what appears to be 1 mol of α-chloro-*p*-cresol (**5**). This is not isolable and attempts at isolation gave only resinous products. However it seems

(1) (a) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960); (b) H. Bredereck, R. Gomper, H. v. G. Schuh, and G. Theilig, *ibid.*, **71**, 753 (1959); (c) M. Matzner, R. P. Kurkjy, and R. J. Colter, *Chem. Rev.*, **64**, 645 (1964).

(2) H. K. Hall, *J. Amer. Chem. Soc.*, **78**, 2717 (1956).

(3) H. Bredereck, R. Gomper, H. Rempfer, K. Klem, and H. Keck, *Chem. Ber.*, **92**, 329 (1959).

(4) H. Bredereck, F. Effenberger, and G. Simchen, *ibid.*, **96**, 1350 (1963).

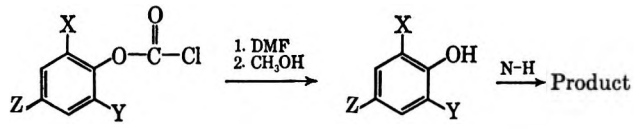
(5) (a) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, No. 25, 9 (1960); (b) A. B. Turner, *Quart. Rev.* (London), **18**, 347 (1964).

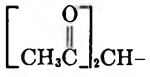
(6) A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961).

(7) G. Martin and M. Martin, *Bull. Soc. Chim. Fr.*, 1637 (1963).

TABLE I

PREPARATION OF α CHLOROCRESOLS AND REACTION WITH NUCLEOPHILES



X	Y	Z	N	Product	Yield, %
H	H	CH_2Cl	$-CH_3O$	α-Methoxy-*p*-cresol	85
H	H	CH_2Cl			78
H	H	CH_2Cl	$N\equiv C-$	α-Cyano-*p*-cresol	45
H	H	CH_2Cl	$[C_2H_5O]_3P$	4-Diethylphosphonomethyl phenol	93
$-CH_3$	$-CH_2Cl$	H	$[C_2H_5O]_3P$	2-Methyl-6-diethylphosphonomethyl phenol	74
$-CH_2Cl$	$-CH_2Cl$	H	$[C_2H_5O]_3P$	2-Ethoxy-2-oxo-7-diethylphosphonomethyl-1,2-benzoxaphosphole	29

to be quite stable in solution. The nmr spectrum shows two benzylic protons at 4.70 ppm suggesting that their environment is unchanged and that the chloromethyl moiety is intact through the series of reactions. The aromatic protons now appear at 6.93 and 7.23 ppm (J = 9 Hz) with the total envelope shifted to higher field than in **1** and **3** owing to the removal of the deshielding positive group.

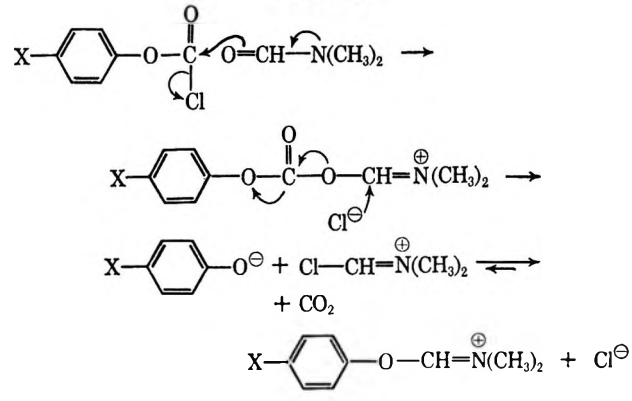
The preparation of simple, unsubstituted α-chlorocresols has been difficult[8] and has been reported infrequently. Thus to further substantiate the above synthesis of **5**, it was desirable to carry out the sequence so that the final product would be a stable, known material.

The reaction of **2** with dimethylformamide gave a product analogous with that formed from **1**, which may be represented by structure **4**. The methyl groups of the dimethylformamide are shifted to 3.36 and 3.65 with the upfield group showing a split of *ca.* 1.5 Hz whereas the aromatic protons are deshielded relative to those in **2** (7.25 ppm) and appear as an A_2B_2 pattern at 7.25 and 7.48 ppm (J = 9 Hz). The protons of the aromatic methyl group remain at 2.35 ppm. On treatment with 1 mol of methanol, the spectrum of a solution of salt **4** disappears and is replaced by one showing 1 mol of methyl chloride, 1 mol of free dimethylformamide, and *p*-cresol (CH_3–, 2.25 ppm; aromatic protons, 7.07 and 6.74 ppm, J = 7 Hz).

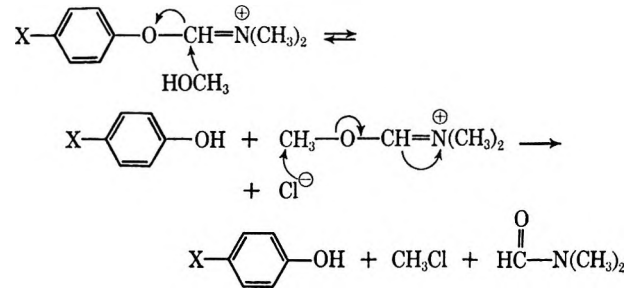
It will be noted that the relationship of the nmr spectra of **2**, **4**, and **6** very closely parallels that of **1**, **3**, and **5** providing further support for the structure of α-chloro-*p*-cresol.

A mechanism for the first reaction may be presented as in Scheme I. The first step, nucleophilic displacement of chloride ion by dimethylformamide, finds analogy in the work of Hall[2] with the reaction of dimethylformamide and acetyl bromide. The second step explains the loss of carbon dioxide and is reasonable since the stability of chloroimonium salts is documented.[7] The final equilibrium should be dependant on the relative basicities of the phenolate and chloride ions and should lie well to the left (in solution) to give the product observed by nmr. Again, in the second reaction (Scheme II) the mechanism accounts for the products and similar mechanisms have been proposed

SCHEME I



SCHEME II



in analogous cases. However, our data do not permit speculation on the more detailed aspects.

Reactions of α-Chlorocresols.—With the preceding spectroscopic evidence that α-chlorocresols could be prepared with ease, it was of interest to demonstrate their synthetic utility. For this reason we prepared several different types from the corresponding chloroformates and utilized them in reaction with nucleophiles. A summary of experimental methods and results is given in Table I.

The reactions were generally carried out by reacting the α-chlorotolyl chloroformate with *ca.* 1 mol of dimethylformamide, then with 1 mol of methanol followed by 1 mol of nucleophile. As shown, the reactions were straightforward and the yields high in most cases. The reaction is general for the preparation of α-substituted cresols. The physical constants for α-methoxy-*p*-cresol and α-cyano-*p*-cresol agree with literature data. Analytical, infrared, and nmr data are consistent with assigned structures in other cases.

(8) G. A. Olah and W. S. Tolgyesi in "Friedel-Crafts and Related Reactions," Vol. 2, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 21.

Experimental Section[9]

Aryl Chloroformates. *p*-Tolyl Chloroformate.—A solution of 1100 g (10.2 mol) of *p*-cresol in 5 l. of toluene was cooled to −10° and 1500 g (15.2 mol) of phosgene was passed into it. The cold solution was then neutralized with 20% sodium hydroxide solution. The product layer was separated and distillation yield 1230 g (71%) of product, bp 97–100° (14 mm) and $n^{25}D$ 1.5100 (lit.[10] bp 108° (30 mm)).

2,6-Xylyl Chloroformate—This material was prepared in the same manner used with *p*-tolyl choroformate using 373 g (3.0 mol) of 2,6-xylenol and 483 g (4.8 mol) of phosgene. Distillation yielded 448 g (81%) of product, bp 155–157° (150 mm) and $n^{25}D$ 1.5023.

Anal. Calcd for $C_9H_9ClO_2$: C, 58.58; H, 4.93; Cl, 19.22. Found: C, 58.58; H, 4.67; Cl, 19.24.

α-Chlorotolyl Chloroformates. α-Chloro-*p*-tolyl Chloroformate.[11]—A mixture of 1110 g (6.5 mol) of *p*-tolyl chloroformate, 23.1 g of phosphorous trichloride, and 2.3 g of benzamide was heated at 135° while a mixture of 12.3 g of benzoyl peroxide and 995 g (7.4 mol) of sulfuryl chloride was added over a period of 6 hr. Distillation yielded 885 g (66%) of product, bp 127–130° (4.5 mm) and mp 60.5–61.5° (from benzene–hexane).

Anal. Calcd for $C_8H_6Cl_2O_2$: C, 46.82; H, 2.95. Found: C, 47.17; H, 3.06.

α-Chloro-2,6-xylyl Chloroformate and α,α′-Dichloro-2,6-xylyl Chloroformate.—These were prepared using the method outlined above in the reaction of 420 g (2.3 mol) of 2,6-xylyl chloroformate, 17 g of phosphorous trichloride, 1.7 g of benzamide, 7 g of benzoyl peroxide, and 740 g (5.5 mol) of sulfuryl chloride. Distillation yielded 124 g (25%) of α-chloro-2,6-xylyl chloroformate, bp 135–145° (10 mm) and $n^{25}D$ 1.5310.

Anal. Calcd for $C_9H_8Cl_2O_2$: C, 49.34; H, 3.68; Cl, 32.4. Found: C, 49.79; H, 3.59; Cl, 32.4.

A second fraction in the distillation yielded 143 g (25%) of α,α′-dichloro-2,6-xylyl chloroformate, bp 162–165° (10 mm) and mp 71.5–73.5 (from benzene–hexane).

Anal. Calcd for $C_9H_7Cl_3O_2$: C, 42.58; H, 2.78; Cl, 42.2. Found: C, 42.02; H, 2.78 Cl, 41.8.

Reaction of Dimethylformamide and α-Chloro-*p*-tolyl Chloroformate.—A mixture of 10.2 g (0.050 mol) of α-chloro-*p*-tolyl chloroformate and 50 ml of dimethylformamide was stirred for 0.5 hr. There was a vigorous reaction, gas was evolved, and a precipitate was formed. The precipitate was collected, washed with ether, and dried *in vacuo*. Spectral data are discussed in the text.

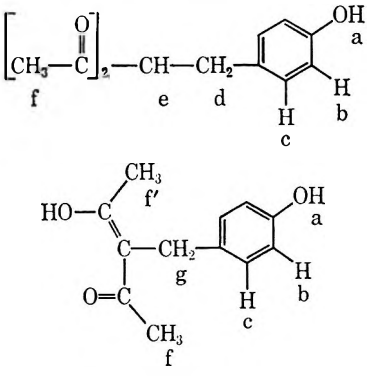
Anal. Calcd for $C_{10}H_{13}Cl_2NO$: Cl, 30.3; N, 6.0. Found: Cl, 30.6; N, 6.0.

In a small-scale experiment, the gas was measured manometrically and amounted to 85% of theory. It was shown to be carbon dioxide by bubbling into limewater and by comparison of the infrared spectrum with that of an authentic sample.

Preparation and Reactions of α-Chloro-*p*-cresol.—As a general procedure 1 mol of α-chloro-*p*-tolyl chloroformate and 1 mol of dimethylformamide were allowed to react for 1 hr in 750 ml of acetonitrile. Methanol (1 mol) was then added and the mixture was stirred for an additional 0.5 hr to form α-chloro-*p*-cresol.

α-Methoxy-*p*-cresol.—A solution of 0.10 mol of the salt of dimethylformamide and α-chloro-*p*-tolyl chloroformate was prepared as above and allowed to react for 1 hr with 125 ml of methanol. The reaction mixture was diluted with water and extracted with ether, and after drying over sodium sulfate, the residue from solvent evaporation was triturated with hexane to yield 14.2 g (85%) of product, mp 79–80° (lit.[12] mp 82.5–83.5°).

3(4′Hydroxybenzyl)-2,4-pentanedione.—A solution of 0.10 mol of α-chloro-*p*-cresol, 10.1 g (0.10 mole) of triethylamine and 10.0 g (0.10 mol) of 2,4-pentanedione was stirred for 1 hr. After the usual treatment the residual oil from solvent evaporation was triturated with benzene to yield 16.0 g (78%) of product, mp 93–94.5° (from ethanol–water). The infrared spectrum was consistent with the assigned structure showing strong hydroxyl absorption and split carbonyl absorption at 1690 and 1720 cm^{-1} (due to keto and enol tautomers). The nmr spectrum is also appropriate and again shows the presence of both the keto and enol structures (δ, ppm (in $CDCl_3$)): a, 8.12; b, doublet, J =

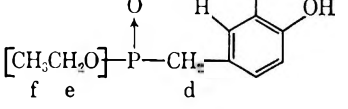


8 Hz, 6.80; c, doublet, J = 8 Hz, 7.12; d, 1.8 protons, doublet, J = 7 Hz, 3.05; e, 0.8 proton, triplet, J = 7 Hz, 4.17; f, 2.12; f′, 2.06; g, 0.4 proton, 3.62.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 70.0; H, 6.84. Found: C, 70.1; H, 6.86.

α-Cyano-*p*-cresol.—A solution of 0.10 mol of α-chloro-*p*-cresol, and 4.9 g (0.10 mol) of sodium cyanide in 75 ml of acetonitrile and 100 ml of methanol was refluxed for 1 hr. The usual procedure yielded 6 g (45%) of product, mp 68–70° (from benzene) and bp 150–155° (1 mm) (lit.[13] mp 69–70°, bp 330.5°).

4-Diethylphosphonomethylphenol.—On addition of 16.6 g (0.10 mol) of triethyl phosphite to a solution of 0.10 mol of α-chloro-*p*-cresol there was a gentle exotherm. The reaction mixture was heated to 175°, removing solvent by distillation. The usual procedure yielded 22.8 g (93%) of product, mp 89–91°

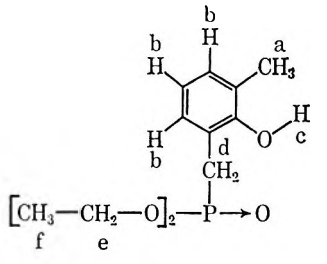


(from tetrahydrofuran–ether–hexane). The infrared and nmr spectra were consistent. Nmr signals (δ, ppm (in $CDCl_3$)) were a, 8.27; b, doublet, J = 8 Hz, 6.65; c, ABX, J_b = 8 Hz, J_P = 3 Hz, 7.05; d, doublet, J = 21 Hz, 3.05; e, ABC, J_f = 8 Hz, J_P = 8 Hz, 3.97; f, triplet, J = 8 Hz, 1.19.

Anal. Calcd for $C_{11}H_{17}O_4P$: C, 54.1; H, 7.03; P, 12.7. Found: C, 54.3; H, 6.98; P, 12.8.

Preparation and Reactions of α-Chloro-2,6-xylenol.—The α-chloro-2,6-xylenol was prepared from α-chloro-2,6-xylyl chloroformate using the same procedure employed for α-chloro-*p*-cresol.

2-Methyl-6-diethylphosphonomethylphenol.—A solution of 0.10 mol of α-chloro-2,6-xylyenol and 16.6 g (0.10 mol) of triethyl phosphite in 75 ml of acetonitrile was heated on a steam bath for 1 hr. Following the usual procedure, distillation of the oil from solvent evaporation yielded 19.0 g (74%) of product,



bp 100–125°(1 μ). The infrared and nmr spectra were consistent. Nmr signals (δ, ppm (in CCl_4)) were a, 2.27; b, 6.5–7.2; c, 8.5; d, doublet, J = 21 Hz, 3.08; e, ABC, J_f = 7 Hz, J_P = 7 Hz, 4.00; f, triplet, J = 7 Hz, 1.24.

(9) All melting and boiling points are uncorrected. Infrared spectra were obtained as Nujol mulls or neat smears using a Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were obtained with a Varian Associates Model A-60 spectrometer. Except where otherwise stipulated, these spectra were obtained in acetonitrile solution. In all spectra TMS was used as the standard.

(10) M. Capisarow, *J. Chem. Soc.*, 251 (1929).

(11) This compound was first prepared by E. D. Weil in these laboratories and the preparative method is presented with his gracious permission.

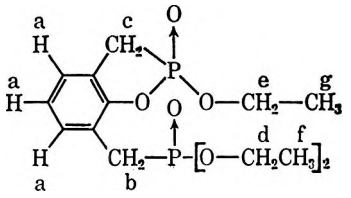
(12) J. deJonge and B. H. Bibo, *Rec. Trav. Chim.*, **74**, 1448 (1955).

(13) H. Will and A. Laubenheimer, *Ann.*, **199**,150 (1879).

Anal. Calcd for $C_{12}H_{19}O_4P$: C, 55.85; H, 7.44; P, 12.0. Found: C, 55.46; H, 7.01; P, 12.1.

Preparation and Reactions of α,α′-Dichloro-2,6-xylenol.—The α,α′-dichloro-2,6-xylenol was prepared from α,α′-dichloro-2,6-xylyl chloroformate using the same procedure employed for α-chloro-*p*-cresol.

2-Ethoxy-2-oxo-7-diethylphosphonomethyl-1,2-benzoxaphosphole.—A solution of 0.10 mol of α,α′-dichloro-2,6-xylenol and 42 g (0.25 mol) of triethyl phosphite in 75 ml of acetonitrile was heated on a steam bath for 45 min. Following the usual procedure, distillation of the oil from solvent evaporation yielded 10.2 g (29%) of product, bp 166–200° (<1 μ). The infrared spectrum shows no hydroxyl absorption and is otherwise consonant. The nmr spectrum (δ, ppm (in $CDCl_3$)) showed a, 6.7–7.3; b, doublet, J = 21 Hz, 3.08; c, doublet, J = 17 Hz, 3.04; d, e, 3.6–4.4; f, triplet, J = 9 Hz, 1.23; g, triplet, J = 9.4 Hz, 1.34.



Anal. Calcd for $C_{14}H_{22}O_6P_2$: C, 48.25; H, 6.12; P, 17.8. Found: C, 48.46; H, 6.42; P, 17.5.

Registry No.—Dimethylformamide, 68-12-2; 2,6-xylyl chloroformate, 876-99-3; **1**, 15451-04-4; α-chloro-2,6-xylylchloroformate, 15451-05-5; α,α′-dichloro-2,6-xylyl chloroformate, 15451-06-6; 3-(4′-hydroxybenzyl)-2,4-pentanedione (keto form), 15451-07-7; 3-(4′-hydroxybenzyl)-2,4-pentanedione (enol form), 15451-10-2; 4-diethylphosphonomethylphenol, 3173-38-4; 2-methyl-6-diethylphosphonomethylphenol, 15451-11-3; 2-ethoxy-2-oxo-7-diethylphosphonomethyl-1,2-benzoxaphosphole, 15451-09-9.

Acid- and Base-Catalyzed Deuterium–Protium Exchange of Some Polyazaindenes

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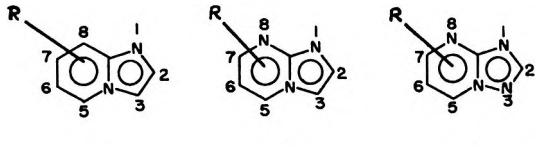
Received August 28, 1967

The acid-catalyzed deuterium–protium exchange of compounds **1**, **2**, and **3** occurs at the positions typical for electrophilic substitutions. These substitutions are shown to occur on the free bases. The base-catalyzed deuterium–protium exchange of compounds **1**, **2**, and **3** occurs at positions adjacent to nitrogen atoms which possess a partial positive charge as indicated by major resonance contributing structures. Proton transfer is shown to be involved in the rate-determining step.

We have recently[1] described some preliminary results of hydrogen–deuterium exchange studies on imidazo[1,2-*a*]pyridine (**1**), imidazo[1,2-*a*]pyrimidine (**2**), and 1,2,4-triazolo[1,5-*a*]pyrimidine (**3**). These studies have shown that electrophilic substitution by D^+ in these ring systems occurs at position 3 in the ring systems **1** and **2** and at position 6 in the ring system **3** (the



numbering of the positions in the manner shown in structure **3** is done for the sake of clarity in comparing the various structures). The positions of deuterium–protium exchange are the same as those involved in the brominations of these compounds.

It now remains to consider if these electrophilic substitutions occur on the protonated or on the free bases. We have previously shown that the methylation, with methyl iodide, of these compounds occurs at the same nitrogen atom (N-1) as protonation does in salt formation.[2–4] If electrophilic substitution occurs on the protonated bases, the deuterium–hydrogen exchange rate of the methiodides should be the same or faster than the exchange in the protonated bases. Table I shows the results of this study and clearly demonstrates that the electrophilic substitution, under the conditions of these experiments, occurs on the free base since the exchange rate on the methiodides is considerably slower than that of the free bases. In view of the fact that the brominations of these compounds are done under milder acidic conditions[2,5,6] (bromine–water) than those employed in the exchange studies, we can say that the electrophilic brominations on these ring systems also occur on the nonprotonated compounds.

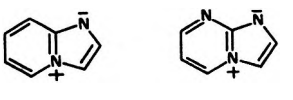
TABLE I

ACID-CATALYZED H–D EXCHANGE[a] ($t_{1/2}$, hr)

Compd	H-3	H-5
1 (R = H)	4.5	
1·CH_3I (R = H)[b]	31	
2 (R = H)	13	
2·CH_3I (R = H)[b]	>300	>300
3 (R = H)		15
3·CH_3I (R = H)[b]		165

[a] 3 *M* D_2SO_4 was used at 100°. [b] The methyl group in the methiodides is at N-1.

In view of the strong contribution of resonance structures such as **4** and **5**, causing an inductive electron



(1) W. W. Paudler and L. S. Helmick, *Chem. Commun.*, 377 (1967); *J. Heterocyclic Chem.*, **3**, 269 (1966). (A typographical error caused the incorrect reporting of the melting points of 1,2,4-triazolo[1,5-*a*]pyrimidine and of 1,2,4-triazolo[4,3-*a*]pyrimidine. The correct melting points are 142–143° and 208–210°, respectively.)

(2) W. W. Paudler and J. E. Kuder, *J. Org. Chem.*, **31**, 809 (1966).

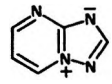
(3) W. W. Paudler and H. L. Blewitt, *ibid.*, **31**, 1295 (1966).

(4) The position of protonation and N-methylation of the 1,2,4-triazolo[1,5-*a*]pyrimidines will be the topic of a forthcoming communication.

(5) W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, **30**, 4081 (1965).

(6) Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), **9**, 804 (1961).

withdrawal at C-3 and C-5, to the ground state of the imidazo compounds **1** and **2**, respectively, base-catalyzed exchange of H-3 and H-5 is to be expected. Similarly, contributions of resonance structures such as **6** to the ground state of the triazole derivative **3** predict facile deuterium–protium exchange at position 5 in this compound. These exchanges have, in fact,



6

been realized and the rate data are presented in Table II. Thus, the observed base exchange processes

TABLE II

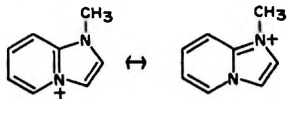
SECOND-ORDER RATE CONSTANTS ($\times 10^3$ l. mol^{-1} sec^{-1}) FOR H–D EXCHANGE IN 0.098 *N* NaOD

	Exchange position				Reacn temp,
Compd[f]	2	3	5	6	°C
1 (R = H)	*a, d*	0.024[a]	0.0072[a]	*a, d*	65
1·CH$_3$I (R = H)[b]	6.1	9.4	0.033	*d*	35
1·CH$_3$I (R = 5-CH$_3$)[c]	5.2	5.2		*d*	35
1·CH$_3$I (R = 6-CH$_3$)	3.3	8.5	*d*		35
1·CH$_3$I (R = 7-CH$_3$)	3.9	7.8	*d*	*d*	35
1·CH$_3$I (R = 8-CH$_3$)	3.3	8.5	*d*	*d*	35
2 (R = H)	0.025[a]	0.15[a]	1.5[a]	0.048[a]	65
	d	0.145	1.64	*d*	65
2·CH$_3$I (R = H)	Decomposes under basic conditions				35
3 (R = H)[e]	*d*		10.9	0.0098	35
	0.037[a]		>50[a]	0.32[a]	65
3 (R = 2-CH$_3$)			6.1	*d*	35
3 (R = 7-CH$_3$)	*d*		3.8	*d*	35
3·CH$_3$I (R = H)	>50		Decomposes too rapidly		35
3·CH$_3$I (R = 7-CH$_3$)	>50		Decomposes too rapidly		35

[a] 0.5 *M* NaOCH$_3$ in CH$_3$OD. These exchanges are too slow at 35° and in 0.098 *N* NaOD to be measured. [b] All methiodides are the 1-N-methyl derivatives. [c] This is the average rate of exchange of H-2 and H-3 since the nmr signals are insufficiently resolved for an individual determination. [d] No measurable exchange at indicated temperature. [e] H-7, under the condition in footnote *a* exchanges at the same rate as H-2. [f] Respective registry no.: 274-76-0; 15562-25-1; 15639-31-3; 15639-32-4; 15639-33-5; 15639-34-6; 274-95-3; 15562-27-3; 275-02-5; 14388-63-7; 15562-30-8; 15562-31-9; 15562-32-0;

confirm the significant contribution of resonance structures such as **4**, **5**, and **6** to the ground state of compounds **1**, **2**, and **3**, respectively.

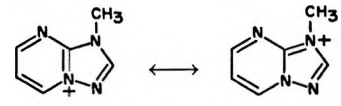
The two major resonance contributing structures of the methiodide of **1** can be pictured as in **7** and **8**.



7 **8**

It is obvious that N-1 no longer possesses a partial negative charge, as is the case in the free bases, and we can consequently predict that base-catalyzed exchange will occur at C-2 in addition to C-3 and C-5. The base-catalyzed exchange in the imidazo[1,2-*a*]pyridine methiodide occurs at a similar rate for H-2 and H-3, with a somewhat faster rate for H-3. The base-catalyzed exchange of H-5 is slower by a factor of about 100 than the H-2 and H-3 exchange. These D–H exchanges do not occur at a measurable rate in the free bases at the conditions employed for the methiodides (65°, 0.098 *N* NaOD). In stronger base, 0.5 *M* NaOMe (65°), the H-3 and H-5 protons of the free base do, however, exchange.[1] Unfortunately, the rate differences in the base-catalyzed exchange reactions of the methiodides and of the free bases is so large, that no suitable set of reaction conditions could be found which allows a direct comparison of the reaction rates. The difference in the reaction rates can, however, be estimated to be in favor of the methiodides by *at least* a factor of 1500. Since the methiodides of the imidazo[1,2-*a*]pyrimidines decompose under basic conditions, no exchange rates can be obtained for these compounds.

The major resonance contributing structures (**9** and **10**) of the methiodides of the 1,2,4-triazolo[1,5-*a*]-pyrimidines suggest that the D–H exchange in these compounds should occur at positions 2 and 5. This



9 **10**

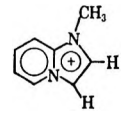
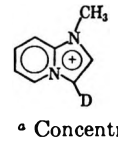
prediction is verified for H-2 by experiment (*cf.* Table II). Unfortunately, these methiodides decompose too rapidly to obtain a valid rate constant for the exchange of H-5. We find that the exchange rate of the methiodides of these compounds is faster, by at least a factor of 1000, than the exchange rate of the corresponding free bases.

The D–H exchange rate of various methiodides of methyl-substituted imidazo[1,2-*a*]pyridines, compared with the exchange rates of the 2 and of the 3 proton of the methiodide of the parent compound itself, is of some interest. The substitution of any of the protons in the six-membered ring by a methyl group has essentially the same rate decreasing effect upon the exchange of H-2, while it has very little, if any, effect upon the exchange rate of H-3 (*cf.* Table II).

The rate data reported in Table II represent second-order rate constants with first-order dependency in both base and heterocycle (see Table III). The results

TABLE III

KINETIC DATA FOR BASE-CATALYZED H–D EXCHANGE AT 35° IN D$_2$O

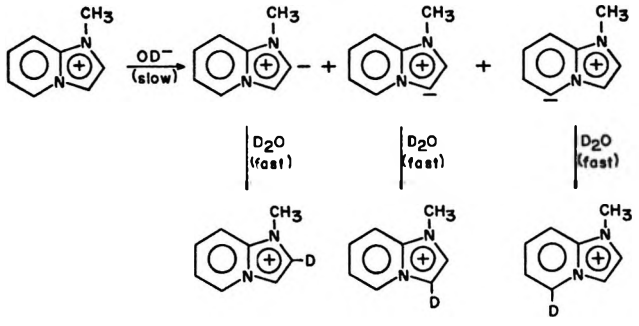
	Concn of methiodide, *M*	Concn of NaOD, *M*	Second-order rate constants ($\times 10^3$ l. mol^{-1} sec^{-1}) H-2	H-3
	0.260	0.098	6.12	9.33
	0.260	0.050	6.22	9.38
	0.260	0.025	6.15	9.60
	0.250	0.098	5.62	8.93
	1.04	0.098	5.95	10.3
	0.262	0.100[a]		4.27

[a] Concentration of NaOH in H$_2$O.

of the base-catalyzed D–H exchanges are certainly consistent with the proposal that an ylide-type intermediate is involved in these reactions. The primary deuterium kinetic isotope effect (see Table III) for the exchange of the methiodide of the 3-deuterioimidazo[1,2-*a*]pyridine as compared to the exchange of the protio compound is 2.19 at 35°. Thus, proton transfer occurs in the rate-determining step. One might

well envision the reaction sequence in Scheme I to account for these base-catalyzed exchange reactions.[7]

SCHEME I



(7) Related studies dealing with some five- and six-membered ring nitrogen heterocyclic compounds have been the subject of several recent publications cited in ref 1. Some more recent publications in this area are Y. Kawazoe and M. Ohnishi, *Chem. Pharm. Bull.* (Tokyo) **15**, 826 (1967); R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Amer. Chem. Soc.*, **89**, 1537 (1967).

Experimental Section

Nmr spectra were obtained with a Varian A-60 spectrometer. Elemental analyses were done on all new compounds by Mrs. K. Decker of this department.

General Procedure of H–D Exchange.—A weighed sample of the appropriate polyazaindene was placed in an nmr tube and dissolved in a measured quantity of standardized acid or base. The nmr spectrum was immediately run and integrated. Exchange was followed by repeated integrations at selected time intervals. Exchange at 35° was obtained by allowing the sample to remain in the nmr probe. Exchange at 65 and 100° was obtained by placing the sample in refluxing methanol or water, respectively, and by removing the sample periodically for nmr analysis. All exchanges were followed to 85% completion.

3-Deuterioimidazo[1,2-*a*]pyridine Methiodide.—Imidazo[1,2-*a*]pyridine was heated at 95° for 19 hr in 3 *M* D_2SO_4, cooled, and neutralized with anhydrous Na_2CO_3 to pH 9. The aqueous solution was extracted with $CHCl_3$, the chloroform extract evaporated to dryness, and the residue dissolved in acetone. Excess iodomethane was added and the solution was allowed to stand overnight. The solution was then filtered, yielding 3-deuterioimidazo[1,2-*a*]pyridine methiodide containing 90% deuterium at position 3 as determined by nmr analysis.

Synthesis of the 6- and 7-Hydroxy-5,8-dioxocarbostyrils[1a]

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Received October 2, 1967

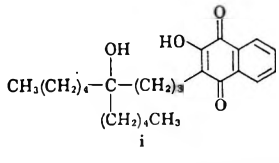
Utilizing a condensation reaction between amine I and methyl propiolate to obtain pyridone III followed by reaction with potassium *t*-butoxide and oxygen in dimethyl sulfoxide, a convenient synthesis of 6-hydroxy-5,8-dioxocarbostyril (V) was achieved. Conversion of 8-hydroxycarbostyril *via* dinitro (XII) and diamino (XIIIa) intermediates provided the isomeric 7-hydroxy-5,8-dioxocarbostyril (XV). The structures assigned to hydroxyquinones V and XV received support from mass spectral and proton magnetic resonance studies.

The potential application[2] of hydroxyquinolinequinones in certain malaria and cancer chemotherapy problems suggested extending our earlier study of carbostyrils[3] to the isomeric 6- (Scheme I) and 7-hydroxy-5,8-dioxocarbostyrils (Scheme II) (V and XV). Whereas syntheses of 6- and 7-hydroxy-5,8-quinolinequinones have been described,[4] no examples of the corresponding carbostyrils appear to have been reported. To allow quinones V and XV to serve efficiently as key intermediates for future studies in this area, initial emphasis was placed upon devising practical routes to both substances.

From a number of potential approaches to quinone V considered, one based on transforming 1,3-dioxocyclohexane to pyridone III appeared most attractive. In 1961, Zymalkowski[5] reported condensing propargyl aldehyde with an amine (I) derivative of 1,3-dioxocyclohexane and obtained the corresponding pyridyl ketone. More recently, the reaction was modified by using methyl propiolate and synthesis of pyridone III by this means was noted, albeit without detail, in a preliminary communication.[6] After brief warming, direct contact between amine I and methyl propiolate led to an exothermic reaction. At the end of 1 hr reaction temperature was raised to approximately 170° to complete cyclization (II → III). Employing lower reaction temperature allowed isolation of *trans*-olefin intermediate IV. The *trans* configuration was supported by a coupling constant of 17 cps for the olefin protons. Heating amino ester IV above 170° caused

(1) (a) This study received support from the U. S. Medical R and D Command under Contract DA-49-193-MD-3010 and National Science Foundation Grant GB-4939. The present manuscript is contribution number 279 from the Army Research Program on Malaria. (b) National Science Foundation Predoctoral Fellow.

(2) For example, from a number of napthoquinones prepared by L. F. Fieser and colleagues for antimalarial evaluation, lapinone (i) proved most promising. For an interesting and valuable review, see L. F. Fieser, J. P.



i

Schirmer, S. Archer, R. R. Lorenz, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967), and L. F. Fieser, "The Scientific Method," Reinhold Publishing Corp., New York, N. Y., 1964, p 190. Furthermore, the metabolic products of certain antimalarials have been shown to be quinolinequinones and carbostyrils: refer to R. R. Holmes, J. Conrady, J. Guthrie, and R. McKay, *J. Amer. Chem. Soc.*, **76**, 2400 (1954), and a review by P. B. Russell, "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 814. These facts augmented by an increasing number of naturally occurring quinones with cytotoxic and antibiotic properties enhanced our interest. Recent studies related to the quinolinequinone antitumor agent streptonigrin have been described by T. K. Liao, W. H. Nyberg, and C. C. Cheng, *Angew. Chem. Intern. Ed. Engl.*, **6**, 82 (1967); T. Kametani, K. Ogasawara, M. Shio, and A. Kozuka, *Yakugaku Zasshi*, **87**, 262 (1967); N. S. Nizuno, *Biochem. Pharm.*, **16**, 933 (1967); and C. W. B. Kremer and J. Laszlo, *Cancer Chemotherapy Rept.*, **51**, 19 (1967).

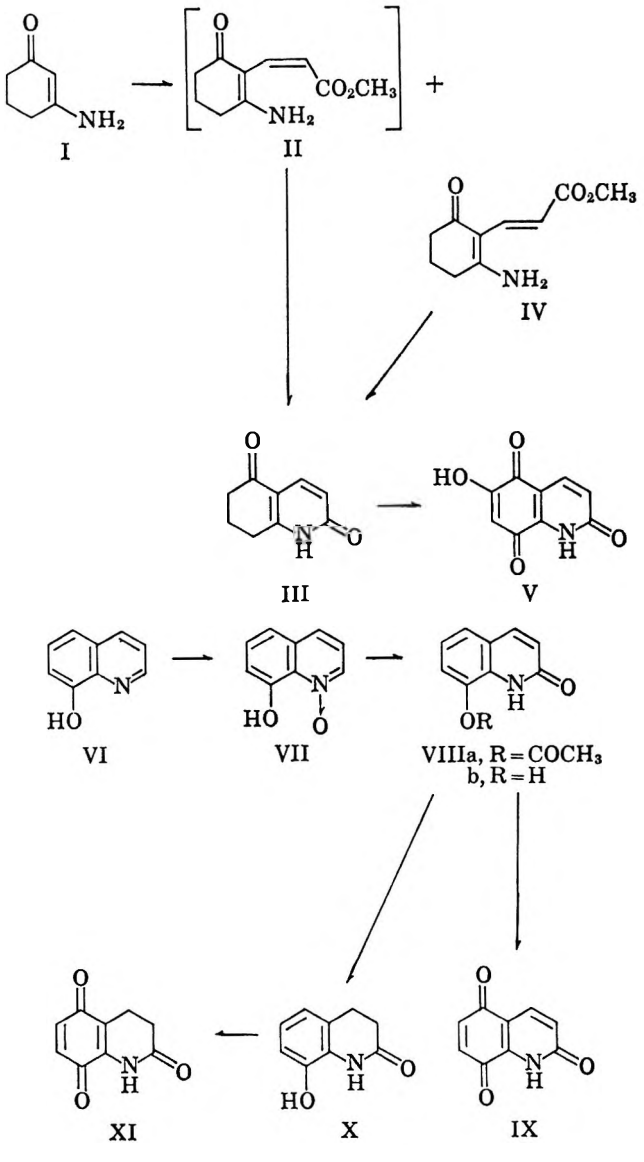
(3) G. R. Pettit and A. B. Neill, *Can. J. Chem.*, **42**, 1764 (1964); G. R. Pettit and M. Kalnins, *J. Org. Chem.*, **25**, 1365 (1960).

(4) The investigations of Drake and colleagues provide a useful summary of prior routes to hydroxyquinolinequinones; *cf.*, Y. T. Pratt and N. L. Drake, *J. Amer. Chem. Soc.*, **79**, 5024 (1957). Interestingly, certain of these quinolinequinones have displayed significant amebicidal activity against induced *E. histolitica* in the guinea pig.

(5) F. Zymalkowski and H. Rimek, *Arch. Pharm.*, **294**, 759 (1961).

(6) M. A. T. Sluyter, U. K. Pandit, W. N. Speckamp, and H. O. Huisman, *Tetrahedron Lett.*, 87 (1966).

SCHEME I



ready cyclization to the pyridone (III). Allowing ketone III to react with oxygen[7] and potassium *t*-butoxide in dimethyl sulfoxide solution afforded a brick-red potassium salt of quinone V. Acidification led to deep orange quinone V, dec pt 285–305°. The two important steps in this sequence, that is, I → III and III → V, proceeded in 39 and 70% yields (pure material), respectively.

The commercial availability of 8-hydroxyquinoline and easy transformation to 8-hydroxycarbostyril[3,8] (VIIIb from N-oxide VII) favored phenol VIIIb as precursor of hydroxy quinone XV. Initial attempts to oxidize phenol VIIIa using a Fremy's[9] salt or 80% hydrogen peroxide[10] procedure proved unrewarding.

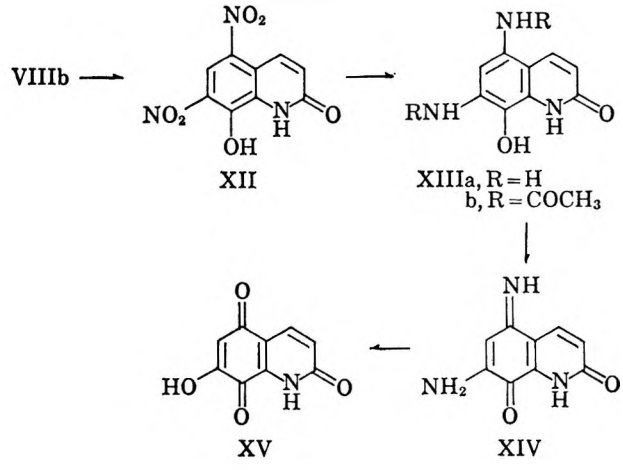
(7) The utility of this approach to hydroxyquinolinequinones was suggested by the excellent application of similar conditions for transformation of α-tetralones to hydroxy napthoquinones: T. R. Kasturi and T. Arunachalam, *Can. J. Chem.*, **44**, 1086 (1966); A. C. Baillie and R. H. Thomson, *J. Chem. Soc., Sect. C*, 2184 (1966). We wish to thank Dr. Kasturi for providing us with experimental details of the reaction prior to publication. A similar reaction has been used to oxidize ketones to diosphenols. For example, see G. R. Pettit, D. S. Alkalay, P. Hofer, and P. A. Whitehouse, *Tetrahedron*, **20**, 1755 (1964), and a reference contained therein.

(8) K. Ramaiah and V. R. Srinivasan, *Proc. Indian Acad. Sci., Sect. A*, **55**, 221 (1962); *Chem. Abstr.*, **57**, 6761*f* (1962).

(9) R. P. Singh, *Can. J. Chem.*, **44**, 1994 (1966); D. J. Cram and A. C. Day, *J. Org. Chem.*, **31**, 1227 (1966); R. Kuhn, *Ber.*, **93**, 2829 (1960).

(10) D. Bryce-Smith and A. Gilbert, *J. Chem. Soc.*, 873 (1964).

SCHEME II



However, a dichromate technique[11] was successful in oxidizing phenol VIIIb to quinone IX. The dichromate method proved even more effective for oxidation of dihydrocarbostyril X to quinone XI. The original purpose for quinone IX was a Thiele acetylation[12] step and thereby to a possible mixture of quinones V and XV. Before this route was adequately evaluated (in two initial attempts only starting material was recovered), treating phenol VIIIb with dilute nitric acid was found to yield (83%) dinitrocarbostyril XII. The structure of carbostyril XII was supported in general by elemental composition and specifically by its proton magnetic resonance spectrum. Protons at C-3 and C-4 appeared as doublets at δ 6.90 and 8.55 with J = 10 cps. A signal corresponding to the C-6 proton appeared at δ 8.50. A possible alternative arrangement involving 3,5-dinitro substituents seemed unlikely because of difficulty experienced in nitrating carbostyrils at C-3.[13]

Reducing nitro compound XII with sodium dithionite[4] in aqueous sodium hydroxide solution, followed by treatment with oxygen led to the green imine XIV. For analytical purposes a specimen of imine XIV hydrochloride was prepared by catalytic (palladium on carbon) reduction of the dinitro compound (XII) suspended in 1 *N* hydrochloric acid and then performing the oxidation step. Unfortunately, the imine proved too insoluble in a variety of solvents for further purification by recrystallization. Amine XIIIa because of its transient existence in air was characterized as acetamide XIIIb. The amide (XIIIb) was easily obtained by subjecting carbostyril XII to catalytic hydrogenation in tetrahydrofuran–acetic anhydride. Owing to the precarious stability of imine XIV and its transformation products under acid conditions, hydrolysis to hydroxyquinone XV required considerable experimentation. Heating imine XIV with 6 *N* sulfuric acid for 20 min followed by continuous extraction of quinone XV from the cool mixture using diethyl ether proved effective. Quinone XV was obtained in 40% yield from XIV (as yellow needles decomposing at 280–300°).

Structural assignments for quinones V and XV received support from results of mass and pmr measure-

(11) H. Gilman, Ed., "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1944, p 375.

(12) V. P. Bhatia and K. B. L. Mathur, *Tetrahedron Lett.*, 4057 (1966); W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 4381 (1965).

(13) A. Kaufmann and V. P. de Petherd, *Ber.*, **50**, 336 (1917); *Chem. Abstr.*, **11**, 2799 (1917).

ments. Molecular ions (M^+ 191) were obtained from both quinones and fragments (loss of C=O) at *m/e* 163, 135, 107, and 79 were in complete agreement.[14] The three distinctive sets of pmr signals shown by each of the isomeric quinones was reassuring.[15] The C-3, C-4 vinyl proton doublets (for example, with V at δ 6.83 and 7.97, J = 9 cps) and a sharp signal (at δ 6.05 for V) assigned to the lone quinone-ring proton was readily apparent in both quinones. The mass and pmr measurements combined with thin layer chromatography proved particularly valuable in dealing with these quinones as assessment of purity by recrystallization and melting point behavior was severely limited.

Experimental Section

Dimethyl sulfoxide was distilled from calcium oxide, redistilled from calcium hydride and stored under nitrogen in the dark. Reagent grade *t*-butyl alcohol was distilled from sodium. Solvent extracts of aqueous solutions were dried over calcium chloride or magnesium sulfate. Thin layer chromatography plates were prepared using silica gel G (E. Merck, AG Darmstadt).

Melting points were observed employing a Kofler melting point apparatus. Ultraviolet (methanol solution, Cary-14 instrument), infrared (in potassium bromide using a Beckman IR-12 instrument), and proton magnetic resonance (Varian Associates, A-60 spectrometer, trifluoroacetic acid as solvent) measurements were performed by Miss K. Reimer. Chemical shifts (δ) are in parts per million relative to tetramethylsilane as external standard. Mass spectra were recorded by Dr. P. Brown and P. A. Whitehouse using an Atlas CH-4B spectrometer equipped with a molecular beam inlet system (70 eV). Elemental microanalyses were provided by Dr. A. Bernhardt, Max Planck Institute, Mülheim, Germany.

1-Amino-3-oxocyclohex-1-ene (I).—The title substance was prepared by treating 89–99-g quantities of 1,3-dioxocyclohexane (Aldrich Chemical) in dry benzene with ammonia essentially as previously described.[5] After the calculated amount of water was collected, the hot solution was cooled and the liquid phase decanted. The residue was triturated with hot dioxane (70 ml) and the hot solution was separated from a dark viscous residue. Upon cooling the yellow crystals of amine I (40–56% yield) which separated were collected and used without further purification.

2,5-Dioxo-1,2,5,6,7,8-hexahydroquinoline (III).—In a typical experiment 1-amino-3-oxocyclohex-1-ene (94.5 g) was ground to a fine powder and mixed with methyl propiolate (95 ml, *caution* potent vesicant). The mixture became homogeneous on warming and by this time the reaction become exothermic. Heating at approximately 105° was continued 1 hr. The condenser was removed and residual methyl propiolate was evaporated over a period of a few minutes by raising the temperature to approximately 170°. The latter increment in temperature promoted cyclization of intermediates II and IV. The solid residue was triturated with two portions (200 ml each) of hot methylene chloride and the pale yellow crystalline product was recrystallized from methanol to yield 53.3 g (39%) of pyridone III. An analytical sample was recrystallized from methanol as colorless plates melting at 285–288° (lit.[6] mp 290–298°): pmr, δ 1.90 (quintuplet, two protons), 2.46 (triplet, two protons), 2.78 (triplet, two protons), 6.74 (doublet, one proton, J = 10 cps) and 8.29 (doublet, one proton, J = 10 cps).

Anal. Calcd for $C_9H_9NO_2$: C, 66.40; H, 5.56; N, 8.52. Found: C, 66.48, 66.23; H, 5.64, 5.70; N, 8.44.

When reaction between amine I and methyl propiolate was conducted without the final period of heating to approximately 170°, it was possible to isolate *trans* olefin IV (in, *e.g.*, 8% yield depending on temperature) by fractional recrystallization of the crude product from methanol. A pure specimen was recrystallized from dioxane as colorless plates: mp 163–166°; pmr, δ 1.77 (quintuplet, two protons), 2.60 (multiplet, four protons), 3.61 (singlet, three protons), 6.36 (doublet, one proton, J = 17 cps), and 7.35 (doublet, one proton, J = 17 cps).

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.56; H, 6.57; N, 7.33.

Heating ester IV at 180° for 15 min readily caused cyclization to pyridone III and elimination of methanol.

6-Hydroxy-5,8-dioxocarbostyril (V).—To a solution prepared from *t*-butyl alcohol (40 ml), potassium *t*-butoxide (freshly prepared from 11.8 g of potassium), and dimethyl sulfoxide (160 ml) was added pyridone III (12.0 g). The flask was quickly stoppered and the mixture stirred until a clear dark red solution was obtained. A slight positive pressure of oxygen was applied and the mixture was stirred and maintained at approximately 30° for 47 hr. During this period 3.3 l. of oxygen was absorbed. Next, the solution was filtered (sintered-glass funnel) and the solid washed with dimethyl sulfoxide (50 ml) and with several portions of dry diethyl ether (600 ml total). The remaining dark solid was dissolved in 500 ml of water. The deep red solution was filtered and cooled and the filtrate acidified with cold 2 *N* sulfuric acid (150 ml). The yellow solid which separated was collected and washed with 0.15 *N* sulfuric acid (30 ml) and 0.05 *N* sulfuric acid (30 ml). Following drying in a vacuum desiccator 9.8 g (70%) of hydroxyquinone V was obtained. Recrystallization from tetrahydrofuran gave an analytical specimen decomposing at 285–305°: λ_{max} 244, 308, and 427 mμ (log ϵ 4.04, 4.35, and 2.62); ν_{max} 3620–3400 (broad), 1680, 1655, 1620, 1551, 1470, 1420, 1270, 1090, and 865 cm^{-1}; pmr, δ 6.05 (one proton at C-7), 6.83 (doublet, one proton, J = 9 cps), and 7.97 (doublet, one proton, J = 9 cps).

Anal. Calcd for $C_9H_5NO_4$ (191): C, 56.55; H, 2.64; N, 7.33. Found: C, 57.03; H, 2.99; N, 7.29; mol wt (mass spec), 191.

8-Acetoxycarbostyril (VIIIb).—A mixture of 8-hydroxyquinoline N-oxide (20 g) and acetic anhydride (120 ml) was heated at steam bath temperature 5 hr.[16] The dark solution was poured into water, cooled, and basified with concentrated ammonium hydroxide. Cooling was continued 30 min and the light brown solid collected to yield 19.9 g (77%) of carbostyril VIIIa melting at 251–254°. Four recrystallizations from ethanol–water gave an analytical sample of shiny leaflets melting at 252–254° (lit.[17,18] mp 247–248° and 250°): pmr, δ 2.15 (three methyl protons), 6.65 (doublet, one proton, J = 9 cps), 7.15 (broad multiplet, three phenyl protons), and 7.85 (doublet, one proton, J = 9 cps).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.17; H, 4.12; N, 6.94.

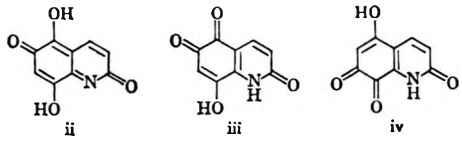
8-Hydroxycarbostyril (VIIIb).—A suspension of 8-acetoxycarbostyril (VIIIa, 20 g) in concentrated hydrochloric acid (200 ml) was heated at steam bath temperature 4 hr. Following dilution with water (200 ml) and cooling (ice bath) the dark tan solid (13.2 g, 84%) was collected. Repeated recrystallization from ethanol (Norit-A)–water and trituration with hot 6 *N* hydrochloric acid gave an analytical sample as light tan needles melting at 297–299° (lit.[17,19] melting points of 250, 287–288 and 260–290° with decomposition): pmr, δ 6.80–7.15 (multiplet, four protons) and 8.15 (doublet, one proton, J = 9 cps).

Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.85; H, 4.82; N, 8.85.

5,8-Dioxocarbostyril (IX).—A solution of sodium dichromate (2.0 g) in water (50 ml) was added dropwise to a stirred mixture composed of chloroform (50 ml), 8-hydroxycarbostyril (0.5 g) and dilute (20%) sulfuric acid (100 ml). Two minutes later the chloroform layer was separated and replaced with another 50-ml quantity of chloroform. Another portion (5 ml) of the dichromate solution was added and the preceding operation was duplicated. The process was repeated four more times using 10-ml

(14) A mass spectral study of hydroxynapthoquinones has been summarized: D. Becker, C. Djerassi, R. E. Moore, H. Singh, and P. J. Scheuer, *J. Org. Chem.*, **31**, 3650 (1966).

(15) Structures ii and iii for quinone V and iv for quinone XV have not been rigorously excluded but seem (spectral evidence) unlikely.



ii iii iv

(16) The reaction is initially exothermic and due care should be exercised in larger scale experiments.

(17) J. P. Phillips, E. M. Barrall, and R. Breese, *Trans. Kentucky Acad. Sci.*, **17**, 135 (1956); *Chem. Abstr.*, **51**, 11349a (1957).

(18) Y. N. Shelnker and I. Y. Postouskil, *Zh. Fiz. Khim.*, **32**, 394 (1958); *Chem. Abstr.*, **52**, 18406i (1958).

(19) K. Inagami, M. Kaihara, and J. M. Price, *J. Biol. Chem.*, **240**, 3682 (1965); *Cancer Research*, **24**, 596 (1954).

quantities of the sodium dichromate solution and waiting 5 min between extractions. The combined chloroform extract was concentrated to a bright yellow powder weighing 0.14 g (26%), dec pt 212–222°. Three recrystallizations from ethyl acetate gave a pure sample of orange-yellow plates decomposing at 218–222°: λ_{max} 265, 303, and 418 mμ (log ε 4.10, 3.92, and 3.11); ν_{max} 1685, 1650, 1618, 1602, 1426, 1331, 1062, and 842 cm^{-1}; pmr, δ 6.55 (singlet, two quinone protons); 6.65 (doublet, one proton); 7.80 (doublet, one proton, J = 9 cps).

Anal. Calcd for $C_9H_5NO_3$: C, 61.72; H, 2.88; N, 8.00. Found: C, 61.92; H, 2.84; N, 8.24.

3,4-Dihydro-5,8-dioxocarbostyril (XI).—A specimen (0.5 g) of 3,4-dihydro-8-hydroxycarbostyril (prepared in 74% yield, mp 195–200° by treating 8-hydroxycarbostyril in ethanol containing 5% rhodium on aluminum oxide and 72% perchloric acid as acid catalyst with a slightly positive atmosphere of hydrogen during 24 hr)[20] was suspended in 10% sulfuric acid (100 ml) and treated over 5 min with a solution of sodium dichromate (1.0 g) in water (20 ml). The solution was stirred 30 min while the carbostyril slowly dissolved and was then extracted with five 25-ml portions of chloroform. The combined extract was concentrated to a bright yellow solid (0.29 g, 54%) melting at 181–185°. Three recrystallizations from ethyl acetate gave an analytical sample of yellow needles melting at 185–188° with decomposition: λ_{max} 249 and 415 mμ (log ε 4.18 and 3.19); ν_{max} 1701, 1650, 1600, 1470, 1364, 1323, 1218, and 851 cm^{-1}; pmr, δ 2.50 (narrow multiplet, four aliphatic protons), and 6.60 (singlet, two quinone protons). The precursor dihydrocarbostyril X displayed pmr signals at δ 1.80 (multiplet, four aliphatic protons), and 5.80–6.40 (multiplet, three aromatic protons).

Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.93; N, 4.06; N, 7.97.

5,7-Dinitro-8-hydroxycarbostyril (XII).—To a stirred solution of 8-hydroxycarbostyril (VIIIb, 5 g) and water (100 ml) was slowly added concentrated nitric acid (100 ml). A yellow solid began to separate in about 1 min and the mixture was heated (steam bath) 10 min, and diluted with water (100 ml). After cooling (overnight), the bright yellow needles (6.5 g, 83%) were collected. Three recrystallizations from ethanol–water provided a pure sample as yellow needles: dec pt 279–280°; ν_{max} 3560 (w), 3440 (w), 3090, 1685, 1670, 1612, 1593, 1532, 1405, 1335, 1183, 1022, 851, and 738 cm^{-1}; pmr, δ 6.90 (doublet, one proton, J = 10 cps), 8.50 (one proton at C-6), and 8.55 (doublet, one proton, J = 10 cps).

Anal. Calcd for $C_9H_5N_3O_6$: C, 43.04; H, 2.01; N, 16.73. Found: C, 43.24; H, 2.22; N, 16.84.

5-Imino-7-amino-8-oxocarbostyril (XIV). Method A.—The following procedure proved more convenient and reliable. To a suspension of 5,7-dinitro-8-hydroxyquinoline (XII, 5 g) in water (200 ml) was added 2 *N* sodium hydroxide (10 ml). Addition of sodium dithionite (40 g) was continued until the initial dark mixture was replaced by an orange solution. Following a 15-min heating (steam bath) period the solution was acidified with 6 *N* hydrochloric acid and heating continued 1 hr. The resulting yellow solution was cooled, filtered, and made basic with sodium bicarbonate. Oxygen was passed into the solution for 20 min and the green solid which separated was collected. The crude product (XIV) was used without further treatment for conversion into quinone XV.

(20) V. G. S. Sidhu, G. Thygarajan, and S. Ansari, *Ann.*, **627**, 218 (1959).

Method B.—A mixture composed of carbostyril XII (0.5 g) 1 *N* hydrochloric acid (60 ml) and 10% palladium on carbon (0.03 g) was stirred under a slightly positive pressure of hydrogen 18 hr. The yellow solution was filtered, adjusted to pH 4 with sodium bicarbonate, and cooled (ice bath). Oxygen was slowly bubbled through the solution during 10 min while green triangular crystals separated. The solid was collected to afford 0.31 g (69%) of amine XIV hydrochloride decomposing at 290–293°. The iminoquinone appeared blue in neutral to acid aqueous solutions and green in aqueous base. Owing to the pronounced insolubility of carbostyril XIV in all solvents investigated, the product could not be effectively recrystallized.

Anal. Calcd for $C_9H_8ClN_3O_2$: C, 47.91; H, 3.57; Cl, 15.71; N, 18.67. Found: C, 47.63; H, 4.16; Cl, 15.61; N, 18.53.

5,7-Acetamido-8-hydroxycarbostyril (VIIIb).—A stirred mixture composed of 5,7-dinitro-8-hydroxycarbostyril (XII, 0.5 g), tetrahydrofuran (100 ml), acetic anhydride (3 ml), and 10% palladium on carbon (0.035 g) was hydrogenated (slightly positive pressure) at room temperature during 24 hr. The grey solid which had slowly separated was collected and partially dissolved in hot methanol (200 ml)–water (50 ml). The solution was filtered and cooled and the colorless solid which separated was collected to yield 0.28 g (51%). Three recrystallizations from methanol–water gave nearly colorless needles: dec pt 324–327°; ν_{max} 3390, 3270, 1670 (broad), 1611, 1557, 1530, 1468, 1379, 1360, 1276, 838, and 730 cm^{-1}; pmr, δ 2.05 (six methyl protons), 7.00 (doublet, one proton, J = 9 cps), 7.20 (one proton at C-6), and 8.30 (doublet, one proton, J = 9 cps).

Anal. Calcd for $C_{13}H_{12}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.34; H, 4.97; N, 15.44.

7-Hydroxy-5,8-dioxocarbostyril (XV).—Among a number of procedures explored, the following was found most effective. A suspension of iminocarbostyril XIV (0.5 g) in 6 *N* sulfuric acid (60 ml) was heated at reflux 20 min. The solution was cooled and transferred (using 60 ml of water) to a continuous extraction apparatus. While stirring the aqueous layer extraction with diethyl ether was allowed to proceed 4 hr. At this point the yellow needles (0.04 g, dec pt 280–300°) which had crystallized from the ether solution were collected. Four hours later another 0.06 g was isolated and after an additional 6 hr, a 0.10-g quantity to provide an over-all yield of 40%. Extending the extraction time led to dark solids. Attempts to further purify quinone XV by recrystallization from a variety of solvents led to less pure material which ranged in color from orange to red. Thus, the yellow needles which initially crystallized from the diethyl ether solution were eventually used for elemental analyses and such specimens displayed λ_{max} 252, 313, and 420 mμ (log ε 4.08, 4.13, and 2.66); ν_{max} 1673, 1635, 1601, 1424, 1382, 1344, 1313, 1201, 1036, 860, and 684 cm^{-1}; pmr, δ 6.00 (one proton at C-6), 6.80 (doublet, one proton, J = 9 cps), and 7.90 (doublet, one proton, J = 9 cps).

Anal. Calcd for $C_9H_5NO_4$(191): C, 56.55; H, 2.64; N, 7.33. Found: C, 56.33; H, 2.72; N, 7.32; mol wt (mass spec), 191.

Registry No.—III, 15450-69-8; IV, 15450-70-1; V, 15450-71-2; VIIIa, 15450-72-3; VIIIb, 15450-76-7; IX, 15450-73-4; XI, 15544-52-2; XII, 15450-74-5; XIIIb, 15450-75-6; XIV hydrochloride, 15444-53-3; XV, 15544-54-4.

Radiotracer Study of a Heterocyclic Ring-Expansion Reaction

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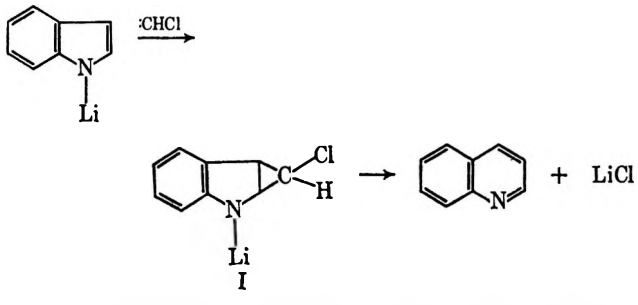
Indole reacts with methyllithium and methylene bromide to form quinoline and 1,2-dihydroquinaldine. The competitive rates of reaction of indole and skatole in this reaction have been compared using carbon-14-labeled methylene bromide reagent and reverse isotope dilution techniques to measure the ratio of the ring-expansion products. The substance isolated in an attempt to obtain the acetyl derivative of the reaction intermediate (in the formation of lepidine from skatole) was shown by carrier techniques to contain a lepidine precursor. The compound, which probably arises by hydrolysis of the anticipated intermediate on the chromatography column, is thought to be 2′-hydroxy-3-methylcyclopropano[2,3:2′,3′]indolenine, which yields lepidine by elimination of a molecule of water. The possibility that an isomeric aziridine is involved in the ring-expansion reaction is discounted as the new carbon atom (originally from the methylene bromide) enters the 3 position in the quinoline ring. The results support the proposal that the addition of a carbene or a carbenoid to the indole 2,3 double bond is the first step in the ring-expansion reaction.

The addition of methyllithium to a solution of indole in methylene chloride yields the ring-expansion product quinoline. Closs and Schwartz[1b] proposed that the reaction proceeds *via* attack of chlorocarbene on the indole 2,3-double bond resulting in the formation of a chlorocyclopropane intermediate (I) that subsequently eliminates lithium chloride to form the ring-expansion product. Several authors[2,3] have invoked the participation of carbenes in other reactions involving the conversion of indoles into quinolines.



The reaction of methylene bromide with methyllithium produces a species that reacts with indole and skatole to yield quinoline and lepidine, respectively.[4] These two quinolines react further with methyllithium to give 1,2-dihydro-2-methylquinoline and 1,2-dihydro-2,4-dimethylquinoline. The ring-expansion products are accompanied by unidentified indoles and a considerable quantity of polymeric material. These reactions have now been studied by ^{14}C tracer techniques.

The electrophilic character of halocarbenes has been postulated and confirmed by relative competitive reaction rate studies. Doering and Henderson[5] examined the reaction of dichlorocarbene with a range of olefins and observed an increase in reactivity with increasing substitution. Skell and Garner[6] observed a similar, although less pronounced, trend with dibromocarbene. Closs and Schwartz[7] measured the yields of chlorocyclopropyl derivatives obtained from a range of olefins in competitive reaction with monochlorocarbene generated from butyllithium and methylene chloride. Their results showed that the magnitude of the differences in reaction rate of chlorocarbene was lower than that of dichlorocarbene. Thus far no comparable study has been reported with bromocarbene.

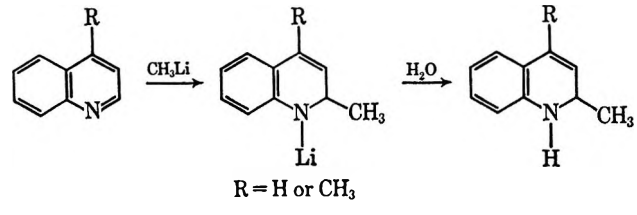
If a true carbene is involved in the ring expansion reaction of indole with methylene bromide and methyllithium the rate of reaction of bromocarbene with skatole should be increased to an observable extent relative to indole by virtue of the electron-releasing properties of the methyl substituent adjacent to the double bond.

The relative rates of the competitive reactions can be expressed as in eq 1 where k_i and k_s are the rate

$$k_i/k_s = R_sP_i/R_iP_s \quad (1)$$

constants for indole and skatole, respectively; P_i and P_s are mole fractions of total ring expansion products; and R_i and R_s are the mole fractions of the competitive reagents, indole and skatole, respectively.

Such an equation applies only if (a) the reactants are present in excess and (b) the product ratio is not changed by further reactions. It is considered that these conditions are fulfilled in the rate study described herein. The low over-all yields of the ring expansion products and the recovery at the completion of similar experiments of considerable quantities of unchanged indoles imply that the competitive reagents are always present in excess. It might be argued, however, that condition b is not fulfilled as the first ring-expansion products react further with the methyllithium to form the corresponding dihydroquinaldine derivatives. The high yields obtained in the preparation of



these subsequent transformation products *per se* (see Experimental Section) indicate that these reactions are virtually quantitative. The measurement of the total ring-expansion products from each indole therefore satisfies condition b.

The three values for k_i/k_s obtained in this study were variable, with a mean value close to unity. Other workers studying the reaction of bromocarbene have observed product dependence upon the reaction condi-

(1) (a) Part of this work was conducted at the U. K. Atomic Energy Research Establishment, Wantage, Berks, England. (b) G. L. Closs and G. M. Schwartz, *J. Org. Chem.*, **26**, 2609 (1961).

(2) B. Robinson, *Tetrahedron Lett.*, No. 4, 139 (1962).

(3) C. W. Rees and C. E. Smithen, *J. Chem. Soc.*, 928 (1964).

(4) H. E. Dobbs, *Chem. Comm.*, 56 (1965).

(5) W. E. Doering and W. A. Henderson, *J. Amer. Chem. Soc.*, **80**, 5274 (1958).

(6) P. S. Skell and A. Y. Garner, *ibid.*, **78**, 5430 (1956).

(7) G. L. Closs and G. M. Schwartz, *ibid.*, **82**, 5723 (1960).

TABLE I

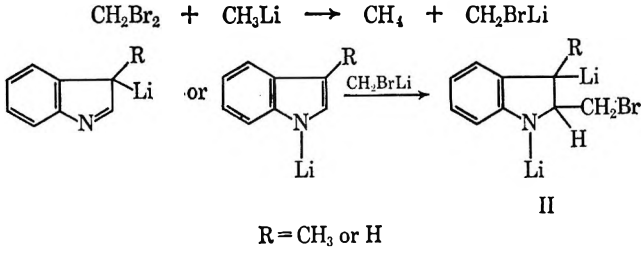
SUMMARY OF COMPETITIVE REACTION RATE STUDIES OF INDOLE AND SKATOLE WITH METHYLLITHIUM AND ^{14}C-LABELED METHYLENE BROMIDE

	Reactants, mmol				% yield of products (based on methylene bromide)					
Experiment	Methylene bromide	Methyllithium	Indole	Skatole	Quinoline	Lepidine	1,2-Dihydroquinaldine	1,2-Dihydro-2,4-dimethylquinoline	Total basic products	k_s/k_i
1	16.4	49.2	8.2	8.2	0.071	0.116	0.019	0.045	0.25	1.8
2	20	60	10	10	0.042	0.033	0.061	0.064	0.20	0.9
3	30	180	30	30	0.207	0.186	0.087	0.088	0.57	0.9
									Mean	1.2

tions.[8] It is possible, therefore, that the variation of the individual values for k_i/k_s (Table I) can be attributed to changes in experimental conditions. The over-all lack of discrimination could be due to the low stability of bromocarbene relative to dibromocarbene (*cf.* chlorocarbene). This result may also be explained in terms of a "carbenoid" intermediate.

Closs and his coworkers,[9-11] postulated the involvement of "carbenoids" in reactions involving alkyllithium compounds, but were unable to confirm their existence by the isolation of derivatives. However, trichloromethyllithium[12] and dichloromethyllithium[13a] were subsequently prepared by other workers at low temperature.

On this evidence it is conceivable that the rate-controlling stage in the ring-expansion reactions discussed herein involves the addition of the carbenoid monobromomethyllithium to indolyllithium to form the adduct II. The same product (II) would be formed by carbenoid reaction with the lithium derivatives of both mesomeric indolyl anions. If bromomethyllithium is involved in the ring-expansion reaction it is likely that it would be less electrophilic than the true carbene, and would be more susceptible to steric hindrance, thus accounting for the similarity of the rates of reaction of indole and skatole.

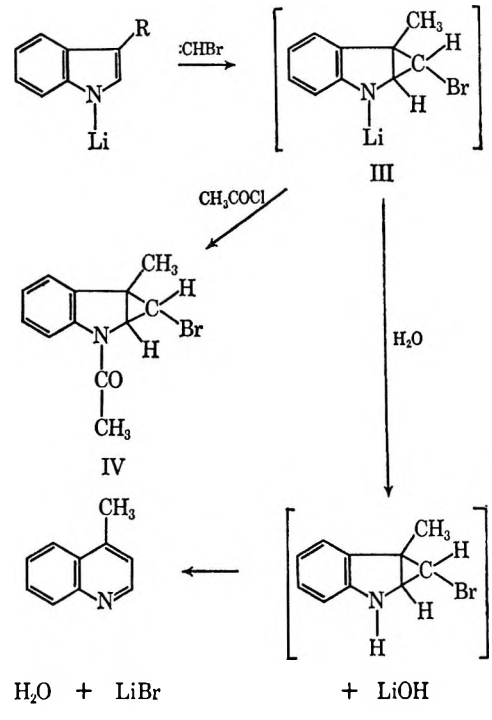


II

R = CH_3 or H

In a preliminary nonradioactive experiment a mixture of lepidine and 1,2-dihydro-2,4-dimethylquinoline was obtained when skatole was allowed to react with methylene bromide in the presence of excess methyllithium for a prolonged period. As lepidine reacts rapdily with methyllithium to form 1,2-dihydro-2,4-dimethylquinoline it was concluded that a metastable intermediate was present in the reaction mixture, and that this compound was converted into the quinoline during the final hydrolysis stage.

In an attempt to produce a stable derivative of the possible anticipated intermediate (III), acetyl chloride was introduced into a reaction conducted with ^{14}C-labeled methylene bromide.[13b] Lepidine carrier was added to a



solution of a substance isolated from this reaction mixture. The lepidine was recovered, converted into the picrate, and after five recrystallizations was shown to be virtually inactive. The lepidine carrier added to another portion of the same solution, that was hydrolyzed with alcoholic potash, became radioactive, thus providing incontravertible evidence for the existence of a lepidine precursor.

The yield of the lepidine precursor from this reaction was very small, however, and it was necessary to repeat the experiment to obtain a sufficient amount of the compound for elemental and spectrophotometric analysis. The combined products were purified by repeated column chromatography, and effluent fractions containing the precursor were identified by hydrolsysis of an aliquot with alcoholic potash in the presence of lepidine carrier. Despite repetition of the experiment, the quantity of intermediate isolated was sufficient only for ir and elemental (and group) analysis, which surprisingly showed it to contain no bromine and no acetyl.

(8) C. W. Jefford, R. Medary, and B. Waegell, Communication to the Chemical Society, Autumn Meeting, Brighton, Sept 1966, paper A19.

(9) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **81**, 4996 (1959).

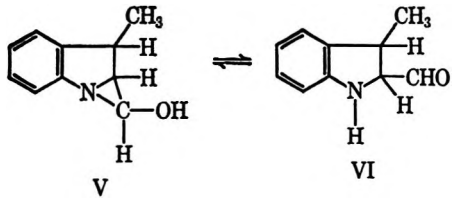
(10) G. L. Closs, *ibid.*, **84**, 809 (1962).

(11) G. L. Closs and L. E. Closs, *Angew. Chem. Intern. Ed. Engl.*, **1**, 334 (1962).

(12) W. T. Miller and D. M. Whalen, *J. Amer. Chem. Soc.*, **86**, 2089 (1964).

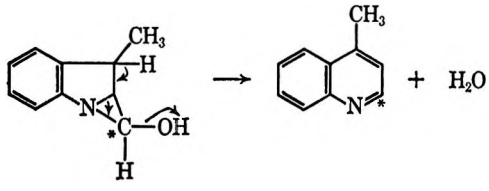
(13) (a) G. Kobrich, K. Flory, and W. Drischel, *Angew. Chem. Intern. Ed. Engl.*, **3**, 513 (1964). (b) Attempts to produce an amount sufficient for detailed analysis of the pure intermediate arising from the reaction of methylene chloride with methyllithium, and indole were not successful. The intermediate derived from [^{14}C]methylene chloride announced in a preliminary communication[4] has subsequently been shown to be impure.

A plausible composition for the product isolated, consistent with the ir and elemental analysis, is a mixture of the aziridine V and the tautomeric indoline aldehyde VI.

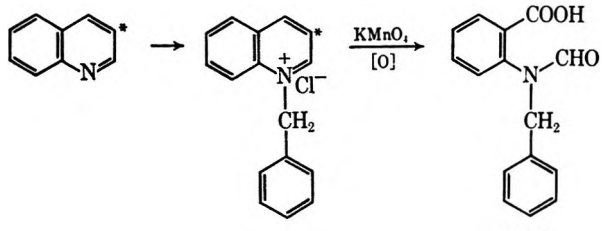


V VI

One possible mechanism for the formation of lepidine from structure V involves the loss of a molecule of water.

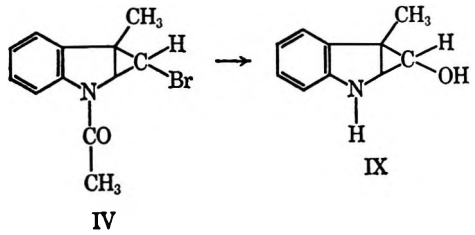


If this route is correct the labeled carbon atom would enter the quinoline ring in the 2 position. To investigate this possibility indole was treated with [^{14}C]-methylene bromide and methyllithium, and hydrolyzed with water. ^{14}C-Labeled quinoline was isolated from the reaction mixture, diluted with carrier, and converted into benzylquinolinium chloride (VII) which was recrystallized to constant specific activity. Oxidation of VII with potassium permanganate to yield nonradioactive N-benzyl-N-formylanthranilic acid (VIII) indicated that the radioactive carbon atom was in the 3 position of the quinoline ring.



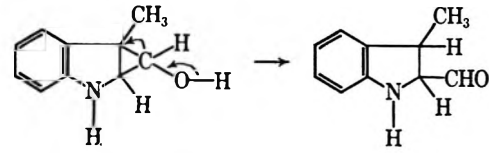
VII VIII + *CO_2

The formation of the ring-expansion product by ring opening and ring closure of the aldehyde VI under basic conditions is unlikely. It is probable, therefore, that the substance isolated is a mixture of the aldehyde VI and the isomeric cyclopropanol IX, which could be derived, by hydrolysis on the column, from the anticipated intermediate derivative IV. Rearrangement of



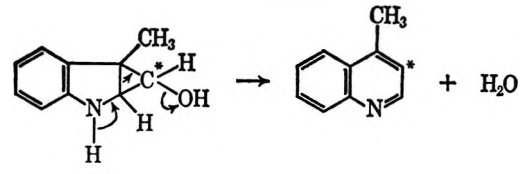
IV IX

the carbinol IX could lead to the formation of the aldehyde VI. Alternatively elimination of a molecule



VI

of water from the carbinol IX would lead to the formation of the ring-expansion product with the new carbon in the 3 position in the lepidine ring.



IX

It is concluded that the ring-expansion reaction of skatole with methyllithium and methylene bromide proceeds *via* addition of bromocarbene or bromomethyllithium to the indole 2,3 double bond. In an anhydrous medium lepidine is formed from the carbene (or carbenoid) adduct intermediate by the elimination of 1 or 2 mol of lithium bromide, respectively. The substance obtained in an attempt to isolate the acetyl derivative of the reaction intermediate is probably a mixture of an indoline aldehyde (VI) and a carbinol (IX) that is transformed to lepidine in boiling alcoholic potash by the elimination of a molecule of water.

The ring-expansion reaction was capricious. The use of radiotracer techniques, however, enabled the yields of selected products to be accurately measured. The use of labeled reagent also provided unequivocal evidence for the presence of small quantities of a ring-expansion precursor and enabled the chromatographic fractions containing it to be identified. The entry of the labeled carbon atom into the 3 position of the lepidine ring provided supporting evidence for the proposed mechanism of the reaction.

Experimental Section

Preparation of Nonradioactive Carriers. 1,2-Dihydroquinaldine.—Quinoline (6.45 g) dissolved in dry ether was added over 5 hr to a solution of methyllithium in ether (100 ml, 1 *M*) under reflux. The reaction mixture was cooled, hydrolyzed, and acidified with 5 *N* hydrochloric acid. Basification of the separated aqueous phase yielded an amber oil (6.3 g, n^{22}D 1.6125) corresponding to a yield of 87.5%. This was distilled at atmospheric pressure and the major fraction (bp 240°, n^{24}D 1.5969) gave a picrate, mp 187° dec.

Anal. Calcd for $C_{16}H_{13}N_4O_7$: C, 51.5; H, 3.49; N, 15.0. Found: C, 51.47; H, 3.38; N, 15.57.

1,2-Dihydro-2,4-dimethylquinoline.—Lepidine (14.3 g) in ether solution was treated with methyllithium (200 ml, 2 *M*) in a manner similar to that used for the preparation of 1,2-dihydroquinaldine to yield 11.5 g of a colorless oil: bp 142–144° (10 mm); n^{18}D 1.5984. It readily formed a picrate, mp 196° dec.

Anal. Calcd for $C_{17}H_{15}N_4O_7$: C, 52.8; H, 3.88; N, 14.5. Found: C, 52.85; H, 3.86; N, 14.59.

Preparation of ^{14}C-Labeled Reagent.—^{14}C-Labeled methylene bromide was prepared *via* bromoform from acetone[1,3-^{14}C] by adapting the methods described by Vogel[14] for the preparation of the nonradioactive compounds.

[^{14}C]Bromoform.—A 250-ml three-necked flask, containing a Teflon-coated magnet, was fitted with a reflux condenser and two dropping funnels, the stem of one of them reaching to the bottom of the flask. Aqueous 20% sodium carbonate solution

(14) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co. Ltd, 1959, pp 299, 300.

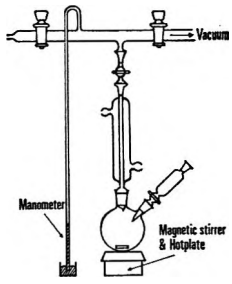


Figure 1.—Apparatus used for reaction-rate studies with methyllithium.

(50 ml) was placed in the flask which was cooled in liquid nitrogen and evacuated. Acetone[1,3-^{14}C] (6.6 g, specific activity 1.04 mCi/mol) was transferred to the flask by vacuum sublimation. The pressure was then rasied to atmospheric and the flask removed from the vacuum manifold and placed in an oil bath at 50°. Bromine (21 ml), placed in the long-stemmed funnel, was added to the warmed aqueous solution with vigorous stirring over a period of 3 hr. After 3 ml of the bromine had been added 180 ml of 11% aqueous sodium hydroxide was run into the reaction mixture, concomitantly with the bromine, at such a rate that the red color discharged if the flow of bromine was reduced. The bath temperature was maintained at 50° throughout the addition. The flask was then cooled in ice and the heavy bromoform layer separated. The aqueous phase was extracted twice with ether. The combined ether washings and bromoform were washed with water, dried with anhydrous calcium chloride, and fractionally distilled to give 19.98 g of the product: bp 149–152°; mp 4°; specific activity 0.47 mCi/mol.

[^{14}C]Methylene Bromide.—A 150-ml, two-necked flask containing a Teflon-coated magnet was fitted with a dropping funnel and a reflux condenser. Freshly prepared bromoform (19.0 g, specific activity 0.41 mCi/mol) was introduced into the flask which was placed in an oil bath. A sodium arsenite solution, prepared by dissolving arsenious oxide (8.9 g) and sodium hydroxide (16.8 g) in 50 ml of water, was introduced into the dropping funnel. A portion of the sodium arsenite solution (10 ml) was added to the bromoform with vigorous stirring, and the bath temperature slowly raised from 20 to 75°. The remainder of the arsenite solution was added over a period of 2.5 hr with the bath temperature maintained at 75°. When the addition was complete the bath temperature was raised to 85° and the mixture stirred for a further 2 hr. The reaction mixture was steam distilled, the methylene bromide was separated, and the aqueous layer extracted twice with ether. The combined ether extracts and methylene bromide were washed with water, dried over anhydrous calcium chloride, and fractionally distilled to give 7.5 g of the product: bp 96°; specific activity 0.39 mCi/mol.

Comparison of Reaction Rates.—The apparatus used in this study is shown in Figure 1. The flask was evacuated before the introduction of the reactants. Methane gas generated by the reaction of the indoles with methyllithium maintained an inert atmosphere (at atmospheric pressure) over the reaction mixture; the excess was allowed to escape *via* the manometer.

Experiment 1.—Indole (1.095 g) and skatole (1.23 g) dissolved in ether (30 ml) were slowly added to a solution of methyllithium in ether (10 ml, 5.62 *M*) and the mixture was heated under reflux for 90 min. [^{14}C]Methylene bromide (3.25 g, 19.14 mCi/mol) dissolved in ether (30 ml) was added over 3 hr. The mixture was stirred and heated under reflux for 19 hr. The flask was then cooled in ice and the reaction mixture hydrolyzed with water (25 ml) and acidified with concentrated hydrochloric acid. The separated ether layer was washed with water, and the washings were combined with the aqueous phase.

Accurately weighed quantities of single nonradioactive carriers (quinoline (0.55 g), lepidine (0.41 g), 1,2-dihydroquinaldine (0.42 g), and 1,2-dihydro-2,4-dimethylquinoline (0.69 g)) were added to known fractions of the total aqueous phase. Each solution was then basified and the basic products were extracted with ether. The extracts were evaporated, converted into picrate, and repeatedly recrystallized (up to 45 times) until the specific activity of the picrate reached a constant value.

The experiment was repeated twice using different quantities of reagents and modified conditions.

The results of all three experiments are contained in Table I.

Isolation of Intermediate.—An ether solution of methyllithium (66 ml, 5.0 *M*) was introduced into a flask connected to a vacuum manifold as in Figure 1. Skatole (8.78 g) dissolved in dry ether (100 ml) was added over 45 min with vigorous stirring and the mixture heated under reflux for 15 min. The flask was then cooled to 24° and methylene bromide (11.6 g, 0.43 mCi/mol) dissolved in dry ether (250 ml) added over 3 hr. The mixture was stirred for a further 1.5 hr, then cooled in ice and acetyl chloride (39.3 g) dissolved in ether (100 ml) added over 15 min. The reaction mixture was allowed to stand overnight at 0°. The ether layer was decanted and evaporated under reduced pressure. The residue was dissolved in acetone (5 ml), adsorbed on an alumina chromatography column (50 cm × 4 cm) cooled to 0°. The effluent was monitored for radioactivity by passage through a cell incorporating an inverted end-window geiger counter.[15] The column was eluted with 100-ml volumes of solvent of gradually increasing polarity. N-Acetyl skatole was eluted with 40–60° petroleum. The lepidine precurson was eluted with ether. Fractions containing the precursor were identified by hydrolysis of an aliquot with alcoholic potash in the presence of 0.5 g of lepidine carrier, which was subsequently converted into the picrate and recrystallized to constant specific activity. Fractions containing the lepidine precursor were evaporated and rechromatographed on alumina.

The above reaction was repeated twice, with modifications, and the lepidine precursor from each reaction was chromatographed twice. The fractions containing lepidine precursor from all of the reactions were combined, evaporated, and chromatographed two more times to yield an amber oil (~50 mg).

A portion of the oil was dissolved in ether (50 ml). Lepidine (0.2 g) was added to 25 ml of this solution. The lepidine was then extracted from the ether solution with dilute acid, converted into the picrate, and recrystallized five times. Assay of the picrate by oxygen flask combustion gave a very small count rate above background, which corresponded to a specific activity of <0.1 μCi/mol for the picrate. The remainder of the ether solution (25 ml) was evaporated in the presence of lepidine (0.2 g) and heated for 16 hr with a solution of potash (0.5 g) in water (1 ml) and ethyl alcohol (10 ml). The lepidine was subsequently extracted, converted into the picrate and recrystallized to constant specific activity (7.7 μCi/mol).

Analysis of the oil showed it to contain no acetyl and no bromine. The ir spectrum of the oil was measured as a thin layer between salts on a Perkin-Elmer "Infracord" spectrophotometer. The very strong absorption band at 3495 cm^{-1} in skatole that is attributed to the N–H stretching frequency was absent.[16] There were broad bands of medium intensity at 3350 and 1110 cm^{-1} that are indicative of a secondary OH. A strong carbonyl stretching band at 1660 cm^{-1} was also present. A band of medium intensity at 1020 cm^{-1} that could perhaps be attributed to a cyclopropane structure was also observed.

Anal. Found: C, 73.62; H, 7.09; N, 8.59; O, 10.7 (by difference).

Determination of the Position of Entry of the New Carbon Atom into the Quinoline Ring. Ring-Expansion Reaction.—Indole (7.25 g) was dissolved in ether and reacted with an equimolar quantity of methyllithium in ether solution (41 ml, 1.5 *M*). The reaction mixture was cooled in ice and methylene bromide (11.0 g, 118 μCi/mol) added concomitantly with another volume of methyllithium solution (41 ml, 1.5 *M*) over 2 hr with vigorous stirring. The reaction mixture was hydrolyzed with water and stirred for 10 min. It was then acidified with concentrated hydrochloric acid. Quinoline carrier (1.53 g) was added to the mixture and subsequently extracted, dried, and fractionally distilled to yield 1.11 g of the product: bp 237–241°; 10.6 μCi/mol.

Benzylquinolinium Chloride.—Quinoline (0.5 g) from the above reaction was diluted with carrier (2.5 g) and heated with benzyl chloride for 5 hr at 100°. The benzylquinolinium chloride was precipitated with ether and recrystallized from alcohol–ethylacetate to yield 2.6 g of pale pink crystals mp (~100) 170°. An aliquot (0.6 g) of this product was recrystallized ten times to constant specific activity. This purified compound, mp (100) 172°, had a specific activity of 0.84 μCi/mol.

(15) H. E. Dobbs, *J. Chromatog.*, **2**, 572 (1959).

(16) This band is not present in the spectrum of indole-3-aldehyde, and its absence is attributed to association of the N–H bond: D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 876 (1959).

Anal. Calcd for $C_{26}H_{14}NCl \cdot H_2O$: C, 70.3; H, 5.85; N, 5.1; Cl, 13.0. Found: C, 70.2; H, 5.65; N, 5.0; Cl, 13.0.

Oxidation.—The remaining benzylquinolinium chloride was oxidized to N-benzyl-N-formylanthranilic acid with potassium permanganate.[17]

Benzylquinolinium chloride (2.0 g) was dissolved in water (400 ml) and warmed to 30°. Potassium permanganate (4.12 g) dissolved in warm water (200 ml) was added over 2 hr with vigorous stirring. The reaction mixture was then made alkaline by the addition of a few pellets of solid potassium hydroxide and filtered. The filtrate was acidified with hydrochloric acid. The pale amber oil, that separated from the aqueous phase on acidification, solidified on standing. The solid was filtered and recrystallized ten times from ethyl alcohol to yield colorless granular crystals, mp 194°.

Anal. Calcd for $C_{15}H_{13}O_3N$: C, 70.6; H, 5.1; N, 5.5. Found: C, 70.5; H, 5.1; N, 5.5.

A sample of this purified product, dissolved in a dioxane-based scintillator, showed no detectable radioactivity.

Radioactivity Measurements.—Radioactivity measurements were made in a coincidence liquid scintillation counter.[18a] Nonquenching radioactive liquids were injected into weighed counting phials containing a suitable phosphor and sealed with rubber serum caps.[18b] Quenching liquids and solids (picrates) were burned in an oxygen flask combustion apparatus and the [^{14}C]carbon dioxide thus formed was dissolved in 2-phenylethylamine premixed with a liquid phosphor and injected into the flask.[18c] Counting efficiencies were measured with an "efficiency stick",[18d] and random samples were checked by "spiking" with a nonquenching standard.[18b]

(17) A. Claus and F. Glyckherr, *Chem. Ber.*, **16**, 1283 (1883).

(18) H. E. Dobbs: (a) U. K. Atomic Energy Authority Memorandum, AERE-M1075 (1962); (b) U. K. Atomic Energy Authority Memorandum, AERE-M1574 (1965); (c) *Anal. Chem.*, **35**, 783 (1963), and **36**, 687 (1963); (d) *Nature*, **200**, 1283 (1963).

Registry No.—1,2-Dihydroquinaldine, 1125-81-1; 1,2-dihydroquinaldine picrate, 15619-45-1; 1,2-dihydro-1,4-dimethylquinoline, 15619-46-2; 1,2-dihydro-2,4-dimethylquinoline picrate, 15619-47-3; benzylquinolinium chloride (VII), 15619-48-4; 1-benzyl-N-formylanthranilic acid (VIII), 15656-73-2; [^{14}C]bromo-form, 7825-2; [^{14}C]methylene bromide, 15619-50-6.

Acknowledgments.—Thanks are extended to Dr. W. A. Waters, F. R. S., Dr. K. W. Bentley, and Dr. G. T. Rogers for their advice and to D. G. Humphreys for technical assistance.

Aziridines. XVIII. Reactions of a 1,3-Diazabicyclo[3.1.0]hex-3-ene with Alkenes, Alkynes, and Diethyl Azodicarboxylate

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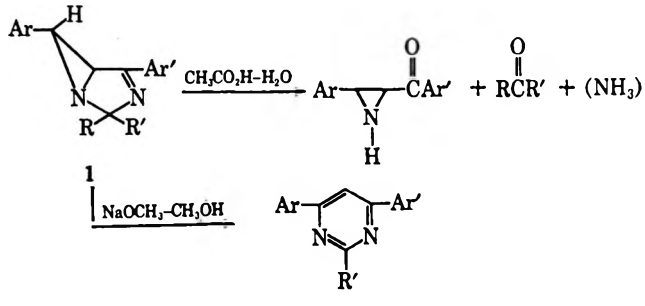
Received October 17, 1967

Adducts of 2,2-dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo[3.1.0]hex-3-ene with diethylacetylene dicarboxylate, diethyl fumarate, *cis*- or *trans*-dibenzoylethene, diethyl azodicarboxylate, and N-phenylmaleimide are formed in refluxing *p*-xylene. The reaction proceeds by carbon–carbon bond scission of the aziridine ring of the 1,3-diazabicyclo[3.1.0]hex-3-ene.

The synthesis of the previously unknown class of compounds, the 1,3-diazabicyclo[3.1.0]hex-3-enes (1), has been described recently.[1] Some of these compounds are converted in moist acetic acid into 2-aryl-3-aroylaziridines and ketones. Other 1,3-diazabicyclo-[3.1.0]hex-3-enes (where R = H) in methanol containing sodium methoxide rearrange and subsequently air oxidize into pyrimidines (Scheme I).

SCHEME I



We now have observed that in refluxing *p*-xylene 1,3-diazabicyclo[3.1.0]hex-3-enes form adducts with various alkenes, alkynes, and diethyl azodicarboxylate. The adducts are novel bicyclic or tricyclic systems and are formed by carbon–carbon cleavage of the aziridine ring. Recent work has demonstrated that carbon–carbon scission of the aziridine ring occurs when 1,2,3-triarylaziridines,[2] 2-aroylaziridines,[3] 2,3-diaroylaziridines,[4] and 2,3-dicarbethoxyaziridines[5] are heated in inert solvents with alkenes and alkynes.

Results

Refluxing a *p*-xylene solution of 2,2-dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (2) and diethylacetylene dicarboxylate formed diethyl 3,3-dimethyl-5-(*p*-nitrophenyl)-1-phenyl-3H-pyrrolo-[1,2-*c*]imidazole-6,7-dicarboxylate (3) (Scheme II). The structure of 3 was confirmed by acid hydrolysis to 2-benzoyl-3,4-dicarbethoxy 5-*p*-nitrophenylpyrrole (4) and presumably acetone. The hydrolysis of the 3-imidazoline moiety of 3 is analogous to the acid hydrolysis of 3-imidazolines to form α-amino ketones, ketones, and ammonium chloride[6] and of 1,3-diazabicyclo[3.1.0]-hex-3-enes to form 2-aryl-3-aroylaziridines and ketones.[1] The structure of 4 was assigned by means of an independent synthesis involving the addition of *trans*-2-*p*-nitrophenyl-3-benzoylaziridine (5) to di-

(1) H. W. Heine, R. H. Weese, R. A. Cooper, and A. J. Durbetaki, *J. Org. Chem.*, **32**, 2708 (1967).

(2) H. W. Heine and R. E. Peavy, *Tetrahedron Lett.*, 3123 (1965); H. W. Heine, R. E. Peavy, and A. J. Durbetaki, *J. Org. Chem.*, **31**, 3924 (1966).

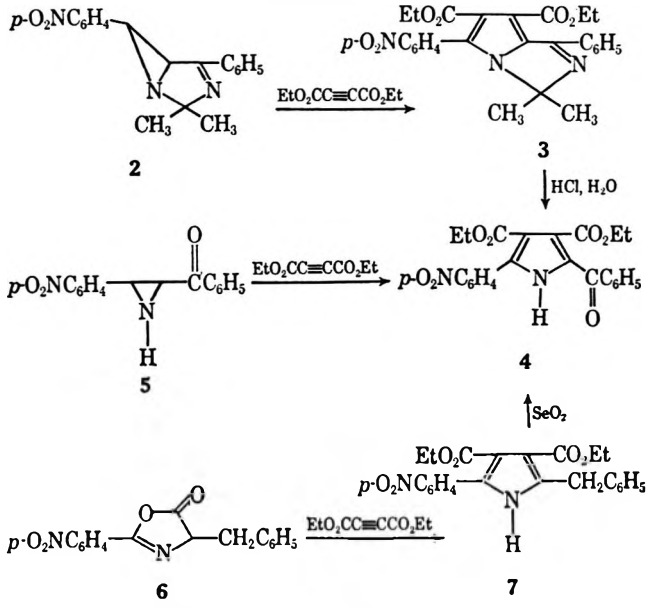
(3) A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965); A. Padwa and L. Hamilton, *J. Heterocyclic Chem.*, **4**, 118 (1967).

(4) R. Huisgen, W. Scheer, G. Szemies, and H. Huber, *Tetrahedron Lett.*, 397 (1966).

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

(6) G. Kirchner, *Ann.*, **625**, 98 (1959).

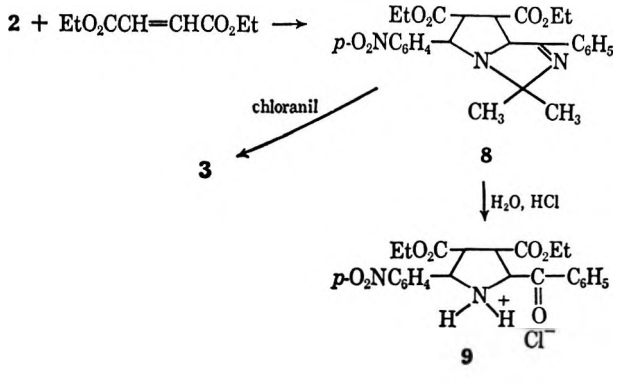
SCHEME II



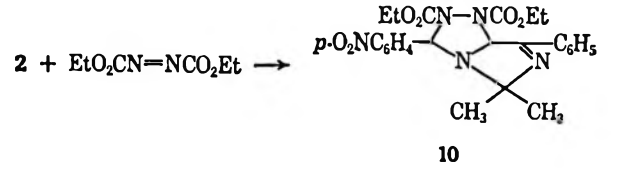
ethylacetylene dicarboxylate. Padwa and Hamilton had previously demonstrated that *trans*-2-phenyl-3-benzoylaziridine adds to dimethylacetylene dicarboxylate by carbon–carbon scission of the aziridine ring to yield 2-benzyl-3,4-dicarbomethoxy-5-phenylpyrrole.[3] Compound **4** was also prepared by a two-step process involving first the heating of 2-*p*-nitrophenyl-4-benzyl-5-oxazolone (**6**) with diethylacetylene dicarboxylate which gave 2-benzyl-3,4-dicarbomethoxy-5-*p*-nitrophenylpyrrole (**7**). Compound **7** was subsequently oxidized by selenium dioxide to **4**. A similar sequence has been employed to prepare 2-benzoyl-3,4-dicarbomethoxy-5-phenylpyrrole.[3]

Compound **2** readily reacted with diethyl fumarate to form the adduct **8**. The structure of **8** was confirmed by the chloranil oxidation of **8** to **3**. Acid hydrolysis of **8** gave the pyrrolidine hydrochloride **9** (Scheme III).

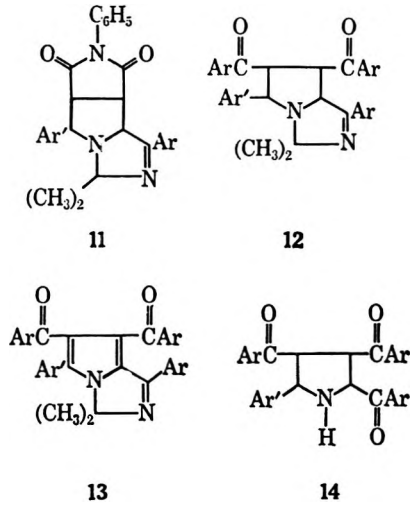
SCHEME III



Refluxing of **2** with diethyl azodicarboxylate in *p*-xylene gave diethyl 5,7a-dihydro-5,5-dimethyl-3-(*p*-nitrophenyl)-7-phenyl-1H-imidazo[5,1-*c*]-*s*-triazole-1,2-(3H)-dicarboxylate (**10**). The structure of **10** was assigned on the basis of elemental analyses and nmr spectroscopy. The nmr spectrum showed the two methyl groups at C-5 as two singlets at 1.57 and 1.69 ppm, the two methine protons as a singlet at 6.51 ppm, and the two ethyl groups as two quartets centered at 4.0 ppm and two triplets clustered at 0.93 ppm downfield from tetramethylsilane as well as a complex pattern of bands from 7.2 to 8.3 ppm characteristic of aromatic protons. If the adduct **10** had been formed by carbon–nitrogen bond cleavage of the aziridine ring, the methine protons would be on adjacent carbon atoms and two doublets should be observed in the nmr spectrum.

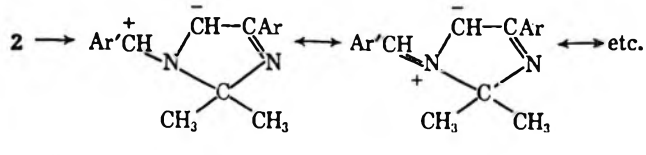


Compound **2** with N-phenylmaleimide in refluxing *p*-xylene gave 5,6,7,7a-tetrahydro-3,3-dimethyl-5-(*p*-nitrophenyl)-N,1-diphenyl-3H-pyrrolo[1,2-*c*]imidazole-6,7-dicarboximide (**11**). Refluxing equimolar quantities of **2** with *cis*- or *trans*-dibenzoylethene gave the identical addition product **12**. Control runs with *cis*- and *trans*-dibenzoylethenes in refluxing *p*-xylene showed that the interconversion of these alkenes does not occur. Compound **12** was oxidized by chloranil to the corresponding pyrrolo derivative **13**. Hydrolysis of compound **12** formed the pyrrolidine **14**. An independent synthesis of **14** was accomplished by the addition of *trans*-2-*p*-nitrophenyl-3-benzoylaziridine to *trans*-1,2-dibenzoylethene.



Ar = C_6H_5; Ar′ = *p*-$O_2NC_6H_4$

A likely mechanism for these additions is the conversion of the 1,3-diazabicyclo[3.1.0]hex-3-ene into a 1,3 dipole (**15**) which subsequently reacts with the unsaturated substrate.



The fact that **2** with *cis*- or *trans*-dibenzoylethene gave the same adduct **12** may be the result of a two-step nonstereoselective addition by the 1,3 dipole **15** to the ethenes. However, most 1,3-dipolar additions are known to be concerted and thus stereospecific.[7] More likely, the formation of the same stereoisomeric

(7) R. Huisgen, *Angew. Chem.*, **2**, 633 (1963).

adduct **12** is the result of the epimerization of one of the initially formed adducts. The addition of diphenyl (nitrileimine) to dimethyl maleate has been shown to involve just such an epimerization.[7,8]

Experimental Section

2,2-Dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo[3.1.0]-hex-3-ene (2) was prepared either by the published procedure[1] or by the following shorter method. A suspension of 40.0 g of 2,3-dibromo-1-phenyl-3-(4-nitrophenyl)-1-propanone in 250 ml of absolute ethanol containing 10 ml of acetone was stirred and saturated with ammonia. When most of the dibromide had dissolved the reaction mixture was stored in a refrigerator overnight. The crude **2** was filtered and washed with a little 95% ethanol and then with water. Recrystallization from 95% ethanol gave 21.5 g (72%) of **2**.

Compound 3.—A mixture of 1.228 g of **2** and 680 mg of diethylacetylene dicarboxylate in 20 ml of *p*-xylene was refluxed for 1 hr. The solvent was evaporated and 4 ml of 95% ethanol was added to the oily residue. The crude **3** which formed on the addition of the ethanol weighed 945 mg (49%) and melted at 160–163°. Four recrystallizations from 95% ethanol gave **3** melting at 168–169.5°.

Anal. Calcd for $C_{26}H_{25}N_3O_6$: C, 65.68; H, 5.30; N, 8.84. Found: C, 66.01; H, 5.26; N, 9.15.

Compound 4. Method A.—A solution of 536 mg of *trans*-2-*p*-nitrophenyl-3-benzoylaziridine and 340 mg of diethylacetylene dicarboxylate in 5 ml of *p*-xylene was refluxed 1 hr. The solvent was evaporated and the oily residue heated with 5 ml of 95% ethanol. The crude **4** was filtered and weighed 125 mg (14%). Four recrystallizations from 95% ethanol gave **4** melting at 159–160°. A 22% yield of **4** was obtained if the oily residue was dissolved in a minimum amount of benzene and the benzene solution chromatographed on a 1.5 × 15 cm alumina column. The column was eluted with a 3% solution of ethyl acetate and 97% benzene.

Anal. Calcd for $C_{23}H_{20}N_2O_7$: C, 63.29; H, 4.62; N, 6.42. Found: C, 63.17; H, 4.56; N, 6.53.

Compound 4. Method B.—A solution of 200 mg of **3** in 10 ml of commercial absolute ethanol and 5 ml of concentrated hydrochloric acid was refluxed 1 hr. The solvent was evaporated and the residue recrystallized several times from 95% ethanol. The residue weighed 110 mg (60%) and melted at 159–160°.

Compound 4. Method C.—A mixture of 900 mg of **7** and 600 mg of selenium dioxide was sealed in a tube which was then heated in an oven at 200° for 75 min. The cooled reaction mixture was dissolved in a minimum quantity of benzene and the benzene solution was chromatographed on a column of alumina. The column was eluted with 3% ethyl acetate–97% benzene. Evaporation of the solvent from the collected fractions gave a heavy dark green oil. The green oil was heated in a minimum amount of hot 95% ethanol. On cooling the crystals of **4** which precipitated were collected (70 mg).

Compound 7.—A mixture of 1.5 g of 2-*p*-nitrophenyl-4-benzyl-2-oxazoline-5-one (**6**)[9] and 1.00 g of diethylacetylene dicarboxylate was sealed in a tube which was heated in an oven at 160° for 3 hr. The reaction mixture was cooled and dissolved in a minimum quantity of benzene. The benzene solution was chromatographed on a 1.5 × 15 cm alumina column. The eluate was 3% ethyl acetate–97% benzene. Evaporation of the eluent gave 700 mg (33%) of crude **7**. Recrystallization from 95% ethanol gave **7**, mp 166–167°.

Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.40; H, 5.25; N, 6.63. Found: C, 65.41; H, 5.04; N, 6.65.

Compound 8.—A mixture of 614 mg of **2** and 344 mg of diethyl fumarate in 20 ml of *p*-xylene was refluxed for 1 hr. The *p*-xylene was evaporated and 10 ml of 95% ethanol was added to the oily residue. The crude **8** was filtered and weighed 657 mg (68%) and melted at 165–167°. Four recrystallizations from 95% ethanol gave **8** melting at 165–167°.

Anal. Calcd for $C_{26}H_{29}N_3O_6$: C, 65.13; H, 6.09; N, 8.76. Found: C, 65.08; H, 6.33; N, 8.77.

Oxidation of 8 to 3.—A solution of 480 mg of **8** and 300 mg of chloranil in 10 ml of *p*-xylene was refluxed for 17 hr. The solvent was evaporated and the residue washed with ether. Recrystallization of the crude **3** with 95% ethanol gave 200 mg (42%) of **3**, mp 168–169°.

Hydrolysis of 8 to 9.—A solution of 1.3 g of **8** in 5 ml of concentrated hydrochloric acid and 5 ml of ethanol was refluxed for 15 min. Evaporation of the solvent and recrystallization of the residue from 95% ethanol gave **9**, mp 184–186°.

Anal. Calcd for $C_{23}H_{25}ClN_2O_7$: C, 57.91; H, 5.28; N, 5.87. Found: C, 57.95; H, 5.23; N, 5.85.

Compound 10.—A mixture of 920 mg of **2** and 600 mg of diethyl azodicarboxylate in 75 ml of decane was refluxed for 30 min. The solvent was evaporated and the crude **10** (1.10 g, 76%) was recrystallized once from 95% ethanol and four times from petroleum ether (bp 100–115°) to give **10** melting at 119–120°.

Anal. Calcd for $C_{24}H_{27}N_3O_6$: C, 59.86; H, 5.65; N, 14.54. Found: C, 60.26; H, 5.66; N, 14.83.

Compound 11.—A mixture of 614 mg of **2** and 346 mg of N-phenylmaleimide in 10 ml of *p*-xylene was refluxed for 1.5 hr. The *p*-xylene was evaporated and to the residual oil was added 20 ml of 95% ethanol. The crude **11** which precipitated was filtered and weighed 685 mg (71%); it melted at 218–219°. Four recrystallizations from ethanol gave **11** melting at 218–220°.

Anal. Calcd for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.20; H, 5.44; N, 11.78.

Compound 12. Method A.—A mixture of 614 mg of **2** and 472 mg of *trans*-dibenzoylethene in 10 ml of *p*-xylene was refluxed for 85 min. The solvent was evaporated and the solid residue recrystallized from 95% ethanol to give 728 mg (67%) of **12**, mp 200–202°.

Anal. Calcd for $C_{34}H_{29}N_3O_4$: C, 75.12; H, 5.37; N, 7.73. Found: C, 75.44; H, 5.59; N, 7.61.

Compound 12. Method B.—The identical procedure was employed as in method A above except 472 mg of *cis*-dibenzoylethene was employed in place of *trans*-dibenzoylethene. A 40% yield of **12** was obtained.

Oxidation of 12 into 13.—A solution of 543 mg of **12** and 600 mg of chloranil in 20 ml of *p*-xylene was refluxed for 17 hr. The solvent is evaporated and the residue washed with ether. The crude **13** weighed 520 mg and was recrystallized from 95% ethanol. The recrystallized **13** melted at 203–204°.

Anal. Calcd for $C_{34}H_{25}N_3O_4$: C, 75.66; H, 4.66; N, 7.78. Found: C, 75.60; H, 4.48; N, 7.63.

Compound 14. Method A.—To 5 ml of *p*-xylene was added 268 mg of *trans*-2-*p*-nitrophenyl-3-benzoylaziridine and 236 mg of *trans*-dibenzoylethene. This mixture was refluxed for 40 min and the solvent was then evaporated. The residue was slurried with a small quantity of ethanol and the crude **14** (322 mg, 65%) was filtered. Recrystallization from 95% ethanol gave **14** melting at 172–173°.

Anal. Calcd for $C_{31}H_{24}N_2O_5$: C, 73.79; H, 4.79; N, 5.55. Found: C, 73.65; H, 4.58; N, 5.71.

Compound 14. Method B.—A mixture of 310 mg of **12**, 10 ml of concentrated hydrochloric acid, and 10 ml of 95% ethanol was warmed for a few minutes on a hot plate. Not all of **12** dissolved. Prolonged heating is very detrimental to the isolation of **14**. The mixture was allowed to stand for 3 days during which time the color of the reaction mixture darkened considerably. The insoluble material was filtered. It presumably was the hydrochloride of **14**. Recrystallization of this material several times from 95% ethanol gave 114 mg of **14** that was identical in all respects with the **14** isolated in method A.

Registry No.—**3**, 15757-44-5; **4**, 15757-45-6; **7**, 15757-46-7; **8**, 15757-47-8; **9**, 15757-48-7; **10**, 15757-49-0; **11**, 15757-50-3; **12**, 15757-51-4; **13**, 15757-52-5; **14**, 15757-53-6; **2**, 15757-54-7.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work and the National Institutes of Health for Grant CA-10015.

(8) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).

(9) P. Karrer and C. Christoffel, *Helv. Chim. Acta*, **27**, 622 (1944).

The Thermal and Photolytic Decomposition of 2,3-Diazido-1,4-naphthoquinone and Certain Related Azidoquinones

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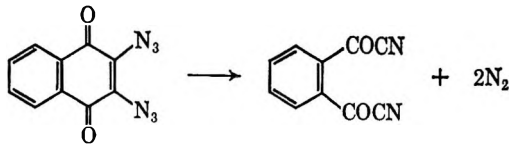
Phthaloyl cyanide was prepared by the decomposition of 2,3-diazido-1,4-naphthoquinone (1) by means of heat or light. The rates of thermal decomposition of 1 and of some related azidoquinones in boiling toluene were determined. The quantum yield for the photolytic decomposition of 1 was 1.04 ± 0.1. Phthaloyl cyanide was photolyzed in ether solution.

The decomposition of solutions of 2,3-diazido-1,4-naphthoquinone (1) by means of heat or light results in a reaction product which is assigned the structure 2.



1 2

The thermal decomposition of 1 was carried out in boiling toluene or xylene. The product (2) was easily hydrolyzed, and if precautions were not taken to exclude moisture during the thermolysis or photolysis, the main product was phthalic anhydride (3) and the secondary product was 2.

Blackstone[1] prepared a compound which he thought was phthaloyl cyanide (2) from phthaloyl chloride and mercuric cyanide. The product was reported to melt at about 300°, its solubility in organic solvents was poor, and it was stable to hot concentrated hydrochloric acid. These data suggest that the material prepared by Blackstone was a polymer rather than 2, and recently it was suggested by Hertler[2] that the material which Blackstone prepared from terephthaloyl chloride and mercuric cyanide was a polymer rather than the *para* isomer of 2. The facts that the nitrile we obtained has properties similar to those of the *para* isomer described by Hertler,[2] that it is readily converted into phthalic anhydride by recrystallization from water, and that physical data, such as the infrared spectrum (carbonyl absorption at 5.83 and 5.91 and cyano absorption at 4.46 μ), nmr spectrum (singlet at δ 8.04), and elemental analysis, are in accord with structure 2 leave little doubt that we have an authentic sample of phthaloyl cyanide (2).

The thermal decomposition of 1 and of the related 2-azido-1,4-naphthoquinone (4) and 2-azido-3-chloro-1,4-naphthoquinone (5) in dry solvents occurs with conveniently measurable rates in the range of 90–120°. This temperature range is much lower than that reported for α-azido ketones,[3] 180–220°, and also considerably lower than the decomposition range for *o*-diazidobenzene,[4] 160–170°. The low thermal stability of the azidoquinone is probably due to the fact that these compounds are vinylogs of acyl azides. Acyl azides have been found[5] to decompose with comparable rates at slightly lower temperatures than those characteristic of the quinone azides.

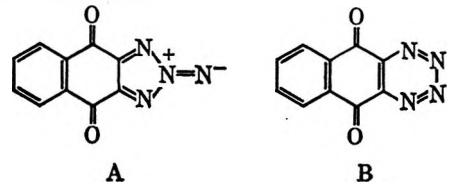
The rates of thermal decomposition of the azidonaphthoquinones, which were measured by means of a nitrometer connected to a rocking thermostated vessel,[6] were accurately first order in terms of nitrogen evolution over the entire range. Rate data for the thermal decomposition in *m*-xylene of 1, 4, and 5 are shown in Table I. Qualitative thermolysis rates of 2,3-diazido-5,6-dimethylbenzoquinone (6) and 2-azido-3-methoxy-1,4-naphthoquinone (7) in boiling toluene were found to be similar to those for the related compounds shown in Table I. The qualitative rates were determined by the disappearance of the characteristic red color of 6 and 7. The products which were obtained by the thermolysis of 4, 5, 6, and 7 were not characterized.

Table I

Rates of Thermolysis

Species	Concn. mol/l. × 10³	Temp, °C	Rate (±5%), sec⁻¹ × 10³	E_a, kcal/mol	Log *A*
1	1.2	85.0	0.140	27	12.63
		94.5	0.476		
		100.0	0.772		
		106.5	1.24		
		110.0	2.24		
		120.0	4.49		
4	1.2	90.0	0.221	26	12.11
		94.5	0.399		
		100.0	0.783		
		105.0	1.15		
		110.0	2.58		
		120.0	3.78		
5	1.2	110.0	0.66		

During the thermolysis or photolysis of 1 in inert dry solvents, there was no spectrophotometric evidence of the presence, in significant amounts, of an intermediate, such as A or B, which could result from



A B

the decomposition of a single azide group. Structures similar to A and B have been postulated as intermediates during the decomposition of *o*-diazidobenzene.[4] The quantum yield for the decomposition of 1 was 1.04 ± 0.1, as determined in dry benzene with

(1) G. Blackstone, *J. Amer. Chem. Soc.*, **34**, 1080 (1912).
(2) W. R. Hertler, H. D. Hartzler, D. S. Acker, and R. E. Benson, *ibid.*, **84**, 3387 (1962).
(3) J. Boyer and D. Straw, *ibid.*, **74**, 4506 (1952); **75**, 1642, 2633 (1953).
(4) J. Hall, *ibid.*, **87**, 1147 (1965).
(5) Y. Yukawa and Y. Tsuno, *ibid.*, **79**, 5530 (1957).
(6) T. Fugley, J. Sutter, and R. Oglukion, *ibid.*, **78**, 5567 (1956).

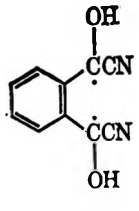
TABLE II
ANALYTICAL AND SPECTRAL DATA

Compd	Empirical formula	Mp, °C	Solvent of crystallization	Calcd over found, % C	H	N	% yield	Electronic spectra, λ (ε × 10⁻³)	Solvent
2	$C_{10}H_4N_2O_2$	103	Ligroin (bp 100–115°)	65.3	2.2	15.2	52	228 (6.3)	
				65.5	2.1	15.0		277 (5.2)	Acetonitrile
4	$C_{10}H_5N_3O_2$	118 dec	Ethanol	60.3	2.5	21.1	85	257 (18.4)	
				60.4	2.8	20.9		296 (14.1)	Methanol
								344 (3.7)	
5	$C_{10}H_4ClN_3O_2$	115	Ethanol	51.4	1.7	18.0	60	404 (2.5)	Chloroform
				51.2	2.0	17.9			
6	$C_8H_6N_6O_2$	75	Ligroin (bp 70–79°)	44.0	2.8	38.5	60	430 (2.4)	Methanol
				43.9	3.1	38.6			
7	$C_{11}H_7N_3O_3$	94	Methanol	57.7	3.0	18.3	71	342 (2.5)	
				57.5	2.9	18.5		430 (2.2)	Acetonitrile

light of 437-mμ wavelength. The measurements were made by following the disappearance of the 455-mμ band of **1** under conditions where the light[7] was totally absorbed by **1**. The amount of light absorbed was determined by ferrioxalate actinometry[8] in parallel experiments.

Several attempts were made to photolyze **1** in aqueous alcohol or dioxane, but the rate of the reaction was much slower than when dry benzene was used as the solvent. The decrease in rate was due to the formation of a red, unidentified product which functions as an internal filter. This species was also photosensitive but disappeared much more slowly than **1**.

The illumination of **2** in ethyl ether resulted in a rapid disappearance of the 270-mμ absorption peak of **2**. The products of this photoreaction have not been identified, but they appear to be largely polymeric. It seems likely on the basis of the recent findings of Raaen,[9] that a photoreduction of **2** proceeds through the radical **8**.



8

Experimental Section

The analytical and spectral data for the compounds are collected in Table II.

2,3-Diazido-1,4-naphthoquinone (1) was prepared by the method of Fries and Ochwatt[10] and showed absorption (in acetonitrile) at 455 mμ (ε 4200).

Phthaloyl Cyanide (2).—A mixture of 100 ml of toluene, 3 g of Linde Type 3A Molecular Sieves, and 5 g of diazidonaphthoquinone (1) was refluxed until no more gas was evolved (about 10 min). The reaction mixture was cooled to room temperature and filtered, the filtrate was evaporated to dryness *in vacuo*, and the residue was recrystallized.

The infrared spectrum of **2** showed an absorption at 4.46 μ for the cyano group and strong carbonyl absorption at 5.83 and 5.91 μ. A once crystallized sample contained a small amount of phthalic anhydride as shown by a weak absorption at 5.42 and 5.63 μ. The latter peaks were eliminated when the sample was recrystallized three times from anhydrous petroleum ether (bp 100–115°) in a drybox.

The nmr spectrum of **2** at 60 MHz in deuteriochloroform with tetramethylsilane as an internal standard showed a single peak at δ 8.04 with a width of 3 Hz at half-height. The single peak is due to accidental equivalence of the two pairs of protons.

A solution of 1 g of **2**, 50 ml of toluene, and 0.1 ml of water was refluxed for 15 min and then evaporated to dryness. The residue was a mixture of **2** and phthalic anhydride. When more water was used and the heating period extended to 1 hr, the only material that was isolated was phthalic acid.

2-Azido-1,4-naphthoquinone (4).—A solution of 1.2 g of sodium azide in 5 ml of water was added to 2.5 g of 2-chloro-1,4-naphthoquinone and the mixture was stirred at 90–100° for 5 min. The mixture was cooled and the precipitate was collected, washed with water, and crystallized.

Alternatively, 2,3-dichloro-2,3-dihydronaphthoquinone[11] can be substituted for 2-chloro-1,4-naphthoquinone in the procedure to give **4**, in 46% yield.

2-Azido-3-chloro-1,4-naphthoquinone (5).—Sodium azide (2.86 g) dissolved in a minimum of water was added all at once, with vigorous stirring, to 10 g of 2,3-dichloro-1,4-naphthoquinone which was dissolved completely in dimethylformamide. After the product had been stirred for 15 min, it was precipitated with water to give 6.2 g of **5**.

2,3-Dichloro-5,6-dimethyl-1,4-benzoquinone.—A solution of 25 g of 2,3-dimethyl-1,4-benzoquinone and 9.5 g of iodine in 250 ml of glacial acetic acid was heated at 90–100° while chlorine gas was passed through for 1 hr. The purple semiquinone precipitated. A solution of 4.5 g of potassium bromate in water was added to the reaction mixture, with vigorous stirring, and the mixture, which became yellow immediately, was cooled and diluted with 500 ml of water. The yellow precipitate was collected and crystallized from ethanol to give 87% yield of product, mp 168°.

Anal. Calcd for $C_8H_6Cl_2O_2$: C, 46.9; H, 29.0. Found: C, 46.9; H, 30.0.

2,3-Diazido-5,6-dimethyl-1,4-benzoquinone (6).—A solution of 5 g of sodium azide in the minimum amount of water was added to a solution of 5 g of 2,3-dichloro-5,6-dimethylbenzoquinone in 50 ml of ethanol, and the mixture was diluted with water. The solid was collected and recrystallized.

2-Chloro-3-methoxy-1,4-naphthoquinone.—A solution of 11.3 g of 2,3-dichloro-1,4-naphthoquinone and 9.0 g of sodium acetate in 100 ml of methanol was heated for 4 hr and cooled; the solid which separated was collected by filtration, washed with water, and crystallized from acetic acid to give 7.2 g (65%) of product, mp 153°.

Anal. Calcd for $C_{11}H_7ClO_3$: C, 59.4; H, 3.1. Found: C, 59.6; H, 3.0.

2-Azido-3-methoxy-1,4-naphthoquinone (7).—The following procedure is a modification of the method of Mosby and Silva.[12] A solution of 4.4 g of 2-chloro-3-methoxy-1,4-naphthoquinone in 100 ml of methanol was heated with 2.0 g of sodium azide in 20 ml of water. After the reaction mixture had been treated it was filtered hot, and the filtrate was cooled, to give 3.2 g of **7**.

(7) The light source was the output of a Bausch and Lomb "high-intensity" monochromator with a 200-W mercury source.

(8) C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc.*, **235**, 518 (1956).

(9) V. F. Raaen, *J. Org. Chem.*, **31**, 3310 (1966).

(10) K. Fries and P. Ochwatt, *Ber.*, **56**, 1299 (1923).

(11) T. Zincke and M. Schmidt, *ibid.*, **27**, 2753 (1894).

(12) W. L. Mosby and M. L. Silva, *J. Chem. Soc.*, 3990 (1964).

Photolysis of 1.—A solution of 0.026 g of **1** in 100 ml of dry ethyl ether was exposed to blue fluorescent light through a Corning 3-72 filter which removes all light of wavelength below 430 mμ. Under this condition of illumination, the sole product was **2**.

Photolysis of 2.—An ether solution of **2**, which was continuously flushed with nitrogen was exposed to the light of a high-pressure, water-cooled mercury arc which was filtered through Pyrex glass. An exposure time of 5 min reduced the 277-mμ absorption peak of **2** to less than one-quarter of its original value.

Registry No.—**1**, 6427-95-8; **2**, 15707-28-5; **4**, 15707-29-6; **5**, 15707-35-4; **6**, 15707-30-9; **7**, 15707-33-2; 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone, 15707-31-0; 2-chloro-3-methoxy-1,4-naphthoquinone, 15007-32-1.

The Preparation of Certain Pyrylium Salts by Using Chalcone and Boron Trifluoride Etherate

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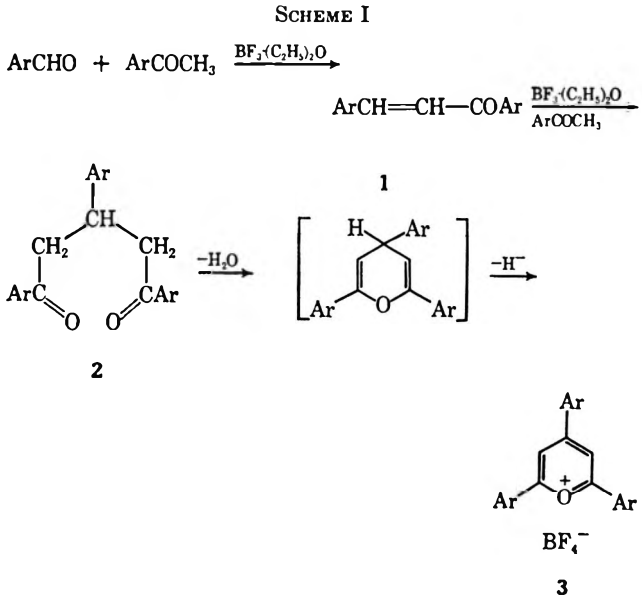
Received September 26, 1967

Some pyrylium salts were prepared from 1,5-diketones by using chalcone as a hydride-abstracting agent and boron trifluoride etherate as a cyclization medium. Under these conditions, 2-carbethoxy-1,3,5-triphenylpentane-1,5-dione (**9**) gave the 3-benzyl-2,4,6-triphenylpyrylium salt (**10**) rather than the expected 3-carbethoxy-2,4,6-triphenylpyrylium salt (**11**). An explanation for this result is proposed. Ethyl acetoacetate, chalcone, and boron trifluoride etherate gave 3-carbethoxy-2-methyl-4,6-diphenylpyrylium salt (**14**). Some 3-substituted 2,4,6-triphenylpyrylium salts were prepared from chalcone, α-substituted acetophenone derivatives, and boron trifluoride etherate.

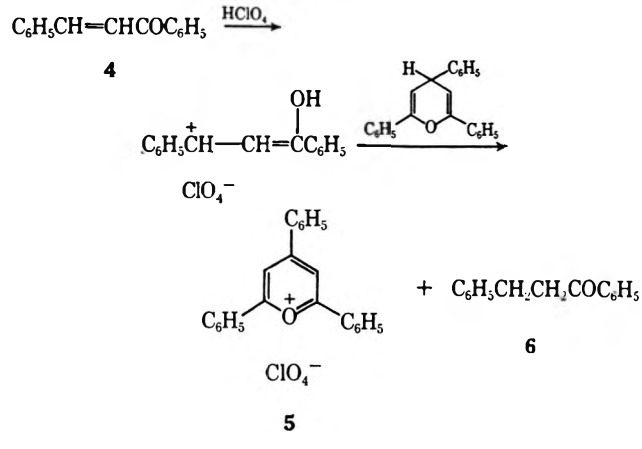
The most common preparative method for synthesizing 2,4,6-triarylpyrylium salts involves the condensation of 1 equiv of an aryl aldehyde and 2 equiv of an arylalkyl ketone in the presence of Lewis acids, strong mineral acids, or dehydrating agents such as polyphosphoric acid. We have found boron trifluoride etherate to be the most generally useful condensing agent for this synthesis. The reaction path is illustrated in Scheme I below. The 1,5-

SCHEME I



diketone **2** is an intermediate during the formation of **3**, since 1,5-diketones of this type readily yield **3** when treated with boron trifluoride etherate or perchloric acid. Inspection of the sequence shows that a dehydrogenation step is required to form **3**, and, since oxidizing agents are not usually present in the reaction medium, the nature of this dehydrogenation has long been a matter of conjecture. Recently it was reported[1] that the conjugate acid of the intermediate chalcone serves as a hydride abstractor in the manner shown in Scheme II. Balaban

SCHEME II



proposed this reaction scheme on the basis of the improved yields of **5** that were obtained by the addition of chalcone (**4**) to 1,3,5-triphenylpentane-1,5-dione (**7**) in perchloric acid, and isolation of **6** from the reaction mixture.

We thought it of interest to investigate boron trifluoride etherate as a condensing agent and chalcone as a hydride abstractor in a synthetic procedure for pyrylium salts. The results obtained when **7** was allowed to react under a variety of conditions are summarized in Table I.

Procedure C (see Table I) was extended to include other 1,5-diketones, and in many cases excellent yields of pyrylium fluoroborates were obtained. For example, **8a** was obtained in 88% yield, **8b** in 93% yield and **8c** in 72% yield.

In some cases, however, this procedure led to un-

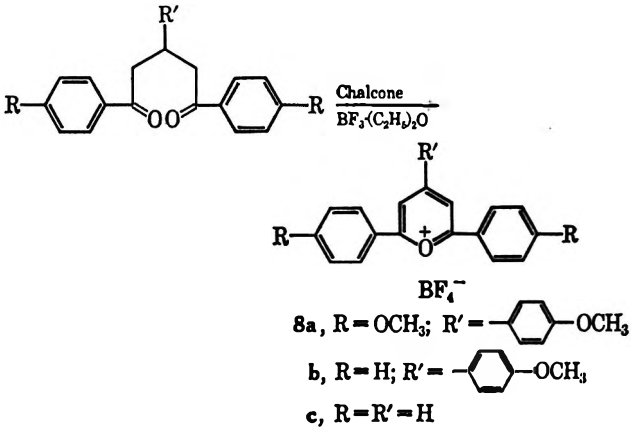
(1) A. T. Balaban, *Comp. Rend.*, **256**, 4239 (1963).

TABLE I

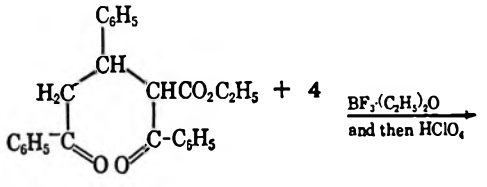
THE EFFECT OF VARYING REACTION CONDITIONS ON THE YIELD OF 5

Procedure	Conditions: Equivalents of 7	Condensing agent	Equivalents of 4	% yield of 5
A	1	$2HClO_4$	1	75
B	1	$2HClO_4$	0	54
C	1	$8BF_3 \cdot (C_2H_5)_2O$	1	96
D	1	$8BF_3 \cdot (C_2H_5)_2O$	0.5	81
E	1	$8BF_3 \cdot (C_2H_5)_2O$	0	59
F[a]	1	$8BF_3 \cdot (C_2H_5)_2O$	0	63
G[b]	1	$(C_6H_5)_3C^+ClO_4^-$	0	86

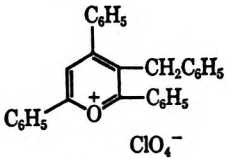
[a] One-half equivalent of chloranil was present in the reaction mixture. [b] Siemiatycki and Fugnetto [*Bull. Soc. Chim. Fr.*, 538 (1961)] have shown that trityl perchlorate is a very useful condensing agent and hydride abstractor for preparing pyrylium salts from 1,5-diketones.



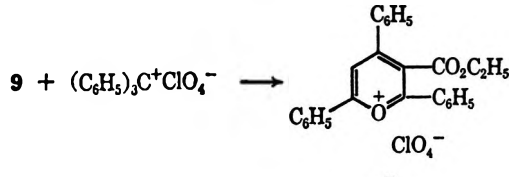
expected results. For example, the substituted 1,5-diketone **9** in the presence of **4** and boron trifluoride etherate gave 3-benzyl-2,4,6-triphenylpyrylium fluoroborate (isolated as the perchlorate salt **10**) rather than the expected 3-carbethoxy derivative **11**, and **9** with trityl perchlorate gave **11**. A rationale for the formation of **10** is that **9** adds to chalcone (**4**) under the influence of boron trifluoride, to give **12** which, in turn, eliminates ethyl benzoylacetate by a reverse Michael reaction to form **13** which is cyclized to **10**. This



9

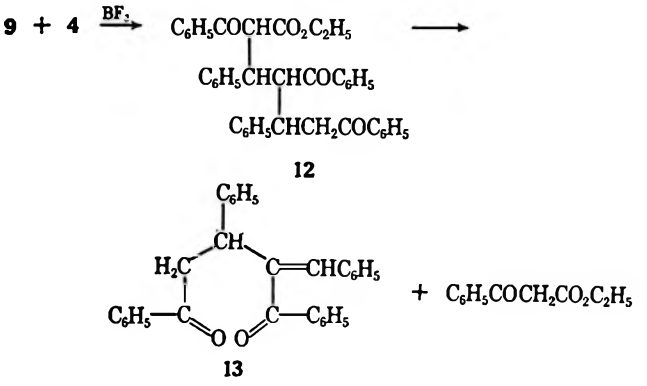


10

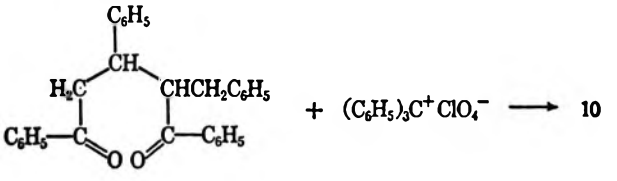


11

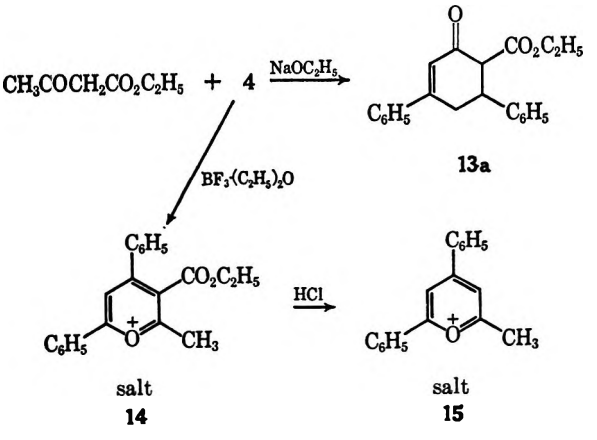
SCHEME III



sequence of reactions is illustrated in Scheme III. The fact that the adduct of chalcone and dimethyl malonate reacts with a further equivalent of chalcone to give **10** is substantiating evidence for the mechanism just proposed for the formation of **10** from **4** and **9**, since it shows that the exact nature of the group that is eliminated in the reverse Michael step is not important. The structural proof for the pyrylium salt **10** follows from its synthesis from 2-benzyl-1,3,5-triphenylpentane-1,5-dione and trityl perchlorate.

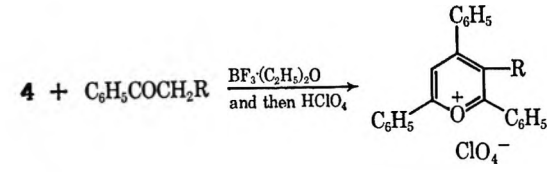


Attempts to treat chalcone with ethyl acetoacetate gave interesting results. It had been shown[2] that basic reaction conditions gave the cyclohexenone **13a**, but we found that the acidic catalyst, boron trifluoride etherate, gave the pyrylium salt **14**. Acid hydrolysis of **14** yielded 2-methyl-4,6-diphenylpyrylium salt (**15**), indicating that the 3-carbethoxy group of the pyrylium salt is readily hydrolyzed and decarboxylated.



The preparation of 3-substituted 2,4,6-triphenylpyrylium salts by the reaction of chalcone (**4**) with acetophenone derivatives in the presence of boron trifluoride etherate is quite general, and **16a**, **b**, **c**, **d**, and **e** were synthesized in this manner.

(2) E. Knoevenagel and H. Schmidt, *Ann.*, **281**, 58 (1894).



16a, R = CH_3
b, R = C_2H_5
c, R = C_4H_9
d, R = C_6H_5
e, R = $OCOCH_3$

Experimental Section

2,4,6-Triphenylpyrylium Salts (Table I). Procedure A.—A mixture of 6.6 g (0.02 mol) of **7**,[3] 4.2 g of chalcone (**4**), and 6 g of 70% perchloric acid was heated on the steam bath for 1 hr. The mixture was diluted with 20 ml of alcohol and chilled, and the solid was collected and recrystallized from acetic acid to give 6.2 g (75% yield) of 2,4,6-triphenylpyrylium perchlorate, mp 293–295°.

Procedure B.—A mixture of 6.6 g (0.02 mol) of **7** and 6 g of 70% perchloric acid was heated on the steam bath for 1 hr, and the product was isolated and purified as described for procedure A.

Procedure C.—A mixture of 0.02 mol of **4** and **7** in 25 ml of boron trifluoride etherate was heated for 2 hr on the steam bath, cooled, and diluted with ether. The solid was collected and recrystallized from ethanol to give 7.6 g (96% yield) of the fluoroborate salt, mp 252–253°.

Procedure D.—The reaction was carried out as described for procedure C, except that 0.01 mol of **4** was used.

Procedure E was the same as procedure C except that no chalcone was used.

Procedure F was the same as procedure E but included 0.01 mol of chloranil in the reaction mixture.

Procedure G.[4]—A mixture of 0.02 mol of **7**, 0.02 mol of trityl perchlorate, and 50 ml of acetic acid was refluxed for 30 min, and, after the mixture had cooled, the product was collected.

2,4,6-Tri(4-methoxyphenyl)pyrylium Fluoroborate (8a).—A mixture of 8.4 g (0.02 mol) of 1,3,5-tri(4-methoxyphenyl)-1,5-pentanedione,[5] 4.2 g (0.02 mol) of chalcone, and 24 ml of boron trifluoride etherate was heated on the steam bath for 2 hr, cooled, and diluted with ether; the solid was collected and recrystallized from acetonitrile to yield 8.6 g (88% yield) of **8a**, mp 346–347° (lit.[6] mp 345–347°).

4-(4-Methoxyphenyl)2,6-diphenylpyrylium Fluoroborate (8b).—The procedure described for the preparation of **8a** was used, except that anisylidenebisacetophenone[7] was employed as the diketone. The yield of **8b** was 7.9 g (93%), mp 238–240° (from a mixture of ethanol and acetonitrile).

Anal. Calcd for $C_{24}H_{19}BF_4O_2$: C, 67.6; H, 4.5. Found: C, 67.9; H, 4.7.

A sample of **8a** was converted into the perchlorate salt which melted at 260° (lit.[8] mp 257–259°).

2,6-Diphenylpyrylium Fluoroborate (8c).—The procedure described for the preparation of **8a** was used with 1,3-dibenzoylpropane[9] as the diketone to yield 4.6 g (72%) of **8c**, mp 206–207°. The product was dissolved in hot acetic acid, 2 ml of 70% perchloric acid was added to the solution, and, after the solution had cooled, the 2,6-diphenylpyrylium perchlorate was collected, mp 224–225° (lit.[4] mp 226°).

3-Benzyl-2,4,6-triphenylpyrylium Perchlorate (10).—A mixture of 7.5 g (0.02 mol) of the diketone **9**,[10] 4.2 g of **4**, and 25 ml of boron trifluoride etherate was heated on the steam bath for 4 hr and then poured into a mixture of 75 ml of ethanol and 5 ml of 70% perchloric acid. The mixture was chilled and the product was collected and recrystallized from acetic acid to yield 4.7 g of **10**, mp 241°. The ultraviolet spectrum in acetonitrile solution showed peaks at λ 273 mμ (ε 15,600) and 383 mμ (ε 21,800).

Anal. Calcd for $C_{30}H_{23}ClO_5$: C, 72.2; H, 4.6; Cl, 7.1. Found: C, 72.2; H, 4.8; Cl, 7.2.

Compound **10** was also prepared by heating 4.8 g (0.025 mol) of ethyl benzoylacetate, 10.4 g (0.50 mol) of **4**, and 30 ml of boron trifluoride etherate on the steam bath for 4 hr. The product was isolated as just described and was obtained in 6.2-g yield.

Compound **10** was also prepared from 17 g of the adduct of **4** and dimethyl malonate, 4,4-dicarbomethoxy-3-phenylpropiophenone,[11] **10** g of **4**, and 30 ml of boron trifluoride etherate. The reaction was carried out as already described, to yield 12 g of **10**.

A mixture of 0.015 mol of 2-benzyl-1,3,5-triphenylpentane-1,5-dione and trityl perchlorate in 35 ml of acetic acid was refluxed for 15 min and cooled; the solid was collected and recrystallized from acetic acid to yield 4 g of **10**.

3-Carbethoxy-2,4,6-triphenylpyrylium Perchlorate (11).—A mixture of 12 g (0.03 mol) of **9**, 10.8 g (0.032 mol) of trityl perchlorate, and 75 ml of acetic acid was refluxed for 5 min, cooled, and diluted with a large volume of ether; the solid that separated was collected. The solid was recrystallized from acetic acid to yield 6.2 g of **11**, mp 235°. The ultraviolet spectrum in acetonitrile showed peaks at λ 235 mμ (ε 13,900), 275 (16,800), 351 (27,200) and 398 (24,000).

Anal. Calcd for $C_{26}H_{21}ClO_7$: C, 65.0; H, 4.4; Cl, 7.4. Found: C, 65.3; H, 4.4; Cl, 7.7.

3-Carbethoxy-2-methyl-4,6-diphenylpyrylium Perchlorate (14).—A solution of 10.4 g (0.05 mol) of **4**, 6.5 g (0.05 mol) of ethyl acetoacetate, and 40 ml of boron trifluoride etherate was heated on the steam bath for 5 hr. The reaction mixture was poured into 30 ml of ethanol and 9 ml of 70% perchloric acid and chilled. The solid was collected and recrystallized from acetic acid to yield 4.6 g of **14**, mp 178°. The ultraviolet spectrum in acetonitrile showed peaks at λ 257 mμ (ε 14,600) and 376 mμ (ε 25,500).

Anal. Calcd for $C_{21}H_{19}ClO_7$: C, 60.2; H, 4.6; Cl, 8.5. Found: C, 60.5; H, 4.7; Cl, 8.4.

2-Methyl-4,6-diphenylpyrylium Perchlorate (15).—A solution of 2 g of **14** in 20 ml of acetic acid and 12 ml of concentrated hydrochloric acid was refluxed for 2 hr. The mixture was cooled and the solid was collected and recrystallized from acetic acid to give 0.8 g of **15**, mp 205°. The product showed an infrared absorption curve which was identical with that of an authentic sample of **15**.[12]

The general procedure employed for the preparation of **16a, b, c, d,** and **e** was the following. A solution of 10.4 g (0.1 mol) of **4**, 0.05 mol of the acetophenone derivative, and 35 ml of boron trifluoride etherate was heated on the steam bath for 2 hr, cooled, and poured into 35 ml of methanol and 10 ml of 70% perchloric acid. The mixture was chilled and the solid was collected and recrystallized from the appropriate solvent.

3-Methyl-2,4,6-triphenylpyrylium Perchlorate (16a). From Propiophenone.—The product was obtained in 13-g yield (62%), mp 236°. The ultraviolet spectrum in acetonitrile showed peaks at λ 229 mμ (ε 14,700), 272 (17,300), 340 (17,900), and 386 (23,200).

Anal. Calcd for $C_{24}H_{19}ClO_5$: C, 68.3; H, 4.5. Found: C, 68.2; H, 4.7.

3-Ethyl-2,4,6-triphenylpyrylium Perchlorate (16b). From Butyrophenone.—This compound was obtained in 13-g (60%) yield, mp 180° (from acetonitrile). The ultraviolet spectrum in acetonitrile showed peaks at λ 248 mμ (ε 10,300), 271 (13,200), ~350 (16,000), and 380 (21,000).

Anal. Calcd for $C_{25}H_{21}ClO_5$: C, 67.2; H, 5.0. Found: C, 67.2; H, 4.8.

3-*n*-Butyl-2,4,6-triphenylpyrylium Perchlorate (16c). From Hexanophenone.—The product was obtained in 9-g yield (39%), mp 201° (from a mixture of acetonitrile and ether). The ultraviolet spectrum in acetonitrile showed peaks at λ 232 mμ (ε 16,500), 275 (9500), 332 (14,300), and 382 (11,200).

Anal. Calcd for $C_{27}H_{25}ClO_5$: C, 70.0; H, 5.4. Found: C, 69.9; H, 5.1.

2,3,4,6-Tetraphenylpyrylium Perchlorate (16d). From Desoxybenzoin.—The yield of product was 11.7 g, mp 261° (from acetic

(3) St. V. Kostanecki and G. Rossbach, *Ber.*, **29**, 1488 (1896).
(4) See Table I, footnote *b*.
(5) W. Schneider and G. Gramms, *ibid.*, **69**, 2543 (1936).
(6) W. C. Dovey and R. Robinson, *J. Chem. Soc.*, 1389 (1935).
(7) W. Dilthey and R. Taucher, *Ber.*, **53**, 255 (1920).
(8) W. Dilthey, G. F. Frode, and H. Koenen, *J. Prakt. Chem.*, **114**, 153 (1926).
(9) F. R. Japp and A. C. Michie, *J. Chem. Soc.*, **79**, 1017 (1901).
(10) R. Connor and D. Andrews, *J. Amer. Chem. Soc.*, **56**. 2713 (1934).
(11) E. P. Kohler, *Amer. Chem. J.*, **46**, 482 (1911).
(12) W. Schneider and F. Seebach, *Ber.*, **54**, 2289 (1921).

acid) (lit.[13] mp 261°). The ultraviolet spectrum in acetonitrile showed peaks at λ 276 mμ (ε 16,400) and 386 mμ (23,100).

3-Acetoxy-2,4,6-triphenylpyrylium perchlorate (16e) was obtained in 7.6-g yield, mp 230° (lit.[14] mp 230°).

(13) W. D. Dilthey and T. Bottier, *Ber.*, **52**, 2046 (1919).
(14) G. Suld and C. C. Price, *J. Amer. Chem. Soc.*, **83**, 1770 (1961).

Registry No.—Chalcone, 94-41-7; boron trifluoride etherate, 109-63-7; **5**, 1484-88-4; **8a**, 75696-46-5; **8b**, 15696-47-6; **8c**, 15696-48-7; **10**, 15707-55-8; **11**, 15707-56-9; **14**, 15707-57-0; **15**, 7654-52-6; **16a**, 3558-70-1; **16b**, 15707-60-5; **16c**, 15707-61-6; **16d**, 3558-71-2; **16e**, 15893-40-0.

Hydrolytic Dimerization of Ethyl 5-Amino-2-furoate[1]

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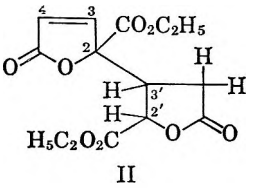
Received August 30, 1967

The acid hydrolysis of ethyl 5-amino-2-furoate (I) is shown to produce two stereoisomers of diethyl [(2,2′,3′,-4′,5,5′-hexahydro-5,5′-dioxo)-2,3′-bifuran]-2,2′-dicarboxylate (II and IIa). A possible mechanism for this hydrolytic dimerization is proposed.

A number of nitrofurans have acquired considerable importance as chemotherapeutic agents.[3] In connection with biochemical studies concerning the metabolism of nitrofurans,[4,5] alkaline and acid hydrolyses of ethyl 5-amino-2-furoate (I) were investigated. The alkaline hydrolysis of I to give α-ketoglutaramic acid has been reported.[6] We now wish to report on a strikingly different reaction observed when I is treated with acid.

In aqueous–alcoholic hydrochloric acid at room temperature, I was found to undergo a rapid reaction resulting in the formation of the crystalline dilactone (II) as the major product. A higher melting isomer (IIa) was obtained simultaneously in low yield. The evidence for the structural assignments is presented.



II

The infrared spectra of II and IIa revealed intense lactone and ester absorptions at 5.55 and 5.73 μ, with a double-bond stretching band of low intensity at 6.25 μ. The 6.25-μ band was absent in the spectrum of the crystalline dihydro compound (III) obtained by catalytic hydrogenation of II in acetic acid over Adams catalyst. Treatment of III with aqueous–alcoholic sodium hydroxide at room temperature gave a saponification equivalent consistent with complete hydrolysis of the lactone and ester groups of III. The high value of the saponification equivalent of II may be due to incomplete hydrolysis of the unsaturated lactonic ester portion of II. The nmr spectrum of II is shown in Figure 1a. The pair of doublets at τ 2.51, and 3.62 may be attributed to the protons on the α,β-unsaturated carbonyl system of II. The doublet at τ 5.12 may be assigned to the proton on the oxygen-bearing carbon at 2′. The simple splitting pattern of the 2′ proton, as well as mechanistic considerations, suggest monosubstitution at C-3′. The 3′ and 4′ protons appear as complex multiplets centered at τ 6.50 and 7.50, respectively. The characteristic ethyl quartet and triplet are shown at 5.71 and 8.67. The nmr spectra of II and IIa are very similar and, since structure II contains three asymmetric centers, it is reasonable to assume that these two compounds are diastereoisomers. Both show a 4-cps coupling constant for the doublet at τ 5.12 (5.42 for IIa) indicating that both have a *trans* relationship between the 2′ and 3′ protons.[7] It would appear, therefore, that the two dilactones differ by their configuration at C-2.

Ultraviolet absorption studies of the reaction of I in aqueous–alcoholic hydrochloric acid show rapid disappearance of I and suggest the formation of an intermediate, which is converted into the final products at a slower rate. Hydrolysis of the amine group during the hydrolytic dimerization of I was determined by liberation of ammonia. The biphasic nature of this hydrolysis suggests the formation of the partially hydrolyzed intermediate V or VI, either of which could be formed *via* the reaction mechanism shown in Scheme I.

Dimerization of I may be considered to proceed *via* a nucleophilic addition of C-2 in one aminofuran molecule to the electrophilic site at C-3 of another. Hydrolysis of the 5′-amino or the 5-imino group of the initially formed intermediate (IV) would lead to V or VI. When the reaction is stopped at a time when most of I has disappeared and only about half the total ammonia has been liberated (2 min), a chloroform extract of the reaction mixture shows nmr signals at τ 3.12 and 3.59 (Figure 1b) which may be assigned to the protons on the α,β-unsaturated imino system of V. When the extracted material was hydrolyzed in the presence of deuterium oxide, II was formed without deuterium substitution. This observation supports the hypothesis that the hydrolytic dimerization of I proceeds *via* V rather than VI, since hydrolysis of the 5′-amino group of VI would result in deuterium substitution at C-4′.

Hydrolytic dimerization of I in a deuterated system results in a mixture of deuterated forms of II (Figure

(1) A preliminary report of this work has been presented at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966.
(2) (a) The Norwich Pharmacal Co.; (b) Cornell University.
(3) H. E. Paul and M. F Paul in "Experimental Chemotherapy," Vol. II, R. J. Schnitzer and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1964, p 307.
(4) H. E. Paul, V. R. Ells, F. Kopko, and R. C. Bender, *J. Med. Pharm. Chem.*, **2**, 563 (1960).
(5) J. Olivard, S. Valenti, and J. A. Buzard, *ibid.*, **5**, 524 (1962).
(6) G. M. Klein, J. P. Heotis, and J. A. Buzard, *J. Biol. Chem.*, **238**, 1625 (1963).
(7) H. Conroy, *Advan. Org. Chem.*, **2**, 311 (1960).

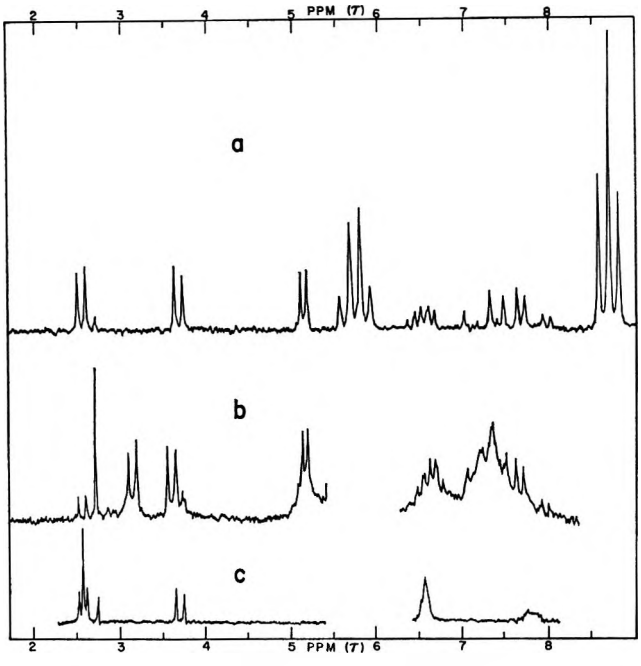
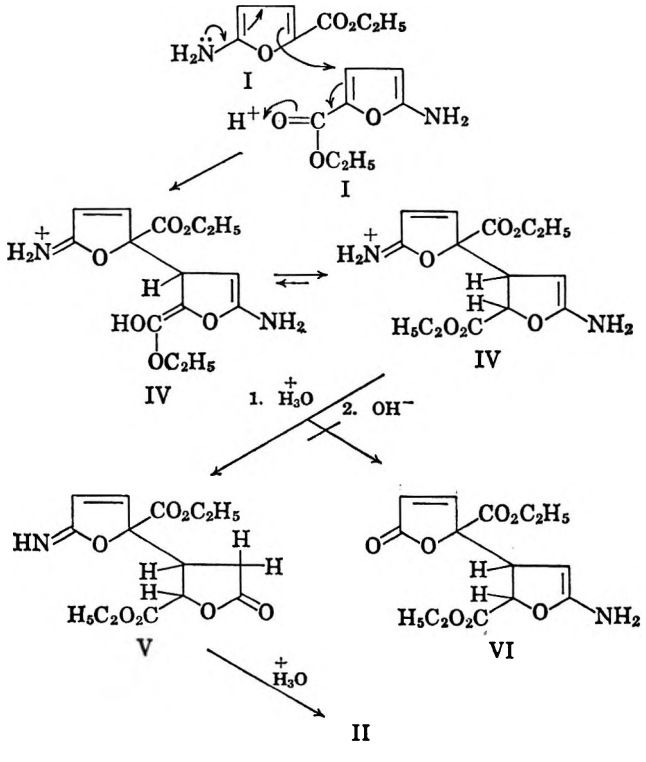


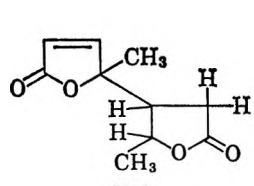
Figure 1.—Nmr spectra in $CDCl_3$ of (a) II, (b) partially hydrolyzed reaction mixture, and (c) II prepared in 0.5 *M* DCl in deuterium oxide–dioxane.

SCHEME I

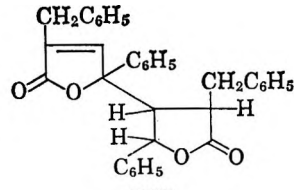


1c). The absence of the τ 5.1 doublet indicates complete deuterium exchange at the 2′ position of II. This result is consistent with a reaction mechanism involving the enolic intermediate IV. The appearance of both a singlet at τ 2.51 and doublets at 2.51 and 3.65 indicates partial deuterium exchange at C-4, which probably occurred in the initial amino ester. On the basis of the relative areas of the peaks at τ 2.51 and 3.65, there is 67% deuterium exchange at C-4. The formation of II with partial deuteration at C-4 is consistent with our proposed reaction mechanism and indicates that, under the reaction conditions investigated, the rate of dimerization of I is competitive with the rate of deuterium exchange α to the amino group.

The 2,3′-bifuran, VII, has been obtained in 11% yield by mixing α-angelica lactone and potassium carbonate in a ball mill for 12 hr.[8] We prepared VII in 9% yield after stirring equal amounts of α- and β-angelica lactones with potassium carbonate for 1 hr. The nmr spectrum of VII shows a symmetrical pair of olefinic proton doublets at τ 2.51 and 3.83, a singlet at 8.47 (C-2 methyl), a doublet at 8.58 (C-2′ methyl), and multiplets at 5.50 and 7.40. The lithium aluminum hydride reduction of α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide has been reported to give VIII *via* a Michael-type condensation.[9]



VII



VIII

Experimental Section

Melting points were determined on a micro hot stage (Fisher-Johns) apparatus and are corrected. Ultraviolet spectra were taken using a Beckman DB spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. The nmr spectra were determined using a Varian A-60 spectrometer.

Diethyl [(2,2′,3′,4′,5,5′-Hexahydro-5,5′-dioxo)-2,3′-bifuran]-2,2′-dicarboxylate. Low-Melting Isomer (II).—A solution of 50 g of ethyl 5-amino-2-furoate in 500 ml of alcohol was added to 750 ml of 0.8 *M* hydrochloric acid. After 20 min, the solution was cooled for 2 hr and the product was collected. The crude product, mp 80–82°, was recrystallized from 600 ml of 95% ethanol resulting in 20 g (40%) of II, mp 95–96°. An analytical sample, mp 95–96°, was prepared by recrystallization from alcohol: $\lambda_{max}^{2\%\ EtOH}$ 200 mμ (ϵ 9600); infrared absorption (Nujol mull) at 5.55, 5.73, 6.25, 7.70, 7.93, 8.13, 8.65, 9.10, 9.30, 9.50, 10.35, 11.00, 12.05 μ; nmr spectrum ($CDCl_3$), doublets at τ 2.51, 3.62, 5.12, a triplet at 8.67, a quartet at 5.71, and complex multiplets at 6.5 and 7.5 with peak area ratios of 1:1:1:6:4:1:2.

Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.85; H, 5.16; mol wt, 312. Found: C, 53.58; H, 4.96; mol wt (osmometer), 323; sapon equiv × 3, 370.

High-Melting Isomer (IIa).—The mother liquor from the preparation of II was cooled overnight at −10° resulting in 4 g of product melting at 81–82°. The mother liquor from the recrystallization of II was concentrated to 100 ml resulting in 7 g of product, mp 90–95°. The combined products were recrystallized from 95% ethanol (20 ml/g) at room temperature and the mother liquor was cooled at −10°. The product from the −10° crystallization was recrystallized four times as above resulting in 1.1 g, mp 106–108°. An analytical sample, mp 108–109°, was prepared by recrystallization from alcohol: infrared absorption (Nujol mull) at 5.58, 5.78, 6.25, 7.75, 7.95, 8.50, 9.30, 10.30, 11.00, 11.80, 11.98 μ; nmr spectrum ($CDCl_3$), doublets at τ 2.58, 3.67, 5.42, a triplet at 8.60, a quartet at 5.70, and complex multiplets at 6.5 and 7.3 with peak area ratios of 1:1:1:6:4:1:2.

Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.85; H, 5.16; mol wt, 312. Found: C, 54.01; H, 5.14; mol wt (osmometer), 300.

Diethyl [(2,2′,3,3′,4,4′,5,5′-Octahydro-5,5′-dioxo)-2,3′-bifuran]-2,2′-dicarboxylate (III).—To a solution of 0.36 g of II in 5 ml of acetic acid was added 67 mg of platinum oxide and the mixture was stirred under a pressure of 70 mm for 18 hr. After filtration of the catalyst and evaporation of the solvent,

(8) R. Lukes and K. Syhora, *Collect. Czech. Chem. Commun.*, **19**, 1205 (1954).

(9) R. Filler and E. J. Piasek, *J. Org. Chem.*, **28**, 3400 (1963).

the residue was recrystallized from 5 ml of 95% ethanol resulting in 0.28 g of III, mp 107–108°. An analytical sample, mp 108–109°, followed by solidification and remelting at 112–113°, was prepared by recrystallization from alcohol: infrared absorption (Nujol mull) at 5.57, 5.75, 7.40 (shoulder), 7.65, 7.88, 8.03, 8.13, 8.33, 8.43, 8.70, 9.15, 9.30, 9.85, 10.20, 10.33, 10.85, 11.95, 13.20 μ; nmr spectrum ($CDCl_3$), a doublet at τ 5.18, a triplet at 8.62, a quartet at 5.70, and complex multiplets at 6.7 and 7.3 with peak area ratios of 1:6:4:1:6.

Anal. Calcd for $C_{14}H_{12}O_8$: C, 53.50; H, 5.77; mol wt, 314. Found: C, 53.24; H, 5.76; sapon equiv × 4, 316.

Reaction Intermediate.—To a solution of 2 g of I in 20 ml of 95% ethanol was added 20 ml of 1 *M* hydrochloric acid. After 2 min, the solution was added to 1750 ml of water and extracted three times with chloroform. The aqueous phase was neutralized with 40 ml of 1 *M* dipotassium phosphate and extracted three times with chloroform. The chloroform extract of the neutralized solution was dried over sodium sulfate and concentrated to 31 ml under reduced pressure. A 3-ml aliquot was evaporated to dryness under reduced pressure, dissolved in 2 ml of $CDCl_3$, evaporated, and dried for 10 min under oil pump vacuum. The residue (0.15 g) was immediately dissolved in $CDCl_3$ for determination of the nmr spectrum (Figure 1b). Absence of the τ 2.78 and 4.65 furanoid proton bands indicates that I is not present in this material. The infrared spectrum of the chloroform extract shows intense absorption at 5.62, 5.80, and 5.98 μ. Purification of the extracted material by crystallization or by thin layer chromatography was not successful. The remainder of the chloroform solution was evaporated, dissolved in 10 ml of dioxane, and treated with 15 ml of 0.8 *M* hydrogen chloride in deuterium oxide. After 15 min the solution was concentrated until an oil separated. After recrystallization from a mixture of chloroform and carbon tetrachloride, 0.35 g of product, mp 93–94°, was obtained. The nmr spectrum was identical with that of II.

Hydrolytic Dimerization of I in Deuterium Oxide.—To a solution of 1.7 g of I in 17 ml of dioxane was added 25 ml of 0.8 *M* deuterium chloride in deuterium oxide. After 15 min at room temperature, the solution was cooled at −10° for 1 hr. The yield of recrystallized product, mp 91–92°, was 0.7 g. The nmr spectrum was determined in $CDCl_3$ (Figure 1c). The peaks at τ 2.51 (triplet), 3.65 (doublet), and 6.55 (singlet) have relative areas of 1:0.33:1.

Ultraviolet Absorption Studies.—A solution of 0.624 g (4.03 mmol) of I in 10 ml of 95% ethanol was prepared. A 1-ml aliquot was added to 1 ml of 1 *M* hydrochloric acid in a 25-ml volumetric flask. After the desired reaction period, the solution was diluted to 25 ml with 1 *M* dipotassium phosphate. After diluting 1:100 with water, the ultraviolet absorption spectrum was determined. The half-life of I under these conditions is 0.5 min. The formation of a reaction intermediate is indicated by the appearance of a peak at 208 mμ. After a 15-min reaction period, only end absorption characteristic of II remains.

Hydrolysis Studies.—Hydrolysis of the amine group during the hydrolytic dimerization of I was determined by liberation of ammonia using the Van Slyke aeration procedure.[10] To a solution of 30 mg of I in 0.5 ml of 95% ethanol was added 0.5 ml of 1 *M* hydrochloric acid. Separate runs were made and in each run 5 ml of 1 *M* sodium hydroxide was added after the desired reaction period. Nitrogen was passed through the solution at 0.5 ft^3/hr for 90 min. The ammonia was absorbed in 10 ml of a 2% boric acid solution containing bromcresol green indicator and was titrated with 0.02 *N* sulfuric acid. The yields of ammonia after 0.5-, 1-, 2-, 5-, and 15-min reaction periods are 32, 40, 44, 57, and 77%.

Registry No.—I, 15856-35-6; II, 15814-68-3; IIa, 15814-69-4; III, 15856-36-7.

Acknowledgments.—The authors are grateful to Mr. Benjamin Stevenson for the preparation of compound I, to Mr. Grant Gustin and Mr. Marvin Tefft for the microanalyses, and to Mrs. Patricia Curtis for the nmr spectra.

(10) P. B. Hawk, B. L. Oser, and W. H. Summerson, "Practical Physiological Chemistry," The Blakiston Co., Philadelphia, Pa., 1947, p 828.

Kinetics of the Reaction of Chloroacetic Acid with Ammonia in an Aqueous Solution[1]

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The kinetics of the consecutive reactions between chloroacetic acid and ammonia in aqueous solutions to form glycine and iminodiacetic and nitrilotriacetic acids have been studied by following the produced chloride ion. The observed second-order rate law, $v = k$[chloroacetic acid][amino compound], together with the relation between the rate constant and the pH of the solution confirms the ordinary SN2 mechanism involving an attack of free ammonia or amino group on the chloroacetate ion. The reactivities of amino compounds are discussed in terms of their rate constants, activation parameters, and basicities of amino groups.

Treatment of chloroacetic acid with ammonia gave glycine, iminodiacetic acid, and nitrilotriacetic acid.

$$NH_3 + ClCH_2COOH \xrightarrow{-HCl} H_2NCH_2COOH \xrightarrow[-HCl]{ClCH_2COOH}$$

$$HN(CH_2COOH)_2 \xrightarrow[-HCl]{ClCH_2COOH} N(CH_2COOH)_3$$

A large excess (*ca.* 60-fold) of ammonia was found to be favorable for the preparation of glycine.[2-4] Cheronis and Spitzmuller have studied qualitatively the effect of pH of the solution on the yield of glycine; they suggested that the formation of secondary and tertiary amino compounds was reduced at pH below 10 and that the reactive species are probably free ammonia and chloroacetate ion.[5] Iminodiacetic acid has been prepared by the reaction of boiling aqueous chloroacetic acid with ammonia.[6] However, no report has appeared on the preparation of nitrilotriacetic acid from these materials. Few kinetic studies have been reported for this type of reaction.[7,8]

The present study was undertaken to obtain some information on the kinetics of the formation of glycine and iminodiacetic and nitrilotriacetic acids from chloroacetic acid and ammonia together with the effect of pH

(1) Contribution No. 101.
(2) K. Kraut, *Ber.*, **23**, 2577 (1890).
(3) G. R. Robertson, *J. Amer. Chem. Soc.*, **49**, 2889 (1927).
(4) J. M. Orten and R. M. Hill, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 300.
(5) N. D. Cheronis and K. H. Spitzmuller, *J. Org. Chem.*, **6**, 349 (1941).
(6) H. Heintz, *Ann.*, **145**, 49 (1867).
(7) J. D. Johnson and L. J. Edwards, *Trans. Faraday Soc.*, **45**, 286 (1949).
(8) N. I. Darienko and N. V. Sapozhinikova, *Izv. Vyssh. Ucheb. Zaved. Khim, Khim. Tekhnol.*, **3**, 461 (1960); *Chem Abstr.*, **54**, 21954 (1960).

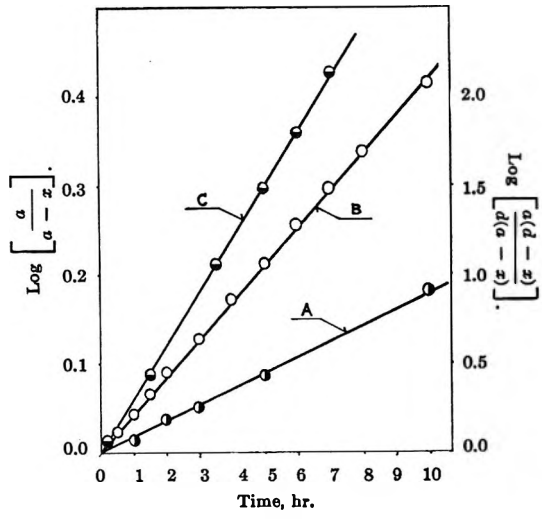

Figure 1.—Pseudo-first-order kinetics (left side of vertical axis) for the reaction of chloroacetic acid with ammonia (A) and with glycine (B) and second-order kinetics (right side of vertical axis) for the reaction of chloroacetic acid with iminodiacetic acid (C) in aqueous buffer solutions at 30 ± 0.1°. Initial concentrations were (A) chloroacetic acid, 0.1 *M*, ammonia, 2.0 *M*; (B) chloroacetic acid, 0.05 *M*, glycine, 0.50 *M*; (C) chloroacetic acid, 0.099 *M*, iminodiacetic acid, 0.05 *M*. The symbol *a* represents the initial concentration of chloroacetic acid and *d*, the initial concentration of iminodiacetic acid. All of the reaction were followed up to over 70% and all plots lie on good straight lines up to this high conversion.

on the rate for the clarification of the reaction mechanism.

Experimental Section

Materials.—Aqueous ammonia, sulfuric acid, nitric acid, sodium hydroxide, sodium sulfate, and sodium nitrate used were of guaranteed reagent grade. Chloroacetic acid was redistilled under vacuum, bp 97–98° (24 mm). Commercial glycine, mp 235.2–237° (effervesces) (lit.[9] 236–239° (dec), and iminodiacetic acid, mp 224–229° (effervesces) (lit.[10] 225° dec), were recrystallized from aqueous methanol.

Rate Measurements.—A solution (5 ml) of chloroacetic acid was pipetted into an aqueous solution of amino compound (100 ml) placed in a glass-stoppered flask which had reached thermal equilibrium in a thermostat. Aliquots (5 ml) were pipetted out at regular intervals and cold dilute nitric acid was added to them to stop the reaction. The concentrations of chloride ion were determined by the Volhard method.[11]

The hydrolysis of chloroacetic acid was negligible under the kinetic conditions at pH below 12, since practically no chloride ion was detected after 8 hr in an aqueous solution of chloroacetic acid in the absence of ammonia even at pH 12 and at 30°. A report[8] that the rate of hydrolysis of chloroacetic acid in an aqueous solution at 60° is *ca.* $^1/_{30}$ of the rate of the ammonolysis under the same conditions was consistent with our observation. Therefore, the rate of appearance of chloride ion may be assumed to be equal to the rates of the corresponding formation of glycine, iminodiacetic acid, and nitrilotriacetic acid. The concentration of ammonia was determined by titration with standard hydrochloric acid.

The pH and the ionic strength of the solution were controlled by adding a mixture of sulfuric acid and sodium sulfate or a mixture of nitric acid and sodium nitrate (for the reaction of chloroacetic acid with ammonia) or by adding a mixture of sodium hydroxide and sodium nitrate (for the reaction of chloroacetic acid with glycine or iminodiacetic acid). The pH of the solution was determined by Hitachi-Horiba pH meter type M 4 which is reliable in the range of pH 0–14.

(9) J. M. Hill and R. M. Hill, *J. Amer. Chem. Soc.*, **53**, 2797 (1931).
(10) K. Polstorff and H. Meyer, *Ber.*, **45**, 1906 (1912).
(11) J. R. Coldwell and H. V. Meyer, *Ind. Eng. Chem. Anal. Ed.*, **7**, 38 (1935).

Although hydrogen chloride was a reaction product, the change in pH of the solution is very small throughout the reaction as shown in Table I.

TABLE I

RATE CONSTANTS FOR THE REACTION OF CHLOROACETIC ACID WITH AMINO COMPOUNDS IN AN AQUEOUS SOLUTION AT 30 ± 0.1°

$ClCH_2COOH$, *M*	NH_3, *M*	H_2SO_4, *M*		Initial pH	Final pH[a]	$k^b \times 10^5$, sec^{-1}
0.1	1.0	0.04		10.0	9.7	0.486
	2.0	0.11		10.2	9.8	1.09
	3.0	0.23		10.2	9.9	1.68
	4.0	0.30		10.3	10.0	2.30
	5.0	0.36		10.4	10.2	3.14
$ClCH_2$-COOH, *M*	NH_2CH_2-COOH, *M*	NaOH, *M*	$NaNO_3$, *M*	Initial pH	Final pH[c]	$k^d \times 10^5$, sec^{-1}
0.05	0.50	0.33	2.42	9.5	9.4	2.66
	0.75	0.50	2.13	9.6	9.5	4.78
	1.00	0.67	1.83	9.8	9.7	6.75
	1.25	0.83	1.55	9.8	9.7	8.45
$ClCH_2$-COOH, *M*	$NH(CH_2$-$COOH)_2$, *M*	NaOH, *M*	$NaNO_3$, *M*	Initial pH	Final pH[e]	$k^f \times 10^5$, M^{-1} sec^{-1}
0.099	0.050	0.50	2.38	13.4	13.2	19.8
	0.075	0.75	2.08	13.1	13.0	18.0
	0.100	1.00	1.78	13.3	13.1	17.4
	0.125	1.25	1.48	13.6	13.1	18.3
	0.150	1.50	1.18	13.5	13.2	18.4

[a] After 38 hr. [b] First-order rate constants for chloroacetic acid at various ionic strengths. [c] After 5 hr. [d] First-order rate constants for chloroacetic acid at ionic strength 3. [e] After 20 hr. [f] Second-order rate constants for chloroacetic acid and iminodiacetic acid at ionic strength 3.

The Preparation of Nitrilotriacetic Acid.—Aqueous ammonia (28%, 1 mol, 70 ml), 100 ml of an aqueous solution of sodium hydroxide (15 g, 0.375 mol), and 100 ml of an aqueous solution of chloroacetic acid (38 g, 0.4 mol) were mixed in a flask equipped with a reflux condenser at room temperature. The solution was then allowed to stand for 24 hr. On heating at 100° (of bath temperature) with vigorous stirring for 3 hr the solution became yellowish. The solution was then cooled and acidified with sulfuric acid. Nitrilotriacetic acid was formed immediately as a white precipitate, which was filtered off, washed with water, and recrystallized twice from water, giving 18 g of colorless crystals of nitrilotriacetic acid, mp 240° (effervesces) (lit.[12] 242° dec); the yield after recrystallization from water was 73.4% based on chloroacetic acid.

The product was identified by similarity in paper chromatographic behavior with an authentic sample.[13] A mixture of 1-butanol–water–acetic acid (4:5:1 in volume) was employed as a developer and an ascending method was used. The R_f values (and the characteristic color) were 0.11 (violet) for the product, 0.19 (reddish violet) for glycine, 0.13 (reddish violet) for iminodiacetic acid, and 0.10 (violet) for nitrilotriacetic acid.

The Measurement of pK_a.—The ionic strength of the solution was controlled to 3 using sodium nitrate. The pK_a value of the conjugate acids of amino compounds was measured using the potentiometric titration method.[14] The pK_a values at 30° were 9.45, 9.60, and 9.15 for the conjugate acid of ammonia, iminodiacetic acid, and nitrilotriacetic acid, respectively.

Results and Discussion

Typical rate data are shown in Table I. The reactions of chloroacetic acid with ammonia to form glycine, iminodiacetic acid, and nitrilotriacetic acid are consecutive.[2-5] The straight lines in the pseudo-first-order plot in Figure 1 show that the reaction rate of chloroacetic acid with formed glycine can be neglected in a large excess (over tenfold) of ammonia. Indeed,

(12) J. V. Dubsky and W. D. Wensink, *Ber.*, **49**, 1042 (1916).
(13) A. E. Martell and F. C. Bersworth, *J. Org. Chem.*, **15**, 46 (1950).
(14) S. Nakamura, *J. Syn. Org. Chem. Jap.*, **24**, 923 (1966).

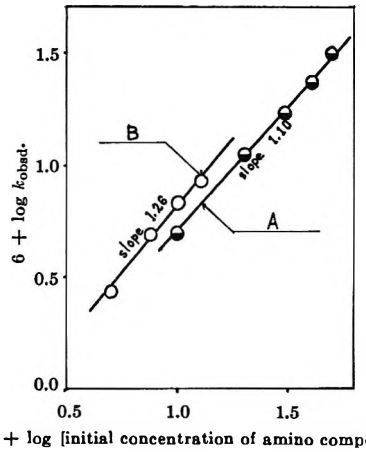

Figure 2.—The relationship between log (pseudo-first-order rate constants) and log (the initial concentration of ammonia) (A) and log (the initial concentration of glycine) (B) at 30 ± 0.1°.

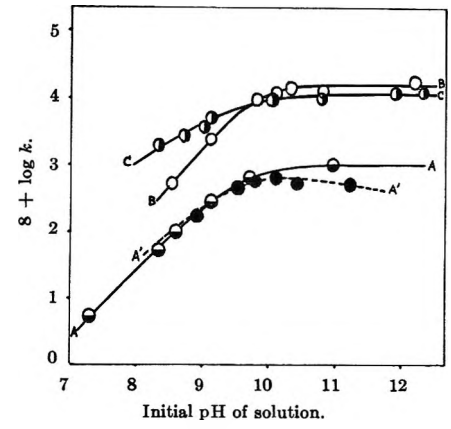

Figure 3.—The effect of pH on the rate of reaction of chloroacetic acid with ammonia (A), glycine (B), and iminodiacetic acid (C) at 30 ± 0.1° and ionic strength 3, and the effect of pH on the rate of reaction of chloroacetic acid with ammonia (A′) at 30 ± 0.1° and various ionic strengths. Initial concentrations were (A) chloroacetic acid, 0.1 M, ammonia, 2.5 M; (B) chloroacetic acid, 0.05 M, glycine, 0.75 M; (C) chlorocetic acid, 0.099 M, iminodiacetic acid, 0.1 M; (A′) chloroacetic acid, 0.1 M, ammonia, 5.0 M.

although the reactivity of glycine is ten times as much as that of ammonia as observed, the reaction with glycine may be neglected even at 50% conversion of chloroacetic acid because of the high molar ratio of ammonia to glycine. It has been reported that besides glycine (a main product) only a small amount of iminodiacetic acid and nitrilotriacetic acid were obtained under these conditions.[2-5] A similar consideration may be applied to the reaction of chloroacetic acid with glycine. If the reactivity of iminodiacetic acid is almost equal to that of glycine as observed, the effect of formed iminodiacetic acid (below 5%) on the rate in a large excess (over tenfold) of glycine can be neglected even if half of the chloroacetic acid is consumed.

Kinetics of the Formation of Glycine.—Curve A in Figure 1 shows that the rate of formation of glycine is first order in chloroacetic acid. For the determination of the order with respect to ammonia, the rate was measured at constant concentration of chloroacetic acid (0.1 M) and at various concentrations of ammonia, *i.e.*, 1.0, 2.0, 3.0, 4.0, and 5.0 M. The logarithm of the observed rate constants was plotted against the logarithm of the initial concentration of ammonia (Figure 2, curve A).

Since the plotted line has a slope of almost unity (1.10), the reaction forming glycine also follows first-order kinetics with ammonia, and the rate equation is expressed in eq 1.

$$v = k_\alpha[\text{ammonia}][\text{chloroacetic acid}] \quad (1)$$

Effect of pH on the Rate of Formation of Glycine.—It is shown in Figure 3, curve A, that the rate of formation of glycine decreases sharply at pH below 10 and gives a line having a slope of unity at pH below 9.5.

If the rate-determining step consists of an attack of free ammonia on chloroacetate ion as postulated by Cheronis and Spitzmuller,[5] the over-all reaction is expressed in eq 2–4.

$$NH_4^+ \underset{\text{mobile}}{\overset{K_2}{\rightleftharpoons}} NH_3 + H^+ \quad (2)$$

$$ClCH_2COOH \underset{\text{mobile}}{\overset{K_3}{\rightleftharpoons}} ClCH_2COO^- + H^+ \quad (3)$$

$$NH_3 + ClCH_2COO^- \underset{\text{slow}}{\overset{k_4}{\longrightarrow}} NH_2CH_2COO^- + H^+ + Cl^- \quad (4)$$

The stoichiometric concentration of ammonia ($b - x$) is the sum of the concentrations of free and protonated amines (see eq 5). In the same way, the stoichiometric

$$(b - x) = [NH_3]\left(1 + \frac{[H^+]}{K_2}\right) \quad (5)$$

concentration of chloroacetic acid ($a - x$) is expressed as in eq 6. The term, $[H^+]/K_3$, may be negligible

$$(a - x) = [ClCH_2COO^-]\left(1 + \frac{[H^+]}{K_3}\right) \quad (6)$$

under all conditions studied (pH >7), since the value of K_3 at 25° is 1.4×10^{-3} and chloroacetic acid may be almost completely anionic; hence ($a - x$) is equal to $[ClCH_2COO^-]$. Therefore, the rate of formation of glycine may be expressed as in eq 7, where k and K are

$$v = k_4[NH_3][ClCH_2COO^-]$$
$$k_4\left(\frac{1}{1 + ([H^+]/K_3)}\right)(b - x)(a - x) \quad (7)$$

rate and equilibrium constants for the subscripted step, respectively.

The comparison of eq 7 with eq 1 leads to an expression for the apparant rate constant k_α (see eq 8). The

$$k_\alpha = k_4\left(\frac{1}{1 + ([H^+]/K_2)}\right) \quad (8)$$

average value of rate constant, k_4, for the rate-determining step was calculated to be $1.12 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$ from eq 6 at pH above 10.5 and ionic strength 3. The solid curve A in Figure 3 is the theoretical curve for log k_α–pH profile calculated from eq 8 assuming k_4 of $1.12 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$ at constant ionic strength 3 and pK_2 of 9.60; the observed values of k_α lie on the curve A. The assumed value of basicity of ammonia, pK_2 = 9.60, agrees within experimental error with the observed value of pK_a (9.45) determined at 30° and ionic strength 3. This agreement shows that the above rate law is sufficient to describe the pH–rate profile.

Therefore, it is concluded that the main reactive species are not $ClCH_2COOH$ but $ClCH_2COO^-$, at least, in this pH range.

The existence of a maximum at pH of *ca.* 10 at various ionic strengths was observed in a plot of log k_α *vs.* pH (Figure 3, curve A'). However, the fact that the salt effect is observed at high ionic strength even in the reaction between neutral and ionic species[15,16] and that the pH of the solution was prepared by adding sulfuric acid, suggests a positive salt effect. Indeed, the maximum rate disappears at constant ionic strength 3 (Figure 3, curve A). It is probable that this positive salt effect appears to be due to the reaction between chloroacetate ion and free ammonia, since a molecule of ammonia having a strong dipole may behave in a manner similar to an anion at high ionic strength.[15,16]

Kinetics of the Formation of Iminodiacetic Acid.—The rate of iminodiacetic acid formation from glycine and chloroacetic acid measured at constant ionic strength 3 follows first-order kinetics with chloroacetic acid (Figure 1, curve B) and with glycine (Figure 2, curve B), respectively. Therefore, the rate is expressed as in eq 9. The slope (1.26) of the plot of

$$v = k_\beta\,[\text{glycine}]\,[\text{chloroacetic acid}] \qquad (9)$$

log k_β *vs.* log [glycine] in Figure 2 is larger than unity. This may be due to a slight increase in pH of the solution with increasing concentration of glycine and hence sodium hydroxide causes an increase in rate as stated below (Table I).

Effect of pH on the Formation of Iminodiacetic Acid.—It has been reported[5] that the formation of iminodiacetic and nitrilotriacetic acids is difficult at pH <10 and that the reaction between glycine and glucose is influenced by the pH of the solution.[17] The effect of pH on the rate of iminodiacetic acid formation may then be discussed in the same way as in the reaction between ammonia and chloroacetic acid. It is apparent in curve B of Figure 3 that the rate of formation of iminodiacetic acid sharply decreases at pH below 10 and gives a straight line having a slope of *ca.* 1 at pH below 9.

Glycine exists in an aqueous neutral solution as a zwitterion, $^+NH_3CH_2COO^-$. Considering that the solution is basic and assuming that the rate-determining step is the reaction between chloroacetate ion and glycine anion, the over-all reaction is expressed as in eq 10 and 11.

$$^+NH_3CH_2COO^- \underset{\text{mobile}}{\overset{K_{10}}{\rightleftharpoons}} NH_2CH_2COO^- + H^+ \qquad (10)$$

$$NH_2CH_2COO^- + ClCH_2COO^- \xrightarrow[\text{slow}]{k_{11}} NH(CH_2COO^-)_2 + H^+ + Cl^- \qquad (11)$$

As in the reaction between ammonia and chloroacetic acid, the rate equation of iminodiacetic acid formation can be derived from eq 10 and 11. The comparison of the rate equation with the observed eq 9 leads to eq 12.

$$k_\beta = k_{11}\left(\frac{1}{1 + ([H^+]/K_{10})}\right) \qquad (12)$$

The average value of the rate constants of the rate-determining step, k_{11}, was calculated to be 1.22×10^{-4} M^{-1} sec^{-1} (ionic strength 3) from eq 10 together with the observed data at pH >10. Assuming k_{11} of 1.22×10^{-4} M^{-1} sec^{-1} and pK_{10} of 9.80, curve B in Figure 3 is drawn by using the value of k_β which is a constant calculated from eq 10 at various pH. The observed rate constants at pH 8–12 lie on curve B as shown in Figure 3. The pK_{10} of 9.80 assumed here agrees with the observed value of pK_{NH^+} (9.60) determined by potentiometric titration at 30° and ionic strength 3. Therefore, it is concluded that the main reactive species in this reaction are $ClCH_2COO^-$ and $NH_2CH_2COO^-$, at least under these conditions. The rate constant of iminodiacetic acid formation was ten times as high as that of glycine formation.

Kinetics of the Formation of Nitrilotriacetic Acid.—The reaction between ammonia and chloroacetic acid in a basic solution produces nitrilotriacetic acid in a good yield (73%). The rate of nitrilotriacetic acid formation is expressed as eq 13 derived from curve C of Figure 1.

$$v = k_\gamma[\text{iminodiacetic acid}]\,[\text{chloroacetic acid}] \qquad (13)$$

Effect of pH on the Formation of Nitrilotriacetic Acid.—Considering the dissociation of reactants, the over-all reaction may be written as eq 14 and 15. Here, the

$$^+NH_2\langle^{CH_2COO^-}_{CH_2COOH} \underset{\text{mobile}}{\overset{K_{14}'}{\rightleftharpoons}} {}^+NH_2\langle^{CH_2COO^-}_{CH_2COO^-} + H^+ \underset{\text{mobile}}{\overset{K_{14}}{\rightleftharpoons}}$$

$$NH\langle^{CH_2COO^-}_{CH_2COO^-} + 2H^+ \qquad (14)$$

$$NH\langle^{CH_2COO^-}_{CH_2COO^-} + ClCH_2COO^- \xrightarrow[\text{slow}]{k_{15}}$$

$$N\langle^{CH_2COO^-}_{CH_2COO^-}_{CH_2COO^-} + H^+ + Cl^- \qquad (15)$$

contribution of K_{14}' is negligible, since this value is more than 10^{-3}.

The relationship between the rate constant and pH of solution expected from this scheme leads to eq 16. This equation agrees with the experimental results as shown in Figure 3. Hence the main reactive species of this

$$k_\gamma = k_{15}\left(\frac{1}{1 + ([H^+]/K_{14}) + ([H^+]^2/K_{14}'K_{14})}\right) \qquad (16)$$

reaction are $NH(CH_2COO^-)_2$ and $ClCH_2COO^-$. The rate constant, k_{15}, was 1.12×10^{-4} M^{-1} sec^{-1} and pK_{14} was 9.15 at 30° and ionic strength 3. The rate constant is comparable with that of iminodiacetic acid.

The Reactivity of Amino Compounds and the Reaction Mechanism.—The rate constants for the reaction of chloroacetic acid with ammonia and amino acids were estimated at various temperatures and are shown in Table II. The activation parameters were calculated and they are listed in Table III together with the pK_a values of the conjugate acids of the amines.

Both glycine and iminodiacetic acid having a carboxymethyl group are about ten times as reactive as ammonia. On the other hand, there is little difference in reactivity between glycine and iminodiacetic acid: $NH_2CH_2COO^- \simeq NH(CH_2COO^-)_2 > NH_3$. This is

(15) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p 151.

(16) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, p 186.

(17) M. Nikonorow and H. P.-Karpinska, *Rocz. Panstwowego Zakladu Hig.*, **11**, 23 (1960); *Chem. Abstr.*, **55**, 10545 (1961).

TABLE II
THE SECOND-ORDER RATE CONSTANT AT VARIOUS TEMPERATURES ($10^5\ M^{-1}\ sec^{-1}$)

Reactants (M)	Temp, °C 60	50	45	40	35	30
$ClCH_2COO^-$ (0.1) + NH_3 (5)	...	10.0	6.13	3.25	2.17	...
$ClCH_2COO^-$ (0.055) + $NH_2CH_2COO^-$ (0.15)	209	90.0	...	36.3	...	13.3
$ClCH_2COO^-$ (0.055) + $NH(CH_2COO^-)_2$ (0.15)	223	96.7	...	28.9	...	15.1

TABLE III
pK_a VALUES FOR THE CONJUGATE ACID OF AMINO COMPOUNDS AND ACTIVATION PARAMETERS FOR THE REACTION OF CHLOROACETIC ACID WITH AMINO COMPOUNDS IN AN AQUEOUS SOLUTION AT 30 ± 0.1° AND IONIC STRENGTH 3

Reactants	pK_a[a]	pK_a[b]	k[c] × 10^5, M^{-1} sec^{-1}	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu
$ClCH_2COO^-$ + NH_3	9.45	9.25	1.12	20.9	−16
$ClCH_2COO^-$ + $NH_2CH_2COO^-$	9.60	9.74	12.2	18.5	−17
$ClCH_2COO^-$ + $NH(CH_2COO^-)_2$	9.15	9.89	11.2	18.7	−17

[a] The acidities of protonated amines were measured at 30° and ionic strength 3. [b] The acidities of protonated amines taken at 30° and lower ionic strength. [c] Second-order rate constant.

apparent from the energy of activation, but not from the entropy of activation which is in the order $NH_2CH_2COO^- \simeq NH(CH_2COO^-)_2 < NH_3$. The observed pK_a values at 30° and ionic strength 3 for conjugate acids of amines are in the order $NH_2CH_2COO^- > NH_3 > NH(CH_2COO^-)_2$, but the basicities and nucleophilicities of these amines at lower ionic strength are in the order: $NH(CH_2COO^-)_2 \simeq NH_2CH_2COO^- > NH_3$. The difference between these values may be due to the difference of ionic strength.

Therefore, the reactivities of these amino compounds depend more on the basicity or nucleophilicity of amino nitrogen. A slight decrease in rate for iminodiacetic acid, compared with the rate for glycine, may have been due to the steric effect. However, the reaction of chloroacetic acid with these amino compounds possesses comparable entropies of activation. Hence, the steric effect of the introduced carboxymethyl group seemed to be negligible.

The rate of reaction is expressed as $v = k[\text{amine}] \times [ClCH_2COO^-]$, where k depends on the basicity (and nucleophilicity) of amino nitrogen. Further, the entropy of activation is *ca.* −16 to −17 eu. These facts suggest that these reactions proceed by the SN2 mechanism.

A mechanism involving carbonium ion or α-lactone is excluded, since the rate did not decrease in spite of the accumulation of chloride ion as the reaction proceeded; *i.e.*, no common ion effect was observed, and the rate of the hydrolysis of substrates compared with ammonolysis is slow.

Registry No.—Chloroacetic acid, 79-11-8; ammonia, 7664-41-7; glycine, 56-40-6; iminodiacetic acid, 142-73-4.

A New Thermal Rearrangement of Allylic Phenylurethans[1]

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On heating to 200–240° with a catalytic amount of sodium hydride, phenylurethans of allylic alcohols rearrange, with expulsion of carbon dioxide, to N-phenylallylamines. Predominant inversion of the allyl moiety occurs and the reaction is considered to proceed by a cyclic electron reorganization process. Rearrangement of optically active Δ^2-cyclohexenylphenylurethan is accompanied by 65% retention of configuration and 35% racemization. Small amounts of imidazolidones are found as by-products and a pathway for their formation, involving base-catalyzed cyclization of N-allylureas, is proposed and supported by testing the presumed intermediates.

Of the thermal reorganization reactions which involve six-membered cyclic transition states,[2] one of the mechanistically most interesting and synthetically most useful families is that whose prototype is the Claisen rearrangement of allyl vinyl ethers (Chart I, reaction a[3]). A number of variations on this theme are known, some of which are listed in Chart I. These include the rearrangement of allylic imidates to amides (b),[4,5] the rearrangement of ketene acetals and their nitrogen analogs to esters and amides (c),[6,7] the pyrolysis of allylic acetoacetates and cyanoacetates (d),[8,9] and the rearrangement of carbanions of allylic esters to α-allyl carboxylic acids (e).[10] Similar rearrangements are observed in reactions which verge on the SNi′ type, such as the thermal isomerization of allyl esters (f),[11,12] and the recently reported conversion of allyl sulfamates into allylamines (g).[13]

(1) This study was initiated with the support of a Research Fellowship to R. K. H. from the Alfred P. Sloan Foundation and supported by a research grant (GP-3811) from the National Science Foundation, to both of whom the authors express their gratitude.

(2) J. Mathieu and J. Valls, *Bull. Soc. Chim. Fr.*, 1509 (1957).

(3) (a) C. D. Hurd and M. A. Pollock, *J. Amer Chem. Soc.*, **60**, 1905 (1938); (b) W. J. Croxall and J. O. Van Hook, *ibid.*, **72**, 803 (1950); (c) A. W. Burgstahler and I. C. Nordin, *ibid.*, **83**, 198 (1961).

(4) O. Mumm and F. Möller, *Ber.*, **70**, 2214 (1937).

(5) R. M. Roberts and F. A. Hussein *J. Amer. Chem. Soc.*, **82**, 1950 (1960).

(6) S. M. McElvain, H. I. Anthes, and S. H. Shapiro, *ibid.*, **64**, 2525 (1942).

(7) (a) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann.*, **641**, 1 (1961); (b) A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964).

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(9) E. C. Kooyman, R. Louw, and W. A. M. de Tonkelaar, *Proc. Chem. Soc.*, 66 (1963).

(10) (a) R. T. Arnold and S. Searles, Jr., *J. Amer. Chem. Soc.*, **71**, 1150 (1949); (b) K. C. Brannock, H. S. Pridgen, and B. Thompson, *J. Org. Chem.* **25**, 1815 (1960).

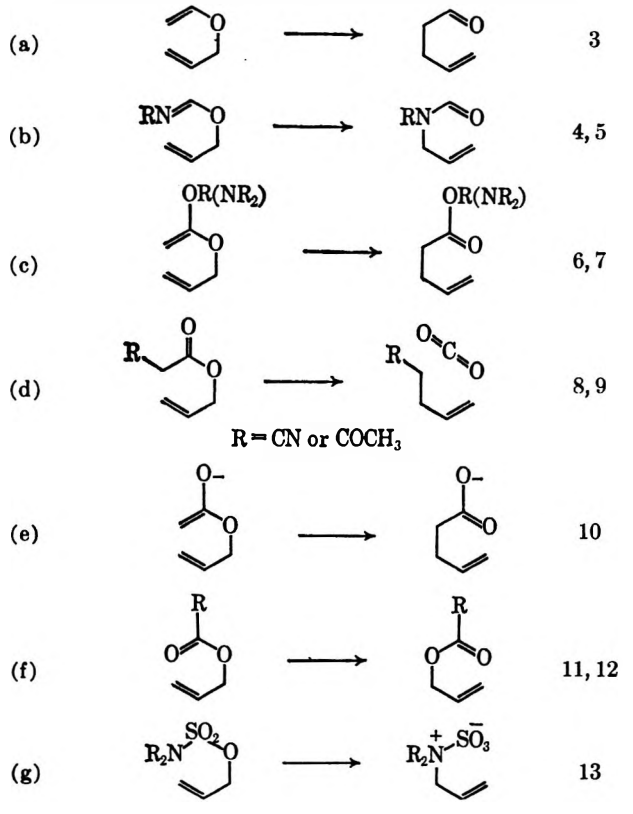
(11) (a) C. S. Marvel and N. O. Brace, *J. Amer. Chem. Soc.*, **70**, 1775 (1948); (b) E. A. Braude, D. W. Turner, and E. S. Waight, *Nature*, **173**, 863 (1954); (c) E. A. Braude and D. W. Turner, *Chem. Ind.* (London), 1223 (1955).

(12) J. Kenyon, S. M. Partridge, and H. Phillips, *J. Chem. Soc.*, 207 (1937).

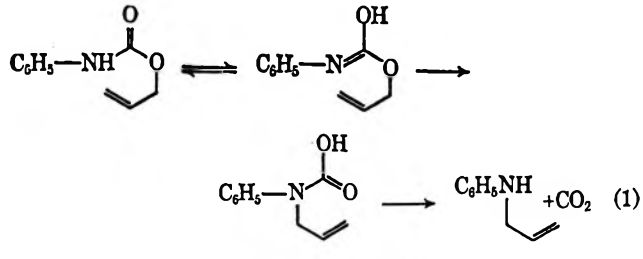
(13) E. H. White and C. A. Elliger, *J. Amer. Chem. Soc.*, **87**, 5261 (1965).

CHART I

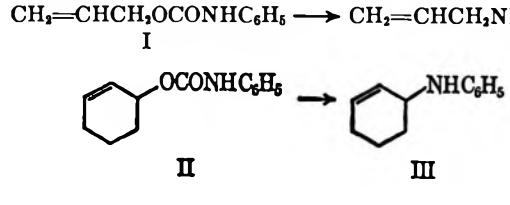
REACTIONS RELATED TO THE CLAISEN REARRANGEMENT



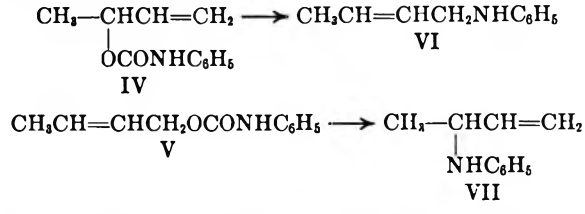
We wish to report a new and practical reaction which belongs in this category, the thermal rearrangement of phenylurethans of allylic alcohols to N-allylanilines. Since urethans are isoelectronic with ester carbanions, it appeared that they might undergo a thermal reaction similar to reaction e in Chart I to produce carbamic acids, which would decarboxylate under the reaction conditions (eq 1).



Rearrangement.—Heating the phenylurethans of several allylic alcohols at 200–240° caused the evolution of carbon dioxide and formation of amines. The reaction occurred much more readily when a catalytic amount of sodium hydride was added, and all preparative experiments involved heating the phenylurethan with 1–2% of its weight of a sodium hydride dispersion in mineral oil for 3–12 hr. Under these conditions the phenylurethan (I) of allyl alcohol yielded N-allylaniline in 24% yield. Δ^2-Cyclohexenylphenylurethan (II) afforded N-phenyl-Δ^2-cyclohexenylamine (III) in 34% yield.



A cyclic rearrangement mechanism requires inversion of the allyl moiety; this was tested with the phenylurethans (IV and V) of α-methallyl and crotyl alcohol. The amine formed in 60% yield by pyrolysis of IV was shown by vpc analysis to be essentially pure N-crotylaniline (VI), accompanied by 1–2% each of aniline and N-phenyl-α-methallylamine (VII). The butenylaniline formed in yields of 56–64% from V was similarly shown to be an 85:15 mixture of VII and VI. The two isomeric amines could be separated by careful distillation through a spinning-band column. Their structures were established unambiguously from infrared and nmr spectra and by hydrogenation of VII to N-*sec*-butylaniline. The predominant product of each rearrangement is consequently the amine in which the allyl group has inverted.



Amines VI and VII are thermally stable. The small amount of allylic isomer which accompanies each in the pyrolysis may have two possible origins: (a) decomposition of the phenylurethan without allylic rearrangement or (b) partial isomerization of the phenylurethan to its allylic isomer prior to decomposition to amine. The latter alternative may be more likely in view of the report[12] of thermal isomerization of arylurethans to allylic isomers. We were unable to recover any phenylurethans from the pyrolysis mixture to test directly the possibility of phenylurethan isomerization in this case.

Though the yields of amines produced in this rearrangement are only moderate, the yields reported here are all for redistilled products, and the ease of preparation of the starting materials and simplicity of the reaction conditions make this a valuable method for the preparation of N-phenylallylamines. It may prove to be of particular utility when one unsymmetrical allylamine, such as VI or VII, is desired, since the most common present method of preparation, the displacement of allyl halides by amines, leads invariably to mixtures of allylic isomers.[14]

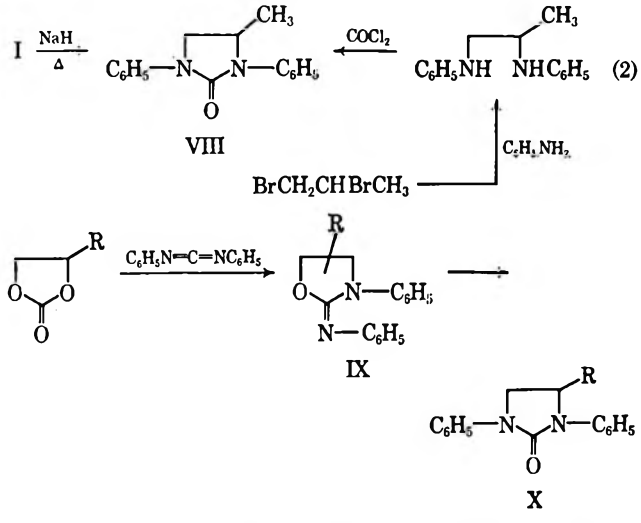
A single attempt to rearrange the *n*-butylurethan of crotyl alcohol under similar conditions gave no amine.

By-products.—Small amounts of aniline and, in some cases, *sym*-diphenylurea, resulting from decomposition of the phenylurethans, were isolated in most runs. From the rearrangement of allylphenylurethan there was isolated, in addition to N-allylaniline, about 5% of a neutral solid, $C_{16}H_{16}N_2O$, mp 122–123°. The infrared spectrum revealed the absence of N–H bands and showed aromatic absorption as well as a strong carbonyl band at 5.87 μ. The nmr spectrum showed a multiplet in the aromatic region centered about 7.3, a multiplet at 3.1–4.4, and a doublet at 1.2 ppm; the three groups of protons were in the ratio 10:3:3. These data led to the suggestion that the compound might be 1,3-diphenyl-4-methylimidazolidone-2 (VIII).

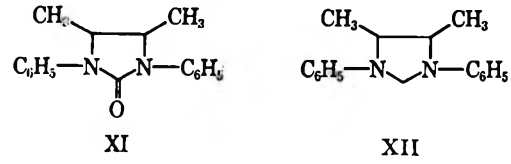
(14) For example, the reaction of α-methallyl chloride with N-methylanilines gives less than 10% of the S$_N$2 displacement product: D. C. Dittmer and A. F. Marcantonio, *J. Amer. Chem. Soc.*, **86**, 5621 (1964).

However, a compound of this structure was reported a few years ago by Gulbins and Hamann,[15] with mp 76–77°. Gulbins and Hamann prepared their compound by reaction of propylene carbonate with diphenylcarbodiimide, and assigned the structure by analogy with the corresponding product from ethylene carbonate, which they showed to be the known 1,3-diphenylimidazolidone-2 (X, R = H).

A sample kindly furnished by Professor Hamann confirmed the nonidentity of the propylene carbonate–diphenylcarbodiimide product with the by-product from the allyl phenylurethan rearrangement. Though the nmr and infrared spectra showed certain similarities, they were distinctly different. In order to decide which substance is the imidazolidone VIII a sample of VIII was prepared by the unambiguous method of Hanssen.[16] 1,2-dibromopropane was heated with aniline and the resulting diamine treated with phosgene (eq 2). Authentic VIII prepared in this way melted at 122–123° and was identical with the allylphenylurethan rearrangement product. The structure of the Gulbins–Hamann compound remains in doubt. These authors had suggested that the reaction of carbonates with diphenylcarbodiimide proceeds *via* the intermediates IX which then thermally isomerize to imidazolidones X, and it may be that their compound is one of the methyl derivatives (R = CH_3) of IX, but we have no further information on this subject.

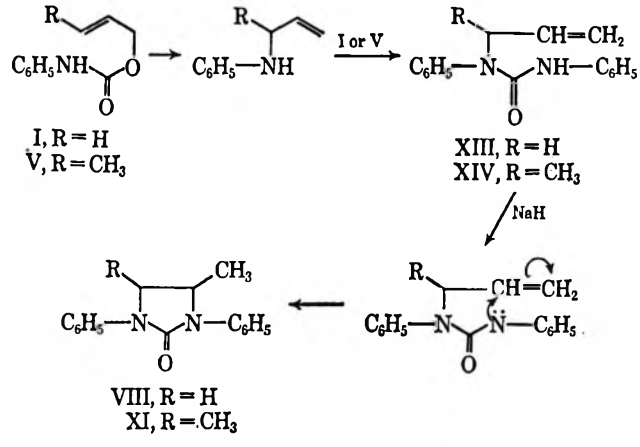


A homolog of VIII, 1,3-diphenyl-4,5-dimethylimidazolidone-2 (XI), was isolated in 2–3% yield as a mixture of stereoisomers from the rearrangement of crotylphenylurethan (V). Neither fractional crystallization nor chromatography effected more than partial separation of the isomers. In one run it was possible to isolate small amounts of two fairly sharp-melting substances, mp 145–146° and 152–153°, but their nmr spectra showed clearly that neither was a pure stereoisomer. The nmr spectrum of the mixture showed aromatic protons (10 H) at 7.0–7.7, overlapping quartets (2 H) centered about 4, and a doublet (6 H) at 1.4 ppm. Synthesis of XI from 2,3-dibromobutane (mixture of stereoisomers) and aniline, followed by ring closure with phosgene, gave a mixture with the same melting point behavior and identical infrared and nmr spectra. Lithium aluminum hydride reduction of XI gave the imidazolidine XII, whose nmr spectrum showed aromatic absorption at 6.5–7.4 (10 H), a singlet at 4.65 (2 H), a quartet at 3.9 (2 H), and a doublet at 1.2 ppm (6 H).



A plausible mechanism for the formation of the imidazolidones VIII and XI is suggested in Scheme I.

SCHEME I



Nucleophilic attack of amine (N-allylaniline or VII) on the carbonyl group of unreacted phenylurethan would lead to the unsymmetrical ureas XIII and XIV. Intramolecular addition of the urea N–H group to the double bond, catalyzed by sodium hydride, could then form VIII and XI. The addition of alkali metal derivatives of organic compounds to unconjugated olefins is a well-documented process.[17]

An obvious test of this proposal is to determine whether the presumed intermediates, ureas XIII and XIV, do in fact cyclize to imidazolidones. The ureas were prepared from the amines and phenyl isocyanate and separately heated with sodium hydride for a few minutes, resulting in the formation of VIII and XI in low yields. In the absence of sodium hydride, only *sym*-diphenylurea resulted from heating XIV.

Stereochemistry.—A stereochemical characteristic of the cyclic mechanism by which the reactions in Chart I take place is the ability to transmit asymmetry from one site on the cycle to another through a transition state of fairly rigid geometric requirements. This sort of internal asymmetric induction has been observed for the reactions a,[18] c,[7b] d,[19] and f.[12] In order to make

(15) K. Gulbins and K. Hamann, *Chem. Ber.*, **94**, 3287 (1961).
(16) A. Hanssen, *Ber.*, **20**, 784 (1887).

(17) (a) J. G. Welch and R. M. Magid, *J. Amer. Chem. Soc.*, **89**, 5300 (1967); (b) H. Pines, J. Veseley, and V. Ipatieff, *ibid.*, **77**, 554 (1955); (c) P. D. Bartlett, S. Friedman, and M. Stiles, *ibid.*, **75**, 1771 (1953); (d) G. G. Eberhardt, *J. Org. Chem.*, **29**, 643 (1964). For a particularly close analogy, see (e) R. F. Brown and N. M. van Gulick, *J. Amer. Chem. Soc.*, **77**, 1092 (1955).

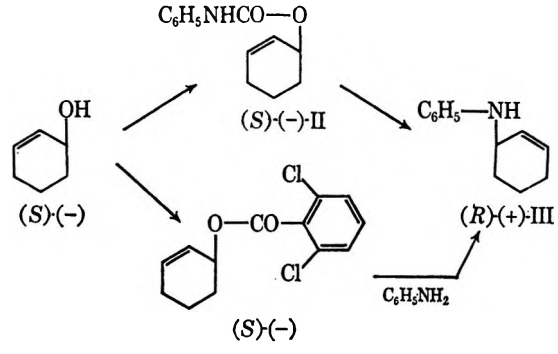
(18) R. K. Hill and A. G. Edwards, *Tetrahedron Lett.*, 3239 (1964). Asymmetric induction has also been observed in the Claisen rearrangement of aryl allyl ethers: E. R. Alexander and R. W. Kluiber, *J. Amer. Chem. Soc.*, **73**, 4304 (1951); H. L. Goering and W. I. Kimoto, *ibid.*, **87**, 1748 (1965).

(19) R. K. Hill and M. E. Synerholm, *J. Org. Chem.*, **33**, 925 (1968).

this stereochemical test in the rearrangement of allylic phenylurethans, we have studied the pyrolysis of optically active Δ^2-cyclohexenylphenylurethan (II). If the rearrangement involves dissociation of the starting material into discrete radicals or ions, then any delocalized intermediate from the cyclohexenyl moiety would be symmetrical and the product racemic.

Pyrolysis of the phenylurethan of (*S*)-(−)-Δ^2-cyclohexenol[20] yielded an amine (III) whose hydrochloride showed no detectable rotation at the D line, but a clear, though small, positive rotation at 300 mμ. To obtain an estimate of the optical purity of III and to establish at the same time its absolute configuration, III was prepared independently from Δ^2-cyclohexenol as shown in Scheme II. The (*S*)-(−) alcohol was converted into the 2,6-dichlorobenzoate and heated with aniline to afford the (*R*)-(+)-hydrochloride of III. The optical rotation of the amine III prepared by the phenylurethan rearrangement was 65% of that of the amine prepared by displacement. Consequently the rearrangement is accompanied by a minium of 35% racemization; if any racemization occurs in the displacement reaction this figure will, of course, be higher.

SCHEME II



It may be noted that regardless of whether the displacement of the allylic dichlorobenzoate is an SN2 or SN2′ process the result is inversion of configuration;[21] the amine prepared in this way from the (*S*) alcohol[22] must have the (*R*) configuration. Amine prepared from phenylurethan rearrangement has the same sign and consequently is also formed with inversion of configuration, a result demanded by the cyclic transition state.

These experiments thus show that the thermal rearrangement of allylic phenylurethans displays the characteristic inversion of the allyl double bond and induction of asymmetry which are typical of concerted cyclic electron-reorganization reactions. The partial racemization accompanying the formation of III may be due to a small degree of nonconcerted rearrangement, or it may be an artifact caused by partial racemization of the starting phenylurethan by allylic isomerization. These alternatives could be distinguished by the use of a suitable unsymmetrical optically active phenylurethan.

(20) D. B. Denney, R. Napier, and A. Cammarata, *J. Org. Chem.*, **30**, 3151 (1965). We are grateful to Professor Denney for furnishing us with the details of his elegant synthetic procedure before publication.

(21) SN2′ displacement on cyclohexenol derivatives involves a *cis* relation of nucleophile and leaving group; see G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).

(22) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).

Experimental Section

Preparation of Phenylurethans.—The allylic alcohol was treated with an equimolar amount of phenyl isocyanate. When the initial reaction had subsided, the mixture was heated on the steam bath for 1 hr. Dilution with 1:1 benzene–petroleum ether (60–70°) and cooling gave the phenylurethan in high yield and purity. Phenylurethans obtained were allylphenylurethan, mp 68–69° (lit.[23] mp 70°); α-methallylphenylurethan, mp 50–52° (lit.[24] mp 50–51°); crotylphenylurethan, mp 78.5–80° (lit.[25] mp 79.4–80.0°); Δ^2-cyclohexenylphenylurethan, mp 107–108° (lit.[26] mp 107°).

Rearrangement of Allylphenylurethan.—The phenylurethan (100 g) was mixed with 2 g of a 55% dispersion of sodium hydride in mineral oil and heated under reflux in a Woods' metal bath at 210–230° for 12 hr. After cooling, the mixture was diluted with an equal volume of ether and kept at 5° overnight. The solid which had precipitated was collected (see below) and the filtrate extracted with 125 ml of 6 *N* hydrochloric acid in several portions. The acidic extracts were made strongly alkaline with sodium hydroxide and extracted with ether. After drying over magnesium sulfate, the ether solution was distilled through a Vigreux column, affording 26 g (35%) of amine, bp 100–115° (15 mm). Careful redistillation through an 18-in. spinning-band column gave 18 g (24%) of **N-allylaniline**, bp 85–87° (3 mm), lit.[27] bp 68–70° (1.3 mm). The **hydrochloride**, after recrystallization from ethanol–ether, melted at 118–119° (lit.[5] mp 110°); no melting point depression was observed when the hydrochloride was mixed with an authentic sample prepared from aniline and allyl bromide.

N,N′-Diphenyl-N-allylurea (XIII), prepared from the amine and phenyl isocyanate, melted at 84–85° after recrystallization from benzene–petroleum ether.

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.96; H, 6.48; N, 11.28.

The solid (4.0 g) which had crystallized from the ether solution of the reaction mixture was recrystallized from alcohol to give **1,3-diphenyl-4-methylimidazolidone-2 (VIII)**, mp 122–123°.

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.21; H, 6.42; N, 11.06.

Preparation of VIII. A. From 1,2-Dibromopropane.—A mixture of 20 g of 1,2-dibromopropane and 50 g of aniline was heated under reflux for 2 hr, poured into a mixture of ice and hydrochloric acid, and extracted with ether. The acidic solution was made alkaline and extracted with ether, and the extracts dried over magnesium sulfate and distilled, yielding 13.9 g (62%) of 1,2-dianilinopropane, bp 220–225° (0.5 mm).

To a cooled, stirred solution of this diamine in benzene was slowly added a benzene solution of 6.2 g of phosgene, followed by 10 g of pyridine in benzene, and the mixture was stirred 30 min at room temperature. The solution was filtered and the filtrate evaporated to dryness. Three recrystallizations of the residue from ethanol gave VIII, mp 123–124°. Infrared and nmr spectra were identical with those of the sample obtained from the allylphenylurethan rearrangement, and the mixture melting point was not depressed.

B. From N,N′-Diphenyl-N-allylurea (XIII).—A mixture of 3.0 g of XIII and 0.2 g of sodium hydride dispersion was heated for a few minutes at 160–180°, cooled, and extracted with boiling cyclohexane. The extracts were filtered hot and concentrated at reduced pressure, and the residual yellow oil crystallized from ethanol, affording 0.1 g of VIII. After four recrystallizations from ethanol it melted at 123–124°, alone or mixed with the product of part A.

Rearrangement of crotylphenylurethan (100 g) was accomplished by heating with sodium hydride as described above for the allyl derivative. From the ether solution of the reaction mixture, on standing overnight at 5°, 1–2 g of a solid (XIa) precipitated and was filtered. The filtrate was extracted with 6 *N* hydrochloric acid; evaporation of the ethereal solution left a mixture of oil and a solid (XIb).

The aqueous acid extracts were made basic with sodium hydroxide and extracted with ether. The combined extracts

(23) H. Pariselle, *Ann. Chim.* (Paris), [8] **24**, 339 (1911).

(24) A. F. Dobrjanski, R. Gutner, and M. Schtschigelskaja, *Zh. Obshch. Khim.*, **7**, 1319 (1937).

(25) E. Galand, *Bull. Soc. Chim. Belges*, **39**, 529 (1930).

(26) R. Willstäter and E. Sonnenfeld, *Ber.*, **46**, 2957 (1913).

(27) J. E. Hyre and A. R. Bader, *J. Amer. Chem. Soc.*, **80**, 437 (1958).

were dried and concentrated; vpc analysis[28a] showed that the amine mixture consisted of 8% aniline, 76% **N-phenyl-α-methallylamine** (VII), and 16% N-crotylaniline (VI). Distillation through a Vigreux column gave a small forerun, bp below 100° (15 mm), identified as aniline by its infrared spectrum and the formation of the hydrochloride, mp and mmp 197–198°. The main fraction, bp 100–115° (15 mm), weighed 43–49 g (56–64%). Vpc analysis[28b] showed this to be a mixture of 85% VII and 15% VI. Redistillation through an 18-in. spinning-band column gave pure VII, bp 107–111° (10 mm), 55–56° (0.35 mm) (lit. bp 130° (20 mm),[5] 63–65° (2 mm)[29]) in 34–45% yield. The infrared spectrum (neat) had N–H absorption at 2.88 and vinyl bands at 6.05, 10.02, and 10.80 μ. The nmr spectrum showed complex aromatic splitting at 6.3–7.2 (5 H), the characteristic vinyl pattern at 4.8–6.1 (3 H), a multiplet at 3.9 overlapping a broad N–H signal at 3.3 (total 2 H), and a doublet (J = 7 cps) at 1.2 ppm (3 H).

Anal. Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.90. Found: C, 81.64; H, 8.88.

The **hydrochloride** melted at 149–151° (lit.[5] mp 150°).

Anal. Calcd for $C_{10}H_{14}NCl$: C, 65.38; H, 7.68; N, 7.63. Found: C, 65.46; H, 7.68; N, 7.57.

The ***p*-nitrobenzoyl derivative**, recrystallized from heptane, melted at 67.5–68°.

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.50; H, 5.65; N, 9.58.

N,N'-Diphenyl-N-(α-methallyl)urea (XIV), prepared from VII and phenyl isocyanate, had mp 56–57° (recrystallized from ligroin).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.58; H, 6.88; N, 10.67.

The minor component of the amine mixture from the rearrangement was identified as **N-crotylaniline** (VI) from the nmr spectrum of a pure sample separated by preparative vpc. The spectrum (in $CDCl_3$) showed a doublet of triplets (3 H) at 1.66 ppm (olefinic methyl), two vinyl protons at 5.5–5.7, five aromatic protons at 6.4–7.2, and overlapping bands due to N–H and $-CH_2-$ (3 H) at 3.5–3.6 ppm. The infrared spectrum showed an N–H band at 2.94 μ and double-bond absorption at 6.2 and 10.4 μ.

Hydrogenation of amine VII by catalysis in ethanol resulted in extensive hydrogenolysis. In benzene, however, hydrogenation over palladium–charcoal gave **N-phenyl-*sec*-butylamine, hydrochloride** mp and mmp 137–140° (lit.[5] mp 136°).

1,3-Diphenyl-4,5-dimethylimidazolidone-2 (XI). Formation of XIa.—The solid which precipitated from the ether solution of the reaction mixture was recrystallized several times from ethanol to give colorless crystals, mp 152–153°.

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.27; H, 6.66; N, 10.37.

Formation of XIb.—The solid left by evaporation of the ether solution after extraction with acid was triturated with ether and recrystallized several times from ethanol, giving 1.0 g of crystals, mp 145–146°. A mixture of XIa and XIb melted at 137–139°.

Anal. Found: C, 76.39; H, 6.63; N, 10.55.

In all other runs than the one described, the imidazolidone isolated was a mixture of XIa and XIb and could not be separated into pure components by repeated recrystallization from ethanol or by chromatography on alumina.

Preparation of XI. A. From 2,3-Dibromobutane.—Using the procedure described above, 21.6 g of 2,3-dibromobutane (Eastman, mixture of stereoisomers) was treated with 50 g of aniline to yield 12.1 g (83%) of 2,3-dianilinobutane, bp 190–195° (1 mm). To a stirred, cooled solution of 5 g of this diamine in 50 ml of benzene was added dropwise a solution of 4 g of phosgene in 12 ml of benzene, followed by 3 ml of pyridine. The mixture was stirred for 30 min at room temperature, filtered, and evaporated to dryness. The residue (3.6 g) was recrystallized twice from alcohol to yield a mixture of XIa and XIb, mp 140–143°. The infrared and nmr spectra were identical with those of the mixture obtained from the rearrangement of crotylphenylurethan.

Anal. Found: C, 76.75; H, 6.96; N, 10.37.

B. From Urea (XIV).—A mixture of 5 g of XIV and 0.1 g of sodium hydride dispersion in mineral oil was heated to 100°. The mixture foamed and the temperature rose to 140°, where it was held for a few minutes. On cooling and dilution with alcohol a solid separated, which was filtered and recrystallized from alcohol. The yield was 0.9 g (18%) of a mixture of XIa and XIb, mp 136–139°, with nmr and infrared spectra identical with those of the product from part A. In the absence of sodium hydride, the only product isolated from heating XIV was *sym*-diphenylurea, mp and mmp 239–240°.

Reduction of XI.—A mixture of 650 mg of the imidazolidone (XI, mixture of isomers) and 500 mg of lithium aluminum hydride in 5 ml of tetrahydrofuran was stirred at room temperature for 6 hr and the excess hydride destroyed by the addition of ethyl acetate. When dilute hydrochloric acid was added to dissolve the salts a solid separated (350 mg), which was collected and recrystallized from ethanol to afford 1,3-diphenyl-4,5-dimethylimidazolidine (XII), mp 98–99°, apparently a single stereoisomer.

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.72; H, 7.97; N, 11.07.

Rearrangement of α-Methallylphenylurethan.—The phenylurethan (IV) was rearranged as described above for V, heating the mixture for 3 hr at 240°. Vpc analysis of the crude basic product showed it to be almost completely N-crotylaniline (VI), contaminated with 1–2% each of aniline and N-phenyl-α-methallylamine (VII). Distillation gave pure VI, bp 58–59° (0.1 mm) (lit.[30] bp 89–90° (3 mm)), in 60% yield. The infrared and nmr spectra were identical with those of the sample of VI obtained as the minor product of rearrangement of V.

Rearrangement of Δ²-Cyclohexenylphenylurethan.—A mixture of 7 g of the phenylurethan II and 0.15 g of a 55% sodium hydride dispersion in mineral oil was heated at 210–220° for 3 hr and worked up as described above. Small amounts of *sym*-diphenylurea, mp and mmp 239–240°, crystallized from the ether solution of the reaction mixture. Distillation of the basic fraction gave 0.5 g of aniline, bp 83–100° (25 mm), and 1.9 g (34%) of **N-phenyl-Δ²-cyclohexenylamine (III)**, bp 153–158° (25 mm). The hydrochloride, mp 172°, did not depress the melting point of an authentic sample prepared by the reaction[31] of Δ²-cyclohexenyl bromide with aniline.

Rearrangement of Optically Active II.—Optically active Δ²-cyclohexenol was prepared by the method of Denney, Napier, and Cammarata.[20] The alcohol, bp 92–97° (50 mm) and $[\alpha]^{23}D$ −5.88° (neat, 5-cm tube), furnished a phenylurethan, mp 107–108° and $[\alpha]^{23}D$ −7.52° (*c* 9.85, chloroform).

Rearrangement of the levorotatory phenylurethan was carried out just as described for the racemic compound and afforded the hydrochloride of III, mp 172°, $[\alpha]^{23}D$ 0°, and $[\alpha]^{23}_{300}$ +2.6° (c 1.84, chloroform).[32] The amine was regenerated from the hydrochloride and converted into N,N'-diphenyl-N-(Δ²-cyclohexenyl)-urea by treatment with phenyl isocyanate. The urea had mp 122–123° and $[\alpha]^{23}D$ −0.85 ± 0.57° (*c* 2.8, chloroform).[32]

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.87; H, 6.79; N, 9.44.

Alternate Preparation of III.—Following the procedure of Stork and White,[21] a solution of 2.1 g of Δ²-cyclohexenol, $[\alpha]^{25}D$ −15.2° (*c* 5.32, chloroform), in 10 ml of pyridine was treated with 5.0 g of 2,6-dichlorobenzoyl chloride and heated on the steam bath for 3 hr. After cooling, the mixture was saturated with gaseous ammonia, poured into 150 ml of 5% hydrochloric acid, and extracted with ether. The ether extracts were washed with dilute acid, water, and aqueous sodium bicarbonate, dried over potassium carbonate, concentrated, and diluted with 100 ml of petroleum ether (bp 30–60°). After standing 2 hr, the mixture was filtered through Celite, then through a short column of alumina, and distilled to afford 3.0 g of the dichlorobenzoate, bp 138–140° (0.5 mm) (lit.[21] bp 163–164° (1.6 mm)) and $[\alpha]^{22}D$ −14.6° (*c* 9.2, chloroform).

A mixture of 3.0 g of the dichlorobenzoate and 5.2 g of aniline was heated to 110° for 46 hr, cooled, and distributed between ether and 10% hydrochloric acid. The acidic aqueous layer was made basic with 6 *N* sodium hydroxide solution and extracted with ether. After the ether extracts were dried (potassium carbonate), fractional distillation gave 1.4 g of amine III,

(28) (a) On a 10-ft column of 15% Carbowax 20M (column temperature, 215°; flow rate, 110 cc of helium/min) the retention times were 3.6 min (aniline), 4.3 min (VII), and 7.2 min (VI). (b) With a 20-ft column of 30% SDC 710 on Chromosorb W, 45–60 mesh (column temperature, 220°; flow rate, 250 cc of helium/min), the retention times were 15 min (VII) and 23 min (VI).

(29) V. Wolf and D. Ramin, *Ann.*, **626**, 47 (1959).

(30) Y. A. Arbuzov, *Dokl. Akad. Nauk SSSR*, **63**, 531 (1948); *Chem. Abstr.*, **43**, 5403 (1949).

(31) Y. A. Arbuzov and T. A. Mastryukova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 665 (1952); *Chem. Abstr.*, **47**, 10493 (1953).

(32) We thank Dr. P. Laur and Mr. G. R. Krow for measuring these rotations on a Cary spectropolarimeter.

bp 88–90° (0.5 mm), which furnished a crystalline hydrochloride, mp 171–174°. The hydrochloride had rotations of $[\alpha]^{23}D$ +1.62° and $[\alpha]^{23}_{300}$ +10.8° (*c* 0.283, chloroform).[32] The infrared spectra of the free base and its hydrochloride were identical with those of authentic III and its hydrochloride.

Calculation of Asymmetric Induction.—The cyclohexenol sample, $[\alpha]D$ −5.88° (neat), used for the phenylurethan rearrangement is calculated to have $[\alpha]^{24}D$ −5.66° (*c* 5.54, chloroform), by comparing the rotation of its phenylurethan with that reported by Denney.[20] If no racemization occurred in the preparation and displacement of the allylic dichlorobenzoate, a sequence in which alcohol of $[\alpha]D$ −15.2° gave amine of $[\alpha]_{300}$ +10.8°, alcohol of $[\alpha]D$ −5.66° should have given amine of $[\alpha]_{300}$ +4.02° if asymmetric induction were quantitative. The experimental amine rotation of $[\alpha]_{300}$ +2.6° corresponds to 65% asymmetric induction.

Registry No.—(*S*)-(−)-Δ²-Cyclohexenol, 6426-24-2; II, 15619-41-7; III, 15619-43-9; III hydrochloride, 15619-44-0; N,N′-diphenyl-N-(Δ²-cyclohexenyl) urea, 15717-36-9; (*S*)-(−)-Δ²-cyclohexenol dichlorobenzoate, 15717-37-0; VI, 6246-96-4; VII, 15645-60-0; VII *p*-nitrobenzoyl derivative, 15717-39-2; VIII, 15645-61-1; XI, 15645-62-2; 1,2-dianilinopropane, 15717-40-5; XII, 15645-63-3; XIII, 15645-64-4; XIV, 15717-41-6.

Phenylcyclohexadienes

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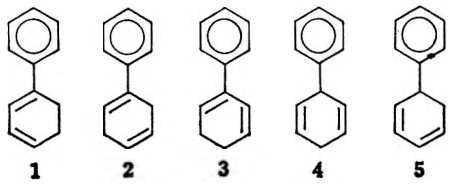
A detailed examination of the published methods for the reduction of biphenyl, *via* the alkali metal adducts, has shown that the phenylcyclohexadienes **3** and **4** may be formed depending on the conditions employed. The more reduced compounds, phenylcyclohexene and phenylcyclohexane, may also be produced. Dienes **1** and **2** can be prepared by the elimination of certain groups from the substituted 1-phenylcyclohexenes (**6**). Dienes **1**–**4** were isolated by glpc and the structures assigned on the basis of ultraviolet, mass, and nuclear magnetic resonance spectroscopic measurements.

During a study of the photochemistry of sodium tetraphenylborate[1] we isolated a compound the analytical data for which indicated that it was one of the phenylcyclohexadienes **1**–**5** and probably **2**.



1 **2** **3** **4** **5**

In the last 40 years, reports of compounds **1**–**4** have appeared but conclusive evidence for the structural assignments has been lacking. Although calculations predict **4** as the product resulting from the addition of alkali metals to biphenyl,[2] the Russian workers,[3] on the basis of spectral evidence, have reported **2** as the product. Their report was claimed as a correction of the earlier work of Schlenk and Bergmann[4] on the addition of lithium to biphenyl. These authors, on the basis of chemical evidence, assigned the structure **4** to the diene which they obtained. In 1939, Hückel and Bretschneider[5] studied the reaction between sodium and biphenyl in liquid ammonia at −70°. The adduct was decomposed with methanol and the diene **3** was claimed as the product on the basis of chemical evidence. In 1956, a further study was conducted[6] and, under conditions that the authors state are not appreciably different from those used previously, a diene was isolated to which the structure **4** was assigned. In this latter reaction the adduct was decomposed with ammonium chloride after a much shorter reaction time More recently, this preparation has been repeated by DeTar and Long[7] to provide an authentic sample of **4** tc compare with the product obtained by the thermal decomposition of benzoyl peroxide in benzene. In an unrelated study,[8] isomer **1** has been reported to be formed by the dehydration of 3-phenyl-2-cyclohexen-1-ol over alumina at 350°. It was pointed out, however, that rearrangement under these conditions was possible.

Our unknown diene (A) had *m/e* 156, mp 89°, λ_{max} 249 mμ (ε 9300), which suggested a phenylcyclohexadiene type **2**. However, the Russian workers[3] claim **2** as a liquid with λ_{max} 250 mμ (ε 12,000). In addition the melting point and ultraviolet spectrum of the unknown compared favorably with the physical data reported for **1**—mp 85°, λ_{max} 248 mμ (ε 9000).[8] We have therefore repeated the earlier preparations of these dienes. In view of the contradictions mentioned earlier, we have isolated *all* the products from the diene syntheses by preparative glpc and examined each peak by mass and ultraviolet spectrometry. Peaks with *m/e* values of 156 were then examined by high-resolution mass spectrometry and elemental analyses were carried out on the more stable compounds. The homogeneity of each diene was tested on a second glpc column. Assignments were made on the basis of the spectroscopic data and in some cases deuterium tagging facilitated the interpretation. By avoiding chemical methods, we hoped to eliminate the possibilities of isomerization and oxidation to biphenyl.

For the reduction of biphenyl, the method of Egerov, *et al.*,[3] yielded phenylcyclohexane, a phenylcyclohexadiene (B), and 1-phenylcyclohexene; the method of Hückel and Bretschneider[5] yielded a similar mixture, together with another phenylcyclohexadiene (C), and the method of Hückel and Schwen[6] yielded the phenylcyclohexadiene (B). Biphenyl was recovered in each

(1) J. L. R. Williams, J. C. Doty, P. J. Grisdale, T. H. Regan, and D. G. Borden, *Chem. Commun.*, 109 (1967); *J. Amer. Chem. Soc.*, **89**, 5153 (1967).
(2) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 425.
(3) Iv. P. Egorov, E. P. Kaplan, Z. I. Letina, V. A. Shliapochnikov, and A. D. Petrov, *J. Gen. Chem. USSR*, **28**, 3284 (1958).
(4) W. Schlenk and E. Bergmann, *Ann.*, **463**, 92 (1928).
(5) W. Hückel and H. Bretschneider, *ibid.*, **540**, 173 (1939).
(6) W. Hückel and R. Schwen, *Chem. Ber.*, **89**, 150 (1956).
(7) D. F. DeTar and R. A. J. Long, *J. Amer. Chem. Soc.*, **80**, 4742 (1958).
(8) G. F. Woods, N. C. Bolgiano, and D. E. Duggan, *ibid.*, **77**, 1800 (1955).

preparation. The ultraviolet spectrum of **4** is reported to be similar to that of toluene[7] and indeed the diene (B) isolated from the above reactions had such a spectrum (Table I).

TABLE I

ULTRAVIOLET SPECTRA OF THE PHENYLCYCLOHEXADIENES AND RELATED COMPOUNDS IN CYCLOHEXANE

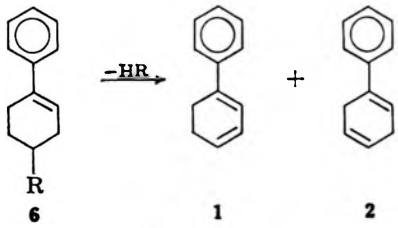
Compd		λ_{max}, mμ(ε)	Comments
1	1-Phenyl-1,3-cyclohexadiene	303 (13,800)	Broad band
2	1-Phenyl-1,4-cyclohexadiene	249 (9,300)	Broad band
3	2-Phenyl-1,3-cyclohexadiene	276 (8,140[a])	Broad band
4	3-Phenyl-1,4-cyclohexadiene	262 (465)	Peaks at 242, 249, 256, 269 mμ
7	1,3-Diphenyl-1,3-cyclohexadiene[b]	314 (11,250)[c]	Broad band

[a] This diene is very sensitive to air; this ε value may be low. [b] See ref 10. [c] This diene had mp 93–95° (lit.[10] mp 98–99°). Our sample had some *m*-terphenyl as impurity; this ε value is low.

The nmr spectrum of B showed protons in the ratios of 1 benzylic, 2 allylic, 4 olefinic, to 5 aromatic, so that the structure must be either **4** or **5**. Initially, we chose **5** since the sum of the two benzylic allylic coupling constants was 18 Hz, suggesting a vicinal relationship. However, the absence of absorption in the ultraviolet characteristic of a 1,3-diene contradicted this and a report in the literature suggested that coupling constants across five bonds in 1,4-cyclohexadienes may be unusually large.[9] Reduction of 4,4′-dideuteriobiphenyl by the Hückel–Bretschneider method[5] provided a sample of B-d_2. The nmr spectrum of this sample had only one allylic proton whose signal was now a skewed *doublet* of multiplets (peak separation 9 Hz). Compound B was therefore unequivocably assigned the structure **4**.

The nmr spectrum of C-d_2, isolated from the same reduction, showed three olefinic protons but only three allylic protons. This enabled us to assign the structure **3** to diene C.

Our failure to isolate a sample of **2** by the Russian method[3] prompted us to attempt to prepare a sample by elimination reactions on various substituted cyclohexene derivatives of type **6**.



6 **1** **2**

a, R = Cl
b, R = $OCOCH_3$
c, R = $OCOC_6H_5$
d, R = $OCSSCH_3$

We had anticipated that such a reaction would produce **1** as the major product and **2** as the minor product. This would be particularly convenient since **1** had been described as a solid, mp 85°.[8] We examined the elimination of hydrogen chloride from **6a**, when attempts to pyrolyze the esters **6b** and **6c** failed to yield dienes. Under rather drastic basic conditions this dehydrohalogenation reaction furnished a mixture of two dienes in poor yield. The fact that a similar mixture was obtained by the pyrolysis of the xanthate ester **6d** led us to assume that no unexpected rearrangements had taken place. The minor product had mp 89° after isolation by preparative glpc and was assigned the structure **2** on the basis of its ultraviolet spectrum, λ_{max} 250 mμ (*cf.* phenylcyclohexene, 250 mμ). It was identical in every respect with the unknown (A). The major product had mp 39° after preparative glpc and was assigned the structure **1** by a process of elimination and because it showed extended ultraviolet absorption (λ_{max} 303 mμ). The nmr spectra (Figure 1) support all these assignments and show the expected ratios of various protons. The methylene absorption of compound **2** falls in a multiplet centered at δ 2.90, at a significantly lower field than **1** or **3**, in keeping with the assignment of the methylenes as diallylic. The olefinic protons fall in two distinct groups: a 1 H multiplet at δ 5.98 and a 2 H multiplet at δ 5.72. The chemical-shift difference between the methylene protons of **1** and **3** on the one hand and **2** on the other is consistent with that found for 1,3-cyclohexadiene (δ 2.1) and 1,4-cyclohexadiene (δ 2.6). The chemical shifts of the methylene protons of **1** and **3** are also in agreement with the shift we have measured for the known compound, 1,3-diphenyl-1,3-cyclohexadiene[10] (δ 2.50). Attempts to repeat the work of Woods, Bolgiano, and Duggan[8] on the dehydration of 3-phenyl-2-cyclohexen-1-ol have failed and only biphenyl has been obtained. As judged by physical constants, the product which Woods and coworkers isolated corresponds to our structure **2**.

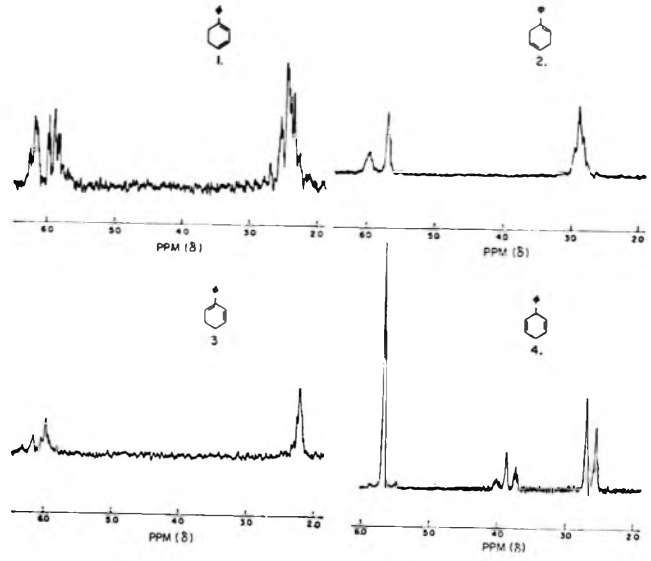


Figure 1.—Portions of the nmr spectra of compounds **1**–**4** in CCl_4.

The work reported here illustrates the fact that in most cases (the work of Hückel and Schwen[6] excepted) the alkali metal reduction of biphenyl leads to a complex mixture of products. This complexity has no doubt contributed to the incorrect assignments in the early work. The most characteristic physical properties of the dienes **1**–**4** are their ultraviolet spectra. These data are listed for reference in Table I.

The present assignments are in accord with the ultraviolet spectral data recorded for the open-chain analogs of **1** and **3**. 1-Phenylbutadiene absorbs at

(9) L. J. Durham, J. Studebaker, and M. J. Perkins, *Chem. Commun.*, 456 (1965).

(10) G. F. Woods, and I. W. Tucker, *J. Amer. Chem. Soc.*, **70**, 2174 (1948).

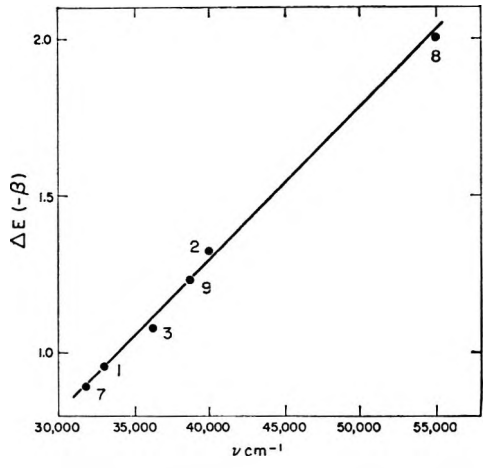


Figure 2.—Calculated transition energies (ΔE) *vs.* observed values (ν) for the compounds indicated.

longer wavelength (279 mμ) than does the 2 isomer (241 mμ).[11]

The transition energies calculated in terms of β by the HMO method[2] for the conjugated dienes correlate well with the experimental values. A plot of such a correlation is shown in Figure 2. 1,3-Diphenyl-1,3-cyclohexadiene (**7**) was prepared according to the method of Woods and Tucker.[10] Cyclohexene (**8**) and 1,3-cyclohexadiene (**9**) are included for reference. An excellent correlation is obtained, which may however be fortuitous, because of the assumptions inherent in the HMO method and our assumption that the interplanar angle between the phenyls and the diene ring can be ignored.

Owing to the limited availability of these dienes, we have made no attempt to study their chemistry, although their sensitivity to oxygen has been observed. The order toward oxidation in air is **3** > **1** > **4** > **2**. Diene **3** decomposes on exposure overnight to air at room temperature, whereas **2** is stable for prolonged periods at room temperature.

Experimental Section

The various spectra were determined on Cary Model 15 (uv), Perkin-Elmer Infracord (ir), and Varian A-60 (nmr) instruments. Tetramethylsilane was used as an internal standard for the nmr measurements. Mass spectra were determined with a 60° sector-type instrument. High-resolution mass spectra were determined with a CEC 21-110B instrument. Both mass spectrometric instruments were equipped with heated inlet systems.[12]

4-Chloro-1-phenylcyclohexene (6a).—4-Chlorocyclohexanone[13] (26 g, 0.2 mol) in dry ether (50 ml) was treated at room temperature, with stirring, with phenylmagnesium bromide solution (0.22 mol). When an oily precipitate appeared, dry benzene (50 ml) was added and the addition of the Grignard solution completed. The resulting solution was stirred for 30 min at room temperature, poured into crushed ice, and acidified with dilute hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ether (100 ml). The combined extracts were dried and evaporated. The pale yellow oily residue showed a strong OH band in the infrared spectrum at 3300 cm^{-1}. This crude 1-phenylcyclohexanol was dehydrated by heating it under reflux in aqueous oxalic acid (200 ml, 15%) for 2 hr. Extraction of the crude product with chloroform and subsequent evaporation of the chloroform extract yielded a pale yellow liquid. It was fractionated through a 6-in. column packed with glass helices to yield the desired cyclohexene derivative (**6a**): 12.6 g (33%); bp 102–105° (0.2 mm); $n^{25}D$ 1.5765. The nmr spectrum shows $\delta^{acetone-d_6}$ 1.8–2.8 (doublet of multiplets, 6 H), 4.1–4.5 (multiplet 1 H), 5.85–6.1 (multiplet 1 H), 7.1–7.5 (multiplet 5 H).

Anal. Calcd for $C_{12}H_{13}Cl$: C, 74.8; H, 6.8; Cl, 18.4. Found: C, 74.7; H, 6.8; Cl, 18.5.

4-Benzoyloxy-1-phenylcyclohexene (6c).—4-Benzoyloxycyclohexanone[14] (150 g, 0.69 mol) was treated with phenylmagnesium bromide in exactly the same manner as that described for 4-chlorocyclohexanone, to yield the crude cyclohexanol derivative (190 g). This oily solid was dehydrated by heating it with 15% oxalic acid solution under reflux for 40 hr to yield the oily solid, crude cyclohexene derivative (6c). A 25-g portion of this material was triturated with petroleum ether (bp 66–75°) and the solid residue crystallized from ethanol–water to yield white needles of 4-benzoyloxy-1-phenylcyclohexene, 4.25 g (18%), mp 114–116°. The nmr spectrum showed δ^{CDCl_3} 1.8–2.8 (doublet of multiplets, 6 H), 5.1–5.6 (multiplet, 1 H), 5.8–6.2 (multiplet, 1 H), 7.1–7.6 (multiplet, 8 H), 7.9–8.2 (multiplet, 2 H).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5. Found: C, 82.0; H, 6.5.

4-Phenyl-3-cyclohexen-1-ol.—Crude 4-benzoyloxy-1-phenylcyclohexene (100 g) in ethanol (300 ml) and water (150 ml) was treated with 40% sodium hydroxide solution (35 ml) and the solution heated under reflux for 1 hr. This solution was then evaporated to near-dryness and the residue extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to give a pale yellow solid, which was crystallized from petroleum ether (bp 65–75°) as colorless needles, 23 g (36% based on the benzoyloxycyclohexanone), mp 82–84°. The nmr spectrum showed δ^{CDCl_3} 1.5–2.8 (doublet of multiplets, plus a signal at δ 2.47, exchangeable H with D_2O, total 7 H), 2.7–4.2 (multiplet 1 H), 5.8–6.1 (multiplet, 1 H), 7.1–7.5 (multiplet, 5 H).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.8; H, 8.0. Found: C, 82.9; H, 8.0.

The acetate (**6b**) had bp 105–110° (0.3 mm), $n^{25}D$ 1.5488.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.7; H, 7.4. Found: C, 77.4; H, 7.6.

S-Methylxanthate Ester of 4-Phenyl-3-cyclohexen-1-ol (6d).—4-Phenyl-3-cyclohexen-1-ol (5 g, 0.028 mol) in dry ether (100 ml) was converted into the lithium salt by the addition of phenyllithium (16 ml, 1.8 *M* solution). Dry carbon disulfide (3.5 g) was then added and after 1.5 hr the solution was treated with methyl iodide (10 g) and stirred overnight. The mixture was filtered. The filtrate was washed with water, dried, and evaporated at room temperature to yield the crude xanthate ester as a yellow oil, 5.0 g (76%). An analytical sample purified by chromatography with benzene–hexane on alumina was obtained as a yellow oil. The nmr spectrum showed δ^{CCl_4} 1.9–2.8 (triplet of multiplets, 9 H), 5.6–6.1 (doublet of multiplets, 2 H), 7.1–7.4 (multiplet, 5 H).

Anal. Calcd for $C_{14}H_{16}OS_2$: C, 63.6; H, 6.1; S, 24.2. Found: C, 63.9; H, 6.3; S, 24.0.

Chromatographic Analysis of the Phenylcyclohexadienes (1–4).—The two techniques which were employed for the analysis, separation, and isolation of the dienes (1–4) produced in the present experiments are described in the following section. Method A, an F & M Model 720 gas chromatograph, equipped with a 1/4 in. × 8 ft long column, packed with 20% SE 30 on Anakrom ABS at 110°, was used. The detector and injector temperatures were 300°. A helium flow of 150 ml/min was used. Method B, an Aerograph Model A90-P gas chromatograph, equipped with a 1/4 in. × 10 ft long column, packed with 25% Carbowax 20M on dimethyldichlorosilane-treated Chromosorb W, was used. The column was maintained at 200°. The helium flow was 60 ml/min. The detector and injector temperatures were 230°.

Under these conditions, the adjusted retention times given in Table II were obtained.

1-Phenyl-1,3-cyclohexadiene (1) and 1-Phenyl-1,4-cyclohexadiene (2). A. From Xanthate Ester (6d).—The crude xanthate ester **6d** was injected into the heated inlet of a gas chromatograph and the resulting pyrolysis products were analyzed under conditions of method A. The composition of the mixture

(11) I. N. Nazarov, Yu. A. Titov, and A. I. Kuznetsova, *Izvest. Akad. Nauk SSSR*, 1270 (1959).

(12) The system is described by V. J. Caldecourt, *Anal. Chem.*, **27**, 1670 (1955), but was constructed of glass.

(13) R. Grewe, W. Lorenzen, and L. Vining, *Chem. Ber.*, **87**, 793 (1954).

(14) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).

TABLE II

Compound	Retention time, min: Method A	Method B
Phenylcyclohexane	16.0	8.5
3-Phenyl-1,4-cyclohexadiene (4)	16.0	11.4
1-Phenylcyclohexene	25.3	13.4
2-Phenyl-1,3-cyclohexadiene (3)	21.5	15.8
Biphenyl	21.0	20.1
1-Phenyl-1,3-cyclohexadiene (1)	25.3	18.1
1-Phenyl-1,4-cyclohexadiene (2)	28.4	20.1

was analyzed as 80 ± 2% 1-phenyl-1,3-cyclohexadiene (1) and 20 ± 2% 1-phenyl-1,4-cyclohexadiene (2). In some runs, only traces of biphenyl were formed; in others, as much as 20% was observed. The use of lower injection port and detector temperatures (230°) had no effect on this ratio. Compound 1 melted at 38–39°. Since 1 reacted rapidly with oxygen, routine elemental analyses of several samples gave consistently low C and H values. The high-resolution mass spectrum of a freshly isolated sample indicated a parent ion peak at *m/e* 156.0929 (duplicate measurements). $C_{12}H_{12}$ requires 156.0939. Diene 2 melted at 89–90°.

Anal. Calcd for $C_{12}H_{12}$: C, 92.3; H, 7.7. Found: C, 91.9; H, 8.0.

B. From the Chloro Compound (6a).—A mixture of 4-chloro-1-phenylcyclohexene (1.0 g) and potassium *t*-butoxide (1.0 g) in *t*-butyl alcohol (50 ml) was heated under reflux for 16 hr. The solution was then poured into cold water and the solid which was isolated by filtration and dried weighed 0.2 g and melted at 40–52°. Glpc analysis (method A) indicated a mixture of biphenyl (3%), 1-phenyl-1,3-cyclohexadiene (80%), and 1-phenyl-1,4-cyclohexadiene (17%).

Alkali Metal Reduction of Biphenyl. A. Sodium in Liquid Ammonia.—Biphenyl was reduced with sodium in liquid ammonia according to the method of Hückel and Bretschneider.[5] The crude product was chilled overnight to remove some unchanged biphenyl. The liquid portion of the chilled product was analyzed by glpc (method B). In addition to unreacted biphenyl, there was obtained phenylcyclohexane, 21%; 3-phenyl-1,4-cyclohexadiene, 4, 52%; 1-phenylcyclohexene, 20%; and 2-phenyl-1,3-cyclohexadiene, 3, 6%. In a second run, traces of a $C_{12}H_{16}$ isomer (mass spectrum *m/e* 160) were eluted after 8.1 min. Diene 3 was extremely sensitive to air, but a freshly isolated sample had a parent ion peak at *m/e* 156.0939 in its high-resolution mass spectrum. $C_{12}H_{12}$ requires *m/e* 156.0939. Diene 4 had $n^{25}D$ 1.5595.

Anal. Calcd for $C_{12}H_{12}$: C, 92.3; H, 7.7. Found: C, 92.6; H, 8.0.

B. Sodium in Liquid Ammonia.—Reduction of biphenyl according to the method of Hückel and Schwen[6] and treatment as just described yielded 3-phenyl-1,4-cyclohexadiene (4) in addition to recovered biphenyl. No other dienes or reduced products were observed.

C. Lithium in Ether.—Reduction of biphenyl with lithium in ether according to the method of Egorov, *et al.*,[3] and treatment as described yielded, in addition to unreacted biphenyl, phenylcyclohexane, 19%; 3-phenyl-1,4-cyclohexadiene, 4, 72%; and 1-phenylcyclohexene, 9%. No diene 3 was detected.

Phenylcyclohexadienes 3-d_2 and 4-d_2.—4,4′-Dideuteriobiphenyl, prepared by treatment of the corresponding dilithio derivative[16] with D_2O, was reduced as under A to yield the dideuterio compounds corresponding to the hydrogen analogs described earlier.

Registry No.—1, 15619-32-6; 2, 13703-52-1; 3, 15619-34-8; 4, 4794-05-2; 6a, 15619-36-0; 6b, 15619-37-1; 6c, 15619-38-2; 6d, 15619-39-3; 7, 10345-94-5; 4-phenyl-3-cyclohexen-1-ol, 15619-51-9.

Acknowledgment.—The authors would like to thank Messrs. G. P. Happ and D. P. Maier for determining the mass spectra.

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Preparation of Mixed Organotin Chlorides by the Redistribution Reaction[1a]

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Under appropriate reaction conditions, organotin dichlorides with two different alkyl or aryl groups can be prepared in good yields by redistribution between organotin trichlorides and tetraalkyltins or trialkyltin chlorides. Some of these organotin dichlorides have been converted into trialkyltin chlorides with three different alkyl groups by alkylation with tetraalkyltins. The following organotin dichlorides have been prepared: butylmethyl, isobutylmethyl, methylphenyl, ethylphenyl, propylphenyl, butylethyl, and butylpropyl. In addition, butylethylmethyl, butylmethylvinyl, butylethylvinyl, and butyldimethyltin chlorides have been prepared.

Organotin halides with two or more different alkyl or aryl groups are usually prepared by alkylation of an organotin halide with Grignard reagent, followed by cleavage of one of the alkyl groups with a halide,[2] *e.g.*, eq 1 and 2.

In many cases special care has to be taken in the cleavage step in order to avoid a mixture of organotin halides (*e.g.*, in eq 2 RR'_2SnX and $R_2R'SnX$). This proved to be extremely difficult, especially when R and R′ are very similar, for example ethyl and butyl. The

$$R_2SnCl_2 \xrightarrow{2R'MgX} R_2R'_2Sn \quad (1)$$

$$R_2R'_2Sn \xrightarrow{X_2} RR'_2SnX \quad (2)$$
$$(X = Cl, Br, I)$$

preparation of organotin dihalides of the type $RR'SnX_2$ or monohalides of the type RR′R″SnX is even more difficult. In order to prepare the latter, a series of alkylations and cleavage reactions has to be carried out.[2] The stepwise addition of different groups by Grignard reagents in most cases is impossible.[2]

A more convenient synthesis of these halides seemed to be desirable and would be a prerequisite in the investigation of asymmetric organotin compounds.

The most frequently applied method for the preparation of organotin halides is the redistribution reaction, first investigated by Kocheshkov.[3,4]

Recently it was observed that these reactions (eq 3–5)

$$3R_4Sn + SnX_4 \longrightarrow 4R_3SnX \quad (3)$$

$$R_4Sn + SnX_4 \longrightarrow 2R_2SnX_2 \quad (4)$$

$$R_4Sn + 3SnX_4 \longrightarrow 4RSnX_3 \quad (5)$$

(1) (a) This research was supported by the National Science Foundation under Grant GP-5285; (b) R. S. thanks the Deutschen Forschungsgemeinschaft for a travel grant.

(2) For a review, see R. K. Ingham, S. D. Rosenberg, and H. Gilman, *Chem. Rev.*, **60**, 459 (1960).

(3) K. A. Kocheshkov, *Ber.*, **62**, 996 (1929).

(4) K. A. Kocheshkov, *ibid.*, **66**, 1661 (1933).

occur stepwise and that it is possible to interrupt them before the final products were formed.[5-7] The first step in eq 4 is the exchange of an alkyl group and a halogen (eq 6), then at higher temperature the two products react to form the organotin dihalide (eq 7).[5]

$$R_4Sn + SnX_4 \longrightarrow R_3SnX + RSnX_3 \quad (6)$$

$$R_3SnX + RSnX_3 \longrightarrow 2R_2SnX_2 \quad (7)$$

Although it has been stated[2] that these redistribution reactions are "undesirable for the preparation of organotin halides in which all of the organic groups are not identical," they have not been investigated in detail.

We find that under appropriate conditions redistributions analogous to that of eq 7 can provide an easy route for the preparation of mixed organotin dihalides, $RR'SnX_2$. In some cases even organotin monohalides with three different alkyl or aryl groups can be prepared. All reactions were monitored by glpc, which proved to be especially valuable, because in some cases further reactions occurred during attempted isolation of the products.

The alkylation of butyltin trichloride with tetramethyltin was exothermic yielding trimethyltin chloride and butylmethyltin dichloride. However, some dimethyltin dichloride and butyldimethyltin chloride were formed (eq 8).

$$Me_4Sn + BuSnCl_3 \longrightarrow Me_3SnCl + BuMeSnCl_2 + Me_2SnCl_2 + BuMe_2SnCl \quad (8)$$

On the other hand, when the tetramethyltin was added slowly to the butyltin trichloride at 0°, the formation of dimethyltin dichloride and butyldimethyltin chloride could be suppressed. Upon distillation, however, large amounts of the two latter compounds were again obtained. It was shown in additional experiments that on heating trimethyltin chloride with butylmethyltin dichloride to 150°, a very rapid reaction occurred, leading to an equilibrium mixture in which about 40% of the trimethyltin chloride had transferred a second methyl group to the butylmethyltin chloride to form dimethyltin dichloride and butyldimethyltin chloride (eq 9). (The same equilibrium

$$Me_3SnCl + BuMeSnCl_2 \rightleftharpoons Me_2SnCl_2 + BuMe_2SnCl \quad (9)$$

mixture was formed from dimethyltin dichloride and butyldimethyltin chloride.)

Butylmethyltin dichloride was obtained in good yield when we used trimethyltin chloride instead of tetramethyltin to alkylate butyltin trichloride (eq 10).

$$Me_3SnCl + BuSnCl_3 \longrightarrow Me_2SnCl_2 + BuMeSnCl_2 \quad (10)$$

Only negligible amounts of side products were formed.

Furthermore, combination of eq 8 and 10 proved to be possible; butylmethyltin dichloride was obtained in 99% yield by adding 1 mol of tetramethyltin to 2 mol of butyltin trichloride at 0° and heating subsequently to 180°.

With isobutyltin trichloride similar results were obtained; alkylation with tetramethyltin led only to a 32% yield of isobutylmethyltin dichloride because of the reaction between trimethyltin chloride and isobutylmethyltin dichloride during distillation. Alkylation of the isobutyltin trichloride with trimethyltin chloride provided isobutylmethyltin dichloride in 80% yield.

Tetramethyltin reacted exothermically with phenyltin trichloride upon addition of the tetramethyltin slowly at 0°. Only trimethyltin chloride and methylphenyltin dichloride were formed. The trimethyltin chloride had to be removed at low temperature in order to avoid further alkylation of the methylphenyltin dichloride which was isolated in 85% yield. Ethylphenyltin dichloride and phenyl-*n*-propyltin dichloride were prepared in a similar manner from phenyltin trichloride and the tetraethyl or tetra-*n*-propyltin. Distillation of the alkylphenyltin dichlorides was not attempted since other mixed alkylaryltin halides disproportionated on distillation.[8,9]

Tetraalkyltins and trialkyltin halides with higher alkyl groups are less reactive toward organotin trichlorides than tetramethyltin and trimethyltin chloride. For this reason it was possible to prepare butylethyltin dichloride in 86% yield from tetraethyltin and butyltin trichloride. No detectable amounts of diethyltin dichloride or butyldiethyltin chloride were formed.

In those cases where the reaction products, R_3SnCl and $RR'SnCl_2$, have boiling points too close together to separate by distillation, the products can be isolated after conversion into the oxides. This was shown with the mixture of tri-*n*-propyltin chloride and butylpropyltin dichloride which resulted from the alkylation of butyltin trichloride with tetra-*n*-propyltin.

Butylethyltin dichloride could be alkylated with tetramethyltin to butylethylmethyltin chloride in 76% yield. In the same way, a methyl group can be introduced into other dialkyltin dichlorides, such as in butylmethyltin dichloride.

Tetravinyltin transfers one vinyl group to an organotin dichloride at 20°. Thus, upon reaction with butylmethyltin dichloride only butylmethylvinyltin chloride and trivinyltin chloride were obtained. On distillation of the reaction mixture, however, the starting materials were recovered nearly quantitatively. This is due to an equilibrium (eq 11) which is shifted upon distillation to the left.

$$Vin_4Sn + BuMeSnCl_2 \rightleftharpoons BuMeVinSnCl + Vin_3SnCl \quad (11)$$

Experimental Section

Boiling points are uncorrected. Carbon, hydrogen, and chlorine analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Tin analyses were carried out by oxidation to stannic oxide with 1:1 (volumes) mixture of concentrated sulphuric and nitric acid in quarz test tubes as described.[10] For analytical glpc separations, an F & M Model 720 temperature programmed gas chromatograph was used, with a flow rate of 60 cc of helium/min, using an 8 ft column of 10% silicone rubber SE 30 on Chromosorb W 60–80. Preparative glpc separations were carried out on an F & M Model 775 using a 13 ft by 0.25 in. i.d. column with the same packing material as above.

Materials.—Tetramethyltin, trimethyltin chloride, and butyltin trichloride were gifts from M & T Chemicals. The other tetraalkyltins were prepared from stannic chloride with trialkylaluminum;[10] vinylmagnesium chloride[11] with stannic chloride

(5) W. P. Neumann and G. Burkhardt, *Ann.*, **663**, 11 (1963).
(6) Metal and Thermit Corp., British Patent 739,883.
(7) E. V. van den Berghe and G. P. van der Kelen, *J. Organometal. Chem.*, **6**, 522 (1966).
(8) S. D. Rosenberg and A. J. Gibbons, Jr., *J. Amer. Chem. Soc.*, **79**, 2138 (1957).
(9) D. Seyferth, *ibid.*, **79**, 2133 (1957).
(10) W. P. Neumann, *Ann.*, **663**, 157 (1962).
(11) S. D. Rosenberg, A. J. Gibbons, Jr., and H. E. Ramsden, *J. Amer. Chem. Soc.*, **79**, 2137 (1957).

TABLE I

PREPARATION OF MIXED ORGANOTIN CHLORIDES BY THE REDISTRIBUTION REACTION

Starting materials				Products (% yield)[a]			Conditions	
							Temp, °C	Time, hr
Me_3SnCl		$BuSnCl_3$		$BuMeSnCl_2$ (88)		Me_2SnCl_2 (96)	180–190	3.5
Me_3SnCl		*i*-$BuSnCl_3$		*i*-$BuMeSnCl_2$ (80)		Me_2SnCl_2 (97)	180–190	3.5
Me_4Sn		*i*-$BuSnCl_3$		*i*-$BuMeSnCl_2$ (32)		Me_3SnCl (54)	0	
				i-$BuMe_2SnCl$		Me_2SnCl_2		
Me_4Sn		$BuSnCl_3$		$BuMeSnCl_2$ (37)		Me_3SnCl (59)	0	
				$BuMe_2SnCl_2$		Me_2SnCl_2	0	
Me_4Sn		$2BuSnCl_3$		$2BuMeSnCl_2$ (99)		Me_2SnCl_2	Then 180	2
$2Me_4Sn$		$BuSnCl_3$		$BuMe_2SnCl$		$2Me_3SnCl$	75–85	3
Me_4Sn		$BuMeSnCl_2$		$BuMe_2SnCl$ (91)		Me_3SnCl (96)	75–85	3
Me_3SnCl	+	$BuMeSnCl_2$	⇄	$BuMe_2SnCl$	+	Me_2SnCl_2	150	5
Me_4Sn		$PhSnCl_3$		$MePhSnCl_2$ (85)		Me_3SnCl (99)	0	
Et_4Sn		$PhSnCl_3$		$EtPhSnCl_2$ (98)		Et_3SnCl	20	1
$Prop_4Sn$		$PhSnCl_3$		$PropPhSnCl_2$ (69)		$Prop_3SnCl$ (98)	60	4.5
							25	3
Et_4Sn		$BuSnCl_3$		$BuEtSnCl_2$ (86)		Et_3SnCl (83)	Then 100	3
$Prop_4Sn$		$BuSnCl_3$		$PropBuSnCl_2$ (62)		$Prop_3SnCl$	180–190	2
Me_4Sn		$BuEtSnCl_2$		$BuEtMeSnCl$ (76)		Me_3SnCl (91)	120–130	4
							20	4
Vin_4Sn	+	$BuMeSnCl_2$	⇄	$BuMeVinSnCl$	+	Vin_3SnCl	60	2
							20	4
Vin_4Sn	+	$BuEtSnCl_2$	⇄	$BuEtVinSnCl$	+	Vin_3SnCl	60	2

[a] Yield after isolation. The actual yields were higher in many cases.

gave tetravinyltin. Organotin halides were prepared from tetraalkyltin and stannic chloride by redistribution (see Table I).[5]

For distillations, either a 30-cm, vacuum-jacketed, silvered column (column 1) or 12-cm heated column (column 2), both packed with stainless steel helices, or a 55-cm, vacuum-jacketed, silvered column, packed with glass helices (column 3), all equipped with heads for liquid–liquid separations, were used unless otherwise indicated.

Butylmethyltin Dichloride from Trimethyltin Chloride and Butyltin Trichloride.—Trimethyltin chloride (59.8 g, 0.3 mol) and 84.7 g (0.3 mol) of butyltin trichloride were heated for 1.5 hr to 180 to 190° and maintained at this temperature for 2 hr. Glpc (100 to 270°, 10°/min) showed that the reaction mixture contained dimethyltin dichloride and butylmethyltin dichloride and a very small amount of butyldimethyltin chloride. The mixture was separated by distillation through column 1, yielding 63.1 g (96%) of dimethyltin dichloride, bp 103–105° (40 mm), solidifying in the condenser. Fraction 2, bp to 116° (16 mm) (9.2 g), contained the rest of the dimethyltin dichloride, the butyldimethyltin chloride, and some butylmethyltin dichloride. Fraction 3, bp 117–119° (16 mm), consisted of 99% pure butylmethyltin dichloride (by glpc, as described above) and 69.2 g (88%) was obtained. It crystallized on cooling, mp 42–43°.

Anal. Calcd for $C_5H_{12}SnCl_2$: C, 22.94; H, 4.62; Cl, 27.09; Sn, 45.35. Found: C, 22.96; H, 4.60; Cl, 27.24; Sn, 45.2.

Butylmethyltin Dichloride from Tetramethyltin and Butyltin Trichloride.—Tetramethyltin (71.4 g, 0.4 mol) was added over a period of 1 hr at 0° to 225.7 g (0.8 mol) of butyltin trichloride. The reaction mixture was stirred for 1 hr at 20° and heated for 2 hr to 180°. Glpc (as above) indicated that only dimethyltin dichloride and butylmethyltin dichloride were formed. Distillation as above yielded 207.5 g (99.4%) of pure butylmethyltin dichloride.

Isobutylmethyltin Dichloride from Trimethyltin Chloride and Isobutyltin Trichloride.—Trimethyltin chloride (39.9 g, 0.2 mol) and 56.4 g (0.2 mol) of isobutyltin trichloride were treated as described for butylmethyltin dichloride. Glpc (100 to 270°, 10°/min) indicated that only dimethyltin dichloride and isobutylmethyltin dichloride were formed. Distillation through column 1 yielded 42.5 g (97%) of dimethyltin dichloride, bp 108–109° (52 mm), which solidified in the condenser, 9.9 g of a fraction containing dimethyltin dichloride, isobutyldimethyltin chloride, and isobutylmethyltin dichloride, bp to 124° (27 mm), and 41.6 g (80%) of isobutylmethyltin dichloride, bp 124–125° (27 mm), of 99.5% purity (by glpc), mp 41°.

Anal. Calcd for $C_5H_{12}SnCl_2$: C, 22.94; H, 4.62; Cl, 27.09; Sn, 45.35. Found: C, 22.75; H, 4.56; Cl, 26.96; Sn, 45.4.

Isobutylmethyltin Dichloride from Tetramethyltin and Isobutyltin Trichloride.—To 56.4 g (0.2 mol) of isobutyltin trichloride were added 35.8 g (0.2 mol) of tetramethyltin at 0° with magnetic stirring over a period of 2 hr. Glpc (100 to 270°, 10°/min) showed that *ca.* 16% of the isobutylmethyltin dichloride, formed in the first step, had reacted further to form isobutydimethyltin chloride. The mixture was distilled through column 1 yielding 21.5 g (54%) of pure trimethyltin chloride, bp 93° (91 mm). Then the boiling point rose slowly to 127° (32 mm). The fractions collected (total 47.5 g) consisted of mixtures containing trimethyltin chloride, dimethyltin dichloride, isobutyldimethyltin chloride, and isobutylmethyltin dichloride. Pure isobutylmethyltin dichloride distilled at 127° (32 mm) in 32% yield (16.5 g), mp 41°. Qualitatively the same results were obtained when *n*-butyltin trichloride was used instead of isobutyltin trichloride.

Methylphenyltin Dichloride from Tetramethyltin and Phenyltin Trichloride.—To 30.2 g (0.1 mol) of phenyltin trichloride 17.9 g (0.1 mol) of tetramethyltin were added under cooling to 0° and magnetic stirring over a period of 0.5 hr. Stirring was continued for an additional hour at 0°. The reaction mixture consisted of trimethyltin chloride and methylphenyltin dichloride, along with negligible amounts of other products. Trimethyltin chloride (22.3 g) was distilled off and collected in a trap cooled with liquid nitrogen at 0.1 mm by heating the flask slowly to 50°. It contained some higher boiling material and was redistilled, bp 154° (760 mm). The residue of the first distillation was nearly pure methylphenyltin dichloride (23.0 g, 85%); after recrystallization from hexane it had mp 43°.

Anal. Calcd for $C_7H_8SnCl_2$: C, 29.84; H, 2.86; Cl, 25.17; Sn, 42.13. Found: C, 29.73; H, 2.71; Cl, 24.90; Sn, 42.3.

When separation of the reaction mixture was attempted at higher pressure (30 mm), further reaction occurred between trimethyltin chloride and methylphenyltin dichloride.

Ethylphenyltin Dichloride from Tetraethyltin and Phenyltin Trichloride.—Tetraethyltin (23.5 g, 0.1 mol) and 30.2 g (0.1 mole) of phenyltin trichloride were treated under the same conditions as described for methylphenyltin dichloride. After stirring for 1 hr at 20°, the reaction mixture consisted of triethyltin chloride and ethylphenyltin dichloride. Triethyltin chloride 24.1 g (100%) was distilled at 0.002 mm up to a bath temperature of 50° and collected in a trap cooled with liquid nitrogen. The residue, 29.1 g (98%) of nearly pure ethylphenyltin dichloride, solidified on cooling and was recrystallized from hexane, mp 66°. (Ladenburg gives a melting point of 45°.[12])

Anal. Calcd for $C_8H_{10}SnCl_2$: C, 32.49; H, 3.41; Cl, 23.97; Sn, 40.13. Found: C, 32.34; H, 3.40; Cl, 24.13; Sn, 40.2.

Phenylpropyltin Dichloride from Tetrapropyltin and Phenyltin Trichloride.—Phenyltin trichloride (30.2 g 0.1 mol) and 29.1 g

(12) A. Ladenburg, *Ann.*, **159**, 251 (1871).

(0.1 mol) of tetrapropyltin were stirred for 1 hr at 25°. Glpc (100 to 290°, 15°/min) showed considerable amounts of unreacted tetrapropyltin. Even after 1.5 hr at 60° the reaction was not yet complete. After additional heating for 3 hr to 60°, 34.3 g of tripropyltin chloride were distilled at 0.01 mm up to a bath temperature of 90°. It contained some higher boiling compounds and was redistilled at 12 mm. The residue, 25.0 g of 95% pure phenylpropyltin dichloride, solidified upon cooling and was recrystallized from heptane at −20 to −30° to yield 20.4 g (69%), mp 37–39°. After several additional recrystallizations from heptane the melting point rose to 40°.

Anal. Calcd for $C_9H_{12}SnCl_2$: C, 34.89; H, 3.90; Cl, 22.89; Sn, 38.31. Found: C, 34.77; H, 4.11; Cl, 23.01; Sn, 37.9.

Butylethyltin Dichloride from Tetraethyltin and Butyltin Trichloride.—Upon mixing 47.0 g (0.2 mol) of tetraethyltin and 56.4 g (0.2 mol) of butyltin trichloride, a slightly exothermic reaction occurred. After stirring for 3 hr at 25° and 3 hr at 90–100°, the mixture consisted only of triethyltin chloride and butylethyltin dichloride as shown by glpc (100 to 270°, 10°/min). Distillation over column 1 yielded 40.2 g (83%) of triethyltin chloride, bp 126–127° (56 mm). Then the boiling point rose slowly from 98 to 126° (14 mm). Several fractions (totaling 14.2 g) taken showed, in addition to triethyltin chloride, increasing amounts of butylethyltin dichloride. This compound (45.5 g) was then distilled without a column, bp 126–127° (14 mm). It solidified on cooling. An additional 2.1 g was obtained from fraction 2 upon cooling to 0° to yield 47.5 g (86%), mp 39° (from hexane).

Anal. Calcd for $C_6H_{14}SnCl_2$: C, 26.13; H, 5.12; Cl, 25.71; Sn, 43.04. Found: C, 26.30; H, 5.35; Cl, 25.90; Sn, 43.3.

Butylpropyltin Dichloride from Butyltin Trichloride and Tetrapropyltin.—Butyltin trichloride (42.3 g, 0.15 mol) and 43.7 g (0.15 mol) tetrapropyltin were mixed and heated slowly for 2 hr to 180–190° and maintained at this temperature for 1 hr. After cooling, the reaction products were taken up in ether and converted into the oxides with 10% sodium hydroxide solution. The solid butylpropyltin dioxide was separated by filtration, washed with ether, and shaken with an ethereal solution of concentrated hydrochloric acid to form the dichloride. This was purified by converting it into the oxide a second time. The resulting dichloride was free from tripropyltin chloride but was contaminated by about 10% of dipropyltin dichloride. This was removed by distillation through column 3 (mp 80°) leaving 99% pure butylpropyltin dichloride (by glpc, 75 to 290°, 10°/min) which was distilled without a column to yield 26.8 g (63%), bp 140–142° (15 mm) and mp 44–45°. A sample was recrystallized from petroleum ether (bp 30–70°), mp 46–47° (lit.[13] mp 67–68°).

Anal. Calcd for $C_7H_{16}SnCl_2$: C, 29.01; H, 5.57; Cl, 24.47; Sn, 40.95. Found: C, 29.06; H, 5.58; Cl, 24.65; Sn, 40.7.

The bis(tripropyltin)oxide was converted into tripropyltin chloride by hydrochloric acid and isolated by distillation.

Butyldimethyltin Chloride from Butylmethyltin Dichloride and Tetramethyltin.—Tetramethyltin (17.9 g, 0.1 mol) and 26.2 g (0.1 mol) butylmethyltin dichloride were heated for 3 hr to 75–85°. Glpc (120 to 280°, 10°/min) indicated that only trimethyltin chloride and butyldimethyltin chloride were present along with negligible amounts of dimethyltin dichloride. Distillation through column 2 yielded 19.1 g (96%) of trimethyltin chloride (bp 83–84° (75 mm)), 0.6 g of a mixture of trimethyltin chloride and butyldimethyltin chloride (bp up to 105° (30 mm)), and 21.9 g (91%)) of butyldimethyltin chloride (99.5% purity, bp 108° (30 mm), $n^{20}D$ 1.4971. The residue (1.4 g) consisted of *ca.* 60% of butyldimethyltin chloride and 40% higher boiling materials.

Anal. Calcd for $C_6H_{15}SnCl$: C, 29.86; H, 6.27; Cl, 14.69; Sn, 49.18. Found: C, 29.72; H, 6.25; Cl, 14.49; Sn, 48.8.

(13) Z. M. Manulkin, *J. Gen. Chem. USSR*, **20**, 2004 (1950); *Chem. Abstr.*, **45**, 5611 (1951).

Butyldimethyltin Chloride from Tetramethyltin and Butyltin Trichloride.—Tetramethyltin (35.8 g, 0.2 mol) and 28.2 g (0.1 mol) of butyltin trichloride gave, by the same procedure as described above, analogous results, *i.e.*, 0.2 mol of trimethyltin chloride and 0.1 mol of butyldimethyltin chloride.

Butylethylmethyltin Chloride from Butylethyltin Dichloride and Tetramethyltin.—Tetramethyltin (17.9 g, 0.1 mol) and 27.6 g (0.1 mol) of butylethyltin dichloride were heated for 4 hr to 120–130°. Glpc (100 to 270°, 10°/min) indicated a few per cent of unreacted tetramethyltin, trimethyltin chloride, butylethylmethyltin chloride, and negligible amounts of one other product. No butylethyltin dichloride was left over. Distillation through column 1 yielded 18.0 g (91%) of trimethyltin chloride, bp 72–74° (47 mm); then the boiling point rose slowly to 127° (35 mm). Fractions collected, totaling 5.2 g, contained mixtures of trimethyltin chloride, small amounts of an unknown compound, and butylethylmethyltin chloride. The latter compound (19.4 g, 76%) was distilled at 127–128° (35 mm) (99.5% purity). The residue contained butylethylmethyltin chloride and higher boiling compounds.

Anal. Calcd for $C_7H_{17}SnCl$: C, 32.93; H, 6.71; Cl, 13.89; Sn, 46.48. Found: C, 33.13; H, 6.75; Cl, 13.68; Sn, 46.3.

Reaction between Tetravinyltin and Butylmethyltin Dichloride.—Tetravinyltin (34.0 g, 0.15 mol) and 39.2 g (0.15 mol) of butylmethyltin dichloride were stirred for 4 hr at 20° and for an additional 2 hr at 60–70°. Glpc (100 to 270°, 10°/min) showed that only trivinyltin chloride and butylmethylvinyltin chloride were formed. A trace of starting materials was left over. Upon distillation through column 3, 31.6 g (93%) of tetravinyltin were recovered, bp 54–56° (20 mm). A higher boiling fraction (5.7 g) contained tetravinyltin, trivinyltin chloride, butylmethylvinyltin chloride, and butylmethyltin dichloride. The main part of the latter was in the residue and was distilled without column to yield 32.5 g (83%), bp 117–119° (16 mm). It contained no detectable amounts of vinyl groups (ir spectroscopy). The butylmethylvinyltin chloride can be isolated by preparative glpc (100 to 170°, 2°/min), bp 96° (16 mm).

Anal. Calcd for $C_7H_{15}SnCl$: C, 33.19; H, 5.97; Cl, 13.99; Sn, 46.85. Found: C, 33.39; H, 6.09; Cl, 14.02; Sn, 46.4.

Reaction between Tetravinyltin and Butylethyltin Dichloride.—Stoichiometric amounts of tetravinyltin and butylethyltin dichloride were treated as above. Glpc (100 to 270°, 10°/min) showed that most of the starting materials had reacted to form only trivinyltin chloride and butylethylvinyltin chloride. Upon attempted distillation redistribution back to the starting materials occurred. The butylethylvinyltin chloride was isolated by preparative glpc (180° isothermal). Under these conditions, the redistribution back occurred only to a small extent.

Anal. Calcd for $C_8H_{17}SnCl$: C, 35.94; H, 6.41; Cl, 13.26. Found: C, 35.86; H, 6.42; Cl, 13.42.

Reaction between Trimethyltin Chloride and Butylmethyltin Dichloride.—Trimethyltin chloride (1.99 g, 0.01 mol) and 2.61 g (0.01 mol) of butylmethyltin dichloride were heated for 5 hr to 150°. Glpc (100 to 250°, 10°/min) showed that 40–45% of the starting materials had reacted to form dimethyltin chloride and butyldimethyltin dichloride. On prolonged heating, this amount did not increase. Equimolar amounts of dimethyltin dichloride and butyldimethyltin chloride formed, on heating for 4 hr to 150°, the same equilibrium mixture with 55–60% trimethyltin chloride.

Registry No.—$BuMeSnCl_2$, 15649-24-8; *i*-$BuMeSnCl_2$, 15649-25-9; $MePhSnCl_2$, 15649-26-0; $EtPhSnCl_2$, 15649-27-1; $PropPhSnCl_2$, 15649-28-2; $BuEtSnCl_2$, 15649-29-3; $PropBuSnCl_2$, 15649-30-6; $BuMe_2SnCl$, 15649-31-7; BuEtMeSnCl, 15649-32-8; BuMeVinSnCl, 15649-33-9; BuEtVinSnCl, 15649-34-0.

Electronic Spectra of Lithium Salts of Substituted Fluorenes. Evidence for the π-Inductive Effect of Unshared Pairs[1]

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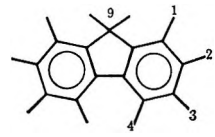
Electronic absorption spectra have been recorded for lithium salts of twelve substituted fluorenes in cyclohexylamine. The compounds include 2-fluorofluorene, 2-dimethylaminofluorene, the five isomeric methylfluorenes, and the five methoxyfluorenes. Relative to lithium fluorenyl itself, salts bearing a substituent at the 1, 2, or 4 position show a hypsochromic shift, whereas those substituted at the 3 or 9 position show a bathochromic shift. Coulson's treatment correctly predicted the direction of the spectral shift for all five methylfluorenyl anions, but on the basis of σ-inductive effects it failed for every anion bearing a lone-pair substituent. The results provide evidence for the electron-repelling π-inductive effect of lone-pair substituents, recently proposed by Clark, Murrell, and Tedder.

The spectral shifts produced when hydrogen is replaced by methyl in an aromatic hydrocarbon have been studied extensively. In even-alternant hydrocarbons (those which have no odd-membered rings), substitution of methyl for hydrogen invariably results in a shift to longer wavelength. In contrast, in the nonalternant hydrocarbon azulene, the direction of the spectral shift for the absorption in the visible region depends on the position at which the methyl is introduced. A methyl group at position 1 or 5 produces a shift to longer wavelength, but methyl at 2, 4, or 6 results in a shift to shorter wavelength.[2]

By comparison to the wealth of reports on stable hydrocarbon compounds, the electronic spectra of hydrocarbon ions have received little attention; until recently the literature contained almost no information about the effect of substituents on the spectra of these ions. Studies of allyl and benzyl cations have shown that introduction of methyl into an odd-alternant hydrocarbon cation can result in either a bathochromic or a hypsochromic shift, depending on the position of the substituent,[3] just as in the case of the neutral species azulene. Waack and Doran recorded spectra of a number of methyl-substituted allyl and benzyl anions and found the direction of the spectral shift to be position dependent.[4] Thus, the effect of methyl substituents on electronic spectra has been examined in neutral hydrocarbon compounds of the even and nonalternant types and in odd-alternant hydrocarbon cations and anions, but studies of this kind on nonalternant hydrocarbon ions have not previously been done.

Streitwieser and his coworkers reported electronic absorption spectra for lithium and cesium salts of a number of nonalternant hydrocarbon anions. These included salts of fluorene, the three benzfluorenes, and 9-methyl-, 9-phenyl-, and 9-benzylfluorene, as well as salts of several other hydrocarbons,[5] but did not include any fluorene derivatives substituted in the 1, 2, 3, or 4 position. This study deals with the relation of spectral shift to position of substitution for lithium salts of twelve substituted fluorenes, with cyclohexylamine as solvent, and substituents including methyl and three groups of the lone-pair type, fluoro, dimethylamino, and methoxy.



The effect of lone-pair substituents on the spectra of even alternants is, like the effect of methyl, well documented. Substitution of halogen, –OR, –SR, or $-NR_2$ for hydrogen on either ethylene or benzene causes a decrease in electronic transition energy.[6] Only a few examples in odd and nonalternant systems have been reported. Halogen at the 1 or 3 position of azulene[7] and amino, dimethylamino, methoxy, or chloro at the *ortho* or *para* position of triphenylmethyl cation[3c] produces all bathochromic shifts. Our search of the literature uncovered only one example of a hypsochromic shift caused by a lone-pair substituent; substitution of chlorine for *meta* hydrogen in triphenylmethyl cation shifts λ_{max} from 431 to 412 mμ.[3c] Clark, Murrell, and Tedder hypothesized that a major and previously unrecognized effect of lone-pair groups is electron donation by a π-inductive mechanism,[8] and suggested that decisive evidence for their hypothesis would be observation of increases in electronic transition energy produced by lone-pair substituents in nonalternant systems. A major objective of our study of spectra of the five isomeric methoxyfluorenyl anions was to provide this test for the π-inductive effect.

Experimental Section

Materials Used.—Several of the compounds used were obtained from the Aldrich Chemical Co. The ones which melted below the literature values were purified by recrystallization from isooctane (spectranalyzed). These samples had the following melting points:[9] 2-fluorofluorene, mp 99.0–100.0°

(1) Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) P. A. Plattner, *Helv. Chim. Acta*, **24**, 283E (1941); P. A. Plattner and E. Heilbronner, *ibid.*, **30**, 910 (1947).

(3) J. A. Grace and M. C. R. Symons, *J. Chem. Soc.*, 958 (1959); (b) J. Rosenbaum and M. C. R. Symons, *ibid.*, 1 (1961); (c) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Org. Chem.*, **19**, 155 (1954).

(4) R. Waack and M. A. Doran, *J. Phys. Chem.*, **68**, 1148 (1964).

(5) (a) A. Streitwieser, Jr., and J. I. Brauman, *J. Amer. Chem. Soc.*, **85**, 2633 (1963). (b) A. Streitwieser, Jr., J. I. Brauman, J. H. Hammons, and A. H. Pudjaatmaka, *ibid.*, **87**, 384 (1965).

(6) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp 175–177 and 248–252.

(7) E. Heilbronner in "Non-benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, Inc., New York, N.Y., 1959, pp 237, 244.

(8) D. T. Clark, J. N. Murrell, and J. M. Tedder, *J. Chem. Soc.*, 1250 (1963); D. T. Clark, *Chem. Commun.*, 390 (1966).

(9) Melting points were taken on a Thomas–Hoover apparatus, and are uncorrected.

(lit.[10] mp 98°); 1-methoxyfluorene, mp 85.0–86.0° (lit.[11] mp 85–86°); 2-methoxyfluorene, mp 109.5–110.5° (lit.[12] mp 110°); 3-methoxyfluorene, mp 83.0–84.0° (lit.[13] mp 84–85°); 4-methoxyfluorene, mp 77.0–78.0° (lit.[14] mp 76.5–77.5°). Melting points of three additional samples[15] were as follows: 1-methylfluorene, mp 84.0–85.0° (lit.[16] mp 85°); 2-methylfluorene, mp 100.5–102.5° (lit.[12] mp 101.5–102.5°); 2-dimethylaminofluorene, 179.5–180° (lit.[17] mp 180.0–180.5°).

The method of DeTar and coworkers[18,19] was used to prepare 3-methyl-9-fluorenone; 1.6 g of this ketone was reduced by the Huang-Minlon modification[20] of the Wolff–Kishner reaction to yield 1.4 g (94%) of 3-methylfluorene, mp 83–85°. Recrystallization from isooctane raised the melting point to 87.5–88.5° (lit.[21] mp 88°). Preparation of 4-methylfluorene was accomplished by a five-step sequence. Commercial 9-fluorenone-4-carboxylic acid (Aldrich Chemical Co.) was reduced to fluorene-4-carboxylic acid by the method of Morrison.[22] The acid was converted to the acid chloride by treatment with thionyl chloride, and the unpurified acid chloride was reduced in the usual way with lithium aluminum hydride to yield 4-hydroxymethylfluorene (75.3% yield from the acid) of mp 126.5–128.5° (lit.[23] mp 129–130°). Treatment with thionyl chloride coverted the alcohol to 4-chloromethylfluorene,[23] and the chloride was reduced to 4-methylfluorene with lithium hydride and lithium aluminum hydride by the method of Streitwieser and Langworthy,[24] mp 70.0–72.0° (lit.[25] mp 69–70°). Preparation of 9-methylfluorene was accomplished by reaction of 9-fluorenone with methylmagnesium iodide, and reduction of the resulting 9-methyl-9-fluorenol with zinc dust and palladium in acetic acid,[26] mp 45.0–46.0° (lit.[27] mp 46–47°). 9-Methoxyfluorene was prepared by lithium aluminum hydride reduction of 9-fluorenone, conversion of 9-fluorenol into 9-bromofluorene with hydrobromic acid in acetic acid, and reaction of the bromide with silver nitrate in methanol,[28] mp 43.0–44.0° (lit.[28] mp 43.5°).

The cyclohexylamine used (Eastman Kodak Co.) was purified by fractional distillation, bp 134.2–134.8° (760 mm). *n*-Butyllithium (Foote Mineral Co.) was approximately 1.6 *M* in heptane.

Spectra.—The solutions were prepared in Pyrex vessels having the following features: (1) a straight-bore stopcock and outer joint at the top for connection to a vacuum system, (2) a side arm with a straight-bore stopcock for injection of butyllithium, and (3) a side arm with a rectangular Pyrex absorption cell. Path lengths of the cells on the three reactors used were calibrated with standard solutions of K_2CrO_4–KOH and found to be 9.97 mm, 10.02 mm, and 1.02 mm (10-mm Pyrex cell with 9.0-mm silica spacer). A quantity of a hydrocarbon was weighed on a Cahn Model M-10 electrobalance, dissolved in isooctane (spectranalyzed), and introduced into the weighed vessel with a syringe. The vessel was attached to a vacuum system and the isooctane was removed. About 5 ml of dry cyclohexylamine was transferred under vacuum into the vessel directly from a stock solution of lithium cyclohexylamide in cyclohexylamine. The vessel was charged to atmospheric pressure with argon and removed from the vacuum line. A syringe was used to inject 0.1 ml of butyllithium solution through a rubber septum and the adjacent stopcock. The volume of the solution was determined from the weight of solution added and the known density of cyclohexylamine.

Preliminary scans of the spectra were made on a Beckman DB recording spectrophotometer. The λ_{max} and ϵ_{max} values reported were determined from more precise measurements on a Beckman DU instrument which had previously been adjusted for maximum accuracy of wavelength calibration. Absorbances were corrected for absorbance by the cell and solvent.

Results

All of the fluorene derivatives used in this study were readily soluble in cyclohexylamine containing lithium cyclohexylamide, giving solutions of substituted fluorenyl anions which absorbed in the region 400–600 mμ; the range below 400 was not examined, as solutions of lithium cyclohexylamide in cyclohexylamine are known to absorb below about 375.[5a] The stability of the anion solutions was evident from the fact that repeated scans showed no change in absorption over periods as long as 10 days. At least two runs were made for each salt, and ϵ_{max} values were reproduced to better than 10% in every case except those of 2-methylfluorenyl and 9-methoxyfluorenyl anions, for which two runs gave results differing by 12 and 14%, respectively. The three extinction coefficients found for lithium fluorenyl and the three for lithium 9-methylfluorenyl were approximately 7% lower than the values reported by Streitwieser and Brauman.[5a] Solutions of fluorene and 9-methylfluorene (as well as those of a number of other fluorene derivatives) in lithium cyclohexylamide–cyclohexylamine are known[5a] to obey Beer's law, indicating that the reaction in eq 1 goes to

$$RH + C_6H_{11}NHLi \longrightarrow RLi + C_6H_{11}NH_2 \qquad (1)$$

completion. Solutions of 3- and 4-methylfluorene and 1-, 2-, 3-, and 4-methoxyfluorene in this medium proved to obey Beer's law; the concentration ranges used with the remaining hydrocarbons were too small to permit any conclusion about the relation between concentration and absorbance.

As the data in Table I show, all of these lithium fluorenyl salts have three maxima between 435 and 555 mμ, spaced from 20 to 40 mμ apart. In every case the middle one is the most intense, with ϵ_{max} values ranging from 937 to 1780, and the long wavelength one is the least, with ϵ_{max} values lying between 591 and

TABLE I

Lithium salt of	λ_{max}, mμ (ϵ_{max})
Fluorene	454 (1040), 480 (1220), 514 (788)
	452 (1080), 477 (1300), 510 (827)[a]
1-Methylfluorene	449 (1210), 472 (1500), 503 (1020)
1-Methoxyfluorene	440 (1470), 461 (1620), 489 shoulder (979)
2-Methylfluorene	450 (910), 476 (982), 505 shoulder (592)
2-Methoxyfluorene	441 (974), 461 (1030), 489 shoulder (643)
2-Fluorofluorene	443 (805), 470 (973), 501 (591)
2-Dimethylaminofluorene	439 (928), 462 (937), 490–495 shoulder
3-Methylfluorene	461 (1070), 489 (1210), 522 (773)
3-Methoxyfluorene	475 (1070), 497 (1260), 528 (838)
4-Methylfluorene	441 (1260), 465 (1480), 496 (958)
4-Methoxyfluorene	428 shoulder (1450), 448 (1780), 474 (1250)
9-Methylfluorene	482 (848), 514 (1080), 553 (706)
	480 (905), 512 (1130), 551 (785)[a]
9-Methoxyfluorene	487 shoulder (972), 513 (1100), 542 shoulder (758)

[a] Values of Streitwieser and Brauman.[5a]

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1250. In a few cases one or the other of the side peaks appears only as a shoulder. The maxima are broad and cannot be located with an accuracy greater than ±1 or 2 mμ. The three λ_{max} values found for the fluorenyl anion and the three for 9-methylfluorenyl differ slightly from those given by Streitwieser and Brauman, all of them being shifted 2–4 mμ to longer wavelength from the earlier values. Several of the salts showed end absorption in the 400–415-mμ region.

Substitution of methyl or methoxy for hydrogen at the 3 position results in a shift of λ_{max} (for the middle of the three peaks) to longer wavelength by 9 and 17 mμ, respectively. At the 9 position these substituents also produce a bathochromic shift, but the effect is more pronounced; the shifts are 34[5a] and 32 mμ. In contrast, methyl or methoxy at position 1 or 4 causes a shift to shorter wavelength; the shifts are as follows: 1-methyl-, 8; 1-methoxy-, 19; 4-methyl-, 15; and 4-methoxy-, 32 mμ. Similarly, all four 2-substituted salts show hypsochromic shifts relative to lithium fluorenyl itself: 2-methyl-, 4; 2-methoxy-, 19; 2-fluoro-, 10; and 2-dimethylamino-, 18 mμ. The hypsochromic shifts found for 2-fluoro-, 2-dimethylamino-, and 1-, 2-, and 4-methoxyfluorenyl anions appear to be the first known examples of increases in transition energy produced in a nonalternant hydrocarbon system by a lone-pair substituent.

Discussion

The fact that these lithium fluorenyl salts all have the same π system suggests that their spectra all involve the same electronic transition or transitions. This suggestion receives strong confirmation from the extremely close similarity of the λ_{max} and ϵ_{max} values and the general shapes of the spectra.

Attempts were made to resolve each of the experimental curves into three overlapping Gaussian curves centered near the observed absorption maxima. In each case good agreement was obtained at the long wavelength end, but discrepancies at the short wavelength end were substantial, and agreement in this region could be accomplished only by inclusion of one or two more Gaussian curves (see Figure 1 for comparison of the observed and calculated spectra of 9-methylfluorene). The resolved curves were spaced at intervals of approximately 1350 cm^{-1}, the intervals being slightly larger at the high-frequency end and smaller at the low-frequency end. These results strongly support the suggestion of Streitwieser and Brauman[5a] that the spectra of lithium fluorenyl salts result from a single electronic transition, with vibronic interaction involving several vibrational levels of the electronic excited state. All 13 salts show very nearly the same spacing, 1400 ± 60 cm^{-1}, between the two Gaussians at the high-frequency end, indicating that the same vibrational mode produces the fine structure in each spectrum.

The transition which produces absorption in the visible range for the fluorenyl anion may be assumed to be promotion of an electron from the highest filled π molecular orbital to the lowest empty one. This transition is allowed by symmetry.

The intensities for the substituted fluorenes show a moderate dependence on the position and nature of the substituent. These effects would be expected to arise from three principal causes. (1) Substituents cause shifts in frequency of absorption and intensity is directly dependent on the frequency. (2) Substituents cause small perturbations in the molecular orbitals at each of the atoms in the π system, thereby affecting the dipole strength, which in turn affects the intensity. (3) The atomic orbitals of the substituent may contribute slightly to the molecular orbitals of the π system and thus make a contribution to the dipole strength. None of these factors correlated the observed changes in even a qualitative way with Hückel wave functions, however; rationalization of the changes in terms of molecular orbital theory would appear to require more refined calculation methods.

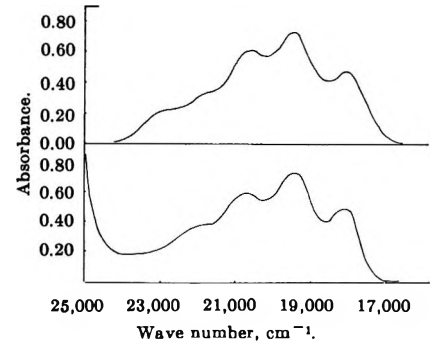

Figure 1.—The upper curve was generated by summation of five Gaussian curves. All five curves were assumed to have the same width at half-height. Taken in order from lower to higher wavenumber, the relative intensities are 1.0, 1.5, 1.2, 0.6, and 0.4, and the maxima of the individual curves are spaced 2.8, 2.4, 2.4, and 2.3 units apart. If the parameter of width at half-height is also varied, slightly better agreement can be obtained, especially at the low wavenumber end. The pronounced difference between the experimental and calculated curves around 25,000 cm^{-1} suggests the occurrence of a second electronic transition (probably either the $\psi_6 \rightarrow \psi_8$ or the $\psi_7 \rightarrow \psi_9$ transition), which is not taken account of in the calculated curve. The lower curve represents the spectrum of lithium 9-methylfluorenyl.

The Methylfluorenyl Salts.—Coulson[29] treated substituent effects on transition energies in π-system hydrocarbons by perturbation methods, and derived an expression for the inductive effect of a substituent at atom r (see eq 2), where c_{ir} and c_{fr} are the coefficients

$$h\Delta\nu = (c_{fr}^2 - c_{ir}^2)\delta\alpha_r \qquad (2)$$

of atomic orbital of atom r in MO's i and f (MO i is the one *from* which the electron is promoted, and MO f is the one *to* which it is promoted), and $\delta\alpha_r$ is the effective change in the Coulomb integral of atom r as a result of the inductive effect of the substituent. The quantity $\delta\alpha_r$ is positive for substituents which are electron donating relative to hydrogen, and negative for those which are electron withdrawing. Application of this expression to the substitution of methyl for hydrogen in azulene correctly predicts the direction of the shift in the visible spectrum for all five isomers; the quantitative correlation, however, is mediocre, no doubt due at least in part to the limitations of the Hückel eigenfunctions.

The method is equally successful for the methylfluorenyls examined in the present work. The assumption that the electron is promoted from ψ_7 to ψ_8, together with the use of the appropriate HMO coefficients, leads to the prediction that methyl at C-3 or C-9 will

(29) C. A. Coulson, *Proc. Phys. Soc.* (London), **A65**, 933 (1952).

lower the transition energy; methyl at C-1, C-2, or C-4 is predicted to raise the energy. The predictions are in agreement with experimental observation for all five isomers.[30] As is apparent from the data in Table II, the correlation is not quantitative, and the use of MO's obtained by the ω technique gives little improvement. It would be interesting to apply Coulson's method, making use of eigenfunctions obtained by less approximate MO techniques, especially those which take electron repulsion into account.

TABLE II

Substituent	ν_{max},[a] cm^{-1}	$c_{fr}^2 - c_{ir}^2$, HMO[b]	$c_{fr}^2 - c_{ir}^2$, ω technique[c]
H	19,430		
1-Methyl	19,760	+0.022	+0.025
1-Methoxy	20,340		
2-Methyl	19,600	+0.108	+0.088
2-Methoxy	20,340		
3-Methyl	19,070	−0.087	−0.065
3-Methoxy	18,780		
4-Methyl	20,050	+0.137	+0.112
4-Methoxy	20,980		
9-Methyl	18,060	−0.347	−0.290
9-Methoxy	18,120		

[a] The frequency given here is that of the maximum of the longest wavelength Gaussian curve, as obtained by resolution of the experimental curve into individual Gaussians. The estimated uncertainty is ±50 cm^{-1}. Because all eleven salts show virtually the same spacing between the two longest wavelength Gaussians, essentially the same shifts can be obtained directly from the λ_{max} values for the middle, or most intense, maximum for each salt. [b] Values calculated from data in A. Streitwieser, Jr., and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Vol. 1, Pergamon Press Inc., New York, N. Y., 1965, pp 247–250. [c] We thank Mr. J. Gatewood and Mr. J. Fahnestock for writing the computer program used for these calculations.

The complete qualitative success of this approach for the nonalternant methylfluorenyl anions is in striking contrast to the observations of Waack and Doran[4] on methyl-substituted allyl and benzyl anions. The direction of the spectral shift in these odd-alternants is incorrectly predicted in three of the four ions studied, 1-methylallyl, 2-methylallyl, and 4-methylbenzyl. The predicted direction is correct for α-methylbenzyl anion, but the low magnitude of the shift, 3 mμ, is in complete disagreement with the very large decrease in charge density at the α position, 0.57 unit. In view of the fact that Hückel wave-functions are generally less accurate for nonalternants than for odd-alternants, it is remarkable that Coulson's treatment works for the former in the two systems studied to date, methylazulenes and methylfluorenyl anions, and not for the latter. That the shift is correctly predicted for nonalternants in ten cases out of ten suggests that the agreement is not fortuitous.

The Methoxyfluorenyl Salts.—Coulson's approach dissects the total effect of a substituent into an inductive and a conjugative contribution. If the inductive effect predominates, the direction of the shift is dependent both on the position of the group and its electronegativity. As the σ-inductive effect of methoxy is electron withdrawal relative to hydrogen, $\delta\alpha_r$ will be negative. The term $c_{fr}^2 - c_{ir}^2$ is negative for positions 3 and 9, and positive for 1, 2, and 4. Thus, the transition is predicted to shift to higher energy for substitution of methoxy at C-3 or C-9, and to lower energy for methoxy at C-1, C-2, or C-4. In fact, the 3 and 9 isomers show shifts to lower energy, and the 1, 2, and 4 isomers show shifts to higher energy; the direction of the change in transition energy is incorrectly predicted for all five isomers. The effect is not limited to the methoxy group; two other lone-pair substituents, fluoro and dimethylamino, also produce an increase in transition energy at the 2 position, again contrary to the expected result.

Comparison with substituent effects in the azulene system[31] is instructive. For four groups which are electron withdrawing both inductively and by resonance (–COOH, $-COOC_2H_5$, $-COCH_3$, and $-NO_2$), the direction of spectral shift is correctly predicted on the assumption of a dominating inductive effect. For Cl and Br, substituents of the unshared-pair type, which are inductively electron withdrawing and electron donating by resonance, the same assumption results in incorrect prediction of the direction of the shift. A possible explanation of these observations is that spectral shifts caused by lone-pair substituents result from a predominating conjugative effect.

Coulson's discussion shows that for a substituent of electronegativity similar to that of aromatic carbon, such as vinyl, an overriding conjugative effect should invariably lead to a red shift. Much evidence from solution chemistry demonstrates that the resonance effect of methoxy does override the opposing inductive effect when the group is located in a conjugating position. Thus, extension of Coulson's argument to the methoxyfluorenyl anions suggests that the spectra of all five isomers will be shifted to lower frequency relative to fluorenyl. In fact, three of the five are shifted to higher frequency. Despite these incorrect predictions based on perturbation theory, it is difficult to rule out unequivocally the possibility that the observed blue shifts are caused by a predominating conjugative effect. Introduction of a methoxy group into a π system can actually result in an increase in the calculated transition energy. Our calculations, done by the Hückel method with $\alpha_O = \alpha_C + 2\beta_{CC}$ and $\beta_{CO} = 0.8\beta_{CC}$,[32] gave the following transition energies: 1-methoxy, 0.981β; 2-methoxy, 1.013β; 3-methoxy, 0.961β; 4-methoxy, 1.014β; 9-methoxy, 0.877β (the value for the parent anion, fluorenyl, is 0.993β). Thus, decreases in transition energy are predicted and observed for 3- and 9-methoxy, and increases are predicted and observed for 2- and 4-methoxy. Of the five isomers, the direction of the spectral shift is incorrectly predicted only for 1-methoxyfluorenyl.

A number of lines of argument indicate that the success of these calculations is apparent rather than real. From the standpoint of theory, there is no assurance that the Hückel eigenvalues are an accurate reflection of the molecular energy levels. The calculated transition energies would be expected to be quite sensitive to the parameters chosen for the oxygen atom and to the approximations involved in the calculation method. Furthermore, the magnitudes of the calcu-

(30) Streitwieser and Brauman[5a] have already pointed out the success of this treatment for the case of lithium 9-methylfluorenyl.

(31) See ref 7, pp 237 and 244.

(32) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N.Y., 1961, p 123.

lated blue shifts are much too small. If β is assigned a normal spectroscopic value of 50 to 60 kcal, an increase of Δm from 0.993 to 1.013 or 1.014 corresponds to a shift of about 400 cm^{-1}; the observed shifts for 2- and 4-methoxyfluorenyl anions are 910 and 1550 cm^{-1}, respectively. Moreover, the discrepancy becomes greater when the opposing σ-inductive effect of methoxy is taken into account. Many kinds of evidence, such as Hammett σ_m constants, acidities of appropriate α-substituted acetic acids, chemical shifts in nuclear magnetic resonance, and the like, demonstrate that relative to hydrogen, methoxy is more effective in withdrawing electrons inductively than methyl is in donating electrons. Thus, the σ-inductive perturbation produced by methoxy should cause a red shift at least as large in magnitude as the opposing blue shift which the calculations suggest may result from conjugation. The net effect on the observed spectrum would then be either no shift at all or a small red shift.

More significant than these theoretical considerations are the experimentally observed effects of lone-pair substituents in spectra of even-alternant hydrocarbons. In compounds of this class, such as ethylene and benzene, inductive effects produce little change in the positions of absorption maxima; the spectrum of anilinium ion is virtually superimposable on that of benzene.[6] Spectral shifts produced by substituents in these systems result from a predominating conjugative effect, and for a variety of lone-pair groups, including methylamino, amino, hydroxy, methoxy, and four halogens, the shift is in every case to lower frequency.[6] Amino derivatives of naphthalene, anthracene, 1,2-benzanthracene, and pyrene are all red shifted relative to the parent hydrocarbons.[33] In view of the fact that the conjugative effect of lone-pair substituents in even-alternant hydrocarbons invariably causes a decrease in transition energy, it is not unreasonable to conclude that it will cause a similar decrease in nonalternant hydrocarbon systems.

If the spectral shifts observed for the five isomeric methoxyfluorenyl anions cannot be convincingly rationalized in terms of conjugation or of the electron-withdrawing σ-inductive effect of methoxy, they can be readily accounted for on the basis of an electron-repelling π-inductive effect. Clark, Murrell, and Tedder[8] proposed that for an electronegative substituent with an unshared pair, while the σ electrons are attracted to the electronegative atom because of the increased nuclear charge, the π electrons may well be repelled by the unshared pair more strongly than they are attracted by the nuclear plus charge. With respect to properties which would be expected to depend markedly on distribution of the σ electrons, such groups would have a net inductive effect of electron withdrawal, but for properties dependent primarily on the π electrons, such as energies of $\pi \rightarrow \pi^*$ transitions, the net inductive effect would be an electron-repelling one. In Coulson's expression for the inductive perturbation, a predominating π-inductive effect corresponds to a positive sign for the quantity $\delta\alpha_r$. When the appropriate HMO coefficients are substituted into the equation, hypsochromic shifts are predicted for methoxy at C-1, C-2, and C-4, and bathochromic shifts are predicted for methoxy at C-3 and C-9. As Table II shows, all five of these predictions are correct. The hypsochromic shifts observed for 2-fluoro- and 2-dimethylaminofluorenyl anions also cannot be rationalized in terms of conjugation or a σ-inductive effect, but are successfully explained by the π-inductive model. If this effect predominates, one can draw the general conclusion that at a given position of an odd- or nonalternant system methyl and lone-pair groups should cause spectral shifts in the same direction. Few examples have been reported, but the generalization does hold for 1-halogenated azulenes[7] and *meta*- and *para*-chlorinated triphenylmethyl cations.[3c]

The observed shifts for 1-, 2-, 3-, and 4-methoxyfluorenyl anion are about two to three times larger than the shifts for the corresponding methyl anions. The similar pattern of magnitudes suggests that the shifts result from the same cause; for methyl the cause seems clearly to be an inductive perturbation, and the implication is that the hypsochromic shifts produced by methoxy at C-1, C-2, or C-4 should be attributed to the π-inductive effect and not to conjugation. The 9 isomers fit the pattern less neatly, as methyl and methoxy at C-9 produce nearly identical shifts. However, scale models show that the hydrogens at C-1 and C-8 force the 9-methoxy group out of the plane of the fluorenyl system.[34] Because of the lack of coplanarity, both the conjugative and the π-inductive effects are probably reduced, and the red shift is less than expected.

Comparison of the blue shifts observed for 2-methoxy- and 2-dimethylaminofluorenyl anions provides further support for the π-inductive effect. Dimethylamino is a far better conjugative electron donor than methoxy, and produces much larger red shifts in benzenoid hydrocarbons.[6] If the blue shifts observed for these 2-substituted fluorenyl anions resulted from a predominating conjugative effect, the perturbation ought to be much greater for the dimethylamino group. In fact the two groups produce virtually identical shifts.

In our judgment, the effects of lone-pair substituents on the electronic spectrum of fluorenyl anion cannot be satisfactorily explained in terms of conjugation; the results constitute solid evidence for the π-inductive effect.

(33) See ref 6, pp 303–337.

(34) Scale models indicate that if the methoxy carbon lies in the plane of the fluorenyl system, the steric interference between the methyl and the C-1 hydrogen is about as severe as the interaction in 1-acetylazulene which would occur between the methyl and the C-8 hydrogen, if the methyl group were directed toward the seven-membered ring. 1-Acetylazulene is believed to have a structure in which the carbonyl group lies on the side toward the hydrogen at the 8 position, so that steric strain is minimized. See E. Heilbronner and R. Gerdil, *Helv. Chim. Acta*, **39**, 1996 (1956).

Conformational Preferences in Diastereomers. III. Addition Products from Unsaturated Nitriles

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The diastereomers resulting from alkylmagnesium halide addition to α-phenylcinnamonitrile were studied. Increasing the steric requirements of the alkyl groups results in a trend toward low vicinal coupling constants in the most stable, crystalline diastereomer, which is assigned to the *erythro* configuration. Conversely, the *threo* diastereomer moves toward high *J* values. The effect of various quenching media on the intermediate carbanion is interpreted in terms of an SEi mechanism.

From earlier work[1-5] on conformational preferences in diastereomers, a fairly clear picture is beginning to emerge concerning the most favored disposition of various groups. This can be seen with the aid of Figure 1, in which L, M, and S refer to the size of the groups. The designation *erythro*-s indicates the assignment of configuration is based on size.[6]

When there is a substantial difference in the steric requirements of the large and medium groups (L and M) it appears the L groups will prefer a *trans* orientation. In the other diastereomer, if the L groups are *trans*, the S groups likewise must be *trans*. If S is hydrogen the nuclear magnetic resonance vicinal coupling constant *J* will be large, *ca.* 10–12 cps. In the diastereomer the S groups will be *gauche* and *J* will be small, *ca.* 1–3 cps.

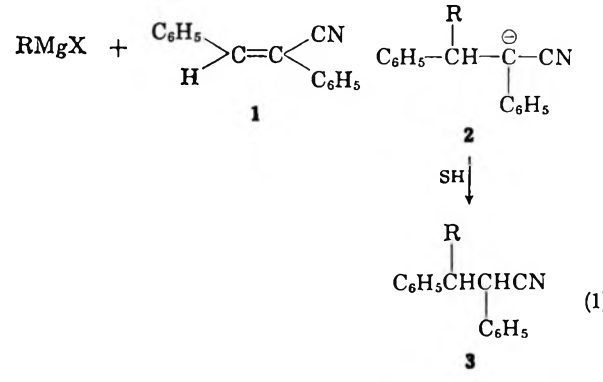
Noteworthy exceptions to this generalization exist. When both L and M groups are similar in steric requirements, *both* diastereomers frequently have quite large coupling constants.[7] In either case, if the hydrogens are *trans*, the total number of *gauche* interactions between sizeable groups is decreased compared to a rotomer involving *gauche* hydrogens.

In other cases, where only one group in the molecule can be considered large, other rotomers than the ones shown in Figure 1 have significant weight. Close to the "averaged" coupling constant, J = 5–8 cps, is frequently observed.[2,7]

In still other cases the interactions of groups may be attractive rather than repulsive, *e.g.*, where intramolecular hydrogen bonding is important.[8-11] In these cases the *erythro*-s *J* value may be lower than the *threo*-s value.

Diastereomers containing the *t*-butyl group frequently represent unexplained anomalies characterized by low coupling constants.[7,12,13]

The present study concerns a series of diastereomers derived from Grignard addition to unsaturated nitriles (eq 1), a reaction first observed by Kohler and Reimer.[14,15]



(1)

It was the purpose of this study to (1) observe the vicinal coupling constants of the two diastereomeric products (**3**) and to assign configurations to the two isomers, (2) observe the relative stabilities of the two isomers, and (3) observe the ratios of the isomers of **3** as a function of quenching of the intermediate **2** by various proton-donating systems.

Results and Discussion

Conformational Preferences and Configurations.— It had been hoped that Grignard addition to a variety of substrates would be possible. Unfortunately attempted addition to an α-methylcinnamonitrile was not successful, as was attempted addition to the β-naphthyl and β-*o*-chlorophenyl analogs of **1**. Addition of alkyllithiums resulted in a plethora of products, very little of which was the desired product **3**.

Addition of alkylmagnesium halides, however, was a smooth reaction providing an excess of the Grignard reagent was used. The intermediates **2** were usually red in color and were quenched to form **3** cleanly except in the case of R = CH_3 when some side products were evident. The nmr resonance absorptions of the two diastereomers of formula **3** were well separated and the coupling constants could be accurately determined from the spectrum of the mixed diastereomers (Figure 2). These data are listed in Table I. In our hands only one of the diastereomers was high melting and easily obtained pure. The second diastereomer was usually an oil and it was very difficult to separate this material completely from the high-melting product and traces of **1**. Chroma-

(1) M. Hanack, "Conformation Theory," Academic Press Inc., London, 1965, pp 331–343.
(2) G. Whitesides, J. Sevenair, and R. Goetz, *J. Amer. Chem. Soc.*, **89**, 1135 (1967).
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(9) J. Sicher and M. Svoboda, *Collect. Czech. Chem. Commun.*, **24**, 2735 (1959), plus related papers.
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(13) C. A. Kingsbury, W. R. Oliver, and G. Underwood, unpublished observations.
(14) E. P. Kohler and M. Reimer, *Amer. Chem. J.*, **33**, 333 (1905).
(15) M. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p 782.

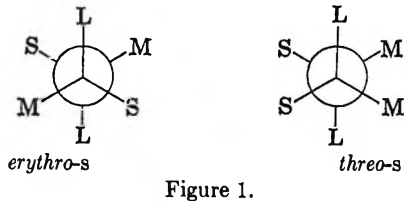
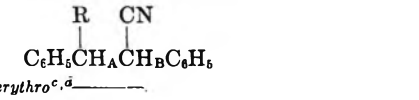


Figure 1.

TABLE I

VICINAL COUPLING CONSTANTS[a] OF THE GRIGNARD ADDITION PRODUCTS 3



	erythro[c,d]			threo[c]		
R	δ_A, ppm	δ_B	J_{AB}, cps	δ_A	δ_B	J_{AB}
CH_3[b]	3.23	3.94	7.2	3.19	3.94	6.8
C_2H_5	2.84	3.98	6.4	*Ca.* 2.8	3.86	7.1
i-C_3H_7	*Ca.* 2.4	4.29	4.8[h]	2.95	4.17	8.4[i]
t-C_4H_9	2.61	4.36	3.7	2.99	4.03	10.2
S-C_6H_5[g]	4.12	4.28	5.5	4.15	4.45	7.1
C_6H_{11}[e]	2.51	4.31	5.3[f]	2.97	4.22	8.3[f]

[a] Spectra taken on a Varian A-60 instrument. Concentration was 10% by wt/v of CCl_4 except as indicated. Coupling constants were determined from expanded spectra. [b] Concentration 10% in $CDCl_3$. [c] For justification of this assignment, see text. [d] High-melting isomer, physical constants are given in the Experimental Section. [e] Cyclohexyl. [f] These *J* values varied ±0.2 cps over a fourfold change in concentration. [g] Anionic addition product rather than Grignard product. [h] This value should be regarded as approximate; some virtual coupling was evident. [i] $J_{\text{isopropyl-A}}$ = 6.0 cps.

tography on silica gel afforded considerable separation, however, the spectrum of all fractions still indicated contamination of the oil by the high-melting product. Chromatography on alumina resulted in equilibration giving a predominance of the high-melting product.

As the data in Table I show, for R = CH_3, there is little difference in the *J* values for the two products. Both values are close to the "averaged" coupling constant indicative of little or no conformational preferences. This represents one more illustration of the fact that phenyl is little different from methyl in effective size. As the bulk of R increases the coupling constants of the high-melting isomer move monotonically toward low values. These values are taken as indicative of a growing predominance of a rotomer with *gauche* protons.

On the other hand, the *J* values of the other isomer move toward high values indicative of a predominant rotomer with *trans* protons. In the case of R = *t*-butyl near conformational purity is evident.

The diastereomers of this study were comparatively well behaved in that there was no discontinuity in *J* in moving from R = isopropyl to R = *t*-butyl as was observed in other studies.[7,13]

With the above data in hand, a tentative assignment of configuration may be made. Here it is convenient to move to the alternate definition of configuration to avoid confusion when groups are of similar size. The *erythro* isomer is taken as the material in which like groups can be eclipsed.[1,3,8] The assignments of configuration are illustrated for R = *t*-butyl in Figure 3.

If one assumes the most stable rotomer has the largest groups *trans*, the low coupling constant product (*gauche* protons), which is also the crystalline product,

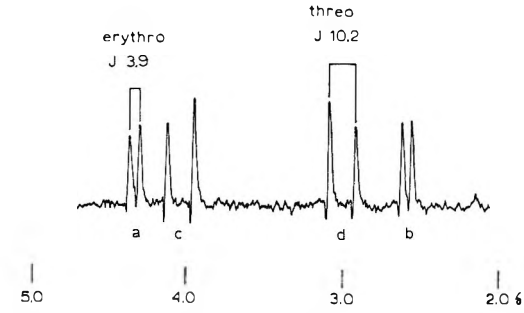


Figure 2.—Partial nmr spectrum of mixed diasteromers of **3**, R = *t*-C_4H_9, resulting from NH_4Cl–ice quench of carbanion **2**. An internal standard, tetramethylsilane, was taken as 0 ppm. The resonance absorptions a, b, c, and d are assigned as shown in Figure 3.

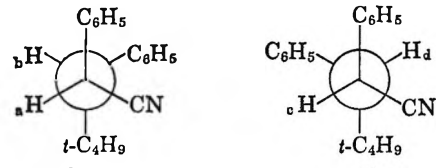


Figure 3.

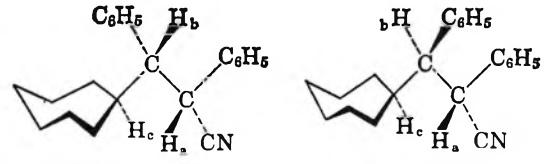


Figure 4.

is the *erythro* diastereomer. The other crystalline products (R = CH_3, etc.) by analogy are also assigned the *erythro* configuration.

It is interesting to compare the R = isopropyl and R = cyclohexyl cases. Previous it had been shown[4,7] that, if J_{ab} is large, J_{bc} would be small and *vice versa*. The cyclohexyl as well as the isopropyl compounds exhibit the same phenomenon. This alternation of *J* values can be explained with the aid of extended conformational diagrams such as in Figure 4. These compounds are less conformationally pure than other examples and only one rotomer of the *erythro* and *threo* is shown. By arranging protons a and b *gauche* and b and c *trans* (or *vice versa*) 1,3 interactions are minimized. In each case H_c is opposite the CN and H_a opposed to one arm of the cyclohexyl ring. If J_{ab} and J_{bc} were both large or both small the conformation would involve a severe 1,3 interaction between sizeable groups.

Equilibrium Experiments.—The base-catalyzed equilibration results for several diastereomers in methanol are listed in Table II.

TABLE II

EQUILIBRATION EXPERIMENTS OF 3[a]

% *erythro* of an *erythro–threo* mixture (temp, °C)			
R = CH_3	R = *i*-C_3H_7	R = C_6H_{11}	R = *t*-C_4H_9
55 (27)	77 (25)	72 (27)	82 (24)

[a] Solution of *ca.* 200 mg of substrate in 20 ml of 0.06 *N* $NaOCH_3$–CH_3OH. [b] These results are considered good to ±5%.

It is evident from Table II that the *t*-butyl compound not only exhibits the strongest conformational preferences but also the greatest difference in stability between the two isomers. This difference is perhaps smaller than anticipated considering the relative sizes of the alkyl groups.

For the R = *t*-butyl case, where the two diastereomers are close to conformational purity, it is instructive to count up the *gauche* interactions in each diastereomer. Assuming the dihedral angles are close to 60°, equivalent *gauche* interactions in the *erythro* and *threo* isomers may be cancelled. The stability of the *erythro* then is associated with a lower energy of interaction of *gauche* C_6H_5–CN and H–H groups over *gauche* C_6H_5–H and CN–H groups in the *threo* isomer. On the basis of steric hindrance this seems unlikely, since in the *threo* both interactions involve hydrogens. However, it is possible that the C_6H_5–CN interaction in the *erythro* is attractive rather than repulsive, since both groups should be "soft" according to the Chatt–Pearson point of view,[16a] and polarizability effects may be significant.[16b]

More likely dihedral angles are not exactly 60°. A slight clockwise rotation of the *t*-butyl, *et al.*, groups is possible (Figure 3). In the *erythro* isomer this rotation does appear to relieve steric interference (from Stuart–Breigleb models). However, the C_6H_5–C_6H_5 interaction is worsened in the *threo* case. This sort of rotation may be denied the *threo* isomer which may account in part for its instability.

Carbanion Quenching Experiments.—Various *erythro–threo* ratios resulted depending on the proton-donating medium used to destroy the carbanion **2**. The media used were NH_4Cl over ice, ethanol, acetic acid, and anhydrous HCl in ether. The data are recorded in Table III. It is seen that the more stable *erythro* isomer is usually the predominant product. As the steric requirements of the R group increase, the trend is toward increasing amounts of the *threo* isomer.

TABLE III

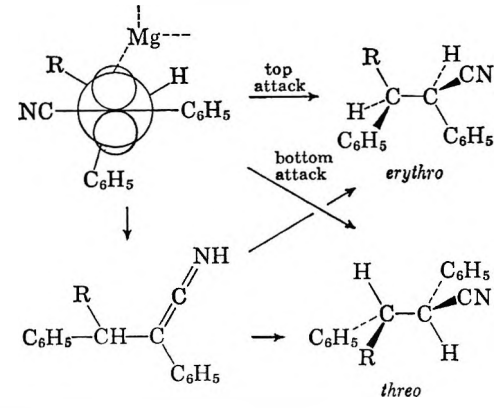
threo–erythro RATIOS[d] IN **3** FROM VARIOUS QUENCHING MEDIA

	R			
Medium	CH_3	*i*-C_3H_7	C_6H_{11}	*t*-C_4H_9
NH_4Cl–ice	0.6[c]	0 68	0.88	1.14
C_2H_5OH	0.5	0 62	0.80	0.92
HOAc–$(C_2H_5)_2O$[a]	0.5	0 50	0.70	0.52
HCl–$(C_2H_5)_2O$[b]	0.3	0 39	0.72	0.53

[a] The mixture was 10 ml of acetic acid in 20 ml of anhydrous ether. [b] Anhydrous HCl was passed into 20 ml of anhydrous ether for *ca.* 10 min. [c] The ratio for HCl–ice was similar. [d] These values are considered good to ±6%, except R = CH_3 (±10%).

The carbanionic center may be either sp^2 or sp^3 hybridized. However, since the negative charge may be delocalized into both cyano and phenyl groups a planar carbanionic center seems more likely.[17,18] However, the following discussion would not be materially changed if an sp^3 center were assumed.

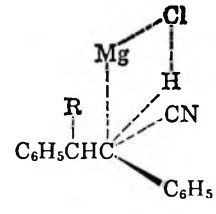
Ignoring for the moment the effect of the magnesium cation, a rationalization for the effect of the R group may be given with the aid of the theoretical model developed by Zimmerman and Chang[6] (Figure 4).



This model seems quite good for R = isopropyl, cyclohexyl, and *t*-butyl. With increasing size of the R group, attack by the proton donor from the top to give *erythro* product becomes increasingly difficult.[19,20] In the extreme case the R = *t*-butyl group shields the top of the molecule to the extent that bottom attack predominates in one case even though this involves momentary eclipsing of groups. Another possible route is initial protonation on nitrogen followed by rearrangement.[21] With exceptions Zimmerman and coworkers have shown such proton transfers often give predominately the least stable isomer,[19,20] which is not observed in this study.

It is somewhat more difficult to rationalize the effects of the various proton donors. Unlike the cases observed by Russell,[21] the acidic media give a more stereoselective product mixture in which the more stable isomer predominates.

It is thought that the influence of the cation is greater in the fairly low dielectric constant ethereal solvents than in the hydroxylic solvents. Extensive ion aggregation appears likely. A four-center mechanism is attractive with coordination between the chloride or acetate and the magnesium. This type reaction bears some similarity to the reactions at carbon–mercury bonds[22,23] and might be termed an SEi reaction.



Experimental Section

The basic procedure used to prepare the substrates **3** was that of Ramart-Lucas.[14,15] The following procedure is illustrative.

2,3-Diphenylbutyronitrile.—To 75 ml of anhydrous ether plus 4.0 g (0.16 g-atom) of magnesium in a dried 500-ml, round-bottom flask was added 10.0 ml (0.17 mol) of methyl iodide in 21 ml of ether dropwise with stirring over a period of 1 hr. To this solution was added 5.0 g (0.024 mol) of α-phenylcinnamonitrile

(16) (a) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967); (b) L. I. Peterson, *ibid.*, **89**, 2680 (1967).

(17) (a) E. Grovenstein, Jr., and G. Wentworth, *ibid.*, **85**, 3305 (1963); (b) D. J. Cram, R. Rickborn, and W. Neilsen, *ibid.*, **82**, 6416 (1960).

(18) See, however, M. Witanowski and J. D. Roberts, *ibid.*, **88**, 737 (1966).

(19) H. E. Zimmerman and M. D. Traxler, *ibid.*, **79**, 1920 (1957).

(20) H. E. Zimmerman and H. Giallombardo, *ibid.*, **78**, 6259 (1956).

(21) G. A. Russell, *ibid.*, **81**, 2016 (1959).

(22) S. Winstein and T. G. Traylor, *ibid.*, **78**, 7592 (1956).

(23) F. R. Jensen and L. H. Gale, *ibid.*, **82**, 148 (1960).

(mp 82–84°) as a solid. The initial reaction was mildly exothermic and red coloration developed over a period of 15 min. The reaction mixture was stirred overnight.

Four quenching mixtures were prepared: (a) *ca.* 10 g of NH_4Cl in *ca.* 200 g of ice, (b) 20 ml of C_2H_5OH, (c) 10 ml of acetic acid in 20 ml of ether, and (d) 20 ml of ether into which anhydrous HCl had been passed for *ca.* 10 min. The reaction mixture was divided into four equal parts and added to each quenching solution (cooled in ice) by pipet. Owing to the excess of Grignard reagent the quenching was extremely exothermic. The C_2H_5OH mixture was immediately acidified and the solvent evaporated. Each reaction mixture was worked up rapidly by adding to ice and ether in a separatory funnel and shaking. The aqueous layer was reextracted with *ca.* 50 ml of ether. The combined ether layers were extracted twice with *ca.* 75 ml of H_2O to which several grams of NH_4Cl had been added. The ether solution was dried with $MgSO_4$ and filtered and the solvent evaporated through a Vigreux column. A small quantity of CCl_4 was added to the oil and this was evaporated. A portion of the oil was taken up in CCl_4 and analyzed by nmr spectroscopy; the results are given in Table III.

All oils were combined and concentrated. Upon standing the material partially crystallized. The crystals were recrystallized twice from $CHCl_3$, mp 132–134° (lit.[14] 133). The remaining oil from which all possible solid has been crystallized was mainly the *threo* isomer contaminated with *ca.* 20% *erythro*. This material was chromatographed on silica gel and eluted with increasing quantities of benzene in hexane. All fractions were oils whose spectrum disclosed increasing quantities of the *erythro* isomer.[24]

2,3-Diphenylvaleronitrile.—This material was prepared similarly again yielding a solid *erythro* isomer, mp 114.0–114.8°, and a noncrystalline mixture, predominately *threo*.

Anal. Calcd for $C_{17}H_{17}N$ (*erythro*): C, 86.9; H, 7.3. Found: C, 86.71; H, 7.43.

2,3-Diphenyl-4-methylvaleronitrile.—The *erythro* isomer was a solid, mp 104.5–105.2°.

Anal. Calcd for $C_{18}H_{19}N$: C, 86.7; H, 7.68. Found: C, 86.63; H, 7.70.

2,3-Diphenyl-3-cyclohexylpropionitrile.—The *erythro* isomer was obtained by chromatography on silica gel with elution by 10% ether in pentane, mp 120–122°.

Anal. Calcd for $C_{21}H_{23}N$: C, 87.3; H, 8.02. Found: C, 87.09; H, 8.20.

The other fractions crystallized in part as mixtures of the two isomers. Repeated crystallization by the triangle scheme afforded little purification. The best *threo* isomer obtained, mp 83–87°, still contained *ca.* 10% *erythro* by nmr.

2,3-Diphenyl-4,4-dimethylvaleronitrile.—The *erythro* isomer had mp 110.8–111.5°.

Anal. Calcd for $C_{19}H_{21}N$: C, 86.6; H, 8.03. Found: C, 86.50; H, 8.01.

The best melting point obtained for the *threo* isomer was 50–53°. Figure 2 shows a partial nmr spectrum of mixed *erythro* and *threo* diastereomers resulting from the NH_4Cl–ice quench.

3-Thiophenoxy-2,3-diphenylpropionitrile.—To 50 ml of a solution of sodium ethoxide (*ca.* 0.1 *M*) was added thiophenol, 10.3 g, 0.084 mol) and **1**, 12.0 g (0.03 mol). The solution was stirred at 50° for 2 days. An unidentified precipitate was filtered off, mp 204° dec. To the remainder $Hg(NO_3)_2$ was added until the smell of thiophenol was no longer evident. This precipitate was washed twice with 25-ml portions of ethanol and the solutions were evaporated to a small volume and crystallization induced yielding 3.0 g of the *erythro* isomer, mp 104–108°. This was taken up in ether, extracted twice with H_2O, dried with $MgSO_4$, filtered and recrystallized three times from ether–pentane, mp 114–115°.

Anal. Calcd for $C_{21}H_{17}NS$: C, 80.0; H, 5.44. Found: C, 79.93; H, 5.49.

The remainder of the ethanol solution was mainly the *threo* isomer by nmr. Crystallization could not be induced. Attempted chromatography produced **1** and thiophenol.

Equilibration Experiments.—Approximately 200 mg of the substrate was placed in a 20-ml portion of 0.06 *M* $NaOCH_3$ in CH_3OH and allowed to stand at room temperature for 2 days. The solution was poured into dilute HNO_3 and extracted twice with 50-ml portions of ether. The ether layer was extracted with three 50-ml portions of H_2O plus $NaHCO_3$, dried over $MgSO_4$, evaporated, taken up in CCl_4, and analyzed by nmr spectroscopy. The data in Table II represent the average of duplicate runs.

Registry No.—*erythro* **3** (R = CH_3), 5558-38-3; *erythro* **3** (R = C_2H_5), 15645-51-9; *erythro* **3** (R = *i*-C_3H_3), 15645-52-0; *erythro* **3** (R = *t*-C_4H_4), 15717-34-7; *erythro* **3** (R = S-C_6H_5), 15645-53-1; *erythro* **3** (R = C_6H_{11}), 15645-54-2; *threo* **3** (R = CH_3), 15645-55-3; *threo* **3** (R = C_2H_5), 15645-57-5; *threo* **3** (R = *i*-C_3H_9), 15645-56-4; *threo* **3** (R = *t*-C_4H_4), 15717-33-6; *threo* **3** (R = S-C_6H_5), 15645-58-6; *threo* **3** (R = C_6H_{11}), 15645-59-7.

Acknowledgment.—Support by the National Science Foundation is greatly appreciated (GP 7800).

(24) Upon acidic hydrolysis, the *erythro* nitrile, mp 132–134°, produced predominately *erythro*-2,3-diphenylbutyric acid, mp 186–188°, whereas a mixture of the *erythro* and *threo* nitriles yielded a mixture of *erythro* and *threo* acids.[6]

Reductions Using Alkoxyaluminum Hydrides. I. Reduction of Epoxides

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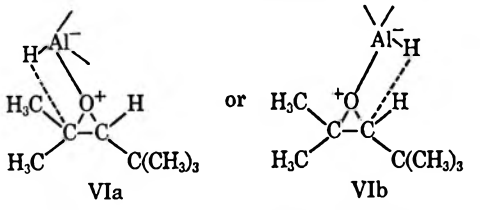
Received September 21, 1967

The reactions of β-diisobutylene oxide and styrene oxide with various alkoxyaluminum hydrides have been studied. This is the first report involving the use of alkoxyaluminum hydrides as selective reducing agents in organic chemistry. Alkoxyaluminum hydrides are less reactive reducing agents toward epoxides than the "mixed hydride reagents," although more reactive than $LiAlH_4$. Whereas mixed hydride reagents, such as $HAlCl_2$, exhibit strong Lewis acidity as evidenced by the substantial production of migration product induced by ring opening with the Lewis acid, alkoxyaluminum hydride reduction of these epoxides produces much less of the migration product, indicating weaker Lewis acidity of these reagents. The differences in Lewis acidity and resulting differences in reactivity between the alkoxyaluminum hydrides and "mixed hydride" reagents can be explained in terms of the different states of association exhibited by the two types of reagents. The role of association through bridging alkoxy groups in reducing the expected Lewis acidity of these reagents is discussed.

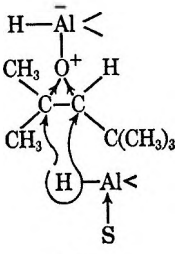
Alkoxyaluminum hydrides have been postulated as intermediates in reductions of epoxides involving mixed hydride reagents.[4,5] Also the assumption has been made that alkoxyaluminum hydrides and hydridoaluminum halides are similar in their behavior as reducing agents[5] for the system studied. This is not an unreasonable assumption since hydriodoaluminum halides, the so-called "mixed hydride reagents,"[6] and alkoxyaluminum hydrides are formally similar. However, previous workers did not prepare authentic alkoxyaluminum hydrides and allow them to react with epoxides. It has been found recently[7] that alkoxyaluminum hydrides can be synthesized by reaction of aluminum hydrides in tetrahydrofuran with the corresponding alcohol in the proper stoichiometric ratios. Dimethoxyaluminum hydride, mono- and diisopropoxyaluminum hydride, and mono- and di-*t*-butoxyaluminum hydride have been prepared in this manner and characterized. The product ratios from reactions of both β-diisobutylene oxide and styrene oxide with these reagents were significantly different from those ratios obtained by reaction with the corresponding hydridoaluminum halides.

Results and Discussion

When β-diisobutylene oxide is treated with a hydride possessing Lewis acidity, the products given in Scheme I are obtained and the pathways shown are operative.[4,8-10] Products II and III are formed by direct reduction *via* a four-center transition state VI[4]

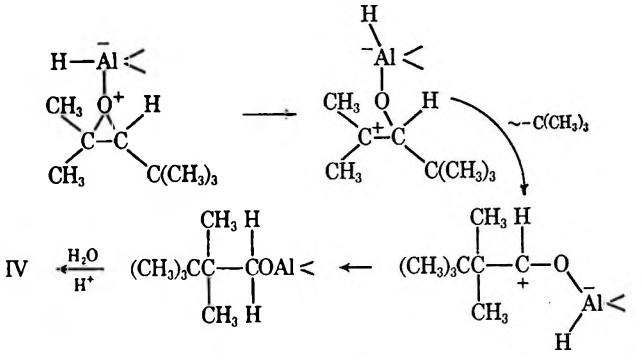


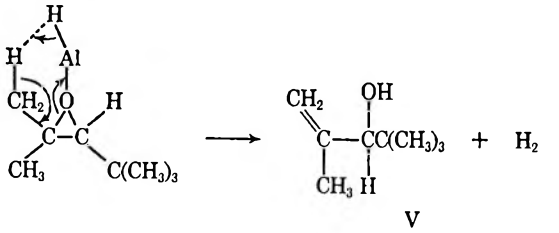
VIa VIb



VII

and by bimolecular backside attack VII.[5] Compound IV is formed by ring opening of the complexed epoxide followed by migration of the *t*-butyl group.[4] Compound V has been proposed as the result of internal elimination[9] and is always formed to some extent in reductions of this type.[6b,10,11] Compound V becomes





V

a major product when the reducing agent employed is a relatively strong hydride donor or weak Lewis acid.[10,11] Zakharkin and coworkers[9] report considerable formation of V in reductions of I using limited amounts of ethereal aluminum hydride in refluxing solvent.

Since compound IV is formed *via* a ring-opening step, any factor that increases the extent of ring opening

(1) Abstracted in part from the M.S. Thesis of B. Cooke, Georgia Institute of Technology, 1967. NASA Predoctoral Fellow 1963–1966.

(2) Alfred P. Sloan Fellow 1965–1967. To whom all inquiries should be sent.

(3) Abstracted in part from the senior thesis of J. Lott, Georgia Institute of Technology, 1966–1967.

(4) E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, **88**, 729 (1966).

(5) P. T. Lansbury, D. J. Scharf, and V. A. Pattison, *J. Org. Chem.*, **32**, 1748 (1967).

(6) (a) E. L. Eliel, *Rec. Chem. Progr.* (Kresge-Hooker Sci. Lib.), **23**, 129 (1961), and references cited therein; (b) M. N. Rerick and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2356 (1962), and references cited therein.

(7) K. Suchy, Dissertation, University of Munich, Munich, Germany, 1966, working under Professor H. Nöth.

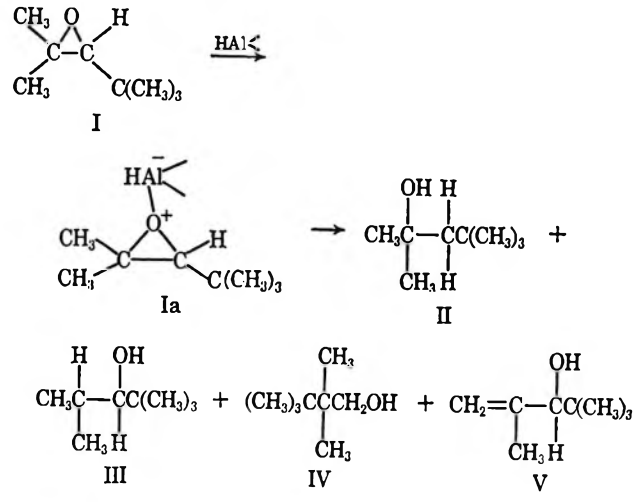
(8) E. L. Eliel and Mark N. Rerick, *J. Amer. Chem. Soc.*, **82**, 1362 (1960).

(9) L. I. Zakharkin and I. M. Khorlina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 862 (1965).

(10) B. J. Cooke and E. C. Ashby, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Division of Organic Chemistry, paper 38.

(11) E. C. Ashby and B. Cooke, *J. Amer. Chem. Soc.*, in press.

SCHEME I



should increase the amount of IV produced. The extent of ring opening should be a function of the Lewis acidity of the aluminum hydride reagent complexed to the epoxide oxygen. Therefore formation of IV should be increased as the Lewis acidity of the reducing agent is increased. Consideration of the data in Table I indicates that these conclusions are valid; *i.e.*, as the Lewis acidity of the reagent increases (AlH_3 < H_2AlCl < $HAlCl_2$, so does the amount of IV produced in the reaction.

TABLE I

PRODUCT RATIOS FROM REDUCTIONS OF I INVOLVING HYDRIDOALUMINUM HALIDES[a]

Reducing agent	II	III	IV	V	Yield of Products, %	Ref
$LiAlH_4$[b]	100	...	...	...	21	6[b]
$LiAlH_4$	...	...	...	...	0	10, 11
AlH_3[c]	19	55	5	21	84	10, 11
H_2AlCl[c]	3	31	60	6	92	10, 11
$HAlCl_2$[c]	1	16	74	9	85	10, 11

[a] Threefold molar excess of hydride to epoxide was employed in diethyl ether solvent at room temperature. [b] These results were obtained under forcing conditions (reflux 24 hr). [c] LiCl present.

Inspection of these data also shows that β-diisobutylene oxide is rather inert to attack by even potent hydride donors, such as lithium aluminum hydride, unless the reagent possesses some Lewis acidity, *i.e.*, prior complexation with resultant weakening of the C–O bonds in the oxirane ring is a prerequisite for the occurrence of hydride reduction to any appreciable extent.

Since alkoxy substituents on aluminum are thought to function solely as inductive electron withdrawers,[12] it would be expected that alkoxyaluminum hydrides should exhibit reactivities similar to the mixed hydrides and that product distributions from the reductions of β-diisobutylene oxide involving alkoxyaluminum hydrides should show the trends outlined in Table I. However, comparison of the data presented in Tables II and III with that in Table I indicates that this is not the case.

These data show that there are important differences between the reducing properties exhibited by the mixed hydrides and alkoxyaluminum hydrides. The following generalities can be made. (1) β-Diisobutylene oxide is reactive toward mixed hydride reagents, but is fairly inert to alkoxyaluminum hydrides, especially the dialkoxyaluminum hydrides. This is shown by the fact that the total product yields are low and that a significant amount of starting material could be detected in the reaction mixtures, even in the case of the reactions run under forcing conditions. (2) The yield of V is significantly higher in the case of the reductions involving alkoxyaluminum hydrides than for those involving the mixed hydride reagents, especially in the case of the reactions run under forcing conditions. (3) The reductions involving alkoxyaluminum hydrides yield significantly less migration product than do those involving mixed hydrides, indicating in general the weaker Lewis acidity of the alkoxyaluminum hydrides. (4) Under normal reaction conditions, the yield of III shows a steady decreasing trend in going from aluminum hydride as the reducing agent to dimethoxyaluminum hydride, whereas the yield of II under the same conditions remains relatively constant. (5) Reductions at room temperature produce trends which are interpretable whereas under forcing conditions trends are distorted due to the high yield of V produced.

In short, the alkoxyaluminum hydrides in general act as weaker Lewis acids than the hydridoaluminum halides. The question that must be answered is how can the substitution of an alkoxy group, which supposedly functions only as an inductive electron withdrawer when bound to aluminum, for hydrogen in aluminum hydride yield a reagent of lesser Lewis acidity than aluminum hydride.

TABLE II

PRODUCT RATIOS FROM REDUCTION OF I WITH ALKOXYALUMINUM HYDRIDES UNDER NORMAL CONDITIONS IN TETRAHYDROFURAN[a]

Reducing agent	II	III	IV	V	Yield of products, %	Recovery of epoxide, %
AlH_3	30	69	...	1	65–100	...
H_2AlO-*t*-Bu	28	59	3	10	12–24	47–64
$HAl(O$-*t*-$Bu)_2$	...	...	...	...	...	65–77
H_2AlO-*i*-Pr	28	49	6	17	16	58
$HAl(O$-*i*-$Pr)_2$	25	25	25	25	1	58
$HAl(OMe)_2$[b]	23	20	27	30	2	64
$HAlCl_2$[c]	2	27	61	9	75–78	...

[a] Threefold molar excess of hydride to epoxide, room temperature, 2 hr. [b] All solutions of the hydrides were clear except this one because of its polymeric nature. $HAl(OMe)_2$ disproportionates to H_2AlOMe and $Al(OMe)_3$. [c] In admixture with LiCl.

TABLE III

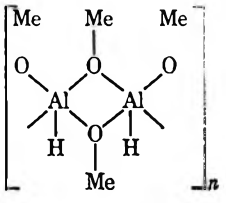
PRODUCT RATIOS FROM REDUCTION OF I WITH ALKOXYALUMINUM HYDRIDES UNDER FORCING CONDITIONS IN TETRAHYDROFURAN[a]

Reducing agent	II	III	IV	V	Yield of products, %	Recovery of epoxide, %
H_2AlO-*t*-Bu	7	25	9	59	53	25
$HAl(O$-*t*-$Bu)_2$	2	2	6	90	51	35
H_2AlO-*i*-Pr	19	45	4	33	76	...
$HAlO$(*i*-$Pr)_2$	9	3	15	73	9	50
$HAl(OMe)_2$[b]	22	14	14	60	4	50

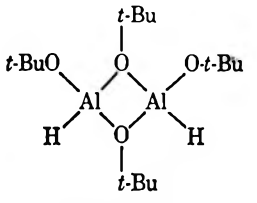
[a] Threefold molar excess of hydride to epoxide, reflux, 6 hr. [b] All solutions clear except this one.

(12) H. C. Brown, E. J. Mead, and C. J. Shoaf, *J. Amer. Chem. Soc.*, **78**, 3616 (1956).

The answer to this question can be found by comparison of the properties of the mixed hydrides and alkoxyaluminum hydrides. Wiberg[13] found that hydridoaluminum halides exist as monomeric etherates in diethyl ether. Nöth and Suchy[7], on the other hand, found that alkoxyaluminum hydrides exist as dimers, trimers, or insoluble polymers in tetrahydrofuran, as shown below, depending on the nature of the alkoxy substituents. These aggregates were found to be associated through bridge bonding involving the alkoxy groups.



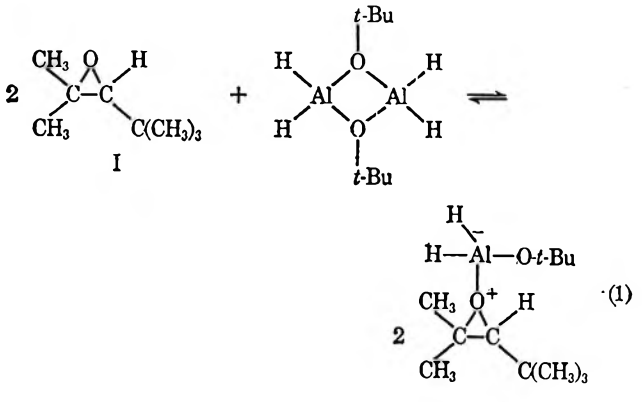
$[AlH(OMe)_2]_n$



$[AlH(O\text{-}t\text{-}Bu)_2]_2$

The difference in association between the two types of reducing agents explains the observed difference in reactivity in the following manner. First of all, it is to be expected that a polymeric species, such as an alkoxyaluminum hydride, would be less reactive than a monomeric species, such as mixed hydride, on steric grounds alone, especially toward a hindered epoxide, such as β-diisobutylene oxide. This would explain the observed over-all low product yields and in particular the high yield of V in these reactions. The fact that product II (direct reduction from least hindered side) remains reasonably constant with an increase in the steric requirement of the reducing reagent whereas product III decreases considerably under the same conditions is reasonable since reduction to product III (direct reduction from more hindered side) should be affected to a greater extent by a bulky reducing agent. The fact that product II is indeed the result of attack from the least hindered side is shown by the fact that only product II is formed when $LiAlH_4$ is the reducing agent (Table I).

The association of alkoxyaluminum hydrides into higher aggregates can also furnish an explanation for the unexpected lack of Lewis acidity exhibited by these reagents. The fact that these compounds were prepared in tetrahydrofuran and yet exist as dimers, trimers, etc., indicates the the alkoxy bridge bonds must be fairly strong and may significantly satisfy the Lewis acidity of the aluminum atom. Also, the first step in the reduction of I involving acidic aluminum reducing agents has been amply demonstrated to be complexation of the type shown (1). Nöth and Suchy



(1)

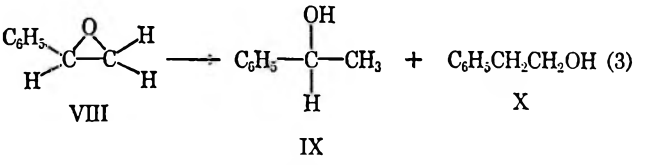
have shown[7] that the equilibrium (2) lies far to the left.

$$(ROAlH_2)_n + n\text{THF} \rightleftharpoons n\text{ROAlH}_2\cdot\text{THF} \qquad (2)$$

As tetrahydrofuran does not cleave the bridge bonds to a detectable extent, it would be unreasonable to expect a bulky epoxide, such as I, to do so; thus, the equilibrium above should lie far to the left, resulting in little activation of the epoxide by complex formation. Therefore more direct reduction rather than migration product is expected and this is what is observed. Approximately ten times more of product II is formed than when mixed hydride reagents are employed. The fact that the migration product (IV) increases from top to bottom in Table II shows that once the complex is formed and the alkoxyaluminum hydrides dissociated, these reagents do show greater Lewis acidity than AlH_3. The increase in product IV from the *t*-butoxy to the methoxy reagent can be explained by assuming that equilibrium 1 (above) lies further to the right when R = CH_3 than when R = *t*-butyl and thus more migration product would be expected. On the other hand, when R = CH_3, the resulting alkoxyaluminum hydride is polymeric producing a lower yield than when R = *t*-Bu and the resulting alkoxyaluminum hydride is dimeric. The fact that when R = *i*-Pr the over-all yields are very low (*e.g.*, when R = CH_3) as compared to when R = *t*-Bu indicates that diisopropoxyaluminum hydride is more highly associated than the corresponding *t*-butyl compound. Unfortunately Suchy did not study the isopropoxyaluminum hydrides.

Aluminum hydride, of course, is strongly solvated to THF. Because aluminum hydride is monomeric in THF this reagent has a low steric requirement. Also since aluminum hydride possesses no electron-withdrawing groups such as halogen or alkoxy it is a very good hydride donor. Thus products II and III are found in high yield and no migration product is observed. The low yield of V indicates facile reaction. In summary then the results reported in Table II are easily explained in terms of the steric requirement of the hydride and the position of the epoxide–hydride equilibrium to form the complex.

An unfortunate aspect of the reactions of I with alkoxyaluminum hydrides is that they proceed to such a limited extent (especially those with the dialkoxyaluminum hydrides). A study of the reactions of these reducing agents with a more reactive epoxide was carried out in order to see if the trends observed in the reactions of I are observable in the reduction of less hindered epoxides. The epoxide chosen was styrene oxide. When this epoxide was treated with hydrides of various types, products IX and X were obtained (eq 3)



(3)

in varying relative yields, depending on the nature of the reducing agent.[14] Since VIII is well known[14] to be

(13) E. Wiberg, K. Modritzer, and R. Uson Lacel, *Rev. Acad. Cienc. Exact. Fis-Quim. Nat. Zaragoza*, **9**, 91 (1954).

(14) (a) L. W. Trevoy and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 1675 (1949); (b) E. L. Eliel and D. W. Delmonte, *ibid.*, **80**, 1744 (1960).

very reactive toward all aluminum-containing hydrides, no statement can be made concerning the role of prior complexation in reductions involving this epoxide. Complexation of styrene oxide by a Lewis acid is obviously not a prerequisite for reduction. Inspection of the data from reductions involving triphenylethylene oxide[6b] shows that there are two pathways involved in the formation of X:[11] (1) complexation followed by direct reduction and (2) complexation followed by hydride migration followed by subsequent reduction of the resulting intermediate. Whichever pathway is involved, the amount of X contained in the reduction products of styrene oxide should be a function of the Lewis acidity of the reducing agent employed. The product ratios from reductions of styrene oxide with various mixed hydrides and alkoxyaluminum hydrides in tetrahydrofuran are shown in Table IV.

TABLE IV

PRODUCT RATIOS FROM REDUCTION OF VIII INVOLVING ALKOXYALUMINUM HYDRIDES AND HYDRIDOALUMINUM HALIDES

Reducing agent	Yield of IX, %	Yield of X, %	Total product yield, %	Recovery of epoxide, %	Ref
$LiAlH_4$	90–95	5–10	82	...	14[b]
$LiAlH_4$[a]	91	9	91	...	*b*
$LiAlH_4$	99	1	93	...	*b*
AlH_3	76	24	...	...	*c*
AlH_3	74	26	55	...	*b*
AlH_2O-*t*-Bu	79	21	97	...	*b*
$AlH(O$-*t*-$Bu)_2$	80	20	76	...	*b*
AlH_2O-*i*-Pr	85	15	53	36	*b*
$AlH(O$-*i*-$Pr)_2$	...	...	0	20	*b*
$HAlCl_2$[a,d]	1	99	69	10	9
$HAlCl_2$[d]	2–5	95–98	71	...	14[b]
H_2AlCl[d]	10	90	75	...	14[b]
AlH_3[e]	72	28	80	...	14[b]

[a] Three moles of hydride per mole of epoxide in diethyl ether at room temperature for 2 hr. [b] This work (THF solvent). [c] H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1464 (1965). [d] Complexed LiCl was present. [e] LiBr and $LiAlH_4$ present. Yield of IX using pure AlH_3 should be lower.

Comparison of the data from reductions involving mixed hydride reagents and alkoxyaluminum hydrides yields the following information. (1) There is a significant solvent effect observed in going from diethyl ether to tetrahydrofuran. This is shown by comparison of the data from reductions of VIII involving lithium aluminum hydride and from previous studies using mixed hydride reagents.[10,11,14b] Thus in a solvent such as tetrahydrofuran, which increases the hydride donor ability of the mixed hydride reagent and using a nonhindered epoxide, it is found that direct reduction is the predominant product. These results also indicate that the majority of the direct reduction must not involve complexed epoxide since this should result in the predominant formation of X. An indication of the strong donor properties of hydrides in tetrahydrofuran was already indicated with the mixed hydride reagents.[10,11] (2) The product ratios arising from the reductions involving all of the alkoxyaluminum hydrides and aluminum hydride are similar with a noticeable decrease in X when proceeding from AlH_3 to AlH_2O-*t*-Bu to AlH_2O-*i*-Pr. Such a trend is easily understood on steric grounds when proceeding from monomeric AlH_3 to dimeric AlH_2O-*t*-Bu to what is believed to be a more highly associated AlH_2O-*i*-Pr. Note in Table IV a product yield of 0% for $AlH(O$-*i*-$Pr)_2$ as compared for the same reduction using $AlH(O$-*t*-$Bu)_2$ (76%). Also Table III shows a lower product yield (9% under forcing conditions) for $AlH(O$-*i*-$Pr)_2$ as compared to $AlH(O$-*t*-$Bu)_2$ (51% under forcing conditions). The product yield from Table III involving $AlH(OMe)_2$ (4%) which is known to be polymeric is very similar to that produced from $AlH(O$-*i*-$Pr)_2$ (9%). Thus the trend observed for both product yield and yield of X in Table IV is to be expected on steric grounds of the hydride reagent.

These observations corroborate the arguments outlined above. Alkoxyaluminum hydrides are significantly weaker as Lewis acids than the "mixed hydride" reagents and are similar to the parent compound, aluminum hydride, of both types of reagents. In short, the following order of increasing Lewis acidity is observed: $HAlOR_2 \simeq H_2AlOR \simeq AlH_3 < AlH_2X < AlHX_2$, where R = CH_3, *i*-Pr, and *t*-Bu and X = I, Br, and Cl.

The data and arguments outlined above amply demonstrate the fact that alkoxyaluminum hydrides and hydridoaluminum halides are dissimilar in exhibited reactivity as reducing agents.

Experimental Section

Materials Used.—Tetrahydrofuran was obtained from Fisher Scientific Co. and purified by distillation from sodium aluminum hydride under a nitrogen atmosphere. Methanol and isopropyl alcohol were distilled from magnesium turnings. *t*-Butyl alcohol was purified by distillation from sodium under a nitrogen atmosphere. Lithium aluminum hydride was obtained from Metal Hydrides Inc. Solutions were prepared by stirring hydride–tetrahydrofuran slurries overnight, filtering the solid material, and standardizing the clear filtrate by titration of aliquots with EDTA. H_2SO_4 (100%) was prepared from water and fuming sulfuric acid was obtained from Fisher Scientific.

Styrene oxide was obtained from the Aldrich Chemical Co. and purified by drying over potassium carbonate, followed by distillation through a Teflon-coated annular spinning-band column. β-Diisobutylene oxide was dried over potassium carbonate and purified by distillation through a spinning-band column. Vapor phase chromatography analysis showed that this epoxide was 97% pure after two distillations.

Reductions of epoxides were carried out under dry nitrogen in a heat-dried and nitrogen-purged round-bottom flask fitted with a magnetic stirrer and a stopper with two inlet tubes. One inlet was fitted with a nitrogen purge and the other with a serum cap. All reagents were introduced into the reaction vessel by injection through the serum cap with the appropriately sized multifit syringes. Reductions of β-diisobutylene oxide were carried out by first preparing the appropriate alkoxyaluminum hydride from a standardized solution of aluminum hydride in tetrahydrofuran and a stoichiometric amount of the appropriate alcohol, according to the method of Suchi.[7] The aluminum hydride was prepared by combining a standardized lithium aluminum hydride solution with 100% sulfuric acid, according to the method of Brown and Yoon.[15] To the resulting reagent was added a measured amount of a standard epoxide solution. Reductions on this epoxide were carried out either at room temperature for 2 hr (normal conditions) or at reflux for 6 hr (forcing conditions). The reactions were carried out in tetrahydrofuran. After the appropriate time had elapsed, the reaction mixtures were subjected to hydrolytic work-up, dried over potassium carbonate, and concentrated at reduced pressure. A measured amount of 1-octanol, the internal standard for vpc analysis, was added.

Reductions of styrene oxide were carried out in an analogous manner, except that all reactions were carried out at room temperatures for 2 hr. The internal standard for vpc analysis was 1-octanol.

(15) See Table IV, footnote *c*.

Method of Analysis of Products.—All product analyses were carried out using an F & M Model 720 dual-column temperature-programming vapor phase chromatograph. Columns packed with Carbowax 20M were found to be suitable for product analyses from reductions involving both β-diisobutylene oxide and styrene oxide. The products were identified by comparison of retention times with those of authentic samples. Product ratios were calculated from the areas under the corresponding peaks and the relative responses of the products with respect to 1-octanol, the internal standard. Over-all product yields and material balances were also determined in this manner. The relative responses of the products with respect to 1-octanol were determined by analysis of mixtures of carefully weighed amounts of the products and 1-octanol. All areas were determined by tracing the peaks with a planimeter.

Products from Reductions of β-Diisobutylene Oxide.—2,2,4-Trimethylpentanol-3 for comparison purposes was synthesized from isobutyraldehyde and *t*-butylmagnesium chloride.[16] 2,2,4-Trimethylpenten-1-ol for comparison purposes was synthesized according to the procedure for Rerick and Eliel.[6b]

Products from Reductions of Styrene Oxide.—1-Phenylethanol and 2-phenylethanol for comparison purposes were obtained from Aldrich Chemical Co., and were purified by distillation through a packed column under reduced pressure.

(16) B. J. Cooke, M.S. Thesis, Georgia Institute of Technology, Atlanta, Ga., 1967.

Registry No.—I, 96-06-0; VIII, 96-09-3; H_2AlO-*t*-Bu, 15649-64-6; $HAl(O\text{-}t\text{-}Bu)_2$, 15649-65-7; H_2AlO-*i*-Pr, 15649-66-8; $HAl(O\text{-}i\text{-}Pr)_2$, 15649-67-9; $HAl(OMe)_2$, 15649-68-0.

Acknowledgment.—The authors are indebted to Professor E. L. Eliel for samples of 2,2,4-trimethylpentanol-3, 2,2,3,3-tetramethylbutanol, and β-diisobutylene oxide. The authors are also indebted to the National Aeronautics and Space Administration for partial financial support of this work.

Imine Photoalkylations. Papaverine, Phenanthridine, and a General Mechanism[1]

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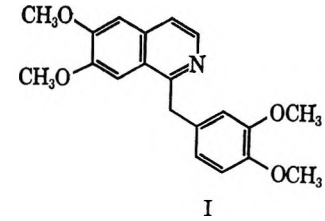
Received September 13, 1967

Irradiation of papaverine (or its hydrochloride) in methanol and ethanol produced 1-methyl-6,7-dimethoxyisoquinoline and 1-ethyl-6,7-dimethoxyisoquinoline, respectively. Irradiation of phenanthridine in ethanol yielded 6-ethylphenanthridine. A mechanism is described which serves to correlate the present results with a number of alcohol incorporations in imine photochemistry.

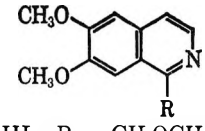
A recent report[2] on the photoalkylation of some pyrimidines and pyrazolopyrimidines prompts us to describe the details of our results[3,4] on alcohol incorporation in the photolysis of papaverine and the photoalkylation of phenanthridine. On the surface, our results and those of Ochiai[2] might appear to involve novel photochemistry. However, closer inspection and consideration of a number of seemingly unrelated literature reports on other imine photochemistry suggested to us that a general mechanism could be written which would correlate a considerable body of C=N photoreactivity. Such a correlation seems valuable at the present time since recent books on photochemistry (with one exception) have largely ignored this topic. This is in spite of the fact that sufficient data is already present in the literature to indicate a versatility of C=N photoreactivity unsurpassed by that of C=O.

Results

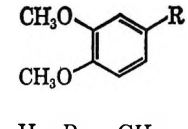
Irradiation of 10^{-3} *M* solutions of papaverine (I) or its hydrochloride in methanol or ethanol for 5–11 days caused 40–60% photolysis and formation of essentially a single basic product (II) in each case, isolated in corresponding yields. With methanol solvent, the product was 1-methyl-6,7-dimethoxyisoquinoline (IIa) and with ethanol solvent, the product was 1-ethyl-6,7-dimethoxyisoquinoline (IIb). Photolysis proceeded only slightly faster in quartz than when a Pyrex filter was used and photolysis did not occur in the same length of time with benzene as solvent. With isopropyl alcohol as solvent, photolysis was relatively rapid (I decreased significantly in hours rather than days) and a mixture of as yet unknown basic products was formed. These products appeared to undergo further photoreactions. In the case of photolysis in methanol and ethanol, the nonbasic products were separated and analyzed. Typical results are given in Table I. The relative yields of methyl and ethyl veratryl ethers (IIIa and IIIb) as compared to veratraldehyde (IIIc) were considerably variable since the former are autoxidizable to the latter. The yields



I



IIIa, R = CH_2OCH_3
b, R = $CH_2OCH_2CH_3$
c, R = CHO
d, R = CH_3
e, R = $COOCH_3$
f, R = $COOCH_2CH_3$
g, R = OCH_3
h, R = H



IIa, R = CH_3
b, R = CH_2CH_3

(1) This work was supported by Grants GM 12407 and GM 15425 from the National Institute of General Medical Sciences (U. S. Public Health Service). The major part of the work was conducted at Utah State University, Logan, Utah, and represented a portion of the Ph.D. thesis submitted to that institution by R.P.S.

(2) M. Ochiai and K. Morita, *Tetrahedron Lett.*, 2349 (1967).

(3) Preliminary results on papaverine photolysis have been reported: Abstracts, the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 40C; see also ref 4.

(4) F. R. Stermitz, R. Pua, and H. Vyas, *Chem. Commun.*, 326 (1967).

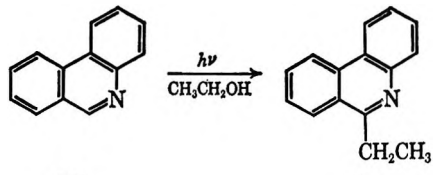
TABLE I

NONBASIC PRODUCTS FROM PAPAVERINE IRRADIATIONS

Reactants	Products, % yield								
	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	IIIh	Unknown
I in CH_3OH	45		Trace	45	Trace		Trace	Trace	Trace
I·HCl in CH_3OH			90		10				
I in CH_3CH_2OH		75		15		Trace		Trace	Trace
I·HCl in CH_3CH_2OH		22	64	7				7	

of IIIa and IIIb are therefore minimum yields and those of IIIc are maximum.

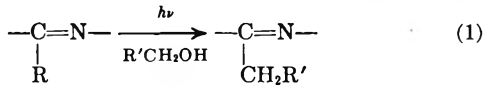
A 5×10^{-2} *M* solution of phenanthridine (IV) in acidified ethanol was irradiated for 14 days (Colorado sunlight) or for 41 hours in a 5-l. immersion reactor with a Hanovia 450-W L lamp, and essentially complete conversion of IV into 6-ethylphenanthridine (V) was achieved.



IV V

Discussion

The reaction we have discovered can be generalized as in eq 1. In our above cases, R = H or veratryl and

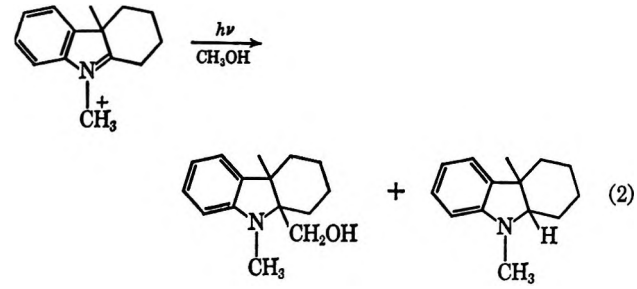


(1)

in the simultaneously discovered[2] photoalkylation of pyrimidines, R = H. A case where R = Cl is also known.[5] In view of the disparity of these R groups, it seems likely that the reaction will prove to be independent of R and therefore of some general applicability. Our results and those of Ochiai[2] indicate that limitations will, however, reside in the alcohol and in the electronic character[2] of the imine.

Mechanistically, the problem presents itself as to how to incorporate this new reaction into our present knowledge of photochemistry. Formally, we seem to be observing alkyl–oxygen cleavage of the alcohols, a manner of photoreactivity for alcohols completely unknown (except in the case of direct irradiation with short wavelength light). Normally, alcohols have been observed to react with photoexcited molecules in only two ways: (1) *via* α-hydrogen abstraction such as in pinacol formation with ketones and (2) *via* O–H bond cleavage such as in the photoaddition to olefins. We believe that our results can best be explained by an initial hydrogen abstraction process, followed by coupling and elimination and that there is, therefore, no need to postulate a new form of alcohol reactivity. Scheme I (path A) presents our suggested mechanism, using the photolysis of papaverine in ethanol as an example.

The first stages in Scheme I (path A) are the same as those which must apply in the reaction observed[6a] by Cerutti and Schmid (see eq 2). Since the non-



(2)

VI

bonded pair on nitrogen is not available in their case or ours in acid, initial excitation must be π–π^*. The papaverine photolysis products are quite similar to those from the hydrochloride photolysis and it seems likely that π–π^* excitation is operable in the case of the free base also. Hydrogen abstraction from the alcohol provides the intermediates necessary for coupling and this is supported by the large rate increase of papaverine photolysis in isopropyl alcohol and the failure in benzene. A similar process must also precede the dimerization of 1-methyl-3,4-dihydroisoquinoline.[6b]

Because of the presence of the good veratryl leaving group, we have not been able to isolate the suspected intermediate VII. However, occurrence of VI, which cannot react further, lends support to the intermediacy of VII. The effectiveness of acid in the alkylations reported[2] by Ochiai is also explained by VII since in his cases (and ours on phenanthridine) the veratryl group is replaced by a hydrogen and acid is necessary to provide facile elimination to an intermediate such as VIII.

Additional evidence for Scheme I (path A) is suggested by the finding of products such as IIIa and IIIb, which are those expected of ionic-type reactions. Postulation of the formation of the veratryl cation X, which is rapidly converted into IIIa or IIIb, provides a logical explanation for many of the III products. Thus, the photolysis[7] of 3-methoxybenzyl acetate in 50% ethanol–water yielded ethyl 3-methoxybenzyl ether (corresponding to IIIb formation) and a mechanism involving an intermediate such as X was suggested. The photochemical autoxidation of ethers (*e.g.*, IIIb to IIIc) is well known[8] and the oxidation is also a dark reaction. The formation of ester products IIIe and IIIf from IIIc irradiation also has ample literature precedence.[9]

One nonbasic product (IIId) was found in relatively high yield only in the case of I photolysis in methanol (see Table I). This product, as well as trace products IIIg and IIIh, did not seem to be explicable in terms

(5) M. Ochiai (Takeda Chemical Industries), private communication (1967).

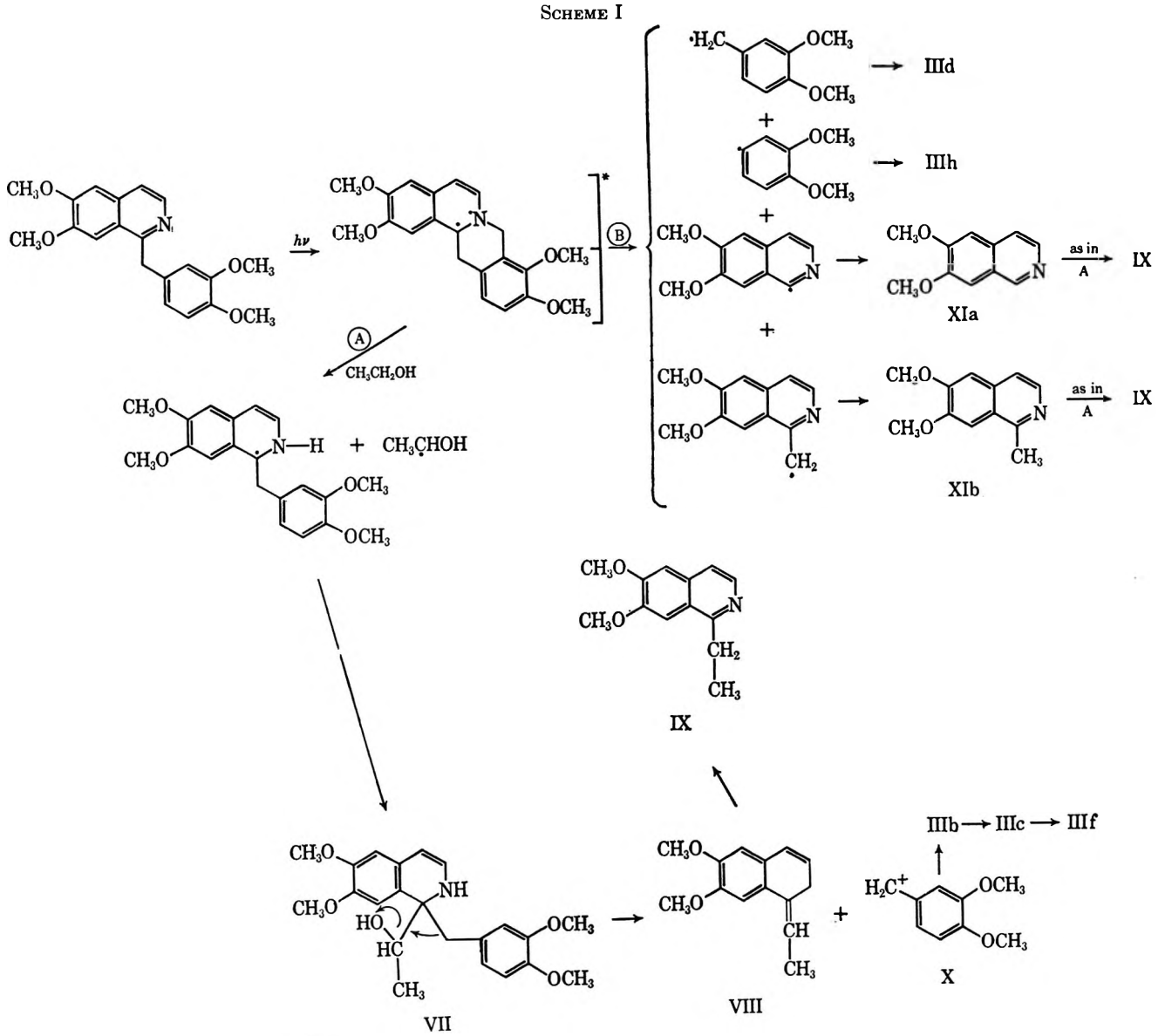
(6) (a) P. Cerutti and H. Schmid, *Helv. Chim. Acta*, **45**, 1992 (1962); (b) *ibid.*, **47**, 203 (1964).

(7) H. E. Zimmerman and V. R. Sandel, *J. Amer. Chem. Soc.*, **85**, 915 (1963).

(8) A. M. Clover, *ibid.*, **46**, 419 (1924); N. A. Milas, *ibid.*, **53**, 221 (1931); D. B. Sharp and T. M. Patrick, Jr., *J. Org. Chem.*, **26**, 1389 (1961).

(9) P. de Mayo, *Advan. Org. Chem.*, **2**, 413 (1960).

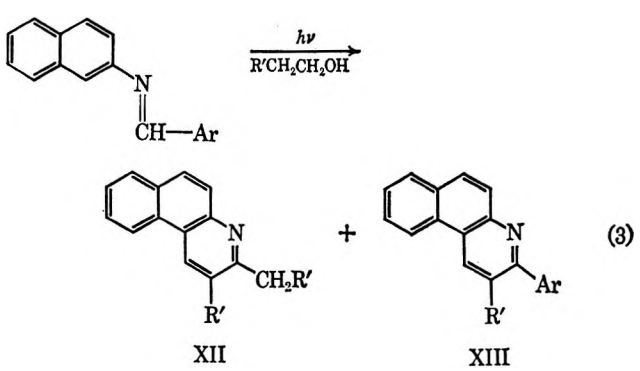
SCHEME I



of path A and, therefore, path B is proposed as a (usually) secondary mode of papaverine photolysis. The isoquinolines XIa and XIb would be readily converted *via* path A into IX and this would explain our failure to find XIa and XIb. Experiments are presently underway to provide further evidence for path B.

We are thus essentially suggesting that imine photochemistry is quite analogous to ketone photochemistry. The dimerization mentioned above[6b] and acridine reductive dimerization[10] are thus analogs of symmetrical pinacol formation (benzopinacol from benzophenone in isopropyl alcohol), whereas our results and others discussed here are analogs of mixed pinacol formation (1,1-diphenyl-1,2-ethanediol from benzophenone in methanol[11]).

Imine photoreduction, however, can apparently lead to one additional type of product involving rearrangement of the abstracted hydrogen prior to coupling. This is, in the first example, exemplified by a mechanism we would like to suggest (Scheme II) for the complex transformation[12] observed recently (eq 3).



(3)

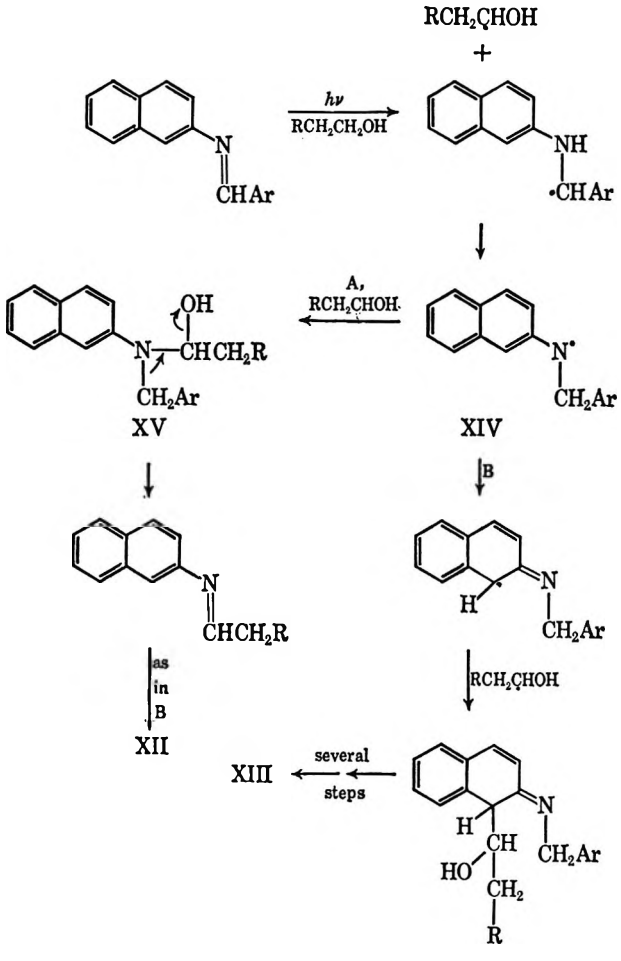
No explanation for this transformation has been given previously and it has only been suggested[10,12] that the alcohol is probably oxidized to aldehyde as a first step. Our mechanism (Scheme II) follows Scheme I with the exception that the hydrogen abstracted from the alcohol by the excited imine first migrates from nitrogen to carbon before the coupling takes place. We feel that it is less likely that intermediate XIV would be formed by direct hydrogen abstraction to the carbon

(10) See, for example, R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., New York, N. Y., 1966, p 225, and references given there.

(11) H. Göth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta*, **48**, 1395 (1965).

(12) P. J. Collin, H. Silberman, S. Sternhell, and G. Sugowdz, *Tetrahedron Lett.*, 2063 (1965); J. S. Shannon, H. Silberman, and S. Sternhell, *ibid.*, 659 (1964).

SCHEME II



end of the C=N, although this remains a possibility. Finally, it should be pointed out that riboflavin photobleaching has been shown[13] to be initiated by the same process proposed here with the exception that in the case of riboflavin an *intramolecular* hydrogen abstraction takes place. In this study[13] a postulated structure for leucodeuteroflavin (a transitory intermediate) was the analog of XV and thus the three steps leading to XV in Scheme II are exactly analogous to the intramolecular ones believed to apply in riboflavin photochemistry.

Experimental Section[14]

General Irradiation Procedure.—Irradiations were conducted in an immersion reactor using an Hanovia Type S (200-W) lamp with a Pyrex filter. (In trial experiments using quartz the typical basic cleavage products were observed to form at only a slightly faster rate, but the total material remaining after solvent evaporation was considerably greater than starting material and there was apparently solvent decomposition during irradiation.) Prior to irradiation, the solution was flushed with nitrogen and nitrogen was bubbled through the solution constantly during irradiation. This prevented the rapid oxidation of papaverine to papaveraldine and other products which occurred when nitrogen was omitted. The solution was stirred magnetically during the entire irradiation. Reagent grade methanol, 95% ethanol, isopropyl alcohol, and benzene were redistilled (discarding initial and final distillates) prior to use.

Papaverine and Papaverine Hydrochloride Photolysis.—A typical complete procedure for papaverine in methanol will be given, followed by whatever different procedures were used in other cases.

A solution of 1.53 g (0.00452 *M*) of papaverine (λ_{max} 324 (log ϵ 3.45) and 316 (log ϵ 3.41)) in 4.5 l. of methanol was irradiated (see above) for 7 days. The progress of photolysis was checked by tlc. Papaverine gave a red-violet spot at R_f 0.60 and a blue-green spot appeared at R_f 0.56 after 24 hr of irradiation. At the end of 7 days, the two spot densities were about equal. The solvent was removed *in vacuo* at room temperature with a rotary evaporator and the residue was dissolved in 50 ml of ether. The ether solution was extracted with three 15-ml portions of 0.1 *N* hydrochloric acid and the acidic layer was brought to pH 3 by the addition of base. The ether layer was dried and evaporated to leave 0.253 g of "nonbasic fraction." The acid solution was extracted with three 50-ml portions of chloroform. The chloroform layer was dried and evaporated to leave 1.08 g of unreacted papaverine. The acidic layer was made basic and extracted with three 50-ml portions of chloroform. The chloroform layer was dried and evaporated to leave 0.249 g of light brown viscous oil which showed (on tlc) only the blue-green spot at R_f 0.56. Upon sublimation of this material, 1-methyl-6,7-dimethoxyisoquinoline (IIa), mp 104–107° (lit.[15] mp 106–107°) was obtained. It formed a hydrochloride salt of mp 224–228° (lit.[16] mp 226–228°) and had an nmr spectrum in agreement with this structure. The "nonbasic fraction" (see above) showed seven peaks on vpc. The nmr spectrum of the mixture before vpc was identical with that obtained by collecting the seven peaks after vpc. Two of the peaks were approximately equal in area and represented about 90% of the nonbasic fraction. These were shown to be homoveratrole (IIId), identified by spectral comparison with an authentic purchased sample (K & K Laboratories), and methyl veratryl ether (IIIa), identified by spectral comparison with an authentic sample prepared from veratryl chloride and sodium methoxide solution. Of the remaining five trace constituents, four could be identified. These were veratrole (IIIh), 1,3,4-trimethoxybenzene (IIIg), veratraldehyde (IIIc), all identified by spectral comparison with authentic purchased samples (Aldrich Chemicals), and methyl veratrate (IIIe), identified by spectral comparison with an authentic sample prepared by esterification of 3,4-dimethoxybenzoic acid.

Irradiation of 1.69 g (0.005 *M*) of papaverine hydrochloride in 4.5 l. of methanol for 11 days and work-up of the products as before yielded 0.663 g of unreacted papaverine, 0.432 g of IIa, and 0.343 g of "nonbasic fraction." The "nonbasic fraction" was found to be composed of 90% veratraldehyde (IIIc) and 10% methyl veratrate (IIIe) as above.

Irradiation of 1.68 g (0.005 *M*) of papaverine in 4.5 l. of 95% ethanol for 11 days and work-up as before yielded 0.271 g of unreacted papaverine, 0.501 g of "nonbasic fraction," and 0.539 g of a basic product having the same R_f on tlc as papaverine. However, the nmr showed the presence of two methoxyl groups and an aromatic ethyl substituent. Sublimation yielded pure 1-ethyl-6,7-dimethoxyisoquinoline (IIb), mp 70–71° (lit.[17] mp 75–76°). Elemental analysis and detailed nmr and mass spectral analysis confirmed the identity. The "nonbasic fraction" consisted of 15% homoveratrole (IIId), 75% ethyl 3,4-dimethoxybenzyl ether (IIIb), identified by spectral comparison with an authentic sample prepared from veratryl chloride and sodium ethoxide, and three trace components. Of the trace components, one was veratrole (IIIh) and a second ethyl veratrate (IIIf). The latter was not obtained pure, but was always contaminated by the third trace component, which has remained unidentified. However, the major portion of the nmr spectrum and infrared spectrum of the mixture was identical with that of authentic ethyl veratrate (prepared by esterification of 3,4-dimethoxybenzoic acid).

Irradiation of papaverine hydrochloride in 95% ethanol in a similar manner yielded, in addition to unreacted papaverine and

(13) W. M. Moore, J. T. Spence, F. A. Raymond, and S. D. Colson, *J. Amer. Chem. Soc.*, **85**, 3367 (1963).

(14) Melting points are uncorrected and were taken on a Mel-Temp apparatus. Nmr spectra were obtained with Varian A-60 and Varian A-60A spectrometers at 60 Mc/sec using tetramethylsilane as an internal reference. Mass spectra were determined with an Hitachi Perkin-Elmer RMU 6-E, ultraviolet spectra with a Cary 15, and infrared spectra in KBr (solids) and CCl_4 (liquids) using a Beckmann IR-8 spectrophotometer. Thin layer chromatography (tlc) was performed on silica gel F254 plates (Brinkmann) with 1:4 methanol–benzene as developing solvent and iodoplatinic acid as the visualizing agent. Vapor phase chromatography (vpc) was performed at 235° using a 10-ft 20% Carbowax on Chromosorb W column in a Varian Aerograph A90P apparatus. Organic solutions were dried with sodium sulfate before evaporation.

(15) A. Ahl and T. Reichstein, *Helv. Chim. Acta*, **27**, 366 (1944).

(16) G. N. Walker, *J. Amer. Chem. Soc.*, **76**, 3999 (1954).

(17) E. Späth and N. Polgar, *Monatsh.*, **51**, 190 (1929).

IIb, a "nonbasic fraction" consisting of 64% veratraldehyde (IIIc), 22% ethyl 3,4-dimethoxybenzyl ether (IIIb), and 7% each of homoveratrole (IIId) and veratrole (IIIh).

A number of trial runs on papaverine irradiation in isopropyl alcohol were attempted using 800 ml of a 10^{-3} *M* solution. For example, after 3 hr of irradiation, tlc showed the presence of five new trace spots positive to iodoplatinic acid. However, upon continued irradiation these spots began to disappear as did that for the papaverine starting material. Evaporation of the solvent left residues weighing two to four times as much as that of the total starting material and preliminary attempts at isolation of any specific pure products were not successful.

Irradiations conducted in a similar manner, except using benzene as solvent, showed no photolysis products on tlc. In one case, an Hanovia Type L (450 W) lamp was used and no new product could be detected after 2 days of irradiation. The solvent was evaporated and the residue found to be only unreacted papaverine. Under these conditions, product spots could be observed using methanol solvent after 2 hr and in less than 1 hr using isopropyl alcohol as solvent.

Irradiation of Phenanthridine.—Phenanthridine (0.91 g or 0.0048 *M*) was dissolved in a mixture of 992 ml of 95% ethanol and 8 ml of concentrated hydrochloric acid and the resulting solution was placed in a 1000-ml Pyrex flask. This was stoppered, inverted, and placed in the sunlight. After 14 days of irradiation, the solvent was removed *in vacuo*, the residue was dissolved in methanol, the solution evaporated, and the residue triturated with benzene–ether. This left a brown oil whose nmr spectrum showed the disappearance of the downfield singlet due to the proton at the 6 position (next to nitrogen) and the appearance of a characteristic upfield triplet and quartet of an ethyl group. Essentially the same result was obtained when 5 l. of the same solution was irradiated for 41 hr in an Hanovia immersion reactor (450-W Type L lamp) under nitrogen and using a Pyrex filter. Gas chromatography showed the residue to be contaminated with about 10% phenanthridine. The gas chromatographic separation yielded a white solid which was then recrystallized from *n*-heptane to give 6-ethylphenanthridine, mp 55° (lit.[18] mp 54–55°). The mass spectrum was exactly analogous with that reported[19] for 2-ethylpyridine (as opposed to other ethylpyridines) and constituted additional proof of structure.

Registry No.—I, 58-74-2; I hydrochloride, 61-25-6; IV, 229-87-8.

Acknowledgment.—The authors are indebted to Drs. R. C. Anderson and W. M. Moore of Utah State University for many helpful discussions and comments.

(18) A. Pictet and A. Hubert, *Ber.*, **29**, 1186 (1896).

(19) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., New York, N. Y., 1962, p 134.

The Electron-Impact Fragmentation of Dimethylaminoacetone and 2-Dimethylaminocyclohexanone

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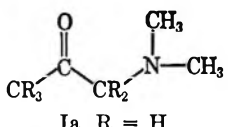
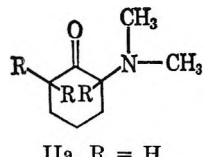
The mass spectra of dimethylaminoacetone and 2-dimethylaminocyclohexanone have been analyzed with the help of their deuterated analogs. Fragmentation patterns are interpreted as being virtually exclusively directed by the nitrogen function with insignificant fragmentation direction by the carbonyl group.

As a prelude to studying the photochemistry of some amino ketones, and particularly the intramolecular interactions of the amino and ketone functions, it was deemed of interest to study the electron impact fragmentation of some model compounds. It has been suggested a number of times in the literature that mass spectra, particularly of aliphatic ketones, can be correlated with photochemistry. The presence of an amino function (strongly directing in electron impact fragmentation) in the same molecule as a carbonyl (highly reactive photochemically) might be expected to test severely this correlation. This paper reports an analysis of the mass spectra of dimethylaminoacetone (Ia) and 2-dimethylaminocyclohexanone (IIa) assisted by the spectra of the deuterio analogs Ib and IIb.



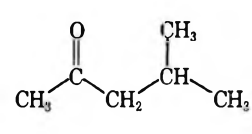
Ia, R = H
b, R = D



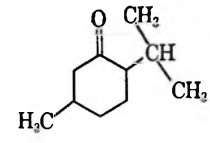
IIa, R = H
b, R = D

Figures 1–4 give the 80-eV mass spectra of Ia, Ib, IIa, and IIb, respectively.

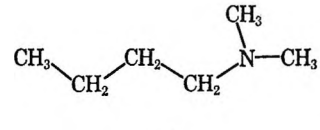
It is perhaps most instructive to compare these spectra with those of similar structure, but in which first the nitrogen is replaced by carbon and, alternatively, the carbonyl group is replaced by CH_2. For the first comparison, mass spectra of 4-methyl-2-pentanone[2] (III) and menthone[3] (IV) are particularly useful. For the second comparison, spectra of dimethyl-*n*-butylamine[4] (V) and a number of dimethylamino steroids[5] (VI) are available. For the



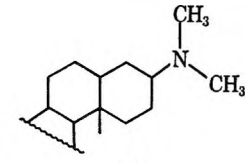
III



IV



V



VI

(1) Public Health Service Research Career Development Awardee (5-K3-GM-16,698) of the National Institute of General Medical Sciences (U.S.P.H.S.) at Utah State University (1963–1967). The experimental portion of this work was conducted at Utah State University under Grant GM-12407 from the N.I.G.M.S.

(2) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, Figure 8.5, p 124.

(3) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc. San Francisco, Calif., 1964, Figures 1-12 and 1-13, p 23.

(4) R. S. Gohlke and F. W. McLafferty, *Anal. Chem.*, **34**, 1281 (1962).

(5) L. Dolejs, V. Hanus, V. Cerny, and F. Sorm, *Collect. Czech. Chem. Commun.*, **28**, 1584 (1963); Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 574 (1965).

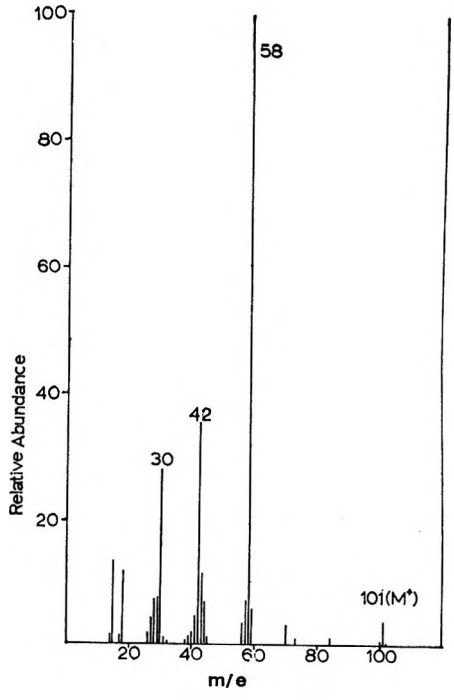


Figure 1.—Mass spectrum of dimethylaminoacetone.

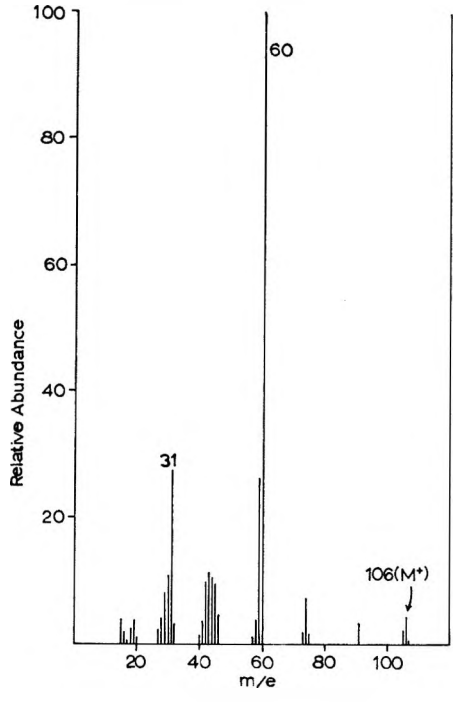


Figure 2.—Mass spectrum of pentadeuteriodimethylaminoacetone.

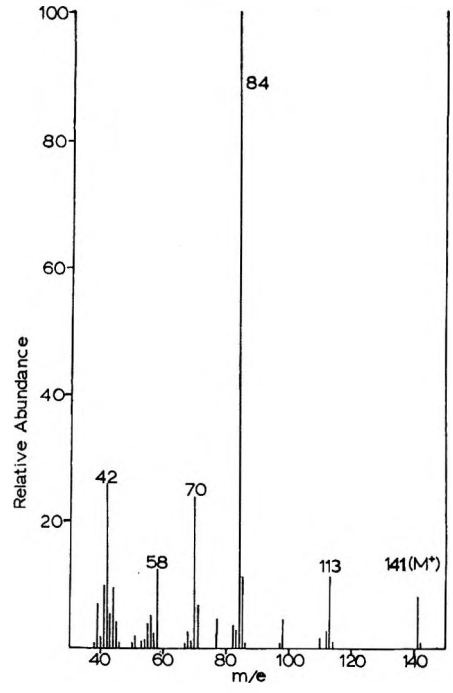


Figure 3.—Mass spectrum of 2-dimethylaminocyclohexanone.

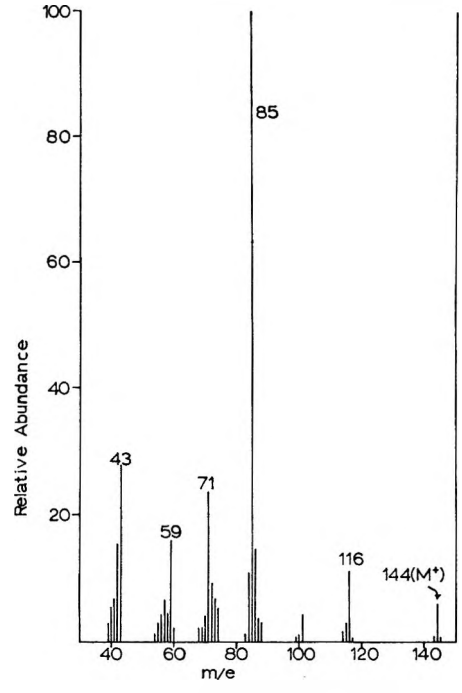
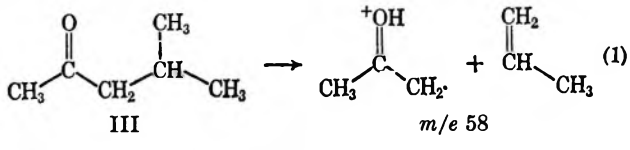


Figure 4.—Mass spectrum of trideuterio-2-dimethylaminocyclohexanone.

first comparison, it is noted[2] that III yields a base peak at m/e 43 for $CH_3C{\equiv}O^+$, which is typical for all methyl ketones and, of second intensity, the m/e 58 McLafferty rearrangement ion (eq 1). The amino



analog Ia, on the other hand, exhibits a relatively minor m/e 43 peak, with the base peak being at m/e 58. Inspection of the Ib spectrum, however, shows that the m/e 58 peak in Ia cannot be that arising from process 1, since there is virtually nothing at m/e 63. The m/e peak has, instead, shifted to m/e 60, indicating the presence of only two deuterium atoms. Based upon comparisons with the spectrum[4] of V, the m/e peak in Ia must be due to the $CH_2{=}N^+(CH_3)_2$ ion. Thus, process 2, the ubiquitous one for methyl

$$CH_3\overset{\cdot O^+}{\overset{\|}{C}}CH_2N(CH_3)_2 \longrightarrow CH_3C{\equiv}\overset{+}{O} + \cdot CH_2N(CH_3)_2 \quad (2)$$

ketones, has been supplanted by process 3 in the

$$CH_3\overset{O}{\overset{\|}{C}}\dot{\overset{+}{C}}H_2N(CH_3)_2 \longrightarrow CH_3\dot{C}{=}O + CH_2{=}\overset{+}{N}(CH_3)_2 \quad (3)$$

present case. If the molecular ion of process 2 were formed at all, some McLafferty rearrangement should

have been observed. The complete absence of this process provides strong evidence for an assumed localized ionization[6] at the nitrogen as the directive force in the fragmentation.

An interesting sidelight in the Ia and Ib spectra is provided by the *m/e* 30 peak of Ia which changes to *m/e* 31 in the deuterio analog. A metastable peak was observed at *m/e* 15.6, with the calculated value of 15.5 being that for a *m/e* 58 to 30 process. The ordinary interpretation of this (CH_2=$N^+(CH_3)_2$ → CH_2=N^+H_2) would predict a shift to *m/e* 32 rather than the observed *m/e* 31. This process will be examined in more detail.

For the second comparison (II *vs.* IV and VI), it is noted[3] that the base peak in the mass spectrum of IV is that resulting from process 1 since we are no longer dealing with a methyl ketone. If this same process held in regard to IIa, the base peak would be expected to appear at *m/e* 98, with a shift to *m/e* 101 in IIb. Examination of Figures 3 and 4 indicates that this is far from being the case, although here this process has not been completely eliminated as in the case of Ia. The base peak of IIa can be assigned to the CH_2=$CHCH$=$N^+(CH_3)_2$ ion (*m/e* 84 in IIa and *m/e* 85 in IIb) in complete accordance with observations[5] in the VI systems where no carbonyl is present.

Our results[7] on the photochemistry of Ia and IIa will be reported subsequently. Those interested in making correlations between electron-impact fragmentation and photochemistry have an opportunity, in the meantime, to predict the latter based upon the spectra reported here.

Experimental Section

The mass spectra were taken using an Hitachi Perkin-Elmer RMU-6E mass spectrometer (80 eV, 100°, all-glass inlet).

Dimethylaminoacetone and 2-dimethylaminocyclohexanone were purchased from Aldrich Chemicals and purified by distillation at reduced pressure.

The deuterated analogs were prepared by warming a mixture of ketone and deuterium oxide with a trace of anhydrous sodium carbonate. The ketone was then isolated by extraction with anhydrous ether and the entire procedure was repeated until complete deuteration (as evidenced by mass spectrometry) of all the protons adjacent to the carbonyl was achieved.

Registry No.—Ia, 15364-56-4; Ib, 15364-57-5; IIa, 6970-60-1; IIb, 15364-59-7.

(6) F. W. McLafferty, "Determination of Organic Structures by Physical Methods," F. C. Nachod and W. D. Phillips, Ed., Academic Press Inc., New York, N. Y., 1962, p 93.

(7) F. R. Stermitz and V. P. Muralidharan, unpublished results.

The Preparation of (+)-N-Methyl-1-(1-naphthyl)ethylamine and the Determination of Its Optical Purity by Nuclear Magnetic Resonance[1a]

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Received September 18, 1967

Optically pure 1-(1-naphthyl)ethylamine (**1**) was converted into the optically pure N-methyl derivative (**2**) by methylation of the benzenesulfonamide, followed by cleavage with sodium naphthalene radical anion. It is suggested that this method is a generally useful one for the N-alkylation of optically active amines without loss of optical purity. The optical purities of **1** and **2** were determined by nmr spectroscopic analysis of the O-methylmandelamides. This approach to the estimation of the optical purity of primary and secondary amines appears to have broad applicability.

In connection with other work in progress in these laboratories, it became necessary to prepare optically pure N-methylamines of type $R_1R_2CHNHCH_3$ from the corresponding primary amines, $R_1R_2CHNH_2$. The purpose of the present paper is to describe, through the example of the conversion of (+)-1-(1-naphthyl)ethylamine ("Resoline," **1**) to (+)-N-methyl-1-(1-naphthyl)ethylamine (**2**), a procedure for N-methylation which results in no loss of optical purity and a method for determining the optical purity of primary and secondary amines by nmr spectroscopy which gives accurate estimates and is simple to apply.

One approach to the preparation of **2** involved reduction of the formamide of **1** (**3**) with lithium aluminum hydride[2] in ether. However, reaction for 18 hr afforded only a low yield of the desired product with the recovery of a considerable amount of unreacted starting material.[3] An alternative approach, the methylation of the benzenesulfonamide of **1** (**4**) and subsequent cleavage of the N-methyl derivative (**5**) by commonly reported procedures,[4] was investigated. Attempted cleavage of **5** with cold, concentrated sulfuric acid,[5] 25% aqueous sulfuric acid at reflux,[6] 25% aqueous hydrochloric acid at reflux,[7] or KOH in dimethyl sulfoxide[8] failed to yield the desired product.[9]

(1) (a) This work was supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-67; (b) Public Health Service Postdoctoral Fellow, 1966–1967; (c) Public Health Service Predoctoral Fellow, 1964–1966.

(2) J. Ehrlich, *J. Amer. Chem. Soc.*, **70**, 2286 (1948).

(3) The difficulty of the reduction of some monosubstituted amides has been noted previously; *cf.* V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

(4) The cleavage of sulfonamides has been discussed by S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959).

(5) T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, **20**, 1021 (1955). This procedure led to extensive decomposition of the starting material.

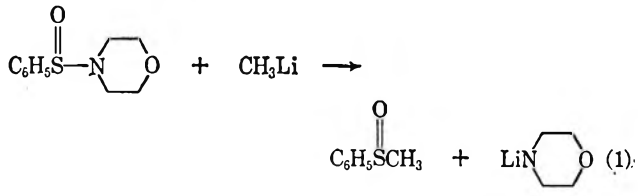
(6) Previous failures to cleave sulfonamides with dilute sulfuric acid (<40%) have been recorded (J. Halberkann, *Ber.*, **54**, 1665 (1921)).

(7) A. Jindra and F. Sipos, *Chem. Listy*, **44**, 235 (1950); *Chem. Abstr.*, **45**, 5569 (1951).

(8) F. C. Chang [*Tetrahedron Lett.*, No. 6, 305 (1964)] has reported the cleavage of toluenesulfonates under similar conditions.

(9) C–N bond cleavage of benzylic sulfonamides has been reported by P. A. Briscoe, F. Challenger, and P. S. Duckworth, *J. Chem. Soc.*, 1755 (1956). The nature of the products (other than recovered starting material) in the present study are unknown.

We recently reported[10] the cleavage of arenesulfinamides with methyllithium as a route to sulfoxides (eq 1), but the anticipated cleavage of **5** under analogous



conditions to yield **2** and methyl phenyl sulfone fails to occur.

The cleavage of sulfonates and sulfonamides with the radical anion of naphthalene has recently been reported.[11] By employing this procedure, we succeeded in cleaving **5** in yields of 75–80%. Since the formation of **4** and the methylation of **4** to **5** are essentially quantitative steps, the over-all yield from **1** to **2** is in the range of 70–80%.

The strongly basic conditions employed in the preparation of **4** and **5**, coupled with the conditions employed in the radical anion cleavage of **5**, might conceivably have led to significant racemization in the course of the conversion of **1** into **2**, by way of abstration of a benzylic α proton.[12] To settle this point, we made use of the nmr method which had been previously applied to the determination of optical purities of alcohols and amines.[13]

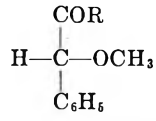
This method depends on the conversion of a mixture of enantiomers ($A_+ + A_-$), using an optically pure reagent, *e.g.*, B_+, into a mixture of diastereomers ($A_+B_+ + A_-B_+$) the ratio of which may be determined by nmr spectroscopy, since, in general, the diastereomers will have similar but distinguishable spectra. The conversion must be carried out in a manner which ensures the equality of the ratios of precursor enantiomers (A_+/A_-) and product diastereomers (A_+B_+/A_-B_+). A reagent previously employed for the determination of the optical purities of alcohols,[14] O-methylmandelyl chloride (**6**), was considered for use with amines. In order to gauge the applicability of the nmr method with the particular reagent under consideration, several amines including **1** and **2** were treated with racemic O-methylmandelyl chloride. In this way mixtures of diastereomers were obtained and their nmr spectra were measured. The use of racemic acid chloride was indicated since an equimolar or nearly equimolar mixture of diastereomers can thus be obtained regardless of the optical purity of the amine used.

In general, when using the nmr method it is advisable to prepare the indicated derivative, here the mandelamides, both from the racemic and from the optically pure reagent, here **6**; if only optically pure acid chloride had been used and no resonance doubling had been observed, it would not have been possible to distinguish between a single diastereomer obtained from reaction with optically pure amine and, given the possibility of accidental coincidence of signals, a mixture of diastereomers obtained from reaction with optically impure amine. Serious errors in interpretation of optical purities may thus be precluded.

The chemical-shift differences of corresponding groups in the resulting mixtures of diastereomeric amides are recorded in Table I. It is seen that in every instance the signals of corresponding protons in the two diastereomeric amides exhibit chemical shift differences of considerable magnitude. The basis was thus laid for the desired determination of optical purity,[13] for if the differences in chemical shift between the diastereotopic[15] O-methyl, C-methyl, methine, and (in the case of **2**) N-methyl groups are large enough and the signals are in a region unencumbered by other resonances, the proportions of the two diastereomers may be determined by integration, each signal affording an independent measure of the diastereomeric ratio.

TABLE I

CHEMICAL-SHIFT DIFFERENCES OF DIASTEREOTOPIC HYDROGENS IN SOME O-METHYLMANDELAMIDES[a]



R	OCH_3[b]	CH_3OCH[c]	CCH_3[d]
$NHCH(CH_3)(\alpha\text{-}C_{10}H_7)$	3.7	2.8	6.5
$N(CH_3)CH(CH_3)(\alpha\text{-}C_{10}H_7)$[e]	5.2	4.8	4.0
$NHCH(CH_3)C_6H_5$	2.3	2.5	4.0
$NHCH(CH_3)CH_2C_6H_5$	2.3	0.8	4.1

[a] Chemical-shift differences are given in hertz for 60 MHz spectra of approximately 10% solutions in deuteriochloroform. [b] Singlets in the region τ 6.5–6.9. [c] Singlets in the region τ 4.8–5.8. [d] Doublets in the region τ 8.2–9.2 (J = 6.5 Hz). [e] NCH_3 singlets at τ 7.67 and 7.71; $\Delta\nu$ 2.4 Hz.

In order to ascertain that no appreciable racemization occurs in the preparation of the acid chloride (or epimerization in the subsequent reactions), optically pure (−)-menthol was reacted with (A) racemic O-methylmandelyl chloride and (B) acid chloride **6** obtained by reaction of optically pure (−)-(*R*)-O-methylmandelic acid with thionyl chloride. The product of reaction A exhibited doubling of resonance signals, with chemical shift differences of 0.4 Hz for the diastereotopic O-methyl protons and of 2.5 Hz for diastereotopic methoxymethine protons (at τ 5.29 and 5.25), whereas the product of reaction B displayed only one resonance for the methine proton, corresponding to the diastereomer which gives the upfield resonance. In an independent experiment,[16] a sample of (+)-(*S*)-O-methylmandelic acid, $[\alpha]^{23}D$ +162° (water), was (A) esterified with diazomethane and (B) converted into (*S*)-O-methylmandelyl chloride which was then reacted with methanol. Methyl (*S*)-O-methylmandelate obtained by these two routes had (A) $[\alpha]^{24}D$ +91.8 ± 0.5° (acetone) and (B) $[\alpha]^{26}D$

(10) J. Jacobus and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 5228 (1967).

(11) W. D. Closson, P. Wriede, and S. Bank, *ibid.*, **88**, 1581 (1966); S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson, and P. Wriede, *ibid.*, **89**, 5311 (1967).

(12) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapters 3 and 4.

(13) M. Raban and K. Mislow, *Tetrahedron Lett.*, No. 48, 4249 (1965); M. Raban and K. Mislow in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., John Wiley and Sons, Inc., New York, N. Y. 1967, p 199. For elegant applications of the method, see H. Gerlach, *Helv. Chim. Acta*, **49**, 2481 (1966), and R. D. Guthrie, W. Meister, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 5288 (1967).

(14) M. Raban and K. Mislow, *Tetrahedron Lett.*, No. 33, 3961 (1966).

(15) K. Mislow and M. Raban in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, Chapter 1.

(16) The experiment was performed by Mr. D. J. Sandman.

+90.9 ± 0.9° (acetone) (lit.[17] $[\alpha]^{13}D$ −96.3° (acetone)).

The method was tested on a sample of partially resolved 1-phenylethylamine, $[\alpha]D$ +22.6° (methanol), which was converted into the amide by reaction with an excess of optically pure (*R*)-O-methylmandelyl chloride (**6**).[18] Integrated intensities of the O-methyl peaks from 50-cycle sweep width scans indicated a diastereomeric ratio of 90:10, corresponding to an optical purity of 80% in the starting amine. From this, the absolute rotation of 1-phenylethylamine is calculated to be $[\alpha]D$ 28.3° (methanol), in satisfactory agreement with the reported value[19] of $[\alpha]D$ 28.5° (methanol).

Reaction of **1** with an excess of optically pure **6** afforded an amide (**7**) whose nmr spectrum consisted of only a single set of signals for the C-methyl, methine, and O-methyl protons, corresponding to the diastereomer which gives the upfield resonance. Reaction of **2** with an excess of optically pure **6** afforded an amide (**8**) whose nmr spectrum consisted of only a single set of signals for the C-methyl, methine, N-methyl, and O-methyl protons, corresponding to the diastereomer which gives the downfield resonance for the first three signals and the upfield resonance for the O-methyl signal. The presence of a single diastereomer in the two O-methylmandelamides demonstrates that **1** and **2** are optically pure within the precision of the nmr measurement and that no racemization takes place in the three-step reaction sequence leading from **1** to **2**.

We believe that the synthesis of **2** from **1** represents a convenient high-yield procedure which is generally useful for the conversion of primary amines of the type $R_1R_2CHNH_2$ to the corresponding N-methyl derivatives without loss of optical purity. The present work further demonstrates the utility of O-methylmandelic acid as an attractive general reagent for the determination of optical purity of amines as well as alcohols by nmr spectroscopy.

Experimental Section[20]

(+)-1-(1-Naphthyl)ethylamine (1) was obtained as "Resoline A" from Crestwood Chemicals, Newport, Tenn., and was purified by distillation and subsequent crystallization of the sulfate salt. The amine had $[\alpha]^{25}D$ +51° (*c* 2.91, absolute ethanol) (lit.[21] $[\alpha]^{19}D$ +61.6° (c 2.22, ethanol)) and $[\alpha]^{23}D$ +81.7° (neat) (lit.[21] $[\alpha]^{17}D$ 82.8° (neat)); the salt had mp 229–232° (lit.[21] mp 230–232°).

(+)-N-[1-(1-Naphthyl)ethyl]formamide (3) was prepared by reaction of **1** with formic acetic anhydride[22] and recrystallized from benzene–petroleum ether (bp 60–70°) to mp 117–118°, $[\alpha]^{25}D$ +121° (*c* 1.18, ethanol). The nmr spectrum featured a doublet at τ 8.34 (J = 6.5 Hz) assigned to CCH_3 (3 H), a multiplet at 3.83–4.33 (CH_3CH, 1 H), a multiplet at 3.41–3.83 (NH, 1 H), and a singlet at 1.86 ($O{=}CH$, 1 H).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.38; H, 6.57; N, 7.03. Found: C, 78.35; H, 6.65; N, 7.13.

(+)-N-[1-(1-Naphthyl)ethyl]benzenesulfonamide (4) was prepared from **1** in the usual manner:[23] mp 150–151° from acetone; $[\alpha]^{26}D$ +23° (*c* 0.96, acetone). The nmr spectrum featured a doublet at τ 8.50 (J = 6.5 Hz) assigned to CCH_3 (3 H), a multiplet at 4.33–4.84 (CH_3CH, 1 H), and a multiplet at 2.75–3.08 (NH, 1 H).

Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.42; H, 5.50; N, 4.50; S, 10.30. Found: C, 69.46; H, 5.35; N, 4.77; S, 10.56.

(−)-N-Methyl-N-[1-(1-naphthyl)ethyl]benzenesulfonamide (5) was prepared by methylation of **4** in the usual manner;[24] mp 174–176° from acetone; $[\alpha]^{25}D$ −40° (*c* 1.59, acetone). The nmr spectrum featured a doublet at τ 8.50 (J = 6.5 Hz) assigned to CCH_3 (3 H), a quartet at 3.80 (J = 6.5 Hz) assigned to CH_3CH (1 H), and a singlet at 7.54 (NCH_3, 3 H).

Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 70.13; H, 5.88; N, 4.30; S, 9.85. Found: C, 70.16; H, 5.86; N, 4.52; S, 10.08.

(+)-N-Methyl-1-(1-naphthyl)ethylamine (2).—Following the general procedure of Closson, Wriede, and Bank,[11] 1 equiv of sulfonamide **5** was added to a solution of the radical anion of naphthalene (3.5 equiv) in THF. The reaction mixture was stirred for 1 hr and then quenched with water. The product was isolated by extraction of the reaction mixture with ether, extraction of the ether layer with dilute hydrochloric acid, neutralization of the acid extract with sodium hydroxide, and extraction of the neutral aqueous layer with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Kugelrohr distillation (100° at 0.1 mm) afforded the pure amine (**2**), $[\alpha]^{25}D$ 74° (*c* 3.885, ethanol). The nmr spectrum featured a doublet at τ 8.57 (J = 6.5 Hz) assigned to CCH_3 (3 H), a quartet at 5.53 (J = 6.5 Hz) assigned to CH_3CH (1 H), and a singlet at 7.66 (NCH_3, 3 H).

Anal. Calcd for $C_{13}H_{15}N$: C, 84.26; H, 8.16; N, 7.56. Found: C, 84.35; H, 8.04; N, 7.80.

Resolution of Mandelic Acid.—*dl*-Mandelic acid (Aldrich) was resolved *via* the (−)-ephedrine salt[25] to give (−)-(*R*)-mandelic acid: mp 130–132.5°; $[\alpha]^{25}D$ −148.5° (*c* 1.18, water) (lit.[25] mp 133.5°, $[\alpha]^{20}D$ −156.9° (water)).

(−)-(*R*)-O-Methylmandelic Acid. Method A.—(−)-Mandelic acid was converted into the O-methyl derivative using dimethyl sulfate in base.[26] The crude product was recrystallized from petroleum ether (bp 60–70°) to constant melting point and rotation. The material had mp 65–67°, $[\alpha]^{23}D$ −161.9°, $[\alpha]^{10.5}D$ −167.9° (*c* 1.66, water) (lit.[27] mp 63–64°, $[\alpha]^{12.5}D$ −165.8° (*c* 1.5686, water)).

Method B.—*dl*-O-Methylmandelic acid (Eastman Organic) was resolved *via* the (−)-ephedrine salt[28] ($[\alpha]^{25}D$ −80° (*c* 1.15, methanol)) to give (−)-(*R*)-O-methylmandelic acid, $[\alpha]^{25}D$ −164° (*c* 1.47, water).

O-Methylmandelyl Chloride.—O-Methylmandelic acid was refluxed on a steam bath with a five- to tenfold excess of thionyl chloride. Benzene was added and the excess $SOCl_2$ was removed on a rotary evaporator under reduced pressure. The evaporation procedure was repeated three or four times to ensure complete removal of excess thionyl chloride. The slightly yellow acid chloride is satisfactory for use without further purification. If desired, the acid chloride may be distilled (70–75° (0.2 mm), Kugelrohr) to give a colorless liquid.

(17) A. McKenzie and H. Wren, *J. Chem. Soc.*, 473 (1910).

(18) The ratio of reagents which was employed depends on their state of optical purity and on the purpose to which the reaction is: if optically pure amine is treated with racemic acid chloride, an excess of the amine is employed in order to ensure complete reaction of the acid chloride and to afford a 1:1 mixture of diastereomeric amides; if a sample of amine whose optical purity is to be determined is treated with optically pure acid chloride (**6**), an excess of **6** is employed in order to ensure complete reaction of the amine and to afford a ratio of diastereomeric amides which equals the ratio of enantiomers in the starting amine; if racemic amine is treated with racemic acid chloride, equimolar portions of amine and acid chloride are employed in order to ensure complete reaction of both components and to afford a ratio of diastereomers which is a function of their relative rate constants of formation.

(19) W. Leitke, *Monatsh. Chem.*, **51**, 381 (1929).

(20) Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Nmr spectra were measured on a Varian A-60A spectrometer and refer to approximately 10% solutions in deuteriochloroform, with tetramethylsilane as internal standard.

(21) E. Samuelsson, Thesis, University of Lund, 1923; *Chem. Abstr.*, **18**, 1833 (1924).

(22) C. W. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

(23) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1959, p 103.

(24) W. H. Carothers, C. F. Bickford, and G. J. Hurwitz, *J. Amer. Chem. Soc.*, **49**, 2908 (1927).

(25) R. Roger, *J. Chem. Soc.*, 1544 (1935); R. H. F. Manske and T. B. Johnson, *J. Amer. Chem. Soc.*, **51**, 1909 (1929).

(26) W. Reeve and I. Christoffel, *ibid.*, **72**, 1480 (1950).

(27) A. McKenzie, *J. Chem. Soc.*, **75**, 753 (1899).

(28) D. G. Neilson and D. A. V. Peters, *ibid.*, 1519 (1962). These authors report that (−)-(*R*)-O-methylmandelic acid has $[\alpha]^{20}D$ −150.7° (*c* 0.574, ethanol). In the present work, the rotation consistently observed by either method A or B was $[\alpha]^{25}D$ −144° (c 1.35, absolute ethanol).

The normal precautions used in handling moisture-sensitive acid chlorides should be exercised. Both racemic and optically pure (6) acid chlorides were prepared by this method.

O-Methylmandelamides were prepared by reaction of the appropriate amine in benzene with a solution of O-methylmandelyl chloride in benzene containing an excess of pyridine. The reaction mixture was allowed to stand at room temperature for 30 min and then poured into a separatory funnel containing ether and water. The ether layer was washed successively with dilute aqueous hydrochloric acid, dilute aqueous sodium bicarbonate, and water. The ether layer was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to yield the crude mandelamide. The mandelamides thus obtained were sufficiently pure for examination by nmr spectroscopy.[29] Analytical samples were crystallized from benzene–petroleum ether (bp 30–60°) mixtures. Nmr properties of the amides and of menthyl O-methylmandelate (which was prepared in the same manner) are given in Table I and the text.

(−)-**N-[1-(1-Naphthyl)ethyl]-O-methylmandelamide** (7), prepared from 1 and optically pure (*R*)-O-methylmandelyl chloride (6), had mp 132–133°, $[\alpha]^{25}D$ −24° (c 1.59, ethanol).

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.96; H, 6.63; N, 4.39. Found: C, 78.91; H, 6.55; N, 4.29.

(+)-**N-Methyl-N-[1-(1-naphthyl)ethyl]-O-methylmandelamide** (8), prepared from 2 and 6, had mp 93–95°, $[\alpha]^{25}D$ +33° (c 0.91, ethanol).

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.96; N, 4.20. Found: C, 79.26; H, 6.85; N, 4.10.

N-[(1-Methyl-2-phenyl)ethyl]-O-methylmandelamide was a diastereomeric mixture (*ca.* 1:1) prepared from racemic amine and racemic O-methylmandelyl chloride and recrystallized three times to mp 59–60°.

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30: H, 7.47; N, 4.94. Found: C, 76.52; H, 7.73; N, 4.66.

N-(1-Phenylethyl)-O-methylmandelamide was a diastereomeric mixture (*ca.* 1:1) prepared from racemic amine and racemic O-methylmandelyl chloride and recrystallized three times to mp 132–137°.

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11; N, 5.20. Found: C, 75.57; H, 7.00; N, 5.26.

Menthyl O-methylmandelate was prepared from an excess of (−)-menthol and racemic O-methylmandelyl chloride. The mixture of diastereomers (*ca.* 1:1) had bp 85° (0.15 mm).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 74.74; H, 9.11.

(29) An nmr spectrum of the crude material should be run prior to any purification in order to ascertain that the ratio of diastereomers is not altered during this procedure.

Registry No.—2, 15297-33-3 3, 15297-34-4; 4, 15297-35-5; 5, 15297-36-6 7, 15297-37-7 8, 15314-01-9; N-[(1-methyl-2-phenyl)ethyl]-O-methylmandelamide, 15297-38-8; N-(1-phenylethyl)-O-methylmandelamide, 17296-90-9; menthyl-O-methylmandilyte, 15296-91-0.

Carbene Reactions from a Diazomethyltriazole. Contrast with the Isosteric Azide[1]

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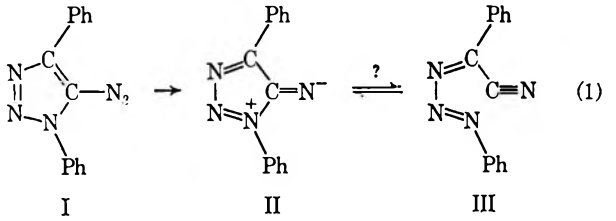
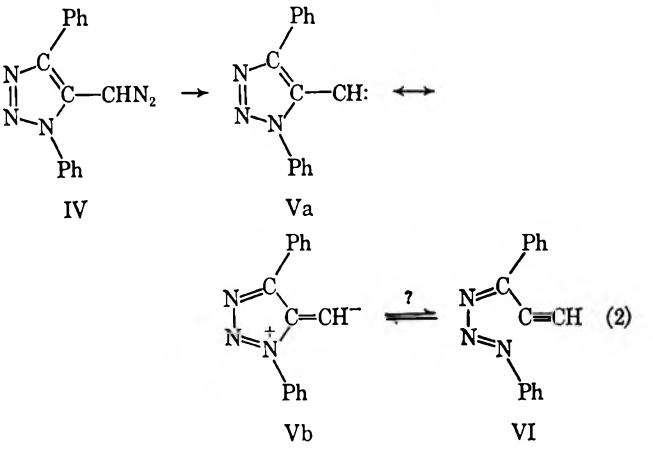
Because 5-azido-1,4-diphenyltriazole loses nitrogen to form an isolable substance that may be an electronically stabilized nitrene, the isosteric diazoalkane was prepared and examined for analogous behavior. No isolable primary decomposition product could be obtained. The crystalline diazo compound lost nitrogen smoothly above 40° without catalysis, attacking the solvent (benzene, cyclohexane, cyclohexene, carbon tetrachloride) to give typical products of carbene insertion or addition in unusually high yields (70%). Decomposition had nearly the same rate in all the hydrocarbon solvents, but was autocatalytic in carbon tetrachloride. The selectivity toward the hydrocarbon solvents was 25:2.1:1 cyclohexene, benzene, and cyclohexane, respectively; the ratio of addition to insertion in reaction with cyclohexene varied from 7.7 to 11. The position isomer, 4-diazomethyl-1,5-diphenyltriazole, lost nitrogen to form a mixture of the corresponding aldazine and the anil of phenyl ethynyl ketone, without detectable attack on any solvent.

We recently reported[2] on the unusual behavior of an azide, 1,4-diphenyl-5-azidotriazole (I), which loses nitrogen from the azido group at relatively low temperatures and forms a product in which neither rearrangement, cyclization, intermolecular insertion, nor hydrogen abstraction have occurred. The structure of this substance, which might be considered as an electronically stabilized nitrene (imidogen), was narrowed down to two possibilities (II and III); its behavior was most readily accounted for by assuming an active equilibrium between the two in solution (eq 1).



The isosteric carbon system, namely, 5-diazomethyl-1,4-diphenyltriazole (IV), became of obvious interest because of the possibility of isolating a substance that might be considered as an electronically stabilized carbene (V) (eq 2), which would bear some analogy to



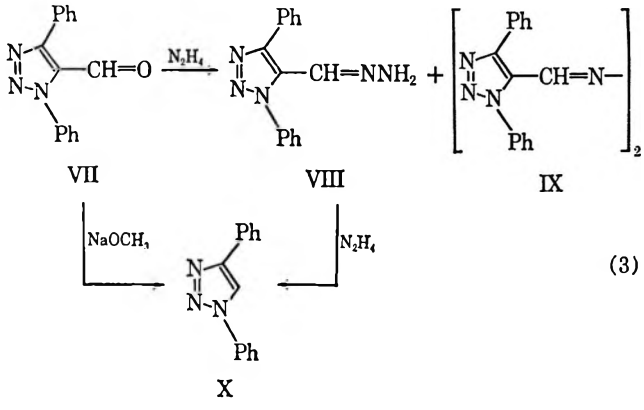
(1) From the Ph.D. Dissertation of J. G. W., Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p 1620.

(2) P. A. S. Smith, L. O. Krbechek, and W. Resemann, *J. Amer. Chem. Soc.*, **86**, 2025 (1964).

isocyanides and to the compound isolated by Wanzlick.[3] Furthermore, the investigation of such a system might shed additional light on the importance of the equilibria II ⇌ III and V ⇌ VI. The question of whether the species initially formed might exist as a triplet carbene distinct from Va, perhaps able to show individual behavior as an ordinary, "unstabilized," carbene before transformation to V or VI, was also of much interest.

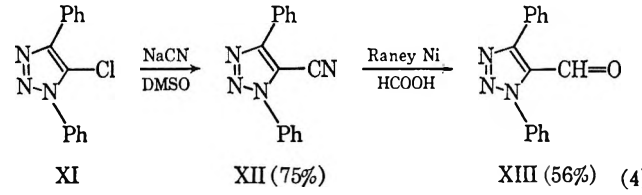
Results

5-Diazomethyl-1,4-diphenyltriazole (IV) was prepared by converting the 5-carboxaldehyde VII into its tosylhydrazone and treating that with butyllithium. The product could be obtained analytically pure as orange crystals, although with some difficulty and concomitant losses (in some experiments it was convenient to utilize the unisolated diazo compound in solution). Several other routes to this substance were tried, but none succeeded except oxidation of the unsubstituted hydrazone, VIII, with mercuric oxide. However, not only was the oxidation highly irreproducible, but the preparation of the hydrazone from the aldehyde was beset with two serious side reactions: formation of the aldazine (IX) and decarbonylation to form 1,4-diphenyltriazole (X). The latter reaction was demonstrated to be a nucleophilic cleavage, analogous to the well-known example of chloral, and could be accomplished quantitatively by treating the hydrazone with excess hydrazine or the aldehyde with sodium methoxide (eq 3).



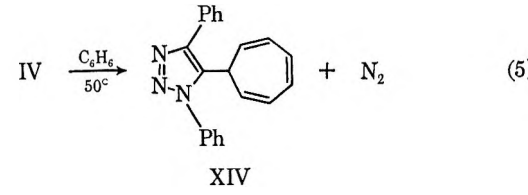
(3)

The preparation of the required 1,4-diphenyltriazole-5-carboxaldehyde (VII) from phenylpropiolaldehyde and phenyl azide[4] also gave a supply of the isomer 1,5-diphenyltriazole-4-carboxaldehyde. This aldehyde was insensitive to nucleophilic deformylation, in contrast to the other isomer. The position isomer of IV, 4-diazomethyl-1,5-diphenyltriazole, was obtained from this aldehyde in good yield with consistent success by conversion into the hydrazone and oxidation with mercuric oxide or activated[5] manganese dioxide, in marked contrast to the analogous route to IV. When IV alone was wanted, there was some advantage in synthesizing the 5-carboxaldehyde by Raney nickel–formic acid reduction[6] of 5-cyano-1,4-diphenyltriazole, obtained by reaction of the 5-chloro compound with sodium cyanide in dimethyl sulfoxide (eq 4).



(4)

The diazomethyltriazole IV lost nitrogen readily in benzene solution at 50° (eq 5). Vapor phase chroma-



(5)

tography revealed no volatile products, but column chromatography on alumina produced, besides some tar, a small amount (8%) of the corresponding aldazine and one other product (66%) whose analysis corresponded to loss of two atoms of nitrogen and addition of the elements of benzene. It added bromine, reduced neutral permanganate, and formed an adduct with maleic anhydride. The nmr spectrum (triplet, 1 H, at τ 6.87; quartet, 2 H, at 4.68; multiplets at 3.77 2 H and 3.40 2 H; and a complex multiplet, 10 H, centered at 2.5) was quite similar to that of cycloheptatriene.[7] The presence of six hydrogens at low field (τ 3.40–4.68) is not consistent with a norcaradiene structure, in which the two equivalent cyclopropane hydrogens would be expected to resonate near 6.5 or higher (*cf.* 7,7-dicyanonorcaradiene[8]). The product is thus presumably 7-(1,4-diphenyl-1,2,3-triazol-5-yl)-cycloheptatriene (XIV). Decomposition of IV in more dilute solution (0.005 *M*) produced none of the azine formed in the more concentrated solution. When oxygen was bubbled through the solution of decomposing IV, the corresponding aldehyde was obtained in only 3% yield in addition to the other products. When carbon monoxide was used instead of oxygen, the products could not be cleanly separated, but the observation of strong bands at 1740 and 1660 cm^{-1} in the infrared spectrum of the residue from the reaction indicated that some carbonyl products had been formed, presumably *via* a ketene initially formed by reaction with the carbon monoxide.

Decomposition of IV in cyclohexane gave some tar, the aldazine (IX) (14%), and a major product (67%) corresponding to loss of two atoms of nitrogen and addition of the elements of cyclohexane. The nmr spectrum (multiplets, 11 H, at τ 9.1 and 8.6; doublet, 2 H, at 7.25; complex multiplet, 10 H, centered at

(3) H. W. Wanzlick and E. Schikora, *Angew. Chem.*, **72**, 494 (1960); D. M. Lemal, R. A. Lovald, and K. I. Kawano, *J. Amer. Chem. Soc.*, **86**, 2518 (1964).

(4) J. C. Sheehan and C. A. Robinson, *ibid.*, **73**, 1207 (1951).

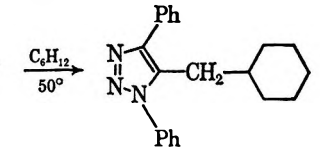
(5) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952); E. F. Pratt and J. F. Van DeCastle, *J. Org. Chem.*, **26**, 2973 (1961).

(6) O. G. Backeberg and B. Staskun, *J. Chem. Soc.*, 3961 (1961).

(7) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 158.

(8) E. Ciganek, *J. Amer. Chem. Soc.*, **87**, 652, 1149 (1965); *cf.* also J. B. Lambert, L. J. Durham, P. Lepoutere, and J. D. Roberts, *ibid.*, **87**, 3896 (1965).

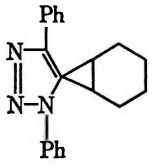
2.5) corresponded with the structure 1,4-diphenyl-5-cyclohexanemethyltriazole (XV) (eq 6).



(6)

XV

In cyclohexene solution at 50°, IV gave rise to a reaction mixture that was not readily resolved by thin layer chromatography, in which it showed R_f values similar to that of XV. The mixture was therefore hydrogenated to saturate the presumed cyclohexenyl groups, and then chromatographed on silica gel, which, however, accomplished only partial separation into two components, mp 143–151° and 127–132°, respectively, in a total yield of 78%. Several recrystallizations of each converted the lower melting fraction into pure XV, and the other fraction into an isomeric compound, mp 150–153°, which reacted sluggishly with bromine and not at all with permanganate. The infrared and nmr spectra were consistent with a triazolylnorcarane structure (XVI); this assignment was confirmed by the formation of the same substance by hydrogenation of the triazolylcycloheptatriene, XIV. The ratio of XVI to XV in the reaction mixture was estimated as 7.7:1 from the nmr spectrum before chromatography.



XVI

The selectivity of attack on the solvents benzene, cyclohexane, and cyclohexene was determined from yields of products from reactions carried out in mixed solvent pairs. From a solution of IV (0.01 *N*) in an equimolar mixture of benzene and cyclohexane, a ratio of XIV (attack on benzene) to XV (attack on cyclohexane) of 2.10 ± 0.05 was obtained by three different methods of estimation. From an equimolar mixture of benzene and cyclohexene, a ratio of XVI (attack on cyclohexene) to XIV of 9 ± 1.5 was obtained. The third solvent combination, cyclohexene and cyclohexane, was used in a mole ratio of 1:10 owing to the large anticipated difference in susceptibility to attack. A ratio of XVI to XV of 2.5 ± 0.5 was estimated from the nmr spectrum of the mixed products; correction for the mole ratio of the solvents leads to a selectivity of 25 ± 5 for cyclohexene–cyclohexane. A further correction for the amount of insertion products (tetrahydrobenzyltriazoles) also formed from cyclohexene (1 part in 8.7) would raise this ratio to about 28.

Two fluorinated solvents were tried in an effort to find an inert medium for the decomposition of the diazo compound IV. Perfluorodioxane did not appear to dissolve significant quantities of IV; heating a vigorously stirred suspension at 60° produced only the corresponding aldazine (76%). Perfluorobenzene dissoved IV satisfactorily. Heating a solution of IV in it produced only tars, from which no pure substance could be obtained. The residue from evaporation of the solvent contained no detectable fluorine, indicating that the tars did not derive from attack on the solvent.

Attempted decomposition of the melted diazo compound IV (under nitrogen) resulted in mild explosions and the formation of tarry residues, from which a small amount of the aldazine was the only pure compound that could be isolated.

Rates of decomposition of IV were determined by following its disappearance spectroscopically. The rates at 50° in cyclohexene, in benzene, and in mixtures of cyclohexane with ether or benzene were first order (the solubility and rate of solution of IV in neat cyclohexane were too low to give satisfactory results). The rate constants obtained are given in Table I. A rate constant for benzene solutions was also determined at 40°, allowing an approximate value of the activation energy, 26 kcal/mol, to be estimated.

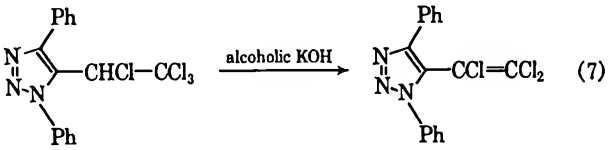
TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE DECOMPOSITION OF 1,4-DIPHENYL-5-DIAZOMETHYL-1,2,3-TRIAZOLE (IV)

Solvent	Temp, °C	10^5k, min^{-1}
Cyclohexene	50.0	17.6
Benzene	50.0	9.2
Benzene	40.0	2.5
Cyclohexane–ether (2:1 mole ratio)	50.0	17.1
Cyclohexane–benzene (equimolar)	50.0	19.3
Cyclohexane–benzene (2:1 mole ratio)	50.0	19.8

The rate of decomposition of IV in carbon tetrachloride solution did not obey either first-order or second-order kinetics over-all. It accelerated rapidly at first, and became first order only in the latter part of each run, from which a rate constant of 122×10^{-3} min^{-1} could be determined.

The products, as well as the kinetics, were different in carbon tetrachloride. In addition to small amounts of hexachloroethane, chromatography separated two colorless, crystalline chlorine-containing compounds (XVII and XVIII) in substantial amounts. Compound XVII, $C_{16}H_{11}N_3Cl_4$, had an infrared spectrum that showed general resemblance to spectra of other 1,4-diphenyltriazole derivatives; its nmr spectrum showed an aromatic multiplet centered at τ 2.5 (10 H) and a singlet at 4.22 (1 H). Treatment with alcoholic potassium hydroxide (see eq 7) produced a new compound, XIX, $C_{16}H_{10}N_3Cl_3$, whose infrared



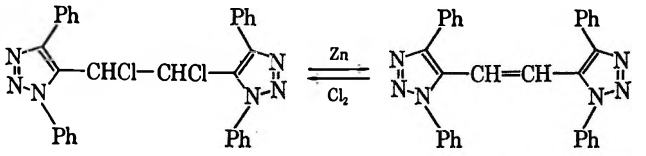
(7)

XVII XIX

spectrum showed a new band at 1625 cm^{-1}, attributable to C=C stretching; the singlet at τ 4.22 in the nmr spectrum was no longer present. XVII is thus presumed to be 1,4-diphenyl-5-(1,2,2,2-tetrachloroethyl)-1,2,3-triazole, and XIX, the 5-trichlorovinyl analog.

Compound XVIII, $C_{30}H_{22}N_6Cl_2$, had an infrared spectrum similar to XVII, but was too insoluble to give a satisfactory nmr spectrum. Treatment with

zinc dust removed the chlorine atoms, producing 1,2-bis(1,4-diphenyl-1,2,3-triazol-5-yl)ethylene (XX), which was converted back into XVIII by treatment with chlorine (eq 8). The structure shown for XVIII,

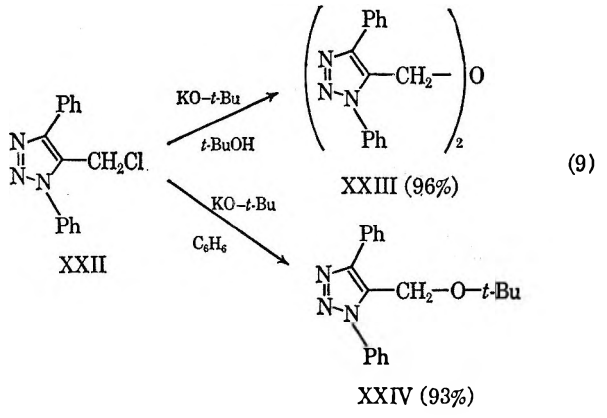


XVIII XX (8)

with uncertain stereochemistry, is consistent with the observations. (A small amount of a high-melting crystalline compound, $C_{30}H_{22}N_6O_3Cl$, which may have been an artifact of the work-up, was also obtained both from the original reaction and from the treatment of XX with chlorine; it was too insoluble to give an nmr spectrum, and was not further investigated.)

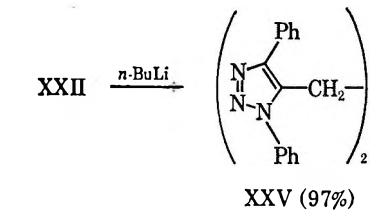
Photolysis of the diazomethyl triazole IV was carried out at 10°, at which temperature thermal decomposition was determined to be negligibly slow. The results were essentially the same as in thermal decomposition. In benzene, XIV was produced in 69% yield, and in cyclohexene the ratio of product from addition to those from insertion was 11.5:1 (combined yield 62%). No reaction with molecular oxygen could be detected in experiments performed with or without the presence of benzophenone as sensitizer.

Some alternative routes were explored for producing the same carbene as is presumably formed from the diazomethyl compound. Dehydrohalogenation of 1,4-diphenyl-5-chloromethyl-1,2,3-triazole (XXII) with potassium *t*-butoxide failed. In *t*-butyl alcohol solution, the principal product was the symmetrical triazolemethyl ether (XXIII) (eq 9), whose structure



XXII XXIII (96%) XXIV (93%) (9)

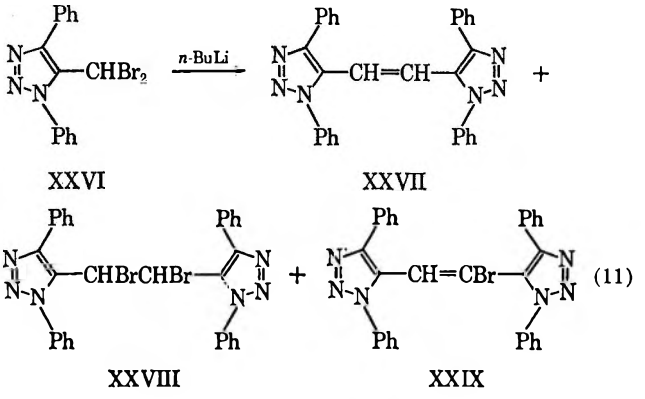
was deduced from its analysis, molecular weight, infrared spectrum (strong C–O–C band at 1060 cm^{-1}), and nmr spectrum (singlet, 2 H, at τ 5.42, and aromatic multiplet, 10 H, centered at 2.5). With dry potassium *t*-butoxide suspended in benzene, the product was the *t*-butyl ether (XXIV) (eq 9), which had a similar infrared spectrum, but whose nmr spectrum showed singlets at τ 8.74 (9 H) and 5.62 (2 H) in addition to the aromatic multiplet (10 H). *n*-Butyllithium produced as the sole product a compound $C_{30}H_{24}N_6$ (eq 10), whose nmr spectrum (singlet, 4 H,



XXV (97%) (10)

at τ 7.03 aromatic multiplet, 20 H, centered at 2.6) was consistent with with *sym*-bis(1,4-diphenyltriazol-5-yl)ethane (XXV). This is the product to be expected of halogen–metal interchange followed by reaction of $ArCH_2Li$ with $ArCH_2Cl$.

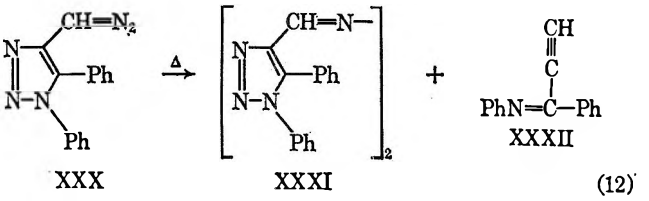
Dehalogenation of the corresponding dibromomethyl compound (XXVI) with *n*-butyllithium (eq 11) was



XXVI XXVII XXVIII XXIX (11)

attempted in a variety of solvents. Essentially the same product mixture was always obtained; the products were of the same type as has been reported for other *gem*-dihalides, and presumably did not arise *via* a carbene intermediate. The major component (54%), $C_{30}H_{22}N_6$, gave normal olefinic reactions with permanganate and bromine, and had an nmr spectrum consistent with *sym*-bis(1,4-diphenyltriazol-5-yl)-ethylene (XXVII) (singlet, 2 H, at τ 3.03, and aromatic multiplet, 20 H, centered at 2.4). Two bromine-containing products were obtained in much smaller amounts. One of them could be dehalogenated with zinc to give XXVII, and is therefore presumed to be the *sym*-dibromoethane derivative XXVIII. The second minor product could be obtained from XXVIII by dehydrohalogenation with alcoholic potassium hydroxide, and is therefore presumed to have structure XXIX. The stereochemistry is in every case unknown, although *trans* configurations can be presumed for the olefins on steric grounds.

When the position isomer of IV, 1,5-diphenyl-4-diazomethyl-1,2,3-triazole, XXX, was heated in benzene, cyclohexane, or cyclohexene, essentially the same result was obtained in each case (eq 12). The major product (64–66%) yield was always the corresponding aldazine, XXXI, accompanied by another substance, XXXII, resulting from loss of four nitrogen atoms from XXX (12–30% yield). An acetylenic function was



XXX XXXI XXXII (12)

indicated by infrared absorption at 2100 cm^{-1}, formation of a copper salt with ammoniacal cuprous chloride, and reaction with bromine and with permanganate. Hydrolysis gave propiolophenone and aniline, demonstrating that XXXII is the corresponding anil. No indication of carbenoid attack on the solvents was observed.

Discussion

It is easily recognized that the products of decomposition of 1,4-diphenyl-5-diazomethyl-1,2,3-triazole (IV) under the influence of either heat or light correspond to those of a carbene intermediate undergoing typical insertion or addition reactions, whereas the products from the position isomer, XXX, do not. Carbene formation as the rate-determining step in the reactions of IV is also indicated by the similarity of the rates of decomposition in benzene, cyclohexene, and cyclohexane, although the character of the product is different in each case. The behavior of IV is thus quite distinct from its nitrogen isostere, the azide I, which does not react with hydrocarbon solvents when decomposed in them, but instead gives a relatively inert primary decomposition product.

The isosteric substance derived from IV, which might be V or VI, is not formed as an isolable product. This suggests that V is much more reactive (as a carbene) than its nitrogen isostere, a circumstance that may reflect the lower stability to be expected of structures bearing a negative charge on carbon (Vb) compared to nitrogen (II), or that transformation to VI is less favored, owing to the higher energy of acetylenes (VI) compared to nitriles (III). Evidence has recently been presented that carboethoxycarbene is much more reactive than carboethoxynitrene, which may indicate a general relationship.[9]

Even when the possibility of intermolecular carbene reactions is denied, as in the decomposition of IV in hexafluorobenzene, no substance corresponding to V (or VI) could be detected; this observation suggests that V (or VI) is inherently unstable under even the mild conditions of the experiments. These considerations raise the interesting question of whether the acetylenic triazene structure (VI) might, when synthesized in an unambiguous manner, react as a triazolylcarbene in suitable media through equilibration with V.

The multiplicity of the carbene as it is initially formed from IV cannot, of course, be determined simply. With some diazoalkanes, evidence suggests that the singlet state is of higher energy and is formed first, subsequently decaying to a triplet ground state[10] as a result of collisions. By virtue of the possibility of such limiting structures as Vb, however, the carbene derived from IV will very likely have a singlet ground state, which may or may not be formed through a triplet-state forerunner. It is therefore worthwhile to examine the behavior of IV for evidence bearing on this point.

Evidence of selectivity, as manifested in the ratio of addition to insertion in reaction with cyclohexene, is interesting but not conclusive. The ratios 7.7:1 (thermolysis at 60°) and 11.5:1 (photolysis at 10°) for diphenyltriazolylcarbene are probably not significantly different, in view of the large estimated error (10–20%) in their determination. It is, nevertheless, clear that diphenyltriazolyl carbene is markedly more selective than methylene, for which ratios of 1:1.54 and 1:2.13 have been determined. Even phenylcarbene[11] gives an addition–insertion ratio of only 1:1, and carboethoxycarbene[12] gives a ratio of about 2:1. Chlorocarbene and bromocarbene,[13] on the other hand, show such high ratios that only the products of addition have been detected. The selectivity of diphenyltriazolylcarbene toward attack on cyclohexene and cyclohexane, ~25:1, may also be compared with that of the halocarbenes toward *cis*-2-butene and pentane, >100:1. Diphenyltriazolylcarbene thus falls between carboethoxycarbene and the halocarbenes in addition–insertion selectivity. The selectivity of diphenyltriazolylcarbene toward benzene (addition) and cyclohexane, 2.1:1, also places it qualitatively in the same position when compared to phenylcarbene,[11] which shows a ratio of 1.6:1.

The nature of the products from reaction with cyclohexene suggests that the foregoing carbenes, including diphenyltriazolylcarbene, react in the singlet state, for no products of hydrogen abstraction were observed. Diphenylcarbene, which is known to be a triplet in the ground state,[14] converts cyclohexene in substantial amounts into bis(cyclohexenyl), becoming itself converted into tetraphenylethane, a reaction attributable to hydrogen abstraction by a triplet species and not paralleled by diphenyltriazolylcarbene.

Relative reactivity toward oxygen and carbon monoxide also suggests a singlet state for diphenyltriazolylcarbene. Both triplet methylene and diphenylcarbene react readily with molecular oxygen,[15] whereas diphenyltriazolylcarbene reacts only to a vary minor extent. Singlet methylene, on the other hand, reacts readily with carbon monoxide,[16] to give ketene and its transformation products, as diphenytriazolylcarbene also appears to do (it is unfortunate that we were unable to characterize the products more satisfactorily, and thus to establish the point firmly, but the over-all reactions form an involved sequence leading to complex products).

In addition to the foregoing similarities of the carbene derived from IV to those derived from other diazo compounds, IV has the notable characteristic of being an unusually clean carbene source. The facts that it gives rise to carbene-derived products in high yield and requires neither light nor catalyst to do so provide obvious opportunities for studying carbene reactions unobscured by the ambiguities engendered by photoexcitation or the possibility of complex formation with heavy metals.

(9) J. E. Baldwin and R. A. Smith, *J. Amer. Chem. Soc.*, **89**, 1886 (1967).

(10) *E.g.*, E. Wasserman, L. Barash, and W. A. Yager, *ibid.*, **87**, 2075 (1965) (cyanomethylene and dicyanomethylene).

(11) H. Nozaki, R. Noyori, and K. Sisdo, *Tetrahedron*, **20**, 1125 (1964); G. L. Closs and L. E. Closs, *Tetrahedron Lett.*, 26 (1960); C. G. Dutsche, G. L. Bachmann, and R. S. Coffey, *Tetrahedron*, **18**, 617 (1962).

(12) K. R. Kopecky, G. S. Hammond, and P. H. Leermakers, *J. Amer. Chem. Soc.*, **84**, 1015 (1962); P. S. Skell and R. M. Etter, *Proc. Chem. Soc.*, 443 (1961).

(13) G. L. Closs and J. J. Coyle, *J. Amer. Chem. Soc.*, **87**, 4270 (1965).

(14) R. M. Etter, H. S. Skovronek, and P. S. Skell, *ibid.*, **81**, 1008 (1959).

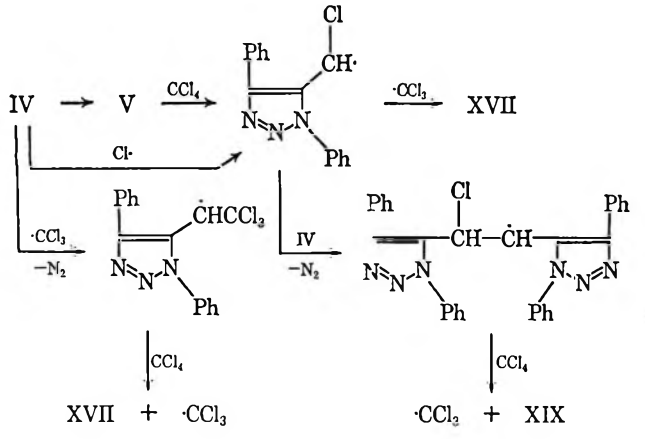
(15) W. Kirmse, L. Horner, and H. Hoffman, *Ann.*, **614**, 19 (1958); R. F. W. Bader and J. I. Generosa, *Can. J. Chem.*, **43**, 163 (1965).

(16) H. M. Frey, in "Carbene Chemistry," W. Kirmse, Ed., Academic Press Inc., New York, N. Y., 1964, pp 217–233.

The decomposition of IV in carbon tetrachloride solution is clearly a different type of process from that in the other solvents studied. The rate is an order of magnitude greater, and the reaction has autocatalytic features. Furthermore, the products are those to be expected of a free-radical process, a possibility for which is shown in Scheme I (the hexachloroethane observed could arise from the trichloromethyl radicals formed).

Similar behavior has been reported for the decomposition of diphenyldiazomethane in bromotrichloromethane,[17] of methyl diazoacetate in chloroform,[17] and of diazomethane in carbon tetrachloride.[17]

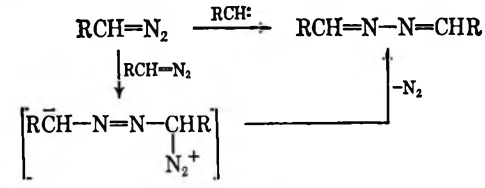
SCHEME I



It is interesting that IV apparently does not cyclize by insertion of the intermediate carbene at one of the *ortho* positions of the adjacent phenyl groups, for *o*-diazomethylbiphenyl, which is structurally very similar, gives high yields of fluorene when decomposed. We believe this to be a steric effect applying to cyclization of 5-substituted 1,4-diaryltriazoles in general, for we were unable to accomplish cyclodehydration of the corresponding carboxylic acid with either polyphosphoric acid or hydrogen fluoride, even though such treatment converts *o*-phenylbenzoic acid into fluorenone. Other examples of vicinal phenyltriazolecarboxylic acids have also been reported to resist cyclization.[18]

It is also of interest that the carbene from IV does not dimerize to an olefin, for such a reaction has been observed with a number of sterically hindered diazoalkanes.[19] Presumably the explanation lies in the fact that V reacts very rapidly with the solvent in which it is generated.

The position isomer of IV, XXX, does not give rise to the insertion and addition products to be expected from a carbene intermediate. Although the formation of aldazine from a diazoalkane, the major reaction in this case, has been attributed to a carbene reacting with undecomposed diazoalkane,[20] there is good evidence that aldazines may be formed by direct dimerization of diazoalkane with loss of nitrogen;[21] the latter path may obtain with XXX.



The second product, the anil of phenyl ethynyl ketone (XXXII), may have arisen from a carbene if the loss of a second molecule of nitrogen (from the triazole ring) is faster than bimolecular reactions of the carbene, but such a situation is not distinguishable from concerted loss of two molecules of nitrogen. On the other hand, it should be noted that there are also marked reactivity differences between the 1,4-diphenyltriazole and 1,5-diphenyltriazole systems that do not involve loss of nitrogen; *e.g.*, the formation of the hydrazones from the aldehydes, the oxidation of the aldehyde hydrazones, the thermal stability of the diazomethyl derivatives, and the base-catalyzed deformylation of the aldehydes. It cannot be said at this time if there is a close relationship between such differences and the formation of carbene intermediates.

Although the yields of acetylenic anil were low, this reaction may have some synthetic interest, for there does not appear to be a feasible alternative route to such a structure (the reaction of aniline with the corresponding ketone gives instead a different type of product, resulting from addition of aniline across the triple bond).

Experimental Section

1,4-Diphenyl-5-cyano-1,2,3-triazole (XII). A. From 1,4-Diphenyl-5-chloro-1,2,3-triazole (XI).[22]—A mixture of 2.00 g (0.00785 mol) of XI[23] with a well-stirred suspension of sodium cyanide (1.47 g) in 25 ml of dimethyl sulfoxide was heated at 140° for 4 hr, whereupon the mixture was poured into cold water and extracted with ether. Drying of the ethereal extract over anhydrous sodium sulfate followed by removal of the ether under reduced pressure gave a white crystalline solid, which was recrystallized from absolute ethanol to give 1.47 g (75%) of the nitrile XII, mp 121–124°. The infrared spectrum showed absorptions at 2260, 1600, 1500, 1080 and 1000 (doublet) cm^{-1}. An analytical sample prepared by three recrystallizations from ethanol–petroleum ether (bp 60–75°) had mp 122–123°. Extending the reaction time to 12 hr resulted in a much lower yield.

Anal. Calcd for $C_{15}H_{10}N_4$: C, 73.15; H, 4.10. Found: C, 73.06; H, 4.20.

B. From 1,4-Diphenyl-1,2,3-triazole-5-carboxaldehyde Oxime.[24]—A solution of 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde oxime (0.50 g, 0.00189 mol) in 10 ml of freshly distilled acetic anhydride was heated under a short Vigreux column so that acetic acid slowly distilled. After 1 hr excess acetic anhydride was removed under reduced pressure leaving a white crystalline solid. Recrystallization from absolute ethanol gave 0.38 g of XII (81%), mp 122–123.5°.

1,4-Diphenyl-1,2,3-triazole-5-carboxaldehyde (VII).[25]—A 2.0-g portion of Raney nickel alloy was stirred for 30 min with 2 *N* sodium hydroxide. The liquid was then decanted and the nickel washed twice with water. A solution of 1.00 g (0.0041 mol) of XII in 75 ml of 90% formic acid was added to the nickel, the suspension was heated to 75°, and 50 ml of absolute ethanol was added. The hot solution was filtered and concentrated to

(17) (a) A. R. M. Murray and A. M. Trozzolo, *J. Org. Chem.*, **27**, 3341 (1962); (b) W. H. Urry and J. W. Wilt, *J. Amer. Chem. Soc.*, **76**, 2594 (1954); (c) W. H. Urry and J. R. Eisner, *ibid.*, **73**, 2977 (1951); **74**, 5822 (1952).

(18) W. Borsche, H. Hahn, and M. Wagner-Roemmick, *Ann.*, **554**, 15 (1943).

(19) H. E. Zimmerman and D. H. Paskovich, *J. Amer. Chem. Soc.*, **86**, 2149 (1964).

(20) H. Reimlinger, *Chem. Ber.*, **97**, 339 (1964).

(21) C. G. Overberger and J. P. Anselme, *J. Org. Chem.*, **29**, 1188 (1964); P. Yates, D. G. Farnum, and D. W. Wiley, *Tetrahedron*, **18**, 881 (1962).

(22) L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

(23) H. W. Carnelly and P. V. Dutt, *J. Chem. Soc.*, **125**, 2476 (1924).

(24) Following the general method given by A. I. Vogel ("Practical Organic Chemistry," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 804).

(25) B. Staskun and O. G. Backeberg, *J. Chem. Soc.*, 5880 (1965).

half the original volume, and water was added to the cloud point. On cooling, 0.46 g (56%) of VII, mp 169–170°, crystallized. It was identical (mixture melting point, infrared spectrum, R_f value) with a sample prepared by the method of Sheehan and Robinson.[4]

1,4-Diphenyl-1,2,3-triazole-5-carboxaldehyde Tosylhydrazone.[26]—A solution of 5.0 g (0.002 mol) of VII and 3.7 g (0.002 mol) of *p*-toluenesulfonylhydrazine in 200 ml of methanol was heated under reflux for 3 hr. The hot solution was filtered to remove traces of the corresponding aldazine[27] and then allowed to cool. The tosylhydrazone crystallized in long white needles, mp 125° with rapid evolution of gas, and weighed 7.7 g (92%). An analytical sample prepared by recrystallization from benzene–petroleum ether mixture below room temperature had mp 128–130°.

Anal. Calcd for $C_{22}H_{19}N_5O_2S$: C, 63.29; H, 4.59. Found: C, 63.48; H, 4.74.

1,5-Diphenyl-1,2,3-triazole-4-carboxaldehyde Tosylhydrazone.—This substance was prepared in the foregoing manner in 95% yield; after recrystallization from chloroform–petroleum ether and benzene–petroleum ether mixtures, it had mp 175–177° with gas evolution.

Anal. Calcd for $C_{22}H_{19}N_5O_2S$: C, 63.29; H, 4.59. Found: C, 62.91; H, 4.66.

1,4-Diphenyl-5-diazomethyl-1,2,3-triazole (IV).[28]—1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde tosylhydrazone (3.0 g, 0.0072 mol) was partially dissolved in 200 ml of anhydrous ether in a carefully dried apparatus, and cooled to −50°. The system was filled with dry nitrogen and protected from moisture while 6.0 ml of a 1.5 *N* solution of butyllithium in pentane was added dropwise by means of a syringe. The reaction mixture was then allowed to warm slowly to 20°, stirred for 24 hr at that temperature, and filtered. Concentration to a small volume in a stream of nitrogen and cooling in a Dry Ice–acetone bath gave 1.04 g (55%) of bright orange crystals which were sufficiently pure for most purposes, mp 110° with rapid gas evolution. The infrared spectrum showed an intense absorption at 2060 cm^{-1} and other maxima at 1600, 1560, 1500, 1080 and 1000 cm^{-1}. The nmr spectrum showed a singlet at τ 5.2 and a multiplet centered at 2.7 (area ratio 1:10). The ultraviolet spectrum in methanol showed λ_{max} 240 mμ (log ϵ 4.35) with a shoulder at 282 mμ, and λ_{max} 462 mμ (log ϵ 1.75). An analytical sample was prepared by three recrystallizations from ether–petroleum ether mixture between room temperature and that of a Dry Ice–acetone bath; the melting–decomposition point was unchanged.

Anal. Calcd for $C_{15}H_{11}N_5$: C, 68.94; H, 4.25; N, 26.81. Found: C, 68.85; H, 4.19; N, 26.74.

Treatment of the diazoalkane with bromine gave a single product identical with 1,4-diphenyl-5-dibromomethyl-1,2,3-triazole prepared from 1,4-diphenyl-5-methyl-1,2,3-triazole (see ahead).

1,4-Diphenyl-1,2,3-triazole-5-carboxaldehyde Hydrazone (VIII).—A solution of 1.00 g (0.004 mol) of VII and 1.33 g (0.042 mol) of anhydrous hydrazine[29] in 50 ml of absolute ethanol was heated under reflux for 4 hr and allowed to cool. A 0.140-g sample of a pale green, insoluble solid (the azine, IX), mp 300–305°, was filtered off, and the mother liquor was diluted with water and extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate, concentrated to a small volume and chromatographed on 50 g of Florisil. Elution with 1% ether in benzene gave 0.035 g (4%) of 1,4-diphenyl-1,2,3-triazole, mp 179–182°. Elution with 2% ether in benzene gave 0.480 g (45%) of a white, somewhat oily, solid (VIII), mp 92–99°. Elution with 5% ether in benzene gave an additional 0.053 g of IX (total yield 19%).

The infrared spectrum of crude VIII had absorptions at 3410, 3310, and 3220 cm^{-1} (N–H), weak absorption at 1640 (C=N), and absorptions at 1600, 1500 and 1080, and 1000 cm^{-1}, indicating the presence of phenyl and 1,2,3-triazole rings. The nmr spectrum contained a broad singlet at τ 4.22 and a complex multiplet centered at 2.5 (relative areas approximately 1:6). An analytical sample prepared by three recrystallizations from ethanol–petroleum ether had mp 106–108°.

Anal. Calcd for $C_{15}H_{13}N_3$: C, 68.42; H, 4.97. Found: C, 68.75; H, 4.64.

Structural assignment was confirmed by oxidation with mercuric oxide to 1,4-diphenyl-5-diazomethyl-1,2,3-triazole (IV).

The infrared spectrum of IX showed C=N absorption at 1625 and other absorptions at 1590, 1550, 1500, 1070, and 990 cm^{-1} (phenyl and 1,2,3-triazole rings); N–H absorption was lacking. The nmr spectrum of IX in trifluoroacetic acid exhibited a singlet at τ 1.63 and an unresolved multiplet centered at 2.2 (relative areas 1:10). An analytical sample, prepared by three recrystallizations each from dimethylformamide and dimethylformamide-*p*-xylene mixture, had mp 302–303°. This substance, the azine of VII, was also prepared in quantitative yield by heating an ethanol solution of 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde and its hydrazone for 3 hr.

Anal. Calcd for $C_{16}H_{11}N_4$: C, 72.85; H, 4.49; N, 22.66. Found: C, 73.04; H, 4.33; N, 22.80.

When a large excess of hydrazine (100-fold) was employed to supress azine formation from the aldehyde, a quantitative yield of the deformylation product, 1,4-diphenyl-1,2,3-triazole (X), was obtained instead.

Deformylation of 1,4-Diphenyl-1,2,3-triazole-5-carboxaldehyde (VII) with Sodium Methoxide.—A solution of 0.23 g of freshly cut metallic sodium and 1.00 g (0.004 mol) of VII in 50 ml of anhydrous methanol was refluxed for 12 hr in a vessel provided with a Dry Ice condenser, after which time 25 to 30 ml of liquid was distilled into a receiver containing 0.435 g of phenylhydrazine. The distillate was then refluxed for 8 hr, after which the methanol was evaporated. The oily residue readily crystallized to give 0.080 g of a white solid, mp 136–140°, identical with an authentic sample of N′-phenylformhydrazide prepared from ethyl formate and phenylhydrazine under the same conditions in 15% yield. (If it can be assumed that the yield of hydrazide is the same in both instances, 98% of the theoretical amount of ethyl formate is accounted for.) On cooling the solution remaining in the original reaction vessel, 0.83 g (93%) of 1,4-diphenyl-1,2,3-triazole (X) was obtained.

Under the same reaction conditions, the position isomer, 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde, was recovered quantitatively.

1,5-Diphenyl-1,2,3-triazole-4-carboxaldehyde Hydrazone.—A solution of 5.0 g (0.02 mol) of 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde and 5.6 g of 95% hydrazine in 50 ml of absolute ethanol was refluxed for 1 hr and then concentrated to one-half its original volume; water was added to the cloud point. The hydrazone separated on cooling, and was recrystallized from benzene–petroleum ether mixture; it weighed 6.9 g (78%) and had mp 150–152° (unchanged by four recrystallizations from benzene–petroleum ether mixture). The infrared spectrum lacked carbonyl absorption but exhibited maxima at 3450, 1600, 1500, and 1080 and 1000 (doublet) cm^{-1}. The nmr spectrum showed singlets at τ 2.60 and 4.67 (broad) and a multiplet centered at 3.1 (relative areas 1:2:10).

Anal. Calcd for $C_{15}H_{13}N_5$: C, 68.42; H, 4.97. Found: C, 68.40; H, 5.09.

1,5-Diphenyl-4-diazomethyl-1,2,3-triazole (XXX).—A suspension of 5.00 g (0.019 mol) of 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde hydrazone, 16.5 g of active manganese dioxide,[5] and 20 g of anhydrous sodium sulfate in 500 ml of anhydrous ether was stirred for 15 min in the dark. A 5-ml portion of saturated alcoholic potassium hydroxide was added and stirring was continued for 5 hr at room temperature. The reaction mixture was filtered and the filtrate evaporated to one-half its original volume in a stream of nitrogen. Petroleum ether was added to the cloud point and the solution refrigerated overnight. A small amount of white solid was filtered off, the solution was concentrated, petroleum ether was added, and the flask was returned to the refrigerator for 24 hr. Repetition of this process gave three crops of orange-red crystals having a combined weight of 2.39 g (48%), mp 110° with rapid evolution of gas (unchanged by three recrystallizations from ether–petroleum ether mixture). The infrared spectrum lacked NH absorption and showed an intense maximum at 2080 cm^{-1} (C=N_2) as well as maxima at 1080 and 100 cm^{-1} (characteristic of 1,2,3-triazoles[30]). The

(26) General method of G. L. Closs, L. E. Closs, and W. A. Boll [*J. Amer. Chem. Soc.*, **85**, 3796 (1963)].

(27) *Cf.* F. C. Chang, *J. Org. Chem.*, **30**, 2053 (1965), for another example of azine formation during the preparation of a tosylhydrazone.

(28) Based on the general method of G. W. Kaufman, J. A. Smith, C. G. Vander Stouw, and H. Shechter, *J. Amer. Chem. Soc.*, **87**, 935 (1965).

(29) L. I. Smith and K. L. Howard, *Org. Syn.*, **24**, 53 (1944).

(30) J. H. Boyer in "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, pp 384–361.

nmr spectrum showed a singlet at τ 5.28 and a complex multiplet centered at 3.1 with relative areas of 1:10.

Anal. Calcd for $C_{15}H_{11}N_5$: C, 68.95; H, 4.24. Found: C, 68.83; H, 4.16.

1,4-Diphenyl-5-hydroxymethyl-1,2,3-triazole.—A solution of 1.0 g (0.004 mol) of VII and 1.5 g of sodium borohydride in 50 ml of methanol was allowed to stand overnight, and was then heated on a steam bath for a few minutes and diluted with 100 ml of 2% hydrochloric acid. The white solid that formed on cooling was recrystallized from an ethanol–water mixture to give 0.78 g of the alcohol, mp 169–170.5° (unchanged by three recrystallizations each from aqueous ethanol and benzene–petroleum ether mixture). Its infrared spectrum showed absorptions at 3320, 1600, 1500, 1260, 1080, 1025, and 1000 cm^{-1} and lacked carbonyl absorption. The nmr spectrum showed singlets at τ 5.25 and 6.90 and a multiplet centered at 2.5; relative areas were 2:1:10.

Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.22; N, 16.72. Found: C, 71.88; H, 5.20; N, 16.82.

1,4-Diphenyl-5-chloromethyl-1,2,3-triazole (XXII).—A solution of 7.0 g (0.0278 mol) of 1,4-diphenyl-5-hydroxymethyl-1,2,3-triazole in 20 ml of thionyl chloride was allowed to stand for 4 hr at room temperature, and thereupon heated for 1 hr on the steam bath. Excess thionyl chloride was removed under reduced pressure, leaving an oil, which crystallized on scratching. Recrystallization from petroleum ether–benzene gave 5.6 g (75%) of the chloromethyl compound, mp 115–117°. Its infrared spectrum lacked –OH absorption and exhibited maxima at 1600, 1500, and 1080, and 1000 cm^{-1} (phenyl and 1,2,3-triazole rings). The nmr spectrum showed a singlet at τ 5.40 and a multiplet centered at 2.4 (area ratio 1:5). An analytical sample, prepared by three recrystallizations from benzene–petroleum ether, had mp 116–117°.

Anal. Calcd for $C_{15}H_{12}N_3Cl$: C, 66.79; H, 4.48; N, 15.58. Found: C, 66.87; H, 4.56; N, 15.44.

1,4-Diphenyl-5-methyl-1,2,3-triazole.[31]—A solution of 5.00 g (0.0372 mol) of phenylacetone, 5.44 g (0.0456 mol) of phenyl azide, and 2.72 g of sodium methoxide in 100 ml of absolute ethanol was heated under reflux for 4 hr. On cooling, a white solid crystallized. Recrystallization from ethanol gave 6.0 g (69%) of product, mp 157–159°. The infrared spectrum showed absorptions at 1600, 1500, 1080, and 1000 cm^{-1} (phenyl and 1,2,3-triazole rings); the nmr spectrum showed a singlet at τ 7.60 (Ar–CH_3) and a complex multiplet centered at 2.5, area ratios 3:10. These data are in good accord with 1,4-diphenyl-5-methyl-1,2,3-triazole. An analytical sample prepared by four recrystallizations from ethanol–petroleum ether had mp 158–159°.

Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; mol wt, 235. Found: C, 76.15; H, 5.69; mol wt (cryoscopic in benzene), 244.

1,4-Diphenyl-5-dibromomethyl-1,2,3-triazole (XXVI).—A solution of 5.25 g (0.0223 mol) of 1,4-diphenyl-5-methyl-1,2,3-triazole, 8.76 g (0.0491 mol) of N-bromosuccinimide and 1.00 g of benzoyl peroxide in 400 ml of carbon tetrachloride was heated under reflux for 24 hr. The solution was filtered hot, washed several times with water, dried over anhydrous sodium sulfate, concentrated, and chromatographed on 250 g of silica gel. The main product (XXVI) was eluted from the column with 1% ether in benzene (following a small band of yellow oil) to yield 5.17 g (70%): mp 144–146°; infrared absorptions at 1600, 1500, 1080, and 1000 cm^{-1} (phenyl and 1,2,3-triazole rings); nmr, singlet at τ 3.25 (Ar–CH) and a multiplet centered at 2.3, relative areas 1:10. An analytical sample prepared by four recrystallizations from carbon tetrachloride–petroleum ether mixture had mp 145–146°.

Anal. Calcd for $C_{15}H_{11}N_3Br_2$: C, 45.83; H, 2.82. Found: C, 45.86; H, 2.78.

The foregoing product was identical with a sample obtained by treating the aldehyde (VII) with phosphorus pentabromide in refluxing methylene chloride (yield 85%).

A sample of XXVI was heated for 3 hr with alcoholic potassium hydroxide; 1,4-diphenyl-1,2,3-triazole (X) was produced essentially quantitatively. A similar experiment conducted at room temperature overnight led to a mixture of X and aldehyde VII.

Thermolysis of 1,4-Diphenyl-5-diazomethyl-1,2,3-triazole (IV). A. In Benzene.—A solution of 0.279 g (0.0011 mol) of IV in 75 ml of anhydrous benzene was heated at 50° under nitrogen for 4 hr, after which time the orange color had completely disappeared. A pale green, insoluble solid, 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde azine (IX), mp 300–304°, wt 0.020 g (8%), was separated by filtration. Thin layer chromatography of the mother liquor showed a single product. Chromatography on 75 g of alumina gave 0.220 g (66%) of XIV as colorless crystals, mp 162–166° (eluted with 75% ether in petroleum ether). Compound XIV decolorized both bromine and potassium permanganate, and showed infrared absorptions at 1600, 1500, 1080, and 1000 cm^{-1} (phenyl and 1,2,3-triazole rings and nmr signals at τ 6.87 (triplet), 4.68 (quartet), 3.77 (multiplet), 3.40 (multiplet), and 2.5 (complex multiplet). An analytical sample prepared by two recrystallizations each from benzene–petroleum ether had mp 167–167.5°.

Anal. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.51; N, 13.50. Found: C, 80.81; H, 5.70; N, 13.42.

On heating XIV under reflux with maleic anhydride in xylene for 0.5 hr, an adduct, mp 257° with decomposition, was obtained, confirming the presence of a conjugated olefin.[32]

Anal. Calcd for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.41; H, 4.46; N, 10.01.

A reaction carried out in more dilute solution (0.005 *M*) differed only in that no azine was formed. When oxygen was bubbled through a 0.005 *M* benzene solution of diazoalkane heated at 50° for 4 hr, a low yield (3%) of 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde (VII), isolated as the 2,4-dinitrophenylhydrazone, was obtained as well. No aldehyde was produced in the absence of oxygen. In a similar experiment using carbon monoxide in place of oxygen, an oily solid remained after evaporation of the excess benzene. No acidic substance could be extracted with base, and no pure substance could be separated. Strong infrared absorptions at 1740 and 1660 cm^{-1} showed that much reaction with the carbon monoxide must have taken place. The nmr spectrum showed peaks characteristic of the cycloheptatriene system, and many other peaks having nonintegral area ratios. Compound XIV was stable under these reaction conditions.

B. **In Cyclohexane.**—A solution of 0.135 g (0.52 mmol) of IV in 35 ml of freshly redistilled cyclohexane was placed in a flask connected to a gas buret, and the system was flushed with dry nitrogen. The solution was heated with stirring for 24 hr at 40°; 0.54 mmol of nitrogen was evolved. A pale green precipitate of aldazine IX (0.018 g, 14%) was removed by filtration. Thin layer chromatography revealed only a single product in the mother liquor. Vapor phase chromatography failed to show any traces of bicyclohexyl. Removal of cyclohexane left an oily yellow solid, from which 0.110 g (67%) of a white solid (XV) was obtained by recrystallization from aqueous ethanol: mp 126–131°; infrared absorptions at 1600, 1500, 1070, and 9955 cm^{-1} (phenyl and 1,2,3-triazole rings); and nmr signals at τ 8.6 (multiplet), 9.1 (multiplet) 7.25 (doublet), and 2.5 (complex multiplet), with relative areas approximately 11:2:10. An analytical sample prepared by three recrystallizations from petroleum ether had mp 132.5–134.0°.

Anal. Calcd for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.65; H, 7.17; N, 13.25.

C. **In Cyclohexene.**—A solution of 0.500 g (0.0019 mol) of IV in 38 ml of freshly redistilled cyclohexene was heated for 4 hr at 50° under dry nitrogen. Thin layer chromatography showed a single, elongated spot with an R_f value approximately the same as for 1,4-diphenyl-5-cyclohexylmethyl-1,2,3-triazole (XV). No 2,2-bicyclohexenyl could be detected by vapor phase chromatography. Cyclohexene was removed *in vacuo*, and the residue was dissolved in ethanol and hydrogenated at room temperature and 35 psi for 3 hr over a platinum catalyst. Chromatography on 80 g of silica gel partially separated the reaction mixture into two components: XVI, mp 143–151°, and a compound, mp 127–132°, identical with XV. A total of 0.466 g of XVI and XV combined were eluted from the column with 2% ether in benzene. Compound XVI was stable to hydrogenation and reacted sluggishly with bromine and not at all with potassium permanganate. Its infrared spectrum had absorptions at 1600, 1500, 1080, and 1000 cm^{-1}. The nmr spectrum had incompletely resolved multiplets at τ 8.0, 8.4, 8.8, and 9.3 and a complex multiplet centered at 2.5 (aliphatic H–aromatic H approximately 11:10). Resonances corresponding to olefinic, allylic, or benzylic protons were completely absent. These data

(31) General method of O. Dimroth, E. Fusoni, and S. Marshall, *Ber.*, **39**, 3920 (1906).

(32) K. Alder, H. Jungen, and K. Rust, *Ann.*, **602**, 94 (1957); N. W. Gordon and I. W. Elliott, *J. Org. Chem.*, **27**, 1445 (1962).

are consistent with 7-(1,4-diphenyl-1,2,3-triazole-5-yl)norcarane. Compound XVI was also obtained by hydrogenation of 7-(1,4-diphenyl-1,2,3-triazole-5-yl) cycloheptatriene (XIV) with a platinum catalyst. An analytical sample prepared by three recrystallizations each from aqueous ethanol and petroleum ether had mp 150–153°.

Anal. Calcd for $C_{21}H_{21}N_3$: C, 79.97; H, 6.72; N, 13.32. Found: C, 79.97; H, 6.71; N, 12.95.

A ratio of 7.7:1 for XV–XVI was determined from the nmr spectrum of the reaction mixture after hydrogenation by comparing the normalized area of the methylene doublet of XV at τ 7.25 with that of remaining aliphatic protons in the region 7.7–9.8. A correction for the contribution of the aliphatic protons of XV estimated from the methylene doublet at τ 7.25, was applied to this latter area. Similar ratios of addition to insertion were obtained by recombining chromatographic fractions containing XVI, XV, and mixtures thereof and from the nmr spectrum of the reaction mixture before hydrogenation. Since the combined yield of XVI and XV was 0.466 g, this ratio corresponds to 0.412 g (69%) of XVI and 0.054 g (9 ± 3%) of XV. The error was estimated by adding a known amount of XV to the mixture and comparing calculated and observed increases in the area of the methylene doublet at τ 7.25.

D. In Carbon Tetrachloride.—A solution of 0.804 g (0.003 mol) of IV in 150 ml of freshly redistilled and deoxygenated carbon tetrachloride was heated under nitrogen for 4 hr at 50°, at which time it had become colorless. The solution was concentrated and examined by vapor phase chromatography, which revealed small amounts of hexachloroethane. Column chromatography on 30 g of Florisil gave 0.505 g (42%) of a white crystalline solid, XVII, mp 132–137°, eluted with 1% ether in benzene. Elution with 10% ether in benzene gave 0.467 g of a second compound, XIX, mp 260° with extensive decomposition. The experiment was repeated several times and varying amounts of aldehyde (XII) were occasionally isolated; careful purification of the diazoalkane eliminated it. Three further potential sources of XII were also eliminated. When oxygen was bubbled through a carbon tetrachloride solution of pure diazoalkane for 4 hr at 50°, no detectable amount of aldehyde was formed, and 1,4-diphenyl-5-dichloromethyl-1,2,3-triazole mp 131–134°, prepared from XII and phosphorus pentachloride, underwent no hydrolysis under the experimental conditions. Compound XVII was also found to be stable under the experimental conditions.

Compound XVII gave a positive test for halogen (sodium fusion). Its infrared spectrum showed absorptions at 1600, 1500, 1080, and 1000 cm^{-1}. The nmr spectrum showed a singlet at τ 4.22 and a multiplet centered at 2.5, relative areas 1:10. Recrystallization from isopropyl alcohol gave an analytical sample, mp 143–143.5°.

Anal. Calcd for $C_{16}H_{11}Cl_4N_3$: C, 49.64; H, 2.87; N, 10.86. Found: C, 49.71; H, 2.95; N, 11.04.

When XVII was heated in an alcoholic potassium hydroxide solution for 0.5 hr, a white, crystalline, chlorine-containing compound, mp 221–223°, precipitated. Its infrared spectrum showed absorption at 1625 (C=C stretching) and at 1600, 1500, 1080, and 1000 cm^{-1} (phenyl and 1,2,3-triazole rings). The nmr spectrum showed only aromatic protons (multiplet centered at τ 2.4). These data are consistent with 1,4-diphenyl-5-trichlorovinyl-1,2,3-triazole (XIX). An analytical sample prepared by two recrystallizations each from ethanol–water and benzene–petroleum ether had mp 221–222°.

Anal. Calcd for $C_{16}H_{10}N_3Cl_3$: C, 54.81; H, 2.88; N, 11.99. Found: C, 55.20; H, 2.95; N, 11.98.

Compound XIX contained halogen, and its infrared spectrum showed absorptions at 1600, 1510, 1080, and 1000 cm^{-1}. It was found to be identical with the 1,2-dichloro-1,2-bis(1,4-diphenyltriazol-5-yl)ethane prepared by addition of chlorine to 1,2-bis(1,4-diphenyltriazol-5-yl)ethylene (XXI) (see below).

When XIX was dissolved in hot acetic acid and heated in the presence of zinc dust for 4 hr, 1,2-bis(1,4-diphenyl-1,2,3-triazol-5-yl)ethylene (XXXI) was produced in good yield. A chloroform solution of XXI (prepared from 1,4-diphenyl-5-dibromomethyltriazole; see ahead) was saturated with chlorine and allowed to stand overnight at room temperature; 1,2-dichloro-1,2-bis(1,4-diphenyltriazol-5-yl)ethane, mp 225–256° with extensive decomposition, identical with XIX, was obtained in 50% yield. In a later experiment, XIX was isolated in a pure state in a yield of 45%, mp 270° with extensive decomposition.

Anal. Calcd for $C_{30}H_{22}N_6Cl_2$: C, 67.04; H, 4.13; N, 15.64. Found: C, 67.32; H, 4.21; N, 15.34.

E. Without Solvent or in the Presence of Inert Diluent.—A suspension of IV in perfluorodioxane (Minnesota Mining and Manufacturing Co. FC-75) heated for 24 hr at 60° yielded only the azine (IX) (76% yield).

A solution of IV in hexafluorobenzene evolved gas when heated, but evaporation of the solvent left a tarry residue from which no pure substance could be isolated; it was free of fluorine.

Thermal decomposition of IV under nitrogen without any solvent led to mild explosions, and left tarry residues from which the only identifiable material obtained was small amounts of the aldazine (IX).

Photolysis of IV.—Experiments were carried out in a thin-walled Pyrex tube with a quartz water jacket. Coolant water was precirculated through a copper coil immersed in an ice–salt bath. An external light source was provided by a Srinivasan-Rayonet-Griffin Photochemical Reactor (Southern New England Ultra-violet Co.) equipped with 16 0.24-W RPR-3500-Å lamps emitting 90% of their energy in the 3500-Å region.

A. In Benzene.—A solution of 0.500 g (0.0019 mol) of IV in 75 ml of anhydrous benzene was photolyzed for 24 hr at 10°, during which time the orange color of the diazoalkane disappeared. In the absence of light, 98% of the diazoalkane remained unreacted under these conditions. Thin layer chromatography revealed a single product. Removal of benzene gave a crystalline residue, which on recrystallization yielded 0.411 g (69%) of 7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene (XIV), mp 159–164°, identical with that obtained from the thermal reaction (mixture melting point after recrystallization).

When the photolysis was conducted while oxygen was bubbled through the solution, no 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde was produced in detectable amounts (infrared; dinitrophenylhydrazone precipitation).

B. In Cyclohexane.—A solution of 0.350 g (0.0013 mol) of IV in 60 ml of freshly redistilled cyclohexene was photolyzed 30 hr at 10°. In the absence of light, 95% of the diazoalkane was unreacted under these conditions. Thin layer chromatography showed a single elongated spot with an R_f value identical with that found in the thermal reaction. Vapor-phase chromatography failed to show any traces of 2,2′-bicyclohexenyl. Chromatography on 50 g of Florisil and elution with 2% ether in benzene partially separated the reaction mixture into two components, 7-(1,4-diphenyl-1,2,3-triazol-5-yl)norcarane (XVI) and 1,4-diphenyl-5-cyclohexylmethyl-1,2,3-triazole (XV). The addition–insertion ratio was determined from the nmr spectrum to be 11.5:1. The combined yield of 0.263 g corresponds to 0.242 g (57%) of the norcarane and 0.021 g (5 ± 3%) of the cyclohexylmethyltriazole (XV).

Competitive Reactions with Hydrocarbons. A. With Benzene and Cyclohexane.—A solution of 0.300 g (0.00115 mol) of IV in 100 ml of of an equimolar mixture of benzene and cyclohexane was heated under nitrogen for 4 hr at 60°. Solvents were removed under reduced pressure, and the residue was redissolved in chloroform. By comparison of the normalized areas of the nmr triplet of XIV at τ 6.87 and the methylene doublet of XV at 7.25, the ratio of XIV–XV was found to be 2.1:1. Chromatography of the reaction mixture on 30 g of Florisil gave 0.311 g of a mixture of XIV and XV, mp 125–155°, eluted with 20% petroleum ether–benzene, and 0.36 g (13%) of the azine (IX), mp 300–305°, eluted with 1:1 ether–benzene. The mixture of XIV and XV was heated 20 min with 0.084 g of maleic anhydride in xylene solution. The solid adduct was filtered from the cooled mixture, the xylene was evaporated from the filtrate, the residue was taken up in hot carbon tetrachloride and filtered from a further small amount of solid. Evaporation left 0.110 g of XV, mp 130–134° (mmp 132–134°). The molar ratio of XIV–XV was therefore 2.05:1. A duplicate experiment using chromatography on silica gel gave 0.264 g of the XIV–XV mixture, from which thorough washing with petroleum ether extracted 0.086 g of XV, mp 125–130°, and left 0.180 g of XIV: molar ratio of XIV–XV = 2.15:1.

B. With Benzene and Cyclohexene.—In a similar experiment using an equimolar mixture of benzene and cyclohexene, relative amounts of XVI and XIV were determined by comparison of the normalized areas of the olefinic protons of XIV at τ 3.40, 3.77, and 4.68 with that of the aliphatic protons of XVI in the region 7.5–9.6. The olefinic protons of XIV at τ 3.40 and 3.77 were cleanly resolved, but those at 4.68 were partially obscured by small amounts of insertion products from the diazoalkane and cyclohexene, causing the combined area of these three groups to be somewhat large, and thus to give only a minimum value for

the ratio of XVI–XIV. A maximum value was obtained by selecting the smallest area from the three groups. The most accurate value of the XVI–XIV ratio, obtained from the cleanly resolved olefinic protons at τ 3.40 and 3.77, was 9.2 ± 1 (average of two determinations).

C. With Cyclohexene and Cyclohexane.—In a similar experiment using a mixture of cyclohexane and cyclohexene in a molar ratio of 10:1, an approximate value for the ratio of XVI and XV was obtained from the relative areas of the methylene doublet of XV at τ 7.25 and the aliphatic protons of XVI in the region of 7.5–9.6. A correction for the contribution of the aliphatic protons of XV to the latter area was calculated from the methylene doublet of XV. The XVI–XV ratio was found to be 2.5 ± 0.5 (average of two determinations), giving a reactivity ratio of cyclohexene–cyclohexane of 25 ± 5 after correction for the 10:1 ratio of the reactants. This value is only approximate, since it is not corrected for products of insertion into C–H bonds of cyclohexene (in pure cyclohexene the addition–insertion ratio was found to be 7.7:1).

Rates of Decomposition of I.—Consumption of IV was followed by the ultraviolet absorbance at 320 or 462 mμ, which was found to vary linearly with concentration.

In the case of reaction in benzene, the rate was also followed by disappearance of the well-resolved infrared peak at 2060 cm^{-1} (log ϵ 1.09), whose intensity was found to vary linearly with concentration.

A. In Cyclohexene.—A solution of 0.050 g of IV in 25 ml of freshly redistilled cyclohexene (preheated to 50°) was immersed in a bath at 50.0 ± 0.1°, and 2-ml aliquots were periodically withdrawn and cooled for a few seconds in an ice bath. Accurate 1.00-ml samples were transferred from these to a 10-ml volumetric flask and immediately frozen in a Dry Ice–acetone bath. Just prior to measurement, samples were thawed and the flask was filled with anhydrous ether. Absorbance of the ether solution was measured at 320 mμ using a reference solution containing 1 ml of cyclohexene in 10 ml of ether solution. Plots of log A *vs.* t were linear. The first-order rate constant calculated from the slope of the plot of log A *vs.* t was 17.6 × 10^{-3} min^{-1} (average of three runs with a range of 3.5 × 10^{-3} min^{-1}).

B. In Benzene.—The reaction of V with benzene was followed as described for cyclohexene. A solution of 1 ml of benzene in 10 ml of solution was used in the reference cell. Although the reaction products showed insignificant absorbance at 320 mμ, the ether–benzene mixture absorbed considerably. Most of this interference was removed by compensation, and the remainder by subtraction of absorbance at $t = \infty$ (A_∞) from A_t. The first-order rate constant calculated from the plot of log A *vs.* t was 9.5 × 10^{-3} min^{-1} (average of two runs with a range 2.6 × 10^{-3} min^{-1}). Representative data are reported in Table II.

TABLE II

KINETIC DATA FOR THE DECOMPOSITION OF 1,4-DIPHENYL-5-DIAZOMETHYL-1,2,3-TRIAZOLE AT 50 ± 0.1°

In benzene			In carbon tetrachloride		
Time, min	Absorbance at 2060 cm^{-1}	$k \times 10^3$,[a] min^{-1}	Time, min	Absorbance,[b] $A_t - A_\infty$	$k \times 10^3$,[a] min^{-1}
30	0.33		6	0.160	
45	0.29	8.7	9	0.150	21
60	0.255	8.5	12	0.125	61
75	0.205	14.5	15	0.080	148
105	0.161	8.3	17	0.060	143
135	0.115	11.0	19	0.045	143
165	0.090	8.2	21	0.035	125
195	0.070	8.4	23	0.025	168
	Average	8.9	25	0.020	111
				Average[c]	139

[a] Calculated for each adjacent pair of points. [b] At 462 mμ. [c] Over last six values.

The reaction rate was also followed by the infrared method. Samples were periodically withdrawn from the reaction mixture by means of a syringe and introduced into a 0.1-mm infrared cell. Absorbances were determined at 2060 cm^{-1} using a reference cell filled with benzene. Runs were conducted at 50.0 ± 0.1° and 40.0 ± 0.1°. First-order rate constants were (50.0°) 9.2 × 10^{-3} and (40.0°) 2.5 × 10^{-3} (calculated activation energy 25.9 kcal/mol).

C. In Carbon Tetrachloride.—Owing to interfering absorbance by reaction products, measurements were made at 462 mμ, using carbon tetrachloride in the reference cell and as the solvent. Plots of log A *vs.* t were initially nonlinear but became linear after approximately 15 min. Second-order plots of the data were also nonlinear. The first-order rate constant calculated from the linear portion of the plots was 122 × 10^{-3} min^{-1} at 50.0°, range 34 × 10^{-3} min^{-1} (average of two runs) (*cf.* Table I).

D. In Cyclohexane.—Owing to the limited solubility and slow rate of solution of IV in cyclohexane, it was necessary to carry out kinetic runs in mixtures containing 1:1 and 2:1 molar ratios of cyclohexane and benzene or a 2:1 molar ratio of cyclohexane and ether. Rates were affected relatively little by changes in the solvent mixture. Experiments were conducted at 50.0 ± 0.1° and absorbances were measured at 462 mμ. First-order rate constants were 17.1 × 10^{-3} min^{-1} (2:1 cyclohexane–ether), 19.3 × 10^{-3} min^{-1} (1:1 cyclohexane–benzene), and 19.8 × 10^{-3} min^{-1} (2:1 cyclohexane–benzene), average value 18.7 × 10^{-3} min^{-1}.

Reaction of 1,4-Diphenyl-5-chloromethyl-1,2,3-triazole (XXII) with Potassium *t*-Butoxide. A. In *t*-Butyl Alcohol. Bis(1,4-Diphenyl-1,2,3-triazole-5-methyl) Ether (XXIII).—A solution of 0.70 g of XXII in 75 ml of *t*-butyl alcohol containing 0.56 g of potassium *t*-butoxide was stirred at room temperature for 20 hr. A white precipitate (XXIII), 0.56 g, was collected on a filter and washed with *t*-butyl alcohol, mp 205–206°. The *t*-butyl alcohol was removed from the mother liquor, the residue extracted with benzene, and the extract washed with water and dried (sodium sulfate). Removal of benzene left 0.18 g of residue, mp 201–204°. The solids were combined and recrystallized from benzene–petroleum ether to give 0.50 g (96%) of XXIII pure by thin layer chromatography. It absorbed in the infrared at 1600, 1500, 1080, and 1000 cm^{-1} (1,4-diphenyl-1,2,3-triazolyl system) and at 1060 cm^{-1} (ether linkages). The nmr spectrum showed a singlet at τ 5.42 and a multiplet centered at 2.5, with relative areas of 1:5. An analytical sample prepared by three recrystallizations from chloroform–petroleum ether mixtures had mp 205–206°.

Anal. Calcd for $C_{30}H_{24}N_6O$: C, 74.37; H, 5.00; N, 17.35; mol wt, 484. Found: C, 74.61; H, 4.86; N, 17.64; mol wt (Rast), 493.

B. In Benzene. 1,4-Diphenyl-5-*t*-butoxymethyl-1,2,3-triazole (XXIV).—To a well-stirred solution of 1.00 g of XXII in 50 ml of anhydrous benzene was added 0.67 g of potassium *t*-butoxide. The initial red color slowly faded during 2 hr while stirring at room temperature, and disappeared completely after heating under reflux for 2 hr more. The hot solution was filtered and the benzene was removed, leaving a residue of 1.20 g, mp 140–150°. Recrystallization from benzene–petroleum ether mixture gave 0.72 g of a white, crystalline solid, XXIV, mp 151–153°. The mother liquor was chromatographed on 20 g of Florisil; 0.012 g of the starting halide, mp 115–117°, was eluted with 1% ether in benzene and 0.34 g of XXIV, mp 145–150°, was eluted with 2% ether in benzene (total yield 93%). Infrared absorptions at 1600, 1500, and 1010 cm^{-1} suggested the 1,4-diphenyl-1,2,3-triazolyl system, and strong absorptions at 1260, 1190, and 1060 cm^{-1} suggested an ether linkage. The nmr spectrum showed singlets at τ 8.74 ($-C-CH_3$) and 5.62 ($Ar-CH_2-$) and a complex multiplet centered at 2.5 (relative areas 9:2:10). An analytical sample prepared by three recrystallizations each from ethanol–water and benzene–petroleum ether mixtures had mp 151–152°.

Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67; mol wt, 307. Found: C, 74.10; H, 6.82; N, 13.72; mol wt (cryoscopic in benzene), 300.

Reaction of 1,4-Diphenyl-5-chloromethyl-1,2,3-triazole (XXII) with *n*-Butyllithium.[33] 1,2-Bis(1,4-diphenyl-1,2,3-triazol-5-yl)-ethane.—To a cold (10°) solution of 1.00 g of XXII in 50 ml of anhydrous benzene was added 1.8 ml of 2.0 *N* *n*-butyllithium in pentane with rapid stirring. After about two-thirds of the *n*-butyllithium was added, a precipitate began to form. The suspension was allowed to warm to room temperature and was stirred overnight. The precipitate was collected on a filter and recrystallized from benzene to give 0.74 g of white solid (XXV), mp 279–280°. Concentration of the mother liquor gave an additional 0.08 g (total yield 97%). Infrared absorption at 1600, 1500, 1080, and 1000 cm^{-1} suggested phenyl and 1,2,3-triazole

(33) General method of G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964).

rings; the nmr spectrum showed a singlet at τ 7.03 and a multiplet centered at 2.6 (area ratio 1:5). No halogen could be detected by sodium fusion, and no reaction was observed with bromine or potassium permanganate. An analytical sample prepared by three recrystallizations from benzene–chloroform and one from ethanol–chloroform had mp 279–280°.

Anal. Calcd for $C_{15}H_{12}N_3$: C, 76.90; H, 5.16; N, 17.94; mol wt, 468. Found: C, 76.76; H, 5.09; N, 18.11; mol wt (Rast), 495.

Reaction of 1,4-Diphenyl-5-dibromomethyl-1,2,3-triazole (XXVI) with *n*-Butyllithium. 1,2-Bis(1,4-diphenyl-1,2,3-triazol-5-yl)ethylene (XXVII).—A solution of 2.00 g of XXVI in anhydrous ether under nitrogen was cooled to 0–5° and 3.0 ml of a 1.5 *N* pentane solution of butyllithium was added dropwise through a rubber septum by means of a syringe. The solution was stirred for 3 hr at room temperature and was then poured into ice water and extracted with benzene. The benzene extract was washed successively with 1 *N* hydrochloric acid and water, dried over anhydrous sodium sulfate, and concentrated to small volme. A white precipitate, XXVII, was collected (0.270 g), mp 236–241°. Chromatography of the mother liquor on 80 g of silica gel gave on elution with 1% ether in benzene 0.602 g of the starting dibromide XXVI (mp 144–147°), 0.30 g each of two additional unknown compounds, XXVIII (mp 220–225°) and XXIX (mp 240° with extensive decomposition), and an additional 0.179 g of XXVII, eluted in the given order. The same product mixture was obtained when reaction was carried out in benzene, cyclohexene, ether–benzene or ether–cyclohexene. No evidence was obtained for reaction with the solvent in any case.

The infrared spectrum of XXVII showed bands at 1600, 1500, 1080, and 1000 cm^{-1} (phenyl and 1,2,3-triazole rings). The nmr spectrum showed a singlet at τ 3.03 and a complex multiplet centered at 2.4, with relative areas of 1:10. Halogen could not be detected by sodium fusion; positive tests for unsaturation were obtained with both bromine and potassium permanganate. Hydrogenation of XXVII in ethyl acetate over platinum oxide gave XXV, identified by mixture melting point. An analytical sample obtained by two crystallizations each from benzene–petroleum ether and ethanol–petroleum ether mixtures, had mp 244–245°.

Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.24; H, 4.75; N, 18.02. Found: C, 77.27; H, 4.71; N, 17.86.

Treatment of XXVII with bromine in chloroform solution gave XXVIII as shown by infrared spectra and mixture melting point. When XXVIII was treated with alcoholic potassium hydroxide, XXIX was produced. Heating an acetic acid solution of XXVIII with zinc dust for 3 hr gave XXVII. Both XXIX and XXVIII gave positive tests for halogen. This evidence suggests that XXVIII is 1,2-bis(1,4-diphenyl-1,2,3-triazol-5-yl)ethylene dibromide and that XXIX is the corresponding vinyl bromide.

Thermolysis of 1,5-Diphenyl-4-diazomethyl-1,2,3-triazole (XXX).—A solution of 0.500 g (0.0019 mol) of XXX in 65 ml of anhydrous benzene was heated under reflux for 5 hr with protection from oxygen. Thin layer chromatography indicated three products; vapor phase chromatography at 180° showed a single volatile product. Column chromatography on 40 g of silica gel gave 0.060 g (17%) of a white solid (XXXII), mp 115–117°, after elution with 50% benzene–petroleum ether, and 0.264 g of a white solid (XXXI), mp 310–315° dec, after elution with 50% ether–benzene.

Compound XXXII reacted readily with both bromine and potassium permanganate and gave a yellow precipitate with ammoniacal cuprous chloride. A monosubstituted acetylene structure was supported by infrared absorptions at 3190 (3300 in chloroform solution) and 2100 cm^{-1}. The nmr spectrum showed a singlet at τ 6.87 and multiplets centered at 2.8 and 1.8 (relative areas 1:8:2). The chemical shifts and splittings of the multiplets were very similar to those of the anil of benzoyl cyanide. An analytical sample prepared by four recrystallizations from petroleum ether had mp 118.5–119.5°.

Anal. Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40. Found: C, 87.88; H, 5.40.

A sample of XXXII was heated for 10 min with 4 *N* sulfuric acid. Steam distillation followed by extraction with ether gave phenyl ethynyl ketone, isolated as its 2,4-dinitrophenylhydrazone, mp 316° dec (lit.[34] mp 314° dec). Neutralization of the acid solution with sodium hydroxide followed by extraction with ether gave aniline, identified by its gas chromatographic retention time at 120°.

The infrared spectrum of XXXI showed a band at 1650 cm^{-1}, attributable to C=N, and bands at 1600, 1500, 1070, and 1000 cm^{-1} (phenyl and 1,2,3-triazole rings). The nmr spectrum contained a singlet at τ 1.44 and a multiplet centered at 2.9 (relative areas 1:10). Confirmation of structure XXXI was obtained by synthesis in quantitative yield from 1,5-diphenyl-1,2,3-triazol-4-carboxaldehyde and an equimolar quantity of its hydrazone. An analytical sample prepared by four recrystallizations from chloroform–petroleum ether had mp 316–318° dec.

Anal. Calcd for $C_{16}H_{11}N_4$: C, 72.86; H, 4.48. Found: C, 72.57; H, 4.64.

Similar results were obtained when XXX was decomposed by heating in freshly redistilled cyclohexane (yields: XXXII, 30%; XXXI, 66%) or in freshly redistilled cyclohexene (yields: XXXII, 12%; XXXI, 64%). No evidence was found for reaction with the solvent in any of these decompositions.

Attempted Cyclization of 1,4-Diphenyl-1,2,3-triazole-5-carboxylic Acid.—Treatment of 1,4-diphenyl-1,2,3-triazole-5-carboxylic acid[4] with anhydrous hydrogen fluoride (24 hr at *ca.* 20°) or polyphosphoric acid[35] (24 hr at 100°) led only to recovered starting material (94–98%).

Registry No.—IV, 15764-89-3; VII tosylhydrazone, 15764-90-6; 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde tosylhydrazone, 15764-91-7; VIII, 15764-92-8; IX, 15764-93-9; 1,5-diphenyl-1,2,3-triazole-4-carboxaldehyde hydrazone, 15764-94-0; XII, 15764-95-1; XIV, 15764-96-2; XIV (adduct with maleic anhydride), 15815-83-5; XV, 15764-97-3; XVI, 15764-98-4; XVII, 15815-84-6; XVIII, 15892-88-3; XIX, 15892-87-2; XXII, 15815-85-7; 1,4-diphenyl-5-methyl-1,2,3-triazole, 15765-00-1; XXIII, 15765-01-2; XXIV, 15765-02-3; 1,2-bis(1,4-diphenyl-1,2,3-triazol-5-yl)ethane, 15765-03-4; XXVI, 15815-86-8; XXVII, 15765-04-5; XXX, 15765-05-6; 1,4-diphenyl-5-hydroxymethyl-1,2,3-triazole, 15765-06-7; XXXI, 15765-07-8; XXXII, 15765-08-9.

Acknowledgment.—We are grateful for support of this work by a grant from the National Science Foundation (GP 3536).

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(35) J. Koo, *J. Amer. Chem. Soc.*, **75**, 1891 (1953).

Terpene–Formaldehyde Reactions. II. *d*-Limonene[1]

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Reaction of *d*-limonene with formaldehyde to give a simple 1:1 product is best achieved in solvent methylene chloride–acetic anhydride at autogenous temperature for 70 min under nitrogen at 1 atm with a complex of boron trifluoride as catalyst, preferably the dihydrate. The principal product fraction (82% yield) is comprised mainly of (84%) 9-acetoxymethyl-1,8(10)-*p*-menthadiene. This acetate and its alcohol are easily converted into the saturated primary alcohol 9-hydroxymethyl-*p*-menthane. The acrylate of the latter alcohol gives a homopolymer and a methyl methacrylate copolymer when polymerized in bulk with initiation by azobisisobutyronitrile.

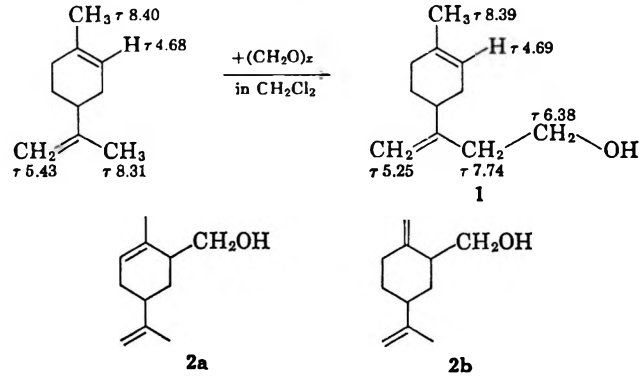
There are many reports in the literature concerned with the reaction of *d*-limonene, or dipentene, with formaldehyde,[3] but none describes the isolation and unequivocal characterization of pure 1:1 reaction products, or simple derivatives thereof. With the modern experimental methods for isolation, purification, and characterization of organic compounds now available, *e.g.*, analytical and preparative glpc, nmr spectroscopy, etc., it was of interest to make a careful, extensive study of the limonene–formaldehyde reaction. The useful synthesis of a primary alcohol from readily available pure *d*-limonene is of importance also.

The limonene–formaldehyde reactions described in this report are those (a) catalyzed by Lewis acids, (b) catalyzed by mineral or strong acids, and (c) so-called "noncatalyzed" thermal condensations. Reactions of the type a proved to be the most broadly useful.

Treatment of *d*-limonene with paraformaldehyde (PFA) (2:1 mole ratio) in methylene chloride containing fuming stannic chloride (0.1 ml/0.22 mol of PFA) for 2 days at room temperature gave, after distillation, a 49% yield of an alcohol fraction that was comprised mainly (80–85%) of the alcohol 9-hydroxymethyl-1,8-(10)-*p*-menthadiene (**1**) and not the alcohols **2a** and/or **2b**. The pure alcohol **1** was obtained by preparative glpc followed by redistillation. The minor products (15–20%) were not examined.

The ir spectrum of the pure alcohol **1** had bands at λ_{max} 3.0 (OH), 5.97 (internal double bond), 6.09 (>C=CH_2), 9.55 (primary OH), 10.90 (internal double bond), and 11.27 μ (>C=CH_2). The nmr spectrum is indicated in Chart I. The triplet at τ 7.74 (-CH_2CH_2OH) was isolated from the other proton signals in the nmr by observing the nmr spectrum of the 3,5-dinitrobenzoate derivative, mp 79.5°, of the alcohol **1** (see Experimental Section), which clearly showed the presence of the group -CH_2CH_2OCO-. The alcohol **1** was converted easily into its acetate, 9-acetoxymethyl-1,8(10)-*p*-menthadiene (**3**), with acetic anhydride.

CHART I



A set of boron trifluoride complexes proved to be very interesting catalysts for the reaction of the title compounds. Thus, reaction of a 2:1 mixture of *d*-limonene and formaldehyde in the solvent system methylene chloride–acetic anhydride (1:1 volume ratio) at autogenous temperature (25–45°) for 70 min and catalyzed by boron trifluoride dihydrate gave an 82% yield of acetates, 84% of which was the acetate **3**. Careful redistillation of this product gave the compound **3** in purity greater than 96%. Under similar conditions the reaction was catalyzed by (a) boron trifluoride etherate, (b) boron trifluoride diphenol, and (c) boron trifluoride diacetic acid to give product acetates in yields of 80, 82, and 78% (with the acetate **3** content found to be, respectively, 80, 88, and 85%). Reaction times for the three reactions were 140, 110, and 60 min at autogenous temperature. Boron trifluoride etherate and diphenol catalyzed reactions of limonene and formaldehyde in the simple solvent methylene chloride afforded decreased yields (47–59%) of product alcohols that contained *ca.* 75–80% of the alcohol **1**.

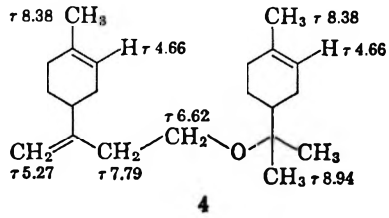
In the latter reactions there was always obtained a substantial amount of higher boiling material. Two components of the high boiling product obtained in the boron trifluoride etherate catalyzed reaction were isolated by careful distillation and column chromatography. Nmr and infrared analyses indicated that they were the ether **4** and the formal **5** (see Experimental Section). The formation of accessory products such as **4** and **5** is clearly reduced in the solvent system methylene chloride–acetic anhydride, probably the consequence of the rapid trapping of alcohols as acetates.

The limonene–formaldehyde reactions catalyzed by acids such as phosphoric, formic, dichloroacetic, and *p*-

(1) For the preceding report from this laboratory on olefin–formaldehyde reactions, see A. T. Blomquist and J. D. Meador, *J. Org. Chem.*, **32**, 3986 (1967).

(2) Abstracted from part of the Ph.D. Dissertation of R. J. Himics, the Graduate School of Cornell University, Ithaca, N. Y., Feb 1967.

(3) (a) G. Ohloff, *Arch. Pharm.*, **287**, 259 (1954); (b) A. T. Blomquist, J. Verdol, C. L. Adami, J. Wolinsky, and D. D. Phillips, *J. Amer. Chem. Soc.*, **79**, 4876 (1957); (c) K. Suga, A. Matsuda, and S. Watanabe, *Nippon Kagaku Zasshi*, **79**, 724 (1958); *Chem. Abstr.*, **54**, 4656 (1960); (d) Y. Matsubara and Y. Watanabe, *ibid.*, **80**, 651 (1959); *Chem. Abstr.*, **55**, 3464 (1961); (e) Y. Watanabe, *ibid.*, **80**, 1063 (1959); *Chem. Abstr.*, **55**, 3591 (1961); (f) Y. Watanabe, Y. Matsubara, and C. Huang, *Kogyo Kagaku Zasshi*, **62**, 1630 (1959); *Chem. Abstr.*, **57**, 13963 (1962); (g) J. Colonge and J. Crabalona, *Bull. Soc. Chim. Fr.*, 102 (1960); (h) K. Suga and S. Watanabe, *Chiba Daigaku Kogakuba Kenkyu Hokoku*, **11**, 29 (1960); *Chem. Abstr.*, **55**, 21159 (1961); K. Suga and S. Watanabe, *Nippon Kagaku Zasshi*, **81**, 1139 (1960); *Chem. Abstr.*, **56**, 507 (1962).



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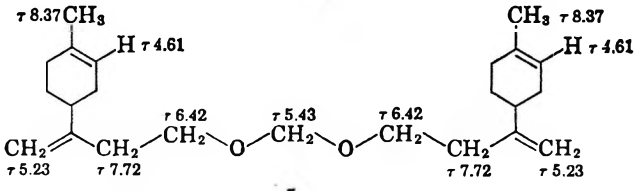

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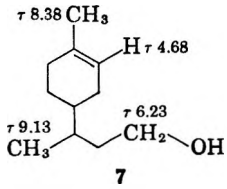
toluenesulfonic were found to be unpromising in that they all afforded inferior yields of complex mixtures of products. Thus, the phosphoric acid-catalyzed reaction in acetic acid–acetic anhydride at 5–15° gave a 34% yield (as acetates) of a mixture that glpc analysis indicated to be composed of three major and at least six minor compounds the formic acid catalyzed reaction in glacial acetic acid at 95–100° afforded a 44% yield of a product mixture that was comprised of three monoacetates in about equal amount (glpc analysis).

For the sake of completeness the classical "non-catalyzed" thermal condensation of *d*-limonene with formaldehyde was reexamined. Reactions effected in a sealed autoclave at 180–200° under autogenous pressure in a variety of solvent systems were uniformly unsatisfactory; all afforded in low yield a complex mixture of products (glpc analysis) whose principal component was the alcohol **1** or the acetate **3**. Reactions in acetic acid in an open vessel at temperatures that ranged from 110 to 125° for 1–7 days gave *ca.* 40–70% yields of complex mixtures whose principal component (55–80%) was the acetate **3**.

With the alcohol **1** and its acetate **3** available in high yield and purity from *d*-limonene it was of interest to examine briefly the polymerization of the saturated primary alcohol 9-hydroxymethyl-*p*-menthane (**6**) derivable from either **1** or **3**. Catalytic hydrogenation of the alcohol **1** occurred smoothly, and stepwise, to afford the alcohol **6** as an inseparable mixture of the expected *cis* and *trans* isomers. The intermediate product of hydrogenation, 9-hydroxymethyl-1-*p*-menthene (**7**),



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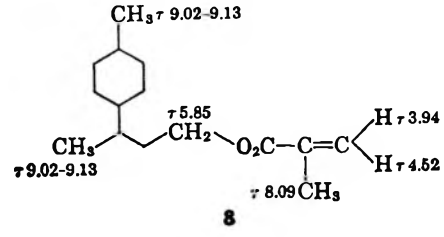

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was obtained by interrupting the hydrogenation after 18 hr (see Experimental Section). Transesterification of methyl methacrylate with the saturated alcohol **6** gave the desired ester **8**, of purity >99%, suitable for polymerization.

The homopolymer of the methacrylate **8** together with a copolymer of **8** and methyl methacrylate were obtained smoothly *via* bulk polymerization initiated by azobisisobutyronitrile. The two polymers, mp 225–230° and 215–225°, respectively, differed markedly in their ease of handling; the homopolymer was soft, caked on standing, and acquired a static charge when ground; the copolymer was a hard, white solid that was easily pulverized. Both polymers were soluble in benzene or toluene and insoluble in acetone or methanol. They showed an intrinsic viscosity in benzene of 3.72 and 3.69 dl/g, respectively.

Experimental Section[4,5]

Materials.—The *d*-limonene used was purchased from Eastman Kodak and showed a purity greater than 99% by glpc analysis.[5a] Fisher "trioxymethylene" (USP) was used as a formaldehyde source; the boron trifluoride catalysts were obtained from the General Chemical Division of the Allied Chemical Corp.

The Stannic Chloride Catalyzed Reaction of *d*-Limonene with Paraformaldehyde.—A mixture of 62.2 g (0.457 mol) of *d*-limonene, 6.6 g (0.22 mol) of paraformaldehyde (PFA), and 400 ml of dry methylene chloride was stirred under nitrogen for 10 min. Fuming stannic chloride (0.3 ml) was then added over 0.5 hr and the mixture stirred at room temperature for 2 days. To the clear, tan solution that resulted there was added, with vigorous stirring, *ca.* 20 ml of cold, dilute sodium hydroxide. The separated aqueous layer was extracted with ether and the ether extracts were combined with the methylene chloride layer. From the dried ($MgSO_4$), combined ether–methylene chloride solution, after removal of solvents *in vacuo*, there was obtained upon distillation two product fractions: (1) 18 g, bp 89–95° (0.5–0.6 mm), $n^{23}D$ 1.4991; (2) 3 g, bp 87–144° (0.3 mm), $n^{23}D$ 1.5086. Fraction 1 (49% yield for a 1:1 limonene–formaldehyde reaction product) was a clear, colorless liquid of 80–85% purity (glpc analysis).[5b] Fraction 2 was not immediately examined.

9-Hydroxymethyl-1,8(10)-*p*-menthadiene (1).—Fraction 1 described above (*ca.* 4 ml) was purified *via* preparative glpc on an 8-ft column (30% Versamid 900 on Chromosorb W) at 180°. Other conditions for the glpc purification were sample size, 1 ml; injector temperature, 330°; detector temperature, 310°; traps manifold, 300°; back pressure value, 310°; head pressure, 15 psi; back pressure, 0 psi; attenuation, 8; flow rates, 7 cm (rotameter). The resulting product, contaminated with Versamid 900, gave the pure alcohol **1** upon redistillation, bp 80–83° (0.2–0.3 mm) and $n^{24}D$ 1.4986. Its ir spectrum showed significant absorptions at 3.0, 5.97, 6.09, 9.55, 10.90, and 11.27 μ. The nmr spectrum showed the following assigned values: τ 4.69 (s, >C=CH–), 5.25 (m, >C=CH_2), 6.38 (t, –CH_2–OH, 7 cps), 7.74 (t, –CH_2CH_2OH, 7 cps), 8.08 (bs), and 8.39 (s, CH_3C=C<).

Anal. Calcd for $C_{11}H_{18}O$: 79.56; H, 10.92. Found: C, 79.40; H, 10.95.

(4) Melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined by a Varian A-60 Spectrometer with carbon tetrachloride used as solvent; integrated area ratios agree well with the structures presented unless otherwise stated. All important distillations were performed using a Nester–Faust Annular Teflon spinning-band column. Analyses were done either by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., or by Galbraith Laboratories, Inc., Knoxville, Tenn.

(5) An F & M Model 770 automatic preparative gas chromatograph was used throughout. For preparative glpc sections of 8 ft × 0.75 in., stainless steel tubing was used that could be coupled to provide a maximum column length of 48 ft. Stainless steel tubing, 4–6 ft × 0.25 in., was used for analytical glpc. The solid support in all glpc columns, unless otherwise stated, was 60-mesh, nonacid-washed Chromosorb W. The liquid phases used in the analytical columns together with the column temperature were as follows: (1) 15% diethylene glycol sebacate (DEGS)–5% Bentone at 85°, (b) 20% diethylene glycol adipate (DEGA) at 190°, (c) same as b at 173°, (d) same as b at 185°, (e) 15% DEGS at 180°, (f) same as a at 190°, (g) 20% silicone gum rubber at 100–200°, (h) 20% Versamid 900 at 195°, (i) same as h at 175°, (j) same as h at 180–225°, (k) same as b at 180°, (l) same as a at 180°, (m) 20% DEGS, (n) 20% Carbowax 20M, (o) same as a at 185°.

Some Derivatives of the Alcohol 1.—The acetate derivative (**3**) of **1**, prepared in a conventional manner *via* reaction with acetic anhydride in the presence of sodium acetate, was a clear, colorless liquid, bp 80–81° (0.3 mm) and $n^{24}D$ 1.4775. Its ir spectrum showed absorption at 5.75 (acetate carbonyl) and 8.0–8.2 μ (acetate group). The nmr spectrum showed significant signals at τ 4.71 (br s, >C=CH), 5.25 (br s, -C=CH_2), 5.92 (t, -CH_2CO-, 7 cps), 7.71 (t, -$CH_2CH_2O_2C$-, 7 cps), 8.09 (s, -O_2CCH_3), and 8.41 (>C=CCH_3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.17; H, 9.79.

The 3,5-dinitrobenzoate derivative of 1, prepared *via* treatment of **1** with 3,5-dinitrobenzoylchloride in the presence of pyridine, mp 79.5° (ethanol–water) showed significant ir absorptions at 5.80 and 8.55 μ; its nmr spectrum showed peaks at τ 2.7 (s, aromatic), 4.6 (br s, -C=C(H)-), 5.13 (br s, -C=CH_2), 5.4 (t, -CH_2CO-, 7 cps), 7.4 (t, -$CH_2CH_2O_2C$-, 7 cps), 7.95 (br s), and 8.4 (s, >C=CCH_3).

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.60; N, 7.78. Found: C, 59.98; H, 5.81; N, 7.54.

The phenylurethan derivative of 1, prepared in a conventional way, had mp 56–57° (from petroleum ether, bp 90–110°) and showed significant ir absorptions at 3.01 (>NH), 5.89 (-CON<), 8.05 (-O_2C-), and 13.34 μ (aromatic). Its nmr spectrum showed peaks at τ 2.73–3.2 (m, aromatic and N-H), 4.57 (s, >C=CH), 5.22 (s, >C=CH_2), 5.28 (t, -CH_2O_2C-), 7.69 (t, -$CH_2CH_2O_2C$-), 8.05 (m), and 8.38 (s, >C=CCH_3).

Anal. Calcd for $C_{18}H_{12}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.87; H, 8.04; N, 4.95.

Reaction of *d*-Limonene with Paraformaldehyde Catalyzed by Boron Trifluoride Complexes. I. With Boron Trifluoride Etherate. A. In Solvent Methylene Chloride.—A solution of 1.0 ml of boron trifluoride etherate in 60 ml of dry methylene chloride was added over a 20-min period to a stirred mixture of 90.5 g (0.665 mol) of *d*-limonene, 9.9 g (0.33 mol) of PFA, and 300 ml of dry methylene chloride at room temperature under nitrogen. This mixture was stirred for 1 hr, treated with 20 ml of saturated sodium bicarbonate solution, and worked up in a conventional way to give a 47% yield (26 g) of the alcohol **1**, bp 81–91° (0.30 mm) and $n^{25}D$ 1.4964, of about 80% purity (glpc analysis).

B. In Solvent Methylene Chloride–Acetic Anhydride.—A solution of 1.0 ml of boron trifluoride etherate in 90 ml of a 1:1 by volume mixture of methylene chloride and acetic anhydride was added to a stirred mixture of 45.2 g (0.332 mol) of *d*-limonene, 5.00 g (0.166 mol) of PFA, 75 ml of methylene chloride, and 75 ml of acetic anhydride at room temperature under nitrogen. After a total reaction time of 142 min (reaction temperature rose to 36° before subsiding) the mixture was worked up in a conventional way to give three principal fractions upon distillation: (1) 19.1 g, bp 35–50° (5.5 mm), $n^{25}D$ 1.4680; (2) 27.6 g, bp 88–95° (0.25 mm), $n^{25}D$ 1.4778; (3) 6.37 g, bp 98–148° (0.25 mm), $n^{25}D$ 1.4845. Fraction 1 was recovered *d*-limonene and corresponded to 84.5% of the excess used. Fraction 2 represented an 80% yield of the expected limonenyl carbinol acetate **3** of *ca.* 80% purity (glpc analysis[5d]).

II. With Boron Trifluoride Diphenol. A. In Solvent Methylene Chloride.—A solution of 5 ml of boron trifluoride diphenol in 95 ml of dry methylene chloride was added over a 45-min period to a stirred mixture of 90.5 g (0.733 mol) of *d*-limonene and 9.9 g (0.33 mol) of PFA in 300 ml of dry methylene chloride at room temperature under nitrogen. The mixture was stirred for another hour, and, after a conventional work-up, gave on distillation unreacted *d*-limonene together with two principal product fractions: (1) 32.5 g, bp 84–91° (0.35 mm), $n^{25}D$ 1.4949, and (2) 17.5 g, bp 140–170° (0.20 mm), $n^{25}D$ 1.5040. Fraction 1 represented a 59% yield of the alcohol **1** of purity 75% (glpc analysis[5e]). Fraction 2 was comprised of high boiling alcohols and ethers.

Upon repetition of the reaction described above using 3.0 and 7.0 ml of catalyst the impure alcohol **1** was obtained in 53 and 49% yield, respectively. The high boiling product, bp 100–190° (0.15–0.40 mm) and $n^{25}D$ 1.5028–1.5055, was obtained in substantial amount in all three reactions.

2,10-Bis(4′-methyl-3′-cyclohexenyl)-5,7-dioxa-1,10-hendecadiene (5).—Examination of the combined high boiling product fraction obtained in the three reactions described in the preceding section (glpc and infrared analysis of redistilled fractions) indicated that it was composed of *ca.* 25% of the alcohol **1** and *ca.* 42% of a complex mixture of alcohols and ethers. Redistillation of a fraction of bp 137–168° (0.20 mm) gave a fraction, bp 152–153° (0.15 mm), whose ir spectrum showed a trace of an hydroxylic component. Column chromatography over neutral alumina with petroleum ether (bp 30–60°) as eluent removed this impurity. Careful redistillation of the chromatographed material gave a center-cut, bp 147–148° (0.15 mm) and $n^{25}D$1 .5029, whose properties indicated it to be the formal **5**. In the infrared it showed strong absorption maxima at 6.10 6.94, 7.26, 9.0, 9.3, 9.7, 11.2, and 12.5 μ; its nmr spectrum showed absorptions at τ 4.61 (br s), 5.25 (br s), 5.43 (s), 6.42 (t), and 8.37 (br s).

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53; mol wt, 344.52. Found: C, 79.99; H, 10.46; mol wt, 345 (chloroform).

2,6-Bis(4′-methyl-3′-cyclohexenyl)-6-methyl-5-oxa-1-heptene (4).—From the high boiling fraction described at the beginning of the preceding section there was obtained, after redistillation, a lower boiling component, bp 124–126° (0.15 mm). This fraction was chromatographed over neutral alumina, benzene–petroleum ether (bp 30–60°) eluent, and redistilled to give a center cut (bp 124–124.5° (0.10 mm) and $n^{25}D$ 1.5019) whose spectral properties were in agreement with the ether structure **4**. In the infrared it showed significant absorption maxima at 5.98, 6.90, 7.23–7.33, 9.33, 11.23, and 12.49 μ. The nmr spectrum showed absorptions at τ 4.66 (br s), 5.27 (br s), 6.62 (t), 7.79 (t), 8.38 (br s), and 8.94 (s).

Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33; mol wt, 302.48. Found: C, 83.35; H, 11.46; mol wt, 310 (acetone).

B. In Solvent Methylene Chloride–Acetic Anhydride.—Reaction was carried out as described in section IB above. A mixture of 46.3 g (0.34 mol) of *d*-limonene and 4.8 g (0.16 mol) of PFA in 100 ml of methylene chloride and 100 ml of acetic anhydride, to which had been added 1.0 ml of boron trifluoride diphenol in 53 ml of the mixed solvent, was stirred under nitrogen at autogenous temperature. The usual work-up gave 27.0 g of a distilled product fraction (bp 87–96° (0.20–0.25 mm) and $n^{25}D$ 1.4780) and corresponded to an 81.5% yield of the acetate of a 1:1 reaction product. Glpc analysis[5f] showed that it contained 88.5% of the acetate **3**.

III. With Boron Trifluoride Dihydrate.—The procedure outlined in sections IB and IIB was followed. From 53 g (0.39 mol) of *d*-limonene and 5.7 g (0.19 mol) of PFA in 100 ml each of methylene chloride and acetic anhydride to which 0.40 ml of boron trifluoride had been added there was obtained, after a total reaction time of 70 min, 32.4 g (82%) of a distilled product fraction (bp 90–102° (0.40–0.45 mm) and $n^{25}D$ 1.4775) that was found by glpc analysis[5d] to be composed mainly (84%) of the acetate **3**. Three redistillations of this product gave a sample of **3** (purity >96% by glpc analysis[5d]) whose ir and nmr spectra as well as elemental analysis were in accord with those given previously for **3** (*supra vide*).

The Phosphoric Acid Catalyzed Reaction of *d*-Limonene with Paraformaldehyde.—To a stirred mixture of 100 g (0.735 mol) of *d*-limonene, 25.5 g (0.750 mol) of PFA, 160 ml of glacial acetic acid, and 25 ml of acetic anhydride cooled to 5° there was added a solution of 25 g of phosphoric acid in 25 ml of acetic acid over a 2-hr period. Stirring was continued at 5–15° for an additional 6 hr and the mixture than allowed to stand overnight. Work-up of the reaction mixture gave unreacted limonene (10.15 g) and three principal product fractions: (1) 1.11 g, bp 30–40° (0.15 mm), $n^{23}D$ 1.4835; (2) 4.5 g, bp 45–47° (0.10 mm), $n^{23}D$ 1.4775; (3) 46.70 g, bp 50–70° (0.10 mm), $n^{23}D$ 1.4868. All three fractions showed very similar infrared spectra with strong absorptions at λ_{max} 2.94, 3.42, 5.81, 7.04, 7.94–8.32, 9.52–9.70, 11.3, and 12.5 μ. The fractions 2 and 3 represented a 34% yield of acetates (such as **1**) derived from limonene. Glpc analysis[5g] of fraction 3 indicated that it consisted of three major and at least six minor components.

The Formic Acid Catalyzed Reaction of *d*-Limonene with Paraformaldehyde.—From a mixture of 89 g (0.655 mol) of *d*-limonene, 9 g (0.30 mol) of PFA, 10.5 g of 98–100% formic acid, and 250 ml of glacial acetic acid stirred for 1–3 days at 95–100° there was obtained two principal product fractions: (1) 27.3 g, bp 78–98° (0.40–0.45 mm), $n^{25}D$ 1.4752; (2) 15.0 g, bp 120–135° (0.40 mm), $n^{25}D$ 1.4820. Fraction 1 amounted to a 44% yield of a mixture of three monoacetates. Glpc analysis[5h] indicated that the three components were present in about equal amounts.

Thermal Reactions of *d*-Limonene with Paraformaldehyde. A. In a Sealed Autoclave.—A mixture of 313 g (2.37 mol) of *d*-limonene, and 62.4 g (2.08 mol) of PFA was heated with shaking for 10 hr at 175–185° in a 4-l., stainless steel bomb. The

cooled, clear product was taken up in ether, washed with water, and dried ($MgSO_4$). Upon distillation there was obtained 194 g of *d*-limonene and three principal product fractions: (1) 11.8 g, bp 71–95° (0.35 mm), $n^{27}D$ 1.4891; (2) 72.3 g, bp 94–95° (0.35 mm), $n^{27}D$ 1.4845; (3) 21.0 g, bp 110–132° (0.20 mm), $n^{27}D$ 1.5029. The undistilled residue was 22.3 g. The combined fractions 1 and 2 represented a 24.4% yield of an alcohol such as **1**; glpc analysis,[6d] showed that it was comprised of four major components in a 9:3:2:1 ratio. The two fractions had similar ir spectra: λ_{max} 2.96, 3.40, 5.71, 6.03, 6.87, 7.28, 8.44, 9.49, 10.85, 11.16, and 12.43 μ as well as 5.71 and 8.44 μ indicative of formate ester. Fraction 3 showed strong ir absorptions for alcohol and ester groups but since glpc analysis[6i] gave ill-defined peaks it was not examined further.

A mixture of 300 ml of anhydrous methanol, 1.5 g of dibutyl tin oxide, and 72 g of fraction 2, estimated by glpc analysis to contain *ca.* 14.5 g (0.0732 mol) of formate ester, was heated for 2 hr at 70–75°. Distillation of the reaction mixture gave three principal product fractions: (1) 5.6 g, bp 60–78° (0.20–0.10 mm), $n^{25}D$ 1.4945; (2) 40.6 g, bp 78–78.5° (0.05 mm), $n^{25}D$ 1.4980; (3) 18.0 g, bp 68–73° (0.025 mm), $n^{25}D$ 1.4995. Infrared analysis showed that fraction 1 contained a trace of formate ester whereas fractions 2 and 3 were formate free; the latter spectra were similar.

The ir spectrum of the major fraction 2 was identical with that of "homolimonenol," ($n^{27}D$ 1.4988) previously reported:[3b] λ_{max} 2.98, 3.49, 6.05, 7.01, 7.25, 9.5–9.9, 11.25, and 12.5 μ. In addition, glpc analysis[6i] of this fraction showed that it was identical with an authentic sample of "homolimonenol" and that it was comprised of *ca.* 75–80% of the limonenyl carbinol **1**.

When the *d*-limonene–formaldehyde experiment described above was carried out in the presence of added sodium acetate (0.01 mol/0.10 mol PFA) no appreciable reaction occurred. Recovery of the initially charged limonene was *ca.* 88%.

B. At Atmospheric Pressure.—A mixture of 81 g (0.50 mol) of *d*-limonene, 9.0 g (0.30 mol) of PFA, and 300 ml of glacial acetic acid heated at 98–101° for *ca.* 2 days gave, after the usual work-up and distillation, two principal product fractions: (1) 8.39, bp 78–83° (0.35 mm), $n^{26}D$ 1.4748; (2) 26.0 g, bp 88–93° (0.35 mm), $n^{26}D$ 1.4780. Glpc analysis of fraction 2[5k] showed that it consisted primarily (*ca.* 80%) of a single component, the expected acetate **3**. This was confirmed by comparison of its ir spectrum and refractive index with those of an authentic sample of **3**.

***cis,trans*-9-Hydroxymethyl-*p*-menthane (6).**—Catalytic hydrogenation, in a Parr apparatus, of 23.0 g (0.138 mol) of the alcohol **1** in 80 ml of ethyl acetate over 0.8 g of Adams catalyst under 35–45 psi of hydrogen for 36 hr at room temperature gave 21 g (88%) of the saturated alcohol **6**, bp 70–77° (0.30 mm) and $n^{25}D$ 1.4692. Glpc analysis[6l] indicated that the product consisted of two major closely eluting components together with a small amount of a lower boiling compound. Ir analysis indicated the absence of unsaturated and ester materials.

Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.53; H, 12.91.

Column chromatography of the alcohol **6** over neutral alumina did not effect separation of the *cis* and *trans* isomers.

A similar hydrogenation of 25.4 g of the alcohol **1** in 100 ml of absolute ethanol over 0.35 g of platinum black for 2 days gave 24.4 g (92%) of **6** (bp 85–93° (0.45 mm) and $n^{25}D$ 1.4692) identical with the alcohol described above.

9-Hydroxymethyl-1-*p*-menthene (7).—Catalytic hydrogenation of 20.3 g of the alcohol **1** in 100 ml of absolute ethanol over 0.3 g of platinum black for 18 hr, under 22–39 psi of hydrogen gave two principal product fractions: (1) 14.8 g, bp 80–90° (0.4 mm), $n^{26.5}D$ 1.4800; (2) 3.4 g, bp 91–92° (0.4 mm), $n^{26.5}D$ 1.4837. Glpc analysis[6m] showed that fraction 2 was *ca.* 95% pure **7**. Ir and nmr analysis were in support of the proposed structure **7**: λ_{max} 3.04, 3.52, 7.05, 7.36, 9.36, 11.0, and 12.5 μ; nmr τ 4.68 (br s, =CH), 6.23 (t, $-CH_2OH$), 6.43 (s, –OH), 8.38 ($>C=CCH_3$), and 9.13 (d, saturated CH_3).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98; mol wt, 168.27. Found: C, 78.59, 78.46; H, 11.91, 12.02; mol wt, 164 (chloroform).

Catalytic hydrogenation of the alcohol **7** with either Adams catalyst or platinum black gave the saturated alcohol **6** that was comprised of the same mixture of *cis* and *trans* isomers previously described.

Methacrylates of the Alcohols 1 and 6. A. 9-Hydroxymethyl-1,8(10)-*p*-menthadiene Methacrylate.—The procedure of Burtle and Turek[6] was used. From 8.3 g (0.05 mol) of the alcohol **1** there was obtained 10.5 g (45%) of the methacrylate derivative, bp 90–93° (0.15 mm) and $n^{24}D$ 1.4900. Glpc analysis[6n] of a redistilled sample of the ester showed but one component. Significant ir absorptions were observed at 5.8–5.9, 6.10, 8.4–8.7, and 11.18 μ. The nmr spectrum had peaks at τ 4.03 (m, $-(CH_3C=C(H)-$), 4.59 (m, $-(CH_3)C=C(H)-$), 4.70 (s, $>C=CH-$), 5.25 (m, $>C=CH_2$), 5.86 (t, $-CH_2O_2C-$), 7.70 (t, $-CH_2CH_2O-$), 8.17 (t, $-(CH_3)C=CH_2$), and 8.45 ($-(CH_3)C=CH-$).

B. 9-Hydroxymethyl-*p*-menthane Methacrylate (8).—Transesterification of 27.2 g (0.26 mol) of methyl methacrylate with 18.6 g (0.108 mole) of the alcohol **6** in the presence of 0.3 g of sulfuric acid and 1.0 g of cupric acetate was carried out at 100° for 16.5 hr. During this period material of bp 55–64° was removed intermittently. Work-up and distillation of the mixture gave two principal product fractions: (1) 1.2 g, bp 50–80° (0.25 mm), $n^{25}D$ 1.4680; (2) 20.5 g, bp 97–104° (0.25 mm), $n^{25}D$ 1.4660. Fraction 2, which corresponded to an 81% yield of the desired methacrylate, gave after redistillation a center cut, (bp 90° (0.35 mm) and $n^{25}D$ 1.4662) of purity >99% (glpc analysis[6o]). The ir spectrum of the latter showed λ_{max} 3.51, 5.91, 7.65, 7.82, 8.62, 10.8, and 12.8 μ; nmr peaks were at τ 3.94 and 4.52 (d, $>C=CH_2$), 5.85 (t, $-CH_2O_2C-$), 8.09 (d, $-(CH_3)C=CH_2$), 9.02–9.13 (m, saturated CH_3-).

Anal. Calcd for $C_{25}H_{26}O_2$: C, 75.58; H, 11.00; mol wt, 238.36. Found: C, 75.62, 75.51; H, 11.01, 11.08; mol wt, 241, 238 (benzene).

Polymerization of the Methacrylate of the Alcohol 6. A. Homopolymerization.—Bulk polymerization of the methacrylate **8**, initiated with azobisisobutyronitrile, was carried out at 47–48° for 3 days. The initially formed (83%) clear, glassy polymer was soluble in benzene and toluene; insoluble in chloroform, acetone, and methanol.[7] (It was difficult to pulverize and dry the polymer because of its tendency to acquire a static charge.) The dried, rather soft polymer showed mp 225–230°. Its intrinsic viscosity in benzene[8] was 3.72 dl/g of polymer. The ir spectrum of the polymer as a film, obtained on slow evaporation of its benzene solution, showed signals at λ_{max} 3.5, 5.8, 7.9, 8.5–9.9, and 12.5 μ.

Anal. Calcd for $(C_{15}H_{26}O_2)_n$: C, 75.58; H, 11.00. Found: C, 75.71, 75.29; H, 11.24, 11.32.

B. Copolymerization with Methyl Methacrylate.—Bulk polymerization of 1.85 g of the methacrylate **8** and 2.0 g of methyl methacrylate (28.3:71.7 mole % ratio), initiated with 0.04 g of azobisisobutyronitrile, was effected at 50° for 24 hr. The crude polymer was dissolved in warm chloroform, the filtered solution added to methanol, and the precipitated copolymer collected and dried at 100° *in vacuo*. The reprecipitation and drying were repeated twice to give 3.29 g (85.5%) of the copolymer as a white tractable powder, mp 215–225°, whose intrinsic viscosity in benzene was 3.69 dl/g of polymer. Elemental analysis indicated that the polymer was indeed a copolymer of **8** and methyl methacrylate.

Anal. Found: C, 67.96, 67.81; H, 9.52, 9.70.

Registry No.—*d*-Limonene, 5987-27-5 **1**, 15766-66-2; **1** 3,5-dinitrobenzoate, 15766-67-3; **1** phenylurethan derivative, 15766-68-4; **3**, 6819-19-8; **4**, 15815-76-6; **5**, 15760-15-3; **6** (*cis*), 15760-16-4; **6** (*trans*), 15760-17-5; **7**, 15760-18-6; **8**, 15760-19-7; 9-hydroxymethyl-1,8(10)-*p*-menthadiene methacrylate, 15760-20-0.

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(6) J. G. Burtle and W. N. Turek, *J. Org. Chem.*, **19**, 1507 (1954).

(7) Criterion for solubility: solution of 50 mg of polymer in 10 ml of solvent after vigorous stirring for 0.5 hr at room temperature.

(8) Intrinsic viscosity measurements were kindly performed in the research laboratory of the Rohm and Haas Co., Bristol, Pa.

The Kinetics of Bromination of 1,5-Dimethylnaphthalene. A Change in Mechanism[1]

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The kinetics of bromination of 1,5-dimethylnaphthalene in 90% aqueous acetic acid in the presence of bromide ion indicates that in this reaction the breaking of the carbon–hydrogen bond is part of the rate-controlling step. In contrast, in bromination of many other hydrocarbons under the same conditions, the first step alone controls the rate. The reversal of the mechanism is ascribed to steric crowding in the intermediate. Two bromo substitution products formed in the reaction have been synthesized and characterized. Addition of acetic acid accompanies substitution.

Aromatic bromination is known to proceed by the sequence

$$ArH + Br_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArHBr^+ + Br^-$$

$$ArHBr^+ \xrightarrow{k_2} ArBr + H^+$$

If the reaction is carried out in aqueous acetic acid and in the presence of an excess of bromide ion, the rate expression is

$$k_{obsd} = kK/(K + Br^-) \quad (1)$$

where K is the dissociation constant of the tribromide ion,[4] and k_{obsd} is obtained from the experimental rate law, $-d(Br_2)_t/dt = k_{obsd}(ArH)(Br_2)_t$.[4] This rate expression has been satisfied in the bromination of many different hydrocarbons and has been interpreted to mean that free bromine is the substituting entity and that the first step is rate-determining ($k_2 \gg k_{-1}$).[4,5] The absence of a significant primary isotope effect[6] and of acetate ion catalysis[4] confirms this view. The constant k refers to bromination by free, uncomplexed bromine and is obtained as the slope from a plot of k_{obsd} against $K/(K + Br^-)$. We now wish to report the results of a kinetic study of the bromination of 1,5-dimethylnaphthalene, where the kinetics reveal that the second step is partly rate controlling.

For a comparison with the reaction of 1,5-dimethylnaphthalene, the bromination of 2,3-dimethylnaphthalene was also studied. The bromination of this compound has the same kinetic characteristics as the reactions of all compounds previously studied. In Table I are listed rate constants for its bromination at varying bromide ion concentrations at a constant ionic strength ($NaClO_4$) and in Figure 1 is shown the plot of k_{obsd} against $K/(K + Br^-)$. The slope, k, is 0.810 ± 0.015 l./mol sec. By contrast, for the bromination of 1,5-dimethylnaphthalene, the corresponding plot shows marked curvature for reaction in both 75 and 90% aqueous acetic acid (Table I, Figure 2). The deviation from a straight line is of such a nature as to suggest that expression 1 should have an additional bromide ion term in the denominator, *i.e.*

$$k_{obsd} = k'K/(K + Br^-)(Br^-) \quad (2)$$

Such a term should result from a mechanism in which a rapid equilibrium is established between reactants and the intermediate, followed by a rate-determining loss of the proton ($k_2 \ll k_{-1}$). A plot using expression 2 results in a straight line, but the points at lowest bromide ion concentrations fall below the line.

If the intermediate $ArHBr^+$ is assumed to be present in a steady-state concentration, the observed rate constant is given by the complete expression

$$k_{obsd} = \frac{k_1k_2K}{(k_{-1}[Br^-] + k_2)(K + Br^-)} = \frac{k_1k_2K/k_{-1}}{(K + Br^-)[Br^- + (k_2/k_{-1})]} \quad (3)$$

In the bromination of 2,3-dimethylnaphthalene, as well as in previous brominations, $k_2 \gg k_{-1}[Br^-]$ and expression 3 reduces to the observed expression 1. If $k_2 \ll k_{-1}[Br^-]$, expression 2 results. Expression 3 will not completely reduce to 2 if the ratio k_2/k_{-1} is not negligible with regard to the bromide ion concentration. Equation 3 can be rewritten in the form $K/[(K + Br^-)(k_{obsd})] = (k_{-1}[Br^-]/k_1k_2) + (1/k_1)$. A plot of the left-hand side of the equation against $[Br^-]$ results in a straight line, from which k_1 and the ratio k_{-1}/k_2 can be obtained (Figure 3). From such plots, k_1 is found to be 0.374 l./mol sec in 90% acetic

TABLE I
KINETIC DATA FOR THE BROMINATION OF 2,3- AND 1,5-DIMETHYLNAPHTHALENE.[a] DEPENDENCE OF RATE ON BROMIDE ION CONCENTRATION[b]

NaBr, mol/l.	2,3-Dimethylnaphthalene–90% acetic acid, $k_{obsd} \times 10^2$	1,5-Dimethylnaphthalene–75% acetic acid, $k_{obsd} \times 10^3$	1,5-Dimethylnaphthalene–90% acetic acid, $k_{obsd} \times 10^3$
0.100	5.50	27.1	9.54
0.125	...	...	6.92
0.150	3.61	12.8	4.93
0.20	2.64	7.70	3.03
0.30	1.85	3.80	1.51
0.40	1.39	2.28	1.03
0.50	1.14	1.60	0.756

[a] All rate constants are in l. mol^{-1} sec^{-1}; T, 25°. [b] The total salt concentration was maintained at 0.50 M with $NaClO_4$ where necessary.

(1) Kinetics of Aromatic Halogenation. XII.

(2) Taken in part from the Ph.D. Thesis of J. B. Kim, Bryn Mawr College; National Science Foundation Cooperative Fellow, 1965–1966; U.S. Steel Fellow in Chemistry, 1966–1967.

(3) Taken in part from the Senior Honors Thesis of M. Link, Bryn Mawr College, May 1964, and from a summer's work as a National Science Foundation Undergraduate Research Participant, 1963.

(4) E. Berliner and M. C. Beckett, *J. Amer. Chem. Soc.*, **79**, 1425 (1957).

(5) (a) L. Altschuler and E. Berliner, *ibid.*, **88**, 5837 (1966); (b) U. P. Zimmerman and E. Berliner, *ibid.*, **84**, 3953 (1962); E. Berliner and J. C. Powers, *ibid.*, **83**, 905 (1961).

(6) E. Berliner, *Progr. Phys. Org. Chem.*, **2**, 253 (1964); H. Zollinger, *Advan. Phys. Org. Chem.*, **2**, 163 (1964). Substantial isotope effects have, however, been observed in the bromination of some crowded substrates. See P. C. Myhre, *Acta Chem. Scand.*, **14**, 219 (1960); E. Helgstrand, *ibid.*, **19**, 1583 (1965); E. Helgstrand and A. Nilsson, *ibid.*, **20**, 1463 (1966).

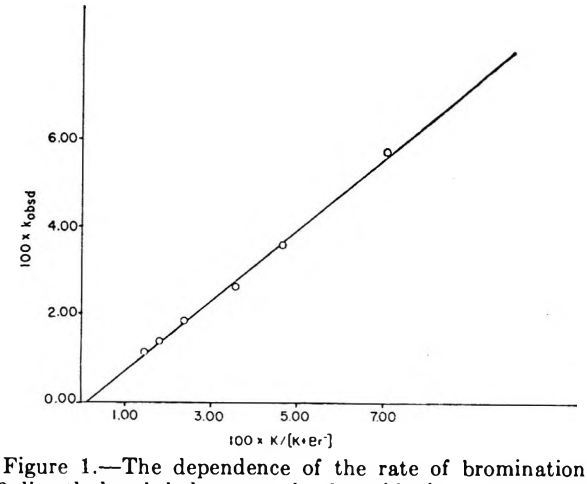

Figure 1.—The dependence of the rate of bromination of 2,3-dimethylnaphthalene on the bromide ion concentration: solvent, 90% acetic acid.

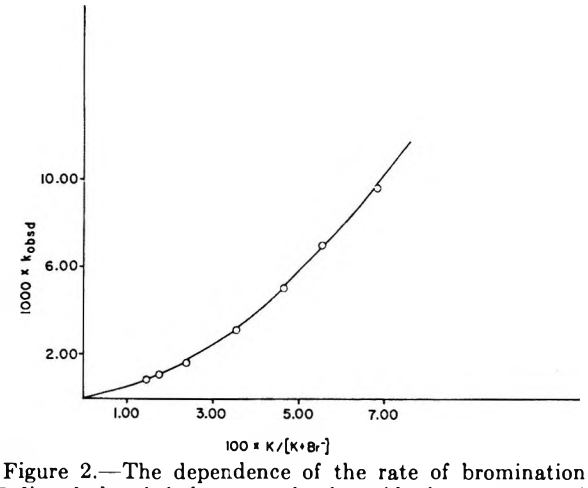

Figure 2.—The dependence of the rate of bromination of 1,5-dimethylnaphthalene on the bromide ion concentration: solvent, 90% acetic acid.

acid and 6.54 l./mol sec in 75% acetic acid and the ratios k_2/k_{-1} are 6.07×10^{-2} and 5.95×10^{-2}, respectively. The ratio k_2/k_{-1} can therefore not be neglected with regard to the bromide ion concentration, particularly when the latter is at its lowest value of 0.1 M. Bond breaking (k_2) becomes part of the rate-controlling step and the intermediate partitions itself between reactants and products in a measurable way. For every molecule of intermediate that goes onto the products, about eight return to reactants in both 90 and 75% acetic acid at a 0.5 M concentration of bromide ion. The constant k_1 is greatly affected by the polarity of the solvent but the ratio k_2/k_{-1} is not. The rate constant k_{-1} should be greater in the less polar solvent, because two ions react to form neutral molecules. Since the ratio k_2/k_{-1} stays the same, k_2 in the less polar solvent is probably also increased, which could happen if the hydrogen bromide in the products is not appreciably dissociated.

Support for the view that in the bromination of 1,5-dimethylnaphthalene the second step is partly rate determining comes from the observation of acetate ion catalysis. Such catalysis might be expected if carbon–hydrogen bond breaking were involved in the rate-determining step. The effect of acetate ion on the rate does not lend itself to a straightforward interpretation, because sodium acetate, like other salts, causes a positive primary salt effect.

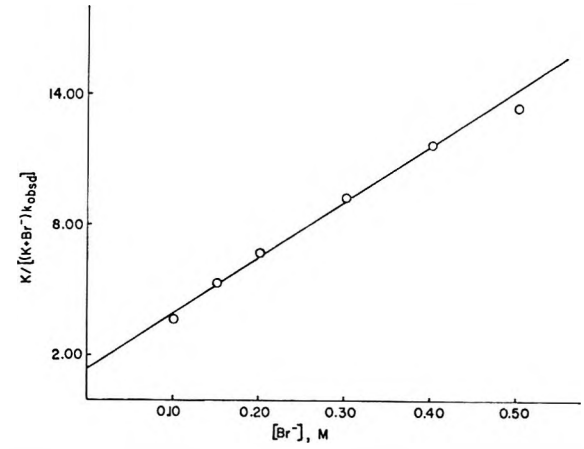

Figure 3.—The dependence of the rate of bromination of 1,5-dimethylnaphthalene on the bromide ion concentration: solvent, 75% acetic acid; slope, 2.57 mol sec $l.^{-1}$; intercept, 0.153 mol sec $l.^{-1}$.

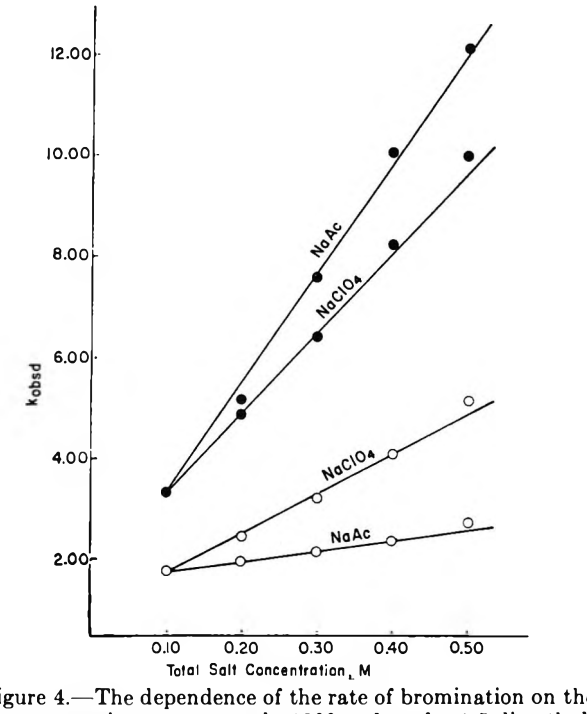

Figure 4.—The dependence of the rate of bromination on the salt concentration: upper graph, 1000 × k_{obsd} for 1,5-dimethylnaphthalene; lower graph, 100 × k_{obsd} for 2,3-dimethylnaphthalene; solvent, 90% acetic acid; [NaBr], 0.10 M in all runs.

It has been observed in previous studies that the effect of acetate ion is less rate enhancing than the effect of sodium perchlorate.[4] This is shown for the bromination of 2,3-dimethylnaphthalene in Figure 4 and is typical of all of the other cases that have been investigated. However, in the bromination of 1,5-dimethylnaphthalene, the effect of acetate ion is considerably greater than that of perchlorate ion (Figure 4). Because this is the only compound for which this reversal of acetate *vs.* perchlorate has so far been observed, it is not unreasonable to assume that it reflects a genuine catalysis by acetate ions.[7]

The results of the bromination of 1,5-dimethylnaphthalene are very reminiscent of Zollinger's

(7) Kinetic characteristics very similar to those observed in the bromination of 1,5-dimethylnaphthalene have now also been found in the bromination of 1,4-dimethylnaphthalene: K. Judd, unpublished results.

studies on the diazo coupling of G-salt[8] and a similar interpretation probably holds. The intermediate in the bromination of the 4 position of 1,5-dimethylnaphthalene is sterically crowded because of the methyl group in the 5 (*peri*) position, just as it is in the diazo coupling of G-salt by the 8-sulfonate group. Steric crowding favors return of the intermediate by loss of bromine to the less hindered reactants, rather than reaction by loss of a proton to the more hindered product. In other words, the condition $k_{-1}[Br^-] \gg k_2$ is the result of the steric requirements of the intermediate. This does not seem to manifest itself in a large decrease of k_1, because k_1 is within a factor of 2 of the value calculated from the additivity principle. Instead, it results in an increase in k_{-1}, in a decrease in k_2 and hence in an over-all decrease of k_2/k_{-1}.

No bromo substitution products of 1,5-dimethylnaphthalene have been described in the literature and authentic samples of two were prepared and identified as follows. In order to avoid the formation of acetoxy addition products (see below), preparative bromination was carried out in chloroform or carbon disulfide in the dark. The product consisted of three monobromo compounds. Separation of the two major isomers was facilitated, because 2-bromo-1,5-dimethylnaphthalene does not form a stable picrate. Other naphthalene derivatives with a methyl group and a bromine atom *ortho* to each other were also found to form unstable picrates, which cannot be recrystallized. Consequently, the reaction mixture from a bromination in carbon disulfide, which contained more of the 4 isomer, was treated with an excess of picric acid. A pure picrate was easily obtained and from it a monobromo compound of mp 41.8–42.6°. This was converted *via* the lithium compound and dimethyl sulfate into the known 1,4,5-trimethylnaphthalene; hence the compound of mp 41.8–42.6° is 4-bromo-1,5-dimethylnaphthalene. The second compound was obtained by crystallization of the crude reaction mixture. This compound of mp 78.0–78.3° was converted into the known 1,5-dimethyl-2-naphthoic acid and its methyl ester and is therefore 2-bromo-1,5-dimethylnaphthalene. The third isomer, which was obtained only in small amounts, was not isolated or characterized but is presumably the 3-bromo compound. The nmr spectrum of 4-bromo-1,5-dimethylnaphthalene confirmed the assigned structure. The assignment was based on the known observation that a bromine atom will shift the *meta* protons to higher fields. The spectrum of 1-bromo-4-methylnaphthalene, for instance, shows a doublet at 394.5 Hz downfield from TMS with a splitting of 7.5 Hz and each component of the doublet is split into a quartet by the 1-methyl group (coupling ~1 Hz). Analogously, the spectrum of 4-bromo-1,5-dimethylnaphthalene contains a doublet at 398 Hz with a splitting of about 8 Hz. The upfield absorptions are absent in the spectrum of 4-bromo-1,2-dimethylnaphthalene and of 1,5-dimethylnaphthalene, which do not possess a proton *meta* to bromine. A complete analysis of the spectrum of the hydrocarbon has since been made.[9]

The reaction mixture of the kinetic runs in 90% acetic acid consisted of 72.6% of 4-bromo-1,5-dimethylnaphthalene, 19.2% of 2-bromo-1,5-dimethylnaphthalene, and 7.7% of the unidentified 3-bromo isomer. These bromo compounds constitute about 60% of the total products. The remaining 40% consists of three other compounds, which are acetoxy compounds, formed from addition of acetic acid to the intermediate and subsequent aromatization during vpc analysis. The acetoxy products were not identified, but their presence was inferred from the typical infrared absorption bands in the reaction mixture prior to vpc analysis. Their formation is analogous to the formation of acetoxy compounds in the bromination of phenanthrene and anthracene.[5a,10] In the present case, loss of a proton has presumably the highest activation energy of the reactions available to the intermediate and addition to the intermediate competes effectively with proton loss. Because of the reaction of the intermediate with acetic acid, the constant k_2, as obtained from Figure 3 (k_{-1}/k_2), is really composite and represents the disappearance of the intermediate not only by loss of a proton but also by reaction with acetic acid. The occurrence of addition during substitution is in itself the result of steric crowding in the intermediate, which is responsible for the increase in k_{-1} and the decrease in k_2. In the bromination of no other of the dimethylnaphthalenes have acetoxy products been observed,[7] but one is also formed in the bromination with bromine and silver perchlorate of the hindered 1,3,5-tri-*t*-butylbenzene.[11]

From k_1 and the isomer distribution and from data obtained previously,[5a] it is possible to calculate partial rate factors ($f_2 = 2.65 \times 10^7$, $f_3 = 1.06 \times 10^7$, $f_4 = 1.00 \times 10^8$), but these do not accurately reflect the reactivities in the three positions. Some of the products are very likely formed by decomposition of acetoxy or dibromo addition compounds. The unusual change of isomer distribution with change in solvent (36.6% of the 2-bromo compound is formed in chloroform, but only 18.8% in carbon disulfide) is possibly the result of such secondary reactions, as is the unexpectedly large amount of 3-bromo isomer. Assuming that the additivity principle holds, and with the help of earlier data, one can calculate that at least 98% of substitution should take place in the 4 position and less than 2% in the 2 position. The large difference between predicted and observed values is probably only partly due to decomposition of addition compounds; it is partly the result of steric hindrance in the intermediate, which reflects itself in less substitution in the 4 position, and consequently more in the 2 position. In the only direct substitution reaction previously reported, namely, the chloromethylation of 1,5-dimethylnaphthalene, only the formation of the 2 isomer has been recorded.[12]

A kinetic expression similar to eq 2, but not 3, would be obtained if the rate-controlling step were to involve an attack by a bromine cation. In view of the difficulty of obtaining bromine cations from

(8) H. Zollinger, *Helv. Chim. Acta.*, **38**, 1597, 1617, 1623 (1955).
(9) J. B. Kim and J. M. Anderson, *Spectrochim. Acta.* in press.
(10) For similar addition during chlorination, see P. B. D. de la Mare, N. V. Klassen, and R. Koenigsberger, *J. Chem. Soc.*, 5285 (1961); P. B. D. de la Mare and R. Koenigsberger, *ibid.*, 5327 (1964); and others in the series.
(11) P. C. Myhre and G. S. Owen, Abstracts of Papers, 150th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1965, 48 S.
(12) W. Ried and H. Bodem, *Ber.*, **91**, 1354 (1958).

bromine molecules,[13] this latter interpretation can be ruled out.

The participation of carbon–hydrogen bond breaking in the rate-determining transition state, as observed here, is usually detected through an isotope effect, but the kinetics of bromination have characteristics such that it can be inferred without the use of isotopically labeled compounds.

Experimental Section

Materials.—All inorganic reagents were best reagent grade chemicals which were dried at 110° before use. The glacial acetic acid was purified with chromium trioxide as described before.[4,5] Percentages of aqueous acetic acid are by volume, before mixing. 2,3-Dimethylnaphthalene was recrystallized three times from an ethanol–benzene (about 6:1) mixture and melted at 104.5–104.9°[14] (lit.[15] mp 104–104.5°). The 1,5-dimethylnaphthalene was recrystallized from ethanol; it melted at 81.2–81.8° (lit.[16] mp 82°).

Separation of the pure bromo compounds was facilitated when, after several attempts at isolation, seed crystals became available and when it was observed that the 2-bromo isomer does not form a stable picrate. It was also found that solutions of picrates could be injected into the vpc injection port without prior isolation of the hydrocarbon; the picric acid remained on the column.

2-Bromo-1,5-dimethylnaphthalene.—To 15 g (0.0975 mol) of 1,5-dimethylnaphthalene in 45 ml of carbon disulfide was added with stirring 6 ml of Br_2 (0.117 mol) in 30 ml of CS_2. Stirring was continued over night, excess Br_2 was destroyed with $NaHSO_3$, and the product was washed with water and dried. Material boiling between 121 and 136° (5 mm) was allowed to solidify in the cold and several crystallizations from ethanol–water afforded 1.13 g (4.93%) of material melting at 77.3–78.5°. A sample, recrystallized further, melted at 78.0–78.3°. *Anal.*[17] Calcd for $C_{12}H_{11}Br$: C, 61.29; H, 4.72. Found: C, 61.12; H, 4.80.

To 200 mg (0.00085 mol) of the above compound, dissolved in 5.0 ml of anhydrous ether, was added 1 ml of *n*-butyllithium in hexane (approximately 0.0034 mol). After 15 min of vigorous stirring, the solution was poured on a Dry Ice–ether slush. After work-up and crystallization from ligroin with 2 drops of glacial acetic acid, there was obtained 75 mg (44%) of 1,5-dimethyl-2-naphthoic acid of mp 207–208° (lit.[18] mp 205–207°). The methyl ester, recrystallized from methanol, had mp 75.9–76.4° (lit.[18] mp 77–78°).

1-Bromo-4,8-dimethylnaphthalene.—A run similar to the one above was conducted in CS_2. A large forerun from the distillation consisted of 95% of unreacted hydrocarbon. The main fraction (8.00 g, 30.6%) consisted of over 70% of the 4 isomer. Preparation and two recrystallizations of the picrate of the distillate afforded a product which was 99% pure on vpc. A total of 2.00 g of picrate was obtained, which, when decomposed on an alumina column, afforded 0.90 g (3.68%) of a white crystalline solid, mp 40.9–42.3°. A sample recrystallized further from ethanol had mp 41.8–42.6°. *Anal.* Calcd for $C_{12}H_{11}Br$: C, 61.29; H, 4.72. Found: C, 61.17; H, 4.72. The picrate, prepared from the pure solid, melted at 122.1–123.6°. It could not be obtained analytically pure, in spite of numerous crystallizations with or without excess of picric acid. It probably contained some free bromo compound. *Anal.* Calcd for $C_{18}H_{14}O_7N_3Br$: C, 46.57; H, 3.04. Found: C, 49.61; H, 3.50. The above bromo compound (300 mg, 0.0013 mole) was converted into the lithium derivative as described for the other isomer. The light yellow solution was treated with a solution of 0.11 ml (0.0015 mole) of dimethyl sulfate in 5 ml of anhydrous ether. The solution became white and turbid. After 15 min of stirring, the mixture was gently refluxed for 1 hr. After work-up, the product was dissolved in the smallest amount of hot ethanol and 0.20 g of picric acid was added. After two recrystallizations from ethanol, a picrate of mp 145.7–147.5° was obtained (lit.[19] mp 144–145°), which was 96.1% pure. The picrate, after decomposition with dilute ammonia, afforded white plates of 1,4,5-trimethylnaphthalene, which after recrystallization from ethanol–water melted at 61.9–62.8° (lit.[19] mp 63°). The literature melting points of the other two possible trimethylnaphthalenes are below 60°.[19,20]

Bromination of 1,5-dimethylnaphthalene in carbon disulfide affords, in the order of their retention times, 9.4% of the 3 isomer, 18.8% of 2 isomer, and 71.8% of 4 isomer, while in chloroform the proportions, in the same order, are 11.3, 36.6, and 52.1%.

Kinetic Determinations.—These determinations were carried out as described in previous work.[4,5] The temperature was 25° for all runs. Rate constants were obtained graphically from the integrated form of the second-order rate equation by the method of least squares. The initial bromine concentration was determined from the intercept of the graphs but the value never differed appreciably from that taken from the initial titer. For very fast reactions the initial titer was determined from a blank. Several blank determinations, which were identical with the kinetic runs except that the hydrocarbon was omitted, showed that loss of bromine was negligible and did not have to be taken into account. The concentration of bromine varied between 0.001 and 0.004 M and that of the hydrocarbons between 0.004 and 0.01 M, depending on the rate of the individual reactions. All runs were done at least in duplicate and the average values listed in Table I rarely had an average deviation of more than 2%. Rate constants were not affected by a change in reactant concentration. For instance, at a concentration of sodium bromide of 0.10 M and of sodium perchlorate of 0.40 M, rate constants of 9.38 and 9.49 $\times 10^{-3}$ were obtained for the bromination of 1,5-dimethylnaphthalene in 90% acetic acid when the concentrations of bromine were 0.00115 and 0.00231 M and those of hydrocarbons 0.00401 and 0.00803 M, respectively.

The equilibrium constant K was taken as 0.0110 mol/l. in 75% and 0.0073 mol/l. in 90% acetic acid.[21]

Product Analyses.—The conditions of typical kinetic runs were reproduced for the product analysis. The reaction mixtures were 0.0040 M in 1,5-dimethylnaphthalene, 0.10 M in NaBr, 0.40 M in $NaClO_4$, and approximately 0.001 M in Br_2; the total volume was usually 100 ml. The completed runs were extracted with five 20-ml portions of petroleum ether and also with three 20-ml portions of benzene. The petroleum ether extracted over 90% of the hydrocarbons and bromo derivatives, but benzene was necessary to extract also the acetoxy compounds. Six products were formed, in addition to excess unreacted hydrocarbon. Comparison with chromatograms of the products of bromination of the hydrocarbon according to their retention times established that the first three were monobromination products. The first was assumed to be the 3-bromo compound and the second and third were identified as the 2- and 4-bromo derivatives, respectively. From three independent kinetic runs, and six chromatographic determinations, the amounts of bromo compounds were established as 7.7 ± 2.3%, 19.2 ± 1.2%, and 72.6 ± 2.7%. Because of the similarity in structure of the bromo compounds, peak areas were taken to represent also weight ratios; the same was done for the acetoxy compounds. The acetoxy peaks overlapped and their relative areas could not be determined with great accuracy. Their percentages, determined from two kinetic runs and four chromatographic determinations, were 23.0% ± 3.0%, 48.3 ± 12.3%, and 28.7 ± 12.4%. The bromination products constituted 59.2 ± 4.2% (two runs, four chromatograms) and the acetoxy compounds 40.7 ± 4.1% of the total. The benzene extract of a run conducted on four times the scale listed above showed, prior to vpc analysis, the typical infrared acetoxy absorptions at 1230 and 1755 cm^{-1}. The same absorption bands were shown by an authentic sample of 2-naphthyl acetate. In kinetic runs extracted only with petroleum ether, the weaker absorption at 1230 cm^{-1} was absent. The acetoxy compounds obtained on vpc analysis

(13) E. Berliner, *J. Chem. Educ.*, **43**, 124 (1966).
(14) All melting points are corrected.
(15) G. Schroeter, L. Lichtenstadt, and D. Irineu, *Ber.*, **51**, 1587 (1918).
(16) O. Kruber and A. Marx, *ibid.*, **72**, 1970 (1939).
(17) All analyses by Galbraith Laboratories, Inc., Knoxville, Tenn.
(18) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2090 (1956).
(19) L. Ruzicka and L. Ehmann, *Helv. Chim. Acta.*, **15**, 140 (1932).
(20) J. Harvey, I. M. Heilbron, and E. D. Kamm, *J. Chem. Soc.*, 3136 (1926); I. M. Heilbron and D. G. Wilkinson, *ibid.*, 2537 (1930).
(21) A. E. Bradfield, G. I. Davies, and E. Long, *J. Chem. Soc.*, 1389 (1949); T. W. Nagakawa, L. J. Andrews, and R. M. Keefer, *J. Phys. Chem.*, **61**, 1007 (1957).

were not characterized further, but, to verify that aromatic acetoxy compounds have longer retention times than bromo compounds, a test mixture was run consisting of 1-methylnaphthalene, 1-bromo-4-methylnaphthalene, and 1-acetoxy-4-methylnaphthalene. The difference in retention time between the bromo and acetoxy derivatives of 1-methylnaphthalene is very similar to that of the derivatives of 1,5-dimethylnaphthalene. Furthermore, when the response factors of the monomethyl compounds were used to calculate weight per cent of a kinetic run, the weight of bromo to acetoxy compounds was found to be 56.9 to 43.1%, in good agreement with the ratio given above.

In the bromination of 2,3-dimethylnaphthalene, a 97.4% yield of 1-bromo-2,3-dimethylnaphthalene was obtained. It was characterized by a comparison with the retention time of an authentic sample, which was prepared according to a literature procedure and had mp 61.8–62.8° (lit.[22] mp 63–64°). The 2.6% constitute another monobromo isomer, most likely the 5 isomer (1-bromo-6,7-dimethylnaphthalene). Material balances on three runs were 97.9, 68.8, and 93.5%. Chromatography of the total reaction product on an SE-30 column showed that no acetoxy products were present. No dibromo substitution products were detected in the bromination of either hydrocarbon.

(22) R. T. Arnold and R. W. Liggett, *J. Amer. Chem. Soc.*, 64, 2875 (1942).

The gas chromatographic analyses were done on a programmed temperature gas chromatograph (F & M Scientific Corp., Model 720). For the separation of the bromo isomers a 4 ft × 0.25 in. column of 5% Apiezon L-5% Bentone 34 on 80–100 Diatoport S was used. Hydrocarbons were analyzed on a 2 ft × 0.25 in. column of Carbowax 20M on 80–100 Diatoport S and acetoxy compounds on a 6 ft × 0.25 in. column of 5% SE-30.

The infrared spectra were recorded in chloroform on a Perkin-Elmer Infracord, Model 137, and the nmr spectra on a Varian Model A-56/60-A spectrometer.

Registry No.—1,5-Dimethylnaphthalene, 571-61-9; 2-bromo-1,5-dimethylnaphthalene, 15095-53-1; 4-bromo-1,5-dimethylnaphthalene, 15095-54-2; 4-bromo-1,5-dimethylnaphthalene picrate, 15153-26-1.

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Reactions of Conjugated Nitro Olefins with Phosphoranes and with Dimethylsulfoxonium Methylide to Give Ylides and Nitrocyclopropanes, Respectively[1a]

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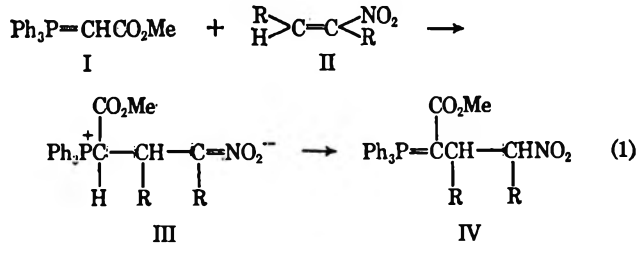
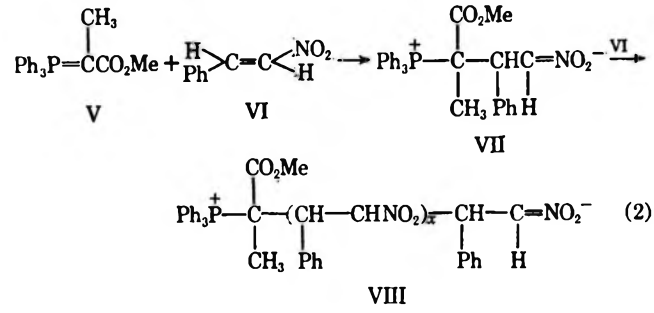
Carbomethoxymethylenetriphenylphosphorane (I) and conjugated nitro olefins (II) react with subsequent proton transfer to give phosphorus ylides, carbomethoxynitroalkylidenetriphenylphosphoranes (IV). The structures of IV were established from their infrared and ultraviolet absorptions. Chemical evidence for the structure of a typical phosphorane (X) was obtained by its bromination and subsequent regeneration by aqueous sodium carbonate. Methylenetriphenylphosphorane (XIV) and dimethylsulfoxonium methylide (XVIII) react with conjugated nitro olefins to yield nitrocyclopropanes; XVIII is the much more efficient and convenient reagent. The spectral properties of various nitrocyclopropanes are described.

Carbomethoxymethylenetriphenylphosphorane (I)[2] has been presently found to add to various conjugated nitro olefins (II, Table I) at 90° in hydrocarbon solvents with subsequent proton transfer (eq 1)



(1)

to give carbomethoxynitroalkylidenetriphenylphosphoranes (IV) efficiently.[3] Reaction of I and II or thermolysis of IV resulting in expulsion of triphenylphosphine to give nitrocyclopropanes, isoxazoline oxides, or related products could not be effected advantageously. Carbomethoxyethylidenetriphenylphosphorane (V)[2] reacts with β-nitrostyrene (VI) to give multiple adducts (VIII, eq 2). Phosphonium nitronates (VII) which do not self-neutralize to nitroalkylphosphoranes (IV) thus may continue Michael addition to conjugated nitro olefins.[3]



(2)

The phosphorus ylides (IV) prepared by the new method are stable greenish white solids which can be recrystallized conveniently from hydrocarbons and from ethyl acetate. The structures of the products as phosphoranes (IV) are assigned from their infrared absorptions (Table I) for nitro (6.48–6.51 μ)[4] and phosphoranocarbonyl (6.13–6.23 μ) groups and from

(1) (a) This research was supported by the Office of Naval Research. (b) To whom inquiries should be addressed.

(2) (a) G. Wittig and G. Geissler, *Ann.*, 580, 44 (1953); (b) O. Isler, H. Guttman, M. Montavon, R. Ruegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, 40, 1242 (1956).

(3) H. J. Bestmann and F. Seng [*Angew. Chem.*, 74, 154 (1962)] have reported a similar reaction in that I reacts with methyl benzoylacrylate to give triphenylphosphine and [(1-carbomethoxy-2-benzoyl)ethyl]carbomethoxymethylene.

(4) J. F. Brown Jr., *J. Amer. Chem. Soc.*, 77, 6341 (1955).

TABLE I

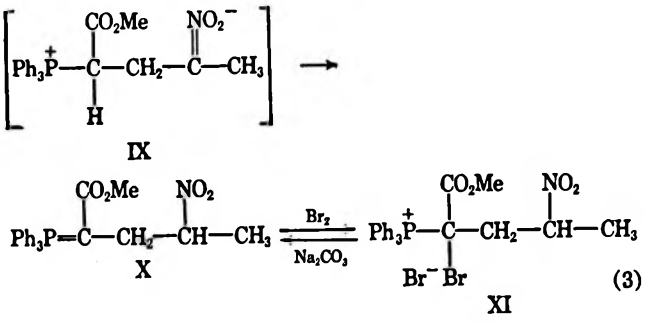
REACTION OF CARBOMETHOXYMETHYLENETRIPHENYLPHOSPHORANE (I) WITH CONJUGATED NITRO OLEFINS (II)

Nitro olefins	Phosphoranes, IV[k]	Mp °C[a]	% yield[b]	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ir absorption,[c] μ >C=O	Ir absorption,[c] μ NO₂
$H_2C{=}C(CH_3)NO_2$	$Ph_3P{=}C(CO_2CH_3)CH_2CH(CH_3)NO_2$	162–164	57	$C_{24}H_{24}NO_4P$	68.50	5.70	3.32	68.21	5.71	3.44	6.13	6.51[d]
$CH_3CH{=}CHNO_2$	$Ph_3P{=}C(CO_2CH_3)CH(CH_3)CH_2NO_2$	164–166	33	$C_{24}H_{24}NO_4P$	68.50	5.70	3.32	68.26	5.55	3.38	6.14	6.49[e]
$CH_2CH{=}C(CH_3)NO_2$	$Ph_3P{=}C(CO_2CH_3)CH(CH_3)CH(CH_3)NO_2$	193.5–195.5	33	$C_{25}H_{26}NO_4P$	68.96	6.00	3.22	68.81	6.12	3.30	6.13	6.51[f]
$PhCH{=}CHNO_2$	$Ph_3P{=}C(CO_2CH_3)CHPhCH_2NO_2$	180–181	23	$C_{29}H_{26}NO_4P$	72.01	5.38	2.90	71.95	5.48	2.85	6.17	6.48[g]
$PhCH{=}C(CH_3)NO_2$	$Ph_3P{=}C(CO_2CH_3)CHPhCH(CH_3)NO_2$	204–207	49	$C_{30}H_{28}NO_4P$	72.43	5.63	2.90	72.15	6.05	2.67	6.17	6.50[h]
$PhCH{=}C(Ph)NO_2$	$Ph_3P{=}C(CO_2CH_3)CHPhCHPhNO_2$	173–174	28	$C_{35}H_{30}NO_4P$	75.13	5.37	2.50	75.16	5.56	2.66	6.14	6.48[i]
$(C_4H_3O)CH{=}CHNO_2$	$Ph_3P{=}C(CO_2CH_3)CH(C_4H_3O)CH_2NO_2$	184.5–185.5	47	$C_{27}H_{24}NO_5P$	68.50	5.08	2.96	68.76	5.24	3.24	6.23	6.48[j]

[a] The phosphoranes melt with decomposition. [b] The actual yields are considerably higher (60–80%); the values reported are those for the analytical samples. [c] Determined in potassium bromide pellets. [d] Uv, λ_{max} (ϵ_{max}) taken in 95% ethanol: 225 (38,700), 261 (5050), 266.5 (5050), and 273.5 (4430). [e] Uv, λ_{max} (ϵ_{max}) taken in 95% ethanol: 225 (37,600), 261 (5770), 266 (5652), and 273 (4800). [f] Uv, λ_{max} (ϵ_{max}) taken in 95% ethanol: 225 (32,222), 260.5 (5160), 267 (5040), and 273.5 (4200). [g] Uv, λ_{max} (ϵ_{max}) taken in 95% ethanol: 225 (39,190), 261 (5787), 266 (6000), 273 (5545), and 304–311 (5400). [h] Uv, λ_{max} (ϵ_{max}) taken in 95% ethanol: 223 (42,666), 262 (5636), 267 (6609), 274 (6913), and 309–312 (10,363). [i] Uv, λ_{max} (ϵ_{max}) taken in 95% ethanol: 223 (38,000), 261 (6200), 267 (5900), and 273 (4800). [j] Uv, λ_{max} (ϵ_{max}) taken in 95% ethanol: 225 (28,400), 260 (4500), 266 (4400), 273 (3700), and 347 (6800). [k] Respective registry no.: 15267-29-5; 15267-30-8; 15267-22-8; 15267-32-0; 15267-33-1; none.

the similarities of their ultraviolet absorptions (Table I) in 95% ethanol (λ_{max} 223–224 (ϵ_{max} 28,400–42,600), 260–262 (1300–6200), 266–267 (1700–6600), and 273 (1400–6900))[5] to that of I (λ_{max} 223–225 (ϵ_{max} 21,200), 260 (1300), 266 (1700), and 272.5 (1400)) and V (λ_{max} 224 (ϵ_{max} 32,100), 260.5 (1800), 266 (2300), and 273 (1900)). If the products were the dipolar adducts III, infrared absorption for the nitronate and carbonyl groups would occur intensely at ~6.2 and 5.7–5.8 μ, respectively, and there should be strong ultraviolet absorption for alkanenitronate groups[6] at 223–234 mμ (9000–11,000) or for arylmethanenitronate ions[6] at 291 mμ (12,000).

The product of reaction of I and 2-nitropropene, methyl 4-nitro-2-(triphenylphosphoranylidene) valerate, was demonstrated chemically (eq 3) to be an

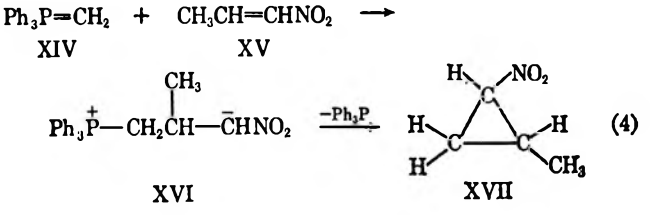


(3)

ylide (X) rather than a phosphonium salt (IX) upon (eq 1) its bromination to a bromophosphonium bromide (XI) exhibiting carbonyl and nitro absorptions at 5.81 and 6.48 μ, respectively, and (eq 2) reaction of XI with aqueous sodium carbonate resulting in regeneration of X. Bromination of the phosphonium nitronate (IX) is expected to occur at the nitronate group. No significant shift in the wave length of the carbonyl absorption would be anticipated as a result of bromination of IX since the carbonyl groups in the reactant and the product should have similar stretching vibrations. Also a shift in the absorption of the nitro group to a lower wave length (~6.37 μ) would be expected upon bromination of IX because of the electron-withdrawing ability of bromine in α-bromo-α-nitro structures.

The utility of methyl 3-methyl-4-nitro-2-(triphenylphosphoranylidene)butyrate (XII) and methyl 4-nitro-3-phenyl-2-(triphenylphosphoranylidene)butyrate (XIII) as ylide reagents for activated aldehydes was investigated. Reactions of XII and XIII with *m*-nitrobenzaldehyde occur slowly to yield the common product, methyl *m*-nitrocinnamate. It is apparent that XII and XIII undergo proton transfer reversal and reverse Michael addition (eq 1) to generate I and the respective nitro olefins. Reaction of *m*-nitrobenzaldehyde and I then yields methyl *m*-nitrocinnamate.

Methylenetriphenylphosphorane (XIV) reacts with 1-nitropropene (XV, eq 4) and with 2-nitro-2-butene in anhydrous dimethyl sulfoxide at 10° to give 2-methyl-1-nitrocyclopropane (XVII) and 1,2-dimethyl-1-nitrocyclopropane[7] in poor (5–7%) yields. Addition of XIV to the nitro olefins occurs with expulsion of triphenylphosphine; however there is extensive Michael polymerization of the nitro olefins under these conditions[8] along with conversion of the phosphorus-containing materials into triphenylphosphine oxide.



(4)

Dimethylsulfoxonium methylide (XVIII)[9] in anhydrous dimethyl sulfoxide is an effective reagent for converting conjugated nitro olefins (II, Table II) into

(5) (a) Aliphatic nitro compounds exhibit a principal absorption band at 270–280 mμ; the absorption is of low intensity (ε *ca.* 15–30).[4] (b) H. E. Ungnade and R. A. Smiley, *J. Org. Chem.*, **21**, 993 (1956).

(6) (a) F. T. Williams, Jr., P. W. K. Flanagan, W. J. Taylor, and H. Shechter, *J. Org. Chem.*, **30**, 2674 (1965). (b) A. Hantzsch and K. Voigt, *Ber.*, **45**, 85 (1912). (c) The intermediate, III, from I and α-nitrostilbene is an arylmethanenitronate.

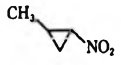
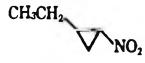
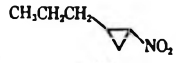
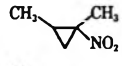
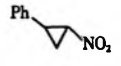
(7) 1-Butylidenetriphenylphosphorane and 9-*n*-butylidenefluorene yield spiro(2,3-dipropylcyclopropane-1,9-fluorene); R. Mechoulam and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 4386 (1958).

(8) Ethylidenetriphenylphosphorane in dimethyl sulfoxide results in extensive polymerization and decomposition of β-nitrostyrene, 1-nitropropene and 2-nitro-1-butene, respectively.

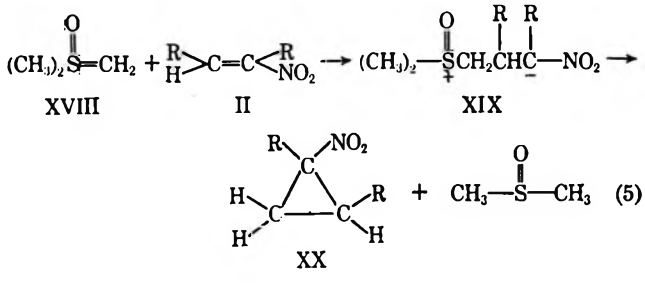
(9) E. J. Corey and M. Chaykovsky, *ibid.*, **84**, 867, 3782 (1962).

TABLE II

REACTIONS OF DIMETHYLSULFOXONIUM METHYLIDE (XVIII) WITH CONJUGATED NITRO OLEFINS (II)

Nitro olefins	Nitrocyclopropanes	Bp, °C (mm)	% yield[a]	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ir absorption,[b] μ NO_2	Uv absorption,[c] mμ (ϵ_{max})
$CH_3CH{=}CHNO_2$		69 (30)	31	$C_4H_7NO_2$	47.52	6.93	13.87	47.67	6.71	14.00	6.48, 7.34	219 (6650)
$CH_3CH_2CH{=}CHNO_2$		62 (10)	40	$C_5H_9NO_2$	52.27	7.82	12.17	52.65	7.79	12.35	6.48, 7.33	219 (6950)
$CH_3CH_2CH_2CH{=}CHNO_2$		76 (11)	43	$C_6H_{11}NO_2$	55.81	8.52	10.85	55.81	8.62	11.01	6.49, 7.33	219 (6445)
$CH_3CH{=}C(CH_3)NO_2$		70 (20)	37	$C_5H_9NO_2$	52.27	7.82	12.17	52.50	7.60	12.35	6.51, 7.39	216 (6236)
$Ph{-}CH{=}CHNO_2$		85–87 (1)	44	$C_9H_9NO_2$	66.26	5.52	8.58	65.93	5.70	8.63	6.49, 7.34	213 (11,230); 252 (8230)

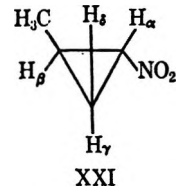
[a] The actual yields are much higher; the values reported are those for multiply distilled analytical samples. [b] Determined in potassium bromide pellets. [c] Determined in 95% ethanol.



XVIII II XIX XX (5)

substituted nitrocyclopropanes (XX) (eq 5).[10-12] The addition reactions are run preparatively by adding the nitro olefins to excess XVIII at 0–10°. The products are usually isolable and purifiable without complication. Conversion of 2-nitro-1-alkenes into nitrocyclopropanes is inefficient, however, because of polymerization of the nitro olefins by XVIII. The nitrocyclopropanes are colorless, pleasant liquids stable to storage, insoluble in aqueous bases,[13] and readily separable from their parent nitro olefins by distillation methods.

The α-nitro-β-substituted cyclopropanes prepared appear to have *trans* stereochemistry.[14] The structure of the product of reaction of XVIII and 1-nitro-1-propene (principally the *trans* isomer) is assigned as *trans*-2-methyl-1-nitrocyclopropane (XXI) on the



XXI

basis of its nmr for two deshielded cyclopropyl hydrogens between τ 8.0 and 8.35 (H_β and H_γ, multiplet, area 1.93),[15a] a methyl group[15b] which is not deshielded and which integrates with cyclopropyl hydrogen (H_δ, not deshielded) between 8.70 and 9.06 (multiplet, area 4.25), and cyclopropyl hydrogen at 5.95 (H_α, quintet, area 1.0) on carbon bearing the nitro group.[15c] Chemical evidence for the stereochemical assignment was obtained in that the nitrocyclopropane is not separated into geometric isomers by gas chromatography on GF-1 (Dow Corning Co.) Chromsorb,[16] and reduction by iron and hydrochloric acid[17] gives 2-methyl-1-cyclopropylamine whose gas chromatographic properties are essentially identical with that of *trans*-2-methyl-1-cyclopropylamine (XXII) prepared as indicated in eq 6 (see Experimental Section) and

(10) The yields listed in Table II are for highly purified nitrocyclopropanes. The actual yields are considerably greater than those given.

(11) (a) XVIII reacts with α,β-unsaturated ketones,[11b] amides,[11c,d] nitriles,[11e] and sulfones[11f] to give cyclopropanes. (b) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965); (c) P. T. Izzo, *J. Org. Chem.*, **28**, 1713 (1963); (d) B. Loev, M. F. Kormendy, and K. M. Snader, *Chem. Ind.* (London), 1710 (1964); (e) C. Kaiser, B. M. Trost, J. Beeson, and J. Weinstock, *J. Org. Chem.*, **30**, 3972 (1965); (f) W. E. Truce and V. U. Badiger, *ibid.*, **29**, 3277 (1964).

(12) It has been reported[11e] that β-nitrostyrene and XVIII do not give the corresponding nitrocyclopropane. In the present experiments the adduct, 1-nitro-2-phenylcyclopropane, is obtained.

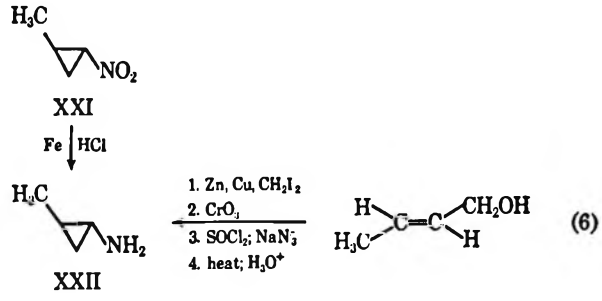
(13) The resistance of conversion of 2-methyl-1-nitrocyclopropane into its corresponding nitronate ion is also indicated by the observation that the ultraviolet absorption of the nitrocyclopropane is unchanged in homogeneous solution upon addition of excess base (also see ref 11e).

(14) Ethyl *trans*-cinnamate and *trans*-N,N-dimethylcinnamamide react with XVIII to give ethyl *trans*-2-phenylcyclopropanecarboxylate (98.9% stereoselective) and *trans*-N,N-dimethyl-2-phenylcyclopropanecarboxamide (100% stereoselective). Ethyl *cis*- and *trans*-2-phenylcyclopropanecarboxylates are not epimerized by the above reaction environment.[11e] *trans*-Cinnamonitrile and XVIII give a mixture of 78% *trans*- and 21% *cis*-2-phenylcyclopropanecarbonitriles.[11e] *trans*-Phenyl ω-styryl sulfone and XVIII yield only *trans*-1-phenyl-2-phenylsulfonylcyclopropane; *cis*-1-phenyl-2-phenylsulfonylcyclopropane is isomerized nearly quantitatively to its *trans* isomer under the conditions for addition of XVIII to the *trans*-sulfone.[11f]

(15) (a) Hydrogen *cis* to a nitro group in a nitrocyclopropane is expected to be highly deshielded. S. Ranganathan (Ph.D. Dissertation, The Ohio State University, Columbus, Ohio, 1962) observed that in 2-nitrospiro[cyclopropane-1,9′-fluorene] the τ values of the β and β′ hydrogens relative to the nitro group of the cyclopropane ring are 8.25 and 8.85, respectively. It is presumed that the β and β′ hydrogens are *cis* and *trans*, respectively, relative to the nitro group. (b) The nmr of shielded and unshielded methyl groups in the following cyclopropanes are 1-methyl- (τ 8.87) *trans*-2-phenylcyclopropane; 1-methyl- (τ 9.20) *cis*-2-phenylcyclopropane; 1-*cis*-2-dimethyl- (τ 8.87) *trans*-3-phenylcyclopropane; 1-*cis*-2-dimethyl- (τ 9.05) *cis*-3-phenylcyclopropane; and 1-*trans*-2-dimethyl- (τ 8.85 and 9.22) *trans*-3-phenylcyclopropane as given by J. P. Freeman [*J. Org. Chem.*, **29**, 1379 (1964)] and G. L. Closs and R. A. Moss [*J. Am. Chem. Soc.*, **86**, 4042 (1964)]. (c) Hydrogen on carbon attached to nitro groups in the present nitrocyclopropanes have τ values of 5.94–5.96. Protons on carbon bearing nitro groups in 2-nitropropane and 2-nitrobutane exhibit resonance at τ 5.33 and 5.48, respectively: Varian Associates NMR Spectra Catalog, Palo Alto, Calif., Spectrum No. 41 and 42.

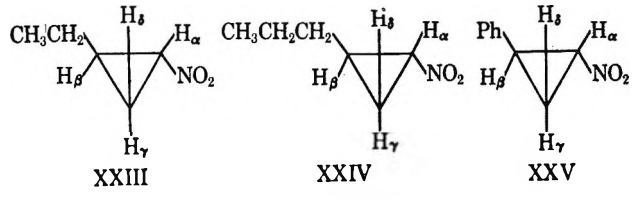
(16) Such columns are effective for separating *cis*- and *trans*-alkylnitrocycloalkanes: G. E. Booth, private communication, 1966.

(17) Iron and hydrochloric acid reduce various *exo*- and *endo*-nitrobicycloalkanes to their corresponding amines without alteration of the initial stereochemistry: P. W. K. Flanagan, Ph.D. Thesis, The Ohio State University, Columbus, Ohio, 1957.

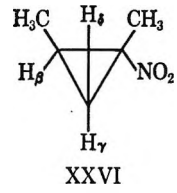


obtained as an authentic sample.[18] It is not yet clear whether XXI is formed from XVIII and 1-nitro-1-propene as a product of kinetic or thermodynamic control.

The products, XXIII, XXIV and XXV, from reaction of XVIII with 1-nitro-1-butene, 1-nitro-1-pentene, and *trans*-β-nitrostyrene, respectively, could not be separated effectively by gas chromatographic methods. The chromatographic traces were symmetrical upon passing each nitrocyclopropane through a variety of columns. Upon attempting to separate the products through long, highly polar, heated columns, there was distortion in the chromatographic responses. It could not be established, however, whether small amounts of initial geometrical isomers were present, whether there was some *cis–trans* isomerization during chromatography, or whether thermal decomposition of initial products led to unsymmetrical broadening of the gas chromatographic peaks.



The structure of XXIII is indicated as *trans*-2-ethyl-1-nitrocyclopropane from its nmr absorption for two deshielded ring protons (H_β and H_γ, multiplet, τ 8.28–8.40, area 2.10), methyl and ring protons (CH_3 and H_δ, multiplet, τ 8.85–9.20, area 4.1), which are not deshielded, alkylmethylene hydrogen (CH_2, sextuplet, τ 8.47–8.85, area 2.10), and hydrogen (H_α, quintet, τ 5.95, area 1.0) on carbon substituted by a nitro group. Similarly XXIV[19a] and XXV[19b] are assigned *trans* stereochemistries from their nmr properties. Although no attempts were made to separate by precision glpc techniques the adduct obtained from 2-nitro-2-butene and XVIII, it is clear from the nmr properties of the product that 1-*cis*-2-dimethyl-1-nitrocyclopropane (XXVI) must be at least the principal component.[20]



XXVI

The spectral properties of the nitrocyclopropanes prepared are of some note. The nitrocyclopropanes in which the nitro groups are at secondary carbon exhibit infrared absorption at 6.48–6.49 and 7.33–7.34 μ (Table II); their absorptions thus occur in general at longer wave lengths than do secondary aliphatic nitro compounds (6.38–6.47 and 7.22–7.35 μ).[21] The tertiary nitrocyclopropanes absorb at 6.51–6.52 and 7.39–7.41 μ and thus more closely approximate tertiary nitroalkanes (6.47–6.53 and 7.36–7.45 μ).[4,21] Ultraviolet absorption of the nitrocyclopropanes (Table II) occurs with intensity (ϵ_{max} ~6,000) in the 213–219 mμ range in 95% ethanol; since nitroalkanes and conjugated nitroalkenes exhibit $\pi \rightarrow \pi^*$ bands at ~210[22] and at 220–250 mμ (ϵ_{max} 3300–12,400),[22] it is apparent that there is an appreciable conjugative effect in the nitrocyclopropanes.

Experimental Section

Reagents and General Procedures.—1-Nitro-1-propene,[23a] 2-nitropropene,[23a,b] 1-nitro-1-butene,[23a] 2-nitro-2-butene,[23c] 1-nitro-1-pentene,[23a] β-nitrostyrene,[23d] 2-nitro-1-phenylpropene,[23e,f] α-nitrostilbene,[23d] 2-(2-nitrovinyl) furan,[23g] methylenetriphenylphosphorane (XIV),[2] ethylidenetriphenylphosphorane,[2] carbomethoxymethylenetriphenylphosphorane (I),[2] carbomethoxyethylidenetriphenylphosphorane (V),[2] and dimethylsulfoxonium methylide (XVIII)[9] were prepared by literature methods. In the subsequent experimental, typical procedures for reactions of conjugated nitroolefins with carbomethoxymethylenetriphenylphosphorane (I) and dimethylsulfoxonium methylide (XVIII) are described. These procedures are almost exact prototypes for the experiments summarized in Tables I and II.

Reaction of 2-Nitropropene and Carbomethoxymethylenetriphenylphosphorane (I).—2-Nitropropene (3.5 g, 0.04 mol), and phenylphosphorane (I) (13.4 g, 0.04 mol) were stirred in anhydrous toluene (80 ml) for 40 hr at 90–100°. The mixture was cooled and the toluene evaporated. Anhydrous ether (200 ml) was added to the dark brown residue, and the resulting solid (9.7 g, 57%) was filtered. Concentration of the ether filtrate afforded no additional product. Recrystallization of the solid from ethyl acetate yielded methyl 4-nitro-2-(triphenylphosphoranylidene) valerate (X), mp 161.5–163.5° dec.

Reaction of β-Nitrostyrene and α-Carbomethoxyethylidenetriphenylphosphorane.—β-Nitrostyrene (2.98 g, 0.02 mol) and this triphenylphosphorane (6.96 g, 0.02 mol) were heated at 90–100° in toluene (100 ml) for 24 hr. The mixture was cooled and concentrated and then ethyl ether (250 ml) was added. Filtration yielded β-nitrostyrene polymer (2.70 g) identified by its infrared absorption and its general properties.

(18) A gift from the Lakeside Laboratories, Inc., Milwaukee, Wis.

(19) (a) The nmr of XXIV indicates H_α (quintet, area 1.0) at τ 5.95, H_β and H_γ (multiplet, area 2.09) between 8.10 and 8.33, alkylmethylene hydrogens ($-CH_2CH_2-$, multiplet, area 4.20) at 8.33–8.86, and H_δ along with methyl protons (multiplet, area 4.14) at 8.86–9.24. (b) XXV exhibits resonance for H_α (quintet, area 1.0) at τ 5.96, H_β (deshielded, multiplet, area 1.06) at 7.07–7.52, H_γ (deshielded, multiplet, area 1.06) at 8.04–8.44, H_δ (quartet, area 1.06) at 8.60–9.02, and H on phenyl (area 4.86) at 2.80–3.24.

(20) The nmr of XXVI reveals methyl protons (singlet, area 2.80) on carbon bonded to the nitro group, H_β and H_γ (multiplet, area 1.80) at τ 8.10–8.33, methyl protons (multiplet, area 3.10) between 8.76–8.96, and H_δ (multiplet, area 1.0) at 9.14–9.33.

(21) (a) N. Kornblum, H. E. Ungnade, and R. A. Smiley, *J. Org. Chem.*, **21**, 377 (1956). (b) Reference 21a reports that 2-methyl-1-nitrocyclopropane absorbs at 6.50 μ and 7.36 μ and that conjugated nitro olefins exhibit absorption at 6.55–6.62 and 7.39–7.46 μ, respectively.

(22) (a) C. N. Rao, "Ultraviolet and Visible Spectroscopy," Butterworth and Co. Ltd., London, 1961, p 20; (b) E. A. Braude, E. R. H. Jones, and G. G. Rose, *J. Chem. Soc.*, 1104 (1947).

(23) (a) E. Schmidt and G. Rutz, *Ber.*, **61B**, 2142 (1928); (b) G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947); (c) H. B. Hass, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950); (d) J. Meisenheimer and F. Heim, *Ann.*, **355**, 275 (1907); (e) L. Bouveault and A. Wahl, *Compt. Rend.*, **134**, 1145 (1903); (f) L. Bouveault and A. Wahl, *Bull. Soc. Chim. Fr.*, [3] **29**, 519 (1903); (g) O. Moldenhauer, W. Irion, D. Mastaglio, R. P. Fluger, and H. Doser, *Ann.*, **583**, 50 (1953).

Concentration of the ether filtrate, and addition of 95% ethanol–ether (1:1, 200 ml) gave triphenylphosphine oxide (1.87 g), identified by its infrared properties. Further evaporation of the filtrate yielded a mixture of triphenylphosphine oxide and α-carbomethoxyethylidenetriphenylphosphorane.

Reaction of Methyl 4-Nitro-2-(triphenylphosphoranylidene) Valerate (X) with Bromine and Then Aqueous Sodium Carbonate.—Bromine (0.48 g, 0.003 mol) in carbon tetrachloride (10 ml) was added dropwise to methyl 4-nitro-2-(triphenylphosphoranylidene) valerate (X, 1.17 g, 0.0028 mol) in carbon tetrachloride (60 ml) at 25–30°. The resulting mixture was stirred 18 hr and then filtered to give bromophosphonium bromide XI (1.46 g, 91%) as a yellow solid, mp 116–120° dec. The infrared spectrum of XI contained strong absorption for carbonyl (5.81 μ) and aliphatic nitro (6.47 μ) groups. Attempts to recrystallize XI from hot absolute ethanol, benzene, carbon tetrachloride, chloroform, or pentane lead to its deterioration.

Compound XI (1.28 g, 0.0022 mol) was dissolved in water (150 ml) at room temperature, filtered, and treated with 10% aqueous sodium carbonate until the aqueous solution was basic. The mixture was filtered to give a green solid (0.51 g, 55%), identified as X by comparison of its infrared spectrum and its mixture melting point with that of initial material.

Reaction of Methyl 4-Nitro-3-phenyl-2-(triphenylphosphoranylidene)butyrate (XIII) and *m*-Nitrobenzaldehyde.—Compound XIII (3.19 g, 0.0066 mol) and *m*-nitrobenzaldehyde (1.00 g, 0.0066 mol) were heated at 100° in dry xylene for 40 hr. The mixture was then cooled and the xylene removed. Anhydrous ether (150 ml) was added to the orange residue and the resulting mixture filtered to give initial phosphorane (XIII, 1.94 g). The filtrate was concentrated *in vacuo* and then dissolved in hot 95% ethanol. Cooling gave methyl *m*-nitrocinnamate (0.34 g), mp 120–122°, identified by comparison of its infrared spectrum and its mixture melting point with those of an authentic sample.[24]

Reaction of Methylenetriphenylphosphorane (XIV) with 1-Nitro-1-propene.—A stirred mixture of sodium hydride (1.20 g, 0.05 mole) and dry dimethyl sulfoxide (75 ml) was heated at 65° under nitrogen until hydrogen was no longer evolved (~90 min). The pale yellow solution was cooled to 15° and then triphenylmethylphosphonium bromide (17.85 g, 0.05 mol) was slowly added. After additional stirring at room temperature for 30 min, the mixture was cooled to −10°; 1-nitro-1-propene (4.35 g, 0.05 mol) in dimethyl sulfoxide (25 ml) was added over a 30-min period, and the mixture was stirred at 75° for 6 hr and then at 25–30° for 12 hr. The mixture was poured on ice and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and concentrated. The orange-black viscous residue was vacuum distilled through a short-path still to give an orange oil which on redistillation afforded 2-methyl-1-nitrocyclopropane (0.23 g, 5%) identified by comparison with a sample prepared from dimethylsulfoxonium methylide (XVIII) and 1-nitro-1-propene.[25]

Reaction of Dimethylsulfoxonium Methylide (XVIII) with 1-Nitro-1-pentene.—Trimethylsulfoxonium iodide (96.8 g, 0.44 mol) was added through Gooch tubing in 30 min to a stirred suspension of sodium hydride (10.56 g, 0.44 mol) in dimethyl sulfoxide (250 ml) under nitrogen. After stirring at room temperature for 4 hr, the mixture was cooled to 10° and 1-nitro-1-pentene (46.0 g, 0.4 mol) in dimethyl sulfoxide was added dropwise in 45 min.[26] The mixture was stirred at 50° for 4 hr and then at 25–30° for 12 hr, poured onto ice, and extracted with ether. The ether extracts were washed with water, dried over magnesium sulfate, and then concentrated at reduced pressure. The orange-red oil was vacuum distilled to give *trans*-2-nitro-1-*n*-propylcyclopropane (XXIV, 22.2 g, 43%) as a colorless liquid (Table II).

2-Methylcyclopropylcarbinol.—A mixture of crotyl alcohol (~80% *trans*, 20% *cis*, 18.0 g, 0.25 mole) and methylene iodide (83.8 g) was added in 2 hr to a stirred suspension prepared by dropwise addition of methylene iodide (10 g, total CH_2I_2, 0.35 mol) to zinc–copper couple[27] (32.7 g, 0.5 mol) in ethyl ether (100 ml). After the stirred mixture had refluxed 25 hr, the ether solution was slowly decanted into a mixture of ice and hydrochloric acid. The ether solution was separated, washed with ice–hydrochloric acid and then water, dried over potassium carbonate, and then concentrated. Distillation of the resulting oil gave 2-methylcyclopropylcarbinol (8.2 g, 38% yield), bp 128–130° (lit.[28] bp 133°). Vapor phase chromatography showed the reaction product to be a 80:20 mixture of *trans*- and *cis*-2-methylcyclopropylcarbinols.

2-Methylcyclopropanecarboxylic Acid.—2-Methylcyclopropylcarbinol (3.3 g, 0.04 mole) was added dropwise to a stirred solution of chromic oxide (15.5 g, 0.15 mol), sulfuric acid (13.6 ml), and water (45 ml) at 0–5°. The mixture was then stirred for 3 hr. The acid solution was extracted with ethyl ether; the ether extracts were dried, concentrated, and distilled to give 2-methylcyclopropanecarboxylic acid (2.4 g, 60% yield), bp 101–102° (22 mm) (lit.[28] bp 97–98° (17.6 mm)). The product upon vapor phase chromatography was found to be a mixture containing 80% of the *trans*- and 20% of the *cis*-2-methylcyclopropanecarboxylic acids.

2-Methylcyclopropylamine.—2-Methylcyclopropanecarboxylic acid (2.2 g, 0.02 mol) and thionyl chloride (10 ml) were stored for 24 hr at 25–30°. The excess thionyl chloride was then removed *in vacuo* to give 2-methylcyclopropanecarbonyl chloride (1.7 g). The acid chloride was dissolved in acetone (40 ml), cooled to 10°, and then treated dropwise with a solution of sodium azide (2.6 g, 0.04 mole) in water (8 ml). The mixture was stirred for 30 min and then poured into ice water (250 ml). The aqueous solution was extracted with ether, and the ether washings were dried over anhydrous magnesium sulfate and concentrated. The residual azide was added to dry toluene (30 ml), heated with steam for 2 hr, and concentrated to give 2-methylcyclopropyl isocyanate. The isocyanate was hydrolyzed in refluxing hydrochloric acid (50 ml) for 12 hr and concentrated *in vacuo* to yield crude 2-methylcyclopropylamine hydrochloride. The hydrochloride was dissolved in water (50 ml), made alkaline with 10% sodium hydroxide, and extracted with ether. The ether extract was dried and concentrated to give 2-methylcyclopropylamine whose infrared spectrum is essentially identical with that obtained for the product of reduction of *trans*-2-methyl-1-nitrocyclopropane (XXI).

Reduction of *trans*-2-Methyl-1-nitrocyclopropane (XXI).—Concentrated hydrochloric acid (8 ml) was added in 3 hr to a refluxing mixture of *trans*-2-methyl-1-nitrocyclopropane (XXI) (1.15 g, 0.011 mol) and iron dust (2.0 g, 0.036 g-atom) in water (20 ml). The mixture was then refluxed for 6 hr, cooled, made alkaline with aqueous sodium hydroxide (10%), and then filtered. The filtrate was extracted with ether; the combined ether extracts were dried over magnesium sulfate and concentrated. The infrared spectrum of the product (XXII) was identical with that of authentic *trans*-2-methyl-1-cyclopropylamine. Its gas phase chromatographic properties revealed that the principal component is identical with that from Curtius reaction of *trans*-2-methylcyclopropanecarboxylic acid.

Registry No.—X, 15267-20-6; XI, 15267-21-7; XIII, 15267-22-8; XVIII, 14407-16-0; XXI, 15267-24-0; XXIII, 15267-25-1; XXIV, 15267-26-2; XXV, 15267-27-3; XXVI, 15267-28-4.

(24) A similar experiment with methyl 3-methyl-4-nitro-2-(triphenylphosphoranylidene) butyrate (XII) and *m*-nitrobenzaldehyde yielded methyl *m*-nitrocinnamate.

(25) A similar experiment with methylenetriphenylphosphorane (XIV) and 2-nitro-2-butene gave 1,2-dimethyl-1-nitrocyclopropane (7%, stereochemistry unestablished). The conditions for formation of nitrocyclopropanes from either methylenetriphenylphosphorane (XIV) or ethylidenetriphenylphosphorane were not optimized because of the greater promise of dimethylsulfoxonium methylide (XVIII) as a reagent.

(26) (a) The reaction is exothermic; (b) addition of XVIII to the nitro olefins resulted in extensive polymerization; (c) under usual circumstances there were no (lachrymatory) nitroolefins in the reaction products.

(27) E. Le Goff, *J. Org. Chem.*, **29**, 2048 (1964).

(28) M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 3671 (1961).

Benzo Derivatives of Nitrocyclopentadiene

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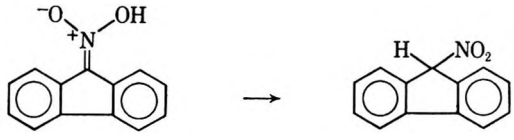
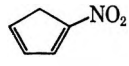
Protonation of the potassium salts of 1-nitroindene and 9-nitrofluorene in water solution occurs fastest at oxygen to yield in both cases the *aci* tautomers. In nonpolar solvents, *aci*-1-nitroindene tautomerizes to 3-nitroindene *via* 1-nitroindene; *aci*-9-nitrofluorene likewise tautomerizes to 9-nitrofluorene. The *aci* compounds do not tautomerize in hydroxylic solvents. On treatment with benzoyl chloride, both salts yield stable O-benzoyl derivatives.

Until recently, it was believed that the only tautomers produced by protonating salts of nitrocyclopentadiene,[1] and its annelated derivatives, 1-nitroindene[2] and 9-nitrofluorene,[3] were uniformly the *aci*-nitro compounds, produced by O protonation. Only in the case of 9-*aci*-nitrofluorene (I) has the *aci* structure been confirmed by spectral methods.[4] However, it has more recently been claimed, on the basis of bromination studies, that 9-*aci*-nitrofluorene (I) is the stable tautomer only in the crystal and in polar media; in nonpolar solvents it is transformed into 9-nitrofluorene (II).[3b]



I II

Because of the uncertainty of the information on the tautomeric forms of the above compounds, and inasmuch as *aci* tautomers are generally less stable thermodynamically than the corresponding nitro tautomers, we decided to reinvestigate these materials in order to establish the true nature of the species involved. Indeed, we have recently shown that the only simple product of protonation of the sodium salt of nitrocyclopentadiene was in fact 1-nitrocyclopentadiene[5] (III) rather than the *aci* compound reported by Thiele.[1]

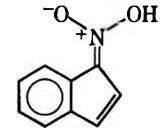


III

Results and Discussion

The potassium salts (IV and V) of 1-nitroindene and 9-nitrofluorene were prepared according to literature methods,[2,6] by treating the potassium salts of indene and fluorene with ethyl nitrate. The structures and spectra of these salts, and particularly their strong dependence on solvent, are reported elsewhere.[7]

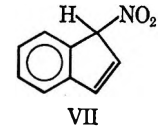
Nitroindenes.—On acidifying an aqueous solution of IV, Wislicenus reported obtaining as a precipitate an unstable material, mp *ca.* 50°, to which he ascribed the *aci* structure, VI.[2] In agreement with his results,



VI

we also found that acidification of a cold aqueous solution of IV yielded a very fine, light yellow precipitate. However, collection of this material by filtration proved difficult owing to its fine particle size. In the time required to accomplish filtration, the material had turned dark orange; it darkened but did not melt on heating to 200°.

Because of this instability of the protonated material,[2] no further attempts were made to isolate it; instead, the water solution was extracted with a suitable organic solvent immediately after acidification and the products were studied in solution. A chloroform-*d* solution of the product of acidification of IV, obtained in this manner and kept cold in a Dry Ice bath, was studied by nmr (see Table I). The spectrum showed a one-proton resonance at τ −0.9, one proton at 2.0, three protons at 2.5–2.8, and two protons at 3.3. This spectrum is uniquely consistent with the *aci* structure VI.[8] After the solution containing VI had stood at room temperature for 3 hr, the resonances of VI were largely replaced by new ones, at τ 2.4, 3.0, and 3.5 (Table I) which, by comparison with the recently reported spectrum of indene-1-carboxylic acid,[9] suggested that a considerable fraction of the VI had tautomerized to 1-nitroindene, VII.[10]



VII

(1) J. Thiele, *Ber.*, **33**, 670 (1900).

(2) W. Wislicenus and K. Pfeilsticker, *Ann.*, **436**, 36 (1924).

(3) (a) C. D. Nenitzescu and C. D. Isacescu, *Ber.*, **63**, 2484 (1930); (b) C. D. Nenitzescu and I. G. Dinulescu, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1228 (1958), as translated in *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1185 (1958).

(4) J. P. Freeman and K. S. McCallum, *J. Org. Chem.*, **21**, 472 (1956).

(5) R. C. Kerber and M. J. Chick, *ibid.*, **32**, 1329 (1967).

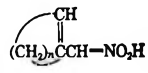
(6) W. Wislicenus and M. Waldmüller, *Ber.*, **41**, 3334 (1908).

(7) R. C. Kerber and A. Porter, *J. Amer. Chem. Soc.*, in press.

(8) Inasmuch as this appears to be the first reported nmr spectrum of an *aci*-nitro compound, it is worth noting that the resonance of the hydroxyl proton at τ −0.9 is similar to that of typical carboxylic acids in nonpolar media [*cf.* J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 91]. This suggests that *aci*-nitro compounds, like carboxylic acids, form hydrogen-bonded dimers in such media. Freeman and McCallum[4] previously proposed that I exists in such a dimeric form in the crystalline state.

(9) O. Meth-Cohn and S. Gronowitz, *Chem. Commun.*, 84 (1966).

(10) A referee has pointed out to us the work of H. B. Fraser and G. A. R. Kon [*J. Chem. Soc.*, 604, (1934)], who also reported obtaining unconjugated products of tautomerization, in their case from the *aci* compounds below.



$n = 3,4$

However, in these cases, the unconjugated tautomers were thermodynamically stable, probably owing to conformational effects. More recent studies in systems free of such effects have found only the conjugated isomers. See, for example, A. T. Nielsen, *J. Org. Chem.*, **27**, 2001 (1962), and H. Shechter and J. W. Shepherd, *J. Amer. Chem. Soc.*, **76**, 3617 (1954).

TABLE I

Compound	τ_1	τ_2	τ_3	τ_{4-6}	τ_7	J_{12}	J_{23}	J_{13}	Ref
Indene	7.01	3.87	3.34	*Ca.* 2.89	*Ca.* 2.89	2.02	5.58	1.98	*a*
syn-Indone oxime	...	3.55	*Ca.* 2.8	*Ca.* 2.8	1.75	...	6.0	...	*b*
anti-Indone oxime	...	3.17	3.02	*Ca.* 2.8	2.3	...	5.8	...	*b*
aci-1-Nitroindene (VI)	...	3.3	3.3	2.5–2.8	2.0	...	...	...	This work
XII	...	3.43	3.08	2.25–2.75	1.9	...	5.7	...	This work
1-Nitroindene (VII)	2.4	3.5	3.0	2.5–2.8	2.5–2.8	2.0	5.8	2.0	This work
3-Nitroindene (VIII)	6.40	2.45	...	2.55–2.85	(τ_4) 1.95	1.9	...	...	This work
Indene-1-carboxylic acid	5.47	3.57	3.24	*Ca.* 2.76	2.45	1.9	5.7	1.9	*c*
Methyl indene-3-carboxylate	6.57	2.67	...	...	(τ_4) 1.97	2	...	...	*d*

[a] D. D. Elleman and S. L. Manatt, *J. Chem. Phys.*, **36**, 234 (1962). [b] Personal communication from Dr. Sylvan E. Forman, FMC Corp; *cf. J. Org. Chem.*, **29**, 3323 (1964); the configuration assignments are our own, based on data in G. Karabatsos, R. A. Taller, and F. M. Vane, *J. Amer. Chem. Soc.*, **85**, 2326 (1963). [c] See ref 9. [d] A. Melera, M. Claesen, and H. Vanderhaeghe, *J. Org. Chem.*, **29**, 3705 (1964).

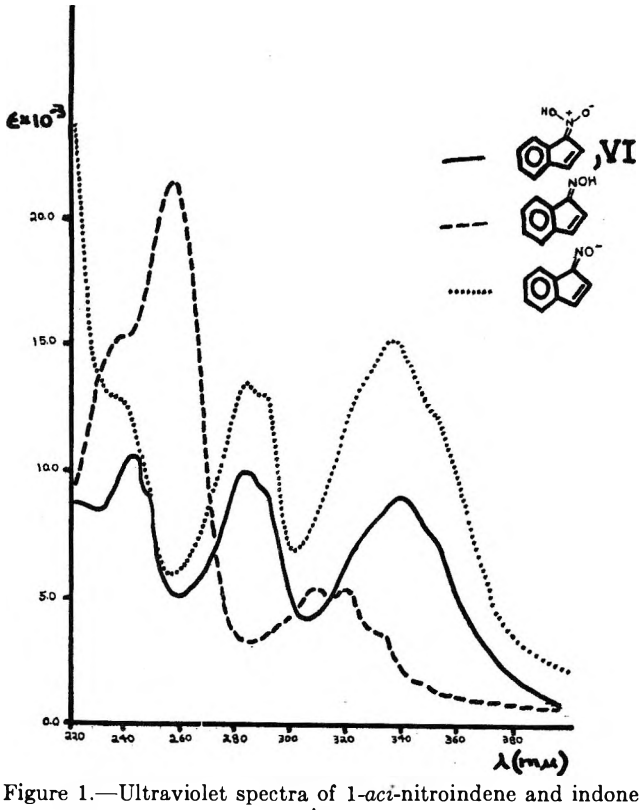
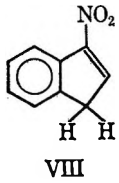


Figure 1.—Ultraviolet spectra of 1-*aci*-nitroindene and indone oxime.

The nmr spectrum of the 3-hr-old sample also showed a doublet at τ 6.40, which continued to increase with time, even as the resonances of VI and VII decreased. After 18 hr a steady state had been reached; the spectrum contained a two-proton doublet at τ 6.40 (J = 1.9 cps), a one-proton multiplet at 1.95, a one-proton triplet at 2.45, (J = 1.9 cps), and a three-proton multiplet at τ 2.55–2.85. These data showed that the ultimate product was 3-nitroindene, VIII.



VIII

The sequence of changes observed in the nmr spectra demonstrates that the rates of protonation at the various positions of the IV anion decrease in the order O > C-1 > C-3[11] and that at equilibrium in nonpolar solution the only isomer detectable by nmr is 3-nitroindene, VIII.

Although the facile interconversion of the nitroindene tautomers makes unambiguous interpretation of other spectra difficult, their origin can usually be inferred from internal evidence. Thus, the same ultraviolet spectrum (Figure 1), due to VI, was obtained either by acidifying an ethanol solution of the salt IV and measuring the spectrum directly or by acidifying an aqueous solution, extracting rapidly with ether, and measuring the spectrum of the diluted ether extract. The attribution to VI is supported by the similarity of the spectrum to that of IV[7] (save for shifts of the maxima to shorter wavelengths) and to that of indone oxime, particularly in basic solution (Figure 1).[12]

As the ether solution of VI stood at room temperature, this spectrum slowly decayed (half-life about 3 hr). After 27 hr, the spectrum showed only broad maxima at 238 and 289 mμ (ε *ca.* 7000 and 3000, respectively), which are presumably due to 3-nitroindene, IX. By comparison, indene absorbs at 252 mμ (ε 9900) in isooctane;[13] 2-nitro-2-butene absorbs at 235 mμ (ε 6100) in hexane.[14]

The infrared spectra of solutions of VI, prepared by extracting a freshly acidified solution of IV with carbon tetrachloride or chloroform, showed O–H absorption as a very broad band between 3600 and 2200 cm^{-1} and C=N at 1654 cm^{-1}.[15] Strong bands not attributable to the hydrocarbon portions of the molecule also appeared at 1253 and 957 cm^{-1}. Similar bands appear in the infrared spectrum of I; these may prove to be characteristic of the *aci*-nitro grouping, $R_2C{=}NO_2H$.

On standing in carbon tetrachloride at room temperature, this spectrum slowly disappeared. After 20 hr,

(11) This assumes that tautomerization in $CDCl_3$ occurs *via* the IV anion; it is presumably catalyzed by small amounts of water present because of the extraction procedure.

(12) The spectra of indone oxime were graciously supplied to us by Dr. Sylvan Forman of F.M.C. Corp. to whom we are very grateful; *cf. J. Org. Chem.*, **29**, 3323 (1964).

(13) A. P. I. Research Project No. 44, I, 321 (1949); *cf.* "Organic Electronic Spectral Data," Vol. 1, M. J. Kamlet, Ed., Interscience Publishers Inc., New York, N. Y., 1960, p 243.

(14) E. A. Braude, E. R. H. Jones, and G. G. Rose, *J. Chem. Soc.*, 1104 (1947).

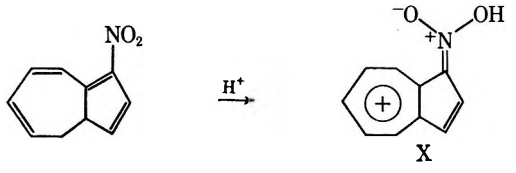
(15) C=N stretching frequencies of other *aci*-nitro compounds fall in the region 1630–1684 cm^{-1}; *cf.* S. S. Novikov, *et al.*, Proceedings of the International Symposium on Nitro Compounds, Warsaw, 1963, T. Urbanski, Ed., MacMillan and Co., Inc., New York, N. Y., 1964, p 119. This paper disputes the existence of covalent *aci* structures, a viewpoint which is inconsistent with the spectra reported herein.

the spectrum showed two strong bands at 1550 and 1359 cm^{-1} due to the nitro group of IX and a medium band at 1460 cm^{-1} due to the CH_2 group.

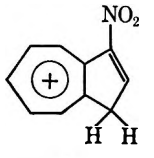
The spectra reported here confirm Wislicenus' conclusion that *aci*-1-nitroindene (VI) is the kinetically controlled product of protonation of IV. However, in nonpolar solvents VI tautomerizes cleanly to 3-nitroindene, IX. None of the other isomers can be detected at equilibrium in these nonpolar solvents.

In contrast to these results, solutions of VI in methanol or ethanol showed no substantial change in ultraviolet-visible absorption on standing at room temperature for several hours. Thus it appears that the tautomeric equilibrium among the nitroindenes is solvent sensitive: *aci*-1-nitroindene (VI) is favored in hydroxylic solvents; 3-nitroindene (IX) is favored in nonpolar solvents.

The thermodynamic preference for *aci* compound VI in hydroxylic media is consistent with the results of Meuche and Heilbronner,[16] who have reported that protonation of 1-nitroazulene in trifluoroacetic–sulfuric acid gave only the *aci* compound X which is isoelectronic with VI. No 3-nitroazulenium ion could be detected by nmr.



X



Nitrofluorene.—Acidification of an aqueous solution of the potassium salt of 9-nitrofluorene (V) produces a light yellow precipitate, which can be collected and dried. This material has been shown to be 9-*aci*-nitrofluorene, I, by both chemical[3] and spectral[4] methods. We report here only those features of the spectra which support our findings in the nitroindene series and which bear upon the question of tautomerism of nitrofluorene.

Dissolution of I in ethanol gives a solution whose electronic spectrum is that of the salt V. In order to obtain a spectrum of I, 1 drop of mineral acid must be added to prevent ionization of I, which is evidently a strong acid in ethanol.[17] The *aci* compound, I, is relatively stable in acidic ethanol; the long wavelength peaks do not change in shape or intensity over a period of at least 1 day.

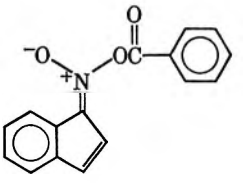
However, in ether or tetrahydrofuran (THF) solution, the spectrum of I is not stable. The long wavelength peaks decay at room temperature leaving maxima at 245, 253, and *ca.* 271 mμ (broad shoulder). The nmr spectrum in THF also behaved in a manner suggesting tautomerism of I to II. The OH resonance of a freshly dissolved sample of slightly wet I appeared at τ 2.1; as the material stood at room temperature, the OH resonance moved upfield toward the free water value, τ 5.0. Simultaneously, the aromatic pattern changed from that of II, which showed three complex multiplets centered at τ 1.85, 2.30, and 2.70 (relative areas 1:1:2) to a single broad multiplet at τ 2.2–3.1.

We interpret the changes in these spectra as being due to tautomerism of I to II in THF,[18] in agreement with Nenitzescu's findings.[3b]

Benzoyl Derivatives.—On treatment with benzoyl chloride, alcohol solutions of IV or V rapidly precipitate bright yellow benzoyl derivatives. In the case of V the product has been shown by chemical means to be O-benzoyl-9-*aci*-nitrofluorene, XI.[19] This is consistent with our observation that the ultraviolet spectra of I and of the benzoyl derivative are nearly superimposable.

The benzoyl derivative of IV was prepared by Wislicenus[2] and assigned the structure 1-benzoyl-3-nitroindene, in part because it was alleged to be soluble in base. We have found, however, that the material is not soluble in 10% aqueous potassium hydroxide; it dissolves in Claisen's alkali to give a solution whose ultraviolet spectrum is that of the salt IV. The ultraviolet spectrum of the benzoyl derivative itself is nearly identical with that of 1-*aci*-nitroindene, VI. The infrared spectrum shows C=O and C=N bonds at 1764 and 1600 cm^{-1}, compared with 1754 and 1616 cm^{-1} for XI. Lastly, the nmr spectrum of the benzoyl derivative (Table I) shows the presence of an unsubstituted double bond in the five-membered ring.

These data show unequivocally that the benzoyl derivative of IV has the structure O-benzoyl-1-*aci*-nitroindene, XII, analogous to that of XI.[20]



XII

Since the O-benzoyl derivatives were obtained in good yield from both IV and V, it is clear that kinetically controlled acylation, like protonation, occurs far faster at oxygen than at any other position of IV or V. It seems probable that other reactions of these anions with electrophiles will also occur preferentially at oxygen, although thermodynamic control may in some cases favor other positions.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Infracord, Model 137B, calibrated with a polystyrene film. Ultraviolet-visible spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Proton magnetic resonance spectra were obtained on a Varian A-60 spectrometer; chemical shifts are reported as τ values relative to tetramethylsilane as internal

(16) D. Meuche and E. Heilbronner, *Helv. Chim. Acta*, **45**, 1565 (1962).

(17) The published spectrum[4] is at least partly that of the anion.

(18) The 9 proton of II was not observed directly in the nmr spectrum, perhaps being buried among the complex aromatic pattern. The aliphatic proton of diphenylnitromethane falls at τ 3.15; that of II should fall at still lower field.

(19) (a) C. D. Nenitzescu and D. A. Isacescu, *Bull. Soc. Chim. Romania*, **14**, 53 (1932); *cf. Chem. Abstr.*, **27**, 964 (1934); (b) E. H. White and W. J. Considine, *J. Org. Chem.*, **22**, 1745 (1957).

(20) This possibility was first suggested in ref 19b, footnote 4.

standard (τ 10.00). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Potassium Salt (IV) of 1-Nitroindene.[2]—Potassium metal (10.0 g, 0.26 g-atom) was added in small portions to a mixture of 40 ml of absolute ethanol and 30 ml of absolute ether in a three-neck flask fitted with nitrogen inlet tube, mechanical stirrer, and dropping funnel. The mixture was stirred under a nitrogen atmosphere until all of the metal dissolved, then a mixture of 25 g (0.22 mol) of freshly distilled indene and 25 g (0.24 mol) of ethyl nitrate in 100 ml of absolute ether was added over a 2-hr period. The temperature was kept within the range 10–30° by use of an ice bath. The mixture was stirred an additional 45 min. Ether was added as necessary to keep the mixture stirable as a voluminous deep yellow precipitate formed. The precipitate was collected by filtration and the solid, which darkened rapidly on exposure to air while wet, was dried in a vacuum desiccator over KOH. The yield was 23.2 g (53%).

The crude salt was purified by dissolving it in 20 ml of acetone, bubbling carbon dioxide through the black solution for 15 min, adding charcoal, and filtering the solution. The precipitate was washed with acetone to give a total of about 50 ml of acetone solution. About 500 ml of chloroform was then added to reprecipitate the salt, as a yellow solid, which was redried *in vacuo*. The product darkened on heating to 200°, but did not melt below 340°. Spectral data appear elsewhere.[7]

The Potassium Salt (V) of 9-Nitrofluorene.[6,21]—V was made in the same manner as IV, using 5.85 g (0.15 g-atom) of potassium, 25.0 g (0.15 mol) of fluorene, and 13.7 g (0.15 mol) of ethyl nitrate. The mixture was filtered after 15 hr, giving the salt as a light yellow powder, in 68% yield. Spectral data appear elsewhere.[7]

Attempted Isolation of Nitroindene.—About 1.0 g of salt IV was dissolved in water and the cold solution was acidified with cold 3% HCl until no further precipitate (a light yellow solid) appeared. Filtration proved slow because of the fine particle size of the precipitate, but eventually resulted in a sticky, dark orange solid, which darkened but did not melt on heating to 200°. No further work was done with this material; rather, the nitroindenes were studied in solution.

***aci*-1-Nitroindene (VI) and 3-Nitroindene (VIII).**—Salt IV was dissolved in water and an equal volume of an immiscible organic solvent was added. The mixture was cooled to 0° and then acidified with cold 3% HCl. The layers were mixed, the organic layer was quickly removed by pipet, and the spectrum was taken. Solvents used included carbon tetrachloride (for ir), chloroform-*d* (for ir and nmr), and ether (for uv).

The ultraviolet spectrum attributed to VI could be obtained either by the above procedure or by acidifying an ethanol solution of IV and measuring the spectrum directly. In ethanol, the spectrum showed peaks at 240 mμ (ϵ 11,100), 248 (shoulder, 9000), 282 (10,000), *ca.* 290 (shoulder, 9200), *ca.* 325 (shoulder, 7800), 338 (9200), and *ca.* 354 (shoulder, 6900). In ether, this spectrum decayed with a half-life of about 3 hr at room temperature; after 2 days the spectrum showed only two peaks at 238 mμ (ϵ *ca.* 7000) and 289 mμ (ϵ *ca.* 3000). In ethanol no substantial change in the ultraviolet spectrum of VI occurred during several hours. Over longer periods, decomposition occurred; no evidence of tautomerism to VIII or VII was found in ethanol solution.

The infrared spectrum of VI showed bands at 3600–2200 (s, broad), 1550 m, 1515 w, 1460 m, 1370 m, 1325 m, 1253 s, and 957 cm^{-1} m. As the sample stood at room temperature these bands disappeared slowly. After 20 hr, the spectrum showed bands at 1603 w, 1553 s, 1481 w, 1460 m, 1439 w, and 1359 cm^{-1} s.[21]

The nmr spectra of VI, VIII, and VII are given in Table I. The solution of VI in chloroform-*d* was kept at −78° between its preparation and obtaining the initial nmr spectrum.

9-*aci*-Nitrofluorene (I) and 9-Nitrofluorene (II).[21]—Compound I was prepared in small quantities as needed by acidification of water solutions of V with dilute hydrochloric or sulfuric acids. It was collected by filtration and dried for up to 1 day *in vacuo* over KOH. The material was a cream solid; typical mp 116–118° (lit.[4] mp 134.5–137°). The only impurity detected by spectral methods was water.[22]

The ultraviolet spectrum of I dissolved in 95% ethanol was identical with that of V.[7] Addition of 1 drop of sulfuric acid to this solution or to a solution made by dissolving V in 95% ethanol gave the spectrum of I, which showed bands at *ca.* 231 mμ (shoulder, ϵ 6200), 236 (6900), 256 (3700), 266 (3600), *ca.* 294 (1700), *ca.* 327 (shoulder, 2100), and 338 (2400). This spectrum persisted with little or no change for at least 18 hr. The same spectrum could be obtained directly by dissolving I in THF or ether; however, the spectrum slowly changed over the course of several hours to one showing maxima at 245, 253, and 271 mμ (broad shoulder). Addition of base after 25 hr did not regenerate the anion VI, showing irreversible changes after tautomerism.[3b]

The infrared spectrum of I as a Nujol mull was similar to that reported,[4] but with fewer small bands in the fingerprint region. I was insufficiently soluble in nonpolar solvents to give usable solution spectra.

The nmr spectrum of I freshly dissolved in THF showed three multiplets centered at τ 1.85, 2.30, and 2.70, relative areas about 1:1:2, due to the aromatic protons, and a somewhat broadened singlet at τ 2.1. After the sample had stood at room temperature for 24 hr, the O–H resonance had moved upfield to τ 3.1; after 3 more days, it had reached τ 4.2 and the aromatic pattern was largely collapsed to a single broad multiplet from τ 2.2 to 3.1. Addition of 1 drop of water moved the O–H resonance to τ 5.0 and raised its intensity.

O-Benzoyl-1-*aci*-nitroindene (XII).—A solution of benzoyl chloride (2.50 g, 0.018 mol) in ether was added slowly to a cooled solution of 3.00 g of the salt IV (0.015 mol) in 20 ml of methanol. Fine orange crystals precipitated almost at once. Filtering, washing with water, and drying gave 3.97 g of XII (78% crude yield). Recrystallization from benzene gave material of mp 118–119.5° dec (lit.[2] mp 121° dec[23]).

Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.07; H, 4.15; N, 5.21. Found: C, 72.16; H, 4.18; N, 5.07.

Compound XII was insoluble in 10% aqueous KOH, but soluble in Claisen's potash. Dilution of this solution with methanol gave a solution whose ultraviolet spectrum was that of the salt IV. Compound XII itself in hexane gave an ultraviolet spectrum very similar to that of VI: λ_{max} 238 mμ (ϵ 15,200), *ca.* 275 (shoulder, 9600), 283 (10,900), *ca.* 292 (shoulder, 9400), *ca.* 325 (shoulder, 7800), 336 (9500), and 351 (shoulder, 6600).

The infrared spectrum of XII as a Nujol mull showed bands at 1764 m, 1600 s, 1447 m, 1370 w, 1346 m, 990 m, broad, 813 m, 752 m, and 699 cm^{-1} m. The nmr spectrum in acetone is described in Table I.

O-Benzoyl-9-*aci*-nitrofluorene (XI).[21]—XI was prepared in the same manner as XII, in 75% yield. Recrystallization from hexane–benzene brought the melting point to 126.5–127.5° (lit.[19b] mp 134–135°[23]).

Anal. Calcd for $C_{20}H_{13}NO_3$: C, 76.20; H, 4.13; N, 4.45. Found: C, 76.40; H, 4.35; N, 4.70.

The ultraviolet spectrum of XI in ethanol was similar to that of I, showing maxima at 231, 254, 263, 321, and 336 mμ with essentially the same intensity relationships as I. Dilution of a solution of XI in Claisen's potash with methanol gave the ultraviolet spectrum of salt V. The infrared spectrum of XI as a Nujol mull showed bands at 1754 s, 1616 s, 1590 sh, 1399 s, 1081 m, 1000 m, 954 m, 775 s, 732 s, and 697 cm^{-1} s. The nmr spectrum showed two groups of aromatic protons, centered at τ 1.78 and 2.5 in about a 1:4 ratio.

Registry No.—I, 15206-29-8; II, 14544-96-8; III, 10236-21-2; IV, 15153-27-2; VI, 15095-56-4; VII, 15095-57-5; VIII, 15095-58-6; XI, 15095-51-9; XII, 15095-59-7.

Acknowledgments.—This work was supported in part by a F. G. Cottrell Grant from the Research Corp. We wish to thank Mr. Albert Porter for performing some of the experiments in the nitrofluorene series.

(21) This experiment was performed by Mr. Albert Porter.

(22) A sample dried for only 10 min after filtration gave a higher melting point, 125–128°. A comparison of our ir spectra (*vide infra*) with that of Freeman and McCallum[4] shows our materials to be the same, save that the O–H band of our material (*ca.* 3500–2500 cm^{-1}) is at higher frequency than theirs (*ca.* 3000–2000 cm^{-1}). Conceivably their higher melting material is a hydrate of I.

(23) The melting point of this compound is strongly dependent on the rate of heating and is not therefore a reliable physical constant.

Synthesis, Stereochemistry, and Solvolysis of 2-Bromobicyclopropyl and Closely Related Structures

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Received September 11, 1967

The syntheses of *cis*- and *trans*-2-ethylcyclopropyl bromide (**10**), *cis*- and *trans*-2-vinylcyclopropyl bromide (**5**), and *cis*- and *trans*-2-bromobicyclopropyl (**8**) have been carried out and stereochemistry has been established for each isomer. The relative rates of solvolysis of each isomer (cyclopropyl bromide ≡ 1) and values for $\Delta H^{\pm}$ (in kilocalories per mole) and $\Delta S^{\pm}$ (in entropy units) are as follows: *trans* **8**, 7340, 23.9, −7.7; *cis* **8**, 379, 25.9, −8.8; *trans* **5**, 1180, 19.9, −25.8; *cis* **5**, 103, 19.3, −27.6; *trans* **10**, 361, 20.6, −22.2; *cis* **10**, 17.8, 22.4, −23.1. The *trans* to *cis* rate ratios of 11.5–20.3 are consistent with orbital symmetry considerations. The rate enhancement upon going from the 2-ethyl to the 2-cyclopropyl substituent is entirely due to a more positive $\Delta S^{\pm}$ and is rationalized in terms of charge delocalization into the substituent ring in the transition state.

Except for recent investigations of the solvolyses of several simple alkyl- and aryl-substituted cyclopropyl derivatives for the purpose of examining Woodward–Hoffmann predictions of the preferred stereochemistry of ring opening,[2] relatively little systematic information exists on the nature of the transition states for such reactions.

Because the cyclopropyl group has an exceptional ability to stabilize an adjacent carbonium ion,[3] its use as a substituent on a second system undergoing limiting solvolysis could lead to interesting data on transition state charge distribution. For example, unique solvolysis behavior has already been reported for 1-chlorobicyclopropyl.[4] In the following study the solvolytic behavior of *cis*- and *trans*-2-cyclopropyl, -2-vinyl, and -2-ethylcyclopropyl bromides will be reported.

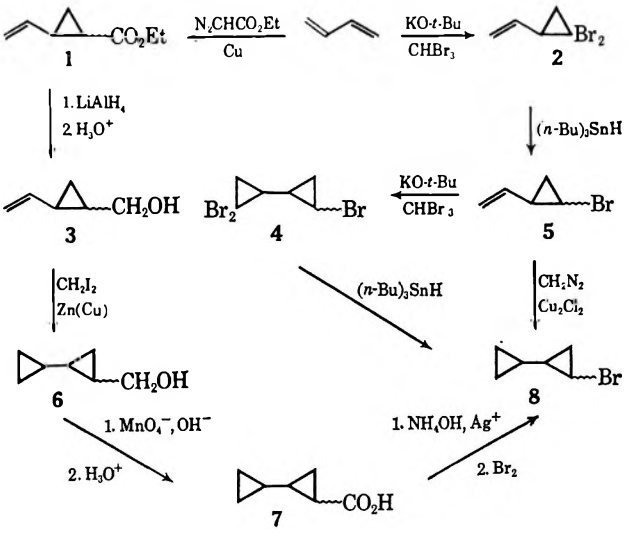
Synthesis and Stereochemistry

Various synthetic routes used for the preparation of 2-bromobicyclopropyl (**8**) and 2-vinylcyclopropyl bromide (**5**) are outlined in Scheme I.

A mixture of 68% *cis*- and 32% *trans*-2-vinylcyclopropyl bromide (**5**)[5] was conveniently converted into *cis*- and *trans*-2-bromobicyclopropyl (**8**) by the cuprous chloride catalyzed addition of diazomethane.

The over-all yield of **8** from 1,3-butadiene was 40%. It is interesting to note that the isomer distributions in **5** and **8** were essentially identical regardless of whether **5** was converted directly into **8** as previously described or by way of 2,2,2′-tribromobicyclopropyl **4**, consistent with the expected similarity in the stereochemical fate of the reaction leading from **2** to **5** with that for the reaction leading from **4** to **8**. The reduction of **2** to **5** with methylmagnesium bromide[6] gave essentially the same product isomer distribution as the tri-*n*-butyltin hydride reduction.

SCHEME I



Because of the complexity of the nmr spectrum of **5**, previous stereochemical assignments[5] were based on the observation that *cis* products predominate during the partial reduction of 1,1-dihalocyclopropanes with tri-*n*-butyltin hydride[7] (Table I), in accord with the belief that the reaction is a radical-chain process in which hydrogen is transferred from tri-*n*-butyltin

TABLE I

SELECTED DATA ON THE PARTIAL REDUCTION OF *gem*-DIHALOCYCLOPROPANES WITH TRI-*n*-BUTYLTIN HYDRIDE

Dihalocyclopropane	*cis* product, %	$\Delta\delta_{CHX}$ (*cis*–*trans*), ppm[a]
1,1-Dibromo-2,2,3-trimethylcyclopropane	80[b]	0.45
7,7-Dibromonorcarane	71.4[b]	0.61
1,1-Dibromo-2-ethylcyclopropane (**10**)	68,[c] 60[d]	0.46
2,2,2′-Tribromobicyclopropyl (**4**)	68[c]	0.42
1,1-Dibromo-2-vinylcyclopropane (**2**)	67.7[b]	0.36
7,7-Dichloronorcarane	65.5[e]	0.55

[a] Stereochemical designation refers to the halogen. [b] See ref 5. [c] This work. [d] G. L. Gloss and J. J. Coyle, *J. Amer. Chem. Soc.*, **87**, 4270 (1965). [e] See ref 2d.

(1) Taken from the Ph.D. Dissertation of L. W. B., University of Kansas, 1967.

(2) (a) P. von R. Schleyer, G. W. Van Dine, U. Schöllkopf, and J. Paust, *J. Amer. Chem. Soc.*, **88**, 2868 (1966); (b) C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966); (c) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *ibid.*, **87**, 4006 (1965); (d) S. J. Cristol, R. M. Sequeira, and C. H. DePuy, *ibid.*, **87**, 4007 (1965).

(3) P. von R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966), and references cited therein.

(4) J. A. Landgrebe and L. W. Becker, *ibid.*, **89**, 2505 (1967).

(5) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963).

(6) D. Seyferth and B. Prokai, *ibid.*, **31**, 1702 (1966).

(7) In contradiction to these observations, Cristol and DePuy[2d] have reported that the reduction of 3,3-dichlorodibenzotricyclo[3.3.2.0^{2,4}]nonadiene with triphenyltin hydride produced the *anti*-monochloride in 61% yield.

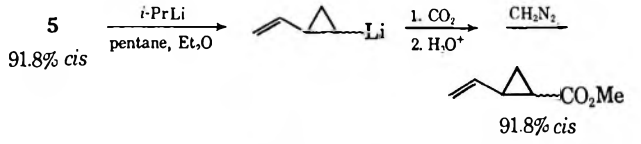
hydride to the least hindered side of a 1-halocyclopropyl radical.[8]

Although proton nmr coupling constants are useful in the assignment of stereochemistry to various substituted cyclopropyl derivatives,[5,2d] the complexity of a spectrum often precludes a straightforward determination of the appropriate values. For this reason it should be noted that the chemical shift of the proton on the halogen-bearing carbon atom for a variety of *cis*-2-substituted cyclopropyl halides (Table I) is ~0.48 ppm further downfield than that for the *trans* isomer and therefore provides a useful additional criterion for the identification of the geometric isomers.

In order to provide a more conclusive chemical proof of the stereochemistry of bromides **5** and **8**, a mixture of *cis* and *trans* **5** was related to ethyl *cis*- and *trans*-2-vinylcyclopropanecarboxylate (**1**), the stereochemistry of which had been previously established by oxidation and hydrolysis of the pure isomers to the well-known *cis*- and *trans*-1,2-cyclopropanecarboxylic acids.[9]

The copper-catalyzed decomposition of ethyl diazoacetate in the presence of 1,3-butadiene produced a 55:45 mixture of *trans* and *cis* **1** in agreement with the previously reported uncatalyzed, thermal reaction.[9,10] As expected, equilibration of the isomers with sodium ethoxide in refluxing ethanol resulted in an increase in the extent of the *trans* isomer from 55 to 91%. The ester mixture was then carefully saponified and by means of diazomethane converted into the methyl esters of the same isomeric composition.

The mixture of bromides **5** (91.8% *cis*) was then allowed to undergo halogen–metal interchange with isopropyllithium in 94% pentane, 6% diethyl ether, conditions for retention of configuration for the resulting cyclopropyllithium,[11] followed by carbonation and



treatment of the carboxylic acid with diazomethane to give a mixture of methyl *cis*- and *trans*-2-vinylcyclopropane carboxylate (91.8% *cis*) which could be directly compared (vpc) with the previously prepared sample.

A second synthetic route to **8** involved the conversion of ester **1** into 2-carboxybicyclopropyl (**7**)[12] followed by a Hunsdiecker reaction on the corresponding silver salt to give a mixture of *cis* and *trans* **8** in a ratio of 28:72. The same reaction carried out on *cis*- and *trans*-2-methylcyclopropanecarboxylic acid by Applequist and Peterson[13] produced a 34:66 ratio of the *cis* to the *trans* product.

(8) (a) H. G. Kuivila, L. W. Menapace, and C. R. Warner, *J. Amer. Chem. Soc.*, **84**, 3584 (1962); (b) H. G. Kuivila and E. J. Walsh, Jr., *ibid.*, **88**, 571, 576 (1966); (c) K. Sisido, S. Kozina, and K. Takizawa, *Tetrahedron Lett.*, 33 (1967).

(9) E. Vogel, R. Erb, G. Lenz, and A. A. Bothner-By, *Ann.*, **682**, 1 (1965).

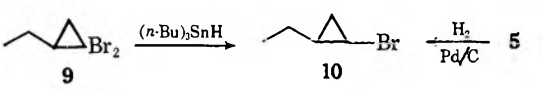
(10) I. S. Lishanskii, A. G. Zak, I. A. D'Yakonov, and T. G. Alievn, *Zh. Org. Khim.*, **1**, 1189 (1965).

(11) D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, **83**, 862 (1961).

(12) Because the Simmons–Smith reaction carried out on **3** gave inconsistent results, it was found advantageous to treat the acetate of **3** with phenyltribromomethylmercury followed by tri-*n*-butyltin hydride reduction of the *gem*-dibromocyclopropane to the acetate of **6**.

(13) D. E. Applequist and A. H. Peterson, *ibid.*, **82**, 2372 (1960).

The synthesis of *cis*- and *trans*-2-ethylcyclopropyl bromides (**10**) was accomplished by the tri-*n*-butyltin hydride reduction of 1,1-dibromo-2-ethylcyclopropane (**9**)[14] to give a 68:32 ratio of the *cis* to the *trans* isomer.



The stereochemical assignments were confirmed by a direct vpc comparison of **10** with the products of catalytic hydrogenation of **5**.

Kinetics

Solvolysis rate data were obtained in 50 vol % aqueous ethanol for *cis*–*trans* mixtures of bromides **5**, **8**, and **10** by means of the usual method for handling parallel first-order processes with a common product (see Experimental Section). In every instance the relative amounts of the *cis* and *trans* isomer present in the mixture as determined from the kinetic data were within ±0.5% of the values determined by vpc methods. Absolute and relative rate constants are tabulated in Tables II and III and the corresponding activation parameters are in Table IV.

TABLE II
SOLVOLYSIS RATES FOR 2-SUBSTITUTED CYCLOPROPYL BROMIDES IN 50 VOL % AQUEOUS ETHANOL

Substituent	Isomer	Temp,[a] °C	k,[b] sec^{-1}
Cyclopropyl (**8**)	*trans*	80.0	2.44×10^{-4}
		95.0	1.02×10^{-3}
	cis	80.0	8.38×10^{-6}
		95.0	3.93×10^{-5}
Vinyl (**5**)	*trans*	95.0	2.65×10^{-4}
		105.0	5.59×10^{-4}
	cis	95.0	2.46×10^{-5}
		105.0	5.08×10^{-5}
Ethyl (**10**)	*trans*	110.0	2.13×10^{-4}
		120.0	4.34×10^{-4}
	cis	110.0	1.01×10^{-5}
		120.0	2.21×10^{-5}

[a] Temperature variation $\leq \pm 0.1°$. [b] All rate constants were determined by the method of least squares with a probable error of $\leq \pm 1\%$. Each value represents the average of two runs with an average deviation of $\leq \pm 2\%$.

TABLE III
RELATIVE RATES OF SOLVOLYSIS OF SUBSTITUTED CYCLOPROPYL BROMIDES IN 50 VOL % AQUEOUS ETHANOL AT 130°

Substituent	k, sec^{-1}	k_{rel}
Hydrogen	2.6×10^{-6} [a]	1.0
1-Methyl	1.05×10^{-4} [a]	40.4
2,2-Propano	2.35×10^{-3} [b]	904
trans-2-Cyclopropyl (**8**)	1.91×10^{-2}	7340
cis-2-Cyclopropyl (**8**)	9.87×10^{-4}	379
trans-2-Vinyl (**5**)	3.08×10^{-3}	1180
cis-2-Vinyl (**5**)	2.67×10^{-4}	103
trans-2-Ethyl (**10**)	9.40×10^{-4}	361
cis-2-Ethyl (**10**)	4.64×10^{-5}	17.8

[a] E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 2719 (1961). [b] J. A. Landgrebe and D. E. Applequist, *ibid.*, **86**, 1536 (1964).

(14) See Table I, footnote *d*.

TABLE IV
SUMMARY OF ACTIVATION PARAMETERS FOR 2-SUBSTITUTED CYCLOPROPYL BROMIDES

Substituent	Isomer	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Cyclopropyl (8)	*trans*	23.9 ± 0.8	−7.7 ± 2.2
	cis	25.9 ± 0.1	−8.8 ± 0.2
Vinyl (5)	*trans*	19.9 ± 0.5	−25.8 ± 1.2
	cis	19.3 ± 0.5	−27.6 ± 1.2
Ethyl (10)	*trans*	20.6 ± 0.9	−22.2 ± 2.2
	cis	22.5 ± 1.1	−23.1 ± 2.7

A significant solvolysis rate enhancement upon introduction of alkyl substituents into the 2 position of cyclopropyl bromide has been observed previously[15] and is entirely consistent with positive charge delocalization to the substituted position in the transition state.

In general agreement with the results for acetolyses of various di- and trimethyl-substituted cyclopropyl tosylates[2a] and 2-phenylcyclopropyl tosylate,[2b,c] the *trans* isomers of **5**, **8**, and **10** all solvolyzed 11.5–20.3 times faster (Table III, 130°) than the corresponding *cis* isomers. Thus one can visualize a slight release of nonbonded strain as the *trans* isomer approaches the transition state and a similar slight increase in strain

in the *cis* isomer.[2a] The *trans* to *cis* rate ratios for the cyclopropyl and ethyl substituents, 19.4 and 20.3, respectively, are in accord with the expected similarity in the size of the two groups.[16,17] The factor of 11.5 for the *trans*-to-*cis* rate ratio for 2-vinylcyclopropyl bromide is again consistent with the known smaller effective size of this group compared to ethyl.[18,19]

In view of the similarity of the reported σ_m values for cyclopropyl, −0.102[20] or −0.07,[21] and ethyl, −0.07,[22] as well as the similarity in size previously mentioned,[16] the rate ratio of *trans* **8** to *trans* **10**, 20.3, and that of *cis* **8** to *cis* **10**, 21.3, cannot be rationalized in terms of steric or inductive differences. Charge delocalization into the cyclopropyl substituent in the transition state is clearly implied. A comparison of activation parameters (Table IV) for bromides **8** and **10** is particularly instructive. While the $\Delta S^{\ddagger}$ values for both *cis* and *trans* **10** are substantially negative, those for *cis* and *trans* **8** are only slightly negative. The $\Delta H^{\ddagger}$ values for both *cis* and *trans* **10** are actually less than those for the corresponding *cis* and *trans* **8**.

(15) See Table III, footnote *b*.

(16) Although the conformational A value for the cyclopropyl group is not known, the corresponding values for ethyl and isopropyl are 1.80 and 2.12, respectively,[17] and one would expect the value for cyclopropyl to be slightly smaller than that for isopropyl.

(17) N. L. Allinger, L. A. Freiberg, and S. E. Hu, *J. Amer. Chem. Soc.*, **84**, 2836 (1962).

(18) The conformational A value for vinyl is ~1.35.[19]

(19) R. J. Ouellette, K. Kiptak, and G. E. Booth, *J. Org. Chem.*, **31**, 546 (1966).

(20) Determined from the pK_a (5.90) of *m*-cyclopropylbenzoic acid in 50 vol % aqueous ethanol at 25.0° by Dr. Ronald H. Rynbrandt.

(21) J. Smejkal, J. Jones, and J. Furkas, *Collection Czech. Chem. Commun.*, **29**, 2950 (1964).

(22) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

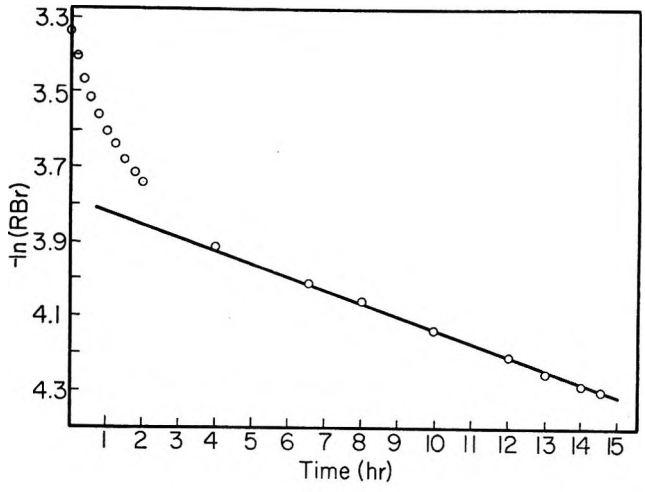


Figure 1.

Thus the increase in rate on going from the ethyl- to the cyclopropyl-substituted system is entirely due to a more positive $\Delta S^{\ddagger}$ in the latter system, a result which can be rationalized by assuming some degree of ring opening of the cyclopropyl substituent at the time of the transition state.

In contrast to bromides **8** are *trans*- and *cis*-2-vinylcyclopropyl bromides (**5**) which solvolyze 3.28 and 5.76 times faster than the corresponding ethyl-substituted compounds. In this case the rate difference can be attributed to the smaller $\Delta H^{\ddagger}$ for **5** compared with **10**, since $\Delta S^{\ddagger}$ for **5** is actually more negative than that for **10**. Because the σ_m for vinyl has been reported as +0.30,[23] the observed increase in rate on going from the ethyl to the vinyl substituent must be caused by favorable charge delocalization in the transition state for solvolysis of the latter system.

Further speculation on the nature of the transition states for solvolyses of **5**, **8**, and **10** must await a detailed product analysis.

Experimental Section[24]

Ethyl *cis*- and *trans*-2-Vinylcyclopropane Carboxylate (1).—Ethyl diazoacetate, generated from 0.893 mole of glycine ethyl ester hydrochloride,[25] was added dropwise (30 min) to 1,3-butadiene (400 ml, 260 g, 4.82 mol). Freshly prepared cuprous chloride[26] (1 g) was then added to the rapidly stirred solution followed by the addition of copper–bronze powder (1 g). Within 15 min, nitrogen evolution began, accompanied

(23) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3452 (1953)

(24) All elemental analyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo. Meeting points were taken on a Thomas–Hoover apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were obtained in carbon tetrachloride solution from a Beckman IR-8 (sodium chloride optics) with a 1603-cm^{-1} peak (polystyrene *vs.* air) as a reference. Mass spectra were obtained on Nuclide Analysis Associates Model 12-90G instrument. Analyses by gas chromatography were done on an F & M Model 700 instrument (thermal conductivity) with the following columns: 20% QF-1 on 30/60 Chromosorb P (15 ft × 0.25 in.); 20% β,β'-oxydipropionitrile on 30/60 Chromosorb P (12 ft × 0.25 in.); 20% Carbowax 1540 on 30/60 Chromosorb P (12 ft × 0.25 in.); 20% Hyprose B on 30/60 Chromosorb P (12 ft × 0.25 in.); 20% tris(cyanoethoxy)propane on 30/60 Chromosorb P (12 ft × 0.25 in.); 7.6% silver nitrate, 8.4% tetraethylene glycol, and 84% 3-nitro-3-methylpimelonitrile on 80/100 Chromosorb W (9 ft × 0.25 in.). All isomeric compounds were assumed to have equal gas chromatographic sensitivity factors. Nuclear magnetic resonance spectra were obtained on a Varian A-60 or A-60-A spectrometer as solutions in carbon tetrachloride with internal tetramethylsilane standard unless otherwise specified. Chemical shifts are expressed in τ units.

(25) N. E. Searle, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, pp 424–426.

(26) R. Q. Brewester, C. A. VanderWerf, and W. E. McEwen, "Unitized Experiments in Organic Chemistry," D. Van Nostrand Co., Inc., Princeton, N. J., 1960, p 151 (procedure a).

by increased reflux rate and a gradual darkening of the solution. After 15 hr, the excess 1,3-butadiene was allowed to evaporate and the residual oil (from two runs) gave 60.0 g (0.43 mol, 24% based on glycine ethyl ester hydrochloride) of a sweet smelling liquid, bp 69–74.5° (10 mm) (lit.[9] bp 61–62° (12 mm)). Fractionation with a short Vigreux column gave 2.0 g, bp 57–69° (10 mm); 38.7 g, bp 69–72° (10 mm); and 18.5 g, bp 72–74.5° (10 mm). Vpc of the distillate before fractionation (Carbowax 1540, 115°) showed two peaks (98% of total) with relative areas of 55:45 in order of increasing retention times assigned to *trans* and *cis* isomers, respectively (see Discussion). High-boiling residue consisted mainly of diethyl fumarate and maleate.

The nmr spectrum of the mixture of isomers showed a complex multiplet at 3.90–5.25 (3 H), a quartet at 5.97 (2 H, J = 7 cps), a triplet at 8.80 (3 H, J = 7 cps), and a complex multiplet at 7.82–9.32 (4 H). The infrared spectrum showed significant absorptions at 3100 (w), 3000 (w), 1725 (s), 1640, 1380, 1175, 1165, 1034 (cyclopropyl), and 905 cm^{-1}. A mass spectrum showed a parent peak at m/e 140.

Equilibration of Ethyl *cis*- and *trans*-2-Vinylcyclopropanecarboxylate.—An isomeric mixture of ethyl 2-vinylcyclopropanecarboxylate (14.0 g, 0.10 mol, 55% *trans*) in absolute ethanol (25 ml) was added to a solution of sodium ethoxide (prepared from 0.10 g-atom of sodium) in absolute ethanol (50 ml) and the yellow solution was maintained at reflux (100 hr). Vpc analysis (Carbowax 1540, 115°) of the isolated ethyl 2-vinylcyclopropanecarboxylate showed 91% of the *trans* isomer (shorter retention time) to be present.

***cis*- and *trans*-2-Vinylcyclopropylcarbinol (3).**—Ester **1** (70.1 g, 0.50 mol, 55% *trans*) in ether (100 ml) was added to an ether slurry of lithium aluminum hydride (20.0 g, 0.53 mol) under a nitrogen atmosphere. After 1 hr at reflux, the reaction mixture was worked up in the usual manner and the product alcohol (42.0 g, 0.43 mol, 87.7%) was distilled, bp 73–74° (9.0 mm). Vpc (Carbowax 1540, 195°) indicated <1% impurity. Several vpc columns failed to separate the *cis* and *trans* isomers.

The nmr spectrum showed a complex multiplet at 4.08–5.33 (3 H), a multiplet at 6.30–6.70 (2 H), a multiplet at 8.15–9.75 (4 H), and the broad singlets (1 H) which shifted with the introduction of a trace of hydrogen chloride. The infrared spectrum showed significant absorptions at 3350, 3020, 2880, 1635, 1510, 1037 (cyclopropane), and 895 cm^{-1}. The mass spectrum showed a parent peak at m/e 98.

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: 73.17; H, 10.16.

***cis*- and *trans*-2-Vinylcyclopropylcarbinyl Acetate.**—Carbinol **3** (9.8 g, 0.10 mol) in dry ether (100 ml) which contained pyridine (7.9 g, 0.10 mol) was treated with acetyl chloride (9.0 g, 0.10 mol) in ether (25 ml) while the flask was cooled in an ice–salt bath. After 30 min, the reaction mixture was poured into water (200 ml) and the ether layer was treated in the usual manner and concentrated to give, after distillation, 10.5 g (0.075 mole, 75.6%) of colorless ester, bp 46–47° (5 mm).

Vpc (QF-1, 143°) showed two components (97%) with relative areas of 55:45 in order of increasing retention times assigned to the *trans* and *cis* isomers, respectively. The nmr spectrum of the isomeric mixture showed a complex multiplet at 4.20–5.33 (3 H, ABC pattern), a doublet at 6.13 (J = 6.8 cps) superimposed on a multiplet at 6.0–6.18 (total 2 H), a singlet at 8.04 (3 H), and a complex multiplet at 8.29–9.70 (4 H). The infrared spectrum showed absorptions at 3100 (w), 3030 (w), 1740, 1640, 1368, 1230, 1040, 1025 (cyclopropane), and 900 cm^{-1}.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.39.

***cis*- and *trans*-2-Hydroxymethylbicyclopropyl (6). Simmons–Smith Method.**—Methylene iodide (300 g, 1.12 mol) was slowly added to a slurry of zinc–copper couple[27] (125 g, 1.91 g-atoms) in dry ether (300 ml) to which a few iodine crystals had been added to initiate the reaction. When the reagent had been prepared, 2-vinylcyclopropylcarbinol (28.5 g, 0.29 mole) in ether (50 ml) was added so as to maintain reflux and the mixture was stirred at reflux for 48 hr. After hydrolysis with saturated aqueous ammonium chloride (300 ml), the excess zinc was removed and the aqueous layer was extracted with ether. The residue after the ether was evaporated was allowed to remain in contact with concentrated sodium methoxide in methanol (50 ml) overnight. After an aqueous work-up the resulting oil was distilled to give 20.0 g of a colorless liquid, bp 67–68° (5 mm). Vpc (Carbowax 1540, 195°) showed a large peak (85–90%) and numerous impurity peaks. There was no separation of *cis* and *trans* isomers.

The nmr spectrum of a purified sample showed a multiplet at 5.55–6.0 (1 H), a multiplet at 6.25–6.83 (2 H), and a complex absorption at 8.3–10.0 (10 H). The infrared spectrum showed significant absorptions at 3400, 3100, 3030, 2880, 1033, and 1015 cm^{-1}.

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.79. Found: C, 74.80; H, 10.74.

Copper-Catalyzed Addition of Diazomethane to Olefins.—Ether (25 ml) and 50% aqueous potassium hydroxide (50 ml) were added to a 100-ml, three-necked flask (nonstandard taper) which was being magnetically stirred and cooled with an ice bath. A capillary tube was placed beneath the ether layer and attached to a nitrogen supply by Tygon tubing. The other outlet of the flask was connected to a potassium hydroxide pellet drying tower which was in turn connected to another three-necked flask with a capillary tube. As the diazomethane precursor was added to the generator, a slow stream of nitrogen was bubbled through the ether layer which carried the diazomethane through the drying tower to the reaction flask and through the capillary tube to the etherate olefin solution. This flask contained the olefin, the solvent, and the cuprous chloride and was also cooled and stirred. The reactions were monitored by vpc and nmr. It was necessary to replenish periodically the ether supply in the generator depending on the flow rate of nitrogen which carried some ether into the reaction flask. The concentration of the diazomethane in the ether layer of the generator was kept low. Usually, 1 g of the diazomethane precursor was added per 25 ml of ether and maintained as such until all the diazomethane had been used as indicated by the absence of yellow color. Depending on the amount of diazomethane passage per unit time, the color of the cuprous chloride in the reaction varied from white to black. Rapid passage caused the salt to turn black, but the black color would gradually change to white in the presence of an olefin if the rate of diazomethane passage was decreased.

***cis*- and *trans*-2-Hydroxymethylbicyclopropyl (6). Diazomethane Method.**—2-Vinylcyclopropylcarbinol (5.0 g, 0.047 mol), cuprous chloride (1 g), and absolute ether (35 ml) were treated with diazomethane as previously described. Complete conversion could be obtained only by the use of a large excess of diazomethane.

***cis*- and *trans*-2-Carboxybicyclopropyl (7).**—2-Hydroxymethylbicyclopropyl (19.0 g, 0.17 mol, 90% purity) was slowly added to a stirred cooled solution of potassium permanganate (5.0 g) and potassium hydroxide (2.0 g) in water (250 ml). Additional permanganate (1-g portions) was added until the color persisted and the excess oxidizing agent was destroyed with 95% ethanol. Water was added to bring the total volume to 750 ml and sodium bisulfite was used to reduce the manganese dioxide. Two ether extracts were discarded and the aqueous layer was acidified with 6 N hydrochloric acid and extracted with ether. Attempts to purify the crude acid product (16.0 g, 0.127 mole, 75%) by distillation resulted in considerable decomposition. The reported boiling point is 100° (4 mm).[28]

The nmr spectrum showed a singlet at −2.05 (1 H) and a complex absorption at 8.0–10.0 (10 H). The infrared spectrum showed absorptions at 3400–2300 (broad), 1670, 1425, 1035, and 1010 cm^{-1}.

***cis*- and *trans*-2-Carbomethoxybicyclopropyl** was obtained by treatment of the acid (10 g, 0.079 mol) with diazomethane in ether. The yellow oil (10.7 g, 0.076 mol, 96.3%), bp 63–64° (4 mm), gave an nmr spectrum which showed singlets at 6.36 and 6.40 (3 H) and a complex multiplet at 8.16–10.0 (9 H). The infrared spectrum showed significant absorptions at 3100, 3030, 2950, 1735, 1440, 1385, 1370, 1195, 1170, and 1148 cm^{-1}. The mass spectrum gave a parent peak at m/e 140 in addition to fragment peaks at 97, 95, 67, 58, 55, 43, 41, and 29. Vpc (Hyprose B, 135°) showed two components (99%) with relative areas 55:45 in order of increasing retention time.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.30; H, 8.57.

(27) R. S. Shank and H. Schechter, *J. Org. Chem.*, **24**, 1825 (1959).

(28) A. P. Meshcheryakov, V. G. Glukhovtsev, and N. N. Lemin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1901 (1961).

cis- and *trans*-2-Bromobicyclopropyl (8). **Hunsdiecker Method.**—The silver salt of 2-carboxybicyclopropyl was prepared from silver nitrate (14.6 g, 0.0856 mol) and the carboxylic acid (10.8 g, 0.0856 mol) by a procedurean alogous to that described by Applequist and Peterson.[13] The yield of dry salt (24 hr at 65° under vacuum) was 17.0 g (0.073 mol) or 85.4%.

The above salt was slowly added to a stirred, cooled (ice–salt bath) solution of bromine (6.9 g, 0.043 mol) in dry, alkene-free pentane (175 ml) under nitrogen, the mixture was allowed to warm to room temperature, the silver bromide was filtered, and the filtrate was evaporated to give the product (2.5 g, 0.0155 mole, 36.1%), bp 76–79° (74 mm).

The nmr spectrum showed multiplets at 7.02 and 7.38 (1 H), the latter absorption being more intense, and a complex multiplet at 8.2–10.0 (9 H). The infrared spectrum showed important absorptions at 3100, 3030, 1440, 1260, 1228, 1218, 1100, 1036, 1020, and 954 cm^{-1}. The mass spectrum showed small parent peaks at *m/e* 160 and 162 and an intense peak at *m/e* 81 ($C_6H_9^+$). The most intense peaks were at *m/e* 119 and 121 ($M^+ - c\text{-}C_3H_5$), with smaller fragments at 132 and 134. Vpc (QF-1, 70°) showed two components (98%) in the ratio 72:28 in order of increasing retention time.

Anal. Calcd for C_6H_9Br: C, 44.74; H, 5.63. Found: C, 45.05; H, 5.72.

1,1-Dibromo-2-vinylcyclopropane (2) was prepared in 60% yield by addition of dibromocarbene to 1,3-butadiene. The bp was 53–56° (10 mm) (lit.[29,30] bp 76–82° (50 mm) and 69.5–70° (26 mm)). The infrared and nmr spectra were consistent with the structural assignment.

cis- and *trans*-2-Vinylcyclopropyl Bromide (5). **Tri-*n*-butyltin Hydride Method.**—Bromides 5 were prepared in 75–80% yield by reduction of dibromide 2 with tri-*n*-butyltin hydride according to the method of Seyferth and coworkers.[5] Vpc (QF-1, 80°) indicated 30–32% of the *trans* isomer (shorter retention time). The nmr spectrum showed a complex multiplet at 4.07–5.20 (3 H), multiplets at 6.7–7.1 and 7.1–7.43 (1 H), and a complex absorption at 7.90–9.33 (4 H). The infrared spectrum showed significant absorptions at 3100, 3030, 1645, 1265, 1230, 1035, 985, and 907 cm^{-1}. The mass spectrum gave small parent peaks at *m/e* 146 and 148 and significant fragments at 67 ($C_5H_7^+$), 65, 44, 41, and 39.

Anal. Calcd for C_5H_7Br: C, 40.75; H, 4.80. Found: C, 40.59; H, 4.63.

Careful fractional distillation gave the following results: bp 60.0–62.5°, 1.2 g, 52.8% *cis*;[31] bp 62.5–65°, 3.8 g, 68.4% *cis*; bp 65.0–69.0°, 2.0 g, 75.8% *cis*; bp 69.0–76.5°, 7.0 g, 91.8% *cis* (lit.[5] bp of mixture 62–74° (90 mm)).

cis- and *trans*-2-Vinylcyclopropyl Bromide (5). **Methylmagnesium Bromide Method.**—Dibromide 5 (3.23 g, 0.022 mol) was slowly (20 min) added to a stirred solution of methylmagnesium bromide in tetrahydrofuran (14.6 ml, 1.51 *N*, 0.022 mol) under nitrogen.[6] The addition was exothermic and a second exothermic reaction occurred at the end of the 20 min together with the formation of a white precipitate. After 30 min, the mixture was hydrolyzed with water (100 ml) and extracted with ether. Vpc (QF-1, 70°) of the isolated bromides (5) indicated 70.9% of the *cis* isomer.

cis- and *trans*-2-Bromobicyclopropyl. **Diazomethane Method.**—2-Vinylcyclopropyl bromide (1.47 g, 0.01 mol, 75% *cis*) was treated with diazomethane and cuprous chloride in ether as previously described. After 90% conversion into the desired product mixture, vpc (QF-1, 70°) showed 77% of the isomer with the longer retention time. Admixture of these products with those from the Hunsdiecker procedure (vpc, QF-1 and β,β′-oxydipropionitrile) showed that they were identical but that the opposite isomer predominated.

Methyl *cis*- and *trans*-2-Vinylcyclopropanecarboxylate.—Ethyl 2-vinylcyclopropanecarboxylate (2.0 g, 0.0143 mol, 91% *trans*) was hydrolyzed with potassium hydroxide solution in the usual manner and the resulting acid was esterified with diazomethane to give the methyl ester (1.2 g, 0.0095 mol, 66.7%), bp 55.5–56.0° (10 mm). The nmr spectrum showed a complex absorption at 4.20–5.12 (3 H), a singlet at 6.34 (3 H), and a complex multiplet at 7.80–9.28 (4 H). The infrared spectrum showed significant absorptions at 3100, 2950, 1730, 1640, 1440, 1380, 1325, 1305, 1285, 1265, 1200, 1170, 980, and 905 cm^{-1}. The mass spectrum showed a parent peak at *m/e* 126 with significant fragments at *m/e* 111, 95, 67 ($M^+ - CO_2CH_3$), and 59 ($COCH_3^+$). Vpc (Carbowax 1540, 145°) showed two peaks in the ratio 91:9 in order of increasing retention times.

Stereospecific Conversion of *cis*- and *trans*-2-Vinylcyclopropyl Bromide to Methyl *cis*- and *trans*-2-Vinylcyclopropanecarboxylate.—The method of Applequist and Peterson[11] was used. A pentane solution of isopropyllithium (20 ml, 0.8306 *N*, 0.0166 mol) was cooled to 0° (N_2 atmosphere) and absolute ether (1.2 ml) was added followed by the rapid addition of 2-vinylcyclopropyl bromide (1.50 g, 0.01027 mol, 91.8% *cis*). After 5 min at 0°, the purple solution was added to finely powdered Dry Ice (100 g). Water (100 ml) was added, the mixture was allowed to warm to 25°, and hydrochloric acid was added to acidify the solution. The acid product was extracted into ether and treated with diazomethane to give 500 mg of ester. Vpc (Carbowax 1540, 145°) confirmed the identity of the ester isomers and indicated that the isomer of longer retention time was present as 91.6% of the mixture. Vpc comparison (Carbowax 1540 and Hyprose B) of the isomer mixture with a similar mixture from the treatment of ethyl diazoacetate with butadiene followed by conversion of the ethyl to the methyl ester confirmed the identity of isomers (see discussion).

cis- and *trans*-2,2,2′-Tribromobicyclopropyl (4).—2-Vinylcyclopropyl bromide (15.0 g, 0.104 mol, 32% *trans*) in dry, alkene-free pentane (100 ml) was added to a solution of potassium *t*-butoxide (prepared from 0.20 g-atom of potassium) under a nitrogen atmosphere. The mixture was stirred and cooled in an ice–salt bath while bromoform (40.0 g, 0.157 mol) was slowly added (1 hr). Stirring and cooling were continued for 12 hr, water (250 ml) was added, the aqueous layer was extracted with ether, and the ether was dried and evaporated to give the expected product (16.6 g, 0.052 mol, 50%), bp 91–95° (1.0 mm).

The nmr spectrum showed multiplets at 6.65–7.08 and 7.08–7.50 (1 H) and a complex multiplet at 7.8–9.5 (7 H). The infrared spectrum showed significant absorptions at 3030, 1425, 1260, 1150, 1035, 1008, and 685 cm^{-1}. The mass spectrum showed no parent peak but substantial fragments at *m/e* 241, 239, 237, 212, 201, 199, 197, 160, 159, 158, 157, 79, 78, and 77.

Anal. Calcd for $C_6H_7Br_3$: C, 22.60; H, 2.21; Br, 75.19. Found: C, 22.71; H, 2.21; Br, 74.98.

cis- and *trans*-2-Bromobicyclopropyl. **Tri-*n*-butyltin Hydride Method.**—Tri-*n*-butyltin hydride (25.0 g, 0.086 mol) was slowly added (2 hr) to cold (ice bath) stirred 2,2,2′-tribromobicyclopropyl (12.0 g, 0.0375 mol) under a nitrogen atmosphere. After being stirred at 25° for 70 hr, the mixture was distilled and redistilled, bp 79–82° (74 mm), to give bromide 10 (2.0 g, 0.0124 mol, 33%), identical in every respect, except isomer distribution, with the previously prepared material. Vpc (QF-1, 80°) indicated 68% of the *cis* isomer (98% over-all purity).

cis- and *trans*-2-Ethylcyclopropyl Bromide (10).—1,1-Dibromo-2-ethylcyclopropane (9) was prepared by the method of Skell and Garner[32] from bromoform, 1-butene, and potassium *t*-butoxide in an over-all yield of 52%, bp 62–64° (12 mm) (lit. bp 68–69° (30 mm)). The dibromide was reduced by tri-*n*-butylin hydride as previously described for 1,1-dibromo-2-vinylcyclopropane to give the final product (22.0 g, 0.148 mol, 74.3%), bp 105–120° (lit.[14] bp 47–52° (66 mm)). Nmr spectral data were consistent with those previously reported.[14] The mass spectrum showed parent peaks at *m/e* 148 and 150 as well as significant fragments at *m/e* 121, 119, 108, 106, 69 ($M^+ - Br$), 53, 42, and 41. Vpc indicate a *cis* to *trans* ratio of 68:32 (lit.[14] 60:40) with the two desired products representing 85% of the total product mixture. Careful fractionation gave the following results: 6.6 g, bp 100–110°, 52.4% *cis*, 27.6% impurity; 5.2 g, bp 110–114°, 57.3% *cis*, 17.8% impurity; 6.7 g, bp 114–117°, 67.5% *cis*, 4.9% impurity; 1.3 g, bp 117–117.5°, 81.9% *cis*, trace of impurity.

Anal. Calcd for C_5H_9Br: C, 40.29; H, 6.09; Br, 53.62. Found: C, 40.46; H, 6.00; Br, 53.36.

Hydrogenation of *cis*- and *trans*-2-Vinylcyclopropyl Bromide.—2-Vinylcyclopropyl bromide (1.47 g, 0.01 mol, 68% *cis*) was hydrogenated at atmospheric pressure in absolute methanol (10 ml) with palladium on charcoal (50 mg, 10%). The reaction was worked up in the usual manner after one-half the

(29) L. Skattebøl, *J. Org. Chem.*, **29**, 2951 (1964).

(30) R. C. Woodworth and P. S. Skell, *J. Amer. Chem. Soc.*, **79**, 2542 (1957).

(31) A low-boiling impurity (40%) was present.

(32) P. S. Skell and A. V. Garner, *ibid.*, **78**, 5430 (1956).

theoretical amount of hydrogen had been absorbed. Vpc analysis (QF-1, 45°) of the product mixture indicated 68% of *cis*-2-ethylcyclopropyl bromide (longer retention time). Vpc analysis of the mixture of these products with those from the previous reaction confirmed these conclusions.

cis- and *trans*-2-Acetoxymethylbicyclopropyl.—2-Vinylcyclopropylcarbinyl acetate (6.0 g, 0.043 mol, 55% *trans*) was treated with phenyltribromomethylmercury[33] (24 g, 0.045 mol) in anhydrous benzene (40 ml) at reflux under nitrogen for 3 hr. Phenylmercuric bromide was filtered from the cold solution and the filtrate was evaporated to give crude product which was not further purified.

The dibromide was reduced with tri-*n*-butyltin hydride (29.1 g, 0.10 mol) over a 72-hr period by the method previously described. The product (4.0 g, 0.023 mol, 60.5%) had a bp 87–91° (3–4 mm). The nmr spectrum showed doublets at 5.9 and 6.2 (2 H, J = 7 cps) with the doublet at 5.9 further split into doublets (J = 2 cps), singlets at 8.02 and 8.04 (3 H), and a complex multiplet at 8.65–10.1 (9 H). The infrared spectrum showed significant absorptions at 3100, 3030, 1745, 1385, 1235, 1025, and 970 cm^{-1}.

cis- and *trans*-2-Hydroxymethylbicyclopropyl from *cis*- and *trans*-2-Acetoxymethylbicyclopropyl.—2-Acetoxymethylbicyclopropyl (3.08 g, 0.02 mol) in ether (10 ml) was slowly added to a suspension of lithium aluminum hydride (1.14 g, 0.03 mol) in ether (25 ml) and maintained at reflux for 1 hr. After hydrolysis and work-up, 1.8 g (0.0184 mol, 80.4%) of crude product was isolated and shown by nmr and infrared spectral comparisons to be identical with the material prepared from 2-vinylcyclopropylcarbinol.

Solvolysis Procedure.—All kinetic experiments utilized a 12 × 12 in. Pyrex bath which contained *ca.* 5 gal. of oil (Cities Service, DC-915), a Lightnin Model L continuous duty stirrer, a hydrogen-jacketed thermoregulator, and a 500-W continuous-heat source which was connected to a Variac. Fine heating was controlled by a 40-W light bulb connected through a transistorized relay to the thermoregulator. The entire bath was surrounded by *ca.* 3 in. (of polyurethan foam and was covered by a 1-in. styrofoam lid.

The appropriate amount of halide was dissolved in *ca.* 50 ml of ethanol–water 50% by volume at 20.0°) and the solution (*ca.* 0.03–0.06 M in halide) was distributed among 19–20 ampoules each containing *ca.* 2.5 ml. The ampoules were sealed and placed in the bath (time started) and at appropriate time intervals ampoules were removed and quenched in ice-water. An exact aliquot (*ca.* 2 ml) was removed with a pipet calibrated with the same ethanol–water solution. The aliquot was diluted with *ca.* 10 ml of cold distilled water and the acid solution was titrated to a phenolphthalein endpoint with a sodium methoxide in methanol solution which had been standardized against potassium hydrogen phthalate. A 5-ml microburet which could be read directly to 0.01 ml was used. Infinity titrations were taken after 10 half-lives. Rate constants were determined by the method of least squares and the activation parameters were calculated from the Eyring equation. Good first-order kinetics were usually observed in ≤60% reaction.

(33) D. Seyferth and J. M. Burlitch, *J. Organometal. Chem.*, **4**, 127 (1965).

The data for a typical run are indicated in Table V and Figure 1 for the 50 vol % aqueous ethanol solvolysis of a mixture of 32% *trans*-2-ethylcyclopropyl bromide and 68% *cis*-2-ethylcyclopropyl bromide at 110 ± 0.1°. (There is a very rapidly solvolyzing 5% impurity present.)

TABLE V[a]

Time elapsed, min	Titrated HBr	−ln (RBr)	Time elapsed, min	Titrated HBr	−ln (RBr)
∞	0.03581	3.3301	120	0.01201	3.7389
10	0.002493	3.4025	240	0.01587	3.9156
20	0.004533	3.4656	390	0.01779	4.0171
30	0.005893	3.5100	480	0.01858	4.0623
45	0.007252	3.5165	600	0.01983	4.1373
60	0.008499	3.6010	720	0.2096	4.2108
75	0.009632	3.6436	780	0.02164	4.2578
90	0.01054	3.6788	840	0.02210	4.2903
105	0.01145	3.7154	870	0.02232	4.3068

[a] $k_{cis} = 1.03 \times 10^{-5}$ sec^{-1}.

The result of the usual analysis of the initial rate data from Table V (see Discussion) is recorded in Table VI.

TABLE VI[a]

Time elapsed, min	$(HBr)_{total} - (HBr)_{cis}$	$-\ln (RBr)_{trans}$	Time elapsed, min	$(HBr)_{total} - (HBr)_{cis}$	$-\ln (RBr)_{trans}$
∞	0.01297		75	0.00428	5.4549
20	0.00862	4.7545	90	0.00354	5.6447
30	0.00740	4.9072	105	0.00285	5.8616
45	0.00624	5.0777	120	0.00250	5.9926
60	0.00519	5.2619			

[a] $k_{trans} = 2.08 \times 10^{-4}$ sec^{-1}.

Registry No.—**1** (*cis*), 2183-89-3; **1** (*trans*), 2183-90-6; **3** (*cis*), 15135-97-4; **3** (*trans*), 15135-98-5; **4** (*cis*), 15135-99-6; **4** (*trans*), 15136-00-2; **5** (*cis*), 15136-01-3; **5** (*trans*), 15136-02-4; **6** (*cis*), 15136-03-5; **6** (*trans*), 15136-04-6; **7** (*cis*), 15136-05-7; **7** (*trans*), 15136-06-8; **8** (*cis*), 15136-07-9; **8** (*trans*), 15136-08-0; **10** (*cis*), 15136-09-1; **10** (*trans*), 15136-10-4; *cis*-2-vinylcyclopropylcarbinyl acetate, 15136-11-5; *trans*-2-vinylcyclopropylcarbinyl acetate, 15186-42-2; *cis*-2-carbomethoxybicyclopropyl, 15186-43-3; *trans*-2-carbomethoxybicyclopropyl, 15215-72-2; methyl *cis*-2-vinylcyclopropanecarboxylate, 15186-44-4; methyl *trans*-2-vinylcyclopropanecarboxylate, 7119-58-6; *cis*-2-acetoxymethylbicyclopropyl, 15186-46-6; *trans*-2-acetoxymethylbicyclopropyl, 15186-47-7.

Aralkyl Hydrodisulfides.[1] VIII. Alkaline Decomposition and Its Competition with Nucleophiles

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By reexamination of the reaction of benzyl hydrodisulfide with potassium hydroxide another mechanism has proved favorable, that involving proton abstraction followed by elimination of the hydrodisulfide ion. When a decreased amount of potassium hydroxide was added to the hydrodisulfide, a mixture of benzyl polysulfides was formed, the formation of which is attributed to hydropolysulfide ion. Nucleophilic attack by cyanide ion appears to proceed competitively with alkaline decomposition in the reaction of benzyl hydrodisulfide with potassium cyanide in aqueous dioxane. The formation of polysulfides in this case is also discussed.

A More Plausible Route for Alkaline Decomposition.—A previous study[2] has confirmed nucleophilic attack on both sulfur atoms of benzyl hydrodisulfide by anions. For the reaction with hydroxide ion, however, it appears that the following sequence also interprets the products, about 0.5 mol each of hydrogen sulfide, dibenzyl disulfide, and sulfur.

$$RSSH + OH^- \longrightarrow RSS^- + H_2O \quad (1)$$

$$RSSH + RSS^- \longrightarrow RSSR + HS_2^- \quad (1a)$$

$$HS_2^- \xrightarrow{H^+} H_2S + {}^1/_8S_8 \quad (1b)$$

Proton abstraction (eq 1) was once abandoned because the products and their amounts did not coincide with those from the assumed sequence[2] subsequent to eq 1. Then the nucleophilic attack on sulfenyl sulfur was considered.

$$RSSH + OH^- \longrightarrow [RSOH] + SH^- \quad (2a)$$

$$RSSH + [RSOH] \longrightarrow RSSR + [HSOH] \quad (2b)$$

$$[HSOH] \longrightarrow H_2O + {}^1/_8S_8 \quad (2c)$$

The objectives of this paper are to determine if the sequence in eq 1 is preferable to that in eq 2 in the reaction of the hydrodisulfide with alkali and to examine whether or not hydroxide ion in the reaction with the hydrodisulfide is competitive with nucleophiles (RS^-, CN^-, and SO_3^{2-}), since they give definite concentrations of hydroxide ion due to hydrolysis in aqueous solutions.

First, benzyl hydrodisulfide solution was added quickly to aqueous potassium hydroxide and immediately the resulting mixture was neutralized. Such treatment shows that the reaction of benzyl hydrodisulfide with alkali was a fast reaction and that benzyl disulfide was formed even before neutralization (expt 1 and 2 in Table I). Thus, the succeeding step (eq 1a) is faster than that of eq 1 and this fact makes it impossible to recover the potassium salt of the hydrodisulfide, which had been expected to be produced in the previous paper.[2]

When the colored aqueous layer in expt 2 was neutralized, its color faded, and at the same time hydrogen sulfide was evolved and free sulfur precipitated. These phenomena show that sulfur had been dissolved in the basic medium, a fact that is well known from other cases.[3] Separate experiments proved that the dioxane–water mixture also dissolves sulfur in the presence of OH^- or SH^- under our experimental conditions and exhibits similar color formation. The absorption maxima resemble well that of the reaction of benzyl hydrodisulfide (Figure 1). Slight dissimilarities seem to result from sulfur chains involving an indefinite number of sulfur atoms.[4-6] All these facts point to the existence of HS_x^-, which was formed from disproportionation of HS_2^- as shown in eq 1a.

When a large amount of potassium hydroxide (at least over 0.5 mol based on the hydrodisulfide) exists in the reaction of the hydrodisulfide, about a half mole each of hydrogen sulfide, the disulfide, and sulfur are produced. Experiments 3 and 4 (Table I) indicate that an insufficient amount of potassium hydroxide produces polysulfidic mixtures at the expense of elemental sulfur. Under these conditions hydroxide was rapidly consumed (eq 1) at earlier stages of the reactions, and the resulting hydrodisulfide ion reacted with remaining benzyl hydrodisulfide to give polysulfides, although the actual paths are not

TABLE I
THE REACTION OF BENZYL HYDRODISULFIDE (1 MOL) WITH POTASSIUM HYDROXIDE AND SODIUM HYDROSULFIDE IN DIOXANE–WATER (20 ML:10 ML) MIXTURE

		Product, mol or g-atom				
Expt	Reactant	H_2S	RSSR	RS_nR[c]	Polysulfidic sulfur,[d] S_x	Free sulfur
1[a]	5KOH	0.45	0.50			0.43
2[a]	5KOH	0.38	0.45[b]			0.79
3	pH 10 (with KOH)	0.41	0.21	0.30	0.46	
4	pH 13 (with KOH)	0.50	0.29	0.22	0.40	
5	NaSH	1.21	0.35	0.18	0.33	
6	NaS_2H (NaSH + S)	1.44	0.19	0.30	0.60	0.59

[a] The products after quick addition of the reactant and immediate neutralization of the mixture. [b] Extracted before the neutralization. [c] The sum of molarities of polysulfides (n = 3–5). [d] S_x in RSS_xSR.

(1) Part VII: T. Nakabayashi, J. Tsurugi, S. Kawamura, T. Kitao, M. Ui, and M. Nose, *J. Org. Chem.*, **31**, 4174 (1966).

(2) S. Kawamura, Y. Otsuji, T. Nakabayashi, T. Kitao, and J. Tsurugi, *ibid.*, **30**, 2711 (1965).

(3) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 11.

(4) Y. Minoura, *Nippon Kagaku Zasshi*, **73**, 133, 244 (1952).

(5) T. Nakabayashi, J. Tsurugi, and T. Yabuta, *J. Org. Chem.*, **29**, 1236 (1964).

(6) P. D. Bartlett, E. F. Cox, and R. E. Davis, *J. Amer. Chem. Soc.*, **83**, 103 (1961).

TABLE II
REACTION OF BENZYL HYDRODISULFIDE (1 MOL) WITH CYANIDE, THIOLATE, AND SULFITE

Expt	Reactant	Solvent	Product, mol or g-atom				
			H_2S	RSH	RSSR	Polysulfidic sulfur, S_x	SCN^- or $S_2O_3^{2-}$
7[a]	KOH	Dioxane–water	0.45	0	0.49	(0.47)[b]	
8	KCN + KOH	Dioxane–water	0.33	0.24	0.37	Trace[c]	0.61
9	KCN + 0.1KOH	Dioxane–water	0.23	0.31	0.33	Trace[c]	0.66
10[a]	KCN	Dioxane–water	0.19	0.33	0.30	0.06	0.70
11	1.2KCN	Dioxane	0.31	0.08	0.45	Trace[c]	0.51
12	1.2RSNa	Dioxane	0.85	0.12	0.89	0	
13	$1.2Na_2SO_3$	Dioxane	0.44	0.18	0.03	0.53[d]	0.03

[a] Cited from ref 2. [b] Free sulfur. [c] From nmr, RS_3R. [d] Bonded as RS_3R, RS_4R, and RS_5R.

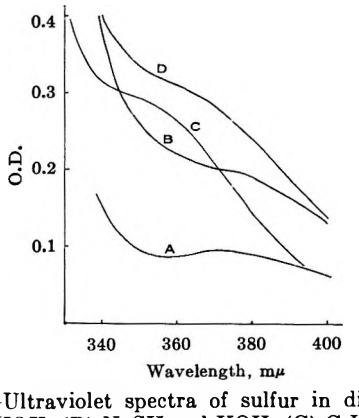

Figure 1.—Ultraviolet spectra of sulfur in dioxane–water. (A) contains KOH, (B) NaSH and KOH, (C) $C_6H_5CH_2SH$ and KOH, (D) benzyl hydrodisulfide and KOH. Each except D contains 10 mg of sulfur. See Experimental Section.

well understood. We therefore offer tentatively the sequence shown in eq 3a–d for the polysulfide formation. Formation of polysulfide by thio anions, HS^-, HS_2^-, HS_3^- · · · HS_x^-, is clear from the results of expt 5 and 6 (Table I). It is concluded from these data that the attack by hydroxide is faster than the attack by the thio anions.

$$HS_2^- \rightleftharpoons HS^-, HS_2^-, HS_3^- \cdots HS_x^- \quad (3a)$$

$$RSSH + HS_x^- \longrightarrow RSS_xH + SH^- \quad (3b)$$

$$RSS_xH \xrightarrow{B} RSS_x^- \quad (3c)$$

$$RSSH + RSS_x^- \longrightarrow RSS_xSR + SH^- \quad (3d)$$

The results appear in Table I and other facts are thus explained by the assumed sequence 1. The sequence 2 based on the initial sulfenyl sulfur attack, on the contrary, tells us nothing about the polysulfide formation at an insufficient concentration of the hydroxide ion or about the color of the reaction mixture mentioned above. Moreover, from the sequence 2, we can expect the formation of at least detectable amounts of stable oxygen-containing compounds such as RS(O)SR, $RS(O_2)SR$, or RSO_3H by the mutual interaction of the intermediate[7,8] RSOH in eq 2a.

Competition of Alkaline Decomposition with Nucleophilic Attack.—In previous papers,[2,9–12] it was concluded that nucleophilic attack on both sulfur atoms of hydrodisulfides occurs (for example, eq 4, 4a, and 5).

$$RSSH + CN^- \longrightarrow RSCN + SH^- \quad (4)$$

$$RSSH + RSCN \longrightarrow RSSR + HSCN \quad (4a)$$

$$RSSH + CN^- \longrightarrow RS^- + HSCN \quad (5)$$

We have tried to determine whether alkaline hydrolysis of hydrodisulfides was also taking place in such aqueous systems. Addition of alkali to the reaction system with cyanide considerably changed the amounts of products (expt 8 and 9 in Table II). We would like to know the reaction with CN^- alone, and tried to carry out reactions under anhydrous conditions. Under these conditions, the reaction proceeded heterogeneously and gave mainly hydrogen sulfide, dibenzyl disulfide, and thiocyanate ion (Table II, expt 11). In the case of the reaction with α-toluenethiolate, hydrogen sulfide and the disulfide were the main products (Table II, expt 12). Therefore, eq 4 and 4a in expt 11 and eq 6 in expt 12 are major reactions.

$$RSSH + RSNa \longrightarrow RSSR + NaSH \quad (6)$$

Formation of polysulfides is attributed to the competitive alkaline decomposition of the hydrodisulfide. Thio anion HS_x^- formed by the decomposition (in sequence 1), will give polysulfenyl ion as in eq 3c which in turn will react with the hydrodisulfide as in eq 3d.

In view of above results, it is likely that nucleophilic attack on both sulfur atoms occur, besides minor alkaline decomposition.

Treatment of sodium sulfite, under anhydrous conditions (Table II, expt 13), with benzyl hydrodisulfide was a sluggish reaction that yielded a large amount of the dibenzyl polysulfides and an extremely small amount of thiosulfate ion which was different from those in aqueous medium.[2] Thus the reaction under anhydrous conditions seems to be a decomposition similar to that of benzhydryl hydrodisulfide induced by sulfite ion as reported in the previous paper.[11]

Experimental Section

Benzyl hydrodisulfide was prepared and purified before use by a method reported elsewhere.[13] Powdered sodium hydrosulfide was prepared from the treatment of sodium ethoxide with hydrogen sulfide in ethanol and its precipitation from ether. Sodium α-toluenethiolate was prepared from the treatment of α-toluenethiol with metallic sodium in a small amount of ether. Inorganic salts were commercial, extra pure. Dioxane was purified before use by boiling with metallic sodium. Dibenzyl disulfide was identified by mixture melting point

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(8) E. Vinkler and F. Klivenyi, *Acta Chim. Acad. Sci. Hung.*, **22**, 345 (1960).
(9) J. Tsurugi, T. Nakabayashi, and T. Ishihara, *J. Org. Chem.*, **30**, 2707 (1965).
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(11) S. Kawamura, T. Nakabayashi, T. Kitao, and J. Tsurugi, *ibid.*, **31**, 1985 (1966).
(12) T. Nakabayashi, J. Tsurugi, S. Kawamura, T. Kitao, M. Ui, and M. Nose, *ibid.*, **31**, 4174 (1966).
(13) J. Tsurugi and T. Nakabayashi, *ibid.*, **24**, 807 (1959).

when it contained little or no polysulfides (expt 1, 2, 8, 9, 11 and 12). Nuclear magnetic resonance spectra were taken on a JNM 3H-60 spectrometer, with tetramethylsilane as an internal standard. Ultraviolet spectra were recorded on a Shimadzu SV-50 spectrometer. Analytical procedures for other reaction products, hydrogen sulfide, α-toluenethiol, and thioanions were the same as in the previous study.[2]

Ultraviolet Spectra of Basic Mixtures.—Three dioxane–water (20 ml:10 ml) mixtures, containing (A) 1.08 g of potassium hydroxide, (B) 0.54 g of sodium hydrosulfide and 1.08 g of potassium hydroxide, and (C) 1.19 g of α-toluenethiol and 1.08 g of potassium hydroxide, were prepared. To each mixture. 10 mg of sulfur was added. A portion of the upper dioxane-rich layer was pipetted and was subjected to uv analysis (Figure 1), Positions of the maxima and their intensities considerably changed depending on temperature and time. The maximum for the sample prepared from 1 drop of the hydrodisulfide and A was also shown in Figure 1. The mixtures A, B, and C dissolved 0.9, 1.2, and 1.4 g, respectively, of crystalline sulfur at equilibrium (with stirring overnight at room temperature).

Procedure for the Reaction with Potassium Hydroxide.—In a three-necked flask on an ice bath equipped with an equilibrated dropping funnel, a thermometer, and nitrogen gas inlet and outlet tubes, the latter of which was connected with absorbing bottles of hydrogen sulfide, are placed 5 g (90 mmol) of KOH and 10 ml of water. Benzyl hydrodisulfide, 2.92 g (18.7 mmol) in 20 ml of dioxane which was bubbled with nitrogen in advance, was added to the flask from the dropping funnel for 3 min with magnetic stirring under a nitrogen atmosphere. The temperature rose to 32° and the reaction mixture became a deep red. After 2 min it was neutralized with 4 *N* hydrochloric acid until it became weakly acidic. Then the color was discharged and hydrogen sulfide evolved. The neutralized mixture was extracted with benzene. Dibenzyl disulfide and sulfur from the extract were analyzed by the previous method.[2] Another aliquot of benzyl hydrodisulfide, 3 g (19.2 mmol), was allowed to react under identical conditions, but this time organic material was extracted with benzene before neutralization. From the extract, dibenzyl disulfide was obtained, mp and mmp 68.5–71°, and sulfur was found in the aqueous layer after neutralization. The products of these experiments were cited in Table I, expt 1 and 2. The reactions with dilute alkalis at room temperature were carried out under similar conditions, where the hydrodisulfide solution was added to 10 ml of water of pH 10 or pH 13. The reaction at pH 10 was so sluggish that it took 2 days to finish the reaction and the reaction mixture did not become colored. The products, dibenzyl di- and polysulfide mixtures were analyzed by nmr spectra as indicated in the following section, and were listed in Table I, expt 3 and 4.

Analysis of Dibenzyl Di- and Polysulfide Mixtures.—It is known[14] that the nmr signals of methylene protons of dibenzyl polysulfides $C_6H_5CH_2SS_xSCH_2C_6H_5$ are distinguishable from each other even in their mixture. Determination of the amounts of dibenzyl di- and polysulfides were as follows. When the benzene extracts from the reaction mixtures contained α-toluenethiol, (*e.g.*, as in expt 8), the amounts were determined by iodometry[11] and the thiol was oxidized to dibenzyl disulfide. Thus benzene solutions containing only di- and polysulfides were obtained. Then the benzene was removed, and to the residues (oil or crystals), appropriate amounts of carbon tetrachloride were added, to make 10–20% solutions whose nmr spectra were taken with integrals by which amounts of the di-, tri-, tetra-, and pentasulfides were determined. Amounts of polysulfidic sulfur, S_x in RSS_xSR, were calculated from the integral values assigned to the respective polysulfides.

Procedure for the Reaction with Sodium Hydro- or Hydropolysulfide.—The reaction condition and procedure were similar to those of the reaction with potassium hydroxide (at room temperature). Aqueous sodium hydropolysulfide NaS_xH (x_{av} = 2) solution was prepared from sodium hydrosulfide and crystalline sulfur. To sulfur (0.62 g, 19.3 mg-atoms) suspended in 10 ml of water and 1.08 g (19.3 mmol) of sodium hydrosulfide, was added 5 ml of dioxane with magnetic stirring under a nitrogen atmosphere. After 5 min, the sulfur dissolved and the solution became colored. To this was added 3 g (19.2 mmol) of the hydrodisulfide in 15 ml of dioxane. Hydrogen sulfide was evolved in both reactions even before neutralization. α-Toluenethiol could not be detected either by usual methods or by nmr spectroscopy. Analytical results are given in Table I, expt 5 and 6.

Procedure for the Reaction under Anhydrous Conditions.—To 1.5 g (23 mmol) of potassium cyanide, 3.35 g (23.1 mmol) of sodium α-toluenethiolate, or 2.42 g (19.2 mmol) of sodium sulfite was added 3 g (19.2 mmol) of benzyl hydrodisulfide in 20 ml of dioxane with vigorous stirring at room temperature under a nitrogen atmosphere, in the same glassware as that used in the foregoing experiments. The reactions proceeded heterogeneously and the reaction mixtures became colored with the evolution of hydrogen sulfide in the case of cyanide and the thiolate. The reaction with sulfite was sluggish but was complete after 1 day. To each reaction mixture was added about 100 ml of benzene, the insoluble material was removed by filtration, and the benzene solution washed with water and dried over magnesium sulfate. The benzene solution was treated as in the previous experiments. Analytical results are cited in Table II, expt 11, 12 and 13.

Procedure for the Reactions with Cyanide in the Presence of Potassium Hydroxide.—The reactions with potassium cyanide in strong basic media were carried out as follows. Using analogous glassware, to benzyl hydrodisulfide (3 g, 19.2 mmol) in 20 ml of dioxane was added 1.25 g (19.2 mmol) of potassium cyanide and 0.108 g (1.92 mmol) or 1.08 g (19.2 mmol) of potassium hydroxide in 10 ml of water with stirring under a nitrogen atmosphere at room temperature. The reaction mixture became red immediately and the color faded after about 10 min. (The reaction mixture with only potassium cyanide was light yellow.[2]) A major portion of hydrogen sulfide was evolved from the reaction mixture containing 1.92 mmol of potassium hydroxide after neutralization and most of hydrogen sulfide from that containing 19.2 mmol after neutralization. Succeeding treatment of the reaction mixtures was the same as that in the previous paper.[2] The amounts of products are shown in Table II, expt 8 and 9.

Registry No.—Benzyl hydrodisulfide, 3492-66-8.

(14) D. Grant and J. R. Van Wazer, *J. Amer. Chem. Soc.*, **86**, 1450, 3012 (1964).

Nucleophilic Displacements α to Sulfonyl Groupings

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Thiophenoxide ion in dimethylformamide solution displaces the halogen atom in halomethyl and α-halobenzyl phenyl sulfones to give high yields of the corresponding phenylthiomethyl and α-phenylthiobenzyl phenyl sulfones. A study of the effect of the nature of the halogen (bromine or chlorine) and the effect of protic solvents on the proportion of displacement *vs.* reduction products was made. Thiophenoxide ion in either dimethylformamide or 33% methanol–67% dimethylformamide solvents reacted with halomethyl phenyl sulfones to give a nearly quantitative yield of phenylthiomethyl phenyl sulfone (**2**). In ethanol solution, thiophenoxide ion reacted with the halomethyl phenyl sulfones to give *ca.* 80% **2** and 20% methyl phenyl sulfone (**3**). In the reaction of thiophenoxide ion with α-halobenzyl phenyl sulfones, α-phenylthiobenzyl phenyl sulfone was obtained in anhydrous dimethylformamide, while this same reaction in the presence of small amounts of protic solvent gave large amounts of benzyl phenyl sulfone (**7**). It is concluded that the halomethyl phenyl sulfones are undergoing SN2 reactions but that the α-halobenzyl phenyl sulfones are probably reacting by a reduction–displacement sequence.

The reaction of bromomethyl *p*-tolyl sulfone with sodium *n*-butyl mercaptide in ethanol has been reported to give 76% of methyl *p*-tolyl sulfone.[1] Displacement on carbon also apparently failed in a similar reaction with sodium *p*-tolyl mercaptide, judging from the isolation of *p*-tolyl disulfide as the major reaction product.[1] These observations and studies of the behavior of compounds like $C_6H_5SO_2CH_2Cl$ and $ClCH_2SO_3Na$ with nucleophiles has led to the conclusion that arylsulfonyl and sulfonate groupings exert a strong retarding effect on SN2 displacements at the α-carbon atom.[2] This effect does not extend to the β or to more distant positions.[3] The retarding effect has been attributed to a steric blocking of the approach of the nucleophile to the α-carbon atom by the sulfonyl oxygen atoms, the radius of which is considerably extended by their residual negative charges.[2,3] In terms of Ingold's classification of structural kinetic effects operating on SN2 reactions, this is a combination of a polar effect and a steric effect.[4] It may alternatively be described as a field effect.[5] In another study we observed what appeared to be a displacement reaction α to a sulfone grouping using dimethylformamide (DMF) solvent. The nucleophilicity of anions in dipolar aprotic solvents like DMF has been found to be greatly enhanced, presumably because of lessened solvation of the anions in this poorly hydrogen-bonding medium.[6] One would also expect a lesser degree of solvation around the sulfonyl oxygen atoms in such solvents. Both of these effects should operate to make SN2 displacements for α-halo sulfones much more facile in dipolar aprotic solvents than in protic solvents. A number of experiments to test this idea have been carried out.

Results

The reaction of potassium thiophenoxide with either bromomethyl phenyl sulfone (**1a**) or chloromethyl phenyl sulfone (**1b**) in dimethylformamide (DMF) gave high yields of phenylthiomethyl phenyl sulfone (**2**). The presence of water in a 10:1 mol ratio to **1** or of methanol in as much as a 100:1 mol ratio did not affect the result.

$$\underset{\mathbf{1},\ X = Br,\ Cl}{C_6H_5SO_2CH_2X} + C_6H_5SK \xrightarrow{DMF} \underset{\mathbf{2}}{C_6H_5SO_2CH_2SC_6H_5} + K^+X^-$$

A slow displacement of the bromine atom in **1a** was also effected by reaction with lithium chloride in DMF (10% conversion in 4 hr at 80°). On the other hand, no reaction occurred under these conditions with sodium cyanide in DMF. After 10 hr at 70–80° with piperidine in DMF 80% of **1a** was recovered and a small amount of methyl phenyl sulfone (**3**) was obtained.

Contrary to the earlier report,[1] the SN2 displacement product (**2**) was the major product from **1a** and sodium thiophenoxide, even in ethanol solution, although about 20% reduction product, methyl phenyl sulfone (**3**), was also obtained. A similar result was obtained in methanol. The products isolated from this latter reaction were **2** (80%), **3** (9%), and phenyl orthothioformate (**4**, 2%).

$$\underset{\mathbf{1a}}{C_6H_5SO_2CH_2Br} \xrightarrow[CH_3OH,\ 12\text{-hr reflux}]{C_6H_5SNa} \underset{\mathbf{2}\ (80\%)}{C_6H_5SO_2CH_2SC_6H_5} + \underset{\mathbf{3}\ (9\%)}{C_6H_5SO_2CH_3} + \underset{\mathbf{4}\ (2\%)}{(C_6H_5S)_3CH}$$

A larger amount of **4** (31%) was obtained in ethanol solvent, and the amount was observed to increase with time. Its source was traced to a slow reaction between **2** and phenyl disulfide; the latter was formed as a consequence of the production of the reduction product (**3**). A 78% yield of **4** was obtained in a separate experiment using **2** and phenyl disulfide in ethanol containing sodium ethoxide.

$$NaOC_2H_5 + \underset{\mathbf{2}}{C_6H_5SO_2CH_2SC_6H_5} + C_6H_5SSC_6H_5 \xrightarrow[(C_2H_5O^-)]{C_2H_5OH} \underset{\mathbf{4}\ (78\%)}{(C_6H_5S)_3CH} + C_6H_5SO_2Na + C_2H_5OH$$

The reaction of **1a** with sodium ethoxide in ethanol gave **3** as the major product. This is in agreement with the results of Ziegler and Conner.[1]

Reaction of α-bromo- or α-chlorobenzyl phenyl sulfone (**5a** and **5b**, respectively) with potassium thiophenoxide in DMF gave *ca.* 95% α-phenylthio-

(1) W. M. Ziegler and R. Conner, *J. Amer. Chem. Soc.*, **62**, 2596 (1940).
(2) F. G. Bordwell and G. D. Cooper, *ibid.*, **73**, 5184 (1951), and references cited therein.
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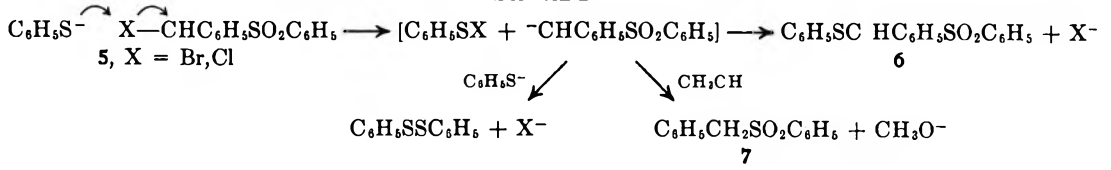
(6) See A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

SCHEME I



benzyl phenyl sulfone (**6**) and 5% reduction product, benzyl phenyl sulfone (**7**). In the presence of a 7.5:1 mol ratio of methanol to **5**, the ratio of **6** to **7** was 65:35 from **5a** and 80:20 from **5b**. When 50% methanol–DMF by volume was used as the solvent, only **7** was obtained from either **5a** or **5b**.

$$C_6H_5CHXSO_2C_6H_5 + C_6H_5SK \longrightarrow$$

5a, X = Br
b, X = Cl

$$C_6H_5CH(SC_6H_5)SO_2C_6H_5 \ (\mathbf{6}) + C_6H_5CH_2SO_2C_6H_5 \ (\mathbf{7})$$

Reaction of **5a** with excess refluxing piperidine gave **7** as the only isolable product (93%).

Discussion

The most likely mechanism for the reactions of **1a** and **1b** with thiophenoxide ion to give **2** in alcohol or DMF solvents is SN2 displacement by thiophenoxide ion on carbon. The only alternative mechanism that needs to be considered is attack of thiophenoxide ion on halogen to produce an α-sulfonyl carbanion and a benzenesulfenyl halide (C_6H_5SX). If these species were to react with one another faster than with solvent or thiophenoxide ion, this could serve as an alternative route to **2**. However, the reaction of the carbanion $C_6H_5SO_2CH_2^-$ with alcohol solvents is extremely fast.[7] Furthermore, the displacement of Br from **1a** by Cl^- seems unlikely to involve attack of the nucleophile on halogen. These data argue against the carbanion mechanism but cannot rule it out completely. It is interesting to note in this connection that in ethanol solution ethoxide ion attacks **1a** exclusively at the bromine atom, whereas thiophenoxide ion attacks **1a** primarily at the carbon atom (assuming the SN2 mechanism). This is just the reverse of what would have been predicted on the basis of the concept of "hard and soft acids and bases."[10] Of course, if **2** is assumed to be formed by attack of thiophenoxide ion on halogen, there would be no conflict with the theory.

The $C_6H_5SO_2CHXC_6H_5$ system (**5**) should be much more prone to nucleophilic attack on halogen than the $C_6H_5SO_2CH_2X$ system (**1**). The $(C_6H_5SO_2CHC_6H_5)^-$ carbanion is much more stable (a better leaving group) than the $C_6H_5SO_2CH_2^-$ carbanion, judging from the fact that the pK_a of $C_6H_5CH_2SO_2CH_2C_6H_5$ is about 5 units lower than that of $C_6H_5SO_2CH_3$,[8] and is, therefore, presumably much more readily produced by nucleophilic attack on halogen. Also, the change from **1** to **5** may retard nucleophilic attack on carbon, judging from the slower rate for displacement of Cl^- by I^- from $C_6H_5CHClCOCH_3$ compared with $ClCH_2COCH_3$.[11] The data show that **5** is indeed much more susceptible to reduction than is **1**. Note, for example, that reduction of **5** by thiophenoxide ion is complete in methanol or ethanol, whereas with **1** only 10–20% reduction occurs. It seems likely, then, that attack of $C_6H_5S^-$ occurs on halogen for **5** in DMF, and that the C_6H_5SX which is produced reacts with the carbanion before the two species diffuse apart. In the presence of methanol (7:5:1 molar ratio to 1) this mechanism requires that C_6H_5SX win out over CH_3OH in competition for the carbanion, since **6** is formed in preference to **7** under these conditions (Scheme I).

There is analogy for this pathway in the reaction in aprotic solvents of triphenylphosphine with α-halo ketones[12,13] and α-halo sulfones[14] to give displacement at halogen followed by rearrangement to the normal SN2 product. Complete reduction occurs in these reactions in the presence of 2 equiv of methanol; α-bromo ketones are far more reactive than α-chloro ketones.[15]

With **5a** or **5b** only partial reduction occurs even with a 7.5:1 ratio of methanol to halide. This requires that C_6H_5SX be far more reactive toward the sulfonyl carbanion than $(C_6H_5)_3PX$ toward the enolate ion or the sulfonyl carbanion, if comparable mechanisms are to operate.

Displacement at the halogen atom would be expected to be more sensitive to the nature of the halogen than would displacement at carbon.[10] Therefore, **5a** would be expected to be much more reactive than **5b**, if attack is on halogen. This prediction was borne out. A qualitative comparison of the rates of reaction of **5a** and **5b** with thiophenoxide ion in anhydrous and methanolic DMF showed that **5a** reacted >300 times as fast as **5b** under the same conditions. This large difference in rates is more compatible with displacement at the halogen atom than with displacement at the carbon center. The leaving-group effect going from chlorine to bromine in normal SN2 displacements is *ca.* 50.[16] These data support the carbanion mechanism for the production of **6**, at least from **5a**. Also, if **6** were being produced from the chloride **5b** solely by displacement at carbon and **7** by displacement at halogen, one might have expected the increase in reduction product in going from the

(7) Using the pK_a value of 27 determined for $C_6H_5SO_2CH_3$ in DMSO,[8] the calculated rate for the combination of $C_6H_5SO_2CH_2^-$ with a proton from methanol would be $k_{-1} = k_1K_{CH_3OH}/K_{C_6H_5SO_2CH_3} \cong 2 \times 10^8\ M^{-1}\ sec^{-1}$.[9]

(8) F. G. Bordwell, R. H. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89**, 3905 (1967).

(9) The rate of exchange for $C_6H_5SO_2CH_3$ in CH_3OD catalyzed by methoxide ion is $2.1 \times 10^{-8}\ M^{-1}\ sec^{-1}$ at 25° (D. A. Schexnayder, unpublished results). The pK_a for $C_6H_5SO_2CH_3$ in methanol is probably not 27, but the order of magnitude is no doubt correct.

(10) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

(11) A. W. Fort, *ibid.*, **84**, 2620 (1962), footnote 17.

(12) I. J. Borowitz and R. Virkhaus, *ibid.*, **85**, 2183 (1963); see, however, I. J. Borowitz and H. Parnes, *J. Org. Chem.*, **32**, 3560 (1967).

(13) P. A. Chopaud, R. F. Hudson, and G. Klopman, *J. Chem. Soc.*, 1379 (1965).

(14) H. Hoffman and H. Förster, *Tetrahedron Letters*, 1547 (1963).

(15) I. J. Borowitz and L. I. Grossman, *ibid.*, 471 (1962).

(16) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw Hill Book Co., Inc., New York, N. Y., 1962, p 30.

chloride (**5b**) to the bromide (**5a**) to be much larger than that observed.

The reaction of **2** with phenyl disulfide to give **4** must occur by way of bis(phenylthio)methyl phenyl sulfone (**8**). Displacements initiated by nucleophiles, like the carbanion derived from **2**, on the sulfur atom of disulfides are common.[17,18] The formation of **4** from **8** can be pictured as a direct displacement (S_N2) or as a solvolysis in which the carbonium ion is captured by thiophenoxide ion. The latter path seems more likely.[19]

$$C_6H_5SO_2CH_2SC_6H_5 \xrightarrow[C_2H_5OH]{C_2H_5O^-} [C_6H_5SO_2CHSC_6H_5]^- \xrightarrow{C_6H_5SSC_6H_5} [C_6H_5SO_2CH(SC_6H_5)_2] + C_6H_5S^-$$
2 **8**

$$\mathbf{8} \xrightarrow{C_2H_5OH} C_6H_5SO_2^- + [(C_6H_5S)_2CH^+] \xrightarrow{C_6H_5S^-} (C_6H_5S)_3CH$$
4

Experimental Section

Analyses were performed by H. Beck, Northwestern University, Evanston, Ill. 60201.

Reaction of Bromomethyl Phenyl Sulfone (1a) with Potassium Thiophenoxide in DMF.—To a solution of 5.00 g (21.3 mmol) of **1a**[20] in 30 ml of dry DMF was added 5.00 g of potassium thiophenoxide. The mixture turned bright yellow, and a precipitate began to form after a few minutes. This mixture was stirred under an atmosphere of nitrogen for 12 hr at room temperature and then poured into water and extracted with ether. From the ether extract was obtained an oil which was crystallized from carbon tetrachloride–hexane to give 4.7 g of phenylthiomethyl phenyl sulfone (**2**), mp 60.5–62.0°. Chromatography of the mother liquor over 60 g of silica gel gave an additional 500 mg (off with 5% ether in hexane) to bring the yield to 5.2 g (93%). The nmr spectrum (carbon tetrachloride) showed aromatic protons (10 H) and a singlet at τ 5.78 (2 H). Breslow and Mohacsi[21] list this peak at τ 5.74 and mp 55–57°.

Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.06; H, 4.58. Found: C, 59.09; H, 4.66.

This same reaction repeated with 2% water (by volume) in DMF gave essentially the same result.

Oxidation of 200 mg of phenylthiomethyl phenyl sulfone with 3 ml of 30% hydrogen peroxide in 10 ml of acetic acid at *ca.* 100° for 3 hr followed by the usual work-up gave 150 mg of bis(phenylsulfonyl)methane, mp 122.5–123° from ethanol (lit.[22] mp 120–121°).

Reaction of 1a with Sodium Thiophenoxide in Alcohol Solvents.—To a solution of 500 mg (4.54 mmol) of benzenethiol in 15 ml of absolute methanol in which 200 mg of sodium metal had been dissolved was added 500 mg (2.13 mmol) of **1a**. This mixture stood at reflux for 12 hr and was worked up by pouring it into water and extracting it with ether. An nmr spectrum of the crude reaction mixture showed there to be present 90% **2** and 10% methyl phenyl sulfone (**3**) along with a small amount of phenyl orthothioformate (**4**). These products could be isolated by column chromatography over silica gel: **4** (15 mg (2%), crystallized from pentane; mp 39–39.5° undepressed on admixture with an authentic sample[23]) was eluted with 15% benzene in hexane; **2** (450 mg, 80%) was eluted with 5% ether in hexane; **3** (30 mg, 9%) was eluted with 10% ether in hexane.

This same reaction in absolute ethanol gave (by nmr analysis) 49% **2**, 20% **3**, and 31% **4**.

Reaction of 1a with Potassium Thiophenoxide in 33% Methanol–DMF.—To a solution of 750 mg (5.2 mmol) of potassium thiophenoxide in 5 ml of methanol (124 mmol) and 10 ml of DMF was added 300 mg (1.28 mmol) of **1a**. This mixture was held at reflux for 8 hr and then worked up as usual. An nmr spectrum of the crude reaction mixture showed no **3** present. Crystallization from ether–hexane gave 310 mg (92%) of **2**, mp 61–63°. This same reaction with **1b**[3] (300 mg) gave the same result.

Reaction of 1a with Sodium Ethoxide in Ethanol.—To a solution of 400 mg of sodium metal dissolved in 20 ml of absolute ethanol was added 300 mg (1.28 mmol) of **1a**. This mixture was held at reflux for 12 hr, and the resulting dark brown mixture was worked up as usual. An nmr spectrum of the crude reaction mixture showed **3** to be the only compound present containing aromatic protons. The oil was then taken up in methanol, treated with charcoal, and cooled, and the resulting precipitate was collected to give 130 mg (65%) of **3**, mp 85–86° (lit.[24] mp 88°).

Attempted Reaction of the Bromo Sulfone 1a with Sodium Cyanide.—Treatment of **1a** with 1 *M* sodium cyanide in DMF at 80–90° for 4 hr followed by the usual work-up gave only recovered starting material (over 50%). This same reaction in DMSO solvent at 80° gave extensive decomposition with a low recovery of starting material.

Reaction of Chloromethyl Phenyl Sulfone (1b)[1] with Potassium Thiophenoxide in DMF.—A solution of 2.0 g (10.6 mmol) of **1b** and 3.0 g (20 mmol) of potassium thiophenoxide in 20 ml of dry DMF under nitrogen was heated at 80° for 1 hr and then worked up in the usual manner. The thio ether was crystallized from ether–hexane to give 2.3 g (83%) of phenylthiomethyl phenyl sulfone, mp 60–62°.

Reaction of Bromomethyl Phenyl Sulfone (1a) with Lithium Chloride in DMF.—A solution of 2.0 g of **1a** and 2.5 g of anhydrous lithium chloride in 20 ml of dry DMF stood at 80° for 4 hr. The usual work-up gave an oil which was shown by nmr analysis to be 90% bromo sulfone **1a** and 10% chloro sulfone **1b**.

Reaction of 2 with Phenyl Disulfide in Basic Ethanol.—To a solution of 1.0 g of sodium metal dissolved in 20 ml of absolute ethanol was added 1.0 g (3.8 mmol) of **2** and 830 mg (4.0 mmol) of phenyl disulfide. This mixture was held at reflux for 5 hr and worked up as usual. An nmr spectrum showed no **2** left and the only proton visible outside the aromatic region was attributable to **4**. Chromatography over silica gel gave **4** as an oil which was eluted with 15% benzene in hexane. The oil was crystallized from pentane to give 1.0 g (78%) of **4**, mp 39–39.5°.

α-Bromobenzyl Phenyl Sulfone (5a).—To a solution of 11.0 g (40.5 mmol) of phenylsulfonylphenylacetic acid[25] dissolved in 100 ml of water containing 27.6 g (200 mmol) of potassium carbonate was added 8.0 g (50 mmol) of bromine dissolved in 50 ml of a 20% potassium bromide solution. The resulting mixture was stirred for 6 hr at room temperature and filtered. The solid was washed with water and a small amount of ethanol and recrystallized from ethanol–chloroform to give 6.5 g (50%) of **5a**, mp 193–194°.

Anal. Calcd for $C_{13}H_{11}BrO_2S$: C, 50.16; H, 3.56. Found: C, 50.18; H, 3.53.

Reaction of α-Bromobenzyl Phenyl Sulfone (5a) with Piperidine.—A solution of 500 mg (1.61 mmol) of **5a** in 10 ml of piperidine was held at reflux for 50 hr. The piperidine was removed *in vacuo* and an nmr spectrum of the resulting solid showed it to be benzyl phenyl sulfone (**7**). Crystallization from ethanol following a treatment with activated charcoal gave 350 mg (93%) of **7**, mp 147–148° (lit.[26] mp 149–150°).

Reaction of 5a with Potassium Thiophenoxide in DMF and Methanol–DMF.—To a solution of 500 mg of potassium thiophenoxide in 10 ml of dry DMF was added 300 mg (0.97 mmol) of **5a**. This mixture stood at room temperature for 1 hr and was then worked up as usual. An nmr spectrum of the resulting oil showed it to be *ca.* 95% α-phenylthiobenzyl phenyl sulfone (**6**) and *ca.* 5% benzyl phenyl sulfone (**7**). This material was passed over 25 g of silica gel and **6** was eluted with 15% ether in hexane to yield 320 mg (89%). This was recrystallized from hexane to a product of mp 92–93°. Further elution with 15% ether in hexane gave 10 mg (4%) of **7**.

(17) A. J. Parker, "Organic Sulfur Compounds," Vol. I, edited by N. Kharasch, Pergamon Press Inc., New York, N. Y., 1961, pp 103.

(18) G. Leandri and A. Tundo, *Ann. Chim.*, **44**, 518 (1954).

(19) Bis(phenylthio)chloromethane is highly reactive toward solvolysis; see H. Böhme and J. Roehr, *Ann.*, **648**, 21 (1961).

(20) F. G. Bordwell, J. M. Williams, Jr., and B. B. Jarvis, *J. Amer. Chem. Soc.*, in press.

(21) R. Breslow and E. Mohacsi, *ibid.*, **84**, 684 (1962).

(22) R. Otto and J. Tröger, *Ber.*, **25**, 3425 (1892).

(23) J. Hine, *J. Amer. Chem. Soc.*, **72**, 2438 (1950).

(24) H. Bohme and H. Fischer, *Ber.*, **75**, 1310 (1942).

(25) K. Fuchs, *Monatsh.*, **53/54**, 438 (1929).

(26) H. Böhme and D. Morf *Chem. Ber.*, **90**, 446 (1957).

Anal. (for **8**). Calcd for $C_{19}H_{16}O_2S_2$: C, 61.27; H, 4.33. Found: C, 61.35; H, 4.31.

This same reaction repeated in 10 ml of DMF (10 ml) containing 0.5 ml (12 mmol) of methanol with 600 mg of potassium thiophenoxide and 500 mg (1.6 mmol) of **5a** at 70° for 30 min gave a 65:35 mixture of **6** and **7**, respectively, while in a 50:50 mixture of methanol–DMF (5 ml each), **5a** gave only **7** in near quantitative yield.

Reaction of α-Chlorobenzyl Phenyl Sulfone (5b) with Potassium Thiophenoxide in DMF and Methanol–DMF.—Reaction of **5b**[27] with potassium thiophenoxide in DMF and in 50% methanol–DMF was carried out in the same manner as that of **5a** and gave identical results. In 5% methanol–DMF the reaction was performed in the same manner as that of **5a** but gave instead 80% **6** and 20% **7** (nmr analysis).

Reaction of 1b with Sodium Ethoxide in Ethanol.—To a solution of 400 mg of sodium metal dissolved in 20 ml of absolute ethanol was added 500 mg (2.6 mmol) of **1b**. This mixture stood at reflux for 18 hr and was then worked up as usual. An nmr spectrum of the resulting oil showed about a 4:1 mixture of recovered **1b** and methyl phenyl sulfone (**3**). The spectrum was contaminated with several smaller peaks which were not readily identifiable.

Reaction of 1a with Piperidine in DMF.—A mixture of 300 mg (1.29 mmol) of **1a** and 200 mg (2.35 mmol) of piperidine were held at 70–80° for 10 hr in 15 ml of dry DMF. The mixture was poured into water and extracted with ether. An nmr spectrum of the crude reaction mixture showed **1a** and piperidine present. When the piperidine was removed by washing with dilute hydrochloric acid, a small amount of methyl phenyl sulfone (**3**) was visible in the nmr spectrum. Crystallization from ethanol of the crude reaction mixture after removal of the piperidine gave 240 mg (80%) of recovered **1a**.

Determination of the Relative Rates of Reaction of 5a and 5b with Thiophenoxide Ion.—Aliquots (5 ml) were taken of a solution of 625 mg (2.0 mmol) of **5a** in 20 ml of dry DMF to which 445 mg (3.0 mmol) of potassium thiophenoxide in 20 ml of dry DMF had been added. The first aliquot (1 min) showed no **5a** present (nmr analysis). This same procedure with **5b** (515 mg 2.0 mmol) showed that the reaction was not complete for *ca.* 10 hr (therefore $k_{Br}/k_{Cl} > 600$).

The procedure for 50% methanol–50% DMF was as follows. To a solution of 315 mg (1.0 mmol) of **5a** in 10 ml of DMF and 7 ml of methanol was added 3 ml of a solution of 120 mg (5.2 mg-atoms) of sodium metal and 550 mg (5.0 mmol) of benzenethiol dissolved in 10 ml of methanol (1.5 mmol of sodium thiophenoxide added). The half-life of this reaction was *ca.* 1 hr. Under these same conditions, **5b** showed no sign of reaction (nmr analysis) after 27 hr.

(27) R. Otto, *J. Prakt. Chem.*, **40**, 505 (1889).

Registry No.—**2**, 15296-86-3; **3**, 3112-85-4; **4**, 4832-52-4; **5a**, 15296-88-5; **7**, 3112-88-7; **8**, 15296-89-6.

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α,β-Unsaturated Aldehydes as Acceptors in the Oxyphosphorane Carbon–Carbon Condensation. Hydrolyses of Five-Membered Cyclic Pentaoxyphosphoranes and Phosphate Esters[1]

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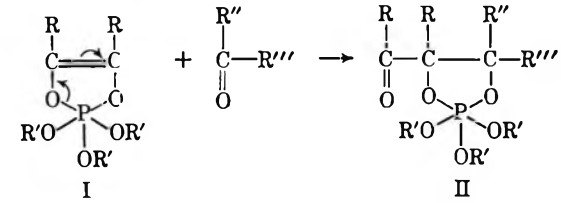
2,2,2-Trimethoxy-4,5-dimethyl-2,2,dihydro-1,3,2-dioxaphospholene performed a nucleophilic 1,2 addition to the carbonyl function and not a 1,4 addition to the olefinic carbon of acrolein. The product was 2,2,2-trimethoxy-4β-methyl-4α-acetyl-5α-vinyl-2,2-dihydro-1,3,2-dioxaphospholane; only the diastereomer with a *cis*-CH_3/H was obtained. Hydrolysis of the five-membered pentaoxyphosphorane gave the two diastereomers at phosphorus of the five-membered cyclic phospho triester. The cyclic phospho triesters underwent an extraordinarily rapid reaction with methanol and gave the corresponding open-chain phospho triester derived from a γ-unsaturated α,β-dihydroxy ketone. The kinetically controlled product had the phosphate at the α position, but the thermodynamically stable product had the phosphate at the β position. The open phospho triester regenerated the cyclic phospho triester upon distillation under vacuum. Hydrolysis of the five-membered pentaoxyphosphorane with an excess of water gave minor amounts of the open-chain β-phospho triester and major amounts of the open phospho monoester derived from the γ-unsaturated α,β-dihydroxy ketone. The kinetically controlled product had the dihydrogen phosphate group at the α carbon, while the thermodynamically stable product had the dihydrogen phosphate group at the β carbon. The five-membered cyclic phospho triester underwent a very rapid hydrolysis with 1 mol equiv of water and gave the five-membered cyclic phospho diester and the open-chain β-phospho triester.

The nucleophilic addition[3] of 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholenes[4] (I) to the carbonyl group of mono- and polycarbonyl compounds constitutes a new and a stereoselective method of making carbon–carbon bonds. This reaction, which can be conveniently named the *oxyphosphorane condensation*,[3] produces derivatives of the 2,2-dihydro-1,3,2-dioxaphospholane ring system, II.



I II

(1) Part XXXVIII: Organic Compounds with Pentavalent Phosphorus.

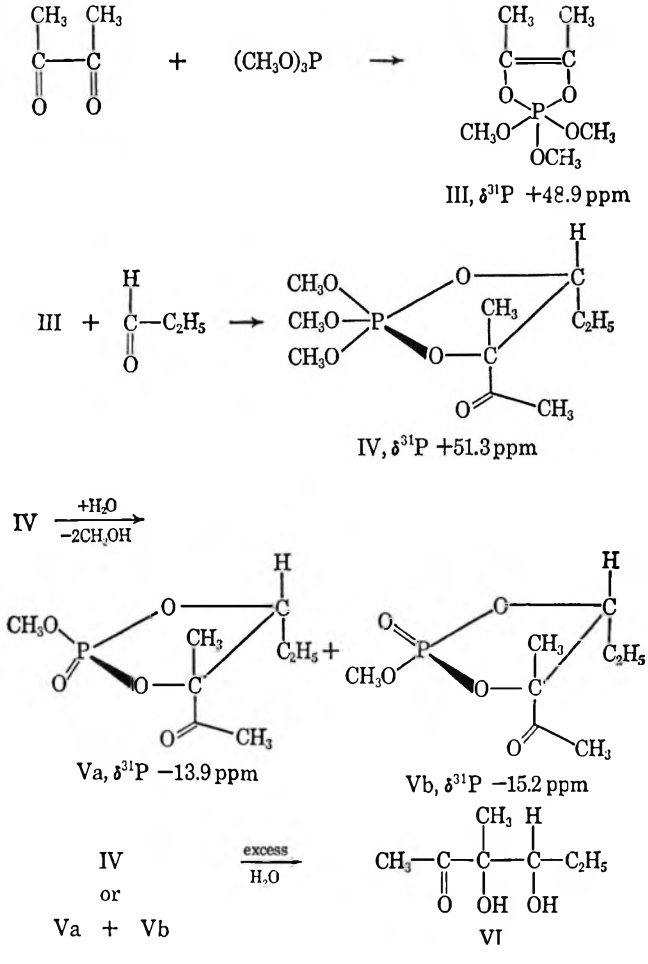
(2) This investigation was supported by Public Health Service Grant CA-04769 from the National Cancer Institute and by the National Science Foundation, Grants GP-3341 and GP-6690-Y.

(3) (a) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961); (b) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Amer. Chem. Soc.*, **84**, 1317 (1962); (c) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964); (d) F. Ramirez, *Bull. Soc. Chim. Fr.*, 2443 (1966).

(4) Derivatives of the 2,2-dihydro-1,3,2-dioxaphospholenes like III were first described by three groups of investigators: (a) G. H. Birum and J. L. Dever, Abstracts, Division of Organic Chemistry, 135th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1958, p 101-P; (b) V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, **121**, 466 (1958); *Chem. Abstr.*, **53**, 1105*b* (1959); (c) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **82**, 2650 (1960). Our discovery of phospholenes III from the reactions of trialkyl phosphites with *o*-quinones and α-diketones was based on our previous discovery of the attack by the phosphorus of trialkyl phosphites on the oxygen of *p*-quinones: *cf.* (d) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 856 (1957); (e) F. Ramirez and S. Dershowitz, *ibid.*, **23**, 778 (1958).

The cyclic, saturated pentaoxyphosphoranes can be hydrolyzed to five-membered cyclic phosphate esters, to open-chain phosphate esters, and to phosphorus-free polyhydroxycarbonyl compounds related to the carbohydrates.[5] For example, the condensation of the α-diketone, biacetyl, with propionaldehyde can be effected by means of trialkyl phosphites according to the sequence of reactions[6] (III → IV → Va + Vb → VI) given in Scheme I.

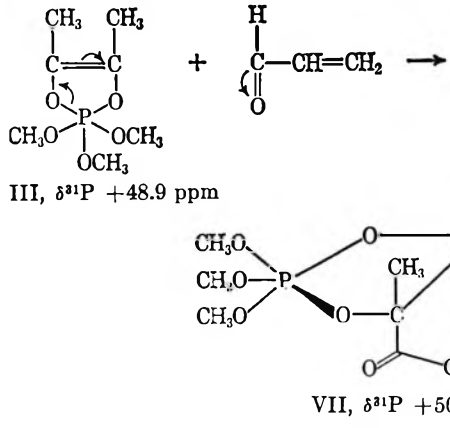
SCHEME I



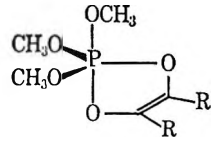
This paper describes the behavior of α,β-unsaturated aldehydes in the oxyphosphorane condensation. We wished to determine whether the dioxaphospholenes are capable of performing a 1,2 addition to the carbonyl function of α,β-unsaturated aldehydes or whether such an addition is of the Michael reaction type, *i.e.*, a 1,4 addition to the olefinic carbon of the unsaturated aldehyde.

Results

Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (III) with α,β-Unsaturated Aldehydes.—Phospholene III reacted with 1 mol equiv of acrolein at 0°. The product of this reaction, which was isolated in 90% yield, was 2,2,2-trimethoxy-4β-methyl-4α-acetyl-5α-vinyl-2,2-dihydro-1,3,2-dioxaphospholane (VII). The phospholane structure, VII, was based on the following data.



(1) The ^{31}P nmr shift was strongly positive relative to H_3PO_4 and was very similar to that of the biacetyl–propionaldehyde phosphite adduct,[6] IV. A positive ^{31}P nmr shift of this magnitude is characteristic of pentaoxyphosphoranes.[3-6] The X-ray analysis[7] of one of these compounds showed that the phosphorus was at the center of a trigonal bipyramid, VIII. The apical P–O bonds were longer than the corresponding equatorial P–O bonds. The apical P–O bond associated with the phospholene ring was longer than the apical P–O bond leading to the alkoxy group. Likewise, the equatorial P–O bond associated with the ring was longer than the equatorial P–O bond leading to the alkoxy groups. These observations suggested that (a) the equatorial bonds had more s character than the apical bonds and thus were somewhat shorter, (b) the P–O bonds associated with the phospholene ring had less p–d π bonding than those leading to the alkoxy groups.[7] The former would be longer since the π bonding should result in bond shortening. The decrease in p–d π bonding could result from delocalization of the unshared electrons of the oxygens into the ring rather than into the d orbitals.



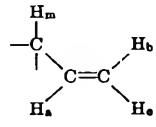
(2) The ^{1}H nmr spectrum of the oxyphosphorane VII is summarized in Table I. The acetyl group on the phospholane ring was assumed to be in a *cis* relationship to the vinyl group by analogy to the configuration assigned previously to the oxyphosphorane IV made from propionaldehyde. The condensation of the phospholene III with the saturated and the unsaturated aliphatic aldehydes gave only one stereomer in high yield. The condensation of phospholene III with benzaldehyde gave two stereomers, but one of them greatly predominated.[6] The major isomer was assigned the configuration with a *cis*-acetyl/phenyl relationship because the nmr signal due to the

(5) (a) F. Ramirez, N. B. Desai, and N. Ramanathan, *J. Amer. Chem. Soc.*, **85**, 1874 (1963); (b) F. Ramirez, A. V. Patwardhan, N. B. Desai, N. Ramanathan, and C. V. Greco, *ibid.*, **85**, 3056 (1963); (c) F. Ramirez, N. Ramanathan, and N. B. Desai, *ibid.*, **85**, 3465 (1963).

(6) (a) F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai C. V. Greco, and S. R. Heller, *ibid.*, **87**, 543 (1965); (b) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *ibid.*, **87**, 549 (1965).

(7) (a) W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *ibid.*, **87**, 127 (1965); (b) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *ibid.*, **89**, 2268 (1967); (c) R. D. Spratley, W. C. Hamilton, and J. Ladell, *ibid.*, **89**, 2272 (1967).

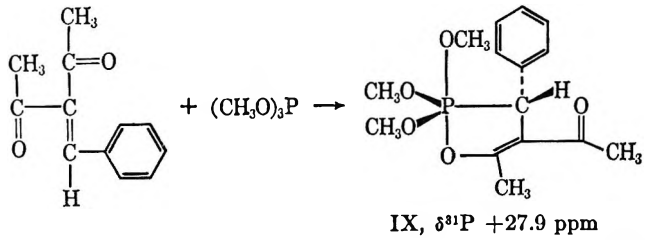
Table I
^{1}H Nmr Signals for the Trimethoxy Biacetylacrolein Phosphite Adduct, VII

τ[a]	No. of ^{1}H	J, cps	Assignment
8.62	3		CH_3C
7.88	3		CH_3CO
6.42	9	J_{HP} = 12.5	CH_3OP
			
5.88	1	J_{HP} = 7.0	H_m
4.42	1	J_{ab} = 15.0 J_{ac} = 8.1	H_a
4.96	1	J_{bc} = 2.8	H_b
4.90	1		H_c

[a] τ in parts per million *vs.* TMS = 10.

acetyl protons was at a higher magnetic field in the major isomer. It was assumed that the strong shielding effect of the *cis*-phenyl was responsible for this effect. As expected, the nmr signal due to the methyl protons was at a higher magnetic field in the minor isomer (*cis*-methyl/phenyl).

The three methoxy groups attached to the phosphorus were magnetically equivalent or indistinguishable since they gave only one doublet. The doublet is due to coupling of the protons with the phosphorus. The apparent magnetic equivalency of the three methoxy groups is a general phenomenon among five-membered cyclic pentaoxyphosphoranes[3-6] in solution at 20°. In a few instances in which the ^{1}H nmr spectrum has been examined at −70°, the same phenomenon was observed. Apparently, a rapid positional exchange occurred among the groups of the trigonal bipyramid as the result of pseudo-rotation.[8,9] It was shown recently[10a,b] that the three methoxy groups of a related cyclic tetraoxyalkylphosphorane,[10c] IX, which were equivalent at 20°, became nonequivalent at −65°.



IX, δ^{31}P +27.9 ppm

(3) The infrared spectrum was consistent with structure VII.

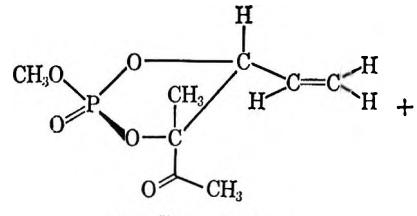
Pentaoxyphosphorane VII was remarkably stable in methanol solution. The ^{31}P nmr spectrum of a solution of VII in methanol at 20° showed no significant changes within 10 min. Prolonged standing led to rather complex changes which are now being investigated.

Attempted Condensations of Phospholene III with α,β-Unsaturated Ketones.—The following unsaturated ketones, methyl vinyl ketone, methyl propenyl ketone, cyclohexenone, and 3-benzylidene-2,4-pentanedione, failed to condense with phospholene III within 5 days at 20 or 60°. Higher temperatures could not be employed since the phospholene itself begins to decompose at an appreciable rate at 100°.

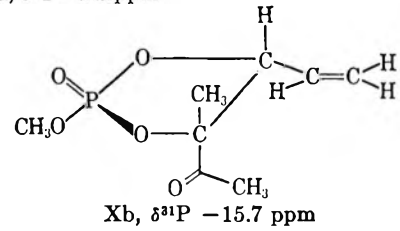
These reactions were carried out under the usual laboratory illuminations. The results of studies of photoinitiated reactions between the phospholene and the unsaturated carbonyl compound will be described elsewhere.[11]

Hydrolysis of Pentaoxyphosphorane VII with 1 Mol Equiv of Water.—The hydrolysis of pentaoxyphosphorane VII was studied in $CHCl_3$ and in $CDCl_3$ using 1 mol equiv of water and of D_2O, respectively. The course of the reaction was followed by ^{1}H and ^{31}P nmr spectrometry. The first product formed was a five-membered cyclic phospho triester, Xa and Xb, together with 2 mol equiv of methanol. The cyclic triester was obtained as two diastereomers at phosphorus, Xa and Xb, in unequal proportions. The configuration at phosphorus was not known with certainty, but, for reasons indicated below, the isomer with the ^{31}P nmr shift at −14.7 ppm was regarded as having the acetyl group *cis* to the phosphoryl oxygen as in formula Xa.

VII phosphorane $\xrightarrow[-2CH_3OH]{+H_2O}$



Xa, δ^{31}P −14.7ppm



Xb, δ^{31}P −15.7 ppm

The ^{1}H nmr signals of the cyclic phospho triesters, Xa and Xb, are listed in Table II. The acetyl signal at the lower magnetic field (τ 7.70) is attributed to the diastereomer Xa with the *cis* relationship of the acetyl and the phosphoryl oxygen. The acetyl signal at higher magnetic field (τ 7.75) would correspond then to the diastereomer Xb with the *trans*-CH_3CO/O. The acetyl signals of the corresponding diastereomers, Va and Vb, in the propionaldehyde series[6] were at τ 7.66 and 7.72, respectively.

(8) (a) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960); (b) E. L. Muetterties and R. A. Schunn, *Quart. Rev.* (London), **20**, 245 (1966), and references therein.

(9) Note Added in Proof.—The stereochemistry of the oxyphosphoranes is discussed further by F. Ramirez, J. F. Pilot, O. P. Madan, and C. P. Smith, *J. Amer. Chem. Soc.*, **90**, 1275 (1968), and F. Ramirez, J. F. Pilot, and C. P. Smith, *Tetrahedron*, in press.

(10) (a) D. G. Gorenstein and F. H. Westheimer, *J. Amer. Chem. Soc.*, **89** 2762 (1967); (b) F. Ramirez, *Trans. N. Y. Acad. Sci.*, in press; (c) F. Ramirez, O. P. Madan, and S. R. Heller, *J. Amer. Chem. Soc.*, **87**, 731 (1965).

(11) While this work was in progress, two preliminary communications dealing with photochemical reactions of the phospholene III have appeared: (a) W. G. Bentrude, *Chem. Commun.*, 174 (1967); (b) W. G. Bentrude and K. R. Darnall, *Tetrahedron Lett.*, 2511 (1967).

TABLE II
^{1}H NMR DATA FOR THE OPEN β-PHOSPHO TRIESTER, XII, AND THE 5-CYCLIC PHOSPHO TRIESTERS, Xa AND Xb

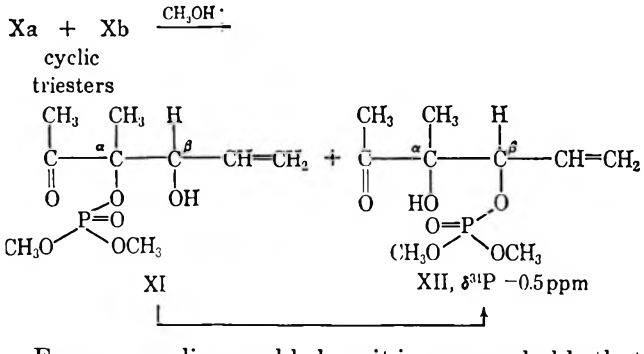
Open triester			Cyclic triester[b]			
τ[a]	No. of ^{1}H	J[a]	τ	No. of ^{1}H	J[a]	Assignment
8.63	3	...	8.43 8.33	3	...	CH_3C
7.74	3	...	7.70 7.75	3	...	CH_3CO
6.26[c]	3	J_{HP} = 10.5	6.10[d]	3	J_{HP} = 11.5	CH_3O
6.20[c]	3	J_{HP} = 11.0	6.08[d]	3	J_{HP} = 11.5	
5.20	1	J_{HP} = 8.0 J_{HH} = 6.0	5.1	1	...	Methine
4.4	3	Multiplet	4.5	3	Multiplet	Vinyl

[a] τ values in parts per million *vs.* TMS = 10; J in cycles per second. [b] Two diastereomers at phosphorus. [c] Two magnetically nonequivalent CH_3O on P. [d] Methoxy of diastereomers at phosphorus.

The signal at τ 8.43 is attributed to the methyl group attached to the phospholane ring in the *cis* isomer Xa, while the signal at τ 8.33 is attributed to the methyl group in the *trans* isomer, Xb. The corresponding signals due to the methyl groups of the *cis* and *trans* isomers, Va and Vb, in the propionaldehyde series were at τ 8.50 and 8.40, respectively. The arguments in favor of the probable configurational assignments to the cyclic phosphates in the propionaldehyde case have already been discussed.[6]

The methanol formed in the hydrolysis of pentaoxyphosphorane VII by 1 mol equiv of water reacted very rapidly with the 5-cyclic phospho triesters, Xa and Xb. The product of this alcoholysis was the open-chain phospho triester, XII, derived from a γ-unsaturated α,β-dihydroxy ketone having the phosphoryl group on the hydroxyl situated at the β carbon.

The ^{31}P nmr signal showed a coupling with the methine proton on the β carbon in addition to the coupling with the six protons of the two methoxy groups attached to the phosphorus. If the phosphoryl group had been on the α-hydroxy group as in XI, the phosphorus nucleus would have been coupled only with the protons of the methoxy groups.



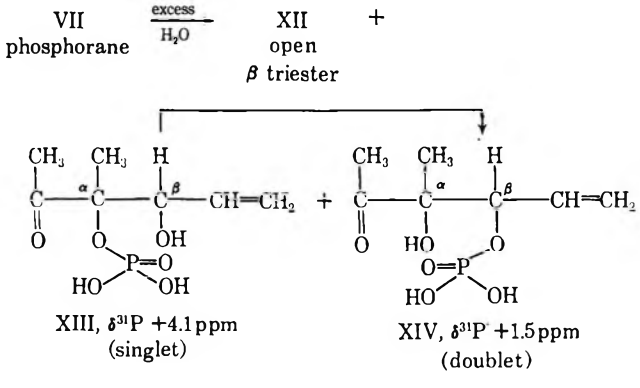
For reasons discussed below, it is very probable that the α-phospho triester XI was the kinetically favored product of the methanolysis of the cyclic triester, X. The α-phosphate, XI, then underwent a rapid rearrangement to the β-phosphate, XII.

The first observations of the ^{1}H and ^{31}P nmr spectra of the hydrolysis product of pentaoxyphosphorane, VII, were made within 5 min. At this point, the two diastereomeric cyclic triesters, Xa and Xb, and the open β triester, XII, were present in an 80:20 proportion, respectively. This proportion had changed to 20:80 within 20 min and to 5:95 after 45 min. *This illustrates the extraordinarily rapid rate of methanolysis of the 5-cyclic phospho triester, X, in solvents of low polarity, like $CHCl_3$.*

The open β triester, XII, was isolated after the methanolysis of the cyclic triester, X, had reached completion. When the open triester, XII, was distilled under vacuum, it lost one molecule of methanol and gave the two diastereomeric cyclic triesters, Xa and Xb.

$$\underset{\substack{\text{open}\\ \beta\text{ triester}}}{\text{XII}} \xrightarrow[\text{vacuum}]{\text{heat}} \underset{\substack{\text{cyclic}\\ \text{triesters}}}{\text{Xa + Xb}} + CH_3OH$$

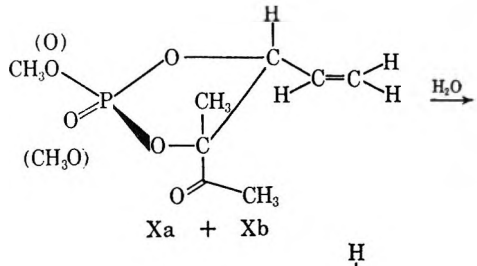
Hydrolysis of Pentaoxyphosphorane VII with an Excess of Water.—Extensive hydrolysis occurred very rapidly when 3 mol equiv of water was added to the solution of pentaoxyphosphorane VII in methylene chloride at 20°. The hydrolysis was instantaneous and exothermic when phosphorane VII was added to an excess of water at 0°. This hydrolysis gave three products. The minor product was the same open β triester, XII, previously described; this material was formed in approximately 20–25% yield. The other two products were the phospho monoesters, XIII and XIV, derived from the γ-unsaturated α,β-dihydroxy ketone, having the phosphoryl groups at the α- and β-hydroxy positions, respectively. Both structural isomers could be observed and *it was possible to follow the isomerization of the α monoester, XIII, into the β monoester, XIV.*



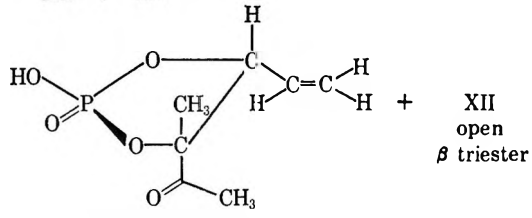
The phosphorus of the α monoester, XIII, gave a singlet while the phosphorus of the β monoester, XIV, gave a doublet, owing to coupling of the phosphorus with the methine protons on the β carbon. The signals for the acetyl and the methyl groups of the α monoester, XIII, were at τ 7.65 and 8.35, respectively. The corresponding signals for the β monoester, XIV, were at τ 7.70 and 8.50, respectively.

Hydrolysis of the Five-Membered Cyclic Phospho Triesters, Xa and Xb. A. With 1 Mol Equiv of H_2O in $CHCl_3$ Solution.—Under these conditions, the 5-cyclic triesters, Xa and Xb, were converted into two types of phosphates in about equal amounts. One of these was the 5-cyclic diester, XV, which was characterized by the large negative ^{31}P nmr shift,[6]

−14.0 ppm. The second product of the hydrolysis was the same open β triester, XII, previously dis-



Xa + Xb

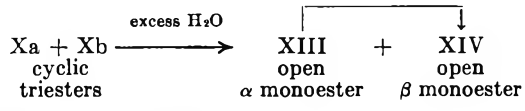


XV, $\delta^{31}P$ −14.0ppm

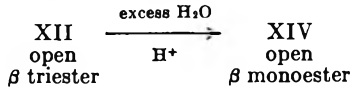
cussed. *This remarkable observation suggested that the 5-cyclic triester, X, underwent hydrolysis to the cyclic diester, XV, and 1 equiv of methanol; the methanol then reacted with the remaining cyclic triester giving the open β triester, XII, as before.*

B. With 2 Mol Equiv of D_2O in $CDCl_3$ Solution.—The hydrolysis was followed by means of ^1H nmr spectrometry and it was shown that after 1 hr at 20° the products were the α- and the β-phospho monoesters, XIII and XIV. Under these conditions, little or no β triester, XII, was produced; the cyclic diester, XV, underwent further hydrolysis to the open monoesters, XIII and XIV.

C. With a Large Excess of Water.—Under these conditions, the formation of the α and the β monoesters, XIII and XIV, was observed within 5 min. The complete conversion of the α into the β monoester was observed after 80 min.



Attempted Hydrolyses of the Open β-Phospho Triester, XII, and the β-Phospho Monoester, XIV.—The open phospho triester, XII, was relatively stable toward water in $CHCl_3$ solution or in an excess of water under neutral conditions at 20°. The addition of acid led to hydrolysis to the β-phospho monoester, XIV. However, no conditions could be found for the complete removal of the phosphorus from the β monoester, XIV, while retaining intact the structure of the sensitive unsaturated dihydroxy ketone.

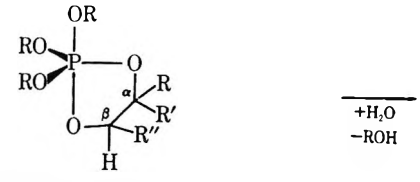


Discussion

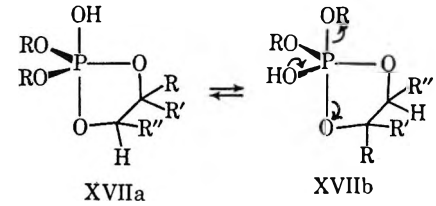
This work showed that derivatives of the 2,2-dihydro-1,3,2-dioxaphospholenes,[4] I, performed a 1,2 addition to the carbonyl group rather than a 1,4 addition to the olefinic double bond of α,β-unsaturated aldehydes. Very mild hydrolyses of the pentaoxyphosphoranes prepared in this manner provided cyclic phospho triesters, Xa and Xb, open phospho triesters, XI and XII, and phospho monoesters, XIII and XIV, derived from γ-unsaturated α,β-dihydroxy ketones.

It was possible to demonstrate experimentally that a phosphate ester adjacent to a carbonyl function as in XI and XIII was a less stable system than a phosphate ester on a β carbon of the α,β-dihydroxy ketone, as in XII and XIV. Apparently, the migration of the neutral dimethoxyphosphoryl group of the triesters from the α to the β positions (XI → XII) was considerably faster than the corresponding migration of a dihydroxyphosphoryl group in the monoesters (XIII → XIV).

The following interpretation accounts for the observations made during the hydrolyses and the methanolysis of the 5-cyclic pentaoxyphosphoranes and phosphate esters.[12] The first step in the hydrolysis of phosphorane XVI with 1 mol equiv of water is a nucleophilic substitution of the methoxy group by a hydroxy group to form a cyclic hydroxytetraalkoxyphosphorane, XVIIa. Little is known about the mechanism and in particular the stereochemistry, of this substitution.[13a] The available evidence tends to exclude an ionization or SN1 mechanism. In this substitution, the longer and probably weaker apical methoxy group is replaced first, but the very rapid positional exchange which results from pseudo-rotation[8-10,12] can lead to other forms of the trigonal bipyramid, for example XVIIb.



XVI, R = CH_3; R′ = CH_3CO; R″ = $CH{=}CH_2$

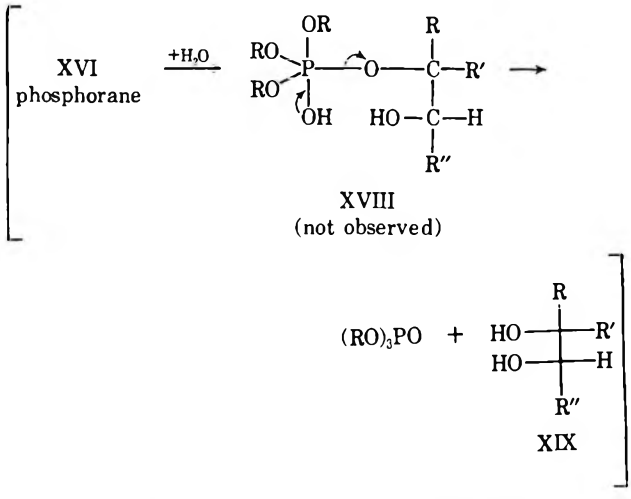


XVIIa XVIIb

If the first substitution on phosphorane XVI had occurred with ring opening to XVIII, the final product would have been trimethyl phosphate and the unsaturated dihydroxy ketone, XIX, since the latter should be more acidic than methanol and, hence, it would be a better leaving group. The retention of the ring during the hydrolysis is an interesting and, apparently, a general phenomenon;[5,6,12] it is, perhaps, related to differences in the strain which may develop

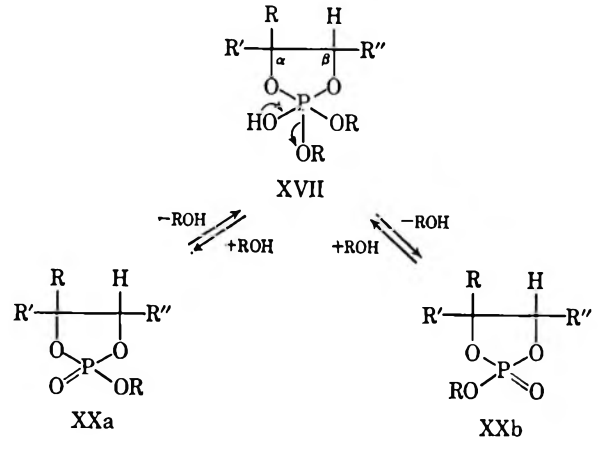
(12) D. Swank, C. N. Caughlan, F. Ramirez, O. P. Madan, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 6503 (1967).

(13) (a) For a comprehensive discussion of the stereochemistry of the reactions of organic phosphorus compounds in general, see W. E. McEwen in "Topics in Phosphorus Chemistry," M. Grayson and E. J. Griffith, Ed., Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1965, pp 1–42. (b) NOTE ADDED IN PROOF.—The retention of the ring in the hydrolysis of the cyclic oxyphosphorane is reasonable if the transition state of the hydrolysis resembles the reactant, *i.e.*, a trigonal bipyramid. The latter is more stable when two of the groups are held together in a ring than when all the groups are free to interfere with each other. Therefore, the transition state which results in ring retention should be of lower energy than that which results in ring opening. (c) NOTE ADDED IN PROOF.—The retention of the ring in the collapse of oxyphosphorane to phosphate is also reasonable if the transition state resembles the reactant, *i.e.*, a trigonal bipyramid. This assumption is reasonable since the reaction is highly exothermic.

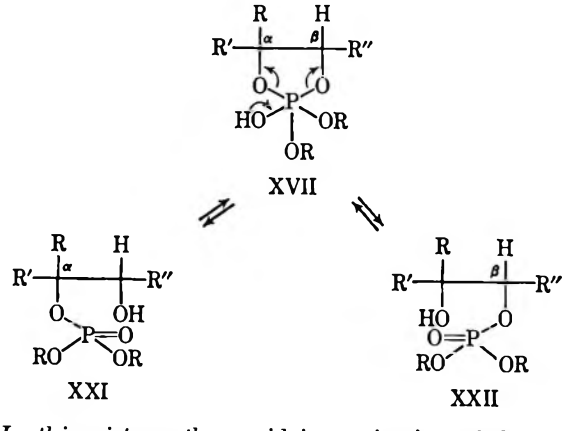


in the transition states leading to ring rupture and to ejection of the methoxy group.[13b]

The cyclic hydroxyphosphorane XVII collapses to the five-membered cyclic triesters XXa + XXb which are stereomers at phosphorus.[13c] Rapid stereomutation among these isomers involves, simply, the readdition of methanol to the phosphoryl group to give the common intermediate XVII.

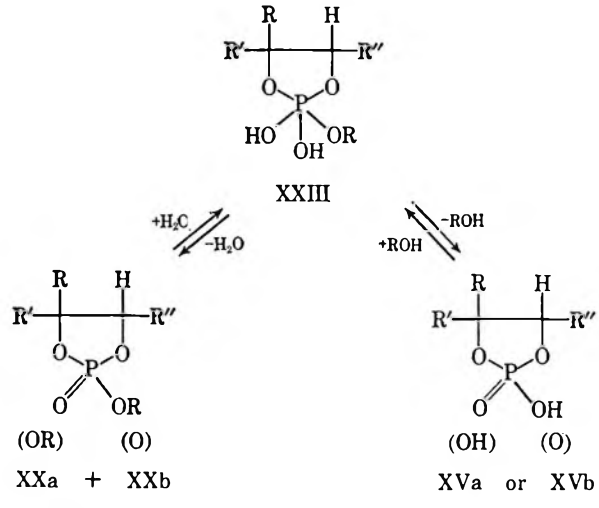


The collapse of hydroxyphosphorane XVII to the α- and the β-phospho triesters, XXI and XXII, eventually occurs.

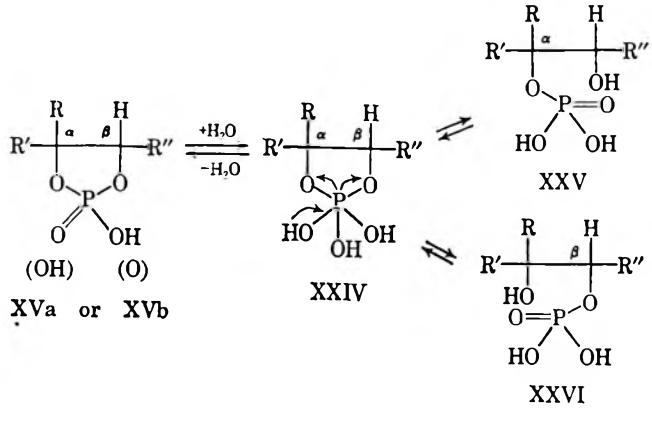


In this picture, the rapid isomerization of the α into the β triesters, XXI → XXII, proceeds through the common intermediate, XVII. Likewise, the rapid methanolysis of the cyclic triesters, XXa and XXb, proceeds through the common intermediate XVII, leading to the open triesters, XXI and XXII. The cyclization of the open triester, XXII → XXa + XXb, involves also the same intermediate, XVII.

The hydrolysis of the cyclic triesters, XXa and XXb, probably involves the addition of water to the phosphoryl group, giving the cyclic dihydroxytrialkoxyphosphorane XXIII which collapses to the cyclic phospho diester, XVa or XVb, plus methanol.[12,14] The results of these experiments suggest that the addition of methanol to the cyclic triesters, XXa and XXb, to form XVII is as fast as, or faster than, the addition of water to the same triesters XXa and XXb to give XXIII.



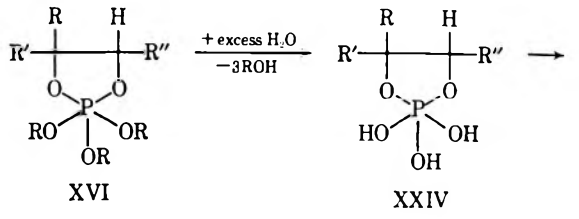
Addition of more water to the cyclic diester XVa or XVb would give the cyclic trihydroxydialkoxyphosphorane, XXIV. The latter should collapse to the α and the β monoesters, XXV and XXVI. The isomerization of the former into the latter proceeds *via* the cyclic intermediate XXIV.



The formation of the α and the β monoesters, XXV and XXVI, from the hydrolysis of pentaoxyphosphorane XVI with an excess of water could occur by the sequence of reactions just discussed. However, a direct path exists from XVI to the trihydroxyphosphorane, XXIV. It is significant that no open-chain phospho diester was observed; this tends to favor the direct mechanism XVI → XXIV → XXV + XXVI when excess of water is used.[15]

(14) F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson, and E. M. Banas, *J. Amer. Chem. Soc.*, **85**, 2681 (1963).

(15) This conclusion assumes that the hydrolysis of the open phospho diester to the open phospho monoester is a relatively slow process. There is no evidence for the addition of water to the phosphoryl group of the *open-chain* phosphate esters.



XVI XXIV XXV + XXVI

An important feature of these mechanisms is the ability of water and of methanol to add to the phosphoryl group of a five-membered cyclic phosphate, XXa, XXb, XVa, XVb. There is no evidence that this can happen to open-chain phosphate esters. The difference is probably due to (1) the lower stability of a 5-cyclic phosphate *vs.* an open-chain phosphate[16] and (2) the higher stability[7] of a 5-cyclic oxyphosphorane *vs.* the open-chain analogs.[17]

Much attention[12,14,16,18-21] has been devoted to the mechanism of hydrolysis of 5-cyclic phosphates.[18] Much of the progress in this field is due to the work of Westheimer and his coworkers.[16,19] We first observed *the complete retention of the ring* when 1 mol of water was added to several 5-cyclic phospho triesters.[14] We related the hydrolysis of the isolated, stable, five-membered cyclic pentaoxyphosphoranes to the hydrolysis of the five-membered cyclic phospho triesters by means of the analogous hypothetical intermediates XXIII and XVII.[5,12,14]

Experimental Section

Analyses were by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (III) with Acrolein.—Acrolein (31.2 g, 0.555 mol) was rapidly added to a solution of 90.0 g (0.428 mol) of phospholene III in 400 ml of dry CH_2Cl_2 at 0° with stirring. Stirring was continued for 2 hr at 0° and then for 2 days at 20°. Solvent and excess acrolein were evaporated at 30° (20 mm). Distillation at 0.2-mm pressure afforded 102 g (90%) of a clear oil, formulated as 2,2,2-trimethoxy-4β-methyl-4α-acetyl-5α-vinyl-2,2-dihydro-1,3,2-dioxaphospholane (VII): bp 96° (0.2 mm); $n^{25}D$ 1.4501.

Anal. Calcd for $C_{10}H_{19}O_6P$: C, 45.0; H, 7.2; P, 11.6. Found: C, 44.9; H, 7.0; P, 11.4.

The ^1H nmr signals are given in Table I. The infrared spectrum had characteristic bands (in CCl_4) at 5.86 (acetyl) and 9.39 μ ($POCH_3$).

Reaction of the Trimethoxy Biacetylacrolein Phosphite Adduct, VII, with 1 Mol Equiv of Water.—Water (1 mol equiv, 1.98 ml) was added to a solution containing 28.7 g (0.108 mol) of phospholane VII in 50 ml of chloroform at 0°. *The mixture was stirred for 2 hr at 20°* and was concentrated at 20° (20 mm). The residue was shown to contain only one type of phosphorus nucleus by ^{31}P nmr spectroscopy. This substance, which was obtained in nearly quantitative yield, was formulated as 4-methyl-1-hexene-3,4-diol-5-one 3-dimethyl phosphate (XII). The ^1H nmr spectrum of the pure liquid is summarized in Table II.

The infrared spectrum in CCl_4 had characteristic bands at 3.03 (OH), 5.87 (C=O), 7.92 (open-chain phosphate ester), and 9.60 μ ($POCH_3$). Attempts to purify this ester by distillation resulted in loss of methanol as described in the next experiment.

Cyclization of the Open-Chain Phospho Triester to the Corresponding Five-Membered Cyclic Triester.—A sample (26 g, 0.10 mol) of 4-methyl-1-hexene-3,4-diol-5-one 3-dimethyl phosphate (XII), described in the previous experiment, was submitted to three successive distillations through a 10-cm Vigreux column at 0.2 mm. Methanol (3 ml, 1 mol equiv) was collected in a trap cooled to −70°. The distillate (21 g, 84% yield) consisted of two diastereomers at phosphorus of 2-methoxy-2-oxo-4β-methyl-4α-acetyl-5α-vinyl-2,2-dihydro-1,3,2-dioxaphospholane (Xa + Xb), bp 116° (0.2 mm).

Anal. Calcd for $C_8H_{13}O_5P$: C, 43.5; H, 6.0; P, 14.1. Found: C, 43.3; H, 6.1; P, 13.9.

The ^1H nmr signals are given in Table II. The infrared spectrum in CCl_4 had characteristic bands at 5.85 (C=O), 7.68 (cyclic phosphate ester, sharp and strong), and 9.50 μ ($POCH_3$).

Reaction of the 5-Cyclic Phospho Triester (Two Diastereomers at Phosphorus, Xa and Xb) with Methanol. A.—Methanol (2 mol equiv) was added to a methylene chloride solution of the 5-cyclic phospho triesters at 20° in an nmr sample tube.

B.—An excess of methanol was added to the cyclic triester in the absence of additional solvent. Measurements of the nmr spectra of these solutions were made at various intervals. The only product observed was the open-chain phospho triester XII which was formed at approximately the same rate in both experiments A and B. The pertinent nmr signals are given in Table II.

Course of the Hydrolysis of the Trimethyl Biacetylacrolein Phosphite Adduct, VII, by 1 Mol Equiv of D_2O in $CDCl_3$ Solution by ^1H Nmr Spectrometry.—The liquid adduct, VII, was diluted with an equal volume of $CDCl_3$ in an nmr sample tube. Deuterium oxide (1 mol equiv) was introduced and the mixture was shaken well for 3 min. The ^1H nmr spectra were examined at 5-min intervals with the following results: after 5 min, 80% 5-cyclic phospho triester (Xa + Xb), 20% open phospho triester (XII); after 20 min, 20% 5-cyclic phospho triester (Xa + Xb), 80% open phospho triester (XII); after 40 min, 5% 5-cyclic phospho triester (Xa + Xb), 95% open phospho triester (XII).

The ^{31}P nmr spectra, examined after 5, 15, and 45 min, showed the following: after 5 min, two peaks, cyclic phospho triester and open phospho triester in a ratio of about 80:20; after 15 min, two peaks, cyclic phospho triester and open phospho triester in a ratio of about 50:50; after 45 min, two peaks, cyclic phospho triester and open phospho triester in a ratio of about 5:95.

Reaction of the Trimethyl Biacetylacrolein Phosphite Adduct, VII, with an Excess of Water. A.—Adduct VII (56.0 g) was added to 150 ml of water at 0° with stirring. An exothermic reaction was observed. The solution was kept 45 min at 20° and was then titrated with 2 *N* NaOH to pH 7. Sodium hydroxide (2 mol equiv) was used in the titration to pH 7, which is consistent with the presence of a dibasic acid. This solution was extracted five times, each with 100 ml of $CHCl_3$. The $CHCl_3$ layer was evaporated at 20° (20 mm). The residue (23% yield) was identified as 4-methyl-1-hexene-3,4-diol-5-one 3-dimethyl phosphate (XII). The water layer was evaporated to dryness at 35° (0.2 mm). The residue (65% yield, mp 158–160°) was identified as the disodium salt of 4-methyl-1-hexene-3,4-diol-5-one 3-dihydrogen phosphate (salt of XIV): $\delta^{31}P$ +1.5 ppm (D_2O).

The ^1H nmr spectrum in D_2O had the following signals: a singlet at τ 8.50 (3 ^1H, CH_3C), a singlet at 7.70 (3 ^1H, CH_3CO), a doublet of doublets at 5.31 with J_{HP} = 8.5 cps and J_{HH} = 6.2 cps (1 ^1H, methine), and the vinyl protons, unresolved, centered at 4.25 (3 ^1H).

B.—The adduct, VII, 3 g, was added to 3 ml of water at 20°. After 10 min, the solution was extracted five times, each with 20 ml of $CHCl_3$, to remove the neutral phospho triester. The

(16) The extensive work of Westheimer and his coworkers has provided evidence for this strain: (a) J. Kumamoto and F. H. Westheimer, *J. Amer. Chem. Soc.*, **77**, 2515 (1955); (b) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *ibid.*, **78**, 4858 (1956); (c) P. C. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961); (d) M. Panar, E. T. Kaiser, and F. H. Westheimer, *ibid.*, **85**, 602 (1963); (e) A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965); (f) D. A. Usher, E. A. Dennis, and F. H. Westheimer, *ibid.*, **87**, 2320 (1965).

(17) Noncyclic pentaalkoxyphosphoranes have been obtained in solutions from the reactions of dialkyl peroxides with trialkyl phosphites. These phosphoranes appeared to have a low degree of stability: *cf.* (a) D. B. Denney and S. T. D. Gough, *ibid.*, **87**, 138 (1965); (b) D. B. Denney and L. Saferstein, *ibid.*, **88**, 1839 (1966).

(18) For recent summaries with bibliographies, see (a) H. Khorana, "Some Recent Developments on the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 3; (b) A. Todd, *Proc. Chem. Soc.*, 199 (1962).

(19) E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, **88**, 3431, 3432 (1966).

(20) (a) G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **19**, 931 (1965); (b) *ibid.*, **20**, 2508 (1966).

(21) R. L. Collin, *J. Amer. Chem. Soc.*, **88**, 3281 (1966).

aqueous solution containing the dibasic phospho monoesters (XIII and XIV) was submitted to ^{31}P and ^{1}H nmr spectrometry at several time intervals. *After 20 min*, two phosphorus nuclei were found: a singlet at +4.1 ppm (phosphate α to carbonyl as in XIII and a doublet at +1.5 ppm (phosphate β to carbonyl as in XIV, signal split by the methine proton).

The ^{1}H nmr spectrum of the same solution showed singlets at τ 8.35 (CH_3C) and 7.65 (CH_3CO) due to the α-phospho monoester (XIII) and singlets at τ 8.50 (CH_3C) and 7.70 (CH_3CO) due to the β-phospho monoester (XIV). The structural isomers were present in about equal proportions.

After 2 hr, the ^{31}P nmr signal of α-phospho monoester XIII (+4.1 ppm) had disappeared almost completely. The doublet due to β-phospho monoester XIV (+1.5 ppm) had doubled its intensity. The ^{1}H nmr signals of the α-phospho monoesters (τ 8.35 and 7.65) had decreased to about 10% of their original intensities, while the signals due to the β-phospho monoester (τ 8.50 and 7.70) had increased by about 90%.

Hydrolyses of the 5-Cyclic Phospho Triesters (Two Diastereomers at Phosphorus, Xa and Xb) with 1 Mol Equiv of Water.—Water (1 mol equiv) was added to a solution of the cyclic triesters, Xa and Xb (3.1 g, 12 mmol), in 12 ml of $CHCl_3$ at 20°. The solvent was removed at 20° and 20 mm, leaving a light brown, oily residue. The ^{31}P nmr spectrum of this liquid had two signals of about equal intensities. One of them at −0.5 ppm was due to the β-open phospho triester (XII). The other at −14.0 was due to the 5-cyclic phospho diester, XVa or XVb.

The ^{1}H nmr signal of the original $CHCl_3$ solution confirmed these assignments and showed the absence of methanol; *i.e.*, the methanol produced in the hydrolysis reacted with the cyclic triester, X, to give the open triester, XII.

Hydrolyses of the 5-Cyclic Phospho Triesters (Two Diastereomers at Phosphorus, Xa and Xb) with an Excess of Water.—The 5-cyclic triesters, Xa and Xb, were mixed with an equal volume of water in an nmr sample tube. After the exothermic reaction had subsided, the solution was analyzed by ^{31}P and ^{1}H nmr spectrometry at various time intervals. The signals due to the α monoester, XIII (+4.1, τ 8.35 and 7.65), which were observed after 30 min, had vanished completely after 2.5 hr. The corresponding signals due to the β-phospho monoester, XIV, had increased in intensity. When the solution was heated 3 min at 100°, it turned dark brown and was not investigated further.

Behavior of the Open-Chain β-Phospho Triester toward Hydrolysis. A.—The open-chain β-phospho triester, XII, was mixed with an equal volume of water at 20°. The ^{1}H nmr spectrum taken at 30-min intervals over a period of 8 hr revealed no significant change.

B.—Addition of 1 drop of phosphoric acid to the aqueous solution caused hydrolysis to the β-phospho monoester (XIV). After 10 min, the extent of the hydrolysis was roughly 5–10%; after 5 hr, approximately 5% of the original signal due to the $POCH_3$ group was present. These results were confirmed by ^{31}P nmr analysis.

Registry No.—VII, 15353-05-6; Xa, 15353-06-7; Xb, 15353-07-8; XII, 15353-08-9; disodium salt of XIV, 15353-09-0.

New Syntheses of β-Keto-α-hydroxy Acid Chlorides, of α-Hydroxy β-Diketones, and of Their Phosphate Esters

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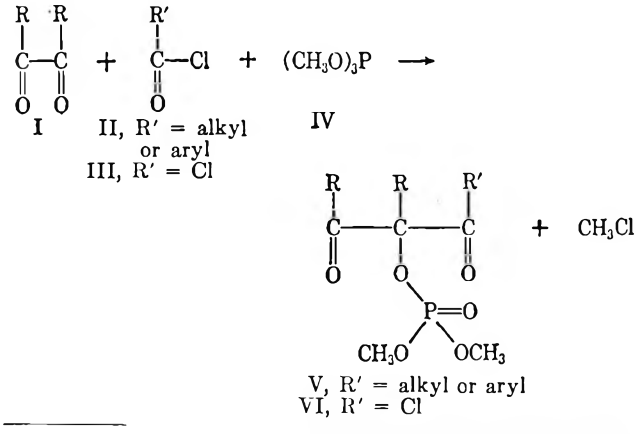
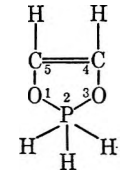
The 1:1 adduct made from biacetyl, $CH_3COCOCH_3$, and trimethyl phosphite, $(CH_3O)_3P$, namely, 2,2,2-trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene, performed a nucleophilic substitution at the carbonyl carbon of carboxylic acid chlorides, R'COCl, and of phosgene, ClCOCl. This new reaction provided a direct synthesis of phosphate esters derived from α-hydroxy β-diketones, R'COC(OH)(R)(COR), and from β-keto-α-hydroxy acid chlorides, ClCOC(OH)(R)(COR). The α-hydroxy β-diketone phosphates underwent an extraordinarily facile hydrolysis to the diketo alcohols.

This paper describes two related new reactions. In one of them, a trialkyl phosphite, IV, was used as the reagent to effect the carbon–carbon condensation of an α-diketone, I, with a carboxylic acid chloride, II, to form the phosphate ester, V, of an α-hydroxy β-diketone. In the second reaction, the trialkyl phosphite, IV, effected the condensation of an α-diketone, I, with phosgene, III, to form the phosphate ester, VI, of a β-keto α-hydroxy acid chloride.



These reactions were carried out in two steps. First, the α-diketone and the phosphite ester were combined in the form of a 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholene,[2,3] VII. Then the phospholene VII was mixed with the acid chloride II or III to give methyl chloride and the corresponding phosphate ester V or VI. It was assumed[4] that a tetra-



(1) This investigation was supported by Public Health Service Grant No. CA-04769-08 from the National Cancer Institute, and by the National Science Foundation Grant CP-6690-Y.

(2) The parent ring system can be named 2,2-dihydro-1,3,2-dioxaphospholene. This name implies the pentacovalency of the phosphorus.

(3) The literature on 2,2-dihydro-1,3,2-dioxaphospholenes has been reviewed: (a) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964); (b) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 2268 (1967).

(4) (a) F. Ramirez, S. B. Bhatia, and C. P. Smith, *ibid.*, **89**, 3026 (1967); (b) F. Ramirez and N. B. Desai, *ibid.*, **82**, 2652 (1960).

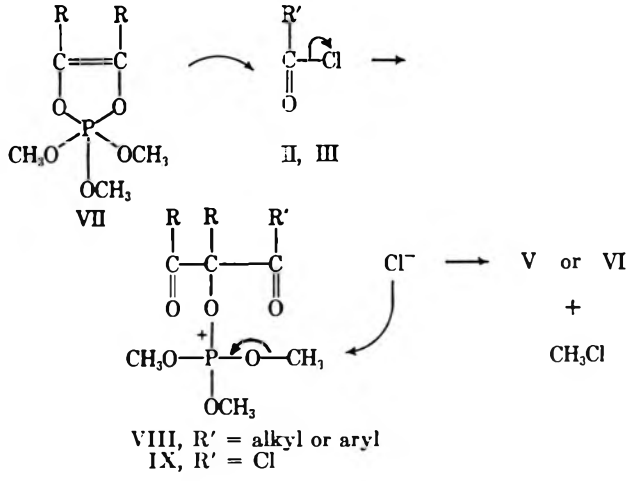
TABLE I

α-HYDROXY β-DIKETONE–DIMETHYL PHOSPHATES FROM THE REACTION OF THE BIACETYL–TRIMETHYL PHOSPHITE ADDUCT, XIII, WITH ACID CHLORIDES,[a] RCOCl

R in RCOCl	Compd	Mp[c] or bp (mm)	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P	Yield, %	Conditions: Solvent	Conditions: Temp, °C	Conditions: Time, hr
CH_3	XVI	87–88 (0.1)	*b*							78	None	55	16
CF_3[c]	XVII	79–80 (0.1)	$C_8H_{12}O_6F_3P$[d]	32.9	4.1	10.6	32.7	4.1	10.5	70[e]	CH_2Cl_2	10	3
C_6H_5	XXVII	74–75[f]	$C_{12}H_{17}O_6P$	52.0	5.7	10.3	51.7	5.7	10.5	71	$C_2H_4Cl_2$	80	30
p-$NO_2C_6H_4$	XXVIII	103–104[f]	$C_{13}H_{16}O_8NP$[g]	45.2	4.6	9.0	44.8	4.6	8.8	90[h]	CH_2Cl_2	40	24
p-FC_6H_4[i]	XXIX	148–153 (0.02)	$C_{12}H_{16}O_6FP$[j]	49.0	5.0	9.7	48.4	5.2	9.7	85	None	70	24
p-$CH_3OC_6H_4$[k]	XXX	*l*								*ca.* 70	None	100	48

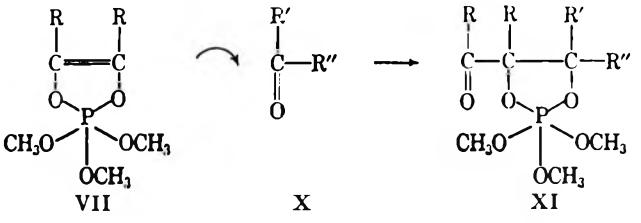
[a] Equimolar amounts of the reagents were allowed to react under the conditions indicated, in a dry N_2 atmosphere. [b] Reference 4a. [c] The gaseous chloride was passed over anhydrous $CuSO_4$ prior to the reaction. [d] Calcd for fluorine: 19.5%. Found: 19.4%. [e] By-products were 15% of $(CH_3O)_3PO$ removed at 50–60° (0.1 mm), 15% of acetyltrifluoroacetylmethylcarbinyl chloride removed below 45° (40 mm), and 5% of dimethyl phosphoacetoin. [f] From benzene–hexane. [g] Calcd for nitrogen: 4.0%. Found: 4.3%. [h] Crude mp 99–102°; 80% after crystallization. [i] By-product, 10% of $(CH_3O)_3PO$. [j] Calcd for fluorine: 5.9%. Found: 5.4%. [k] Two molar equivalents of the adduct XIII were used. The excess of XIII was removed below 70° at 0.1 mm. [l] The phosphate XXX could not be purified by distillation or crystallization; it was hydrolyzed to the hydroxy diketone.

alkoxyphosphonium chloride,[5] VIII or IX, was formed as a fleeting intermediate.

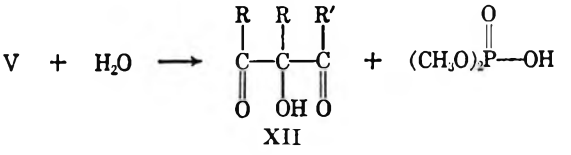


VIII, R′ = alkyl or aryl
IX, R′ = Cl

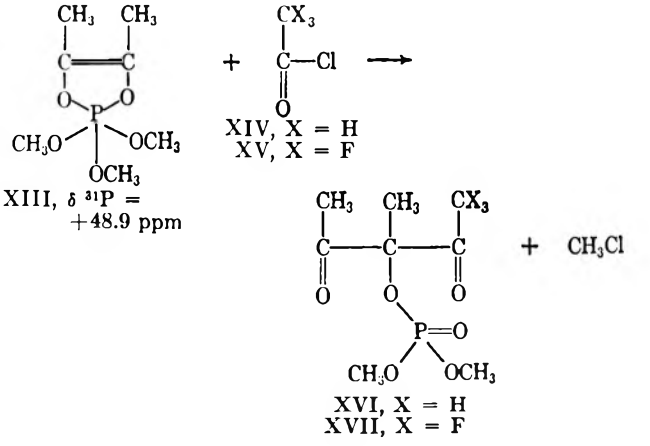
The reaction of the phospholene, VII, with the acid chlorides is a nucleophilic substitution at an unsaturated carbon and should be compared with the related nucleophilic additions of the phospholene to a variety of carbonyl compounds that have been discovered in this laboratory,[6,7] for example, VII + X → XI.



The synthetic scope of the new condensation of phospholenes of type VII with acid chlorides is widened by the extraordinary ease with which phosphate esters of α-hydroxy β-diketones, V, undergo hydrolyses.[4a,8]



Reaction of the Biacetyl–Trimethyl Phosphite 1:1 Adduct, XIII, with Aliphatic Acid Chlorides.—Acetyl chloride reacted smoothly with the biacetyl–trimethyl phosphite adduct XIII under the conditions given in Table I. The product was diacetylmethylcarbinol dimethyl phosphate XVI which had the spectral characteristics listed in Table II.



The hydroxy diketo phosphate, XVI, was identical with a sample made by a new procedure which involved the nucleophilic addition of the phospholene XIII to ketene.[4a] This reaction gave a cyclic pentaoxyphosphorane, XVIII, having an exocyclic enol-ether function. Treatment of this phosphorane with hydrogen chloride afforded the hydroxy diketo phosphate, XVI, *via* the same intermediate tetraalkoxyphosphonium chloride (VIII, R = CH_3) previously discussed.

(5) (a) J. S. Cohen, *J. Amer. Chem. Soc.*, **89**, 2543 (1967); (b) K. D. Berlin, M. Nagabhushanam, and E. T. Gaudy, *Tetrahedron*, **22**, 2191 (1966); (c) D. B. Denney and J. Giacini, *Tetrahedron Lett.*, 1747 (1964); (d) A. Schmidpeter, B. Wolf, and K. Düll, *Angew. Chem. Intern. Ed. Engl.*, **4**, 712 (1965); (e) H. Teichmann, M. Jatkowski, and G. Hilgetag, *ibid.*, **6**, 372 (1967).

(6) (a) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961); (b) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Amer. Chem. Soc.*, **84**, 1317 (1962); (c) F. Ramirez, N. B. Desai, and N. Ramanathan, *Tetrahedron Lett.*, 323 (1963).

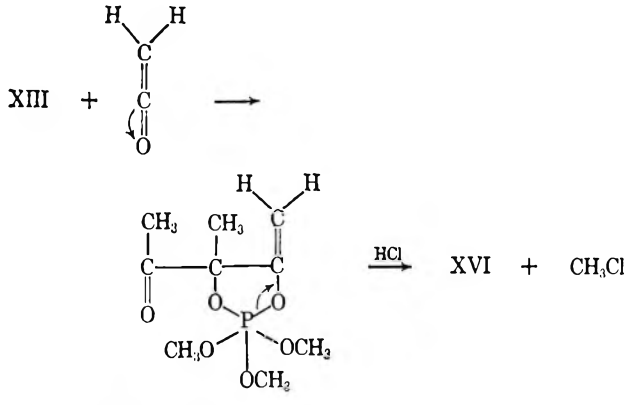
(7) The literature on 2,2-dihydro-1,3,2-dioxaphospholanes has been reviewed: (a) F. Ramirez, *Bull. Soc. Chim. Fr.*, 2443 (1966); (b) F. Ramirez, S. B. Bhatia, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **32**, 2194 (1967); (c) F. Ramirez, S. B. Bhatia, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 3030 (1967).

(8) F. Ramirez, B. Hansen, and N. B. Desai, *ibid.*, **84**, 4588 (1962).

TABLE II
SPECTRAL PROPERTIES OF β-HYDROXY β-DIKETONE DIMETHYL PHOSPHATES[a]

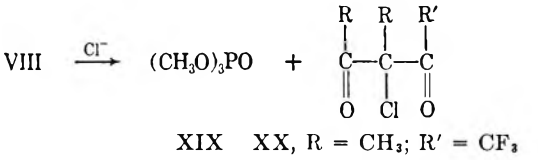
R derived from RCOCl	Compd	δ ^{31}P, ppm	^{1}H nmr[b] τ (CH_3CO)	τ (CH_3)	τ (CH_3O)	J_{HP}, cps	τ (CH_3O)	J_{HP}, cps	Ir, μ[c] (C=O)
CH_3	XVI	+3.0	7.75	8.27	6.20	11.2			5.80, 5.83
CF_3	XVII	+3.2	7.59	8.15	6.17	11.5	6.19	11.5	5.62, 5.80
C_6H_5	XXVII	+3.0	7.65	8.07	6.30	11.4	6.51	11.4	5.80, 5.90
p-$NO_2C_6H_4$	XXVIII	+2.7	7.55	8.02	6.22	11.5	6.41	11.5	5.80, 5.90
p-FC_6H_4	XXIX	+2.9	7.57	8.03	6.23	11.5	6.42	11.5	5.80, 5.90
p-$CH_3OC_6H_4$[d]	XXX	+3.0	7.66	8.05	6.23	11.5	6.42	11.5	5.80, 5.90

[a] ^{31}P nmr are given in parts per million *vs.* H_3PO_4 in CH_2Cl_2 at 40.5 Mcps. ^{1}H Nmr are given in parts per million *vs.* TMS = 10 in $CDCl_3$ at 60 Mcps. Infrared spectra in CH_2Cl_2. [b] The aromatic hydrogens gave the expected signals. [c] All phosphates had strong bands at 7.85 micron (PO) and 9.6 μ ($POCH_3$). [d] Singlet at τ 6.15 (CH_3O on aromatic ring).



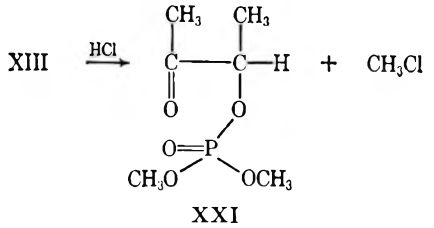
XVIII, δ ^{31}P = +51.4 ppm

Trifluoroacetyl chloride[9] (XV) was extremely reactive toward the phospholene XIII, as can be seen by the conditions given in Table I. Acetyltrifluoroacetylmethylcarbinol dimethyl phosphate (XVII) was isolated in satisfactory yield. Two by-products were also isolated from this reaction, namely, trimethyl phosphate (XIX) and acetyltrifluoroacetylmethylcarbinyl chloride (XX). The formation of these minor products is readily explained as a nucleophilic substitution by chloride ion on the α carbon rather than the methyl group of the tetraalkoxyphosphonium salt, VIII → XIX + XX.

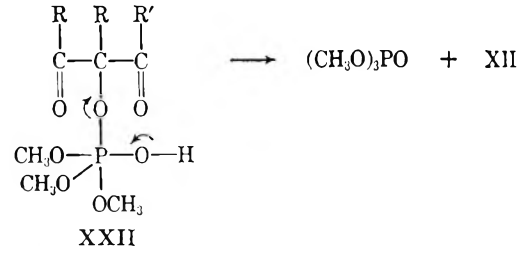


XIX XX, R = CH_3; R′ = CF_3

It should be emphasized that the success of this reaction, and of related ones, requires the absence of hydrogen chloride from the carboxylic acid chloride. It is known[4] that the phospholene XIII is converted into dimethyl phosphoacetoin (XXI) by hydrogen chloride. Strictly anhydrous conditions are demanded by the sensitivity of the reagents to water and by the decomposition of the intermediate VIII into trimethyl phosphate and the hydroxy diketone as shown in formula XXII.

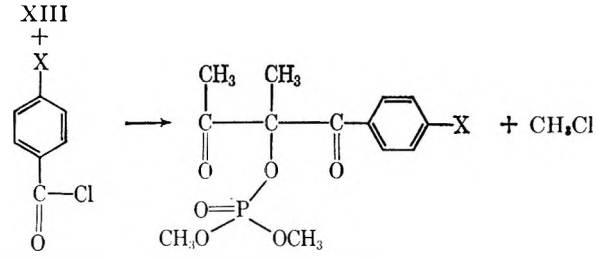


XXI



XXII

Reaction of the Biacetyl–Trimethyl Phosphite 1:1 Adduct with Aromatic Acid Chlorides.—The reaction of benzoyl chloride with the phospholene XIII gave acetylbenzoylmethylcarbinol dimethyl phosphate (XXVII) using the conditions given in Table I. The spectral properties are listed in Table II.



XXIII, X = H XXVII, X = H
XXIV, X = NO_2 XXVIII, X = NO_2
XXV, X = F XXIX, X = F
XXVI, X = OCH_3 XXX, X = OCH_3

Electron-withdrawing groups on the aromatic acid chloride, XXIV and XXV, increased their reactivity toward the phospholene. This was illustrated by the syntheses of acetyl-*p*-nitrobenzoylmethylcarbinol dimethyl phosphate (XXVIII) and of acetyl-*p*-fluorobenzoylmethylcarbinol dimethyl phosphate (XXIX); *cf.* Tables I and II. Less than 10% of trimethyl phosphate was formed as a by-product in these reactions.

Acid chlorides with electron-releasing groups on the aromatic ring were distinctly less reactive toward the phospholenes. Note the preparation of acetyl-*p*-methoxybenzoylmethylcarbinol dimethyl phosphate (XXX) from anisoyl chloride (XXVI).

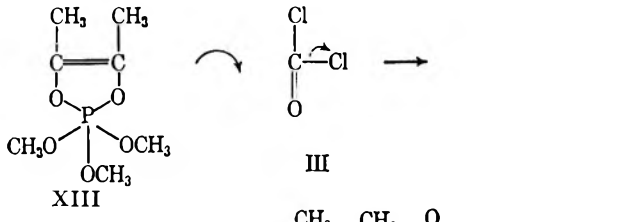
Reaction of the Biacetyl–Trimethyl Phosphite Adduct with Phosgene.—This reaction was carried out at 0° in methylene chloride and afforded α-methyl

(9) A. L. Henne, R. M. Alm, and M. Smoak, *J. Amer. Chem. Soc.* **76**, 1968 (1948).

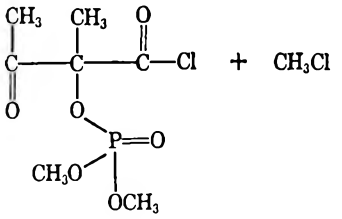
TABLE III
ANALYSES AND SPECTRAL PROPERTIES OF α-HYDROXY β-DIKETONES[a]

R derived from RCOCl	Compd	Bp° (mm)	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	^{1}H nmr[b] τ (CH_3CO)	^{1}H nmr[b] τ (CH_3)	Ir, μ[c]
CH_3	XXXIII	43–44 (4)	*d*					7.76	8.48	5.84
CF_3[e]	XXXIV	71–72 (58)	$C_6H_7O_3F_3$[f]	39.1	3.8	39.4	3.8	7.66	8.32	5.66, 5.80
C_6H_5	XXXV	73–74 (0.01)	$C_{11}H_{12}O_3$	68.7	6.3	67.9	6.3	7.82	8.32	5.80, 5.95
p-$NO_2C_6H_4$	XXXVI	118–119 (0.02)	$C_{11}H_{11}O_5N$[g]	55.7	4.6	55.2	4.8	7.65	8.25	5.80, 5.90
p-FC_6H_4	XXXVII	75–76 (0.01)	$C_{11}H_{11}O_3F$	62.8	5.2	62.5	5.2	7.78	8.30	5.80, 5.92
p-$CH_3OC_6H_4$[h]	XXXVIII	125–126 (0.05)	$C_{12}H_{14}O_4$	64.9	6.3	64.9	6.6	7.82	8.32[i]	5.80, 5.97

[a] A mixture of the phosphate ester, benzene, and water was kept 12 hr at reflux temperature. The water layer was extracted with benzene. The combined benzene solution was extracted with 5% aqueous sodium bicarbonate and distilled. The hydroxydiketones were isolated in about 60–70% yield. [b] Given in parts per million *vs.* TMS = 10 (τ values) in $CDCl_3$; the signals due to the hydroxylic proton were in the range τ 4.75–τ 5.14. [c] The bands due to the OH group were at 2.95 μ. [d] Reference 4a. [e] The phosphate ester, XVII, was very sensitive to water; see Experimental Section. [f] Calcd for fluorine: 31.0%. Found: 31.0%. [g] Calcd for nitrogen: 5.9%. Found: 6.2%. [h] The crude dimethyl phosphate ester was subjected to hydrolysis; the hydroxy diketone was obtained in 40% yield based on the phospholene, XIII. [i] τ 6.16 ($CH_3OC_6H_4$).



XIII III

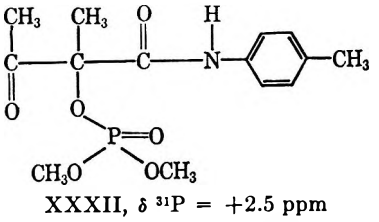


XXXI, δ ^{31}P = +3.2 ppm

α-hydroxyacetoacetyl chloride dimethyl phosphate (XXXI) in satisfactory yield.

It was, of course, necessary to remove hydrogen chloride from the phosgene[10] to prevent the conversion of the phospholene XIII into dimethyl phosphoacetoin (XXII). The acid chloride XXXI was quite stable at 20°, in the presence or in the absence of inert solvents. However, the chloride was rapidly transformed into a variety of products when heated above 80°. These transformations, as well as other aspects of the chemistry of this new type of polyfunctional phosphate ester, will be discussed elsewhere.

The structure of the acid chloride XXXI was based on the following. (1) The ^{31}P nmr shift was typical of a phosphate ester. (2) The ^{1}H nmr spectrum had singlets at τ 7.61 and 8.15 due to the protons of the acetyl and the C-methyl groups, respectively;[11] the spectrum also had two doublets, one at τ 6.11 and the other at 6.17, both with J_{HP} = 11.5 cps, which were due to the nonequivalent methoxy groups on phosphorus. (3) The infrared spectrum had bands at 5.60 and 5.80 due to the carbonyl functions, and at 7.82 and 9.6 μ due to the phosphate group. (4) The crystalline *p*-toluide derivative, XXXII, had the



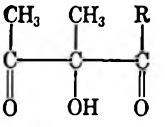
XXXII, δ ^{31}P = +2.5 ppm

(10) I. G. Farbenind A.-G., Belgian Patent 450,648 (June 1943); *Chem. Abstr.*, **41**, 7063*d* (1947).

expected elemental analysis and spectral properties.

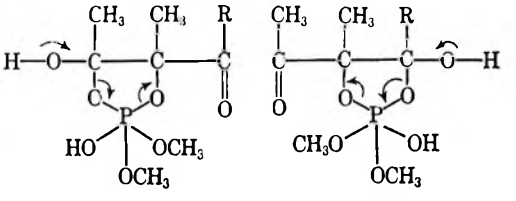
The acid chloride XXXI failed to react with an excess of the phospholene XIII in the temperature range where the chloride was stable.

Hydrolysis of the Phosphate Esters of α-Hydroxy β-Diketones.—These phosphate esters were converted into the α-hydroxy β diketones, XXXIII–XXXVIII, with extraordinary ease. The procedure used and the properties of the alcohols are given in Table III.



XXXIII, R = CH_3
XXXIV, R = CF_3
XXXV, R = C_6H_5
XXXVI, R = p-$NO_2C_6H_4$
XXXVII, R = p-FC_6H_4
XXXVIII, R = p-$CH_3OC_6H_4$

We have suggested[4a,8] that the rapid hydrolysis of the α-ketol phosphates may be due to carbonyl participation and pentaoxyphosphorane formation as shown in formulas XXXIXa and XXXIXb.



XXXIXa XXXIXb

Experimental Section

The analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The instrumentation was described previously.[12]

Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (XIII) with Carboxylic Acid Chlorides.—The phospholene XIII was prepared as described.[4b,12a] It must be protected against moisture and air; it should be redistilled after storage for several weeks. The acid chlorides were freshly distilled or crystallized.

The reactions of the liquid phospholene XIII with the acid

(11) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **31**, 3159 (1966).

(12) (a) F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco, and S. R. Heller, *J. Amer. Chem. Soc.*, **87**, 543 (1965); (b) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *ibid.*, **87**, 549 (1965).

chlorides were carried out under the conditions indicated in Table I. The reagents were mixed in the absence or in the presence of solvents, depending on the reactivity of the chlorides and on their physical state. The course of the reaction was followed by means of infrared spectrometry on small aliquots. At the end of the reaction, the solvent was evaporated under vacuum. When the products were liquids, purification was effected by vacuum distillation. When the products were solids, the crude phosphates, usually of an acceptable degree of purity, were obtained by addition of cold ether. The phosphates were crystallized from the solvents indicated in Table I.

Reaction of the Phospholene XIII with Phosgene.—The phosgene was condensed in a trap at −70° and was then passed[10] through anhydrous $CuSO_4$ and led into a 5 *M* solution of the biacetyl–trimethyl phosphite adduct, XIII, in methylene chloride at 0°. The addition of the phosgene was carried out over a 2-hr period; the chloride was used in excess (*ca.* 1.7 mol equiv). The solution was kept overnight at 20° and was then freed from solvent at 20° and 10 mm, with protection against moisture. The residue was analyzed by ^1H and ^{31}P nmr and infrared spectrometry. This material consisted of 95% acid chloride XXXI and 5% dimethyl phosphoacetoin. *The acid chloride should be handled with care since it may have a high degree of toxicity.*

The acid chloride XXXI (33 mmol) in benzene (80 ml) was treated at 0° with *p*-toluidine (67 mmol) in benzene (25 ml). The mixture was kept 1 hr at 25° and was then filtered. The filtrate was evaporated at 25° (10 mm) and the residue was washed with pentane. The crude *p*-toluide XXXII (76% yield) had mp 102–103°. The analytical sample had the same melting point (from benzene–hexane).

Anal. Calcd for $C_{14}H_{20}O_6NP$: C, 51.1; H, 6.1; N, 4.2. Found: C, 51.1; H, 6.2; N, 4.3.

The infrared spectrum in CH_2Cl_2 had bands at 3.00, 5.78, 5.95, and 7.80 μ. The ^1H nmr spectrum in $CDCl_3$ had singlets at τ 7.66 ($CH_3C_6H_4$–), 7.70 (CH_3CO), and 8.03 (CH_3C); it had doublets at 6.12 and 6.17, both with J_{HP} = 11 cps; it had aromatic protons near 2.7.

Hydrolysis of the Phosphate Esters of α-Hydroxy β-Diketones.—The procedure used and the properties of the resulting alcohols are given in Table III.

Acetyltrifluoroacetylmethylcarbinol dimethyl phosphate (XVII) was very sensitive to water, therefore, the following procedure was used. The phosphate (9.10 g) was dissolved in ether (30 ml) and the solution was cooled to 0°. One molar equivalent of water was added and the mixture was stirred for 30 min at 0° and for 30 min at 20°. The solution was submitted to fractional distillation and gave the hydroxy diketone, XXXIV, in 65% yield; *cf.* Table III.

Acetyltrifluoroacetylmethylcarbinyl Chloride (XX).—As stated in Table I, the reaction of the biacetyl–trimethyl phosphite adduct, XIII, with trifluoroacetyl chloride (XV) gave a by-product which was removed by distillation below 45° at 40 mm. This liquid was distilled and gave the chloro diketone, XX, bp 79–80° at 80 mm.

Anal. Calcd for $C_6H_6O_2F_3Cl$: C, 35.6; H, 3.0; F, 28.2; Cl, 17.3. Found: C, 35.9; H, 3.1.

The infrared spectrum in CH_2Cl_2 had bands at 5.62 and 5.80 with a shoulder at 5.70 μ. The ^1H nmr spectrum in $CDCl_3$ had singlets at τ 7.53 (acetyl) and 8.16 (methyl on C).

Registry No.—XIII, 1665-79-8; XVI, 15088-11-6; XVII, 15186-04-6; XVIII, 15088-10-5; XX, 15138-14-4; XXVII, 15138-15-5; XXVIII, 15138-16-6; XXIX, 15138-17-7; XXX, 15186-02-4; XXXI, 15138-18-8; XXXII, 15215-70-0; XXXIII, 7338-73-0; XXXIV, 15138-20-2; XXXV, 15138-21-3; XXXVI, 15138-22-4; XXXVII, 15186-03-5; XXXVIII, 15138-23-5.

Reaction of Hydriodic Acid with Tertiary Ketols[1]

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Received May 18, 1967

The reaction of hydriodic acid in refluxing acetic acid on tertiary ketols can bring about reduction to saturated ketones, rearrangements, and/or eliminations. Many ketols undergo these reactions whereby an intermediary carbonium ion can explain these reaction sequences. If the ketone cannot enolize no reaction takes place.

Recent publications[3–5] by Reusch, *et al.*, on the reduction of saturated and unsaturated α-diketones and secondary α-ketols with hydriodic acid in refluxing acetic acid prompted this publication on the reaction of the same reagent on tertiary ketols. *A priori*, we were interested in a versatile method for the reduction of 17α-hydroxy 20-keto steroids and also in the reduction of the 17,21-dihydroxy 20-keto side chain as an addition to already well-established methods[6–8] of reduction with zinc and acetic acid. Further examples for the study of tertiary ketol reduction by hydriodic acid were carried out in order to assess this method.

Most materials were allowed to react under the same conditions described by Reusch,[3–5] except in the case of 1-acetyl-1-hydroxycyclohexane which required increased temperature and duration of reaction. In all cases an immediate release of iodine was observed which rendered the solution dark. All conversions were free of tar formation[9] and gave in most cases readily separable mixtures.

Thus, 17α-hydroxyprogesterone (1) was first rearranged[10] to 17aα-methyl-17aβ-hydroxy-D-homoandrost-4-ene-3,17-dione[11] (2), which in turn was reduced to 17aβ-methyl-D-homoandrost-4-ene-3,17-dione (3) (see Scheme I). The isomerization[10] of 17α-hydroxyprogesterone with base and the isolation of the resulting isomeric hydroxymethyl-D-homo ketones is described in detail in the Experimental Section.

Both 3β-methyl-3α-hydroxy-5α-androstane-2,17-dione[12] (7) and 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one[12] (10) gave the identical product, 3β-methyl-5α-androstane-2,17-dione (6) (see Scheme II).

(1) Supported, in part by grants AM-01934 and AM-07280 from the National Institute of Arthritis and Metabolic Diseases.

(2) Ayerst Laboratories, Montreal, Que.

(3) W. Reusch and R. LeMahieu, *J. Amer. Chem. Soc.*, **85**, 1669 (1963).

(4) W. Reusch and R. LeMahieu, *ibid.*, **86**, 3068 (1964).

(5) W. Reusch, R. LeMahieu, and R. Guynn, *Steroids*, **5**, 110 (1965).

(6) J. K. Norymberski, *J. Chem. Soc.*, 517 (1956).

(7) H. L. Slates and N. L. Wendler, *J. Org. Chem.*, **22**, 498 (1957).

(8) R. S. Rosenfeld, *J. Amer. Chem. Soc.*, **79**, 5540 (1957).

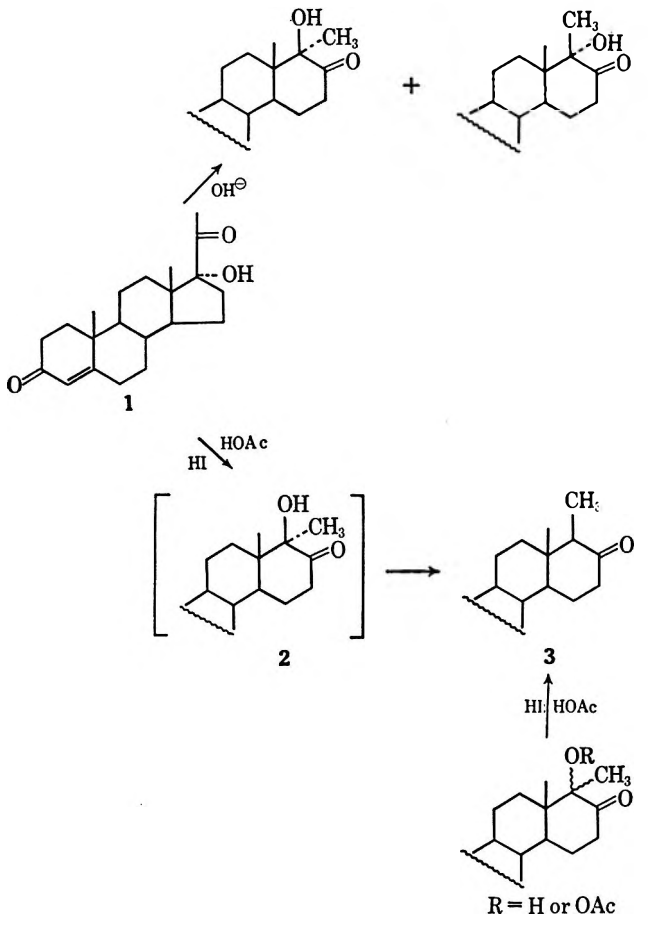
(9) Additional hydroxyls (besides the ketol itself) lead to extensive tar formation.

(10) For pertinent discussion of this rearrangement, see N. L. Wendler in "Molecular Rearrangements II," de la Mare, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 1114–1121, and references therein.

(11) C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 201 (1943).

(12) The synthesis of this compound is described in the experimental part.

SCHEME I



Compounds **7** and **10** were prepared as follows. 2α-Ethynyl-A-nor-5α-androstane-2β,17β-diol[13] (**4**) was hydrated and the product acetylated by treating[14] it with acetic anhydride, acetic acid, boron trifluoride etherate, and mercuric oxide. The resulting 2α-acetyl-A-nor-5α-androstane-2β,17β-diol diacetate (**5**) was hydrolyzed with a 1.1 equiv of base to a mixture of 2α-acetyl-A-nor-5α-androstane-2β,17β-diol (**9**) and of the rearranged 3α,17β-dihydroxy-3β-methyl-5α-androstan-2-one (**8**). The relative configuration of hydroxyl and methyl at carbon 3 follows from reagent control of the reaction and from the bathochromic shift[15] of the optical rotatory dispersion curves of this hydroxy ketone from the corresponding 3-methyl-5α-androstane-2,17-dione (**6**). Both **8** and **9** were oxidized with chromic acid in acetone to their respective 17-ketones **7** and **10**.

Treatment of 5α-hydroxyandrostane-6,17-dione[12] (**14**) with hydriodic acid gave 5α-androstane-6,17-dione (**17**). **14** was prepared in the following fashion. Treatment of 3β-hydroxyandrost-5-en-17-one (**11**) with thionyl chloride gave the known 3β-chloroandrost-5-en-17-one[16] (**12**) (see Scheme III). This product was reduced with lithium in liquid ammonia and the androst-5-en-17β-ol (**13**) was epoxidized with *m*-chloroperbenzoic acid. The resulting 5α,6α-epoxyandrostan-17β-ol (**16**) was treated with acid, and the triol **15** then oxidized with chromic oxide to give the desired 5α-hydroxyandrostane-6,17-dione (**14**).

17α,21-Dihydroxypregn-4-ene-3,20-dione (**18**) was reduced (*via* Mattox rearrangement)[17] to deoxycorticosterone (**19**) (see Scheme IV). Some time ago Slates and Wendler[7] suggested that the reduction of the dihydroxyacetone side chain with zinc and acetic acid must proceed through an enol aldehyde intermediate **20**, and H. L. Herzog, *et al.*,[18] have shown that by treatment of this intermediate with zinc and acetic acid the corresponding 21-hydroxy 20-ketone could be obtained. Upon reduction of the dihydroxyacetone side chain with hydriodic acid the enol aldehyde intermediate could be isolated from the reaction mixture. This compound was reduced further to progesterone or was esterified to deoxycorticosterone acetate. Deoxycorticosterone (**19**) gave as reaction product in good yield progesterone (**21**) and a small amount of deoxycorticosterone acetate (**22**). The latter could be reduced further to furnish progesterone exclusively. 17α,21-Dihydroxypregn-4-ene-3,20-dione 21-acetate (**23**) gave a mixture of 80% deoxycorticosterone acetate (**22**), 5% deoxycorticosterone (**19**), and 15% progesterone (**21**).

1-Acetyl-1-hydroxycyclohexane gave acetylcyclohexane and in addition a small amount of 1-acetylcyclohexene.

17α-Hydroxy-5β-D-homopregnane-3,11,20-trione (**24**) and 3β-hydroxy-3α-acetyl-5α-androstan-17-one (**25**) did not react (see Scheme V).

Discussion of Results

The reduction and/or rearrangement of tertiary ketols by hydriodic acid seems to be effected in several steps. This is evidenced in some examples by the isolation of intermediates. Most cases can be explained by initial protonation of the carbonyl function[19] to give a carbonium ion as common intermediate. This can be followed (loss of proton) by enolization, in analogy with the Mattox rearrangement.[17] The allylic alcohol can be attacked by a nucleophile as hydride or iodide ion which will then readily lead to the parent ketone (see Scheme VI).

Such a reaction sequence would explain the results obtained by reduction of 1-hydroxy-1-acetylcyclohexane to acetylcyclohexane, the reduction of 17α,21-dihydroxypregn-4-ene-3,20-dione (**18**) to 21-acetoxypregn-4-ene-3,20-dione (**22**), the reduction of deoxycorticosterone (**19**) to progesterone (**21**), the reduction of 5α-hydroxyandrostane-6,17-dione (**14**) to 5α-androstane-6,17-dione[20] (**7**), and others. Such a mechanism would also explain the recovery of starting material from a nonenolizable ketone as 17β-hydroxy-17α-methyl-D-homo-5α-androstane-3,17a-dione (**26**). The resistance to reduction of 3β-hydroxy-3α-acetyl-5α-androstan-17-one[21] (**25**) is most likely caused by the

(13) M. Minssen and J. Jacques, *Bull. Soc. Chim. Fr.*, 71 (1965).

(14) Compare L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **21**, 1760 (1938).

(15) R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.* 352 (1955); G. Baumgartner and C. Tamm, *Helv. Chim. Acta*, **38**, 441 (1955).

(16) E. S. Wallis and E. Fernholz, *J. Amer. Chem. Soc.*, **59**, 764 (1937).

(17) V. R. Mattox, *ibid.*, **74**, 4340 (1952).

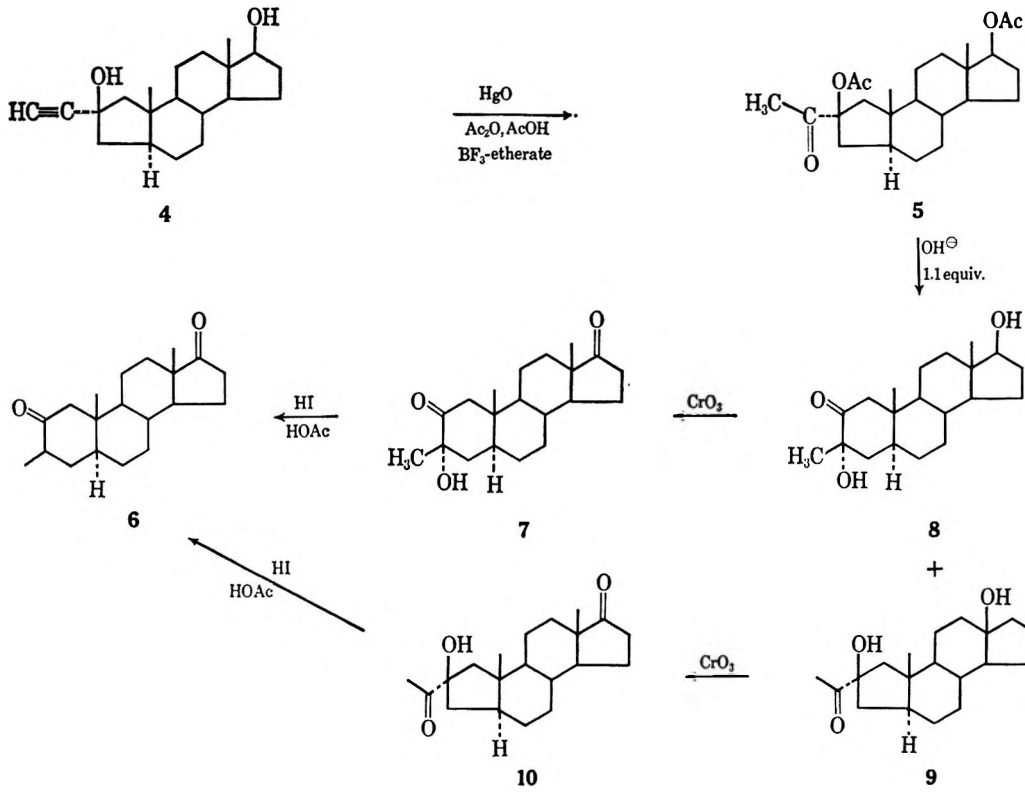
(18) Compare H. L. Herzog, M. J. Gentles, H. Marshall, and E. B. Hershberg, *ibid.*, **83**, 4073 (1961).

(19) This differs from the proposed protonation of the hydroxyl function; compare ref 4.

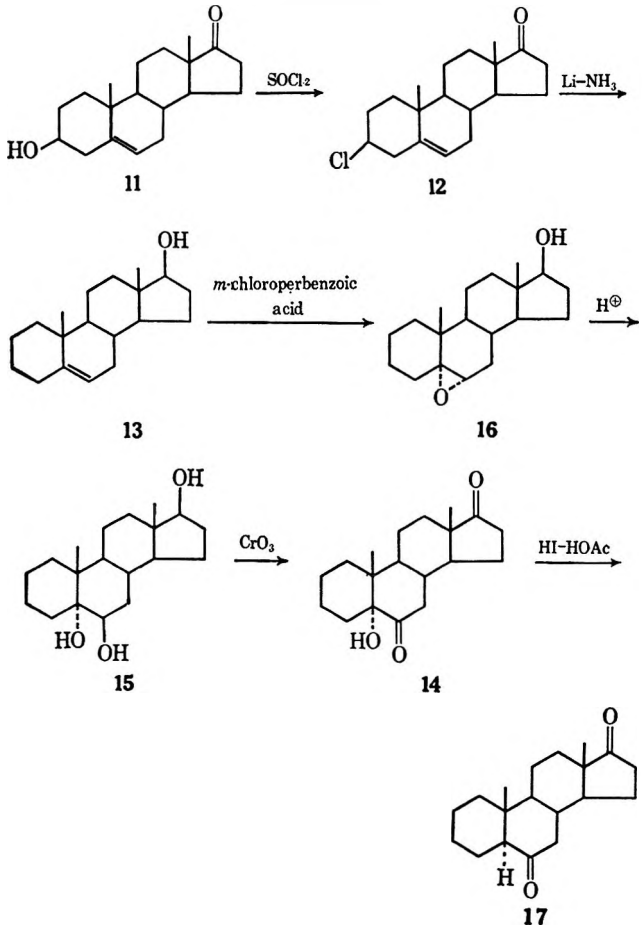
(20) A. Butenandt and L. A. Surang, *Chem. Ber.*, **75**, 591 (1942), and also G. Rosenkranz, M. Velasco, and F. Sondheimer, *J. Amer. Chem. Soc.*, **76**, 5024 (1954).

(21) 3β-Hydroxy-3α-acetyl-5α-androstan-17-one 17-ethylene ketal could not be brominated. Private communication of Dr. Andrée Marquet, Collège de France Paris.

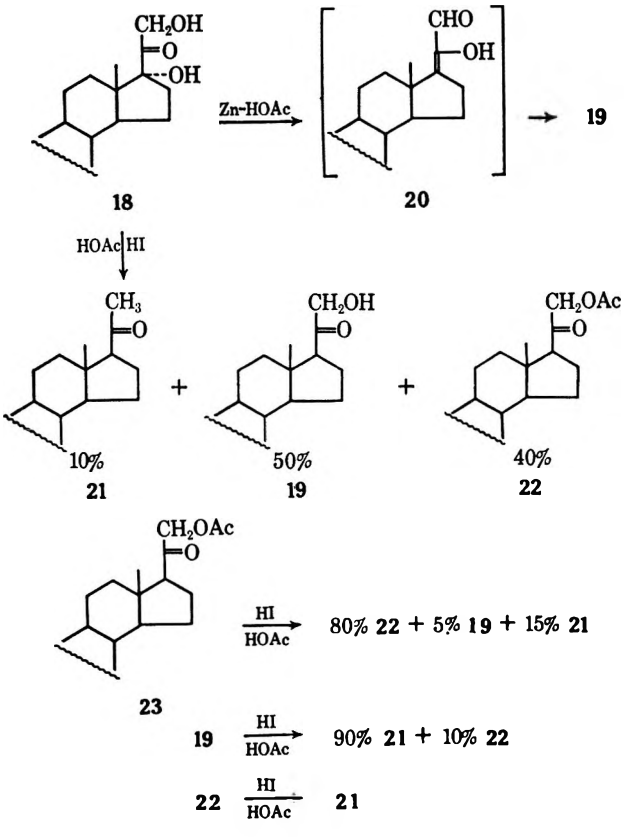
SCHEME II



SCHEME III



SCHEME IV

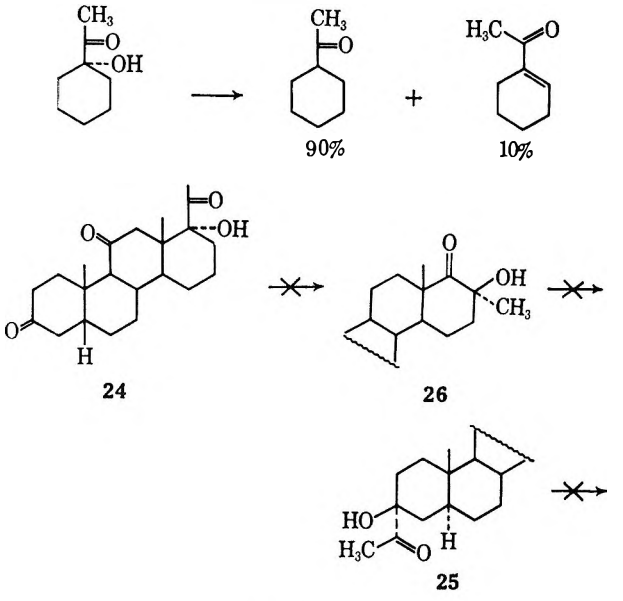


apparent inability of the ketone to enolize. The 17aα-hydroxy-D-homo-5β-pregnane-3,11,20-trione[22] (24) would give a 20-enol readily, but suffers from the interaction[23] between either OH group and C-12 or between the $-CH_2I$ moiety and C-12 of this hypothetical enolic intermediate.

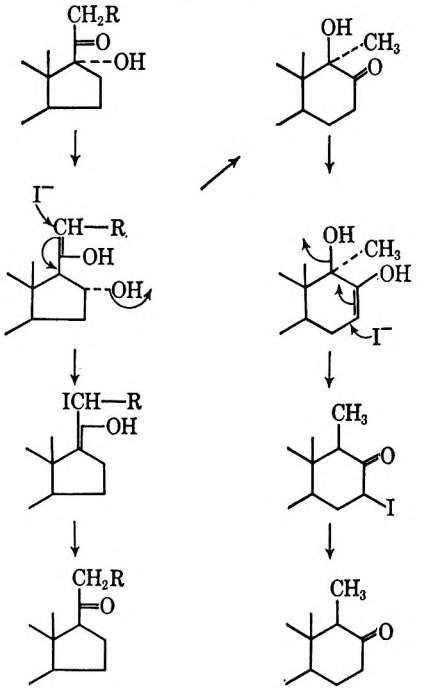
(22) R. O. Clinton, H. C. Neumann, A. J. Manson, S. C. Laskowski, and R. G. Christiansen, *J. Amer. Chem. Soc.*, **80**, 3395 (1958).

(23) Compare F. Johnson and S. K. Malhotra, *ibid.*, **87**, 5492 (1966); S. K. Malhotra and F. Johnson, *ibid.*, **87**, 5493 (1966).

SCHEME V



SCHEME VI



The reaction of 17α-hydroxyprogesterone (**1**) with hydriodic acid proceeds also through initial formation of a carbonium ion which is then followed by ring D expansion (migration of the C_{13-17} bond). The intermediate 17aβ-hydroxy-17aα-methyl-D-homopregn-4-ene-3,17-dione[24] (**2**) can then be reduced *via* formation of an allylic alcohol, as suggested above, to give 17aβ-methyl-D-homopregn-4-ene-3,17-dione (**3**). The transformation of 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**) to 3β-methyl-5α-androstane-2,17-dione (**6**) is analogous.

Experimental Section

Reaction of Hydriodic Acid on 17α-Hydroxyprogesterone.—A solution of 500 mg of 17α-hydroxyprogesterone (**1**) in 20 ml of glacial acetic acid and 1 ml of 47% hydriodic acid was heated on a steam bath. Samples were taken every 5 min and added to an aqueous sodium hydrogen sulfite solution. The precipitated solids were collected and dried. Then a 0.01-mg aliquot of each fraction was chromatographed on paper, using a Bush B_3 system [mobile phase Skellysolve C–benzene (2:1 v/v), stationary phase methanol–water (4:1 v/v)]. The results, obtained by inspection of the paper with an ultraviolet lamp, are tabulated in Table I.

TABLE I

Sample after x min	R_f values (relative amount of absorbance) I, 17α-Hydroxyprogesterone (**1**)	II, 17aβ-Hydroxy-17aα-methyl-D-homopregn-4-ene-3,17-dione (**2**)	III, 17aβ-Methyl-D-homopregn-4-ene-3,17-dione (**3**)
5	0.54 (faint)	(0)	(0)
10	0.54 (faint)	(0)	(0)
15	0.54 (++)	0.7 (++)	0.85 (+)
20	0.54 (+)	0.7 (++)	0.85 (++)
25	(0)	0.7 (++)	0.85 (+++)
30	(0)	(0)	0.85 (+++)

The solution of a 100-mg aliquot of the 25-min fraction in 5 ml of acetic acid was heated on a steam bath with 0.5 ml of 47% hydriodic acid for 30 min. The brown solution was poured into an aqueous sodium hydrogen sulfite solution and the precipitate collected by filtration. After washing and drying there was obtained 90 mg of crystalline material which was found to be a single compound and corresponded to spot III, judged by its migration on a Bush B_3 paper system. This fraction and the 30-min fraction were combined to give 190 mg of a substance which did not show any hydroxyl band in the infrared spectrum. The nmr spectrum showed the presence of two methyl peaks on tertiary carbon (46 and 74.5 cps corresponding to 18- and 19-CH_3 groups, respectively) and one methyl group on a secondary carbon (doublet centered at 61 cps, J_{AB} = 7.0 cps). No peak for a CH_3–CO– type methyl was present. A portion was crystallized for analysis from methylene chloride–ether: mp 210–212°; $\lambda_{max}^{methanol}$ 240 mμ (ϵ 12,500); ν_{max}^{KBr} 1700 (hexacyclic ketone), 1680, 1610 (conjugated ketone) cm^{-1}; nmr 46.0 (18-CH_3), 61 (d) (17α-CH_3, J_{AB} = 7 cps), 74.5 (19-CH_3) cps.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.13; H, 9.83.

Isolation of the Intermediate from the Hydriodic Acid Reaction on 17α-Hydroxyprogesterone.—An aliquot of 60 mg of the 15-min and 20-min fractions from the hydriodic acid reaction product was chromatographed on celite using the Bush A system. After collecting 60 fractions the chromatography was stopped and identical fractions combined. Thus fractions 1 to 17 gave the 17aα-methyl-17-ketone **3**, fractions 20 to 25 gave 15 mg of the intermediate **2**, and fractions 28 to 60 yielded unreacted 17α-hydroxyprogesterone (**1**). The intermediate showed a hydroxyl band in the infrared and its nmr spectrum showed the absence of a CH_3C=O type methyl and the presence of three methyl groups on a tertiary carbon at 46.5, 70, and 80 cps. An aliquot was crystallized for analysis: mp 189–191°; $\lambda_{max}^{methanol}$ 240 mμ (ϵ 13,000); $[\alpha]_D$ +40° (c 1.0 in $CHCl_3$); nmr, 46.5 (18-CH_3), 70.0 (19-CH_3), 80.0 (17a-CH_3) cps.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.15.

Isomerization of 17α-Hydroxyprogesterone with Base.—To a solution of 1 g of 17α-hydroxyprogesterone (**1**) in 95 ml of methanol, 5 g of potassium hydroxide in 5 ml water was added and the solution was refluxed under nitrogen. Samples were withdrawn from the reaction mixture after 30 min, 1 hr, 2 hr, 4 hr, and 20 hr of reaction. They were worked up by pouring them into water and extracting with ethyl acetate. After washing, drying, and evaporation, each fraction was chromatographed on paper using a Bush B_3 system. The results are tabulated in Table II.

Isolation of the Isomeric Hydroxymethyl Ketones.—A portion of fraction 5 weighing 50 mg was distributed between two phases of a Bush B_3 system in a countercurrent apparatus equipped with 99 tubes. After countercurrent extraction the solvents from each tube were removed by evaporation and the fractions were combined according to their R_f values, in the following manner: tubes 2 to 20 (15 mg, mp 284–286°, R_f 0.32),

(24) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941).

TABLE II

Fraction	Time of withdrawal, hr	Spots and their R_f value
1	0.5	0.54
2	1	0.54
3	2	0.54; 0.71
4	4	0.54, 0.71; 0.33
5	20	0.71; 0.33

tubes 21 to 23 (mixture, 9 mg, R_f 0.32, 0.71), tubes 24 to 35 (25 mg, mp 185–186°, R_f 0.71).

The more polar fraction of mp 284–286° was identified as 17aα-hydroxy-17aβ-methyl-D-homoandrost-4-ene-3,17-dione.[22]

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.49; H, 9.21.

The nmr spectrum showed signals at 45.0 (18-CH_3), 70.0 (19-CH_3), 72.5 (17a-CH_3) cps.

The less polar major fraction was identified as 17aβ-hydroxy-17aα-methyl-D-homoandrost-4-ene-3,17-dione:[11,22] mp 189–191°; $[\alpha]_D$ +40° (c 1.0 in $CHCl_3$); nmr 46.5 (18-CH_3), 70.0 (19-CH_3), 80.0 (17a-CH_3) cps. This product was identical in all respect with the intermediate of the hydriodic acid reaction product of 17α-hydroxyprogesterone.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.15.

2α-Acetyl-A-nor-5α-androstane-2β,17β-diol.—To a solution of 400 mg of 2β,17β-diacetoxy-2α-acetyl-A-nor-5α-androstane in 15 ml of methanol, 2.2 ml of 1 *N* sodium hydroxide solution was added during a period of 15 min and the solution heated on a steam bath for another 40 min. Then the solution was cooled, poured into ice, and neutralized with acetic acid. The precipitate was collected, washed, and dried to yield 350 mg of a substance showing no acetate band in the infrared. A silica gel, thin layer chromatogram using 30% ethyl acetate in benzene showed two spots with R_f values of 0.7 and 0.6, respectively. The product was chromatographed on a silica gel column. Elution with 12% ethyl acetate in benzene yielded fractions melting between 172–176°. Elution with 15% ethyl acetate yielded fractions melting between 165–170° and then fractions melting between 200–203°. Investigation of the chromatographic fractions by thin layer chromatography indicated that the fractions melting at 172–176° were one single component, the fractions melting at 165–170° were a mixture, and those melting at 200–203° were one single component. The fractions with mp 172–176° were combined to give 250 mg of 2α-acetyl-A-nor-5α-androstane-2β,17β-diol. A portion was crystallized three times from ether for analysis: mp 182–184°; ν_{max}^{KBr} 3700, 3500 (–OH), 1705 cm^{-1}; nmr, 45.5 (18-CH_3), 62.0 (19-CH_3), 135.0 (–C=OCH_3) cps.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.02; H, 10.21.

The fractions melting at 200–206° were combined to give 25 mg of 3α,17β-dihydroxy-3β-methyl-5α-androstan-2-one (**8**). A portion was recrystallized from ether–hexane to give an analytical sample: mp 206–208°; ν_{max}^{KBr} 3400, 3510 (–OH), 1700 (ketone) cm^{-1}; nmr, 45.0 (18-CH_3), 52.5 (19-CH_3, $W_{1/2}$ = 0.9 cps), 79.0 (3β-CH_3) cps; ORD, λ in mμ ([ϕ] in degrees); 450, (+293), 425, (+378), 400, (+506), 375, (+685), 350, (+1083), 325, (+2698), 300, (−135), 321, (+2881, peak).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.76; H, 9.94.

2β-Hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**).—To a cooled solution of 200 mg of 2α-acetyl-A-nor-5α-androstane-2β,17β-diol (**9**) in 20 ml of acetone was added 0.2 ml of 8 *N* chromic oxide (Jones reagent) solution and the mixture stirred at 0–5° for 5 min. Then the excess of chromic acid was decomposed by methanol and the solution poured into water. The crystalline precipitate was collected, washed, and dried to give 192 mg of 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**), mp 146–148°. A portion was crystallized from ether–hexane for analysis: mp 148–150°; ν_{max}^{KBr} 3500 (–OH), 1705 (ketone), 1740 (pentacyclic ketone) cm^{-1}; nmr, 53.5 (18-CH_3), 62.5 (19-CH_3), 134 (–$COCH_3$) cps.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.20; H, 9.63.

3β-Methyl-5α-androstane-2,17-dione (**6**).—A solution of 200 mg of 2β-hydroxy-2α-acetyl-A-nor-3α-androstan-17-one (**10**) in 10 ml of acetic acid was heated on a steam bath with 2 ml of 47% hydriodic acid for 30 min. The dark brown solution was cooled and poured into a cold 10% solution of sodium bisulfite. The precipitate was collected, thoroughly washed, and dried to yield 180 mg of 3β-methyl-5α-androstane-2,17-dione (**6**), mp 145–147°. A portion was crystallized for analysis from ether–hexane: mp 148–150°; ν_{max}^{KBr} 1745 (17-ketone), 1700 (2-ketone) cm^{-1} (no –OH stretching); nmr, 45.0 (19-CH_3, $W_{1/2}$ = 0.9 cps), 53.0 (18-CH_3), 63 (3β-CH_3, $-J_{AB}$ = 6.0 cps); ORD, λ in mμ ([ϕ] in degrees), 450 (+640), 425 (+818), 400 (+1124), 375 (+1649), 350 (+2366), 325 (+7330), 300 (+1678), 290 (+526), 320.5 (+8778 shoulder), 316 (+9205 peak).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00 Found: C, 79.61: H, 9.81.

3α-Hydroxy-3β-methyl-5α-androstane-2,17-dione (**7**).—Precisely as described for 2α-acetyl-A-nor-5α-androstane-2β,17β-diol (**9**), 100 mg of 3α,17β-dihydroxy-3β-methyl-5α-androstan-2-one (**8**) were oxidized to give 90 mg of 3α-hydroxy-3β-methyl-5α-androstane-2,17-dione (**7**): mp 192–193°; ν_{max}^{KBr} 1750 (17-ketone), 1700 (2-ketone) cm^{-1}.

3β-Methyl-5α-androstane-2,17-dione (**6**) **from 3α-Hydroxy-3β-methyl-5α-androstane-2,17-dione** (**7**).—When 50 mg of 3α-hydroxy-3β-methyl-5α-androstane-2,17-dione (**7**) was treated with hydriodic acid as described in the case of 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**), 40 mg of a substance, mp 147–149°, was obtained which was proved to be identical with 3β-methyl-5α-androstane-2,17-dione (**6**), obtained previously, by its infrared and nmr spectrum.

5α,6α-Epoxyandrostan-17β-ol (**16**).—To a solution of 4.09 g of androst-5-en-17β-ol (**13**) in 40 ml of dichloromethane, was added during a period of 2 min a solution of 2.8 g of *m*-chloroperbenzoic acid (FMC, 85% assay) in 30 ml of dichloromethane. The mixture was stirred at 25° for a period of 45 min and then left at −15° for 2–3 hr. The *m*-chlorobenzoic acid, which started to precipitate after 20 min of stirring, was removed by filtration. The *m*-chlorobenzoic acid in solution and the excess peracid were removed by extraction with 2 *N* aqueous sodium hydroxide solution. The dichloromethane extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was triturated with ether and the crystalline slurry filtered. The crystals were washed with little ether, collected, and dried. There was obtained 3.14 g of colorless prisms.

Recrystallization of this material with ether by means of a Soxhlet extraction apparatus furnished the analytical sample: mp 140–142°; ν_{max}^{KBr} 3280, 1180, 1075, 1050, 1025, 968, 958, and 920 cm^{-1}.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.78; H, 10.56.

Androstane-5α,6β,17β-triol (**15**).—To a suspension of 2.0 g of 5α,6α-epoxyandrostan-17β-ol (**16**) in 30 ml of acetone was added 2 ml of a 1.5 *N* aqueous perchloric acid solution. The mixture was stirred at 25° for a period of 45 min, after which time the clear solution was left for 18 hr at −15°. The product was precipitated by pouring the solution into a mixture of 600 g of ice and 150 ml of saturated saline solution and then the mixture was left standing until the ice had melted. The microcrystalline precipitate was filtered and washed with water to give 1.52 g of colorless crystals, mp 182–185°. The analytical sample was obtained by recrystallization from dichloromethane–acetone: mp 188–190°; ν_{max}^{KBr} 3450, 1075, 1052, 1010, 960, and 920 cm^{-1}.

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.64; H, 10.69.

5α-Hydroxyandrostane-6,17-dione (**14**).—A solution of 300 mg of androstane-5α,6β,17β-triol (**15**) in 10 ml of acetone was oxidized with 0.3 ml of Jones reagent in the usual fashion. Work-up yielded 270 mg of the dione, mp 230–234°. Recrystallization from ether gave the analytical sample: mp 236–238°; ν_{max}^{KBr} 3400 (–OH), 1750 (17-ketone), 1702 (6-ketone) cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.94; H, 9.50.

5α-Androstane-6,17-dione (**17**).—A solution of 200 mg of 5α-hydroxyandrostane-6,17-dione (**14**) in 10 ml of acetic acid was heated on a steam bath with 2 ml of hydriodic acid. Work-up as described for 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**) yielded 180 mg of solids, mp 128–130°. Thin layer chromatography of the product in 30% ethyl acetate in benzene showed one spot, R_f 0.75. The crude product was recrystallized from hexane to give pure 5α-androstane-6,17-dione:[20] mp 132–135°; $[\alpha]^{23}D$ +96° (c 1.0 in chloroform); nmr 45.5 (19-CH_3, $W_{1/2}$ = 0.6), 52.5 (18-CH_3) cps.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.20; H, 9.49.

Treatment of 17α,21-Dihydroxypregn-4-ene-3,20-dione with Zinc and Acetic Acid.[18]—A solution of 1 g of 17α,21-dihydroxypregn-4-ene-3,20-dione (**18**) in 100 ml of 50% aqueous acetic acid was refluxed with 10 g of zinc powder. Samples were collected every 10 min (for a total period of 90 min); the reaction product was worked up by filtering into water and collection of the resulting precipitate. Each fraction was chromatographed on a thin layer plate using 30% ethyl acetate in benzene, and the results are tabulated in Table III.

TABLE III

	R_f values		
Fractions	**18** ("S")	**19** (DOC)	**20** intermediate
1	0.15	×	0.6
2	0.15	0.2	0.6
3	0.15	0.2	0.6
4	0.15	0.2	0.6
5	0.15	0.2	0.6
6	0.15	0.2	0.6
7	0.15	0.2	0.6
8	×	0.2	0.6
9	×	0.2	0.6

A 100-mg aliquot of the combined fractions was chromatographed on a thin layer plate. The fraction 3 (R_f 0.6) was isolated from the plate. Three such plates yielded 75 mg of this intermediate. It was crystallized from methanol–ether to give an analytical sample: mp 185–187°; ν_{max}^{KBr} 3500 (–OH), 1675, 1650, 1600 (Δ⁴-3-ketone and Δ¹⁷⁽²⁰⁾-21-aldehyde); λ_{max}^{EtOH} 242 mμ (ε 17,000), 285 mμ (ε 14,000); nmr 62.5 (18-CH_3), 73.5 (19-CH_3), 335.0 (enolic proton), 345.0 (>C=CH), 576.0 (–C(H)=O) cps.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.56; H, 8.47.

This intermediate was identified as 20-hydroxy-21-oxopregna-4,17(20)-dien-3-one (**20**).

Treatment of Deoxycorticosterone (19) with Hydriodic Acid.—A solution of 500 mg of 21-hydroxypregn-4-ene-3,20-dione (**19**) in 25 ml of acetic acid was heated on a steam bath for 1 hr with 5 ml of hydriodic acid. Usual work-up gave 450 mg of solids which showed two spots on a thin layer plate chromatography corresponding to progesterone (**21**) and to deoxycorticosterone acetate (**22**). The crude product was chromatographed on a silica gel column whereby elution with ethyl acetate–benzene mixtures (5:95 and 7:93) yielded 400 mg of progesterone (**21**). Elution with an ethyl acetate–benzene mixture (15:85) yielded 35 mg of deoxycorticosterone acetate (**22**).

Treatment of Deoxycorticosterone Acetate (22) with Hydriodic Acid.—A solution of 500 mg of deoxycorticosterone acetate (**22**) was treated similarly as in the case described for deoxycorticosterone, except that the reaction time was reduced to 30 min. Usual work-up yielded 480 mg of progesterone (**21**). No other compound was detected.

Treatment of 17α,21-Dihydroxypregn-4-ene-3,20-dione (18) with Hydriodic Acid.—The amount of 500 mg of 17α,21-dihydroxypregn-4-ene-3,20-dione (**18**) was treated in the same manner as described for deoxycorticosterone acetate. A thin layer plate chromatography of the crude product showed three spots corresponding to progesterone, deoxycorticosterone acetate, and deoxycorticosterone (R_f 0.6, 0.35, and 0.2), respectively. A 100-mg aliquot of the crude product was separated on a thin layer plate (30% ethyl acetate in benzene). The bands were visualized with an ultraviolet lamp and then the appropriate zones scraped off the plate. The elution of these fractions yielded 5 mg of progesterone (**21**), 29 mg of deoxycorticosterone acetate (**22**), and 35 mg of desoxycorticosterone (**19**).

Treatment of 17α,21-Dihydroxypregn-4-ene-3,20-dione 21-Acetate (23) with Hydriodic Acid.—The amount of 500 mg of 17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate was subjected to hydriodic acid treatment as described for the case of desoxycorticosterone acetate. Thin layer plate chromatography of the reaction product showed three spots corresponding to progesterone (**21**) (R_f 0.6), deoxycorticosterone acetate (**22**) (R_f 0.35), and deoxycorticosterone (**19**) (R_f 0.2). A 100-mg aliquot of the crude product, separated on a thin layer plate, yielded 60 mg of deoxycorticosterone acetate (**22**), 5 mg of deoxycorticosterone (**19**), and 12 mg of progesterone (**21**).

Reaction of 1-Hydroxy-1-acetylcyclohexane with Hydriodic Acid.—A solution of 100 mg of 1-hydroxy-1-acetyl-cyclohexane in 10 ml of acetic acid was refluxed for 2 hr with 2 ml of 47% hydriodic acid. This was poured into a solution of sodium bisulfite and sodium hydroxide and the mixture was extracted with ether. The ether extract was washed with a solution of sodium hydroxide and water and dried over anhydrous sodium sulfate. Removal of the solvent yielded 75 mg of an oil which, in its infrared spectrum, did not show any hydroxyl band, but had a strong band at 1700 cm^{-1} (saturated ketone) and less intense bands at 1680 and 1660 cm^{-1} for the unsaturated enone system.

The thin layer plate chromatogram of the crude oil showed the presence of two products and one spot absorbed in the ultraviolet.

The extinction (at 232 mμ) of the crude reaction product indicates 1-acetyl-cyclohexene to amount to approximately 10%.

The ultraviolet-absorbing zone was eluted from the silica gel and showed in the infrared bands at 1680 and 1660 cm^{-1}. The ultraviolet had a λ_{max}^{MeOH} 232 mμ (ε 12,000), in agreement with the literature value.[25] The infrared spectrum of the non-absorbing product was identical with the one of authentic acetylcylohexane.

Registry No.—**1,** 68-96-2; hydriodic acid, 10034-85-2; **2,** 2328-80-5; **3,** 15296-76-1; 17aα-hydroxy-17aβ-methyl-D-homoandrost-4-ene-3,17-dione, 14510-23-7; **6,** 15313-99-2; **7,** 15314-00-8; **8,** 15296-62-5; **9,** 15296-63-6; **10,** 15296-64-7; **14,** 15296-65-8; **15,** 15296-66-9; **16,** 6197-92-8; **17,** 13713-89-8; **18,** 152-58-9; **19,** 64-85-7; **20,** 6762-52-3; **22,** 56-47-3; **23,** 640-87-9; 1-hydroxy-1-acetylcyclohexane, 1123-27-9.

(25) L. Ruzicka, D. R. Koolhaas, and A. H. Wind, *Helv. Chim. Acta*, **14**, 1151 (1941); R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951).

Investigations in the 3,4-Dihydrocoumarin Melilotic Acid Series

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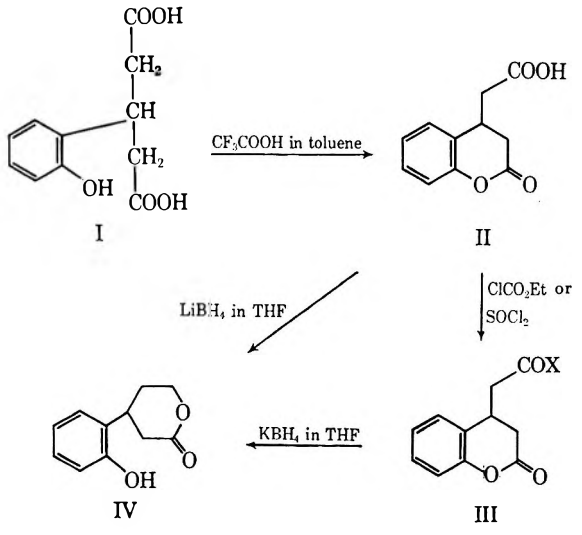
Selective reduction of 3,4-dihydrocoumarin-4-acetic acid (II) leads to 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) by either one of the described two methods. Lactonization of the intermediate 4-hydroxycarboxylic acid to form the above δ-carboxylic acid lactone is preferred over the formation of the phenolic lactone 3,4-dihydro-4-(β-hydroxyethyl)coumarin (XVI). Electrophilic reagents convert 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) into 4-substituted 3,4-dihydrocoumarins. The phenolic lactone 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII), reacts with primary or secondary amine to form 4-substituted chroman derivatives.

Although a great number of natural products related to coumarin are known[1] and coumarins can be characterized by reduction to dihydrocoumarins, relatively little work has been done on 3,4-dihydrocoumarins.[2]

Dihydrocoumarins are hydrolyzed to acids, like melilotic acid (*o*-hydroxyhydrocinnamic acid) which does not cyclize at room temperature to dihydrocoumarin. A number of theories on the biosynthesis and metabolism of coumarin have been proposed which indicate that opening of the heterocyclic ring of coumarin takes place readily, giving rise to melilotic acid as an important product of the coumarin metabolism.[3]

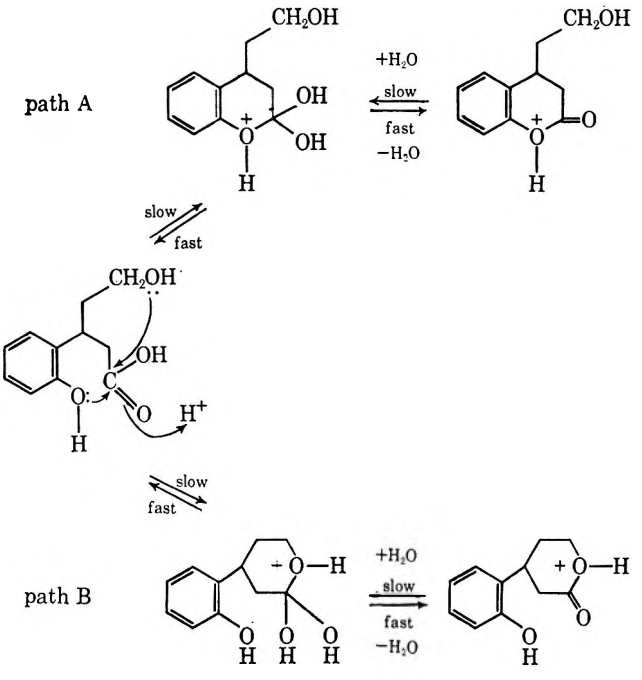
Selective reduction of 3,4-dihydrocoumarin-4-acetic acid, as already reported in a preliminary communication,[4] leads to 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone by either one of the described two methods (Scheme I).

SCHEME I



The rate of acid-catalyzed lactonization reaction of a hydroxy acid bearing a primary alcohol is expected to be faster than that bearing a phenolic hydroxyl, itself an acidic group, particularly in view of the known fact that melilotic acid (*o*-hydroxyhydrocinnamic acid) does not cyclize at room temperature to dihydrocoumarin.[5] Thus, kinetically controlled lactonization should favor formation of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone. Furthermore, the mechanism of the acid-catalyzed lactone formation is pictured as an internal ester formation of the protonated acid and hydroxyl group[6] (Scheme II).

SCHEME II

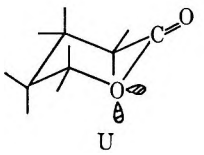


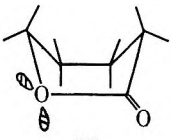
In phenols the delocalization of electrons of the benzene ring is extended to include the OH group. The transition state leading to the dihydrocoumarin system (pathway A) carrying a positive charge on this OH group prevents it from being part of the aromatic system having delocalized electrons. On the other hand, the transition state leading to the δ-lactone will not. Electronic factors should therefore favor formation of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (pathway B).

Lemieux[7] considered δ-valerolactone to possess a chair conformation (U) in which the carbonyl group is eclipsed with a *para* orbital of the lone pair of

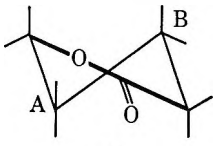
(1) T. O. Soine, *J. Pharm. Sci.*, **53**, 231 (1964).
(2) For some recent references, see T. Amakasu and K. Sato, *J. Org. Chem.*, **31**, 1433 (1966).
(3) T. Kosuge and E. E. Conn, *J. Biol. Chem.*, **234**, 2133 (1959).
(4) J. A. Vida, *Chem. Ind.* (London), 1344 (1966).
(5) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IV, Part B, Elsevier Publishing Co., The Netherlands, 1959, p 874.
(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 320.
(7) R. U. Lemieux in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 709.

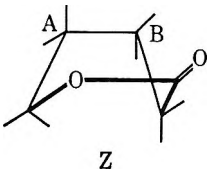
electrons of the ring oxygen. However, Mathieson[8] presented evidence based on X-ray crystallographic analyses that the characteristic shape of the group CC=OOC of a lactone is planar. According to Mathieson, this condition can be satisfied in a six-membered lactone ring by adopting the boat conformation (W).


U


W

In contrast, Overton, *et al.*,[9] have outlined that two conformations satisfy the condition of planarity: (Y) a half-chair conformation having carbon atom A below and carbon atom B above the plane of the lactone function; (Z) a half-boat conformation having carbon atoms A and B displaced to the same side of the plane of the lactone function.


Y


Z

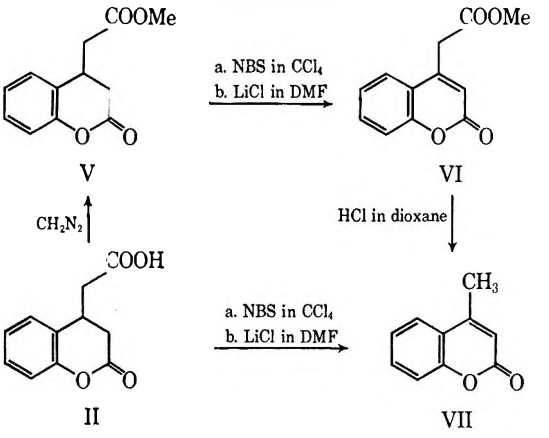
Overton, *et al.*, have suggested that δ-lactones normally adopt the half-chair conformation if other restrictions do not apply. According to Overton, *et al.*, unattached δ-lactones and δ-lactones fused to six-membered saturated carbocyclic rings exist in the half-chair conformation, while δ-lactones fused to five-membered rings exist in the half-boat conformation.

In our case, the δ-lactone, 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, exists in the half-chair conformation and the 3,4-dihydrocoumarin ring probably in the half-boat conformation. Since the half-chair conformation is more stable than the half-boat conformation,[10] formation of the δ-lactone in preference to the dihydrocoumarin ring is sterically favored.

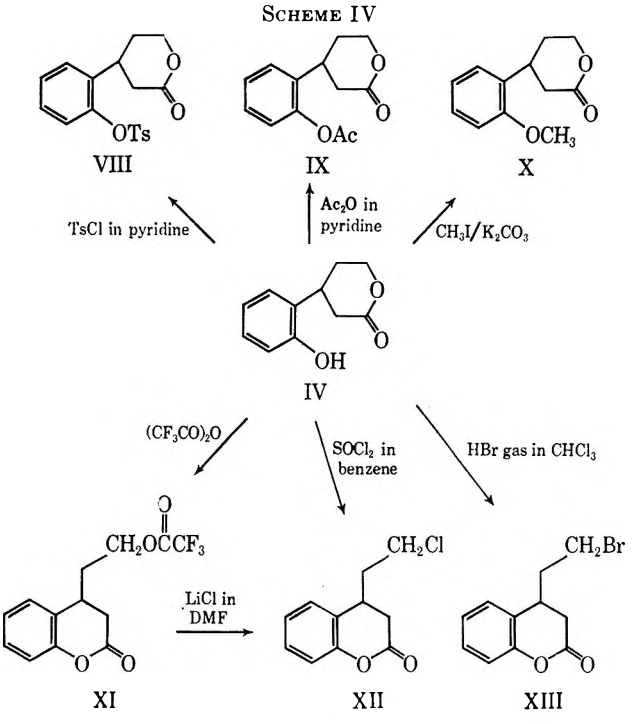
3,4-Dihydrocoumarin-4-acetic acid, upon treatment with diazomethane, was converted into the methyl ester which was brominated and dehydrobrominated to yield 4-carbomethoxymethylcoumarin. Coumarin-4-acetic acids are vinylogs of malonic acid; they lose carbon dioxide at high temperatures; *e.g.*, when the methyl ester was hydrolyzed in boiling aqueous dioxane with hydrochloric acid, the already known 4-methylcoumarin[11,12] was obtained. Similarly the latter compound was obtained from bromination, followed by dehydrobromination of coumarin-4-acetic acid (Scheme III).

Some of the reactions of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone are summarized in Scheme IV.

SCHEME III

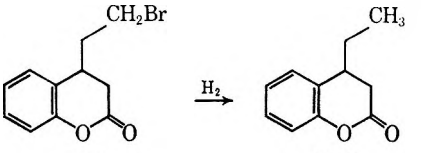


SCHEME IV



Cleavage of the δ-carboxylic acid lactone ring and the subsequent ring closure to form the dihydrocoumarin ring system can be effected with electrophilic reagents, *e.g.*, trifluoroacetic anhydride, thionyl-chloride in benzene,[13] and gaseous hydrobromic acid in chloroform.[14]

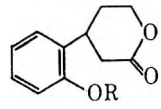
Upon catalytic hydrogenation of 3,4-dihydro-4-(β-bromoethyl)coumarin, there was obtained 3,4-dihydro-4-ethylcoumarin. Treatment of 3,4-dihydro-4-



(β-bromoethyl)coumarin with sodium iodide in a 2:1 mixture of xylene–acetic acid gave a quantitative yield of the 3,4-dihydro-4-(β-iodoethyl)coumarin which in turn could be converted into 3,4-dihydro-4-(β-trifluoroacetoxyethyl)coumarin with silver oxide in

(8) A. M. Mathieson, *Tetrahedron Lett.*, 81 (1963).
(9) K. H. Overton, N. G. Weir, and A. Wylie, *J. Chem. Soc., Sect. C*, 1482 (1966).
(10) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965, p 147.
(11) E. H. Woodruff, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., J. Wiley and Sons, Inc., New York, N. Y., 1955, p 581.
(12) C. E. Wheelock, *J. Amer. Chem. Soc.*, **81**, 1348 (1959).
(13) M. Julia, S. Julia, and B. Bemont, *Bull. Soc. Chim. Fr.*, 304 (1960).
(14) R. Lukes and A. Zobacova, *Collection Czech. Chem. Commun.*, **22**, 1649 (1957).

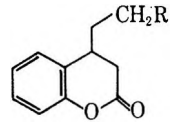
TABLE I[a]



Compound no.	Substituent	Neutral solution				Alkaline solution			
IV	H	280 (2260)	274 (2500)		215 (6300)	293 (3000)	283 (2600)		238 (6400)
X	CH_3	278 (2260)	272 (2480)		218 (7900)		No change		
IX	Ac	268 (254)	262 (281)	255 (261)	208 (8550)	293 (2220)	283 (2700)	276 (2460)	238 (4300)
VIII	Tos	274 (660)	263 (980)	256 (875)	227 (14000)		No change		

[a] Ultraviolet absorption maxima are expressed in millimicrons in the order of decreasing wavelength and in parentheses are given the values of the molecular extinction coefficient (ϵ).

TABLE II[a]

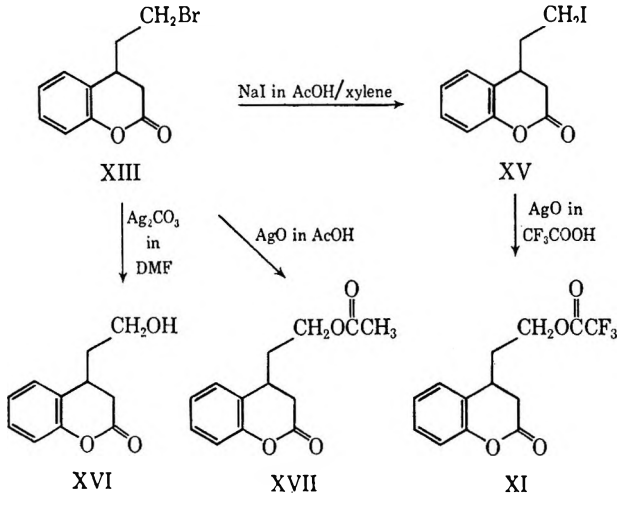


Compound no.	Substituent	Neutral solution				Alkaline solution			
XI	$OCOCF_3$	280 (1080)	273 (1440)	267 (1140)	212 (6120)	293 (2480)	283 (2400)		238 (5570)
XII	Cl	273 (660)	266 (690)	258 (500)	224 (5000)		283 (2400)	276 (2470)	205
XIII	Br	273 (637)	266 (665)	258 (475)	224 (4760)		283 (2360)	276 (2440)	205
XV	I	273 (650)	266 (680)	259 (490)	224 (4775)		283 (2375)	276 (2455)	205
XVI	OH	273 (650)	267 (680)	260 (490)	222 (4900)	293 (1990)	283 (2100)		238 (3780)
XVII	OAc	273 (600)	266 (630)	259 (480)	222 (4500)	293 (1800)	283 (1910)		238 (3600)
XX	NHC_6H_5	283 (2060)	273 (2440)	267 (1990)	220 (8700)	293 (2620)	283 (2270)		237 (7100)

[a] Ultraviolet absorption maxima are expressed in millimicrons in the order of decreasing wavelength and in parentheses are given the values of the molecular extinction coefficient (ϵ).

trifluoroacetic acid. When 3,4-dihydro-4-(β-bromoethyl)coumarin was treated with silver carbonate in dimethylformamide, 3,4-dihydro-4-(β-hydroxyethyl) coumarin was obtained (Scheme V).

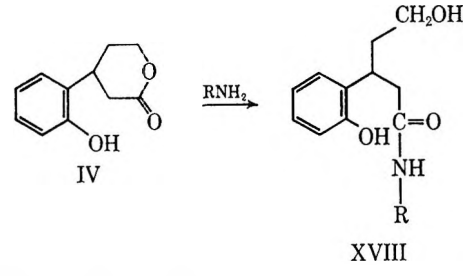
SCHEME V



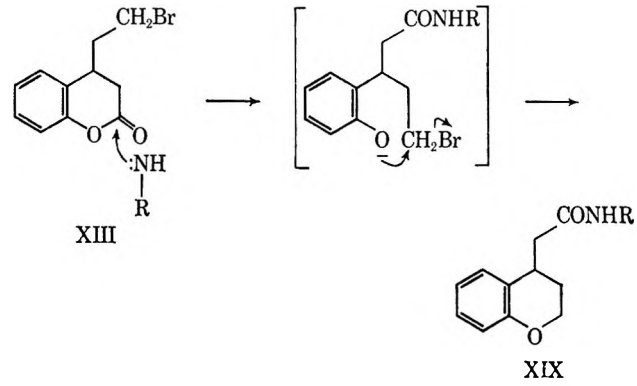
Since the reactions of silver salts with alkyl halides are ordinarily considered[15] to be concerted processes, it is not surprising to find that displacements of the halides proceed with the retention of the 3,4-dihydrocoumarin system.

The reaction of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid with a primary or secondary amine gave amides.

(15) N. Kornblum and D. E. Hardies, *J. Amer. Chem. Soc.*, **88**, 1707 (1966), and references cited therein.

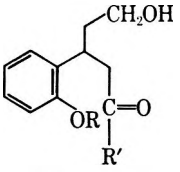


Chromans were the only products isolated from the reaction of 3,4-dihydro-4-(β-bromoethyl)coumarin with a primary or secondary amine, indicating that the nucleophile attacks the lactone carbonyl; *i.e.*, ring opening takes place first with the formation of amide followed by ring closure with the expulsion of the



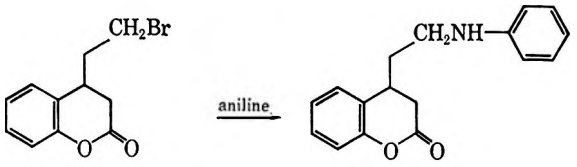
bromide. However, the reaction of 3,4-dihydro-4-dihydro-4-(β-bromoethyl)coumarin with aniline did not lead to the chroman ring system; nucleophilic substitution took place instead, a result which can be explained by the diminished nucleophilicity of aniline compared to a primary or secondary aliphatic amine.

Table III[a]



Compound no.[b]	Substituent R′	Substituent R	Neutral solution				Alkaline solution			
XVIIIc	H	$NHCH_2C_6H_5$	280 (1930)	274 (2140)		206 (16100)	293 (2780)			238 (5350)
XVIIId	H	NHC_6H_{11}	280 (1820)	274 (2000)		215 (5950)	293 (2640)	283 (1640)		238 (4820)
XVIIIa	H	NC_5H_{10}	280 (1580)	274 (1740)		209 (10400)	293 (1820)	283 (1640)		238 (3300)
XVIIIb	TOS	NC_5H_{10}	274 (635)	263 (975)	256 (850)	226 (15300)		No change		

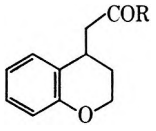
[a] Ultraviolet absorption maxima are expressed in millimicrons in the order of decreasing wavelength and in parentheses are given the values of the molecular extinction coefficient (ϵ). [b] See Experimental Section.



XIII XX

The ultraviolet absorption data are summarized in Tables I–IV. The highly reactive 4-(β-halogenoethyl)-3,4-dihydrocoumarins show ultraviolet absorption representative of the dihydrocoumarin system[16] in neutral solution; on addition of a few drops of dilute sodium hydroxide solution, immediate change of the spectra revealed the newly formed chroman system.[17]

Table IV[a]



Compound no.[b]	Substituent	Neutral and alkaline solution		
XIXa	$NHCH_2C_6H_5$	283 (2300)	276 (2380)	220 (5,850)
XIXb	NHC_6H_{11}	283 (2200)	276 (2250)	220 (5,900)
XIXc	NC_5H_{10}	283 (2470)	276 (2520)	220 (11,500)
XIXd	$N(C_2H_5)_2$	283 (2470)	276 (2520)	220 (8,900)
XXI	OH	283 (2400)	276 (2520)	218 (6,750)
XXII	OCH_3	283 (2450)	276 (2550)	218 (7,000)

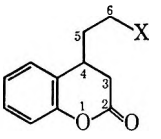
[a] Ultraviolet absorption maxima are expressed in millimicrons in the order of decreasing wavelength and in parentheses are given the values of the molecular extinction coefficient (ϵ). [b] See Experimental Section.

The nmr spectra are summarized in Tables V–VII. The appearance of the aromatic regions for the three groups of compounds are markedly different, but very similar within one group. This provided an easy method for categorizing other compounds having similar structures. Chemical shifts characteristic of certain groups were used for the structural assignments. Thus a sharp singlet in $CDCl_3$ at 139 cps corresponding to three protons characteristic of acetates attached to phenyl groups established the δ-lactone structure of compound IX (Table VII). A doublet in DMSO-d_6 at 462.2 cps, J = 7.6 cps, of compound XIX, R = C_6H_{11}, and a signal at 302 cps in $CDCl_3$ and at 508 cps in DMSO-d_6 of compound XIX, R = $CH_2C_6H_5$ (Table VI), is characteristic of an amide rather than an amine proton, thus establishing the chroman structure. The familiar pattern of ethyl group of compound XIV established the dihydrocoumarin system (Table V). It was also found that the signals of aromatic protons in the dihydrocoumarin and chroman systems are relatively insensitive to solvent or substituent changes, while in the δ-lactone the pattern is influenced by both solvent and substituent changes.

(16) R. H. Goodwin and B. M. Pollock, *Arch. Biochem. Biophys.*, **49**, 1 (1954).

(17) T. J. Webb, *et al.*, *J. Org. Chem.*, **4**, 389 (1939).

Table V[a]



Substituent	Solvent	C-3	C-4	C-5	C-6
OH	DMSO-d_6	174	194	111	248
$OCOCH_3$	$CDCl_3$	169	188	115	246.2
$OCOCH_3$	DMSO-d_6	175	193	109.4	241.6
H	$CDCl_3$	168	200	98	107.5
$OCOCF_3$	DMSO-d_6	176	195	118.2	266
Cl	$CDCl_3$	170	200	120	212
Br	$CDCl_3$	170	200	125	203
I	$CDCl_3$	170	200	122	189
NHC_6H_5	$CDCl_3$	155	210	126	217

[a] Centers of multiplets, in cycles per second, for protons on indicated carbon.

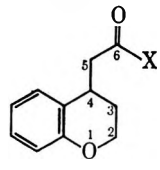
Experimental Section[18,19]

2-*o*-Hydroxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (IV). A.—To the solution of 10.0 g (0.05 mol) of 3,4-dihydrocoumarin-4-acetic acid (II)[4] in 50 ml of benzene 16.4 g (10 ml) of thionyl chloride was added and the solution was refluxed for 2 hr. The excess reagent and the solvent was evaporated under reduced pressure. Benzene (100 ml) was added to the oil and the solvent was evaporated under reduced pressure. The oily residue III was dissolved in 100 ml of dry tetrahydrofuran and 10 g (0.2 mol) of potassium borohydride was added. The reaction mixture was refluxed for 2 hr with stirring. The solvent was evaporated under reduced pressure, 100 ml of 2 *N* hydrochloric acid solution was added to the precooled residue, and the mixture was allowed to stand over-

(18) Melting points were taken on a Fisher-Johns hot stage and are corrected. Ultraviolet absorption spectra were determined in methanol on a Cary Model 14 recording spectrophotometer. Infrared spectra were recorded on a Beckman IR-7 spectrophotometer and on a Perkin-Elmer Infracord. The nmr spectra[19] were run on a Varian Associates DA-60 spectrometer in deuteriochloroform ($CDCl_3$) or deuteriodimethyl sulfoxide (DMSO-d_6) using tetramethylsilane as internal reference. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Chromatographic separations were done with silica gel, Davison Type 923, 100–200 mesh.

(19) We thank Dr. T. A. Wittstruck for the nmr spectra.

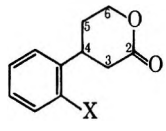
TABLE VI[a]



Substituent	Solvent	C-2	C-3	C-4	C-5[b]		
OH	$CDCl_3$	251.4	122	200.4	153.1 (9.6)	170.5 (4.8)	[−16.0]
OH	DMSO-d_6	247.4	114	192	146.9 (9.4)	162.1 (5.0)	[−16.0]
$N(C_2H_5)_2$	$CDCl_3$	251.2	123	205.2	150.4 (9.0)	162.8 (5.2)	[−15.0]
$N(C_2H_5)_2$	DMSO-d_6	247.2	111	194	...	...	
NHC_6H_{11}	$CDCl_3$	248.8	...	203	136.5 (8.4)	154.1 (6.0)	[−14.4]
NHC_6H_{11}	DMSO-d_6	246.8	...	190.2	133.1 (9.4)	149.3 (5.4)	[−14.2]
OCH_3	DMSO-d_6	247.0	114	193	151.0 (9.4)	167.0 (4.8)	[−15.0]
NC_5H_{10}	DMSO-d_6	247.2	112	...	151.5 (10.0)	161.9 (5.4)	[−15.8]
$NHCH_2C_6H_5$	$CDCl_3$	251.6	122	202	...	...	
$NHCH_2C_6H_5$	DMSO-d_6	247.8	115	194	...	...	

[a] Centers of multiplets, in cycles per second, for protons on indicated carbon. [b] Calculated chemical shift, followed by coupling constant with C-4 proton. The geminal coupling constant is given in brackets. In certain cases the entry is left blank because that portion of the spectrum was obscured by other peaks or the resolution was insufficient for complete determination.

TABLE VII[a]



Substituent	Solvent	C-6	C-5	C-4	C-3 (axial)[b]	C-3 (equatorial)[b]
OH	DMSO-d_6	261.8	118.9	209	156.1 (10.0)	162.7 (7.0) [−17.2]
OCH_3	$CDCl_3$	267.5	119.0	212	152.0 (9.4)	176.0 (6.2) [−17.6]
$OCOCH_3$	$CDCl_3$	272.0	126.0	200	148.0 (10.4)	176.0 (5.0) [−17.0]
$OCOCH_3$	DMSO-d_6	265.0	117.0	207	153.1 (10.0)	160.1 (7.2) [−17.0]
OTos	$CDCl_3$	256.5	114.0	207	144.6 (10.0)	156.6 (6.2) [−17.0]

[a] Centers of multiplets, in cycles per second, for protons on indicated carbons. [b] Calculated chemical shift, followed by coupling constant with C-4 proton. The geminal coupling constant is given in brackets.

night at room temperature. The organic compounds were extracted into ethyl acetate and the acidic fractions were separated by washing the ethyl acetate solution with sodium bicarbonate solution. The remaining ethyl acetate solution containing the neutral fraction was concentrated to dryness and the oily residue was dissolved in benzene and chromatographed on 300 g of silica gel. Elution with 10% ethyl acetate in benzene gave, after evaporation of the solvent, 4.8 g (51.5% yield) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, mp 102–103°. The analytical sample was prepared by recrystallization from acetone: mp 103–104°; ν_{KBr} 3235 (OH), 1602, 1592, 1503 (aromatic ring), 1687 (C=O), and 1255 cm^{-1} (CO). (Both the OH and C=O exhibit strong hydrogen bonding.)

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.63; H, 6.48.

B.—The solution of 10.0 g (0.05 mol) of 3,4-dihydrocoumarin-4-acetic acid (II)[4] in 100 ml of tetrahydrofuran was cooled to −10°. After the addition of 5.42 g (0.05 mol) of ethyl chloroformate the solution was stirred at −10° for 2 hr. Then 7.8 of sodium borohydride was added in small portions and the reaction mixture was stirred for 1 hr at room temperature and refluxed for 1 hr. The reaction mixture containing III was worked up in the same way as described in example A, yielding 4.4 g (47%) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, mp 102–103°.

C.—To the solution of 2.06 g (0.01 mol) of 3,4-dihydrocoumarin-4-acetic acid (II)[4] in 150 ml of dry tetrahydrofuran was added 2 g (0.09 mol) of lithium borohydride. The mixture was refluxed for 16 hr, then the solvent was evaporated under reduced pressure, and 50 ml of 2 *N* hydrochloric acid solution was added to the precooled residue. The reaction mixture was worked up in the same way as described above, yielding 1.700 g (90%) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, mp 102–103°.

4-Carbomethoxymethylcoumarin (VI).—To the suspension of 2.2 g (0.01 mol) of 3,4-dihydrocoumarin-4-acetic acid in dry ether was added a solution of diazomethane in ether at room temperature until the color of the diazomethane solution persisted. All the solid had dissolved at the end of the esterification procedure. The excess of diazomethane and the solvent was evaporated under reduced pressure and the residual oil, 3,4-dihydro-4-carbomethoxymethylcoumarin (V), was dissolved in a mixture of 44 ml of carbon tetrachloride and 8 ml of pentane. After the addition of 2.1 g (0.012 mol) of N-bromosuccinimide the reaction mixture was refluxed for 1 hr while illuminating with a 120-V photospot lamp. The solvent was evaporated under reduced pressure and the mixture dissolved in 25 ml of dimethylformamide, 2.5 g of lithium chloride was added, and the mixture was kept at 100° in a nitrogen atmosphere for 4 hr. The mixture was poured into 500 ml of cold water and the product was extracted into ethyl acetate. After evaporation of the solvent under reduced pressure, 1.87 g of crude product was obtained which was chromatographed on 100 g of silica gel. Elution with 10% ethyl acetate in benzene gave 1.78 g of 4-carbomethyoxymethylcoumarin, mp 124°. The analytical sample was crystallized from acetone: mp 124–125°; λ_{max} 313 mμ (ε 4700), 274 (ε 8250); ν_{KBr} 1750–1695 broad (ester C=O and lactone C=O), 1625 (C=C), 1610, 1563 (aromatic ring), 1250, 1225 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; 4.62. Found: C, 65.81; H, 4.64.

4-Methylcoumarin (VII). A. From 3,4-Dihydrocoumarin-4-acetic Acid.—To the solution of 500 mg (0.0025 mol) of 3,4-dihydrocoumarin-4-acetic acid in a mixture of 25 ml of carbon tetrachloride and 5 ml of pentane, 550 mg (0.003 mol) of N-bromosuccinimide was added and the mixture was refluxed for 40 min while illuminating with a 120-V photospot lamp. The solvent was evaporated under reduced pressure and the residue was dissolved in 10 ml of dimethylformamide. After the addition of 1 g of lithium chloride the mixture was kept at 100° in a mitrogen atmosphere for 4 hr. The mixture was poured into 300 ml of cold water and the product was extracted with ethyl acetate. After evaporation of the solvent 400 mg of crude product was obtained which was chromatographed on 250 g of silica gel. Elution with 20% ethyl acetate in benzene

gave 380 mg of 4-methylcoumarin, mp 80–81°. The analytical sample was crystallized from ether, then from ethanol: mp 82°; λ_{max} 310 mμ (ε 6000), 271 (ε 9900);[12] ν_{KBr} 1725 (C=O), 1618 (C=C), 1608, 1563 (aromatic ring), 1220 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.98; H, 5.11.

B. From 4-Carbomethyoxymethylcoumarin (VI).—To the solution of 100 mg of 4-carbomethoxymethylcoumarin in 10 ml of dioxane 5 ml of 20% aqueous hydrochloric acid was added and the solution was refluxed for 4 hr. The mixture was poured into 500 ml water, the product was extracted into ethyl acetate, and after evaporation of the solvent the residue was chromatographed on 50 g of silica gel. Elution with 20% ethyl acetate in benzene gave 65 mg of 4-methylcoumarin, identical with the above sample.

2-*o*-Tosyloxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (VIII).—To the solution of 750 mg (0.004 mol) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) in 10 ml of pyridine 1 g (0.005 mole) of *p*-toluenesulfonyl chloride was added and the solution was allowed to stand overnight at room temperature. The solution was poured into ice containing 10 ml of 38% hydrochloric acid and the organic compounds were extracted into ethyl acetate. The ethyl acetate solution was washed with sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated under reduced pressure. The residual oil was chromatographed on 90 g of silica gel. Elution with 5% ethyl acetate in benzene and evaporation of the solvent gave 950 mg (70%) of 2-*o*-tosyloxyphenyl-4-hydroxybutane-1-carboxylic acid lactone, mp 130°. The analytical sample was crystallized from acetone: mp 130°; ν_{KBr} 1720 (C=O), 1618, 1582 (aromatic ring), 1360, 1150 (sulfonate), 1250 cm^{-1} (CO).

Anal. Calcd for $C_{18}H_{18}O_5S$: C, 62.41; H, 5.23; S, 9.25. Found: C, 62.40; H, 5.41; S, 9.48.

2-*o*-Acetoxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (IX). To the solution of 960 mg (0.005 mol) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone in 15 ml of pyridine 5 ml (0.05 mol) of acetic anhydride was added and the solution was allowed to stand at room temperature overnight. The solution was poured into ice containing 15 ml of 38% hydrochloric acid and the mixture was allowed to stand for 3 hr. The solid was removed by filtration, washed with water, and dried in the air. There was obtained 1.050 g (90%) of 2-*o*-acetoxyphenyl-4-hydroxybutane-1-carboxylic acid lactone. The analytical sample was crystallized from acetone: mp 137–138°; ν_{KBr} 1750 (C=O), 1695 (C=O), 1587, 1567 (aromatic ring), 1250 cm^{-1} (CO).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.76; H, 5.87.

2-*o*-Methoxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (X).—To the solution of 1.0 g (0.005 mol) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone in 100 ml of absolute ethanol 3 g of anhydrous potassium carbonate and 25 ml of methyl iodide was added and the mixture was refluxed for 20 hr with stirring. After the solvent was evaporated under reduced pressure, 2 *N* hydrochloric acid was added to the residue (to pH 1) and the organic compounds were extracted into ethyl acetate. The solvent was evaporated and the residual oil was chromatographed on 90 g of silica gel. Elution with 10% ethyl acetate in benzene gave 360 mg of 2-*o*-methoxyphenyl derivative. Elution with 30% ethyl acetate in benzene gave 650 mg (65% recovery) of unchanged starting material. The 2-*o*-methoxyphenyl derivative was rechromatographed on 90 g of silica gel. Elution with 10% ethyl acetate in benzene gave 332 mg of pure 2-*o*-methoxyphenyl-4-hydroxybutane-1-carboxylic acid lactone as an oil: ν_{film} 1730 (C=O), 1587, 1575 (aromatic ring), 1235 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.90, H, 6.92.

3,4-Dihydro-4-(β-trifluoroacetoxyethyl)coumarin (XI). A. From 2-*o*-Hydroxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (IV).—The solution of 1.3 g of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) in 20 ml of trifluoroacetic anhydride was refluxed for 16 hr. The excess trifluoroacetic anhydride was removed under reduced pressure, 100 ml of benzene was added, and the solution was evaporated under reduced pressure to dryness. The residual oil was chromatographed on 100 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 1.894 g (96.5%) crystals: mp 61°; ν_{KBr} 1786 (C=O), 1613, 1587 (aromatic ring), 1220 (CO), 1150 cm^{-1} (CF).

Anal. Calcd for $C_{13}H_{11}O_4F_3$: C, 54.17; H, 3.85; F, 19.77. Found: C, 54.38; H, 3.83; F, 19.68.

B. From 3,4-Dihydro-4-(β-iodoethyl)coumarin.—To the solution of 622 mg of 3,4-dihydro-4-(β-iodoethyl)coumarin in 25 ml of trifluoroacetic acid 1.0 g of silver oxide was added and the mixture was heated at reflux with stirring in a nitrogen atmosphere for 16 hr. Most of the solvent was evaporated under reduced pressure, the residue poured into ice, and the product extracted into ethyl acetate. After evaporation of the solvent the residue was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 510 mg (85% yield) of 3,4-dihydro-4-(β-trifluoroacetoxyethyl)coumarin, identical with the compound obtained as described above.

3,4-Dihydro-4-(β-chloroethyl)coumarin (XII). A. From 2-*o*-Hydroxyphenyl-4-hydroxybutane-1-carboxylic Acid Lactone (IV).—To the solution of 576 mg (0.003 mol) of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone in 150 ml benzene, 1.8 g (0.015 mol) of thionyl chloride was added and the solution was heated at reflux for 3 hr. The solvent was evaporated under reduced pressure and 100 ml of benzene was added and evaporated under reduced pressure. The residual oil was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 582 mg (92%) of 3,4-dihydro-4-(β-chloroethyl)coumarin, mp 61°. The analytical sample was crystallized from pentane: mp 61°; ν_{KBr} 1724 (C=O), 1587, 1575 (aromatic ring), 1250 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{11}O_2Cl$: C, 62.71; H, 5.26; Cl, 16.83. Found: C, 62.90; H, 5.09; Cl, 16.75.

B. From 3,4-Dihydro-4-(β-trifluoroacetoxyethyl)coumarin (XI).—To the solution of 288 mg of 3,4-dihydro-4-(β-trifluoroacetoxyethyl)coumarin in 25 ml of dimethylformamide 2.0 g of lithium chloride was added. The mixture was held at 100° in a nitrogen atmosphere for 4 hr. The solution was cooled and poured into ice, the organic compound extracted into ethyl acetate, the solvent evaporated, and the residual oil chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 203 mg (96%) of 3,4-dihydro-4-(β-chloroethyl)coumarin, identical with the compound obtained as described under A.

3,4-Dihydro-4-(β-bromoethyl)coumarin (XIII).—The solution of 576 mg of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) in 25 ml of chloroform was cooled to 0°. At this temperature hydrogen bromide gas was introduced until the solution became saturated with the gas. The solution was allowed to stand at 0° overnight. The solution was diluted with ether and poured into ice, and the product was extracted into ether. The combined organic solution was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene gave 758 mg (99% yield) of crystals, mp 63–64°. The analytical sample was crystallized from pentane: mp 65°; ν_{KBr} 1770 (C=O), 1610, 1580 (aromatic ring), 1220 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{11}O_2Br$: C, 51.78; H, 4.44; Br, 31.33. Found: C, 51.86; H, 4.39; Br, 31.60.

3,4-Dihydro-4-ethylcoumarin (XIV).—To the solution of 333 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 25 ml of acetic acid 100 mg of platinum dioxide was added and the mixture was hydrogenated in a Parr hydrogenator overnight at 45 psi. The catalyst was filtered off and the solution was diluted with benzene. The solution was washed with water, sodium bicarbonate solution, and water. The benzene solution was dried over sodium sulfate and the solvent was evaporated under reduced pressure to give an oil. This was chromatographed on 90 g of silica gel. Elution with 10% ethyl acetate in benzene gave 216 mg (94%) of oil, which contained no bromine. The structural assignment was made on the basis of the nmr spectrum (Table V).

3,4-Dihydro-4-(β-iodoethyl)coumarin (XV).—To the solution of 500 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 20 ml of xylene and 10 ml of acetic acid 300 mg of sodium iodide was added and the mixture was stirred at reflux temperature in an atmosphere of nitrogen for 16 hr. The mixture was added to 300 g of ice, 300 ml of aqueous saturated sodium sulfate solution was added, and the product was extracted into ethyl acetate. The combined organic layer was dried over

sodium sulfate and the solvent was evaporated under reduced pressure. The residual oil was chromatographed on 90 g of silica gel. Elution with 10% ethyl acetate in benzene gave 592 mg (100% yield) of 3,4-dihydro-4-(β-iodoethyl)coumarin as an oil: ν_{film} 1770 (C=O), 1618, 1565 (aromatic ring), 1220 cm^{-1} (CO). The compound gave a positive halogen test.

3,4-Dihydro-4-(β-hydroxyethyl)coumarin (XVI).—To the solution of 510 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 25 ml of dimethylformamide 550 mg of silver carbonate was added and the mixture was kept at 100° with stirring in a nitrogen atmosphere for 16 hr. The mixture was poured into ice containing 2 *N* hydrochloric acid, the product was extracted into ethyl acetate, the solvent was evaporated under reduced pressure, and the residue was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene gave 332 mg (86% yield) of 3,4-dihydro-4-(β-hydroxyethyl)coumarin as an oil, which showed a single spot on a tlc plate: ν_{film} 3580 (OH), 1770 (C=O), 1610, 1580 (aromatic ring), 1220 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29; Found: C, 68.83; H, 6.20.

3,4-Dihydro-4-(β-acetoxyethyl)coumarin (XVII).—To the solution of 510 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 25 ml of glacial acetic acid 510 mg of silver oxide was added and the mixture was kept boiling with stirring in a nitrogen atmosphere for 16 hr. The mixture was cooled, diluted with ethyl acetate, and poured into a sodium bicarbonate solution. The product was extracted into ethyl acetate, the solvent evaporated under reduced pressure, and the residue chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene gave 444 mg (95% yield) of 3,4-dihydro-4-(β-acetoxyethyl)coumarin, as an oil, which showed a single spot on a tlc plate; ν_{film} 1776 (C=O), 1745 (C=O), 1610, 1580 (aromatic ring), 1240 cm^{-1} (CO).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.77; H, 6.06.

Ortho Substituted Phenyl-2-hydroxyethyl-N-alkylhydrocinnamamides (XVIII). General Procedure.—The solution of *o*-hydroxy- (or tosyloxy-) phenyl-4-hydroxybutane-1-carboxylic acid lactone in a tenfold volume of freshly distilled primary or secondary amine was kept at 100° in an atmosphere of nitrogen for 16 hr. The solution was diluted with ethyl acetate, poured into ice containing hydrochloric acid, and the acidic solution was extracted with ethyl acetate. The solvent was evaporated and the oily residue was chromatographed on a 100-weight silica gel column. Elution with 30% ethyl acetate in benzene and evaporation of the solvent gave an oily product which was crystallized.

a. *o*-Hydroxy-2-hydroxyethyl-N-piperidylhydrocinnamamide.—From 1.0 g of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) and piperidine there was obtained 1.257 g (82% yield) of product, which was crystallized from acetone–hexane. The analytical sample was crystallized from ether: mp 99–100°; ν_{KBr} 3330 (OH), 1603 (CON=), 1235 cm^{-1} (CO).

Anal. Calcd for $C_{16}H_{23}O_3N$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.01; H, 8.55; N, 4.99.

b. *o*-Tosyloxy-2-hydroxyethyl-N-piperidylhydrocinnamamide.—From 1.0 g of 2-*o*-tosyloxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (VIII) and piperidine there was obtained 1.205 g (96% yield) of product, which was crystallized from ether: mp 108°; ν_{KBr} 3300 (OH), 1603 (CON=), 1235 (CO), 1360, 1150 cm^{-1} (sulfonate).

Anal. Calcd for $C_{23}H_{29}O_5NS$: C, 64.01; H, 6.77; N, 3.24; S, 7.43. Found: C, 63.80, H, 6.59; N, 3.53; S, 7.52.

c. *o*-Hydroxy-2-hydroxyethyl-N-benzylhydrocinnamamide.—From 1.0 g of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) and benzylamine there was obtained 1.420 g (91% yield) of product, which was crystallized from acetone–hexane. The analytical sample was crystallized from tetrahydrofuran: mp 132–132.5°; ν_{KBr} 3509 (NH), 3333 (OH), 1618 (CONH), 1587, 1563 (aromatic ring), 1225 cm^{-1} (CO).

Anal. Calcd for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.56; H, 7.07; N, 4.64.

d. *o*-Hydroxy-2-hydroxyethyl-N-cyclohexylhydrocinnamamide.—From 1.0 g of 2-*o*-hydroxyphenyl-4-hydroxybutane-1-carboxylic acid lactone (IV) and cyclohexylamine there was obtained 1.257 g (83% yield) of product, which was crystallized from pentane. The analytical sample was prepared from ether: mp 128–129°; ν_{KBr} 3390 (NH), 3280 (OH), 1600 (CONH), 1563, 1538 (aromatic ring), 1235 cm^{-1} (CO).

Anal. Calcd for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.05; H, 8.60; N, 4.62.

4-Carboalkylamidomethylchromans (XIX). General Procedure.—The solution of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in a 10-fold volume of freshly distilled primary or secondary amine was kept at 100° in an atmosphere of nitrogen for 16 hr. The solution was diluted with ethyl acetate and poured into ice containing hydrochloric acid; the acidic solution was extracted with ethyl acetate. The solvent was evaporated and the oily residue was chromatographed on a 100-fold weight silica gel column. Elution with 30% ethyl acetate in benzene and evaporation of the solvent furnished a solid product, which was crystallized from different solvents.

a. 4-Carbobenzylamidomethylchroman.—From 300 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) and benzylamine there was obtained 280 mg (83% yield) of product, which was crystallized from ether: mp 201–202°; ν_{KBr} 3175 (NH), 1626 (CONH), 1585 (aromatic ring), 1220 (CO), 1070 cm^{-1} (COC).

Anal. Calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.65; H, 6.77; N, 5.23.

b. 4-Carbohexylamidomethylchroman.—From 180 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin(XIII) and cyclohexylamine there was obtained 180 mg (93% yield) of product, which was crystallized from ether: mp 147–148°; ν_{KBr} 3322 (NH), 1618 (CONH), 1600, 1567 (aromatic ring), 1220 (CO), 1078 cm^{-1} (COC).

Anal. Calcd for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.70; H, 8.69; N, 4.97.

c. 4-Carbopiperidylmethylchroman.—From 400 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) there was obtained 300 mg (73% yield) of product, which was crystallized from ether: mp 98°; ν_{KBr} 1626 (CON=), 1610, 1585 (aromatic ring), 1220 (CO), 1075 cm^{-1} (COC).

Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.36; H, 8.39; N, 5.50.

d. 4-Carbodiethylamidomethylchroman.—From 280 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) there was obtained 200 mg of syrupy product which could not be crystallized: ν_{film} 1634 (CON=), 1610, 1575 (aromatic ring), 1220 (CO), 1075 cm^{-1} (COC).

Anal. Calcd for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.60; H, 8.78; N, 5.45.

3,4-Dihydro-4-(β-phenylaminoethyl)coumarin.—The solution of 500 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 10 ml of freshly distilled aniline was kept at 110° in an atmosphere of nitrogen for 20 hr. The excess aniline was removed by evaporation under reduced pressure and the remaining oil was dissolved in benzene and chromatographed on 90 g of silica gel. The column was washed with 500 ml of benzene. Elution with ethyl acetate after evaporation of the solvent gave 425 mg (82.5%) of 3,4-dihydro-4-(β-phenylaminoethyl)coumarin, mp 222°. The analytical sample was crystallized from ether: mp 222–223°; ν_{KBr} 3333 (NH), 1639 (CONH), 1610, 1575 (aromatic ring), 1220 (CO), 1075 cm^{-1} (COC).

Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.51; H, 6.63; N, 5.25.

4-Carbohydroxymethylchroman (Chroman-4-acetic Acid) (XXI).—The solution of 510 mg of 3,4-dihydro-4-(β-bromoethyl)coumarin (XIII) in 50 ml of methanol containing 500 mg of potassium hydroxide was kept at reflux in a nitrogen atmosphere for 16 hr. The solution was concentrated under reduced pressure to a small volume and diluted with ethyl acetate; the solution was washed with dilute hydrochloric acid. Evaporation of the solvent gave an oil, which was chromatographed on 90 g of silica gel. Elution with 20% ethyl acetate in benzene and evaporation of the solvent gave 366 mg (95%), mp 90° of 4-carbohydroxymethylchroman, free of halogen. The analytical sample was crystallized from ether–hexane: mp 91–92°; ν_{KBr} 3125 broad (COOH), 1695 (acid) 1587, 1563 (aromatic ring), 1075 cm^{-1} (COC).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.81; H, 6.47.

4-Carbomethoxymethylchroman (XXII).—To the solution of 1.0 g of 4-carbohydroxymethylchroman (XXI) in 100 ml of ether was added a solution of diazomethane in ether at room temperature until the color of the diazomethane solution persisted. The excess of diazomethane and the solvent was

evaporated under reduced pressure and the residue was purified on a 100 g of silica gel column. Elution with 10% ethyl acetate in benzene and evaporation of the solvent gave 1075 mg (100% yield) of 4-carbomethoxymethylchroman as an oil: ν_{film} 1740 (C=O), 1610, 1585 (aromatic ring), 1075 cm^{-1} (COC).

Registry No.—IV, 10513-48-1; VI, 15364-61-1; VII, 607-71-6; VIII, 15364-63-3; IX, 15364-64-4; X, 15364-65-5; XI, 15364-66-6; XII, 15364-67-7; XIII, 15364-68-8; XIV, 15523-38-3; XV, 15364-69-9; XVI, 15364-70-2; XVII, 15364-71-3; XVIIIa, 15364-72-4; XVIIIb, 15364-73-5; XVIIIc, 15364-74-6; XVIIId, 15364-75-7; XIXa, 15364-76-8; XIXb, 15364-77-9; XIXc, 15364-78-0; XIXd, 15364-79-1; XX, 15364-80-4; XXI, 5655-26-5; XXII, 15364-82-6.

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Synthesis of L-α-Methyldopa from Asymmetric Intermediates

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Two procedures for the synthesis of L-α-methyldopa from asymmetric intermediates are described. The substrates for the resolution and racemization processes are DL-α-amino-α-vanillylpropionitrile and DL-α-acetamido-α-vanillylpropionitrile. Hydrolysis of the L isomer yields L-α-methyldopa in high yield.

The hypotensive activity of α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa)[1] (VI) has been shown to reside only in the L isomer.[2] To eliminate the therapeutically impotent D isomer, DL-α-methyldopa has been resolved by conventional methods,[3] and, more recently, by a selective crystallization technique not involving a resolving agent.[4] However, resolution at the amino acid stage results in equal production of the unwanted D isomer which cannot be racemized by usual means because of the absence of an α hydrogen. Practical utilization of the D isomer has been limited to degradation to 3,4-dihydroxyphenylacetone followed by resynthesis of the amino acid.[5]

The asymmetry of the molecule is introduced on formation of the α-aminonitrile or hydantoin intermediates. Of these two intermediates, the α-aminonitrile, being a base[6] and formed in an equilibrium reaction,[7] is uniquely suited for both resolution[8,9] and racemization.[10] The resolutions hitherto reported have all been impaired by the facile hydrolysis of the salts of α-aminonitriles with weak acids. This leads to irreversible decomposition of the aminonitriles to the parent ketones and ammonia, which is captured by the resolving agent.

The optical instability of α-aminonitriles suggested that, in addition to the two general types of resolution process developed for DL-α-methyldopa, it would be possible to develop an asymmetric transformation,[11] initiated in this case by seeding with optically active α-aminonitrile which would result in the crystallization of only the desired L isomer in greater than 50% yield. This ultimate process requires not only a preliminary resolution to produce the seeds, but a favorable solubility relationship between the optically active forms, a rapid rate of crystal growth on the seed bed relative to nucleation of the inactive form, and, finally, a rate of racemization faster than the rate of crystallization.[12]

This approach was tested on the α-aminonitrile II prepared from 3-methoxy-4-hydroxyphenylacetone I (Scheme I). The initial resolution experiments[13] were frustrated by the tendency of its salts to dissociate. However, continued screening of the salts of II with strong acids, using the phase solubility analysis technique,[14] revealed that the *d*-10-camphorsulfonate could be resolved in dioxane, thanks to the formation of a crystalline solvate, $[\alpha]_D$ 15.6°. The absolute configuration and purity were determined by hydrolysis to D-α-methyldopa of known configuration.[3] The other enantiomer of II was obtained *via* the *l*-10-camphorsulfonate[15] dioxanate V, $[\alpha]_D$ −14.7°.

The optically active α-aminonitrile L-II, $[\alpha]_D$ 8.90°, was liberated from its salt with ammonia in ether. It melted completely at 86–88°, then immediately crystallized, and remelted at 125–128°; the melting point remained at 125° thereafter. Hydrogen cyanide

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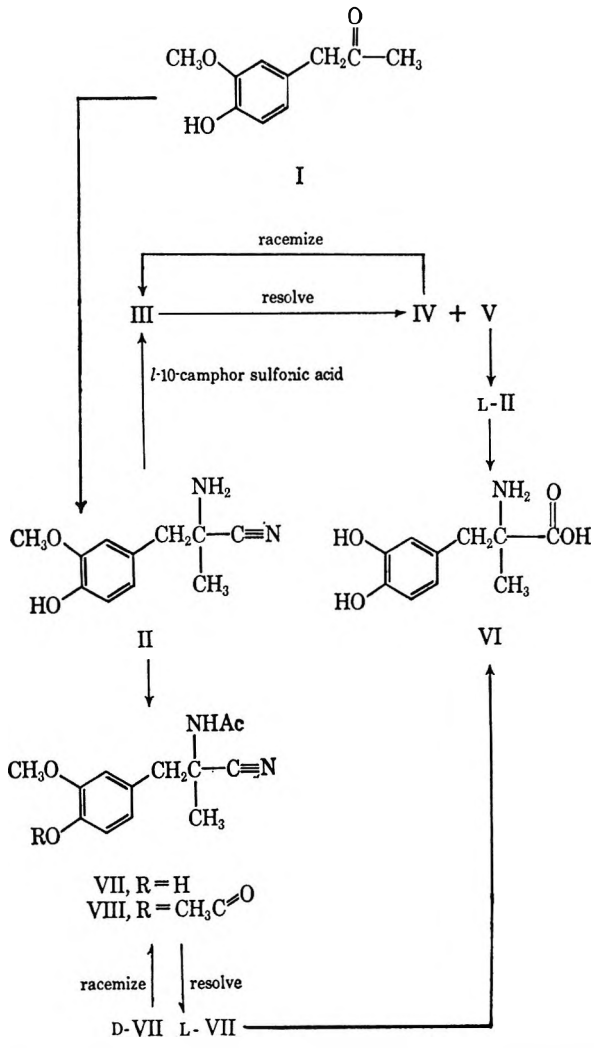
SCHEME I



was not evolved during the melting. L-II racemized 50–60% on melting at 86° and was completely racemized after having melted at 125–128°.

Determination of the solubilities of the optically active and racemic α-aminonitriles in nonionizing solvents, in which racemization was very slow, such as benzene, chloroform, and acetonitrile showed that the optically active form was five to nine times more soluble than the racemate. Thus, the prime requirement for a crystallization resolution was not met.[16]

In polar solvents in which L-II had limited solubility, the rate of racemization was too fast for solubility measurements. However, addition of optically pure seed to an aqueous solution of L-II gave a crystalline product which was extensively racemized. Unfortunately the unfavorable solubility relationship carried over into ionizing solvents and, with II, an asymmetric transformation leading to production of a single isomer would not be possible. Therefore, only the resolution by fractional crystallization of the diastereoisomeric salts was successful.

To complete this route for the synthesis of L-VI, L-II was treated with fortified HCl, simultaneously hydrolyzing the nitrile and cleaving the 3-methoxy group.

The search for a derivative which could be resolved by crystallization techniques was extended to the O,N-diacetyl (VIII) and N-acetyl (VII) derivatives, prepared by standard methods. In addition, racemic VII could also be synthesized in 86–90% yield directly from I by using acetonitrile or 2-propanol as the reaction solvent for formation of the α-aminonitrile, removal of the excess ammonia, and addition of acetic anhydride. This procedure, not involving the isolation of the α-aminonitrile, should be of general utility for the synthesis of N-acylated α-aminonitriles, which can be hydrolyzed in near-quantitative yield to the racemic N-acetylated amino acid (see Experimental Section), one of the preferred derivatives for resolution with optically active bases.

Comparison of the X-ray patterns and solubility data of the racemic and optically active diacetates indicated that VIII formed a *racemic compound* that was less soluble than the D or L form and, therefore, not suitable for resolution by crystallization techniques. On the other hand, a similar comparison of VII and L-VII revealed that the DL and L forms had identical X-ray patterns and that the DL form was exactly twice as soluble as the L form, which are the conditions for a *racemic mixture*. Thus fractional crystallization of VII seeding with either enantiomorph effected resolution.

The ease with which VII could be resolved now prompted a study of its racemization, so that the unwanted D isomer could also be utilized. Like VI, VII possesses no enolizable α-hydrogen atom, and consequently the breaking and re-forming of a C–C or C–N bond is required for racemization. This is easily accomplished thermally with α-aminonitriles in which the unshared electrons on the nitrogen assist the ionization of the cyanide group, but evidently these electrons are much less available in the case of α-acetamidonitriles such as VII, which was found to be optically completely stable even at its melting point, 204°. Even in solvents, such as methanol and methanol–water, which most strongly promote the ionization of α-aminonitriles, VII was optically stable under all conditions compatible with its chemical stability. At 200–225° in these solvents, hydrolysis of the N-acetyl group sets in, affording mixtures of 3-methoxy-4-hydroxyphenylacetone, α-aminonitrile, and cyanohydrin, but all samples of VII recovered from such partially hydrolyzed mixtures were found to be optically pure. The presence of an acidic catalyst, mercuric cyanide, was without effect in these solvents, while bases, as expected, simply catalyzed the hydrolysis reaction.

It thus was apparent that, if racemization rather than hydrolysis were to be the major reaction, the media would be limited to aprotic solvents. Of possible modes of racemization, the elimination and readdition of cyanide still appeared to be the most promising approach.

Refluxing D-VII in DMSO returned optically pure material in near-quantitative yield. It was anticipated that increasing the electron density on the amide nitrogen would facilitate the dissociation of the cyanide ion, and so this experiment was repeated in the presence of sodium cyanide. Under these conditions, racemization was at last achieved, rapidly and in good yield.[17]

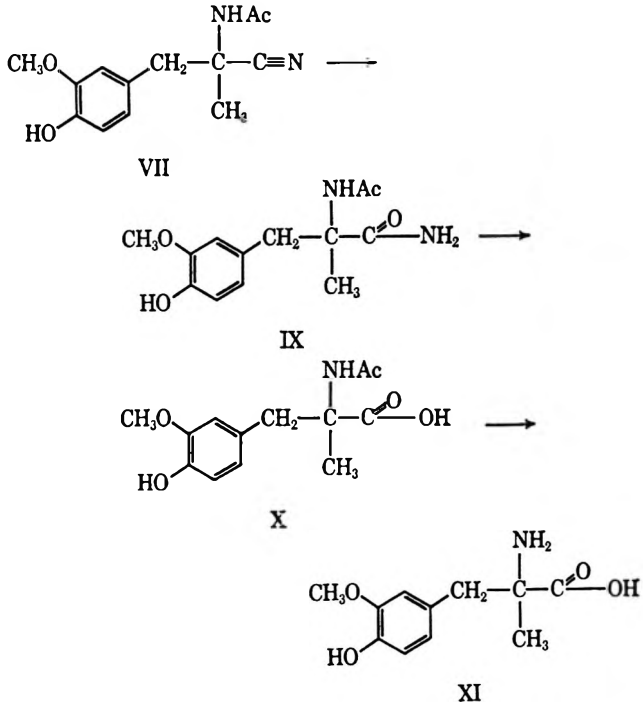
(16) R. M. Secor, *Chem. Rev.*, **63**, 297 (1963).

(17) R. A. Firestone, D. F. Reinhold, W. A. Gaines, J. M. Chemerda, and M. Sletzinger, *J. Org. Chem.*, **33**, 1213 (1968).

The demonstration of the resolution of VII by crystallization, followed by racemization of the D isomer, completed a second pathway for the efficient utilization of II. To complete the synthesis, L-VII was hydrolyzed with HCl to optically pure VI in nearly quantitative yield.

The hydrolysis of L-VII or DL-VII could also be accomplished in stepwise manner permitting isolation of any one of the three optically active or inactive intermediates, α-acetamido-α-vanillylpropionamide (IX), α-acetamido-α-vanillylpropionic acid (X), and α-methyl-3-methoxy-4-hydroxyphenylalanine (XI) (see Scheme II).

SCHEME II



L- or DL-VII dissolved exothermically in cold concentrated hydrochloric acid. Immediate dilution with ice water and adjustment of the pH to 5 with ammonium hydroxide precipitated L-IX as the monohydrate in 83% yield and the DL-IX in 86.5% yield. Tlc of the mother liquors indicated that VII was 100% hydrolyzed with X the only by-product. Extension of the hydrolysis period to 16 hr gave a 91 and 93% yield of L- or DL-X. L- or DL-XI could be obtained in good yield by selective hydrolysis with HCl.

The extremely facile conversion of VII to IX suggested that the N-acetyl was participating in the hydrolysis. However, the lifetime of the intermediate, if present at all, is too short to be detected by nmr methods at 0° in hydrochloric acid.

Experimental Section[18]

DL-α-Amino-α-vanillylpropionitrile (II). Procedure A.—3-Methoxy-4-hydroxyphenylacetone I (350 g, 1.94 moles) was added to a solution of ammonia (33.2 g, 1.95 moles) in 2-propanol (850 ml). Hydrogen cyanide (77 ml, 1.95 moles) was then added over 15 min while maintaining the temperature between 20–30°. The mixture was stirred at 25° for 18 hr, cooled at 0–5° for 1 hr, and filtered. Washing with two 100-ml portions of 2-propanol at 0° and drying at 10 mm and 40° gave 374 g (93.5% yield) of II: mp 125.5–127°; equiv wt 206; λ_{max}^{MeOH} 2800 mμ (ε 3070), 2300 mμ (ε 7090); solubility (mg/g), benzene, 2.83, acetonitrile, 51.4, chloroform, 21.0.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.90; H, 6.82; N, 13.78.

Procedure B.—To a solution of 3-methoxy-4-hydroxyphenylacetone (20 g, 0.11 mole) in 28% ammonium hydroxide (100 ml) was added potassium cyanide (8.0 g, 0.123 mole) and ammonium chloride (6.57 g, 0.123 mole). The mixture was stirred for 3 hr at 25° and 1 hr at 0–5°. The α-aminonitrile II was filtered, washed successively with cold 28% ammonium hydroxide (15 ml) and two 15-ml portions of 2-propanol at 0°, and vacuum dried at 25° to give 20.4 g (89.5% yield): mp 123–125°; equiv wt 208 (theory 206).

L-α-Amino-α-vanillylpropionitrile *l*-10-Camphorsulfonate–Dioxane Solvate (V).—DL-α-Amino-α-vanillylpropionitrile (158 g, 0.77 mole) was added to a solution at 40° of *l*-10-camphorsulfonic acid[16] (187 g, 0.80 mole) in water (490 ml). The mixture was cooled at 5° for 16 hr and the diasterioisomeric salt mixture III filtered, washed with ice water (150 ml), and dried in a vacuum to give 310 g (92% yield), $[\alpha]_D$ −20.5°.

The diasterioisomeric salts III were separated by digesting at 25° in dioxane (14 l.) for 90 hr. The insoluble salt V was filtered and redigested in dioxane (3250 ml) and water (32.5 ml) for 40 hr. Filtration and drying at 40° gave 101 g of pure V: $[\alpha]_D$ −14.7°; ν_{max}^{Nujol} 867 and 892 cm^{-1} (dioxane bands).

Anal. Calcd for $C_{25}H_{38}N_2O_8S$: C, 57.01; H, 7.27; N, 5.32. Found: C, 56.72; H, 7.25; N, 5.40.

Repetition of the above procedure with *d*-10-camphorsulfonic acid gave the D-α-amino-α-vanillylpropionitrile *d*-10-camphorsulfonate dioxane solvate.

L-α-Amino-α-vanillylpropionitrile (L-II).—A slurry of L-α-amino-α-vanillylpropionitrile *l*-10-camphorsulfonate dioxane solvate V (20.0 g) in ether (200 ml) was treated with ammonia gas under a pressure of 1 in. of mercury for 2 hr. The ammonium *l*-10-camphorsulfonate was removed by filtration and excess ammonia was removed by evaporation of the ether to a volume of 25 ml. Ether (175 ml) was added and hydrogen chloride passed into the solution to precipitate the α-aminonitrile hydrochloride. The hydrochloride salt (6.48 g) was slurried in ether (130 ml) and ammonia gas passed into the mixture for 2 hr. The ammonium chloride was filtered and the filtrate evaporated at reduced pressure below 25°. The oily residue crystallized on trituration with ether. Filtration and drying at 30° in a vacuum gave 5.3 g (68% yield) of L-II: mp 86–88°, resolidified and melted at 125–128°; $[\alpha]_D$ +8.9° (*c* 2, dioxane); solubility (mg/g of solvent), benzene, 32.6, acetonitrile 282.6, chloroform, 180.8.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.96; H, 6.78; N, 13.45.

An Attempt to Maintain the Optical Purity of L-II under Racemizing Conditions.—To a solution of L-α-amino-α-vanillylpropionitrile *l*-10-camphorsulfonate dioxane solvate V (1.0 g) in water (3 ml) was added seeds of L-II (10 mg). The pH of the slurry was immediately adjusted to 8 with concentrated NH_4OH and it was placed in an ice bath. The precipitate after aging 1 hr, filtering, and drying in vacuum below 25° weighed 65 mg: $[\alpha]_D$ +3.5° (*c* 2, dioxane), 35% optically pure. The filtrate was again seeded with L-II (10 mg) and aged at 0° for 2 hr. A second crop (100 mg) was obtained: $[\alpha]_D$ +1.4°,

(18) All optical rotations were determined on a Carl Zeiss photoelectric precision polarimeter Model 005. Unless specified, a 1% solution in methanol at 25° was used for all rotations. The $[\alpha]_D$ was calculated using the simplified formula

$$[\alpha]_D = [\alpha]_{578} - [([\alpha]_{578} - [\alpha]_{546}) \times 0.294]$$

Melting points are uncorrected and were determined with a Thomas–Hoover capillary melting point apparatus.

Infrared spectra were determined on a Model 137 Infracord. Equivalent weights were determined in glacial acetic acid by titrating potentiometrically with 0.1 *N* $HClO_4$ in dioxane using a Sargent Model D titrator equipped with the following electrode system: (1) a platinum ring electrode #S30440, and (2) a Calomel sleeve-type Sargent S30084-15 which has had the aqueous electrolite removed, rinsed with water, rinsed with acetic acid, and filled with 0.1 *N* lithium perchlorate (available from G. S. Smith & Co.) in acetic anhydride.

Microanalyses were done through the courtesy of Mr. R. N. Boos and associates. Infrared data were compiled by Dr. N. R. Trenner and Mr. R. W. Walker. Nmr analyses were by Dr. N. R. Trenner, Dr. B. A. Arison, and Mr. B. Singleton. Titrations were by Mr. B. Singleton, Mr. J. P. Gilbert, and associates. Ultraviolet and solubility data were compiled by Mr. E. A. MacMullen and associates.

14% optically pure. The filtrate was again seeded (10 mg) and aged overnight at 0° to give a third crop (130 mg) which was 100% racemic.

Racemization of D-α-Amino-α-vanillylpropionitrile *l*-10-Camphorsulfonate (IV).—Optically impure salt IV (10.0 g), obtained by evaporation of dioxane mother liquors of V, was dissolved in water (20 ml) and concentrated ammonium hydroxide (1.3 ml, 0.019 mole) added. After standing 6 hr, concentrated hydrochloric acid (1.6 ml, 0.019 mole) was added. The mixture was cooled at 0–5° for 18 hr, filtered, washed with ice water, and dried to give 6.0 g of III: $[\alpha]_D$ −20.5°.

Racemization of D-α-Amino-α-vanillylpropionitrile (D-II).—A thick slurry of D-II (510 mg) in 2-propanol (1 ml) was heated in a 40° water bath for 7 hr. Evaporation of the solvent below 40° in a vacuum gave a crystalline residue (510 mg) which was 96% racemic: mp 123.5–126.5°; $[\alpha]_D$ −0.14° (*c* 1, dioxane).

L-O,N-Diacetyl-α-amino-α-vanillylpropionitrile (L-VIII).—A solution of L-II (2.0 g) in pyridine (10 ml) and acetic anhydride (10 ml) was heated for 15 min at 90°, cooled to 20°, poured into water (100 ml), and extracted with chloroform. The chloroform solution was washed successively with cold 2.5 *N* hydrochloric acid and water. The chloroform solution was dried over magnesium sulfate and evaporated to give an oil. Crystallization from 2-propanol–petroleum ether (30–60°) gave 2.7 g (96% yield) of L-VIII: mp 121.5–123.5°; $[\alpha]_D$ −40.7°; $\nu_{max}^{CHCl_3}$ 1770 (OAc), 1685 cm^{-1} (NAc).

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.96; H, 6.32; N, 9.66.

DL-O,N-Diacetyl-α-amino-α-vanillylpropionitrile (VIII).—Synthesis of VIII was accomplished in 95% yield using the same procedure as used for L-VIII: mp 166–168°; infrared in chloroform identical with that of L-VIII.

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.90; H, 6.06; N, 9.58.

DL-α-Acetamido-α-vanillylpropionitrile (VII). Procedure A.—To a slurry of DL-α-amino-α-vanillylpropionitrile (20 g) in 2-propanol (40 ml) at 20° was added acetic anhydride (20 ml). The exothermic reaction and crystallization raised the temperature to 48°. The slurry was slowly cooled to 0–5° and aged at 0–5° for 1 hr. The precipitate was filtered, washed twice with 10-ml portions of cold 2-propanol, and dried, to give 24.0 g (97% yield): mp 176–178°; ν_{max}^{Nujol} 1667 cm^{-1} (NAc); solubility in 2-propanol, 8.5 mg/g.

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.96; H, 6.50; N, 11.20.

Procedure B.—Ammonia (1.9 g, 0.11 mole) was dissolved in 2-propanol (45 ml) at 5°, followed by addition of 3-methoxy-4-hydroxyphenylacetone I (18.0 g, 0.10 mole) and hydrogen cyanide (4.15 ml, 0.105 mole). After stirring for 18 hr, toluene (110 ml) was added and the mixture evaporated at reduced pressure to a volume of 75 ml. Acetic anhydride (20 ml) was added to the slurry which was then heated to the boiling point. The mixture was cooled at 0–5° for 1 hr, filtered, and washed with two 15-ml portions of toluene. Vacuum drying at 45° gave 22.85 g (91.4% yield) of VII: mp 176–178°; λ_{max}^{MeOH} 2810 mμ (ε 3050), 2320 mμ (ε 7800).

L-α-Acetamido-α-vanillylpropionitrile (L-VII). By Synthesis from L-VIII.—A solution of L-VIII (1.0 g) in ethanol (10 ml) and 10% sodium hydroxide (1.5 ml) was stirred at 25° for 2 hr. The solution was diluted with water (10 ml) and acidified with hydrochloric acid. The product L-VII was filtered, washed with water, and dried to 800 mg (93.5% yield): mp 204–206°; $[\alpha]^{30}_D$ −42.4°; ν_{max}^{Nujol} 1665 cm^{-1} (N-Ac), solubility in 2-propanol, 4.2 mg/g.

By Resolution of VII.—VII (1.0 g) was dissolved at 50° in 2-propanol (25 ml) and filtered to remove any potential seeds. The filtrate was cooled to 40° and finely pulverized L-VII (50 mg) was added with stirring. The slurry was cooled to 30° in 5 min and rapidly filtered to give 300 mg of L-VII, $[\alpha]_D$ −25.8° (63% optically pure). Crude L-VII (200 mg) was digested with 2-propanol (10 ml) for 16 hr at 25°, filtered, and washed with 2-propanol to give 110 mg of optically pure material: mp 203–204°; $[\alpha]^{30}_D$ −42°.

Anal. Calcd for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.30; N, 11.49.

Unsuccessful Racemization Studies on D-α-Acetamido-α-vanillylpropionitrile (D-VII). A.—D-VII (20.0 mg) was heated in an oil bath at 207° for 1 min, until completely melted. After cooling, the entire sample retained 100% optical purity.

B.—D-VII (20.3 mg) was heated with 0.5 ml of methanol in a sealed tube for 8 hr at 225°. The total sample then showed 39% of its original optical activity. The residue from evaporation of the solvent crystallized on treatment with chloroform. It was filtered and washed with a little 2-propanol, then had a weight of 5.3 mg and an optical purity of 98%. The filtrate after evaporation weighed 11.8 mg and was *ca.* 80% pure ketone I by ir; the purity would be 78% if all but 39% of the original L-VII had been hydrolyzed to I rather than racemized. Using the 78% figure, the calculated yield of ketone (11.8 × 0.78) is *ca.* 62%, for a mass balance of *ca.* 101%. Thus the loss of optical activity in the total sample is quantitatively accounted for by hydrolysis to I.

Similar results were obtained with 50% aqueous methanol. A similar reaction was run for 9 hr at 200° with 0.5 mg of mercuric cyanide present. The total reaction mixture had 81% retention of optical activity, and from it was isolated 63% of off-color crystalline D-VII, 97% optically pure.

Racemization of D-α-Acetamido-α-vanillylpropionitrile (D-VII).—A mixture of D-VII (2.0 g, 0.008 mole) and sodium cyanide (0.20 g, 0.004 mole) in dimethyl sulfoxide (8.0 ml) was subjected alternately to a vacuum and nitrogen source three times. The flask was placed in a preheated (200°) oil bath. After reaching the boiling point, which required 2 min to attain, the mixture was allowed to reflux 3 min, then immediately was cooled in an ice bath. The dimethyl sulfoxide was distilled under reduced pressure to a syrupy residue. Dilute hydrochloric acid (15 ml) was added to crystallize the light tan product. The racemized product was filtered, washed with water, and vacuum dried to give 1.84 g (91.8% yield): mp 173–176°; $[\alpha]^{30}_D$ 0°. The material was identical in all respects with VII obtained by acetylation of II.

L-α-Methyl-3,4-dihydroxyphenylalanine Sesquihydrate (VI). From L-VII.—A solution of L-VII (24.8 g, 0.1 mole) in concentrated hydrochloric acid (46 ml) in a bomb tube was purged with nitrogen, sealed, and heated at 130° for 5 hr. The tube was cooled in a Dry Ice–acetone bath and opened; the contents were transferred to a round-bottom flask. The hydrochloric acid was distilled at reduced pressure and the residual acid removed by dissolving in water (100 ml) and evaporating again to dryness. The residue was dissolved in water (35 ml), treated with Darco G-60 (1.0 g), and the pH adjusted to 4.5 with concentrated ammonium hydroxide under a nitrogen atmosphere. The mixture was cooled at 0–5° for 1 hr and the white product filtered, washed with two 10-ml portions of ice water, and vacuum dried at 40° to give 21.9 g: mp 302–304° dec; equiv wt 238.1; H_2O, 11.3% (Karl Fischer) (calcd, 11.3%); $[\alpha]_{546}$ +154.5° (*c* 0.5, copper sulfate solution).[3]

From L-II.—The α-aminonitrile L-II was hydrolyzed and the product isolated in the same way except that 45% hydrochloric acid was used as the hydrolysis medium.

L-α-Acetamido-α-vanillylpropionamide (L-IX).—The N-acetylaminonitrile L-VII (20.0 g) was dissolved in concentrated hydrochloric acid (40 ml) at 0°. The solution was immediately diluted with ice water (100 ml) and the pH adjusted to 5.0 with concentrated ammonium hydroxide. The crystals were filtered, washed with ice water, and vacuum dried at 40°. The amide L-IX weighed 18.78 g (82%) and was obtained as the monohydrate: 6.23% (Karl Fischer) (calcd, 6.34%). Crystallization of the monohydrate from 2-propanol gave the anhydrous amide: mp 186–187°; $[\alpha]_D$ −69.2°.

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.40; H, 6.92; N, 10.23.

DL-α-Acetamido-α-vanillylpropionamide (IX).—Hydrolysis of VII (20.0 g), using the same procedure as described above for the optically active material gave 18.56 g (86.5% yield) of anhydrous material: mp 217–222°; ν_{max}^{Nujol} 1695 (N-Ac) and 1630 cm^{-1} C(=O)-NH_2.

The analytical sample was prepared by recrystallization from aqueous methanol, mp 224–228°.

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.81; H, 6.85; N, 10.38.

L-α-Acetamido-α-vanillylpropionic Acid (L-X).—L-VII (20.0 g) was dissolved in cold concentrated hydrochloric acid and stirred for 16 hr at 25°. Addition of water (100 ml) completed the crystallization of the product. Filtration, followed by washing with water and forced air drying, gave 20.9 g (91% yield) of L-X as the monohydrate: H_2O, 6.54% (Karl Fischer) (calcd, 6.39%); $[\alpha]_D$ −50.9°.

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.75; H, 6.72; N, 4.91. Found: C, 54.50; H, 6.65; N, 5.19.

DL-α-Acetamido-α-vanillylpropionic Acid (X).—Hydrolysis of VII using the identical procedure as used for L-VII gave 20.0 g (93% yield), mp 213–216°. Crystallization from water provided the analytical sample, mp 218–220°.

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.56; H, 6.21; N, 5.38.

L-α-Methyl-3-methoxy-4-hydroxyphenylalanine (L-XI).—L-VII (100 g) was added portionwise to cold concentrated hydrochloric acid (200 ml). The solution was diluted with water (1 l.) and the mixture refluxed for 5 hr. After cooling to 20°, the pH was adjusted to 5.0 with concentrated ammonium hydroxide. The product was filtered, washed free of chlorides with water, and vacuum dried to yield 87.7 g, mp 307° dec. The analytical sample was prepared by dissolving crude L-XI in dilute hydrochloric acid, treating with Darco G-60, and reprecipitating as the monohydrate by adjusting to pH 5.5: mp 313° dec; $[\alpha]_{546}$ +166° (c 0.5, copper sulfate solution);[3] H_2O, 8.0% (Karl Fischer) (calcd 7.5%). A single spot appeared on paper strip chromatography using a *n*-BuOH–H_2O–HOAc system (120:50:30). The sample (spotted as 1% solution in water saturated with sulfur dioxide) was detected by spraying with diazotized *p*-nitroaniline, drying, and spraying with 5% sodium carbonate solution.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71. Found: C, 58.66; H, 6.42. (Sample dried at 100°.)

DL-α-Methyl-3-methoxy-4-hydroxyphenylalanine (XI).—The DL-N-acetylaminonitrile VII (20.0 g) was dissolved in concentrated hydrochloric acid (40 ml), diluted with water (40 ml), and heated at 90° for 4 hr until solution was complete. The water was removed at reduced pressure and the residue dissolved in water. Adjustment to pH 6.0 with concentrated ammonium hydroxide resulted in the precipitation of the amino acid. The product was filtered, washed with water, and vacuum dried to give 17.75 g (97.5% yield), mp 318–320° dec.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71. Found: C, 58.40; H, 6.60.

Registry No.—II, 6555-27-7; L-II, 14818-96-3; III, 15073-71-9; V, 15073-82-2; VI, 555-30-6; VII, 14818-97-4; L-VII, 14818-98-5; VIII, 15073-74-2; L-VIII, 15073-76-4; IX, 15156-57-7; L-IX, 15073-77-5; X, 15073-78-6; L-X, 15073-79-7; XI, 15073-80-8; L-XI, 6739-31-7.

The Racemization of α-Methyl-α-acetamidonitriles

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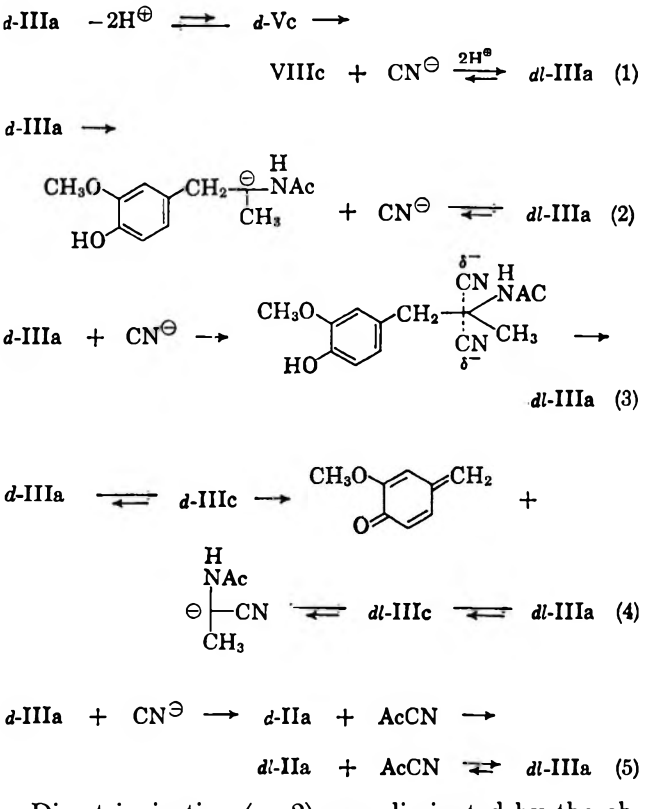
The mechanism of base-catalyzed racemization of α-acetamidonitriles bearing no enolizable α hydrogen has been studied and found to proceed *via* elimination and readdition of the elements of HCN; the amide nitrogen must bear a hydrogen atom. The rate-determining step is not deprotonation but expulsion of cyanide from the amide anion.

In the production of L-α-methyldopa *via* the aminonitrile route, resolution can be accomplished on either the amino acid itself,[1] the α-amino-2-vanillylpropionitrile IIa,[2] or the α-acetamido-α-vanillylpropionitrile IIIa.[2] Both enantiomers can be utilized if the unwanted D isomer can be racemized. This cannot be done at present with I, and, although racemization of II is facile, its resolution is not. Compound IIIa, however, crystallizes as a *dl* mixture, and its resolution by spontaneous crystallization has been accomplished; thus racemization of D-IIIa became a paramount goal.

This was eventually achieved using sodium cyanide in DMSO. A preliminary description of this method is contained in the accompanying paper,[2] and we here report details of the reaction and its mechanism. The first portion of the study was concerned with the scope of the reaction, and the second with kinetics.

Although it was found that IIIa could be racemized by any base of sufficient strength and solubility, sodium cyanide was used in most of the work because it gave the best yields, presumably by suppressing loss of cyanide from the product. In dry DMSO, IIIa could be conveniently racemized in high yield at temperatures ranging from about 140° to reflux (189°). The rate increased about threefold for each 10° rise in temperature. A selection of racemization data obtained in DMSO is presented in Table I.

Five mechanisms were originally considered for the reaction (eq 1–5).



Direct ionization (eq 2) was eliminated by the observation that racemization did not occur in the

(1) E. W. Tristam, J. ten Broeke, D. F. Reinhold, M. Sletzinger, and D. E. Williams, *J. Org. Chem.*, **29**, 2053 (1964).

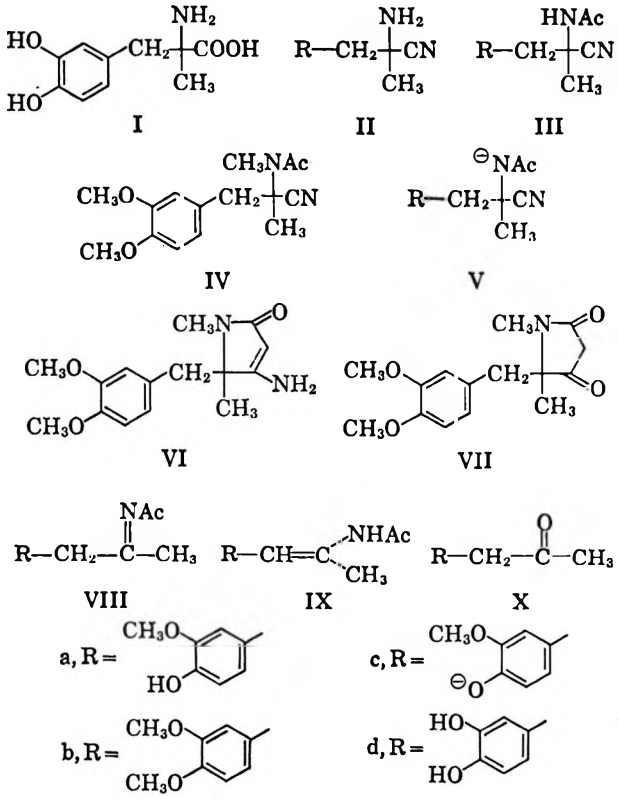
(2) D. F. Reinhold, R. A. Firestone, W. A. Gaines, J. M. Chemerda, and M. Sletzinger, *J. Org. Chem.*, **33**, 1209 (1968).

TABLE I[a]
RACEMIZATION OF VARIOUS α-METHYL-α-ACETAMIDONITRILES

Run no.	Compd	Base (moles)	Temp, °C	Time, min	% racemization	% yield
1[b]	IIIa	NaCN (2)	160	10	54	83
2	IIIa	NaCN (2)	160	10	83	86
3	IIIa	NaCN (0.5)	160	10	64	94
4	IIIa	NaH (0.5)	160	10	94	82
5	IIIa	Na_2CO_3 (0.5)	160	10	18	80
6	IIIa	CaO (excess)	160	10	0	94
7	IIIa	$Hg(CN)_2$ (0.5)	189	3	0	50
8	IIIa	NaCN (0.5), NaH (1)	140	10	67	89
9	IIIa	NaCN (0.5), HCN (1)	160	10	36	83
10	IIIa	NaCN (0.5)	150	10	18	90
11	IIIa	KCN (0.5)	150	10	17	89
12	IIIb	NaCN (0.5)	160	10	100	92
13	IIIb	NaH (0.5)	160	10	100	75
14	IIIb	None	160	10	0	95
15	IV	NaCN (0.5)	160	10	0	75[c]
16	IIIa	NaH (2)	25	120	12	94
17	IIId	NaCN (0.5)	160	30	38	>90
18	IIIa	NaCN (0.5)	189	1.5	100	91
19[d]	IIIa	NaCN (0.5)	210	5	45	50
20[b]	IIIa	NaCN (0.5)	189	1.5	100	96

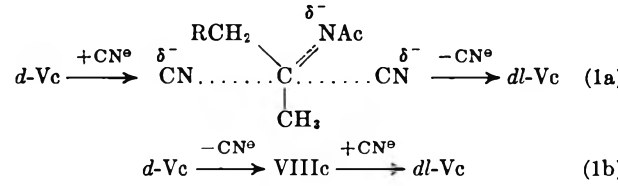
[a] 20% in DMSO. [b] 33% in DMSO. [c] 91% yield taking cyclization into account. [d] No solvent.

absence of base (compare runs 14 with 12 and 13). The case in eq 4, which requires that the dimethoxy derivative IIIb be optically stable under our conditions, was disproved by the finding that IIIb actually racemized much faster than IIIa (compare runs 12 and 3).



If eq 1 is correct, replacement of the N–H by N–methyl must completely suppress the reaction. This is not the case with eq 3 and 5, although they might suffer some steric retardation. When IV was subjected to the usual racemization conditions (run 15), no loss of optical activity was observed; thus the amide N–H is essential for racemization.

These experiments left the mechanism in eq 1 as the only important possibility left from the group. However, the question still remained whether the incoming cyanide approaches the molecule before (eq 1a) or after (eq 1b) complete separation of the outgoing cyanide. A clear choice can be made by comparing



the rate of racemization with that of exchange with external radioactive cyanide. In the mechanism of eq 1a, each exchange of cyanide requires an inversion and racemizes two molecules, while with that of eq 1b only one molecule racemizes per exchange.

The kinetic expressions[3] for the two cases given in eq 1a and b are, respectively

$$1 - F_{ex} = (1 - F_r)^{3/2}$$
$$1 - F_{ex} = (1 - F_r)^3$$

In these expressions, F_r = fraction racemized and F_{ex} = radioactivity at time t divided by radioactivity at time ∞. A sample of pure IIIa reacted in the presence of C^{14}-labeled cyanide ion and was recovered in 90.4% yield with 17.8% racemization. The calculated F_{ex} for cases in eq 1a and b are 0.256 and 0.444, respectively, and the F_{ex} observed was 0.460. This result unequivocally supports mechanism of eq 1b, the elimination–addition route.

The chronology of this elimination remains to be established. It seemed intuitively obvious that the removal of the proton on the amide nitrogen atom would be rate controlling, because elimination of cyanide ion from the resulting anion would surely be rapid compared with the neutral molecule IIa, which loses cyanide ion so readily.[2] This analogy, in the event, proved misleading.

It was found that compound IIIa could be treated with 2 moles of sodium hydride for 2 hr at 25° in DMSO and recovered in 94% yield in 88% of its original optical activity (run 16). To show that all of the hydride was reacting, the hydrogen evolved was collected in 96% yield. Finally, the possibility that 1 mole of the hydrogen came from reaction with DMSO rather than with the amide N–H was eliminated by dimethylation. Compound IV could be prepared from IIIa in >72% yield by treating IIa with 2 moles of sodium hydride in DMSO followed by dimethyl sulfate.

We conclude, then, that IIIa can maintain its optical asymmetry even with anionic amide nitrogen and that deprotonation of this atom is not rate controlling. The most probable mechanism for the racemization of III has the elimination of cyanide ion from the amide anion as the rate-determining step.

A more complete picture of the reaction can now be written (eq 6–8).

$$\text{IIIa} + \text{CN}^\ominus \rightleftharpoons \text{IIIc} + \text{HCN} \quad (6)$$

$$\text{IIIc} + \text{CN}^\ominus \rightleftharpoons \text{Vc} + \text{HCN} \quad (7a)$$

$$2\text{IIIc} \rightleftharpoons \text{Vc} + \text{IIIa} \quad (7b)$$

$$\text{Vc} \overset{\text{slow}}{\rightleftharpoons} \text{VIIIc} + \text{CN}^\ominus \quad (8)$$

(3) These expressions were derived for us by Dr. R. T. Mullen.

Kinetic Studies.—Rate constants were determined for the racemization of IIIa, IIIb (see Table II), IIIc, and Vb.

TABLE II
KINETICS OF RACEMIZATION OF IIIa AND IIIb

Run no.	Temp, °C	Substrate	Concn, M	NaCN, M	k_1, hr^{-1}	k_2, l. mole^{-1} hr^{-1}
K1	124.8	IIIa	0.815	0.0787	0.034	0.47
K2	138.6	IIIa	0.815	0.0787	0.18	2.5
K3	131.2	IIIa	0.815	0.0787	0.076	1.06
K4	138.8	IIIa	0.814	0.0409	0.097	2.6
K5	139.2	IIIa	0.402	0.0392	0.27	7.7
K6	117.4	IIIb	0.802	0.0787	0.17	2.3
K7	117.5	IIIa	0.798	0.847[a]	0.95	1.21
K8	110.2	IIIa	0.798	0.847[a]	0.44	0.56

[a] Flushed twice *in vacuo* with DMSO before racemization. This converts IIIa into IIIc (*vide infra*).

During the first portion of the work, reactions were run in sealed tubes, using DMSO and NaCN. Under these conditions, several acid–base equilibria must be brought into existence before the appearance of V, the amide anion, whose expulsion of cyanide ion is the slow step in the racemization.

The second portion of the kinetic study was concerned with this reaction. Conditions were chosen where all ionizable protons were removed so that all preequilibria were forced completely to the right. The base employed was sodium methylsulfinylmethylide (dimsylsodium) in 1% molar excess, which was prepared and standardized daily. Kinetic runs were performed in volumetric flasks, using a constant-temperature bath good to ±0.02°. For reasons discussed below, these runs did not produce linear plots, but the initial curvature was slight enough to permit the determination of fairly accurate initial rate constants. In these experiments, Vb was used rather than Va, which oxidizes rapidly in very strong base. It may be noted that the return of cyanide to the molecule after elimination is far from quantitative under these conditions; this does not, however, diminish the significance of the results, since departure of the cyanide leads directly to symmetric products, whose subsequent fate is kinetically not significant.

All but one of the sodium cyanide runs were pseudo first order as far as they were carried (20–92% completion). The one exception, run K4, was first order to about 40% reaction, after which the rate began to diminish. We attribute this to the exceptionally low base concentration in this run, 5 mole %; even a very small loss of base by side reactions (*vide infra*) would be magnified in relation to the total.

That the reaction is actually first order in base concentration as well as in substrate can be seen by comparing runs K2 and K4. The second-order rate constants (corrected for the small temperature difference) are the same despite a twofold change in the amount of catalyst.

The very high rates of racemization of Vc (run 16) and of Vb (K13, K14, and K16) (see Table III) compared with those of IIIa and IIIb (runs 1–14), indicate that the steady-state concentration of intermediates V is very low under normal racemization conditions. Chiefly responsible for this is the unfavorable equilibrium in eq 7a and b because equilibrium 6 lies considerably to the right. This was deduced from the following facts: first, if the equilibrium constant for eq 6 were very small, the addition of molar quantities of HCN to the reaction would have a much larger effect on the rate than it actually does (compare runs 3 and 9), which is to reduce it about twofold; second it is possible to remove cyanide by distillation very easily from reaction mixtures containing IIIa and NaCN. This fact made it possible to run kinetics on the vanillyl phenoxide sodium salt IIIc (runs K7 and K8), which has been difficult to prepare by other methods.

TABLE III
KINETICS OF RACEMIZATION OF Va

Run no.	Temp, °C	Concn, M	k_1, hr^{-1}
K13	30.06	0.793	0.18
K14	30.06	0.402	0.18
K16	37.06	0.855	0.42

TABLE IV
ACTIVATION CONSTANTS

Reaction	E_a, kcal/mole	A, sec^{-1}	S^*, eu
IIIa + NaCN	39	1.5×10^{16}	13
IIIc + NaCN	30	1.1×10^{13}	−1.4
Vb racemization	23	2.2×10^{12}	−4.1

As expected, successively by-passing the preequilibria (eq 6 and 7) results in stepwise diminution of the activation energy (see Table IV).

Effect of Hydrogen Bonding.—The reactivity of anions is very great in polar aprotic solvents relative to protic ones,[4] and their basicity is markedly diminished by the introduction of even small amounts of proton donors.[5] This was borne out strongly in our work.

Large rate accelerations are brought about by the successive removal of active hydrogens from the vanillyl system. The most active hydrogen is the phenolic one, and methylation of the free phenol in IIIa, converting it into IIIb, results in a rate increase of 12 (run K6 compared with K1–3 extrapolated to 117.4°; compare also runs 3 and 12). Removal of this same active hydrogen by sodium salt formation, giving IIIc, also accelerates the reaction, in this case by a factor of 6.4 (run K7; see also runs 3 and 4). It is interesting that IIIc is not so active as IIIb (matching second-order rate constants k_2), showing that the expected superiority in reactivity of the dianion Va over that of the monoanion Vb is more than offset by the extra energy required to remove a second proton from anion IIIc. Conversely, the addition of an active hydrogen donor, HCN, reduces the rate of racemization; runs 3 and 9 show a rate factor of about 2. For the same reason, the dihydroxy derivative IIId is about one-sixth as reactive as IIIa (runs 3 and 17).

Upon withdrawal of the last active hydrogen the greatest acceleration is produced; Vb racemizes more than 5000 times as fast as IIIb, comparing runs K13 and K16, extrapolated to 117.4°, with run K6. It is recognized that this large rate increase is not due solely to the active hydrogen effect, but it must nevertheless be a large factor.

(4) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).
(5) E. C. Steiner and J. M. Gilbert, *J. Amer. Chem. Soc.*, **85**, 3054 (1963).

Another system with no active hydrogen is IV–DMSO, in which the normally unreactive α hydrogen of the acetamide function became readily removable with base. Cyclization to VI was quite facile with sodium cyanide, and rapid with sodium hydride. Compound VI was characterized from physical data and also by hydrolysis to VII.

Effect of Solvent.—Although DMSO appears to be the best solvent for the reaction, other polar aprotic solvents have been used successfully. In DMF at 153° the rate is about the same as in DMSO. Diglyme was a much poorer racemization medium, affording only 15% reaction after 10 min at 162° (*cf.* run 3).

With no added solvent, *i.e.*, with IIIa itself as reaction medium at 210°, racemization occurs, but slowly; compare runs 18 and 19. It was observed as a general phenomenon in the concentration range studied that the over-all velocity increased with dilution (run 1 *vs.* run 2) despite a second-order kinetic effect in the opposite direction. Runs K2 and K5 provide a quantitative comparison; at constant substrate–catalyst ratio, an increase of the per cent of DMSO from 80 to 90 gave rise to a second-order rate factor, corrected for temperature, of 2.7. This effect presumably stems not only from the lower polarity of IIIa but also from its possession of hydrogen bond donors.

It can be concluded, then, that an important function of DMSO in promoting our reaction is to tie up hydrogen bonds, thereby liberating a greater proportion of unencumbered base;[6] this, in turn, produces an augmented concentration of Vc by pushing equilibria (eq 7) to the right. Once the dianion Vc has been formed, however, polarity might have a *retarding* effect on its rate of dissociation, a transformation which dissipates charge. In the case of Vb, a monoanion, the solvent effect is small (*cf.* K13 and K14).

As expected, no racemization whatever was observed in diisobutyl carbinol after 30 min at 160°. This alcohol is sufficiently hindered that the carbonyl attack normally observed with bases in alcohols[2] could be at least partially suppressed, although only 45% recovery was obtainable.

Side Reactions.—The curvature of the semilog plots of runs K4, K13, K14, and K15, described previously, correspond to a slow diminution of the base concentration. In the dimsylsodium runs this is much more marked, and we attributed it to elimination and/or tautomerization reactions promoted by the exceptionally basic species present (*e.g.*, Vb, $CH_3SOCH_2^{\ominus}$, and $CN^{\ominus}$ unencumbered by hydrogen bonds), in which relatively acidic protons are created. An obvious possibility is the isomerization of VIIIb to the enamide IXb. This was confirmed in the case of IIIa which, on standing with 2 equiv of dimsylsodium, afforded IXa. Its structure was established by analysis, spectra, and hydrolysis to the known vanillyl ketone Xa and acetamide.

Under more normal racemization conditions, such as run 20, this side reaction is negligible, since the total yield of ketone Xa after hydrolysis in aqueous acid, which includes not only IXa but also any Xa which may have been directly formed, is less than 1%.

(6) For an example of a similar phenomenon but with a different explanation, see C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).

Experimental Section[7]

Reagents.—Dimethyl sulfoxide (Matheson Coleman and Bell) was kept over molecular sieves. The water content never exceeded *ca.* 0.05% by Karl Fischer titration. Redistilled DMSO, kept over sieves, was used for the kinetic measurements.

Sodium cyanide was reagent grade, 98.9% NaCN by Volhard titration, 96.5% alkali (as NaCN) by HCl titration using phenol red (pH 7.0). α-Acetamido-α-vanillylpropionitrile IIIa[2] had mp (*dl*) 176–178°, (*d* or *l*) 202–204° (the *dl* form is a mixture, not a compound); rotation values are 578 mμ, 43.1°; 546, 49.6; 436, 93.4; 405, 117.5; 365, 167.3. It was recrystallized from methanol for the kinetic work.

α-Acetamido-α-veratrylpropionitrile IIIb had mp (*d*) 142–144°, (*dl*) 142–143° (the *dl* form is a compound); rotation values are 578 mμ, 36.8°; 546, 42.6; 436, 79.7; 405, 99.6; 365, 141.2. For the kinetics it was recrystallized from benzene–hexane.

Optical rotations were determined on a Zeiss polarimeter at 578, 546, 436, 405, and 365 mμ. All were 1% in methanol at 30° and all showed correct ORD's for known materials, except as noted.

Infrared spectra were determined on a Perkin-Elmer Model 137 Infracord.

Racemization of α-Acetamido-α-vanillylpropionitrile (IIIa) at 160° Using 0.5 Mole of NaCN.—A mixture of 0.5061 g of *d*-IIIa (0.00204 mole), 0.0502 g of NaCN (0.001 mole), and 2.0 ml of DMSO was warmed until solution was complete, purged thoroughly with nitrogen, and heated with stirring for 10 min in an oil bath at 160°. Most of the solvent was then removed at *ca.* 50° at 1.5 mm. The residue was diluted with 20 ml of water, acidified with HCl, and chilled 0.5 hr. The crystalline precipitate was filtered, washed twice with cold isopropyl alcohol, and once with petroleum ether (30–60°), and dried to give 0.4268 g (84.3%). The optical purity was 40%.

From the mother liquor was obtained a second crop of racemic IIIa, 0.0472 g. Thus the total recovery was 93.6% and the average optical purity 36%.

In another run using the same proportions of reagents but half as much DMSO (1.5 min at reflux, 189°; yield 96% in two crops), the aqueous mother liquor was analyzed, after standing acidified overnight, for ketone. Six chloroform extracts were combined, dried with $MgSO_4$, filtered, stripped, and made accurately to volume. Quantitative vpc comparison with pure Xa solution established that the yield of ketone was only 0.84%.

Racemization of IIIa Using 0.5 Mole of NaCN and 1 Mole of HCN.—Optically pure α-acetamido-α-vanillylpropionitrile IIIa (0.5042 g, 0.002 mole), and 0.0499 g (0.001 mole) of NaCN were dissolved in 2.0 ml of DMSO which was 1.07 N in HCN (0.002 mole). After purging with nitrogen, the mixture was stirred and heated for 10 min in an oil bath at 160°. A strong red color developed.

The reaction was worked up as before, affording 0.4198 g (83.4%) of recovered IIIa, mp 174–198°, whose optical purity was 64%.

Preparation of Optically Active α-Acetamido-α-veratryl propionitrile (IIIb).—Sodium hydride (0.96 g, 50% in mineral oil, 0.02 mole) was washed three times with hexane and brought together with 4.96 g (0.02 mole) of *d*-IIIa in a mixture of 50 ml of dioxane and 15 ml of DMSO. The reaction was allowed to proceed mainly at room temperature and was completed by brief warming.

To the cooled reaction mixture was added 1.89 ml (0.02 mole) of dimethyl sulfate; heat was briefly evolved. It was then heated 10 min on the steam bath, cooled, and stripped under vacuum at *ca.* 1 mm. An oil separated upon addition of 200 ml of water which was extracted four times with methylene chloride. The extracts were washed three times with water, dried with $MgSO_4$, filtered, and evaporated under vacuum, leaving 5.58 g of oil which was crystallized from benzene. The product was filtered, washed with benzene–petroleum ether, and dried to yield 4.36 g (83.3%), mp 139–144°. The mixture melting point with *dl*-IIIb (mp 142–143°) was 134–140°. The ir spectra of *d*- and *dl*-IIIb were identical as chloroform solutions but not as Nujol mulls. The preparation of *dl*-IIIb had previ-

(7) Melting points are uncorrected. Nmr spectra were by courtesy of Drs. N. R. Trenner and B. A. Arison and microanalyses were by R. N. Boos and associates.

ously been carried out in the same way. The ir spectrum was in accord with the structure.

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.99; H, 6.93; N, 10.53.

Racemization of α-Acetamido-α-veratrylpropionitrile (IIIb) with 0.5 Mole of NaCN.—To 2.0 ml of DMSO were added 0.5305 g (0.002 mole) of *d*-IIIb and 0.0517 g (0.001 mole) of NaCN. These were dissolved, and the mixture was purged with nitrogen and heated 10 min at 160°. After vacuum distillation of the solvent, the residue was diluted with water and extracted four times with chloroform. The combined extracts were dried with $MgSO_4$, filtered, and stripped, and the residue was crystallized from benzene, filtered, washed with benzene–petroleum ether, and dried to give 0.4865 g, 91.6% recovery. This was pure racemic IIIb, rotation 0.00°.

Preparation of IV (N-Methyl)-α-acetamido-α-veratrylpropionitrile.—To a cooled and stirred solution of 7.44 g of *dl*-IIIa (0.03 mole) in 90 ml of DMSO was added, first a slurry of NaH (from 2.88 g of 50% NaH, 0.06 mole, which had been washed three times with hexane) in 10 ml of DMSO, and then 5.67 ml (0.06 mole) of dimethyl sulfate. After 0.5 hr, glacial acetic acid was added until the mixture was neutral, the solvent was stripped at 1 mm, and 100 ml of benzene was added. The mixture, which formed two layers, was washed with three 10-ml portions of water, dried with $MgSO_4$, filtered, and stripped. The product was crystallized from 1:1 benzene–cyclohexane, filtered, washed, and dried to yield 5.95 g (71.7%). After recrystallization the melting point was 101–103°; ir and nmr spectra were correct.

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.49; H, 7.18; N, 9.96.

A sample of *l*-IV, prepared in the same way, had the same ir as the *dl* modification in chloroform but a slightly different one in Nujol, mp 99–105° and mmp *ca.* 90–100°. Rotation values were 578 mμ, −41.5°; 546, −47.2; 436, −82.9; 405, −101.6; 365, −133.4.

Cyclization of IV to VI.—A sample of IV was prepared as above from 7.44 g of *l*-IIIa. After addition of the dimethyl sulfate the reaction mixture was aged overnight at room temperature and heated briefly at about 50°; the solvent was removed under vacuum. The solution was strongly alkaline throughout.

The residue was treated with 200 ml of water and extracted ten times with chloroform. The extracts were washed with aqueous KOH, dried with $MgSO_4$, filtered, and evaporated. The residue, which crystallized readily, was recrystallized from benzene–cyclohexane, affording 5.38 g (72.3%) of VI, mp 200–207°. After recrystallization from chloroform–benzene, it exhibited the following properties: ir (Nujol), multiple bands at *ca.* 2.9, 6.01 (w), 6.13 (s), and 6.24 μ (w), plus other bands (8.60, 8.78, 9.75 μ) typical of the veratryl system (no other carbonyl absorption); uv (MeOH), λ_{max} 271 mμ (*E* 341); nmr ($CDCl_3$), τ 3.32 (Ar), 5.75 (HC=), 5.48 (NH_2), 6.22 (OCH_3), 7.14 (NCH_3), 7.17 ($ArCH_2$), 8.63 (CH_3C); rotation, 578 mμ (12.6°), 546 (12.3), 436 (0.0), 405 (−15.8), 365 (−72.7).

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 64.91; H, 7.35; N, 9.70.

Hydrolysis of VI to VII.—Compound VI (0.1166 g) was heated on the steam bath with 10 ml of water and 1 drop of HCl. The pH rose from 3 to 7 over 1 min. Heating another minute with a second drop of HCl did not raise the pH again. On cooling, the product crystallized and was filtered, washed, and dried to yield 0.0406 g: mp 148–150°; ir ($CHCl_3$), 5.67 (m), 5.95 (s), nothing below 3.3 μ; nmr ($CDCl_3$), τ 3.21, 3.35, 3.46, 3.59 (Ar), 6.18 (OCH_3), 6.96 (NCH_3), 7.10 (=CCH_2C=), 7.49, 7.86 with possibly 7.10, 8.23 ($ArCH_2$), 8.56 (CH_3C).

Anal. Calcd for $C_{15}H_{19}O_4N$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.50; H, 7.02; N, 5.10.

Attempted Racemization of IV.—A solution of 0.5527 g of *l*-IV (0.002 mole) and 0.0487 g of NaCN (0.001 mole) in 2.0 ml of DMSO was heated under nitrogen for 10 min at 160° (touched 170° briefly). The mixture was cooled, neutralized with AcOH, diluted with 20 ml of benzene, washed with three 3-ml portions of water, dried with $MgSO_4$, filtered, and stripped under vacuum. The residue (0.55 g of oil) was crystallized from benzene–cyclohexane, taking two crops of IV, 0.3118 and 0.0509 g (total 0.3627 g, 65.7%). These were 99 and 96% optically pure, respectively, with ORD's identical with that of pure IV. As a duplicate run on *dl*-IV gave VI in 18% yield in addition to recovered IV, the yield of recovered *l*-IV above, corrected for this amount of cyclization, is 80%.

Racemization of IIIa with Radioactive Cyanide.—A solution of 0.4968 g of optically pure IIIa (0.002 mole) and 0.0492 g (0.001 mole) of NaCN labeled with C^{14} (64,300 cpm/mg or 3,153,000 cpm/mole) in 2.0 ml of DMSO was heated under nitrogen for 10 min at 150°. The solution was cooled, stripped under vacuum (not over *ca.* 35°), diluted with water, acidified with HCl, and chilled. The product was filtered, washed successively with cold water and isopropyl alcohol, and dried to yield 0.4490 g (90.4%).

To remove any possible trace of cyanide ion, the product was dissolved in warm methanol, acidified with a trace of HCl, and stripped under vacuum. The residue was redissolved and stripped again. The product was dried and showed 82.2% optical purity. Its radioactivity was 483,000 cpm/mole, 15.3% of that of the starting NaCN.

Kinetic Experiments.—The sealed-tube runs (K1–K8) were done in tubes 180 mm long, 2 mm i.d., filled to 120 mm (*ca.* 0.6 ml), unpurged, with DMSO as the solvent. They were held over refluxing liquid in a specially constructed apparatus in which they were immersed in the vapor and could not touch either the side walls or the condensate return. Temperature was measured by Anschutz thermometers, fully immersed with the tubes. Within each run, good temperature constancy was obtained (within 0.1°), but temperatures could not be maintained from day to day owing to variations in the atmospheric pressure. Readings were obtained by acidifying with acetic acid to pH 5.5–6.0, diluting to 10.00 ml with methanol, and reading the rotation at 30.0° at all five wavelengths in the Zeiss polarimeter. Some samples had a slight yellow cast from oxidation in the upper 2–3 mm of the solution in the sealed tubes and could only be read at the higher 3–4 wavelengths; none gave less than two secure readings, and in all cases the ORD's were identical with that of the starting material. All runs gave good linear semilog plots, except as noted, and duplication of identical tubes was very close.

The results are presented in Tables II–III, and for the sake of brevity only one run will be described in detail, no. K2, for which acetic anhydride was used as the refluxing solvent (see Table V); in other runs, *n*-octane, chlorobenzene, 1-butanol and toluene were also employed. The stock solution, whose total volume was 10.00 ml, contained 2.0238 g of IIIa and 0.0402 g of NaCN, total weight 11.1966 g.

TABLE V
DATA FOR RUN K2

Time, hr	Net wt, g	% optical purity
0	0.5791	100.00[a]
1	0.5897	82.7 ± 0.4
2	0.5698	70.0 ± 0.2
4	0.5648	49.5 ± 0.5
6	0.5616	35.4 ± 0.3

[a] An unheated tube served as reference point for the run; its rotation was 98.5 ± 0.2% of the value calculated for pure IIIa, reflecting the slight effect of the *ca.* 2.4% DMSO in the methanol.

Calculation of k_2's required a knowledge of the expansion of the reaction mixture with temperature. This was measured at various temperatures for pure DMSO and for several of the stock solutions, and all were about the same. The expansion factors were 113°, 1.07; 117°, 1.08; 139°, 1.11; 131°, 1.10 (calculated).

Run K4 was linear through the first four points (4 hr), and then showed a slight diminution in rate. Run K7 was so fast that only one experimental point, in addition to the zero point, could be obtained.

Runs K7 and K8 were done with a stock solution containing 1.9807 g of IIIa and 0.4235 g of NaCN. These were dissolved in *ac.* 10 ml of DMSO and stripped at *ca.* 0.5 mm below 50° to a syrup. This was repeated, the syrup made up to 10.00 ml (net weight 11.2896 g), and the normal procedure followed henceforth.

For the dimsylsodium runs, K13–K16, the reagent was prepared and titrated daily by dissolving 4.8 g of 50% NaH (washed four times with hexane) in 75 ml of DMSO under nitrogen at 58°. Normalities ranged from 1.50 to 1.57. A 2% molar excess of dimsylsodium was used in all runs to take care

of possible errors in titration and transfer of the somewhat viscous reagent. The reaction vessel was a 10-ml volumetric flask with a lengthened neck, which was suspended in a water bath controlled to ±0.02°. Temperature was read with an NBS certified thermometer. Since racemization began at room temperature immediately upon mixing the reagents, the first sample, withdrawn after 30 min in the bath, was taken as zero time. Samples were taken in 1-ml pipets and discharged into 10-ml volumetric flasks containing a freshly prepared mixture of 2 ml of methanol and sufficient acetic acid to be slightly in excess (0.10 ml for K13 and K16, 0.05 ml for K14). These were filled to the mark with methanol and read as before.

The data for one run, K14 (see Table VI), are given. The stock solution, (total volume, 10.00 ml) contained 1.0549 g of IIIb and 2.71 ml of 1.50 *N* dimsylsodium.

TABLE VI
DATA FOR RUN K14

Time, hr	% optical purity
0.0	100
0.72	87.5 ± 0.4
1.25	80.2 ± 0.2
1.97	73.5 ± 0.5
3.07	65.6 ± 0.4
4.48	58.6 ± 0.3

Volatility of HCN in Racemization Mixtures.—A solution of 2.00 g (0.00806 mole) of IIIa and 0.1912 g (0.00378 mole) of NaCN in 4 ml of DMSO was partially stripped at 0.5 mm to a net weight of 5.0701 g. A sample of 1.0604 g (20.9%) of this mixture was titrated for cyanide by the Volhard method, and contained 0.000132 mole, or 16.7% of the original amount. Another sample (3.9291 g, 77.5%) was diluted with 15 ml of DMSO and then stripped thoroughly at 50° (0.5 mm). The residue contained 0.0001034 mole of cyanide, or 3.53% of the original amount.

In another experiment, a similar solution was subjected, at 60°, five times alternately to 0.1 atm for 5 sec and then nitrogen at 1 atm. After this treatment the solution was found to contain 100 ± 1% of the original charge of cyanide.

This experiment was performed in order to demonstrate that nitrogen purging, or lack of it, did not affect the relative rates of the various reactions described in this paper.

Isolation of Enamide IXa.—A solution of 2.48 g of IIIa (0.01 mole) in 10 ml of DMSO was treated with 13.30 ml of 1.52 *N* dimsylsodium (0.202 mole). The solution was stored at 25° for 4 days. Then 1.16 ml (0.202 mole) of acetic acid and 50 ml of water were added, but no IIIa precipitated, even after seeding and cooling. After further dilution with 25 ml of water, the mixture was extracted four times with methylene chloride, and the extracts dried with $MgSO_4$, filtered, and evaporated, leaving an oil which crystallized to give 1.26 g. After two recrystallizations from isopropyl alcohol, the melting point was 152–155°. The product had no optical activity. Ultraviolet bands are at λ_{max} 271 mμ (*E* 659); ir ($CHCl_3$) bands are OH at 2.8 and 2.9, C=O and C=C at 5.97 (s) and *ca.* 6.05 μ (shoulder), respectively. Nmr data was in accord with the structure.

Anal. Calcd for $C_{12}H_{15}O_3N$: C, 65.1; H, 6.83; N, 6.34. Found: C, 65.30; H, 7.18; N, 6.43.

A few milligrams of IXa was heated on the steam bath for 10 min with a few drops of water containing a trace of HCl; it dissolved slowly. After removal of the water under vacuum, the residue was taken up in chloroform, dried with $MgSO_4$, filtered, and stripped. The ir spectrum of the resulting oil matched a mixture of 3-methoxy-4-hydroxyphenylacetone Xa and acetamide. Analysis by vpc of this oil also showed the presence of these two substances in *ca.* equimolar amounts.

The recrystallization mother liquors of IXa above were chromatographed by the "dry column" technique on silica gel G (E. Merck), developing and eluting with 4:1 chloroform–acetone, affording more single-spot, though somewhat gummy, material whose R_f was the same as that of IXa. The oily component went readily into benzene, in which IXa is insoluble, and its ir spectrum was so similar to that of IXa that it was apparently the other *cis,trans* isomer. This conjecture was supported by hydrolysis in aqueous acid by the above procedure, which produced the same mixture of ketone and acetamide.

Registry No.—*dl*-IIIa, 14818-97-4; *dl*-IIIb, 15188-49-5; *dl*-IIIc, 15188-50-8; *dl*-IIId, 7754-92-9; *dl*-IV, 15158-48-2; *l*-IV, 15158-49-3; *dl*-Va, 15158-50-6; *dl*-Vb, 15158-51-7; VI, 15158-52-8; VII, 15158-53-9; IXa, 15158-54-0.

The Synthesis of Some Quinazoline Nucleosides[1]

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The synthesis of 1-(β-D-ribofuranosyl)-2,4-quinazolinedione (IV) has been accomplished in above 80% yield by treatment of 2,4-bis(trimethylsilyloxy)quinazoline with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide followed by removal of the benzoyl groups with methanolic ammonia or sodium methoxide. Proof of the β-configuration was obtained by stepwise conversion of IV into O², 5'-anhydro-1-(2', 3'-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone (XI). The site of sugar attachment was established as N_1 by methylation of IV followed by acidic hydrolysis of the product to yield 3-methyl-2,4-quinazolinedione. This assignment was confirmed by ultraviolet and infrared absorption data. Treatment of 1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione with phosphorus pentasulfide provided the 4-thio derivative (V) which upon reaction with methanolic ammonia at 100° resulted in replacement of the 4-thio group with concomitant debenzoylation to yield 4-amino-1-(β-D-ribofuranosyl)-2-quinazolone (VII). Compounds IV and VII may be regarded as 5,6-benzouridine and 5,6-benzocytidine, respectively, with a fused planar aromatic system. The possible biochemical significance of greater electron interaction in the stacking of heterocyclic bases is discussed. Using similar procedures, 1-(2'-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (XIX) and 4-amino-1-(2'-deoxy-β-D-ribofuranosyl)-2-quinazolone (XXI) have also been prepared. 1-(β-D-Ribofuranosyl)-2,4-quinazolinedione (IV) has successfully been converted into O²,2'-anhydro-1-(β-D-arabinofuranosyl)-4-quinazolone (XII) which yielded 1-(β-D-arabinofuranosyl)-2,4-quinazolinedione (XIII) upon ring opening with dilute sodium hydroxide. Acetylation of XIII followed by thiation and treatment with methanolic ammonia gave 4-amino-1-(β-D-arabinofuranosyl)-2-quinazolone (XVI). The reaction procedure for nucleoside formation in such good yields would indicate that this procedure might well be the method of choice for nucleoside synthesis with other unusual heterocyclic systems.

The use of trimethylsilyl derivatives of nitrogen heterocycles in nucleoside synthesis was first introduced by Birkofer, *et al.*,[2] in a novel synthesis of 3-ribofuranosyluric acid. The use of 2,4-bis(trimethylsilyloxy)pyrimidine in a fusion procedure with 2,3,5-tri-O-benzoylribofuranosyl chloride was employed by Nishimura, Shimizu, and Iwai[3] to give uridine in 35% yield. Initial attempts to condense trimethylsilyloxypyrimidines and acetohalo sugars directly in boiling benzene were unsuccessful.[4] The use of polar solvents[5] and milder reaction conditions[5,6] has been more successful. In the present study it was desired to attach the D-ribofuranosyl ring to position 1 of 2,4-quinazolinedione (I). Treatment of I with trimethylchlorosilane in the presence of toluene and triethylamine gave 83% yield of distilled colorless oil, 2,4-bis(trimethylsilyloxy)quinazoline (II) (see Scheme I). Pmr spectra indicated the presence of six methyl groups. Treatment of II with freshly prepared 2,3,5-tri-O-benzoylribofuranosyl bromide in dry acetonitrile for 2 days at room temperature gave 90% yield of crystalline 1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (III). Treatment of III in a refluxing solution of sodium methoxide in methanol removed the benzoyl groups to provide an 88% yield of crystalline 1-(β-D-ribofuranosyl)-2,4-quinazolinedione (IV). Proof of the structural assignment as β was obtained by the stepwise conversion of IV to O²,5'-anhydro-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone (XI) (see Scheme II). The nucleoside IV was converted to 1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)-2,4-quinazolinedione (IX) and then to the 5'-O-mesyl derivative (X). Treatment of X with sodium iodide gave the 5'-iodo compound which was not isolated but cyclized directly to O²,5'-anhydro-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone (XI) with silver acetate in absolute methanol. The cyclonucleoside XI was also prepared directly from X by the action of potassium *t*-butoxide in dimethylformamide at 100° for 1.5 hr.

The fact that XI was actually a cyclonucleoside was established by treatment of XI with liquid ammonia which gave 2-amino-1-(2',3'-O-isopropylidene β-D-ribofuranosyl)-4-quinazolone. All attempts to remove the isopropylidene group resulted in concomitant hydrolysis of the nucleoside and 2-amino-4-quinazolone was isolated instead of 2-amino-1-(β-D-ribofuranosyl)-4-quinazolone.

The position of attachment of D-ribose was determined in the following manner. A comparison of the ultraviolet absorption spectrum of IV with that of 3-methyl-2,4-quinazolinedione[7] and 1-methyl-2,4-quinazoline,[8] respectively, showed that at a pH of 1 or in neutral solution (see Table I) 1-(β-D-ribofuranosyl)-2,4-quinazolinedione (IV) and the 1-methyl- and 3-methyl-2,4-quinazolinediones possessed very similar spectra with a λ_{max} in the region of 306–312 mμ. However at pH 11, 3-methyl-2,4-quinazolinedione exhibited a bathochromic shift to λ_{max} of 326 mμ while at pH 11, 1-methyl-2,4-quinazolinedione and the nucleoside IV exhibited no such shift (Table I).

Additional evidence for assignment of the sugar moiety to the 1 position was obtained by methylation of IV with methyl iodide in N,N-dimethylformamide in the presence of potassium carbonate. The crude 3-methyl-1-(β-D-ribofuranosyl)-2,4-quinazolinedione was hydrolyzed with 10% hydrochloric acid to yield 3-methyl-2,4-quinazolinedione which was identical with an authentic sample[7] as judged by uv spectra, ir spectra, and mixture melting point data.

Synthesis of the cytidine analog, 4-amino-1-(β-D-

(1) This research was supported by Research Grant GB-5446 from the Molecular Biology Division of the National Science Foundation.

(2) L. Birkofer, A. R. Ritter, H. P. Kulthau, *Angew. Chem.*, **75**, 209 (1963).

(3) T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **11**, 1470 (1963).

(4) T. Nishimura and I. Iwai, *ibid.*, **12**, 357 (1964).

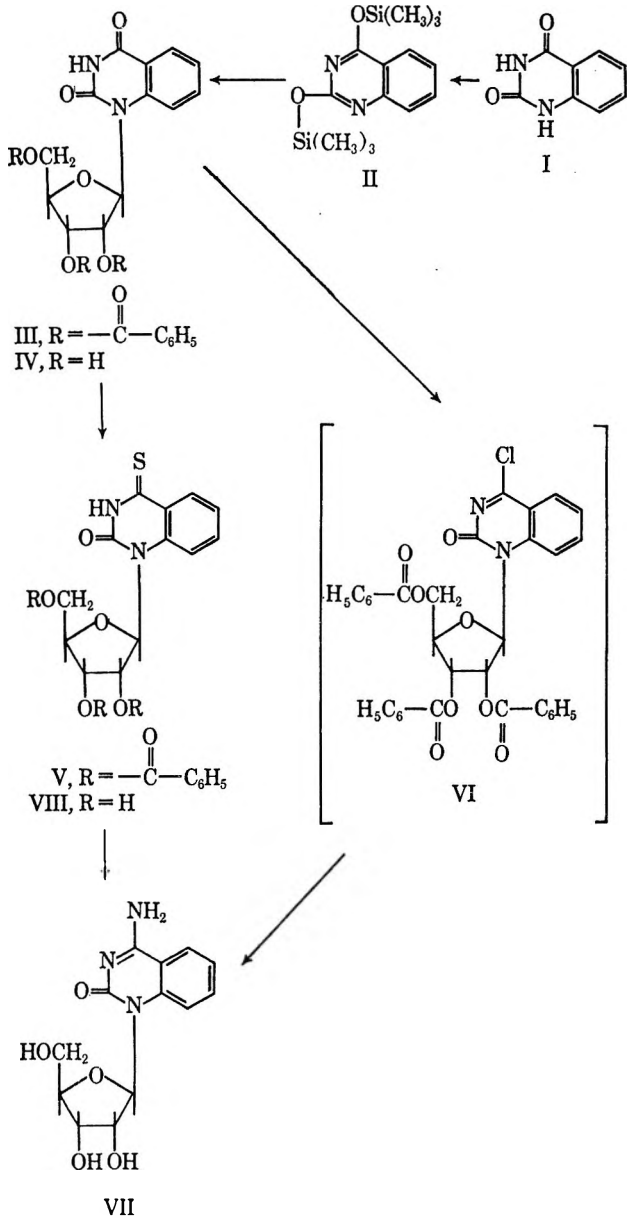
(5) E. Wittenberg, *Z. Chem.*, **4**, 303 (1964).

(6) K. J. Ryan, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **31**, 1181 (1966).

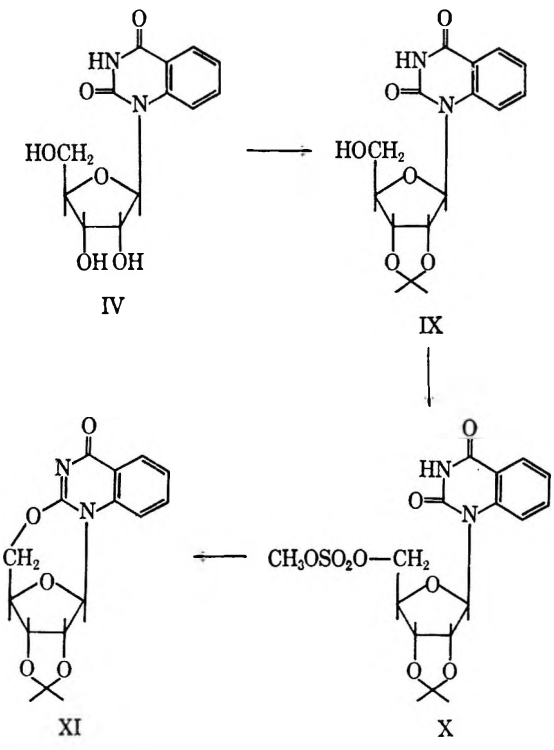
(7) R. P. Steiger and E. C. Wagner, *ibid.*, **18**, 1427 (1953).

(8) A. Chatterjee and S. G. Majumdar, *J. Amer. Chem. Soc.*, **76**, 2459 (1954).

SCHEME I



SCHEME II



ribofuranosyl)-2-quinazolone (VII), was accomplished in two steps by treatment of 1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (III) with phosphorus pentasulfide in pyridine to give a 93% yield of 4-thio-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (V), and then reaction of V with methanolic ammonia at 100° gave simultaneous deblocking and replacement of the 4-thio group to provide 4-amino-1-(β-D-ribofuranosyl)-2-quinazolone (VII), in 82% yield. This general method for the introduction of an amino group was first utilized in nucleoside chemistry by Fox, *et al.*[9] A second route to VII involved the treatment of 1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (III) with phosphorus oxychloride and N,N-diethylaniline, to give the presumed 4-chloro intermediate VI which was not isolated but treated directly with methanolic ammonia to give 4-amino-1-(β-D-ribofuranosyl)-2-quinazolone (VII) in 52% yield. This latter procedure, however, gave a mixture of VII contaminated with IV and in general was not as useful as the thiation route.

Preparation of 1-(β-D-arabinofuranosyl)-2,4-quinazolinedione (XIII) was accomplished in two steps from the uridine analog IV (see Scheme III). The method of Nichol and Hampton[10] for inversion of the 2′-hydroxyl was employed. Treatment of IV with diphenyl carbonate and sodium bicarbonate in N,N-dimethylformamide gave O²,2′-anhydro-1-(β-D-arabinofuranosyl)-4-quinazolone (XII) in 90% yield. Treatment of XII with dilute sodium hydroxide on the steam bath gave 1-(β-D-arabinofuranosyl)-2,4-quinazolinedione XIII in quantitative yield. Acid hydrolysis of XIII gave D-arabinose which was characterized by chromatography.

Acetylation of XIII gave 1-(2′,3′,5′-tri-O-acetyl-β-D-arabinofuranosyl)-2,4-quinazolinedione (XIV). Treatment of XIV with phosphorus pentasulfide in pyridine gave 4-thio-1-(2′,3′,5′-tri-O-acetyl-β-D-arabinofuranosyl)-2-quinazolone (XV) which was in turn treated with methanolic ammonia at 100° to give a good yield of 4-amino-1-(β-D-arabinofuranosyl)-2-quinazolone (XVI), the benzo analog of "cytosine arabinoside."

For the synthesis of 1-(2′-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione (XIX), 2,4-bis(trimethylsilyloxy)quinazoline (II) was treated with 1-chloro-3,5-di-O-*p*-tolyl-2-deoxyribofuranose[11] in acetonitrile (see Scheme IV). An anomeric mixture of nucleosides was obtained which was separated on an alumina column. A 25% yield of pure 1-(3′,5′-di-O-*p*-tolyl-β-D-2′-deoxyribofuranosyl)-2,4-quinazolinedione (XVIII) was obtained plus an additional 35% of mixed anomers. Deblocking XVIII with refluxing sodium methoxide–methanol gave 1-(2′-deoxy-β-D-ribofuranosyl)-2,4-quinazolinedione XIX in 69% yield. Treat-

(9) J. J. Fox, D. Von Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Amer. Chem. Soc.*, **81**, 178 (1959).

(10) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).

(11) M. Hoffer, *Chem. Ber.*, **93**, 2777 (1960).

TABLE I
ULTRAVIOLET ABSORPTION SPECTRA OF VARIOUS QUINAZOLINE NUCLEOSIDES

	λ_{max}^{pH1}		λ_{max}^{pH11}		λ_{max}^{EtOH}	
	mμ	ε	mμ	ε	mμ	ε
I	309	(3,700)	310	(3,500)	309	(3,800)
	240 (infl)	(9,500)	260 (infl)	(5,300)	241	(9,600)
IV	306	(3,900)	306	(4,200)		
VIII	355	(13,100)	348	(12,300)		
	325 (sh)	(7,300)	274	(5,300)		
	310 (sh)	(6,000)				
	270	(5,400)				
	239	(13,200)				
VII	326	(4,700)	317	(4,500)		
	258	(6,900)				
XIX	307	(4,000)	307	(4,400)		
XXI	326	(4,900)	316	(4,800)		
	258	(6,800)				
XII	309 (infl)	(4,000)	309 (infl)	(4,300)	309	(4,600)
	299.5	(5,000)	300	(5,200)	298	(5,500)
XIII	308	(2,600)	307	(4,300)		
XVI	328	(4,900)	318	(4,900)		
	257	(7,100)				
IX	306	(3,800)	307	(4,000)		
			356 (infl)	(4,800)		
X	305	(3,800)	306	(4,100)		
	240	(8,700)	256	(4,700)		
XI	304	(4,200)	307 (infl)	(5,200)		
			301	(5,600)		
3-N-Methyl-2,4-quinazolinedione	309	(3,700)	326	(3,400)		
	240 (infl)	(9,300)	266	(8,100)		
3-N-Methyl-2,4-quinazolinedione[a]	309	(3,500)	326	(3,300)		
	240 (infl)	(9,000)	266	(7,800)		
1-N-Methyl-2,4-quinazolinedione[b]	312	(4,100)	313	(4,500)		
	242 (infl)	(9,100)				

[a] See ref 7. [b] See ref 8.

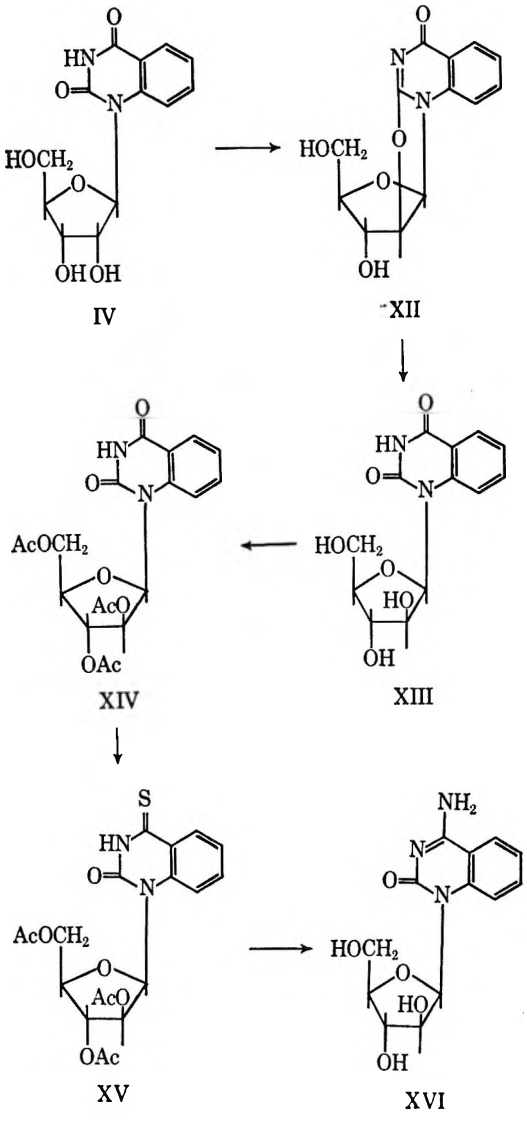
ment of XVIII with phosphorus pentasulfide in pyridine gave XX which in turn gave 4-amino-1-(2′-deoxy-β-D-ribofuranosyl)-2-quinazolone (XXI) with methanolic ammonia. Although no chemical evidence was obtained, the anomeric configuration of XIX (and therefore XXI) was tentatively assigned as β on the basis of the pseudo triplet, $J = 7.5$ cps and peak width was 15.0 cps, due to the anomeric proton.[12] The ultraviolet absorption spectral data for various quinazoline nucleosides are given in Table I.

The spatial limitations for the enzymatic incorporation of a substituted pyrimidine nucleoside into nucleic acid have not been defined although pyrimidines containing groups as large as iodine at the 5 position have been incorporated.[13] In this regard it may be noted that 3-"iso"-adenosine diphosphate is polymerized by azotobacter polynucleotide phosphorylase to yield 3-"iso"-polyadenylic acid.[14] In the present study the fusion of a benzene ring at the pyrimidine positions 5 and 6 results in addition of an aromatic ring in the same plane as the pyrimidine moiety. These derivatives should provide very interesting nucleosides for biochemical study. If the corresponding nucleotides are not incorporated into nucleic acids due to the presence of the benzene ring it is quite possible that these nucleotides may inhibit the polymerase enzymes involved in nucleic acid biosynthesis.

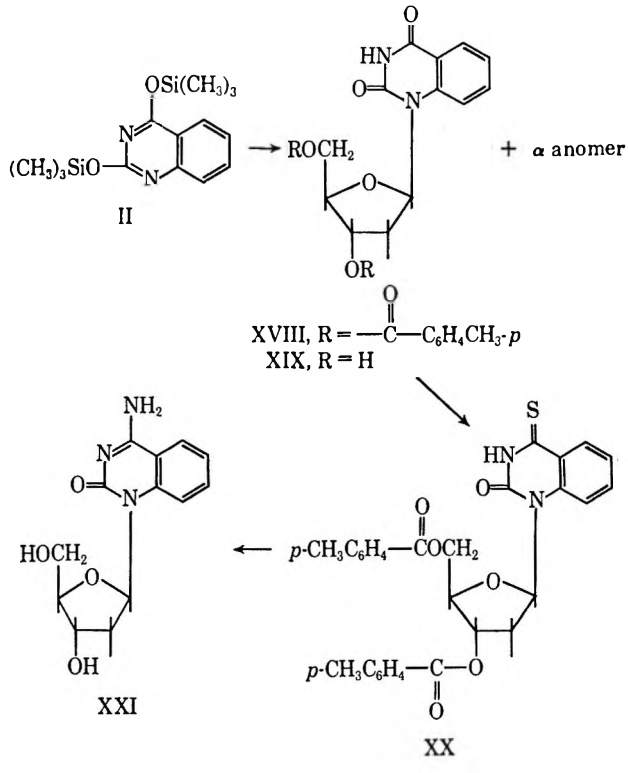
The recent work of Ts'O and coworkers[15-17] has established that vertical stacking of purine with

(12) M. J. Robins and R. K. Robins, *J. Amer. Chem. Soc.*, **87**, 4934 (1965).
(13) W. H. Prusoff, J. J. Jaffe, and H. Gunther, *Biochem. Pharmacol.*, **3**, 110 (1959).
(14) A. M. Michelson, C. Monny, R. A. Laursen, and N. J. Leonard, *Biochim. Biophys. Acta*, **119**, 258 (1966).
(15) P. O. P. Ts'O, I. S. Melvin, and A. C. Olsen, *J. Amer. Chem. Soc.*, **85**, 1289 (1963).
(16) P. O. P. Ts'O and S. I. Chan, *ibid.*, **86**, 4176 (1964).
(17) A. D. Broom, M. P. Schweizer, and P. O. P. Ts'O, *ibid.*, **89**, 3612 (1967).

SCHEME III



SCHEME IV



pyrimidine nucleosides occurs extensively in aqueous solution. It has been recently postulated "that the stacking energy involved in the interaction of the neighboring bases is the major force contributing to the stability of nucleic acid helices." [18] The additional stacking energy due to electron interaction of the benzene ring in the pyrimidine nucleosides described in the present work could contribute significantly to greater stability of a nucleic acid molecule into which these nucleosides are incorporated. Such interactions could well be determined by magnetic resonance spectroscopy. The quinazoline nucleosides described may prove to be important tools for future biochemical studies.

Experimental Section

Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected.

2,4-Bis(trimethylsilyloxy)quinazoline (II).—2,4-Quinazolinedione[19] (I) (50 g, 0.31 mole) was azeotropically dried in 2.4 l. of refluxing toluene for 1.5 hr employing a Dean–Stark trap. The solution was cooled to *ca.* 60° and 90 ml of trimethylchlorosilane added. Reflux was again attained and 114 ml of triethylamine dissolved in 400 ml of toluene was added dropwise over a 30-min period. The mixture was refluxed with stirring for an additional 6 hr and left at room temperature overnight. The triethylammonium chloride was removed by filtration and the toluene solution evaporated under reduced pressure. The residue was transferred to a small flask for distillation. The silyl derivative distilled at 93–98° at 0.08 mm and a bath temperature of 178° to yield 78.5 g (83%) of colorless oil.

1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (III).—2,3,5-Tri-O-benzoyl-D-ribofuranosyl bromide from 25 g (0.05 mole) of 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose was dissolved in 350 ml of dry acetonitrile and 15 g (0.05 mole) of 2,4-bis(trimethylsilyloxy)quinazoline (II) was added. The cloudy solution was stirred for 0.5 hr during which time the solution became clear. The reaction was allowed to proceed at room temperature for 50 hr and the solution then evaporated to dryness under reduced pressure. The resulting foam was dissolved in 180 ml of boiling absolute ethanol and 45 ml of water was added. This solution was stirred and heated on the steam bath for 15 min to achieve crystallization of the product. The mixture was cooled and filtered and the product dried to yield 26.9 g (90%) of III, mp 180–182°. Further recrystallization from 80% ethanol gave fine colorless needles which melted at 180.5–181.5°.

Anal. Calcd for $C_{34}H_{26}N_2O_9$ (mol wt 606.56): C, 67.32; H, 4.32; N, 4.62. Found: C, 67.53; H, 4.40; N, 4.31.

1-(β-D-Ribofuranosyl)-2,4-quinazolinedione (IV). Method A.—1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (III) (12 g, 0.02 mole) was added to a solution of 1.15 g of sodium in 250 ml of absolute methanol. The solution was refluxed for 0.5 hr then evaporated to dryness under vacuum. The resulting solid was partitioned between 500 ml of water and 150 ml of ether. The aqueous portion was extracted twice more with 100 ml of ether each and the combined ether extracts were washed with 50 ml of water. The aqueous phases were combined and acidified to pH 5 with approximately 60 ml of Dowex 50 × 2 (H^+) resin. The resin was removed by filtration and the aqueous phase concentrated to approximately 40 ml. The cooled solution was filtered and the product recrystallized from a mixture of 700 ml of methanol and 40 ml of water which was concentrated to 150 ml and cooled. The product was filtered and dried to yield 5.08 g (88%) of product, mp 226–227°.

Method B.—1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (III) (10 g, 16.5 mmole) was heated with 150 ml of methanol (previously saturated with ammonia at

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(19) N. A. Lange and F. E. Sheibley, "Organic Synthesis," *Coll. Vol. II*, John Wiley and Sons, Inc., New York, N. Y., 1943, p 79.

0°) in a sealed bomb at 100° for 8 hr. The bomb was cooled overnight, the methanol solution evaporated to dryness and the residue triturated with 400 ml of dichloromethane. The resulting solid was recrystallized from a mixture of 500 ml of methanol and 10 ml of water which was concentrated to 250 ml. The product was removed by filtration and dried to yield 4.43 g (91%) of needles with mp 226–226.5° and $[\alpha]^{28}D$ +16° (*c* 1.0, dimethylformamide). This product was identical with that prepared by method A.

Anal. Calcd for $C_{13}H_{14}N_2O_6$ (mol wt 294.26): C, 53.06; H, 4.80; N, 9.52. Found: C, 53.05; H, 4.96; N, 9.37.

1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribofuranosyl)-4-thio-2-quinazolone (V).—To a solution of 6.0 g (0.01 mole) of 1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (III) in 100 ml of pyridine was added, with stirring, 8.9 g (0.038 mole) of phosphorus pentasulfide. The solution was refluxed gently (bath temperature 130–140°) for 17 hr. Completion of reaction was determined by tlc on alumina HF 254 plates with methanol–ethyl acetate (1:20) as solvent. The pyridine solution was evaporated to one-third the original volume and poured into 2 l. of water at 60°. The mixture was stirred for 2–3 hr then left at room temperature overnight. The resulting solid was filtered, dissolved in chloroform, which was dried and removed under vacuum. The resulting foam was boiled with 150 ml of methanol to induce crystallization. The solid was filtered and dried to yield 5.75 g (93%) of yellow solid which melted at 180–181°. Tlc on silicAR 7GF with chloroform–ethyl acetate (9:1) showed *ca.* 3–5% unconverted III. The analytical sample was prepared by preparative plate chromatography on silicAR 7GF with the same solvent and V recrystallized from ethanol–benzene (10:1). The analytical sample melted at 179.5–180.5°.

Anal. Calcd for $C_{34}H_{26}N_2O_8S$ (mol wt 622.63): C, 65.58; H, 4.21; N, 4.50. Found: C, 65.81; H, 4.47; N, 4.66.

4-Amino-1-(β-D-ribofuranosyl)-2-quinazolone (VII). Method A.—1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribofuranosyl)-4-thio-2-quinazolone (V) (2 g) was heated in 150 ml of methanol (previously saturated with ammonia at 0°) in a bomb at 100° for 7 hr and then cooled to room temperature overnight. The resulting solution was concentrated under vacuum. The residue was triturated with 250 ml of dichloromethane and the resultant solid was recrystallized from 180 ml of methanol and 15 ml of water concentrated to *ca.* 25 ml. The product weighed 0.77 g (82%) and melted at 259–260° dec.

Method B.—1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (III) (6 g, 0.01 mole) was refluxed in a solution of 60 ml of phosphorus oxychloride and 3 ml of N,N-diethylaniline for 10 min. The phosphorus oxychloride and N,N-diethylaniline were removed under vacuum and the resulting foam was dissolved in 20 ml of chloroform. This solution was poured slowly into a vigorously stirred ice-cold solution of 2% sodium hydroxide (200 ml). Dilute sodium hydroxide was added as necessary to keep the pH greater than 11 at all times. The basic solution was extracted with two 100-ml and two 50-ml portions of chloroform. The combined chloroform solution was then washed with ice water and saturated salt solution and dried over sodium sulfate containing a little potassium carbonate. The yellow solution was evaporated to dryness; the oil was placed in a sealed bomb with 170 ml of methanolic ammonia and heated at 100° for 7 hr. The cooled methanol solution was evaporated, the residue triturated with dichloromethane, and the solid, mp 140–180°, crystallized from 400 ml of methanol and 50 ml of water which was concentrated to *ca.* 80 ml. This solution was cooled to room temperature and filtered. The product was a mixture of 4-amino-1-(β-D-ribofuranosyl)-2-quinazolone (VII) and 1-(β-D-ribofuranosyl)-2,4-quinazolinedione (IV). Separation of VII from IV was easily achieved by fractional crystallization since VII crystallizes first from a methanol–water mixture. Yield of the cytidine analog VII was 1.52 g (52%) and of the uridine analog IV was 0.90 g (31%). One additional recrystallization of VII from methanol–water gave material which melted at 259–260° dec; $[\alpha]^{28}D$ −3° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{13}H_{15}N_3O_5$ (mol wt 293.27): C, 53.24; H, 5.16; N, 14.33. Found: C, 53.25; H, 5.24; N, 14.33.

1-(β-D-Ribofuranosyl)-4-thio-2-quinazolone (VIII).—A solution of 0.5 g (1.7 mmoles) of 1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-4-thio-2-quinazolone (V) and 0.1 g (4.3 g-atoms) of sodium in 15 ml of absolute methanol was refluxed gently for 70 min. The methanol was evaporated and the residue partitioned between 100 ml of water and 25 ml of ether. The aqueous phase was extracted with two 10-ml portions of ether then acidified to pH 6 with 10% hydrochloric acid. The solution was concentrated to *ca.* 5 ml and the solid filtered. This solid was recrystallized twice from ethanol and melted at 179–180°, $[\alpha]^{28}D$ +53° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{13}H_{14}N_2O_5S$ (mol wt 310.32): C, 50.31; H, 4.55; N, 9.03. Found: C, 49.96; H, 4.88; N, 8.69.

3-N-Methyl-2,4-quinazolinedione from Methylation of IV.—1-(β-D-Ribofuranosyl)-2,4-quinazolinedione (IV) (0.29 g, 1 mmole) was stirred in 2 ml of dry dimethylformamide containing 0.1 g of dry potassium carbonate and 0.01 ml of methyl iodide for 20 hr at room temperature. The potassium carbonate was filtered and washed with 1 ml of dimethylformamide. The filtrate was diluted with 25 ml of dichloromethane and the resulting solid removed by filtration. This filtrate was taken to dryness and the residue refluxed in 10 ml of 10% hydrochloric acid for 1 hr. The solution was filtered hot and gave tan needles on cooling. The needles were recrystallized from ethanol–water using charcoal. The resulting needles were sublimed for analysis (bath temperature 175–180°), and melted at 240–241°.

Anal. Calcd for $C_9H_8N_2O_2$ (mol wt 176.17): C, 61.36; H, 4.58; N, 15.90. Found: C, 60.82; H, 4.43; N, 16.10.

This material on mixture melting point determination with authentic material prepared by the method of Steiger and Wagner[7] was undepressed and the ir and uv curves were identical.

1-(2′,3′-O-Isopropylidene-β-D-ribofuranosyl)-2,4-quinazolinedione (IX).—A solution of 450 ml of dry acetone, 1.60 ml of 2,2-dimethoxypropane, and 2.0 ml of 70% perchloric acid was prepared and left at room temperature for 5 min. To this solution was added 1.32 g (4.5 mmoles) of 1-(β-D-ribofuranosyl)-2,4-quinazolinedione (IV) and the mixture was stirred for 0.5 hr. Pyridine (1.6 ml) was added and the solution was concentrated to *ca.* 70 ml where 23 ml of 10% sodium carbonate was added. The solution was again concentrated to remove the remaining acetone. The aqueous solution was then extracted four times with dichloromethane (one 25-ml portion and three 10-ml portions). The combined dichloromethane solution was dried and evaporated. The resulting glass was crystallized by solution in 30 ml of benzene followed by the addition of 20 ml of cyclohexane to yield 1.43 g (95%) of material which melted at 120–123°. Crystallization of IX from benzene–cyclohexane gave pure product which melted at 125–127°.

Anal. Calcd for $C_{16}H_{18}N_2O_6$ (mol wt 334.32): C, 57.48; H, 5.43; N, 8.38. Found: C, 58.05; H, 5.80; N, 8.17.

1-(2′,3′-O-Isopropylidene-5′-methanesulfonyl-β-D-ribofuranosyl)-2,4-quinazolinedione (X).—A solution of 0.85 g of 1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-2,4-quinazolinedione (IX) and 0.21 ml of methanesulfonyl chloride (1.1 moles) in 15 ml of dry pyridine was left in the refrigerator for 15 hr and then at room temperature for an additional 7 hr. Water (0.45 ml, 10 moles) was then added and the solution stirred at room temperature for 45 min. At this time 25 ml of water was added and the solution extracted with three 25-ml portions of chloroform. The chloroform was washed with six 10-ml portions of ice-cold 3 *N* sulfuric acid until the washes were distinctly acidic and then twice with 5% sodium bicarbonate (20 ml and 5 ml) until the washes were basic. The chloroform solution was then dried over sodium sulfate and taken to dryness. The foam was crystallized by solution in 8 ml of benzene followed by the addition of 1 ml of cyclohexane to yield 0.95 g of crystals which melted at 190–192° with some softening *ca.* 125°. The product was recrystallized from benzene–methanol and melted at 190–192°.

Anal. Calcd for $C_{17}H_{20}N_2O_8S$ (mol wt 412.41): C, 49.51; H, 4.89; N, 6.79. Found: C, 49.16; H, 4.99; N, 6.71.

O²,5′-Anhydro-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone (XI). Method A.—To a refluxing mixture of 0.4 g (0.97 mmole) of 1-(2′,3′-O-isopropylidene-5′-methanesulfonyl-β-D-ribofuranosyl)-2,4-quinazolinedione and 0.3 g of anhydrous sodium iodide in 6 ml of dioxane was added six drops of water and an additional 6 ml of dioxane. After 1.5 hr refluxing the bumping from precipitated salts was such that six more drops of water and 2 ml of dioxane were added and reflux continued 1 hr. To the cooled solution was added 50 ml of dichloromethane and this solution was extracted with three 10-ml portions of water. The water was back extracted with 5 ml of dichloromethane and the combined organic phases were washed with saturated salt solution and then dried over sodium sulfate.

The dichloromethane was removed under vacuum and the resulting oil plus 0.7 g of silver acetate was refluxed for 15 min in 100 ml of absolute methanol. The precipitated silver iodide was filtered and the filtrate saturated with hydrogen sulfide to remove any residual silver. Again the methanol was filtered and the filtrate concentrated to *ca.* 2 ml. The resulting precipitate was recrystallized from 15 ml of benzene and 0.5 ml of methanol concentrated to 10 ml and then 1 ml of cyclohexane added. The compound began to darken at 270° and melted at 280–285° dec.

Anal. Calcd for $C_{16}H_{16}N_2O_5$ (mol wt 316.30): C, 60.75; H, 5.10; N, 8.86. Found: C, 60.55; H, 5.25; N, 8.88.

Method B.—A solution of 0.81 g (0.002 mole) of 1-(2′,3′-O-isopropylidene-5′-O-methanesulfonyl-β-D-ribofuranosyl)-2,4-quinazolinedione (X) in 30 ml of dry dimethylformamide and 4 ml of 0.5 *M* potassium *t*-butoxide in *t*-butyl alcohol was heated at 100° for 1.5 hr. The gellike solution was taken to dryness and the residue extracted twice with boiling chloroform. The chloroform was taken to dryness and the residue crystallized from 30 ml of benzene and 4 ml of methanol concentrated to 10 ml. This gave 0.43 g of product (90%) which melted at 280° after softening at 245°. This product (XI) was identical with that prepared by method A.

1-(3′,5′-Di-O-*p*-tolyl-β-D-2′-deoxyribofuranosyl)-2,4-quinazolinedione (XVIII).—3,5-Di-O-*p*-tolyl-2-deoxyribofuranosyl chloride[11] (14 g, 0.035 mole) and 15 g (0.05 mole) of 2,4-bis(trimethylsilyloxy)quinazoline (II) were reacted in 300 ml of dry acetonitrile. The solution remained cloudy throughout the reaction period. After 42 hr the reaction mixture was evaporated to dryness. The trimethylsilyl groups were hydrolyzed by dissolving the product in 100 ml of boiling ethanol and adding 20 ml of water. This solution was boiled for several minutes then evaporated to dryness under vacuum. The solid was triturated with 500 ml of dichloromethane, filtered, and evaporated leaving 16.61 g of mixed deoxynucleosides plus some sugar. The α and β anomers could be separated by tlc on silicAR 7GF using chloroform–ethyl acetate (4:1).

Purification was achieved by column chromatography on neutral alumina (Merck). The column was 2 in. in diameter by 22 in. high and contained 800 g of alumina. The column was packed in benzene. The nucleoside mixture was dissolved in benzene and applied to the column. The sugar was washed through in 550 ml of 20% benzene–ethyl acetate and an additional 1100 ml of 20% benzene–ethyl acetate eluted nothing more. The eluent was changed to ethyl acetate and after 1700 ml of ethyl acetate the β anomer began to be eluted. The following 4450 ml contained pure anomer which weighed 4.7 g on evaporation of the solvent. From this point the α anomer was eluted with the β anomer.

Total weight of material eluted from the column was 14.9 g (90%) with 3.8 g of sugar, 4.7 g of pure β anomer (25.4%), 6.2 g of mixed anomers, and 0.2 g of α anomer. The over-all yield of α and β anomers was 60%.

The pure β anomer was recrystallized from benzene–cyclohexane and gave 4.21 g which melted at 126–131°. Further crystallization from the same solvent gave material which melted at 129–134°.

Anal. Calcd for $C_{29}H_{26}N_2O_7$ (mol wt 514.41): C, 67.69; H, 5.09; N, 5.45. Found: C, 67.47; H, 5.12; N, 5.45.

1-(β-D-2′-Deoxyribofuranosyl)-2,4-quinazolinedione (XIX).—1-(3′,5′-Di-O-*p*-tolyl-β-D-2′-deoxyribofuranosyl)-2,4-quinazolinedione (XVIII) was added to a solution of 0.1 g (4.3 g-atoms) of sodium dissolved in 21 ml of absolute methanol and the solution was allowed to reflux gently for 30 min. After evaporation of the solvent the residue was partitioned between 100 ml of water and 25 ml of ether. After two more extractions with ether the organic phases were combined and back extracted with 15 ml of water. The aqueous phases were combined and carefully acidified to pH 5 with 6 ml of Dowex 50 × 2 (H^+) resin. The resin was removed by filtration and the filtrate concentrated to 3 ml, cooled and filtered and the solid dried leaving 0.34 g of colorless needles which melted at 159–164°. This material was recrystallized from benzene–methanol to yield 0.26 g (69%) which melted at 167.5–168°, $[\alpha]^{28}D$ +39° (*c* 1.0 dimethylformamide).

Anal. Calcd for $C_{13}H_{14}N_2O_6$ (mol wt 278.26): C, 56.11; H, 5.07; N, 10.07. Found: C, 56.14; H, 5.22; N, 10.23.

1-(3′,5′-Di-O-*p*-tolyl-β-D-2′-deoxyribofuranosyl)-4-thio-2-quinazolone (XX).—To a solution of 1.57 g (3.05 mmoles) of 1-(3′,5′-di-O-*p*-tolyl-β-D-2′-deoxyribofuranosyl)-2,4-quinazolinedione (XVIII) in 45 ml of pyridine was added 2.1 g (9.4 mmol) of phosphorus pentasulfide and the solution gently refluxed for 13 hr (bath temperature 120–130°). Completion of the reaction was determined by tlc on alumina HF 254 plates using methanol–ethyl acetate (1:9) as solvent. At this point there was some unreacted XVIII but also there was some cleavage of the nucleoside. The solution was reduced by *ca.* two-thirds under vacuum and the remaining pyridine solution poured into 700 ml of water at *ca.* 45°. The solution, after cooling, was extracted seven times with chloroform (one 100-ml and six 50-ml portions). The chloroform extracts were combined and washed with ice water and saturated salt solution and then dried over sodium sulfate. The chloroform was removed under vacuum and the residual foam crystallized by boiling in 50 ml of methanol with vigorous stirring. This yielded 1.22 g (75%) of yellow crystals which melted at 194–196°. Purification was achieved by preparative layer chromatography on silicAR 7GF with ethyl acetate–chloroform (1:20) as solvent and the product was crystallized from benzene–ethanol. The analytical sample melted at 195.5–196°.

Anal. Calcd for $C_{29}H_{26}N_2O_6S$ (mol wt 530.58): C, 65.64; H, 4.94; N, 5.28. Found: C, 65.43; H, 5.07; N, 5.31.

4-Amino-1-(β-D-2′-deoxyribofuranosyl)-2-quinazolone (XXI).—A mixture 0.75 g (1.4 mmoles) of 1-(3′,5′-di-O-*p*-tolyl-β-D-2′-deoxyribofuranosyl)-4-thio-2-quinazolone (XX) in 100 ml of methanolic ammonia (saturated at 0°) was left at room temperature in a pressure bottle for 3 days. The methanolic solution was taken to dryness and the residue triturated with 10 ml of dichloromethane and 50 ml of ether. The solid was filtered and recrystallized from a methanol and water mixture. The deoxycytidine analog XXI melted at 212.5–213°; $[\alpha]^{28}D$ +72° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{13}H_{15}N_3O_4 \cdot {}^1/_2H_2O$ (mol wt 286.28): C, 54.54; H, 5.63; N, 14.68. Found: C, 54.19; H, 5.65; N, 14.70.

O²,2′-Anhydro-1-(β-D-arabinofuranosyl)-4-quinazolone (XII).—A mixture of 3.0 g (1.02 mmoles) of 1-(β-D-ribofuranosyl)-2,4-quinazolinedione (IV), 2.85 g (1.33 mmoles) of diphenyl carbonate, and 0.05 g of sodium bicarbonate in 10 ml of dry dimethylformamide was heated at 150° for 30 min. There was an initial vigorous evolution of gas which subsided after 5 min. Tlc on silicAR 7GF with ethyl acetate–methanol (9:1) as solvent showed very little starting material after 10 min. The refluxing solution was allowed to cool for a few minutes and then poured slowly into 800 ml of vigorously stirred ether. The precipitate was filtered and recrystallized from 200 ml of methanol concentrated to 100 ml. The filtered and dried solid weighed 2.53 g (90%) and melted at 259–259.5°.

Anal. Calcd for $C_{13}H_{12}N_2O_5$ (mol wt 276.24): C, 56.52; H, 4.38; N, 10.14. Found: C, 56.56; H, 4.42; N, 10.12.

1-(β-D-Arabinofuranosyl)-2,4-quinazolinedione (XIII).—O²,2′-Anhydro-1-(β-D-arabinofuranosyl)-4-quinazolone (XII) (1 g) was heated on the steam bath in 50 ml of 0.05 *M* sodium hydroxide for 15 min. Completion of the hydrolysis was determined by tlc on silicAR 7GF with water as developing solvent. The solution was cooled and neutralized to pH 5–6 with Dowex 50 × 2 (H^+). The resin was filtered and the aqueous solution concentrated to dryness. The solid was recrystallized from 50 ml of methanol and 7 ml of water concentrated to 5 ml. The thick colorless rods weighed 1.03 g (98%) and melted at 209–211° but resolidified as it apparently lost the sugar, $[\alpha]^{28}D$ −18° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{13}H_{14}N_2O_6$ (mol wt 294.26): C, 53.06; H, 4.80; N, 9.52. Found: C, 52.99; H, 4.80; N, 9.70.

1-(2′,3′,5′-Tri-O-acetyl-β-D-arabinofuranosyl)-2,4-quinazolinedione (XIV).—A solution of 0.90 g (3.05 mmoles) of 1-(β-D-arabinofuranosyl)-2,4-quinazolinedione (XIII) in a mixture of 10 ml of pyridine and 10 ml of acetic anhydride was left at room temperature overnight. The clear solution was poured into a well-stirred mixture of ice water (200 ml). The mixture was stirred at 0° for 2 hr then filtered. The solid was recrystallized from methanol by the addition of water to give 1.30 g (100%) which melted at 205–206°.

Anal. Calcd for $C_{19}H_{20}N_2O_9$ (mol wt 420.37): C, 54.28; H, 4.80; N, 6.66. Found: C, 54.40; H, 4.85; N, 6.53.

1-(2′,3′,5′-Tri-O-acetyl-β-D-arabinofuranosyl)-4-thio-2-quinazolone (XV).—1-(2′,3′,5′-Tri-O-acetyl-β-D-arabinofuranosyl)-2,4-quinazolinedione (XIV) (1.30 g, 3.1 mmoles) was dissolved in 50 ml of pyridine and 2.9 g (12.5 mmoles) of phosphorus pentasulfide was added. The solution was stirred at reflux for 7 hr (bath temperature 140°). Completion of the reaction

was determined by tlc on alumina HF 254 with methanol–ethyl acetate (1:20) as solvent. One-half to two-thirds of the pyridine was removed under vacuum and the remaining solution was poured into 900 ml of water at 65–70°. This solution was stirred and cooled as the thione crystallized. The yield was 1.02 g (77%) which melted at 149–150°.

4-Amino-1-(β-D-arabinofuranosyl)-2-quinazolone (XVI).—1-(2′,3′,5′-Tri-O-acetyl-β-D-arabinofuranosyl)-4-thio-2-quinazolone (XV) (0.90 g, 2.05 mmoles) was heated in 125 ml of methanolic ammonia at 100° for 6 hr in a bomb. The reaction was cooled and filtered and the filtrate taken to dryness. Crystallization of the residue from 60 ml of methanol and 10 ml of water concentrated to 13 ml gave 0.38 g (63%) of XV. The product was crystallized from methanol–water. The melting point was 217–219° dec; $[\alpha]^{28}D$ −24° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{13}H_{15}N_3O_5 \cdot H_2O$ (mol wt 311.29): C, 50.15; H, 5.50; N, 13.50. Found: C, 50.28; H, 5.43; N, 13.48.

2-Amino-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone.—O^2,5′-Anhydro-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone (XI) (660 mg) was treated with 50 ml of liquid ammonia in a sealed bomb at room temperature for 50 hr. After removal of the ammonia the product was crystallized from benzene–methanol and gave colorless needles which melted at 171–172° after sintering at 168°.

Anal. Calcd for $C_{16}H_{19}N_3O_5$ (mol wt 333.34): C, 57.65; H, 5.75; N, 12.61. Found: C, 58.35; H, 5.92; N, 12.33.

2-Amino-4-quinazolone.—All attempts to remove the isopropylidene group from 2-amino-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone proved futile as the sugar linkage was too labile under the conditions necessary to remove the isopropylidene group. The nucleoside (200 mg) was hydrolyzed by heating on the steam bath in 25 ml of 20% formic acid for 10 min. The resulting 2-amino-4-quinazolone which was isolated was identical with the product described by Trattner, *et al.*[20]

Hydrolysis of 1-(β-D-Arabinofuranosyl)-2,4-quinazolinedione (XIII).—A solution of 5–10 mg of XIII in 2 ml of 10% hydrochloric acid was heated on the steam bath for 1 hr. The cooled solution yielded 2,4-quinazolinedione (I) as a precipitate. The filtrate was chromatogrammed against D-ribose, 2-deoxy-D-ribose, D-arabinose, and D-xylose on Whatman No. 1 paper using the ethyl acetate–*n*-propyl alcohol–water (4:1:2) system described by Hall.[21] A second chromatogram was run using butanol saturated with water as solvent. Both chromatograms were run for 40 hr and gave good separation of the known sugars with the unknown sugar at the same R_f as arabinose. The sugars were detected using the aniline hydrogen phthalate spray of Partridge.[22]

Registry No.—I, 86-96-4; II, 15135-19-0; III, 15135-20-3; IV, 15135-21-4; V, 15180-27-5; VII, 15135-22-5; VIII, 15135-23-6; IX, 15185-75-8; X, 15185-76-7; XI, 15135-24-7; XII, 15135-25-8; XIII, 15135-26-9; XIV, 15185-77-0; XV, 15180-28-6; XVI, 15135-27-0; XVIII, 15135-28-1; XIX, 15135-29-2; XX, 15135-30-5; XXI, 15135-31-6; 3-N-methyl-2,4-quinazolinedione, 607-19-2; 2-amino-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)-4-quinazolone, 15135-33-8.

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Notes

The Isolation and Structural Elucidation of Voacristine Hydroxyindolenine

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Earlier reports have described the isolation from *Ervatamia dichotoma* (Roxb.) Blatter of coronaridine[4] and heyneanine.[5] We report herewith the isolation and characterization of voacristine hydroxyindolenine and its synthesis from voacristine.

Partition of the ethanol extract of *E. dichotoma* root bark between ether and 4% hydrochloric acid gave a crude alkaloid fraction upon neutralization of the acid and extraction with ether. The ether extract was washed with 1% sodium hydroxide to remove the phenolic bases and the nonphenolic bases were chromatographed on neutral alumina. Elution with benzene–chloroform (1:1) yielded a fraction which was further fractionated by partition chromatography.[6] Six purple bands were visible on the partition column. After elution, the third band yielded heyneanine (I).[5] The fourth band was rechromatographed on a partition column and yielded four bands. Treatment of the third band with benzene–Skellysolve B gave a crystalline material. Recrystallization from the same solvent system yielded colorless crystals, $C_{22}H_{28}N_2O_5$ (by high resolution mass spectrometry), mp 176–179° dec, $[\alpha]^{26}D$ −22° (*c* 0.51, chloroform). The ultraviolet spectrum (λ_{max}^{EtOH} 229.5, 268, 291, 300 (sh), 314; 12,380, 4400, 4780, 4410, 3810) and infrared spectrum suggested an indole-type alkaloid bearing substituents in the aromatic ring. The infrared spectrum showed broad bands at 2.80 (w) and 3.10 μ (m), indicative of the presence of hydroxyl groups, and a band at 5.76 μ (s), indicative of the presence of a carbomethoxy group. The nmr spectrum contained a doublet (1 H) centered at τ 2.66 (J_{ortho} = 8 cps), a doublet of

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(3) University of Wisconsin. The investigation at the University of Wisconsin was supported by Public Health Service Grant No. HE-02952 from the National Heart Institute.
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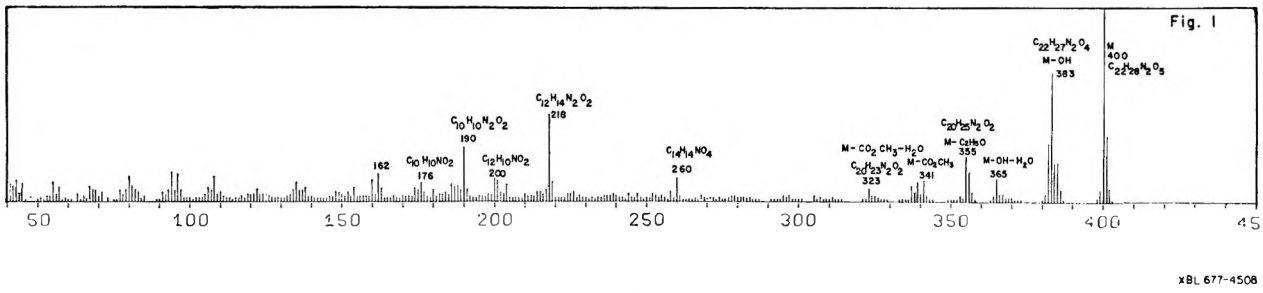
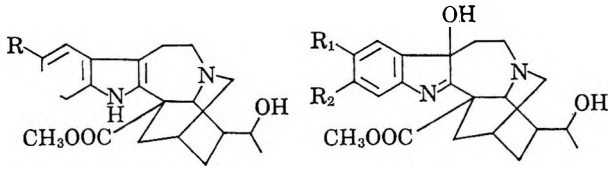


Figure 1.

doublets (1 H) centered at 3.24 (J_{ortho} = 8 cps, J_{meta} = 2.5 cps), and a doublet (1 H) centered at 3.12 (J_{meta} = 2.5 cps). This pattern is consistent with a 1,2,4-trisubstituted benzene ring. In addition, the nmr spectrum showed sharp singlets at τ 6.18 (3 H) and 6.30 (3 H), confirming the presence of a methoxyl and carbomethoxy group, respectively, a doublet (3 H) centered at 8.93 (J = 6.5 cps), and a broad multiplet (1 H) centered at 5.97, indicative of the presence of the $-CHOHCH_3$ group.



I, R = H
III, R = OCH_3

IIa, R_1 = OCH_3; R_2 = H
b, R_1 = H; R_2 = OCH_3

The conventional and high resolution mass spectral data (Figure 1) strongly supported the assignment of a hydroxyindolenine structure of the iboga type to the alkaloid. Peaks at *m/e* 383 (M − OH), 365 (M − OH − H_2O), 355 (M − C_2H_5O), and 341 (M − $COOCH_3$) confirmed the presence of two hydroxy functions, a hydroxy-substituted C_2 side chain and the carbomethoxy grouping. This pattern, together with the peaks at *m/e* 260, 218, 190, 176, and 162 (Figure 1), is entirely analogous to that of other hydroxyindolenines[7,8] of the iboga series. Since the position of the methoxy grouping was limited to C_{12} or C_{13} by the characteristic coupling constants observed in the nmr spectrum (see above), the mass spectral pattern established that the alkaloid should be represented by structures IIa or IIb. Structure IIa for the alkaloid was proven unambiguously by its synthesis[9] from voacristine[10–12] (III). Passage of oxygen through an irradiated solution of III in benzene, followed by chromatography on alumina, yielded an amorphous product with spectral properties essentially identical with those of the natural product. Further purification by partition chromatography furnished a product which, upon crystallization from benzene–Skellysolve B, proved identical with the hydroxyindolenine isolated from the alkaloid mixture.[13]

(7) (a) D. W. Thomas, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1966; (b) D. W. Thomas and K. Biemann, manuscript in preparation. The interesting mass spectral fragmentation of these hydroxyindolenines is discussed in detail in these reports.

(8) D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Paszek, and W. I. Taylor, *J. Amer. Chem. Soc.*, **80**, 123 (1958).

(9) For the synthesis of other hydroxyindolenines in this series, see ref 7a and 8, and also, M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *ibid.*, **80**, 126 (1958).

(10) U. Renner and D. A. Prins, *Experientia*, **15**, 456 (1959).

(11) D. Stauffacher and E. Seebeck, *Helv. Chim. Acta*, **41**, 169 (1958).

(12) U. Renner and D. A. Prins, *Experientia*, **17**, 106 (1961).

Experimental Section

Melting points were determined with a Thomas–Hoover Unimelt apparatus, and are corrected. Ir spectra were measured in $CHCl_3$ solution (10%) on a Beckman double-beam recording spectrophotometer, Model IR-5A. Nmr spectra were determined in $CDCl_3$ at 60 Mc on a Varian Associates A-60 recording spectrophotometer using TMS as the internal standard, and were electronically integrated. The uv spectrum was determined in 95% EtOH on a Beckman recording spectrophotometer, Model DK2A. The optical rotation was determined in $CHCl_3$ solution with a Zeiss-Winkel polarimeter and is approximated to the nearest degree. High resolution mass spectra were obtained on a C. E. C. 21-110 instrument, with photoplate recording. Elemental compositions for all ions were determined; low resolution mass spectra were obtained both on a C. E. C. 21-103 and a C. E. C. 21-110 instrument. Skellysolve B refers to petroleum ether distilling at 60–68°. The solvent system used for partition chromatography consisted of ethylene chloride–Skellysolve B–methanol–water (2.5:15:2:0.3), using bromcresol purple as the indicator in the stationary (lower) phase. We are grateful to Smith Kline and French Laboratories for the alcohol extract of *E. dichotoma*.

Extraction and Preliminary Fractionation.—The dried ground root bark (4.6 kg) was extracted with ethanol after preliminary extraction with petroleum ether. The ethanol extract was concentrated and the residue was taken up in dilute HCl. The insoluble material was removed and the filtrate brought to pH 7. The solid that separated was collected and dried (crude alkaloid fraction, 50 g). A portion (18.2 g) of the crude alkaloid fraction was partitioned between ether (125 ml) and four 80-ml portions of 4% HCl. The combined acid solutions were treated with $(NH_4)_2CO_3$ until alkaline and thoroughly extracted with four 200-ml portions of ether. The combined ether solutions were extracted with four 100-ml portions of 4% HCl. The combined acid solutions were again treated with $(NH_4)_2CO_3$ until alkaline and extracted with five 100-ml portions of ether. The combined ether solutions were washed with five 20-ml portions of 1% NaOH to remove the phenolic bases. The ether solution was washed with water, dried over fused K_2CO_3, and concentrated to yield the nonphenolic bases (8.8 g).

Isolation of Alkaloids.—The nonphenolic bases (8.8 g) were treated with benzene–Skellysolve B (4:1) and filtered to remove insoluble material (0.1 g). The filtrate was added to a column of neutral Woelm grade I alumina (210 g). Elution with benzene–Skellysolve B (1:1, 3000 ml) followed by benzene–Skellysolve B (3:1, 3000 ml) yielded a clear syrup (fraction 1, 1.51 g). Elution with benzene (3000 ml) yielded fraction 2 (0.51 g). Elution with benzene–chloroform (1:1, 3000 ml) yielded a solid yellow foam (fraction 3, 5.42 g). Partition chromatography of the third fraction (5.42 g) on a Celite 545 column (495 g) yielded six bands. Treatment of band 3 (1.33 g) with Skellysolve B yielded heyneanine.[5] Rechromatography of band 4 (460 mg) on a Celite 545 partition column (495 g) yielded four bands. Treatment of band 3 (145 mg) with benzene–Skellysolve B yielded a colorless crystalline material. Recrystallization from the same solvent system yielded voacristine hydroxyindolenine (IIa, 53 mg), $C_{22}H_{28}N_2O_5$:

(13) In view of the relatively facile autoxidation of indole alkaloids of the iboga series, the isolation of these products from the plant does not necessarily prove their natural occurrence.

mp 176–179° dec; $[\alpha]^{26}D$ −22° (c 0.51, chloroform); $\lambda_{max}^{CHCl_3}$ 2.80 (w), 3.10 (m), 5.76 (s), 5.90 (m), 6.25 (m), 6.45 (w), 6.78 (s), 6.98 μ (s); λ_{max}^{EtOH} 229.5, 268, 291, 300 (shoulder), 314 mμ (ε 12,380, 4400, 4780, 3810, 4410); nmr, τ 2.66 (one proton, doublet, J_{ortho} = 8 cps), 3.12 (one proton, doublet, J_{meta} = 2.5 cps), 3.24 (one proton, doublet of doublet, J_{ortho} = 8 cps, J_{meta} = 2.5 cps), 5.97 (one proton, broad multiplet), 6.18 (three protons, $-OCH_3$), 6.30 (three protons, $-CO_2CH_3$), and 8.93 (three protons, doublet, J = 6.5 cps); the mass spectrum is given in Figure 1.

Synthesis of Voacristine Hydroxyindolenine from Voacristine.—Voacristine (III, 500 mg) in 5 ml of benzene was illuminated by an ultraviolet lamp ("Blak-Ray", UVL-22, U.V. Products, Inc., San Gabriel, Calif.) while oxygen was slowly bubbled through the solution. Benzene was periodically added to maintain the volume. After 8 hr the product was chromatographed on 50 g of Woelm alumina III. Benzene–chloroform eluted unchanged voacristine, and chloroform eluted a 150 mg fraction containing the hydroxyindolenine together with a small amount of voacristine. Purification by tlc on silica gel H provided 116 mg of amorphous material which gave infrared, mass, and nmr spectra identical with data from the isolated product IIa. A portion of this material (16.4 mg) was subjected to gas–liquid partition chromatography on a Celite 545 column (5 g) which yielded a colorless solid (11.4 mg). Crystallization from benzene–Skellysolve B yielded colorless crystals (6.7 mg), mp 178–179° dec. This material was shown to be identical with the isolated material (mixture tlc, mixture melting point).

Registry No.—IIa, 15215-86-8.

Acknowledgments.—H. K. S. thanks Professor A. L. Burlingame (Berkeley) and D. W. T. thanks Professor Biemann (M. I. T.) for the use of their respective laboratory facilities.

Syntheses of Rosefuran and Dehydroelsholtzione

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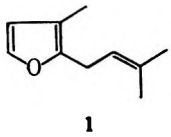
Since ancient times oil of rose has been one of the most valuable materials in perfumery. Its high price made it an obvious target for chemical examination which was begun at the beginning of the last century.[1] The major constituents were already identified by early investigators and used, without delay, for the adulteration of natural oil. The trace constituents to which the essence owes its characteristic and powerful odor were not detected by the inadequate analytical tools then available and are only now being isolated. In the course of a detailed analysis of Bulgarian rose oil (*Rosa damascena* Mill.), E. s. K. isolated a compound to which structure **1** was assigned and which was named rosefuran. To evaluate the importance of this constituent as regards the odor of rose oil, it was decided to produce rosefuran by total synthesis.



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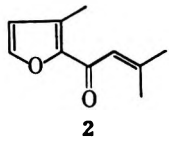
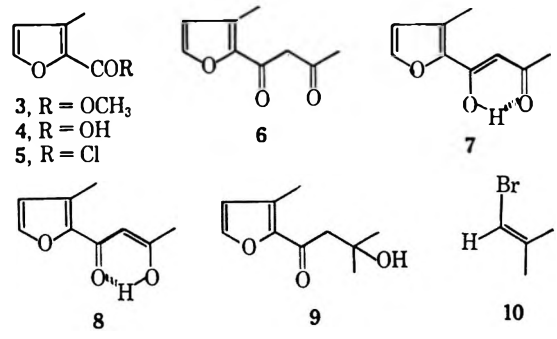


2

(1) E. Guenther, "The Essential Oils," Vol. 5, D. Van Nostrand Co. Inc., New York, N. Y., 1949, p 1.

Our investigation was commenced with a synthesis of dehydroelsholtzione (**2**)[2,3] (naginata ketone[4]) which we hoped to reduce to rosefuran (**1**). Efforts to prepare this ketone by a previously described procedure[5] involving condensation of 3-methylfuran with β-methylcrotonoyl chloride in the presence of boron trifluoride failed to give more than trace amounts of the desired product.[6] In any event, the exclusive formation of a 2-substituted furan seemed improbable and, after finding that the Vilsmeier reaction with 3-methylfuran did indeed give a mixture of substitution products containing 85% of 3-methyl-2-furfuraldehyde[7] and 15% of 4-methyl-2-furfuraldehyde, we made no further efforts to prepare dehydroelsholtzione (**2**) by this procedure.

Condensation of the readily accessible methyl 3-methyl-2-furoate (**3**)[8] with acetone in the presence of sodium hydride gave the anticipated compound. A nuclear magnetic resonance spectrum in carbon tetrachloride (see Experimental Section) revealed the presence of 88% of either of the two enols **7** or **8** and 12% of the diketone **6**. When subjected to the action of methylmagnesium iodide, the diketone was transformed to a mixture of products containing 85% of the hydroxy ketone **9** and 15% dehydroelsholtzione (**2**). Simple heating in hot benzene was sufficient to transform the remainder of the hydroxy ketone **9** to the unsaturated ketone **2**. The spectral properties of synthetic dehydroelsholtzione **2** were identical with those of natural material.[3]



3, R = OCH_3
4, R = OH
5, R = Cl

6

7

8

9

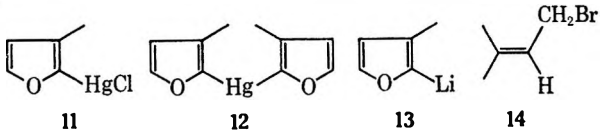
10

In a second, but much less satisfactory method, the ketone **2** was prepared by condensing the acid chloride **5** with the Grignard reagent of 1-bromo-2-methyl-1-propene.[9] Numerous attempts to transform synthetic dehydroelsholtzione (**2**) to rosefuran (**1**) by Wolff–Kishner reduction, by hydrogenolysis of the corresponding allylic alcohol and by reduction of the tosylhydrazone with metal hydrides failed.

It was then decided to approach the synthesis by way of 2-lithio-3-methylfuran (**13**). By heating an aqueous solution of the sodium salt of 3-methyl-2-furoic acid (**4**) with mercuric chloride we obtained the

(2) Y. R. Naves and P. Ochsner, *Helv. Chim. Acta.*, **43**, 406 (1960).
(3) Y. R. Naves and P. Ochsner, *ibid.*, **43**, 568 (1960).
(4) Y. Fujita and T. Ueda, *Chem. Ind.* (London), 236 (1960).
(5) P. A. Finan and G. A. Fothergill, *J. Chem. Soc.*, 2262 (1962).
(6) We have not repeated the synthesis of T. Ueda, *Nippon Kagaku Zasshi*, **83**, 341 (1962); *Chem. Abstr.*, **59**, 3857 (1963), because low yields were reported.
(7) T. Reichstein, H. Zschokke, and H. Goerg, *Helv. Chim. Acta*, **14**, 1277 (1931).
(8) D. M. Burness, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 649.
(9) H. Normant in "Advances in Organic Chemistry: Methods and Results," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp 1–65.

chloromercurifuran **11** in 86% yield.[10] Coupling brought about with sodium thiosulfate[10] afforded the corresponding difurylmercury **12** (97%). Treatment with finely dispersed lithium in ether produced 2-lithio-3-methylfuran (**13**)[11] readily converted to rosefuran (**1**) (35%) by condensation with 1-bromo-3-methyl-2-butene (**14**).[12] The infrared and nuclear magnetic resonance spectra of synthetic rosefuran (**1**) were identical with those of the natural product.



11 **12** **13** **14**

Experimental Section

Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind., and Dr. S. M. Nagy at the Massachusetts Institute of Technology. Melting points were determined on a hot-stage microscope and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237 instrument; only selected high-intensity bands are listed. Ultraviolet spectra were obtained on a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are given in parts per million downfield from tetramethylsilane as internal standard; coupling constants (J) are given in cycles per second. The abbreviations s, d, t, q, and m indicate singlet, doublet, triplet, quartet, and multiplet, respectively. The nmr data are given by listing the chemical shift, number of protons, multiplicity, and coupling constants. Thin layer chromatography (tlc) was used routinely for monitoring reactions and chromatographic separations.

Vilsmeier Condensation with 3-Methylfuran.—A three-necked flask charged with 8.15 g (110 mmoles) of dimethylformamide was cooled in an ice bath and 8.5 g (55 mmoles) of phosphorus oxychloride was added with stirring over a period of 0.5 hr and the mixture kept at 0° for 20 min. 3-Methylfuran[8] (4.1 g, 50 mmoles) was added at such a rate that the temperature did not rise above 15°. The mixture was kept at 0° for 1 hr and then at room temperature for an additional hr. The solution was poured into 100 ml of water and crushed ice, neutralized with sodium carbonate, extracted with ether twice, washed with water, dried over sodium sulfate, evaporated, and the product distilled. A mixture of aldehydes (3 g), bp 78–80° (15 mm), was obtained in 55% yield. Vapor phase chromatography using a 10% Carbowax 12-ft column at 140° revealed two compounds in a ratio of 17:3 with retention times of 7.3 and 9.2 min. An nmr spectrum (CCl_4) showed the two aldehydes in the same ratio: 3-methyl-2-furfuraldehyde (85%) had signals at 2.33 (3 H s), 6.39 (1 H d, J = 1.8), 7.52 (1 H d, J = 1.8), 9.73 (1 H s); 4-methyl-2-furfuraldehyde (15%) had signals at 2.07 (3 H s), 7.00 (1 H s), 7.42 (1 H s), 9.55 (1 H s).

1,3-Butanedione-1-(3-methyl-2-furyl) (6).—To a stirred mixture of 24 g (1 mole) of sodium hydride (washed from mineral oil) in 100 ml of dry ether was added at room temperature 70 g (0.5 mole) of methyl 3-methyl-2-furoate[8] (**3**) in 100 ml of ether and then, dropwise, 58 g (1 mole) of acetone in 100 ml of ether at such a rate that the temperature remained between 27 and 30°. A slow stream of nitrogen was passed through the apparatus and the mixture was stirred for 1 hr, boiled for 2 hr and then allowed to stand at room temperature overnight. Excess sodium hydride was destroyed by the dropwise addition of 25 ml of ethyl alcohol. The mixture was stirred for 30 min, cooled in an ice bath, and 400 ml of 20% sulfuric acid at 0° was added and the mixture stirred for 30 min. The ether extract was washed six times with aqueous sodium bicarbonate, and six times with 10% sodium hydroxide solution at 0°. The sodium hydroxide extracts, after acidification at 0° with 15% HCl, were extracted with ether twice, washed with aqueous sodium bicarbonate and with water, and dried over sodium sulfate. A yellow oil (49.1 g) was obtained after distillation, bp 88–92° (1 mm), yield 59%. A sample purified through the copper salt, $n^{25}D$ 1.5735, had uv absorption (isooctane) at 311 mμ (ε 19,800); the nmr (CCl_4) spectrum of the enol form had signals at 2.06 (3 H s), 2.38 (3 H s), 6.00 (1 H s), 6.30 (1 H d, J = 1.8), 7.34 (1 H d, J = 1.8), 15.30 (1 H s); the nmr spectrum of the diketone form had signals at 2.18 (3 H s), 2.38 (3 H s), 3.80 (2 H s), 6.30 (1 H d, J = 1.8), 7.34 (1 H d, J = 1.8). Infrared absorptions in CCl_4 were at 1725 (w), 1600 (very broad), 1480, 1400 cm^{-1}.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.78; H, 5.90.

Butan-1-one-3-methyl-3-hydroxy-1-(3-methyl-2-furyl) (9).—A solution of 47 g (0.283 mole) of 1,3-butanedione-1-(3-methyl-2-furyl) in 200 ml of ether was added dropwise to a stirred, ice-cold solution of methylmagnesium iodide prepared from 14.4 g (0.59 mole) of magnesium and 87.3 g (0.59 mole) of methyl iodide in 250 ml of ether, at such a rate that the temperature remained below 5°. After addition, a slow stream of nitrogen was passed through the apparatus, the temperature maintained at 0° for 2 hr and the mixture was stirred overnight at room temperature. The reaction product was cautiously poured on 500 ml of 20% HCl and crushed ice, extracted with ether twice, washed with aqueous sodium bicarbonate, water, dried over sodium sulfate and evaporated. The residue was distilled giving a main fraction, bp 83–90° (1 mm), 33.5 g, 65% yield. The nmr (CCl_4) spectrum gave signals at 1.23 (6 H s), 2.36 (4 H s), 2.93 (2 H s), 6.35 (1 H d, J = 1.8), 7.38 (1 H d, J = 1.8). Infrared absorptions in CCl_4 were at 3500, 1655, 1640, 1580 cm^{-1}.

Dehydroelsholtzione (2). A.—Butan-1-one-3-methyl-3-hydroxy-1-(3-methyl-2-furyl) (32 g, 0.176 mole) in 120 ml of benzene was refluxed for 2 hr in a flask fitted with a water separator. The solution was cooled, extracted with ether, washed with aqueous sodium bicarbonate, water, dried over sodium sulfate and the solvent removed *in vacuo*. The residue was distilled and the main fraction, bp 70–75° (1 mm), fractionated through a Vigreux column giving 23.9 g (yield 83%) of pure ketone: bp 78° (1 mm); $n^{26}D$ 1.5403; uv (isooctane) 284 mμ (ε 16,200), 291.5 mμ (ε 17,200); nmr (CCl_4), 1.93 (3 H s), 2.21 (3 H s), 2.37 (3 H s), 6.28 (1 H d, J = 1.8), 6.68 (1 H m), 7.28 (1 H d, J = 1.8). The infrared spectrum was identical with that published in ref 3.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.89; H, 7.28.

Synthetic dehydroelsholtzione gave a deep red 2,4-dinitrophenylhydrazone: mp 163° (lit.[3] mp 163–164°); ultraviolet absorption ($CHCl_3$) 407 mμ (ε 27,400) [lit.[3] 406 mμ (ε 27,700)].

B.—A solution of Grignard reagent prepared from magnesium (2.55 g) and 1-bromo-2-methyl-1-propene[9] (13.5 g) in tetrahydrofuran (50 ml) was slowly added to a solution of 3-methyl-2-furoylchloride (13 g) in 50 ml of tetrahydrofuran cooled to −40°. The mixture was maintained at this temperature for 1 hr and was then allowed to remain at 0° overnight. Work-up in the conventional manner gave an oil which was distilled and the fraction with bp 77–85° (1 mm) was chromatographed on silicic acid. Distillation of the appropriate fractions gave dehydroelsholtzione (**2**) 1.85 g (12% yield), bp 78° (1 mm), whose spectral properties were identical with those of material prepared as described under A.

3-Methyl-2-furoic acid (4) was prepared according to Burness,[8] mp 135–136° (lit.[8] mp 134–135°).

3-Methyl-2-chloromercurifuran (11).—To a solution of 3-methyl-2-furoic acid (6 g) and sodium hydroxide (1.9 g) in water (120 ml) was added mercuric chloride (13 g) in water (220 ml). The mixture was allowed to stand with occasional agitation for 4 hr at room temperature. The resulting precipitate was filtered off and the filtrate refluxed until the evolution of carbon dioxide was complete. After cooling, the mercurial was filtered off and added to the former precipitate which was then recrystallized from alcohol to give the required product (13 g, 86%) as colorless needles, mp 143–144°.

Anal. Calcd for C_5H_5OHgCl: C, 18.92; H, 1.59. Found: C, 18.98; H, 1.70.

2,2′-Di-3-methylfurylmercury (12).—3-Methyl-2-chloromercurifuran (6.3 g) was added to a solution of sodium thiosulfate (10 g) in water (40 ml). After stirring for 2 hr at room temperature, the reaction mixture was added to ether (20 ml). The ether layer was washed with water and dried and the solvent removed. The crude product was recrystallized from

(10) Method of H. Gilman and G. F. Wright, *J. Amer. Chem. Soc.*, **55**, 3302 (1933).

(11) We are indebted to Professor G. Whitesides, M. I. T., for useful advice on this reaction.

(12) H. Staudinger, W. Kreis, and W. Schilt, *Helv. Chim. Acta*, **5**, 750 (1922).

acetone–water to give 3.5 g (97%) of pure material. A sample for analysis was chromatographed on aluminum oxide (Woelm, neutral, activity grade II) and eluted with ether to afford colorless crystals: mp 54.5–55°; ir (CCl_4), 1575, 1480, 1460, 1390, 1150, 1060, 890, 730 cm^{-1}; nmr (CCl_4), 2.20 (6 H s), 6.41 (2 H d, J = 2), 7.53 (2 H d, J = 2).

Anal. Calcd for $C_{10}H_{10}O_2Hg$: C, 33.08; H, 2.77. Found: C, 32.83; H, 2.76.

3-Methyl-2-(3-methylbutene-2)furan (Rosefuran) (1).—2,2′-Di(3-methylfuryl)mercury (**12**) (5.50 g) in absolute ether (10 ml) was dropped, during 1 hr, into a suspension (−20°) of lithium sand (0.36 g, >50% excess) in ether (10 ml). After the addition was complete the reaction mixture was stirred at −20° for 1 hr. This mixture was then allowed to warm to room temperature and was then stirred for an additional 30 min. The solution of the organolithium compound was forced by helium pressure through a sintered glass disk into a second reaction vessel kept at −20°. 1-Bromo-3-methylbutene (4.50 g) in absolute ether (6 ml) was added through a dropping funnel in the course of 30 min. After the reaction mixture had reached room temperature it was poured into ice cold 15% ethanolic potassium hydroxide (20 ml). The ether was carefully distilled off, and after the mixture had been allowed to reflux for 1.5 hr the hydrolysis of unreacted bromide was complete. To the cold reaction mixture was added ether (30 ml) and the ether solution was washed with water until neutral and free of ethanol. After the solvent had been removed *in vacuo* the residue was distilled giving 1.64 g (36% yield) of rosefuran (**1**): bp 39–40° (1.0 mm); ir absorptions, 1675, 1625, 1510, 1460, 1380, 1160, 1090, 900, 860, 730 cm^{-1}; nmr ($CDCl_3$), 1.74 (6 H d, J = 1), 1.98 (3 H s), 3.31 (2 H d, J = 7.5), 5.34 (1 H t of heptet, J = 7.5, J' = 1), 6.22 (1 H d, J = 2), 7.28 (1 H d, J = 2), mass spectrum, M^+ 150, intense peak at 135.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.99; H, 9.45.

Registry No.—**1**, 15186-51-3; **2**, 6138-88-1; **6**, 15135-45-2; **9**, 15135-46-3; **11**, 15136-36-4; **12**, 15136-37-5.

Acknowledgment.—We are indebted to Firmenich et Co., Geneva for generous financial support.

Greenheart Alkaloids. III. Sepeerine (Ocoteamine) and Demerarine[1,2]

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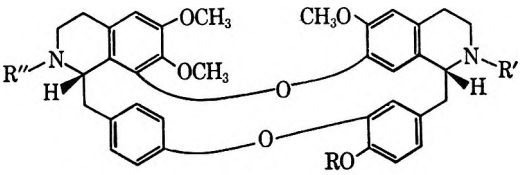
Received April 14, 1967

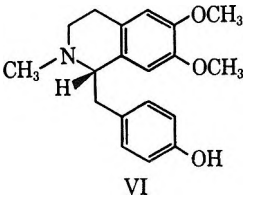
The seven alkaloids which had been isolated from the ether-soluble alkaloids of greenheart bark (*Ocotea rodiaei*) had properties pointing to biscoclaurine structures. Three of these alkaloids, rodiasine, norrodiasine, and dirosine, appeared to have one diphenyl ether linkage[1] and such a structure has recently been determined for rodiasine.[3] The four other alkaloids, ocoteamine, otocamine, demerarine, and ocodemerine, appeared to have two diphenyl ether linkages.[1] The latter alkaloids each had one secondary amino group and ocoteamine and demerarine each had one free phenolic group.

Ocoteamine has an infrared spectrum very similar to that of oxyacanthine (I), a phenolic alkaloid with no secondary amino groups. Methylation with formaldehyde and formic acid gave N-methylocoteamine whose hydrochloride was indistinguishable from that of oxyacanthine (based on infrared spectral comparisons, specific rotations, and distribution coefficients in acetate buffer–chloroform). Ocoteamine is thus a de-N-methyloxyacanthine (II or III).



	R	R′	R″	
I	H	CH_3	CH_3	oxyacanthine
II	H	H	CH_3	ocoteamine, sepeerine
III	H	CH_3	H	
IV	CH_3	H	CH_3	dimethyldaphnoline
V	CH_3	CH_3	H	hydroepistephanine-A

Methylation of the phenolic group of ocoteamine with diazomethane should give O-methylocoteamine of structure IV or V. The hydrochloride of O-methylocoteamine differed from that of authentic hydroepistephanine-A (V)[4] (in specific rotation, distribution coefficient, and R_f in paper chromatography). O-Methylocoteamine, therefore, had to be the same as O,O-dimethyldaphnoline (O,O-dimethyltrilobamine, IV)[5,6] and the specific rotation of the hydrochloride was indeed the same as that reported in the literature. The structure of O-methylocoteamine (IV) was further confirmed by reductive cleavage with sodium in liquid ammonia. This cleavage gave armepavine (VI), which can be obtained from a structure such as IV, but not from V.



VI

Ocoteamine therefore has structure II and is identical with sepeerine, which Grundon and McGarvey isolated from Greenheart.[7] Ocoteamine has a higher melting point (222.5° *vs.* 199°), but the specific rotations are the same and the infrared spectra are practically indistinguishable. The name ocoteamine should therefore be superseded by sepeerine.

Turning now to demerarine, this alkaloid has several properties closely resembling those of ocoteamine. These include the molecular composition, the distribution coefficients in acetate buffer and chloroform, the R_f values in multibuffer chromatography, the infrared spectrum of the phenolic peak,

(1) Part II: P. J. Hearst, *J. Org. Chem.*, **29**, 466 (1964).

(2) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963.

(3) M. F. Grundon and J. E. B. McGarvey, *J. Chem. Soc., Sect. C*, 1082 (1966).

(4) M. Tomita and Y. Watanabe, *Pharm. Bull. (Tokyo)*, **4**, 124 (1956); and H. Furukawa, *Yakugaku Zasshi*, **86** (3), 253 (1966).

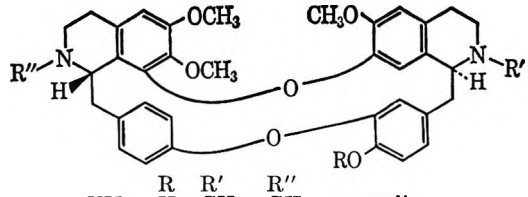
(5) Y. Inubushi, *Pharm. Bull.* (Tokyo), **3**, 384 (1955).

(6) I. R. C. Bick, P. S. Clezy, and M. J. Vernengo, *J. Chem. Soc.*, 4928 (1960).

(7) M. F. Grundon and J. E. B. McGarvey, *ibid.*, 2739 (1960); 2077 (1962).

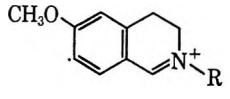
and the number of functional groups (OH, NH, and CH_3O).[1] It therefore appeared that the difference between the two bases could be due simply to a different configuration of one of the two asymmetric carbon atoms.

To clarify this point, demerarine was N-methylated by the Clarke–Eschweiler method and the N-methyldemerarine obtained was found to be identical with repandine (VII) (as shown by corresponding infrared spectra, practically identical mass spectra, and identical R_f values in thin layer chromatography using 12 different solvent systems). Demerarine is thus a de-N-methylrepandine (VIII or IX).

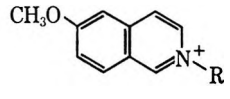


	R	R′	R″	
VII	H	CH_3	CH_3	repandine
VIII	H	H	CH_3	demerarine
IX	H	CH_3	H	

The mass spectrum of demerarine has an important peak at *m/e* 160 which is due to fragment X (R = H) less a hydrogen atom, or possibly XI (R = H). Either fragment could have been obtained from demerarine or from the moiety XII (R = H). The presence of this *m/e* 160 fragment shows that the secondary nitrogen of demerarine must be on the right-hand side of the molecule so that demerarine is VIII and not IX.

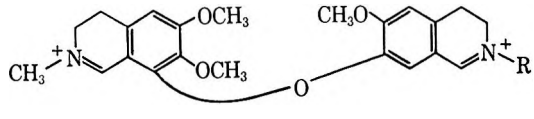


X

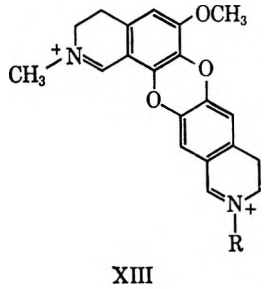


XI

Other peaks in the mass spectrum of demerarine are consistent with structure VIII and include a molecular ion peak at *m/e* 594 ± 1 (calcd for VIII, 594.7) and a base peak at *m/e* 191 with an isotope peak at *m/e* 191.5. The latter must be due to the doubly charged species XII (R = H) and the corresponding singly charged species gives a peak at *m/e* 382 and also at 381 through loss of a hydrogen atom. Doubly charged fragments of type XII are known to cyclize with elimination of CH_3OCH_3 to



XII



XIII

(8) D. C. DeJongh, S. R. Shrader, and M. P. Cava, *J. Amer. Chem. Soc.*, **88**, 1052 (1966).

give XIII[8] and the resultant peak at *m/e* 168 (XIII, R = H) is evident.

The above assignments are confirmed by the mass spectrum of N-methyldemerarine (repandine, VII). This spectrum gives peaks at *m/e* 608 (calcd for VII, 608.7), at 198 and 198.5 (XII, R = CH_3), at 396 and 395, at 175 and 175.5 (XIII, R = CH_3), and at 174. The latter peak probably is due to the fragment X (R = CH_3), less a hydrogen atom, or possibly XI (R = CH_3). These spectral values are all 14 mass units higher than those of the corresponding singly charged fragments from demerarine and 7 mass units higher than those of the corresponding doubly charged fragments from demerarine.

Experimental Section[9]

Ocoteamine.—Ocoteamine hydrochloride[1] had $[\alpha]^{25}D$ + 250° and $[\alpha]^{25}_{5461}$ + 303° (*c* 1.0, water). Treatment of an aqueous solution with ammonium hydroxide gave ocoteamine, which on crystallization from acetone or from benzene melted in a broad range near 180°; recrystallization from methanol gave platelets: mp 221.5–222.5°; $[\alpha]^{25}D$ + 392° (*c* 0.29, chloroform). The infrared spectrum of ocoteamine in chloroform was similar to that of oxyacanthine but lacked a peak at 1380 cm^{-1} and a doublet at 1360 cm^{-1}.

Anal. Calcd for $C_{36}H_{38}N_2O_6$: C, 72.7; H, 6.44; N, 4.71; O, 16.1; $4CH_3O$, 15.7; $1NCH_3$, 2.5. Found: C, 72.7; H, 6.49; N, 4.81; O, 16.7; CH_3O, 15.4; NCH_3, 2.3.

N-Methylocoteamine Hydrochloride.—Ocoteamine (350 mg) was dissolved in 1 ml of 90% formic acid and 1 ml of 37% formalin and was heated on a steam bath under reflux for 3 hr. Water and ammonium hydroxide were added to the reaction mixture and the resultant precipitate was freeze-dried to give 332 mg of crude product. The infrared spectrum of the product in chloroform was very similar to that of oxyacanthine. The product in very dilute hydrochloric acid was treated with saturated sodium sulfate solution and the resultant crystalline product was recrystallized to give 248 mg of the hydrogen sulfate salt. Recrystallization from dilute hydrochloric acid gave 161 mg of long needles of the hydrochloride: $[\alpha]^{25}D$ + 186° (*c* 1.0, water); *K* = 2.59.

O-Methylocoteamine Hydrochloride.—Ocoteamine (1.5 g) in methanol was treated with ethereal diazomethane for 2 days. The product was dissolved in dilute hydrochloric acid and washed with ether. Further addition of hydrochloric acid produced 951 mg (54%) of crystalline product. Recrystallization to constant specific rotation gave 685 mg of long platelets: $[\alpha]^{25}D$ + 263° (*c* 1.0, water); $[\alpha]^{26}D$ + 268° (*c* 0.50, water); $[\alpha]^{26}D$ + 279° (*c* 0.27, water) (lit.[4] $[\alpha]^{20}D$ + 272°, *c* 0.47, water); *K* = 0.47; R_f 0.62 for the free alkaloid with the system amyl alcohol–pyridine–water (110:110:90) on paper impregnated with potassium dihydrogen phosphate.[10]

Anal. Calcd for $C_{37}H_{40}N_2O_6 \cdot 2HCl \cdot H_2O$: C, 63.5; H, 6.34; O, 16.0; $4CH_3O$, 17.8. Found: C, 63.4; H, 6.34; O, 16.4; CH_3O, 17.6.

Cleavage with Sodium in Liquid Ammonia.—O-Methylocoteamine (300 mg obtained from the hydrochloride) in 10 ml of benzene–toluene (1:1) was added in seven portions to 150 ml of liquid ammonia at −40° to which a total of 500 mg of sodium was added to maintain a lasting blue color. Extraction with ether and 5% sodium hydroxide solution gave 21 mg of nonphenolic product and 279 mg of phenolic product. The latter product in 2 ml of ethanol was treated with 2 ml of a saturated alcoholic solution of oxalic acid. Obtained were 196 mg of crystals, which were recrystallized to give 165 mg of armepavine oxalate, mp 215–216° dec. A similar cleavage of cycleanine, mp 274–276°, which had been prepared by the O-methylation[10]

(9) Melting points were corrected and were determined in evacuated capillaries or on a hot stage under a blanket of nitrogen; microanalyses were performed by Dr. W. Zimmermann, University of Melbourne, Australia; distribution coefficients, *K*, were determined according to the method of ref 1, using 0.5 *M* acetate buffer, pH 4.15, and chloroform. The mass spectra were obtained on a Nuclide single beam spectrometer, 12-90-G1.1.

(10) D. A. A. Kidd and J. Walker, *J. Chem. Soc.*, 669 (1954).

of isochondrodendrine[11] in benzene–methanol, gave armepavine oxalate, mp 211–213° (lit. mp 211–212° uncor[5] and mp 209° [6]).

Demerarine.—Demerarine hydrochloride[1] had $[\alpha]^{25}D$ − 181°, $[\alpha]^{25}_{5461}$ − 219° (*c* 1.0, water). Treatment of an aqueous solution with ammonium hydroxide gave demerarine which crystallized in needles from methanol: mp 222–223°; $[\alpha]^{25}D$ − 162° (*c* 0.35, 5% methanol in chloroform). The mass spectrum exhibited a molecular ion peak at *m/e* 594 ± 1 in accord with the molecular formula $C_{36}H_{38}N_2O_6$. Other important peaks were at *m/e* 168, 191, 381, and 382.

N-Methyldemerarine.—Demerarine (100 mg) in 0.5 ml of formic acid and 0.5 ml of formalin was heated in a steam bath for 4 hr. Treatment with water and ammonia gave a precipitate which on drying weighed 91 mg. The infrared spectrum in a KBr pellet was the same as that of a sample of repandine. In thin layer chromatographic comparisons on silica gel (Adsorbosil-1), using 12 different solvent systems, N-methyldemerarine and repandine had the same R_f values. The mass spectra of the two alkaloids were identical showing a molecular ion peak at *m/e* 608 ± 1 in accord with the molecular formula $C_{37}H_{40}N_2O_6$.

Oxyacanthine Hydrochloride.—The addition of saturated sodium sulfate solution to a solution of commercial "oxyacanthine hydrochloride tetrahydrate" (Fluka AG. Buchs, Switzerland) gave platelets of oxyacanthine sulfate. The product was recrystallized from water and was converted into oxyacanthine hydrochloride by the addition of hydrochloric acid to an aqueous solution: $[\alpha]^{25}D$ + 188° (*c* 1.0, water); *K* = 2.36.

Hydroepistephanine-A Hydrochloride.—A sample of epistephanine in sulfuric acid and ethanol was reduced with zinc dust by the method of Tomita and Watanabe.[4] Hydroepistephanine-A hydrochloride was obtained in small, long rods: $[\alpha]^{24}D$ + 300° (*c* 0.27, water) (lit.[4] $[\alpha]^{29}D$ + 298°, *c* 0.24, water); *K* = 1.03; R_f 0.58 for the free alkaloid with the system amyl alcohol–pyridine–water (110:110:90) on buffered paper.[10]

Registry No.—II, 6787-93-5; VIII, 15353-21-6; N-methylocoteamine HCl, 15352-74-6; O-methylocoteamine HCl, 15352-75-7; N-methyldemerarine, 15352-76-8.

Acknowledgments.—The authors wish to thank Dr. Yasuo Watanabe, First College of Pharmacy, Fukuoka City, for a sample of epistephanine, Dr. I. R. C. Bick, University of Tasmania, for a sample of repandine, and Dr. M. F. Grundon, The Queen's University, Belfast, for a sample of sepeerine. M. S. wishes to acknowledge financial support from the National Institutes of Health through Grant GM-10608.

(11) H. McKennis, Jr., P. J. Hearst, R. W. Drisko, T. Roe, Jr., and R. L. Alumbaugh, *J. Amer. Chem. Soc.*, **78**, 245 (1956).

Solvent Effects in the Chlorination of Isobutyl Chloride and *t*-Butyl Chloride[1]

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Russell[2] reported that in the photochlorination of 2,3-dimethylbutane at 25° the relative reactivities of the primary and tertiary hydrogen atoms varied from 4.2 in pure carbon tetrachloride to 225 in 12 *M* carbon disulfide. The relative reactivities of covalently bound hydrogen atoms to photochlorination in different solvents have been determined for other compounds such as *n*-pentane,[3] *n*-butyl chloride,[4] hexanoyl chloride,[5] *n*-heptane,[6] octanoyl chloride,[6] and chlorocyclopentane;[7] relationships between the nature of the solvent and the relative reactivities of the hydrogen atoms being abstracted have been developed. Our purpose in this investigation was to apply these principles to the chlorination of isobutyl chloride in order to obtain a better understanding of the transition state.

Isobutyl chloride in mixed solvents of different compositions was allowed to react photochemically with a small amount of chlorine and the products were separated and measured quantitatively by gas chromatography. The results are shown in Table I.

TABLE I
SOLVENT EFFECTS IN THE CHLORINATION OF ISOBUTYL CHLORIDE[a]

$(CH_3)_2CHCH_2Cl + Cl_2 \xrightarrow{k_1} (CH_3)_2CClCH_2Cl$
$\xrightarrow{2k_2} (CH_3)_2CHCHCl_2$
$\xrightarrow{6k_3} CH_3CH(CH_2Cl)_2$

Solvents	Concn of second solvent, mol/l.	k_1/k_3[b]	k_1/k_2[b]	k_3/k_2[b]
CCl_4	...	4.5	6.1	1.35[c]
CCl_4–CS_2	1.2	8.8	8.7	0.99
CCl_4–CS_2	2.2	11.4	10.2	0.90
CCl_4–CS_2	3.8	14.4	11.6	0.81
CCl_4–CS_2	6.2	19.7	13.6	0.69
CCl_4–CS_2	8.5	24.3	14.6	0.60
CCl_4–CS_2	9.2	24.3	14.8	0.61
CCl_4–CS_2	11.2	27.2	15.0	0.55
CS_2	...	29.1	15.3	0.53
CCl_4–C_6H_6	1.3	8.4	9.2	1.10
CCl_4–C_6H_6	2.5	11.2	10.6	0.95
CCl_4–C_6H_6	3.7	13.3	11.7	0.88
CCl_4–C_6H_6	5.0	15.7	12.5	0.80
CCl_4–C_6H_6	6.3	17.4	12.6	0.72
CCl_4–C_6H_6	7.4	19.6	*d*	*d*

[a] Each solution contained 0.87 g of isobutyl chloride and 0.024 g of chlorine in a total volume of 4.2 ml. [b] Each value is the result of four or five determinations; the average deviation of each value is ±3%. [c] E. M. Hodnett and P. S. Juneja, *J. Org. Chem.*, **32**, 4114 (1967). [d] Not determined because of experimental difficulties.

For further comparison, mixtures of isobutyl chloride and *t*-butyl chloride were chlorinated in the same solvents under the same conditions; the results are shown in Table II.

Russell[2,8] has suggested that relative reactivities that are determined mainly by the availability of electrons in the carbon–hydrogen bond are not particularly sensitive to solvent effects while relative reactivities that are determined mainly by the stabilities of the incipient free radicals are very sensitive to changes in solvent. This is because in solvents which complex chlorine atoms the transition state has more radical character and therefore is influenced

(1) Abstracted in part from the Ph.D. dissertation of P. S. J., Oklahoma State University, May 1967.
(2) G. A. Russell, *J. Amer. Chem. Soc.*, **80**, 4987 (1958).
(3) G. A. Russell, *ibid.*, **80**, 4997 (1958).
(4) C. Walling and M. F. Mayahi, *ibid.*, **81**, 1485 (1959).
(5) H. J. den Hertog and P. Smit, *Proc. Chem. Soc.*, 132 (1959).
(6) P. Smit and H. J. den Hertog, *Rec. Trav. Chim.*, **83**, 891 (1964).
(7) G. A. Russell, A. Ito, and R. Konako, *J. Amer. Chem. Soc.*, **85**, 2988 (1963).
(8) G. A. Russell, *Tetrahedron*, **8**, 101 (1960).

TABLE II

SOLVENT EFFECTS IN THE COMPETITIVE CHLORINATION OF ISOBUTYL CHLORIDE AND *t*-BUTYL CHLORIDE[a]

$$(CH_3)_2CHCH_2Cl + Cl_2 \xrightarrow{2k_2} (CH_3)_2CHCHCl_2$$
$$\xrightarrow{6k_3} CH_3CH(CH_2Cl)_2$$

$$(CH_3)_3CCl + Cl_2 \xrightarrow{9k_6} (CH_3)_2CClCH_2Cl$$

Solvents	Concn of second solvent, mol/l.	k_3/k_6[b]	k_2/k_6[b]
CCl_4	...	2.25[c]	1.78[c]
CCl_4–CS_2	2.1	2.09	2.33
CCl_4–CS_2	4.2	2.38	3.12
CCl_4–CS_2	6.3	2.18	3.19
CCl_4–CS_2	8.4	1.83	3.30
CS_2	...	1.98	3.94
CCl_4–C_6H_6	1.2	2.12	1.97
CCl_4–C_6H_6	2.5	2.05	2.13
CCl_4–C_6H_6	3.7	1.91	2.18
CCl_4–C_6H_6	5.0	1.98	2.50

[a] Each solution contained 0.42 g of *t*-butyl chloride, 0.44 g of isobutyl chloride, and 0.017 g of chlorine in a total volume of 4 ml. [b] Each value is the result of four or five determinations; the average deviation of each value is ±3%. [c] See footnote *c*, Table I.

by the stability of the incipient radicals. These principles seem to have been observed in other investigations of solvent effects[3-7] and have been applied to the results of this study.

The reactivities of the hydrogen atoms of isobutyl chloride in photochlorination in mixed solvents are compared with one another in Table I and with the reactivity of the hydrogen atoms of *t*-butyl chloride in Table II. The absolute reactivity of the hydrogen atoms of *t*-butyl chloride may change with each solvent. It is possible that the chlorine atom of *t*-butyl chloride may participate in the stabilization of the incipient radical $(CH_3)_2\dot{C}Cl\dot{C}H_2$.[9] The results given in Tables I and II are summarized in Table III.

TABLE III

CH_3 | CH_3–CH–CH_2Cl			CH_3 | CH_3–CCl–CH_3	Solvent
2.25	8.02	1.78	1.00[a]	Carbon tetrachloride
1.98	31.2	2.50	1.00[a]	Benzene (5.0 *M*) and carbon tetrachloride
1.98	60.3	3.94	1.00[a]	Carbon disulfide

[a] Assumed value.

The greatest solvent effect is demonstrated by the tertiary hydrogen atom of isobutyl chloride; the relative reactivity varies from 8.02 in carbon tetrachloride to 60.3 in carbon disulfide solutions. This large effect probably results from the stability of the radical $(CH_3)_2\dot{C}CH_2Cl$ which is formed by abstraction of the tertiary hydrogen atom; that is, hyperconjugative stabilization of the incipient radical rather than polar effects probably determines the reactivity of this hydrogen atom.

The inductive effect of a chlorine atom normally results in deactivation of the hydrogen atoms on the same and adjacent carbon atoms as shown by the relative reactivities of the hydrogen atoms on carbons 1 and 4 of *n*-butyl chloride.[4,10] However, the hydrogen atoms on carbon 1 of isobutyl chloride are more reactive than the hydrogen atoms of *t*-butyl chloride in carbon tetrachloride and become even more reactive in carbon disulfide. Although the solvent effect on the reactivity of the hydrogen atoms on carbon 1 of isobutyl chloride is not so great as that for the tertiary hydrogen atom of isobutyl chloride, these hydrogen atoms do become more reactive in the solvent which is more capable of complexing with chlorine. The incipient free radical, $(CH_3)_2CH\dot{C}HCl$, is significantly stabilized by conjugation of the forms[11]

$$(CH_3)_2CH\dot{C}\text{—}\ddot{Cl}: \leftrightarrow (CH_3)_2CH\dot{C}{=}\ddot{Cl}: \leftrightarrow (CH_3)_2CH\dot{C}\text{—}\ddot{Cl}:$$
$$\mathbf{1} \qquad\qquad \mathbf{2} \qquad\qquad \mathbf{3}$$

Structure **3** may also be stabilized by dipole-induced dipole interaction with solvents having easily polarizable π electrons. Thus to the extent that structure **3** contributes to the resonance hydrid of the incipient radical one would expect some solvent stabilization. Walling and Wagner[12] have suggested that the solvation of the organic free radical which is being formed is an important factor in determining the selectivity of the reaction.

The relative reactivity of the hydrogen atoms on carbon 3 of isobutyl chloride varies least of all with changes in solvents. This is to be expected since it is most like the hydrogen atoms of *t*-butyl chloride with which it is being compared. The greater reactivity of the hydrogen atoms on carbon 3 of isobutyl chloride compared to those of *t*-butyl chloride may be due to (1) hyperconjugative stabilization of the incipient radical $CH_2\dot{C}H(CH_3)CH_2Cl$ (not possible for *t*-butyl chloride) or (2) the inductive effect of the chlorine atom of *i*-butyl chloride (which is closer to the reaction site than the chlorine atom of isobutyl chloride).

Experimental Section

Materials.—The benzene used in this work was obtained from J. T. Baker Co. as their reagent grade; gas chromatography showed that it contained no more than 0.4% impurities, of which 0.33% was toluene. Carbon disulfide was also a reagent grade from J. T. Baker Co. and was gas chromatographically pure. The sources and purities of other materials used were described previously.[13]

Procedure.—The procedures were also described previously.[13] The solutions contained known quantities of the compound or compounds to be chlorinated, a limiting amount of chlorine, and known ratios of solvents. After the reaction mixture was degassed it was irradiated at room temperature with an incandescent light until all the chlorine had reacted. The reaction mixture was shaken with solid sodium bicarbonate, dried with Drierite, and analyzed quantitatively by gas chromatography; the peak area (peak height times width at half-peak height) was assumed to be proportional to the concentration of products.[14] The three dichloro isomers from isobutane were considered to have the same thermal conductivity response and hence no calibration was employed.[13]

(9) P. S. Skell, R. G. Allen, and N. D. Gilmour, *J. Amer. Chem. Soc.*, **83**, 504 (1961); W. Thaler, *ibid.*, **85**, 2607 (1963); P. S. Skell, D. L. Tuleen, and P. D. Readio, *ibid.*, **85**, 2849 (1963); W. O. Haag and E. I. Heiba, *Tetrahedron Lett.*, **41**, 3678, 3683 (1965); P. S. Juneja and E. M. Hodnett, *J. Amer. Chem. Soc.*, **89**, 5685 (1967).

(10) P. S. Fredricks and J. M. Tedder, *J. Chem. Soc.*, 144 (1960).

(11) G. A. Russell and A. Ito, *J. Amer. Chem. Soc.*, **85**, 2983 (1963); J. M. Tedder, *Quart. Rev.* (London), **14**, 336 (1960).

(12) C. Walling and P. J. Wagner, *J. Amer. Chem. Soc.*, **86**, 3368 (1964).

(13) See footnote *c*, Table I.

(14) R. P. W. Scott and D. W. Grant, *Analyst*, **89**, 179 (1964).

Identification of Products.—The products of the reaction were identified by nmr spectra and retention times on the gas chromatograph.[13]

Registry No.—Isobutyl chloride, 513-36-0; *t*-butyl chloride, 507-20-0.

Acknowledgments.—We thank Dr. Stuart Scheppele for helpful discussions in the interpretations of these results. This work was supported financially by the U. S. Atomic Energy Commission under Contract AT(11-1)-1049 and by the Research Foundation of Oklahoma State University.

A β Secondary Isotope Effect in the Photochlorination of 2-Methylpropane-2-*t*[1]

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The primary hydrogen atoms of 2-methylpropane-2-*t* are removed by photochlorination less rapidly than are the primary hydrogen atoms of isobutane. This difference in rates indicates that tritium has a β-secondary isotope effect in this free-radical chlorination. Secondary β-isotope effects of deuterium have been reported,[2-9] but few of these are for reactions with free-radical mechanisms.[10-12]

The photochlorination of hydrocarbons occurs by a chain reaction. For the chlorination of methane, the

$$RH + Cl\cdot \rightarrow R\cdot + HCl \quad (I)$$

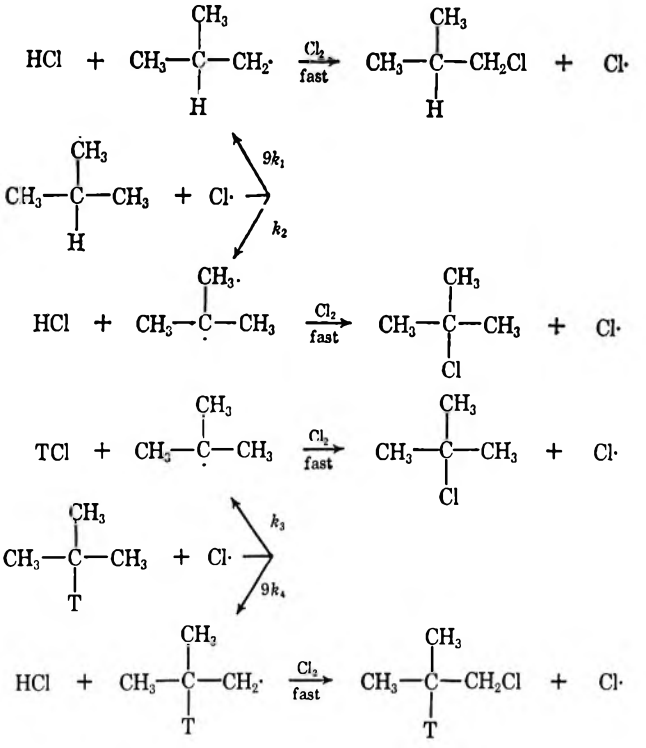
$$R\cdot + Cl_2 \rightarrow RCl + Cl\cdot \quad (II)$$

calculated heat of reaction of step I is −1 kcal/mole and that of step II is −23 kcal/mole;[13] step I is probably rate determining. The rate of chlorination of a mixture of isobutane and tracer amounts of 2-methylpropane-2-*t*, therefore, is determined by the first step of each of the four reactions given in Scheme I.

Equations 1–3 may be used to compare the four reaction rate constants with each other: eq 1

$$\frac{\log N_A/N_{A_0}}{\log A/A_0} = \frac{9k_4 + k_2}{9k_1 + k_2} - 1 \quad (i)$$

SCHEME I



where N_{A_0} and N_A are the specific radioactivities of the isobutane-*t* at the start and at the end of the experiment and A/A_0 is the fraction of isobutane remaining at the end of the experiment; eq 2 shown below

$$k_2/9k_1 = B/C \quad (2)$$

where B/C is the ratio of *t*-butyl chloride and isobutyl chloride formed in the reaction (under these conditions k_2/k_1 has a magnitude[14] of 3.5); and eq 3

$$k_1/k_4 = N_{A_0}/N_B \quad (3)$$

(for low extents of reaction) where N_B is the specific activity of the isobutyl chloride formed at low extents of reaction. Equation 3 assumes that the specific radioactivity of the isobutane-*t* does not change for low extents of reaction. However, if one assumes that the primary isotope effect has a magnitude[15] of 5 and the β secondary isotope effect has a magnitude of 1.04, the radioactivity of the remaining isobutane-*t* after 1.5% reaction can be calculated by eq 1 to have increased by 0.37%. Since the isobutyl chloride was formed from isobutane-*t* with an initial radioactivity of 59.92 μcuries/mmole and a final one of 60.14 μcuries/mmole, an average value of 60.03 μcuries/mmole is used in the calculations of the β secondary isotope effect shown in Table I.

2-Methylpropane-2-*t*, prepared from *t*-butylmagnesium chloride and tritiated water, was treated in carbon tetrachloride solution with enough chlorine to react with 1.5% of the isobutane. The reaction mixture was irradiated at room temperature until the chlorine color disappeared and the hydrogen chloride and part of the remaining isobutane were removed. Samples of the remainder were injected into a gas chromatograph which was attached to an ionization chamber. The components of the mixture were sep-

(1) These results were presented at the Oklahoma Tetrasectional Meeting of the American Chemical Society, Tulsa, Okla., March 1967; abstracted from a portion of the Ph.D. dissertation of P. S. J., Oklahoma State University, May 1967.

(2) P. Laszlo and Z. Welvart, *Bull. Soc. Chim. France*, 2412 (1966).

(3) V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, **75**, 2925 (1953).

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(5) V. J. Shiner, Jr., *Tetrahedron*, **5**, 243 (1959).

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TABLE I
CHLORINATION OF 2-METHYLPROPANE-2-*t* IN CARBON TETRACHLORIDE AT 24° (INITIAL CONCENTRATION OF ISOBUTANE-*t*, 2.2 *M*; AVERAGE RADIOACTIVITY OF ISOBUTANE-*t*, 60.03 ± 0.13 μCURIES/MMOLE)

Expt no.	Radioactivity of isobutyl chloride, μcuries/mmole[a]	k_1/k_4[a]
E109	57.63 ± 0.38	1.041 ± 0.007
E110	56.94 ± 0.40	1.054 ± 0.004
E113	57.64 ± 0.49	1.041 ± 0.009
	Av	1.045 ± 0.004

[a] With standard deviations.

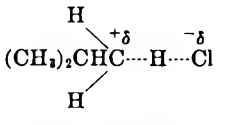
arated by the gas chromatograph and their radioactivities were recorded immediately by means of a vibrating reed electrometer. Owing to experimental difficulties, a good value for the radioactivity of the hydrogen chloride produced in the runs was not obtained and therefore the primary isotope effect in the reaction was not determined exactly. The radioactivity of the isobutyl chloride that was formed in the runs conducted in benzene solution could not be determined exactly because of the small quantity of isobutyl chloride produced in these experiments. This part of the problem is being investigated further.

Although the average value of the β secondary isotope effect shown in Table I is not large, it is significantly greater than the experimental error. The value of 1.045 for the β secondary tritium isotope effect in this reaction may be compared with the value of 1.018 per deuterium atom which Seltzer[10] reported for the β secondary effect in the homolysis of azobis(α-phenylethane-β,β,β-d_3). For this purpose the following equation, developed by Swain, *et al.*, and Bigeleisen[16] for primary isotope effects, may be used,

$$k_H/k_T = (k_H k_D)^{1.442}$$

although it does not necessarily apply to secondary isotope effects. Calculated by this equation, the β secondary effect for tritium in the homolysis of azobis(α-phenylethane-β-*t*) would be 1.026, which is significantly lower than the β secondary isotope effect of tritium obtained in the chlorination of 2-methylpropane-2-*t* in this work.

Secondary β-isotope effects of deuterium in reactions having carbonium ions as intermediates may be as great as 20%.[17] Seltzer[10] has suggested that hyperconjugative delocalization in a free radical is not so extensive as that in the corresponding carbonium ion and therefore the isotope effect in the free-radical reaction would be expected to be much less than that in a reaction involving a carbonium ion. We feel that in the photochlorination of isobutane there may be a small contribution to the transition state by a polar form such as



which would tend to increase the isotope effect.

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Experimental Section

Preparation of 2-Methylpropane-2-*t*.—*t*-Butylmagnesium chloride was prepared by the method of Whitmore and Badertscher[18] from 31.8 g (0.333 mole) of pure *t*-butyl chloride and 8.16 g (0.333 mole) of magnesium turnings in anhydrous ether. After the reaction was complete, tritiated water (100 μl, 171 mcuries/g) dissolved in 1.5 ml of isopropyl alcohol and 10 ml of ether was added dropwise to the stirred mixture. Dilute hydrochloric acid (1:100) was added to the reaction mixture until the Grignard reagent was completely decomposed; the mixture was heated to reflux for 1 hr. During these additions and subsequent reflux, the evolved isobutane was passed through an efficient reflux condenser cooled to 0.5° and was collected in a trap cooled to −78°.

Gas chromatographic analysis of the condensate showed that the ratio of isobutane to ether was 3:1. The condensate was redistilled slowly through a vertical condenser cooled to 0.5°; the ratio of isobutane to ether in the distillate was 6:1. This solution was passed three times through a 10% sulfuric acid solution and a tower containing anhydrous calcium chloride and potassium hydroxide pellets. Analysis of the purified isobutane showed 3.5% isobutylene and 0.6% ether. When a sample of this 2-methylpropane-2-*t* was chlorinated, the *t*-butyl chloride was not radioactive, indicating that all the tritium was on the tertiary carbon atom. The yield of isobutane was 25 ml (14 g, 0.24 mole, 72.3% of the theoretical yield, with a radioactivity of 60 μcuries/mmole (radioactivity yield) 84%).

Preparation of 1-Chloro-2-methyl-1-propene-*t*.—This compound, needed for comparison of radioactivities, was prepared by a procedure suggested by the work of Burgin, Hearne, and Rust on the isomerization of methallyl chloride (3-chloro-2-methyl-1-propene) with sulfuric acid.[19] Methallyl chloride (48 ml, practical grade) was stirred at 25–26° while 6.12 g of 80% sulfuric acid containing 50 μl of tritiated water (172 mcuries/g) was added dropwise. The reaction mixture was then stirred for 2.5 hr at 40°. The organic layer was separated, washed with sodium bicarbonate solution and water, dried with anhydrous sodium sulfate, and distilled. The product boiling at 58–72° contained 1-chloro-2-methyl-1-propene-*t* and methallyl chloride-*t* in the ratio of 93.6:6.4. Pure 1-chloro-2-methyl-1-propene-*t* was obtained by preparative chromatography (column temperature, 75°; carrier gas flow, 100 ml/min; Resoflex 728 on firebrick).

Radioactivity Assays.—2-Methylpropane-2-*t* was assayed by placing a known volume of the gas at a known pressure in an ionization chamber and filling to atmospheric pressure with methane. Since the mole fraction of methane was always much greater than that of the other gas, the chemical composition of the latter did not affect the results.[20] The ion current was then measured on an Applied Physics vibrating reed electrometer. A sample of 1-chloro-2-methyl-1-propene-*t* was weighed in an ampoule and transferred to the same ion chamber as a vapor; measurement of the ion current under identical conditions gave a direct comparison of the radioactivities of the two compounds. Each radioactive gas was assayed at least three times alternately with the other gas; a standard chamber was used to test the vibrating reed electrometer before and after each measurement in order to discover any variation in operation of the instrument.

The 1-chloro-2-methyl-1-propene-*t* was also injected into an Aerograph A90P gas chromatograph which was joined to a heated ionization chamber for flowing gases. The ratio of the peak height on the recorder of the gas chromatograph to the peak height on the recorder of the vibrating reed electrometer was proportional to the specific activity of the 1-chloro-2-methyl-1-propene-*t*. That this ratio was not dependent on the size of the sample used was shown by many injections of the same sample. After the chlorination mixture was freed of excess isobutane-*t* and all the hydrogen chloride, it was injected into the gas chromatograph and the peak heights on both recorders for the pure isobutyl chloride-*t* were measured under the same conditions used to measure those of 1-chloro-2-methyl-1-propene-*t*. Comparison of these ratios of peak

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heights gave the relative specific radioactivities of 1-chloro-2-methyl-1-propene-*t* and isobutyl chloride-*t*.

Photochlorination of 2-Methylpropane-2-*t*.—A known volume of gaseous 2-methylpropane-2-*t* (approximately 0.45 g) measured at a known temperature and pressure was condensed on the vacuum line into 3 ml of previously degassed carbon tetrachloride. A portion (0.25 ml) of the reaction mixture was removed in order to measure the initial specific radioactivity of the isobutane. Enough chlorine in 0.5 ml of carbon tetrachloride was added to the reaction mixture to react with 1.5% of the isobutane and all of the isobutylene and the mixture was again degassed on the vacuum line.

The unopened reaction tube was irradiated at 24° with a 200-w incandescent bulb until the color of chlorine had disappeared (30 min). The reaction tube was returned to the vacuum line where most of the unreacted isobutane and all of the hydrogen chloride were removed. The remaining solution, containing some 2-methylpropane-2-*t* and most of the isobutyl and *t*-butyl chlorides, was used for determination of the specific radioactivity of the isobutyl chloride. The results of three runs are shown in Table I.

Registry No.—2-Methylpropane-2-*t*, 7101-09-9.

Acknowledgment.—We wish to thank Dr. Stuart Scheppele for his interest in this investigation.

A Highly Selective Allylic Bromination in a Bicyclic System

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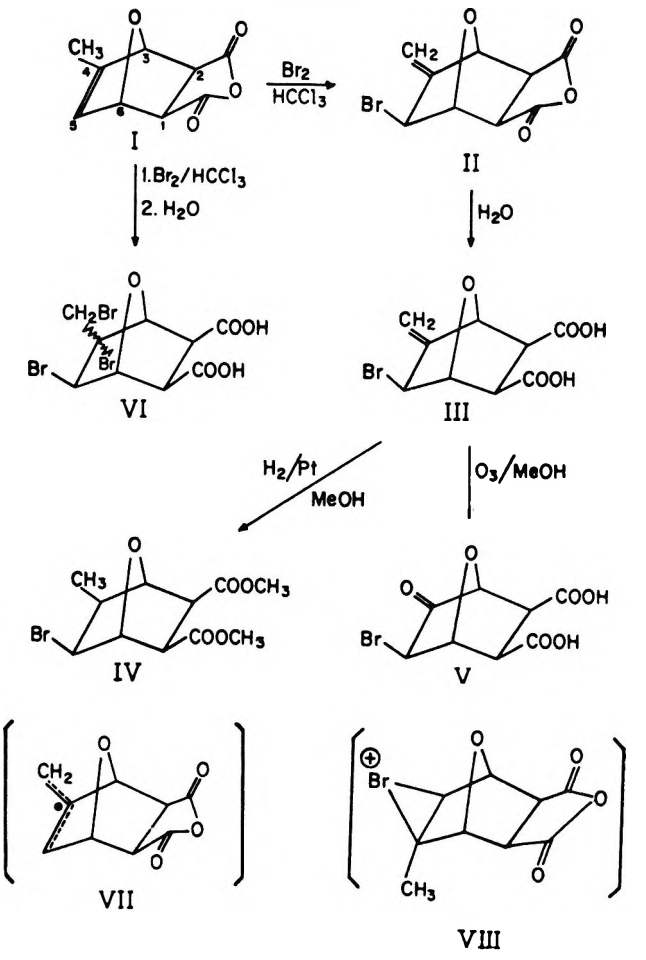
The study of bromination reactions in oxobicyclic analogs of norbornene has attracted our attention lately. The system of our choice has been the *exo-cis*-3,6-endoxo-Δ^4-tetrahydrophthalic anhydride and its methyl derivatives.[2] Bromination of these compounds in inert solvents (CCl_4, $HCCl_3$, H_2CCl_2), under sunlight, leads to *cis*- and *trans*-dibromo compounds when the unmethylated, the 3-methylated, and the 3,6-dimethylated substrates are used. The results of that study will be published elsewhere.

We now wish to report the bromination of the *exo-cis*-3,6-endoxo-4-methyl-Δ^4-tetrahydrophthalic anhydride (I). When I is treated with an equimolecular amount of bromine in $HCCl_3$ solution, only one product is isolated, in very high yield. The main features of this compound are the following: it contains only one bromine atom; its nmr spectrum shows the absence of methyl groups and the disappearance of the 4,5-unsaturation; nmr spectroscopy also indicates that one hydrogen atom has been lost during the reaction. This information allowed the tentative assignment of structure II to the bromination product. Scheme I shows the path selected in order to prove the validity of the assignment made.

The stereochemistry around C-4 was established on the basis of the nmr spectra of compounds IV and V which show the absence of coupling between hydrogens at C-5 and C-6, implying that hydrogen at C-5

SCHEME I



is at the *endo* side of the system.[2,3] The same criterion was used in ascertaining the stereochemical course of the reduction III → IV.

The nmr data for all compounds studied are collected in Table I. Compounds II and III present a complicated spectrum where assignment of bands is difficult due to the great number of couplings between the vinylic hydrogens, which are nonequivalent, and hydrogens at C-3 and C-5. Nevertheless, the main features previously mentioned are clear-cut and unambiguous.

There are two additional relevant points. First, the reaction is catalyzed by addition of a very small amount of water and, second, when it is carried out in the presence of 2 equiv of bromine further bromination occurs and compound VI is formed. If one takes the dimethyl ester of III in $HCCl_3$ solution and treats it with an equivalent amount of bromine, the dimethyl ester of VI is obtained. Unfortunately, the stereochemistry at C-4 in compound VI is not known.

Two possible pathways may be postulated to explain the course of this reaction, namely, a free radical and an ionic-type mechanism. The free radical mechanism, through an allylic intermediate (VII) originated by hydrogen abstraction from the methyl group, is strongly supported by two important facts. First, all efforts to isolate the bromo compound II failed when the reaction was carried out in the dark; in contrast to bromination reactions of similar Diels–

(1) To whom correspondence should be addressed: Escuela de Química, Facultad Ciencias, Universidad Central, Caracas, Venezuela.

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TABLE I
NMR SPECTRAL DATA FOR COMPOUNDS III, IV, V, AND VI

Compound	Protons	Chemical shift, ppm	Integral protons	Multiplicity[a]	Coupling constants, cps
III[b]	C-1,2	2.90	2	bs	
	$=CH_2$	4.86	2	bd	
	C-5	5.08	1	bs	
	C-3,6	5.42	2	bs	
IV[c]	C-1,2	3.05	2	s	
	4-CH_3	1.22	3	d	$J_{CH_3,4} = 7.2$
	C-4	2.18	1	m	$J_{4,5} = 7.2$
					$J_{4,6} = 0.6$
	C-5	4.28	1	d	$J_{4,5} = 7.2$
	C-3	4.52	1	d	$J_{3,6} = 1.5$
	C-6	5.00	1	q	$J_{6,4} = 0.6$
					$J_{3,6} = 1.5$
V[d]	C-1,2	3.35	2	m(AB)	$J_{1,2} = 11.8$
	C-3,6	4.90	2	m(AB)	$J_{3,6} = 1.4$
	C-5	4.47	1	s	
VI[b]	C-1,2	3.36	2	m(AB)	$J_{1,2} = 9.8$
	$-CH_2Br$	4.32	2	s	
	C-3,6	5.20	2	m(AB)	$J_{3,6} = 1.6$
	C-5	4.48	1	s	

[a] bs, broad singlet; bd, broad doublet; s, singlet; d, doublet; q, quartet; m, multiplet. [b] In D_2O–K_2CO_3 solution and TMS as external standard. [c] In $DCCl_3$ solution and TMS as internal standard. [d] In DMSO-d_6 solution and TMS as internal standard.

Alder adducts that follow an ionic pathway[4] and, second, when the reaction was carried out in the presence of a small amount of hydroquinone, it was not possible to detect even traces of the bromination product by the use of nmr spectroscopy.

Once the allylic intermediate VII has been formed, the results indicate that the reaction is completed by attack at the 5 position of the intermediate in a highly selective manner. This selectivity could be rationalized considering the nature of the two products of possible formation from intermediate VII. Attack of bromine at the 5 position gives the product actually isolated experimentally (II) which has only one sp^2 carbon atom in the bicyclic system, whereas attack at the other end of the allylic system would retain the unsaturation between carbon atoms 4 and 5 and, therefore, the product formed would have had two sp^2 carbon atoms in the bicyclic system. Apparently the latter situation is a more energetic one and the course leading to II is preferred. The increase in energy content of the endocyclicly unsaturated structure must be due to internal strain in the bicyclic skeleton. If the preceding considerations are correct, the transition state for this reaction should resemble very closely the final products where the energy differences created by the internal strain factor should be more decisive.

However, the fact that the reaction is water-catalyzed strongly suggests an ionic mechanism which may occur through a bromonium ion intermediate (VIII). The latter, instead of being attacked by a bromide ion in the usual way, simply loses a proton to yield product II. The relief of strain due to the methyl group when going from an sp^3—in the bromonium ion—to an sp^2 hybridization of the product might be the driving force for this reaction. It should be mentioned, however, that in the bromination of the Diels–Alder adduct from maleic anhydride and 2,4-dimethylfurane the formation of the expected dibromo derivatives has been observed[5] in spite of the fact that the above-mentioned compound also has a methyl group in position 4. The observed water catalysis may be visualized, in the case of a free radical mechanism, as a simple mechanical action that facilitates the separation of the product.

Referees of this article have suggested that the ionic pathway is the more feasible, since that mechanism is in agreement with the observed water catalysis. We consider that, with the available information, it is very difficult to dismiss in a definite manner either of the two possible mechanisms proposed.

Experimental Section

***exo-cis*-3,6-Endoxo-4-methyl-Δ^4-tetrahydrophthalic anhydride** (I) was prepared from 3-methylfuran[6] and maleic anhydride following the procedure described by Rinkes.[7]

***exo-cis*-3,6-Endoxo-4-methylene-5-*exo*-bromotetrahydrophthalic Acid** (III).—To a solution of I (5.7 g, 0.031 mole) in $HCCl_3$ (150 ml) bromine (1.8 ml, 0.035 mole) was added with vigorous stirring in an ice bath. Small pieces of ice were added to the reaction mixture. After a few minutes the solution became clear and a white solid precipitated. Recrystallization from water afforded 8 g (9[illegible]%) of III, mp 182–186°.[8]

Anal. Calcd for $C_9H_9O_5Br$: C, 39.01; H, 3.27; Br, 28.87. Found: C, 38.75; H, 3.35; Br, 28.65.

Dimethyl *exo-cis*-3,6-Endoxo-4-*exo*-methyl-5-*exo*-bromotetrahydrophthalate (IV).—A solution of III (3 g, 0.011 mole) in methanol (70 ml) to which 5% Pt/C catalyst (0.15 g) had been added was left overnight under a hydrogen pressure of 45 psi. Filtration of the reaction mixture and evaporation of the solvent afforded 0.9 g (27%) of IV, mp 151–154° (water–acetone).

Anal. Calcd for $C_{11}H_{15}O_5Br$: C, 43.01; H, 4.92; Br, 26.02. Found: C, 43.23; H, 5.08; Br, 26.12.

***exo-cis*-3,6-Endoxo-4-one-5-*exo*-bromotetrahydrophthalic Acid** (V).—Ozonolysis of 2.5 g (0.009 mole) of III dissolved in 200 ml of methanol afforded 0.6 g (24%) of V, mp 173–175° (acetone). The 2,4-dinitrophenylhydrazone of the dimethyl ester of V was prepared, mp 253–256° dec.

***exo-cis*-3,6-Endoxo-4-bromo-4-bromoethyl-5-*exo*-bromotetrahydrophthalic Acid** (VI).—To a solution of I (5.7 g, 0.031 mole) in $HCCl_3$ (70 ml) placed in an ice bath, bromine (3.5 ml, 0.070 mole) was added with vigorous stirring. The white precipitate formed was crystallized from water to yield 12 g (88%) of VI, mp 241° dec.

Anal. Calcd for $C_9H_9Br_3O_5$: C, 24.74; H, 2.07; Br, 54.87. Found: C, 24.38; H, 2.05; Br, 55.01.

Dimethyl *exo-cis*-3,6-Endoxo-4-methylene-5-*exo*-bromotetrahydrophthalate (IX).—A suspension of 8.6 g (0.031 mole) of II in 150 ml of ether was sterified with an excess of diazomethane in ether. The white needles formed were crystallized from 1:1 water–acetone mixture to yield 8.6 g (90%) of IX, mp 113–114°.

Anal. Calcd for $C_{11}H_{13}BrO_5$: C, 43.30; H, 4.29; Br, 26.19. Found: C, 43.51; H, 4.47; Br, 26.31.

Dimethyl *exo-cis*-3,6-Endoxo-4-bromo-4-bromomethyl-5-*exo*-bromotetrahydrophthalate (X).—To a solution of IX (1.5 g, 0.0049 mole) in chloroform (20 ml) placed in an ice bath, bromine (0.5 ml, 0.01 mole) was added. After completion of the reaction and removal of the solvent, the remaining solid was crystallized from a 1:1 water–acetone mixture to yield 2.1 g (93%) of X, mp 151–154°.

Anal. Calcd for $C_{11}H_{13}Br_3O_5$: C, 28.41; H, 2.82; Br, 51.56. Found: C, 28.49; H, 2.98; Br, 51.71.

Nmr spectra were run at approximately 34° on a Varian A-60 spectrometer unless otherwise stated. The information obtained is collected in Table I.

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(5) E. Payo, *et al.*, unpublished results.

(6) D. M. Burnes, "Organic Synthesis," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 628.

(7) I. Rinkes, *Rec. Trav. Chim. Pays-Bas*, **50**, 1127 (1931).

(8) All melting points are uncorrected. The microanalyses were performed by Franz Pascher, Mikroanalytisches Laboratorium, Bonn, Germany.

Registry No.—III, 15292-78-1; IV, 15292-79-2; V, 15292-80-5; 2,4-DNPH of Me ester of V, 15292-81-6; VI, 15292-84-9; IX, 15292-82-7; X, 15292-83-8.

Acknowledgments.—We wish to thank the referees for their helpful suggestions and comments.

The Solvolysis of 1-Chlorobicyclo[3.3.1]nonane[1]

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Ever since the pioneering work on reactions of bridgehead substituted bicyclic systems by Bartlett and Knox in 1939,[3] many studies of a wide variety of bicyclic compounds have provided valuable information about mechanisms and transition-state geometries of nucleophilic substitution reactions.[4] Recently, Gleicher and Schleyer[5] reported a correlation of experimental rate constants with the calculated energy difference between the hydrocarbon and the respective carbonium ion for five compounds. In addition, they used the correlation to predict the solvolytic rate constants of three bridgehead substituted compounds for which rate data had not been reported. One of these compounds was 1-bromobicyclo[3.3.1]nonane, whose predicted rate was approximately half the rate predicted for *t*-butyl bromide; the predicted rate of the latter compound was one-fifth the known experimental rate. We should like to report our results on the related 1-chlorobicyclo[3.3.1]nonane.

Recent work in this laboratory, related to the solvolysis of bicyclo[3.3.0]octane-1-carbinyl tosylate,[6] provided a convenient synthesis of bicyclo[3.3.1]nonan-1-ol. The methyl ester of 1-carboxybicyclo[3.3.0]octane[7] was converted into 1-hydroxymethylbicyclo[3.3.0]octane,[6] mp 41–42°, with lithium aluminum hydride. The toluenesulfonate ester,[6] mp 22–23°, was prepared in 91% yield from the bicyclic carbinol and tosyl chloride in pyridine at 0°. Hydrolysis of bicyclo[3.3.0]octane-1-carbinyl *p*-toluenesulfonate in 60% aqueous acetone gave bicyclo[3.3.1]nonan-1-ol[6] (88%), mp 182.5–184°. The alcohol was easily converted in 84% yield into 1-chlorobicyclo[3.3.1]nonane, mp 87–88.5°, with thionyl chloride. Solvolytic studies were carried out in 60% aqueous ethanol, following a procedure similar to that of Winstein and Fainberg.[8] Rate constants were calculated by the method of nonlinear least squares[9] and are presented in Table I. Activation parameters were determined by a least-square analysis:[9] $\Delta H^{\ddagger}_{25^\circ} = 22.8 \pm 0.4$ kcal/mol and $\Delta S^{\ddagger}_{25^\circ} = -8.2 \pm 1.0$ eu. Preparative scale solvolysis at 55° in 60% aqueous ethanol gave bicyclo[3.3.1]nonan-1-ol (90%) and 1-ethoxybicyclo[3.3.1]nonane (10%). The infrared spectrum of the alcohol was identical with that of an authentic sample and the ether was prepared from bicyclo[3.3.1]nonan-1-ol by a modified Williamson synthesis.

TABLE I
FIRST-ORDER RATE CONSTANTS[a] IN 60% AQUEOUS ETHANOL

Substrate[b]	Temp,[c] °C	$k_1 \times 10^5$,[d] sec^{-1}
t-Butyl chloride	25.0	12.1[e]
1-Chlorobicyclo[3.3.1]nonane	25.0	0.202 (calcd)
	44.9	2.34
	55.0	7.67
	65.0	21.2

[a] Determined from two runs at each temperature. [b] $0.0008\ M \leq$ [substrate] $\leq 0.0011\ M$. [c] ±0.1. [d] ±3%. [e] Previously reported as $12.3 \pm 0.10 \times 10^{-5}$ sec^{-1}.[8]

The experimental solvolytic rate of 1-chlorobicyclo[3.3.1]nonane is 1/60 that of *t*-butyl chloride. The relative rates of a large number of tertiary alicyclic and bridged substrates with different halide leaving groups have been studied[10,11] and no large variations in the halide rate ratios were reported. Also, a large body of evidence exists which suggests that solvent variations have little effect on the relative reactivities of alicyclic tertiary halides to bridgehead halides.[4c] Thus, the difference in rates between *t*-butyl chloride and 1-chlorobicyclo[3.3.1]nonane should be a good approximation for the corresponding bromides. Consequently, the estimated rate of 1-bromobicyclo[3.3.1]nonane at 25° in 80% aqueous ethanol is 5.6×10^{-6} sec^{-1},[12] a rate which is seven times slower than predicted by Gleicher and Schleyer.[5]

A comparison of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the solvolysis of the 1-chlorobicyclo[3.3.1]nonane with the values reported for *t*-butyl chloride[13] indicates that in the former compound both terms make significant contributions to the decreased rate at 25°. The small difference in the free energies of activation (2.4 kcal/mol, 25°) of these two compounds may be anticipated in view of the conformation of the bicyclic system. The infrared spectrum of 1-chlorobicyclo[3.3.1]nonane had four sharp bands at 1484, 1464, 1449, and 1441 cm^{-1}, which were characteristic of the substituted bicyclo[3.3.1]nonanes encountered in this study. The band at 1490 cm^{-1} in the infrared spectrum of bicyclo[3.3.1]nonane has been assigned[14] as a scissoring methylene vibration ($\delta(CH_2)$) which

(1) (a) This work was supported in part by Grant GP-3890, National Science Foundation. (b) After completion of this work, Professor P. von R. Schleyer kindly informed us of his study using the 1-bromo derivative; these two studies are being published simultaneously.

(2) National Institutes of Health Predoctoral Fellow, 1966–1967.

(3) P. D. Bartlett and L. H. Knox, *J. Amer. Chem. Soc.*, **61**, 3184 (1939).

(4) For excellent reviews, see (a) D. E. Applequist and J. D. Roberts, *Chem. Rev.*, **54**, 1065 (1954); (b) U. Schollkopf, *Angew. Chem.*, **72**, 147 (1960); (c) R. C. Fort, Jr., and P. von R. Schleyer, *Advan. Alicyclic Chem.*, **1**, 283 (1966).

(5) G. J. Gleicher and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967).

(6) R. A. Flath, Thesis, University of California at Berkeley, Berkeley, Calif., 1964.

(7) A. C. Cope and E. S. Graham, *J. Amer. Chem. Soc.*, **73**, 4702 (1951).

(8) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).

(9) We are indebted to Professor A. Streitwieser for providing copies of LSKIN1 and ACTENG computer programs, both of which were developed by Professor D. F. DeTar, Florida State University.

(10) A. Streitwieser, *Chem. Rev.*, **56**, 571 (1956).

(11) P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 2700 (1961).

(12) A value of 3.38×10^{-4} sec^{-1} was used for the rate of *t*-butyl bromide in 80% aqueous ethanol at 25°.[10]

(13) For *t*-butyl chloride in 60% aqueous ethanol, $\Delta H^{\ddagger} = 21.7$ kcal/mol and $\Delta S^{\ddagger} = -3.7$ eu [S. Winstein and A. H. Fainberg, *ibid.*, **79**, 5937 (1957)].

(14) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965).

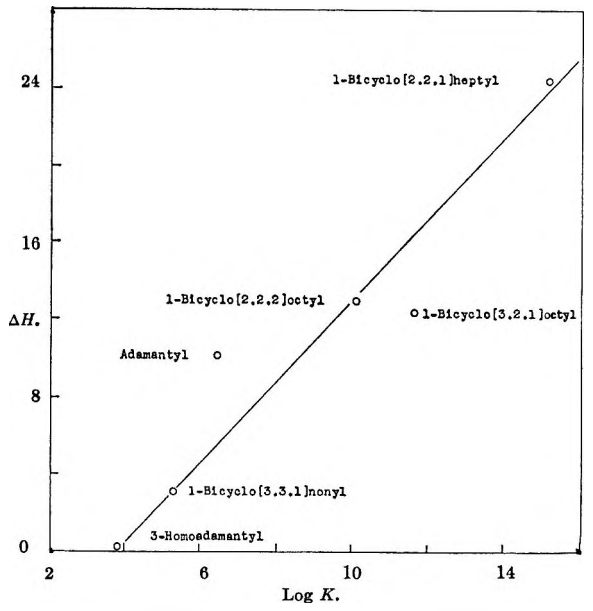

Figure 1.—Plot of the calculated hydrocarbon–carbonium ion strain differences (ΔH) against $-\log$ rate constants at 25°.

had been shifted to shorter wavelength because of steric interaction between C_3 and C_7 methylene groups in the chair–chair conformation. This shift is observed in both solid- and liquid-phase spectra. X-ray studies of substituted bicyclo[3.3.1]nonanes[15,16] indicate that interactions between C_3 and C_7 methylene groups cause considerable "flattening" of the cyclohexane rings and distortion of the bond angles. In such a conformation, a developing bridgehead sp^2 center does not appear to introduce much additional strain into the bicyclic system.

Gleicher and Schleyer[5] noticed an excellent linear correlation for 1-bromohomoadamantane, 1-bromobicyclo[2.2.2]octane, and 1-bromobicyclo[2.2.1]heptane and discussed, in detail, possibilities for the "anomalous" behavior of *t*-butyl bromide and 1-bromoadamantane; however, all five experimental rates were used for predictive purposes because of the limited rate data which were available. The rate predicted for 1-bromobicyclo[3.3.1]nonane by this method is in good agreement with our results. If the two "anomalous" points are excluded, the predicted rate calculated from eq 1, which represents the best

$$-\log k = 0.472\Delta H_{\text{strain}} + 3.78 \quad (1)$$

straight line through the three original points as determined by least-squares analysis, is 5.6×10^{-6} sec^{-1}, identical with the experimental rate. From a recent report by Bly and Quinn,[17] the extrapolated acetolysis rate of bridgehead substituted bicyclo[3.2.1]octyl *p*-bromobenzenesulfonate at 25° is 33 times slower than the corresponding [2.2.2] isomer, which represents a significant deviation from the predicted value, as shown in Figure 1. The validity of this comparison is somewhat mitigated by the series of long extrapolations necessary for a comparison of rates. The omission of the "anomalous" rate data might be open to question in view of the approximations which accompanied the strain calculations. It is evident, however, that the correlation of estimated strain energy differences with experimental rate constants is remarkable when factors which are not included in the calculations (*i.e.*, inductive effects, entropy of activation, etc.) are minimized by considering a family of similar compounds.

(15) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).

(16) M. Dobler and J. D. Dunitz, *Helv. Chem. Acta*, **47**, 695 (1964).

(17) R. S. Bly and E. K. Quinn, Abstracts of the 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, p 91O.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer as a 10% solution in carbon tetrachloride and nmr spectra were recorded on a Varian A-60 spectrometer as a 10% solution in carbon tetrachloride using tetramethylsilane as an internal standard.

Bicyclo[3.3.1]nonan-1-ol.—A solution of 3.741 g (0.013 mol) of bicylo[3.3.0]octane-1-carbinyl tosylate and 2.0 g of calcium carbonate in 100 ml of 60% aqueous acetone was heated at 75° for 93 hr. The mixture was diluted with water and extracted with four portions of diethyl ether. The ether solution was washed with saturated sodium chloride solution and dried. The solvent was removed at reduced pressure and the remaining material sublimed at 85° (3 mm) to yield 1.607 g (88.4%) of a white solid: mp 182.5–184.0°; $\nu_{max}^{CCl_4}$ 3559, 3322, 2890, 2825 (sh), 1486, 1464, 1435, 1085, 1001, 932 cm^{-1}; nmr (δ, ppm) 1.6 and 2.1 (15 H, multiplets), 3.6 (1 H, broad singlet, hydroxyl group).

1-Chlorobicyclo[3.3.1]nonane.—A solution of 0.999 g (7.15 mmol) of bicyclo[3.3.1]nonan-1-ol in 5 ml of thionyl chloride was heated at 34° for 14 hr. The solution was diluted with 150 ml of ice–water and extracted with four portions of pentane. The pentane solution was washed with two portions of saturated sodium bicarbonate solution and one portion of saturated sodium chloride solution. After drying, the pentane was removed at reduced pressure and the residue sublimed at 85° (20 mm) to give 0.948 g (84%) of a white solid: mp 87.0–88.5°; $\nu_{max}^{CCl_4}$ 2924, 1484, 1464, 1449, 1441, 1048, 963 cm^{-1}; nmr (δ, ppm) 1.8 and 2.2 (multiplets).

Anal. Calcd for $C_9H_{15}Cl$ (158.69): C, 68.11; H, 9.55; Cl, 22.34. Found: C, 67.92; H, 9.35; Cl, 22.48.

Ethanolysis of 1-Chlorobicyclo[3.3.1]nonane.—Mixed ethanol–water solvent which consisted of 60% ethanol by volume was prepared from freshly distilled water and anhydrous ethanol.

A 100-ml volumetric flask which contained 1-chlorobicyclo-[3.3.1]nonane (between 0.8×10^{-4} and 1.1×10^{-4} mol) and solvent was allowed to equilibrate. The reaction was followed through four half-lives by removing aliquots with a pipet and titrating liberated acid with 4.9×10^{-4} *N* potassium hydroxide in 90% aqueous ethanol, using half-neutralized brom phenol blue as an indicator.[8]

In a preparative ethanolysis, a solution of 21.5 mg (0.136 mmol) of 1-chlorobicyclo[3.3.1 nonane in 4 ml of 60% aqueous ethanol was heated at 55° for 37 hr in a sealed tube. The solution was diluted with water and extracted with four portions of pentane. The pentane solution was washed with two portions of water and dried. Solvent was removed at reduced pressure to give 20 mg of a colorless semisolid, which consisted of bicyclo[3.3.1]nonan-1-ol (90%) and 1-ethoxybicyclo[3.3.1]-nonane (10%).

1-Ethoxybicyclo[3.3.1]nonane.—A solution of 61 mg (0.44 mmol) of bicyclo[3.3.1]nonan-1-ol in 6 ml of anhydrous benzene was injected into a flask, under nitrogen, which contained 27 mg (1.13 mmol) of sodium hydride (obtained as a mineral oil dispersion from Metal Hydrides, Inc.). The suspension was heated at reflux for 1 hr and 0.624 g (4.00 mmol) of ethyl iodide was added. Heating was continued for 21 hr before the mixture was diluted with water and extracted with three portions of pentane. The pentane solution was washed with saturated sodium chloride solution and dried. Removal of solvent at reduced pressure gave 58 mg of a semisolid residue which consisted of bicyclo[3.3.1]nonan-1-ol (69%) and 1-ethoxybicyclo[3.3.1]nonane (31%). The components were separated by preparative vpc (10 ft × 0.25 in. 10% Carbowax 6000 10% KOH, 150°); the ether was a colorless liquid: $\nu_{max}^{CCl_4}$ 2924, 1488, 1471, 1453, 1439, 1115, 1093 cm^{-1}; nmr (δ, ppm) 1.05 (3 H, triplet, methyl group, J = 7 cps), 1.65 (13 H, multiplet),

2.1 (2 H, multiplet), 3.36 (2 H, quartet, ethoxymethylene group, J = 7 cps).

Anal. Calcd for $C_{11}H_{20}O$ (168.27): C, 78.51; H, 11.98. Found: C, 78.75; H, 12.00.

Registry No.—1-Chlorobicyclo[3.3.1]nonane, 15158-55-1; bicyclo[3.3.1]nonan-1-ol, 15158-56-2; 1-ethoxybicyclo[3.3.1]nonane, 15158-57-3.

Bridgehead Reactivity in Bicyclo[3.3.1]nonane Systems

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Received July 17, 1967

Bridgehead substituted derivatives provide excellent substrates for the study of the relationship between structure and reactivity.[2] Variations in reactivity are extreme; more than twelve powers of ten separate the solvolysis rates of 1-bicyclo[2.2.1]heptyl (I) and 3-homoadamantyl bromides (II).[2] While qualitative rationalizations for such large differences can easily be given,[2] it was only recently that an attempt to achieve quantitative understanding has been made.[3]

By using an approach based on computer conformational analysis, Gleicher and Schleyer examined four bridgehead bromides: I, II, the 1-adamantyl (III), and the 1-bicyclo[2.2.2]octyl (IV). The calculated increases in strain in going from ground states (models, the parent hydrocarbons) to transition states (models, the carbonium ions) when plotted against $-\log$ of the relative solvolysis rates gave a satisfactory correlation; the average deviation was $10^{\pm 0.8}$. This result seemed encouraging in view of the many assumptions which were required.[3]

Calculations were made on three additional bridgehead systems. For one compound, 1-bicyclo[3.2.1]-octyl bromide (V), some solvolysis data was already available in the literature[2] and an additional investigation has since been reported.[4] A second system, the 1-bicyclo[3.3.1]nonyl, was unknown in the literature and the rate calculated[3] for the bromide was thus a true prediction. This note deals with the preparation of 1-bicyclo[3.3.1]nonyl bromide (VI), the determination of its solvolysis rate constants, and an interpretation of the results.[5]

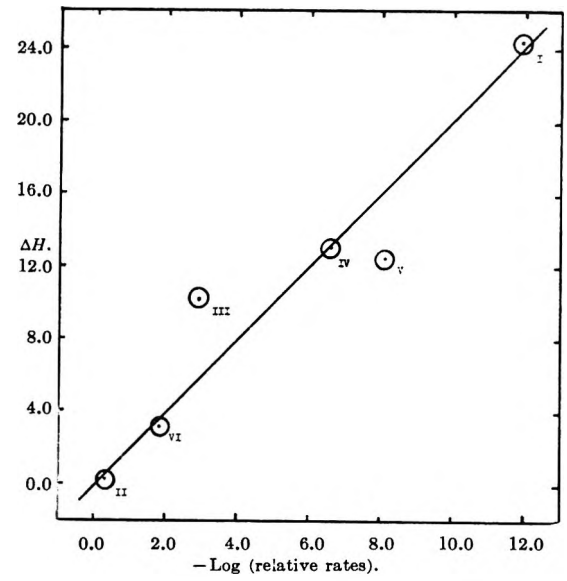
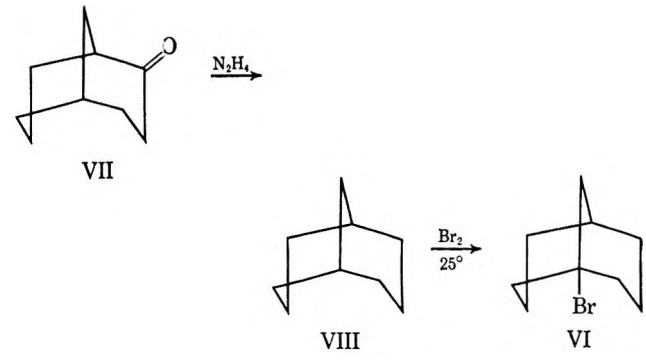


Figure 1.—Plot of the calculated hydrocarbon–carbonium ion strain differences (ΔH) plotted against $-\log$ of the experimental relative solvolysis rate constants.[2]

Bicyclo[3.3.1]nonan-2-one (VII)[6] was reduced by the modified Wolff–Kishner method[7] to give the parent hydrocarbon, VIII.[8] Bicyclo[3.3.1]nonane (VIII)



could be brominated at the bridgehead position by stirring the hydrocarbon and bromine together at room temperature for 1 day. This observation provided the first indication of the relative reactivity of the bicyclo[3.3.1]nonane and adamantane systems, for adamantane is inert under these conditions and can only be brominated with elemental bromine at the reflux temperature.[9] These brominations presumably are ionic reactions.[9] 1-Bicyclo[3.3.1]nonyl bromide (VI), mp 52–53°, had an nmr spectrum somewhat reminiscent of that of 1-adamantyl bromide (IV).[10] No C*H*Br resonance characteristic of primary or secondary bromides was present, but rather two main absorptions centered at about δ 1.75 and 2.35 with some fine structure in the latter absorption (VIII, like adamantane,[10] had essentially but one absorption position for the various kinds of protons, at δ 1.70). Hydrogenation of VI in the presence of Raney nickel[11] regenerated the parent hydrocarbon in 62% yield,

(1) Taken, in part, from the A.B. Thesis of P. R. I., Princeton University, 1967.

(2) R. C. Fort, Jr., and P. von R. Schleyer, *Advan. Alicyclic Chem.*, 1, 283 (1966).

(3) G. J. Gleicher and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 89, 582 (1967).

(4) R. S. Bly and E. K. Quinn, 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, Abstracts, 91-0; and personal communication from Professor Bly. The extrapolated acetolysis rate of V-OBs at 25° is 33 times slower than IV-OBs.

(5) During the course of this work, we were informed of the completion of a similar study on 1-bicyclo[3.3.1]nonyl chloride [W. G. Dauben and C. D. Poulter, *J. Org. Chem.*, 33, 1237 (1968)]. The results of the two investigations are in excellent agreement. We would like to thank Professor Dauben for the information and for his courtesy in agreeing to simultaneous publication of our results.

(6) M. Hartmann, *Z. Chem.*, 6, 182 (1966).

(7) Huang-Minlon, *J. Amer. Chem. Soc.*, 68, 2487 (1946).

(8) *Cf.*, A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *ibid.*, 87, 3130 (1965), and references therein cited.

(9) For a review, see R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Rev.*, 64, 277 (1964).

(10) R. C. Fort, Jr., and P. von R. Schleyer, *J. Org. Chem.*, 30, 789 (1965).

(11) A procedure similar to that used by H. Stetter and P. Goebel, *Ber.*, 96, 550 (1963), for the reduction of 3-homoadamantyl bromide was used.

thereby demonstrating the absence of skeletal rearrangement. Preparative hydrolysis of VI in boiling 60% aqueous acetone for 0.5 hr gave an 84% yield of 1-bicyclo[3.3.1]nonanol, mp 180–182° (lit. mp 182.5–184°).[5] In 80% ethanol a mixture of this alcohol (60%) and, presumably, the corresponding ethyl ether (40%) was obtained.[5]

The rate constants for solvolysis of 1-bromobicyclo[3.3.1]nonane (VI) in 80% ethanol follow: at 24.1°, $(3.04 \pm 0.04) \times 10^{-6}$ sec^{-1}; at 50.1°, $(9.26 \pm 0.08) \times 10^{-5}$ sec^{-1}; at 74.9°, $(1.31 \pm 0.01) \times 10^{-3}$ sec^{-1}. These data gave $\Delta H^{\ddagger} = 23.9$ kcal/mol, $\Delta S^{\ddagger} = -3.2$ eu, and a calculated rate constant at 25° of 3.53×10^{-6} sec^{-1}. From data on the solvolysis of 1-chlorobicyclo[3.3.1]nonyl chloride in 60% ethanol, Dauben and Poulter[5] estimated this rate constant to be 6×10^{-6} sec^{-1}, a value in good agreement with our findings.

Gleicher and Schleyer predicted the rate constant of VI in 80% ethanol at 25° to be one-eighth that of *t*-butyl bromide, or 4.30×10^{-5} sec^{-1}. This predicted value is 12.2 times larger than the value we have found experimentally by interpolation and seven times larger than Dauben and Poulter's less directly estimated value. This agreement certainly is creditable.

When a plot of the calculated strain differences *vs.* the experimental rate data (Figure 1) is examined, the situation appears even better. Included in this plot are all the data for the bridgehead systems previously examined (I–IV),[3,12] the new datum for VI, as well as a point estimated for V.[4] Four points, those for compounds I, II, IV, and VI, lie very close to the correlation line; the point for V deviated by about $10^{1.9}$ and that for 1-adamantyl bromide (III) by $10^{2.2}$.[13] The average deviation of all six points is only $10^{\pm 0.78}$. This approach to the quantitative prediction of reaction rates, despite its rather crude assumptions, seems to have promise. We plan to test it further in a number of systems.

Experimental Section

Bicyclo[3.3.1]nonane (VIII).—A solution of bicyclo[3.3.1]nonan-2-one[6] (14 g), 85% hydrazine hydrate (55 ml), and potassium hydroxide (15 g) was heated at reflux in 350 ml of diethylene glycol.[8] The water formed and the excess hydrazine were removed by means of a Dean–Stark trap, enabling the reflux temperature to rise to about 180°. Crystals, which consisted of starting material and product, sublimed onto the condenser and were recycled until no further carbonyl absorption was detected in the infrared. Final sublimation of the product gave 7.4 g (54%) of the parent hydrocarbon: mp 143–146° (lit.[14] mp 145–146°); nmr (CCl_4), broad singlet at 1.75 ppm with a small shoulder at 1.55 ppm; $\nu_{max}^{CCl_4}$ 2975, 2900, 2845, 1450 cm^{-1}.

1-Bicyclo[3.3.1]nonyl Bromide (VI).—A solution of 1 g of bicyclo[3.3.1]nonane in 2 ml of neat bromine was stirred at room temperature for 20 hr. At the end of this period the mixture was dissolved in 20 ml of CCl_4, poured into 100 ml of H_2O, and the excess bromine destroyed with sodium thiosulfate solution. The organic layer was separated, dried over $MgSO_4$, and the solvent was evaporated. Upon standing in the refrigerator, the residual yellow oil solidified. Sublimation and recrystallization from pentane gave a white crystalline product: 52% yield, mp 52–53°; nmr ($CDCl_3$), two main absorptions centered at 1.75 and 2.35 ppm; $\nu_{max}^{CCl_4}$ 2975, 2920, 2850, 1450, 1340, 1300, 1045, 950, 650 cm^{-1}.

The elemental analysis of this compound, even after purification by gas chromatography and by other means, was not satisfactory, the bromine being consistently high.

Anal. Calcd for $C_9H_{15}Br$: C, 53.20; H, 7.39; Br, 39.41. Found: C, 52.57; H, 7.25; Br, 40.17.

Hydrogenolysis of VI.—A solution of 500 mg of 1-bicyclo[3.3.1]nonyl bromide in 10 ml of methanol containing 0.2 g of NaOH and 1 g of Raney nickel catalyst was hydrogenated at 50 psi for 2 hr. The catalyst was then filtered and the reaction mixture was diluted with 50 ml of H_2O. The solid product was extracted with ether, dried, and the solvent was removed under vacuum, leaving 180 mg (62.2%) of a white solid whose physical and spectroscopic properties were identical in every respect with bicyclo[3.3.1]nonane.

1-Bicyclo[3.3.1]nonanol.—A solution of 105 mg of 1-bicyclo[3.3.1]nonyl bromide in 50 ml of a 60:40 acetone–water mixture was refluxed (85°) for 0.5 hr. After cooling, the reaction mixture was extracted with petroleum ether (bp 30–60°), the extracts were dried, and the solvent was removed under vacuum leaving 60 mg (84%) of white needle-shaped crystals. Two recrystallizations from petroleum ether (bp 30–60°) gave a mp of 180–182° (lit.[5] mp 182.5–184°); $\nu_{max}^{CCl_4}$ 3600, 3350, 2985, 2905, 2850, 1485, 1470, 1450, 1090, 1000, 930, 870 cm^{-1}; nmr (δ, ppm) 1.6 and 2.1 multiplets in a ratio of 15:1 with the hydroxyl proton presumably coming beneath the main absorption.

Kinetic and Product Studies.—The kinetics were measured in the usual manner[15] in 80% aqueous ethanol.

The ethanolic solution of solvolyzed alkyl bromide was refluxed for 1 hr with 1 g of Na_2CO_3. An equivalent amount of water was added and this solution was extracted with petroleum ether (bp 30–60°) and dried over $MgSO_4$. The solvent was evaporated and the residue sublimed. Gas chromatographic analysis showed three peaks: a minor component of about 3% (not identified); a second component of about 40% (presumably the ethoxide); and the major product (60%) positively identified as the 1-bicyclo[3.3.1]nonanol by comparison of its vpc retention time and nmr with that of an authentic sample.

Registry No.—VI, 15292-76-9; VIII, 280-65-9; 1-bicyclo[3.3.1]nonanol, 15158-56-2.

Acknowledgments.—This research was supported by the National Science Foundation, the National Institutes of Health, and the Petroleum Research Fund, administered by the American Chemical Society.

(12) On a variety of grounds, discussed in the original paper,[3] the point for *t*-butyl has been omitted from Figure 1.

(13) Our continuing efforts to improve these calculations have yielded favorable results and an average deviation of $10^{\pm 0.37}$ has been achieved with the point deviating most (III) off the correlation line by $10^{1.1}$ (J. Williams and R. Bingham, unpublished observations).

(14) A. C. Cope and M. E. Synerhold, *J. Amer. Chem. Soc.*, **72**, 5228 (1950).

(15) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **77**, 3619 (1955).

A Photochemical Cycloaddition of Thiobenzophenone to Conjugated Dienes

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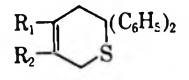
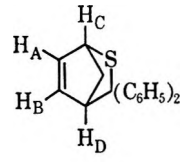
Although the photochemical cycloaddition to form a four-membered ring system[1] and the photochemical Diels–Alder addition of olefins to 1,2-dicarbonyl

(1) H. Kataoka, K. Yamada, and N. Sugiyama, *Bull. Chem. Soc. Japan*, **38**, 2027 (1965); N. Sugiyama, K. Yamada, Y. Watari, and T. Koyama, *Nippon Kagaku Zasshi*, **87**, 737 (1965).

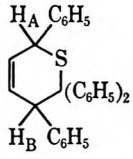
compounds[2] are well-known, few reports on the photochemical Diels–Alder addition of dienes have been found in the literature; *e.g.*, 1,4 addition of maleic



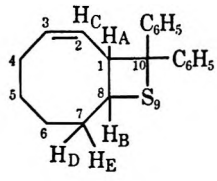
I, $R_1 = H, R_2 = CH_3$
II, $R_1 = CH_3, R_2 = H$



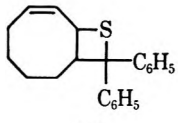
III



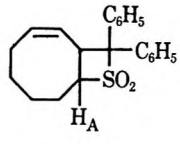
IV



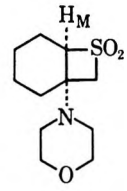
V



VI



VII



VIII

anhydride to anthracene,[3] that of maleic anhydride or dimethyl maleic anhydride to conjugated dienes,[4] that of oxygen to dienes,[5] and that of benzoquinone to 2,3-dimethylbutadiene[6] have been reported. Thus, maleic anhydride, dimethyl maleic anhydride, oxygen, and benzoquinone can be added to conjugated dienes to form a six-membered ring system. We have recently found that thiobenzophenone can be added to α-phellandrene to afford 1,2 and 1,4 adducts by ultraviolet irradiation.[7] This was the first example of the photochemical cycloaddition of thiocarbonyl compounds to conjugated dienes, though the photochemical cycloaddition of thiobenzophenone to some monoenes to afford 2:1 adducts has been recently reported by Tsuchihashi and coworkers.[8] In the present paper we report the results of the application of this new reaction to isoprene, cyclopentadiene, 1,4-diphenylbutadiene, and 1,3-cyclooctadiene.

When a mixture of thiobenzophenone and an excess of conjugated diene was irradiated with Pyrex filtered ultraviolet light, gradual fading of the ultraviolet absorption maximum of thiobenzophenone at 314 mμ, accompanied by the disappearance of the blue color, was observed. At −78°, thiobenzophenone reacted with isoprene or cyclopentadiene by ultraviolet irradiation, but did not react in the dark. However, at room temperature, thiobenzophenone reacted with isoprene or cyclopentadiene, both under irradiation and in the dark. On the other hand, even at room temperature, thiobenzophenone did not react with 1,4-diphenylbutadiene or 1,3-cyclooctadiene. The photoproducts were separated by chromatography. All products were proved to be 1:1 adducts of thiobenzophenone to diene by elemental analyses. It was shown by thin layer chromatography with two solvent systems (*n*-hexane–benzene 5:1 v/v; CS_2) and the mixture melting point that the photoproducts (1,4 adducts) isolated from the reaction (at −78°) mixture of thiobenzophenone and isoprene or cyclopentadiene were the same as the photoproducts isolated from the reaction (at room temperature) mixture. Furthermore, by the kinetic studies of the reactions which were carried out at −78° and at room temperature, it was found that they were both first-order reactions.[9] These facts indicated that the possibility of initia l1,2 adducts rearranging 1,4 adducts was eliminated.

Photochemical Adduct of Thiobenzophenone to Isoprene (I and II).—The nmr spectrum is given in Table I. The peaks between τ 2.50 and 3.05 cor-

TABLE I
NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA OF THE ADDUCTS

Compd	Chemical shift (τ)	Multiplicity[a]	Proton assignment		Coupling constants, cps
	2.50–3.05	m	10 H	Phenyl	
I and II	4.45	m	1 H	Vinyl	
in CCl_4	7.20	m	4 H	Methylene	
	8.20	s	1.2 H	Methyl	
	8.32	s	1.8 H		
	2.60–3.10	m	10 H	Phenyl	
III	3.73	dd	1 H	H_A or H_B	
in CS_2	4.57	dd	1 H	H_A or H_B	
	6.00	m	2 H	H_C and H_D	
	8.05	m	2 H	Methylene	$J_{AB} = 5.2$, $J_{AC} = J_{BD} = 2.5$
	2.30–3.55	m	20 H	Phenyl	
IV	3.96	m	2 H	Vinyl	
in CS_2	5.85	m	1 H	H_A	
	6.25	m	1 H	H_B	
	2.35–3.20	m	10 H	Phenyl	
V	4.65	m	2 H	Vinyl	
in CS_2	5.46	dd	1 H	H_A	
	6.70	se	1 H	H_B	
	7.50–9.20	m	8 H	Methylene	$J_{AB} = 3.3$, $J_{AC} = J_{BD} = J_{BE} = 10.0$
	2.50–3.10	m	10 H	Phenyl	
VII	4.45	m	2 H	Vinyl	
in CS_2	5.85	m	2 H	Methyne	
	7.40–8.70	m	8 H	Methylene	

[a] Abbreviations used are as follows: m = multiplet; s = singlet; dd = doublet of doublets; se = sextet.

respond to ten aromatic protons, and a multiplet centered at τ 4.45 corresponds to one vinyl proton. The presence of only one vinyl proton indicates that the photoproduct is not the 1,2 adduct but the 1,4 adduct. If it were the 1,2 adduct, it would show two or three vinyl protons. The two possible 1,4 adducts

(2) C. R. Masson, V. Bockelheide, and W. A. Noyes, Jr., in "Technique of Organic Chemistry," Vol. II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p 257.
(3) J. P. Simons, *Trans. Faraday Soc.*, **56**, 391 (1960).
(4) G. O. Schenck, J. Kuhls, and C. H. Krauch, *Ann.*, **693**, 20 (1966).
(5) G. O. Schenck and K. Ziegler, *Naturwiss.*, **32**, 157 (1944).
(6) J. A. Barltrop and B. Hesp, *Proc. Chem. Soc.*, 195 (1964); *J. Chem. Soc.*, 5182 (1965).
(7) Y. Omote, M. Yoshioka, K. Yamada, and N. Sugiyama, *J. Org. Chem.*, **32**, 3676 (1967).
(8) G. Tsuchihashi, M. Yamauchi, and M. Fukuyama, *Tetrahedron Lett.*, 1971 (1967).
(9) M. Yoshioka, H. Kataoka, K. Yamada, and N. Sugiyama, VIIIth Symposium of Organic Radical Reactions, Nagoya, 1967, No. D-25.

of thiobenzophenone to isoprene are 3-methyl-6,6-diphenyl-1-thiacyclohexene-3 (I) and 4-methyl-6,6-diphenyl-1-thiacyclohexene-3 (II). Since two singlets at τ 8.20 (1.2 H) and 8.32 (1.8 H) were assigned together to the three protons of a methyl group, the photoproduct must be a mixture of I and II. Owing to similar chromatographic behavior, they could not be separated. The same product composition was obtained by the thermoreaction of the corresponding mixture at 100°.

Photochemical Adduct of Thiobenzophenone to Cyclopentadiene (III).—The nmr spectrum of III shows ten aromatic protons between τ 2.60 and 3.10, a doublet of doublets centered at 3.73 for one vinyl proton, a doublet of doublets centered at 4.57 for another vinyl proton, a multiplet centered at 6.00 for two methyne protons, and a multiplet centered at 8.05 for two methylene protons. The fact that each vinyl proton shows the same pattern indicates that the photoproduct is a 1,4 adduct, *i.e.*, 3,3-diphenyl-2-thiabicyclo[2.2.1]hept-5-ene (III). H_A gave a quartet by coupling with H_B and H_C, and H_B also gave a quartet by coupling with H_A and H_D, J_{AB} = 5.2 cps, $J_{AC} = J_{BD}$ = 2.5 cps. The thermoreaction of the corresponding mixture at 100° afforded the same product, III.

Photochemical Adduct of Thiobenzophenone to 1,4-Diphenylbutadiene (IV).—In this case the photochemical adduct could be either the 1,2 adduct styrene derivative, or the 1,4 adduct. The latter is preferable, because the ultraviolet spectrum of the product did not show a strong absorption maximum near 250 mμ which is characteristic of styrene derivatives. Thus, the photochemical adduct was assumed to be the 1,4 adduct, 2,5,6,6-tetraphenyl-1-thiacyclohexene-3 (IV). This assumption was supported by the nmr spectral data. The nmr spectrum showed 20 aromatic protons between τ 2.35 and 3.55, a multiplet centered at 5.85 for H_A, a multiplet centered at 6.25 for H_B and a multiplet centered at 3.96 for two vinyl protons. If this compound were the 1,2 adduct, the chemical shifts of the vinyl protons should be distinctly different from each other, because one of them is adjacent to a phenyl group. The thermoreaction of the corresponding mixture at 100° gave the same product as IV.

Photochemical Adduct of Thiobenzophenone to 1,3-Cyclooctadiene (V).—The nmr spectrum of V shows ten aromatic protons between τ 2.35 and 3.20, a multiplet centered at 4.65 for two vinyl protons, a doublet of doublets centered at 5.46 for one methyne proton, a sextet centered at 6.70 for another methyne proton, and a multiplet between 7.50 and 9.20 for eight methylene protons. This nmr pattern indicates that this compound is not the 1,4 but is the 1,2 adduct. The coupling patterns of two methyne protons should be the same in the two possible 1,2 adducts, V and VI. The nmr spectrum of the corresponding sulfone obtained by peracetic acid oxidation showed a multiplet centered at τ 5.85 for two methyne protons. Since H_A of VII is approximately in the same situation as H_M of VIII, H_A and H_M may appear at approximately the same field strength. In fact the chemical shift of H_M was reported as τ 5.6.[10] Thus the chemical shifts of H_A and H_M are regarded as approximately the same. Therefore, the structure of this sulfone must be VII, so that our photoproduct is 10,10-diphenyl-9-thiabicyclo[6.2.0]decene-2 (V). Furthermore, if the structure of our photoproduct were VI, the chemical shift of the proton on C-1 of the corresponding sulfone would appear at a lower field than that of VI, but, as pointed out above, such an effect was not observed. This compound was not obtained by thermoreaction at 100°.

As the two double bonds in the starting substance, 1,3-cyclooctadiene, are not in the same plane, it cannot act as a conjugated diene compound. The reason the 1,4-adduct was not formed from the mixture of thiobenzophenone and 1,3-cyclooctadiene may be attributed to this situation.

Kaiser and Wulfers[11] reported the photolytic reaction of thiobenzophenone in the presence of ethylene derivatives through a four-membered ring system by irradiation with 210–280-mμ light. They did not isolate the intermediate four-membered ring system. But, from the results of the present research, its isolation would be succeeded if light of lower energy, Pyrex filtered light, is used.

Experimental Section

All melting points are uncorrected. The infrared spectra were determined on a Hitachi EPI-2 spectrophotometer, and the ultraviolet spectra were recorded on a Hitachi EPS-033 spectrophotometer. The nmr spectra were determined on a Hitachi H-6013 spectrometer (60 Mc). Tetramethylsilane was used as an internal standard. The irradiation was carried out with a high pressure mercury lamp (Taika, Type H, 150 W) in a Pyrex tube under a nitrogen atmosphere. The per cent yields of all products are based on thiobenzophenone.

1:1 Addition of Thiobenzophenone to Isoprene. Photoreaction.—A mixture of 5 g of thiobenzophenone and 5 ml of isoprene was irradiated for 45 min at room temperature. The blue color of thiobenzophenone faded gradually with irradiation, and after 45 min, it disappeared completely. After removal of the unreacted isoprene from the irradiation mixture, the residual oil was chromatographed on 50 g of silica gel (Merck, 0.05–0.20 mm) with 5:1 *n*-hexane–benzene. A fraction which showed the same R_f value on a thin layer chromatogram was collected to yield 6.3 g (94%) of a mixture of I and II. They could not be separated from each other on account of their identical R_f value. The infrared spectrum (liquid film) showed strong bands at 2950, 2900, 1600, 1490, 1445, 750, and 700 cm^{-1}. The nmr spectrum is shown in Table I.

Anal. Calcd for $C_{18}H_{18}S$: C, 81.15; H, 6.81. Found: C, 80.93; H, 6.89.

They decomposed by heating into a blue oil, which was shown to be thiobenzophenone.

Thermoreaction.—From 5 g of thiobenzophenone and 5 ml of isoprene, 5.6 g (84%) of the addition product (the mixture of I and II) was obtained by heating at 100° for 45 min in a sealed tube under nitrogen atmosphere.

1:1 Addition of Thiobenzophenone to Cyclopentadiene. Photoreaction.—A mixture of 2 g of thiobenzophenone and 1.34 g of cyclopentadiene was irradiated at room temperature for 10 min. At the end of this time the complete disappearance of the blue color of thiobenzophenone was observed. The reaction mixture was worked up as described above to give 1.1 g (41%) of colorless leaflets (from ethanol–water), mp 133–134° dec. The structure of this compound was proved as III by the following spectral data and elemental analysis. The infrared spectrum (KBr pellet) showed strong bands at 1590, 1480, 1440, 760, 735, and 700 cm^{-1}. The nmr spectrum is shown in Table I.

Anal. Calcd for $C_{18}H_{16}S$: C, 81.79; H, 6.10. Found: C, 81.09; H, 6.01.

Irradiation of a solution of 200 mg of thiobenzophenone and

(10) I. J. Borowitz, *J. Amer. Chem. Soc.*, **86**, 1146 (1964).

(11) E. T. Kaiser and T. F. Wulfers, *ibid.*, **86**, 1897 (1964).

excess cyclopentadiene in 600 ml of *n*-hexane at −78° for 52 hr gave 60 mg of colorless leaflets. This product was identified as III by the mixture melting point and spectral data.

Thermoreaction.—The mixture of 2 g of thiobenzophenone and 1.34 g of cyclopentadiene was heated at 100° for 10 min in a sealed tube. The product, 1.1 g (41%), from the reaction mixture was identified as III by the spectral data and the mixture melting point.

1:1 Addition of Thiobenzophenone to 1,4-Diphenylbutadiene. Photoreaction.—A solution of 2 g of thiobenzophenone and 1.94 g of 1,4-diphenylbutadiene in 10 ml of benzene was irradiated at room temperature for 95 hr. Although, at the end of this period, the complete disappearance of the blue color of thiobenzophenone was not yet observed, the solvent was evaporated and the residual oil was worked up as described above to afford 720 mg (18%) of colorless prisms. The structure of this compound was proved to be IV by the following spectral data and elemental analysis. The infrared spectrum (KBr pellet) showed strong bands at 1600, 1490, 1445, 840, 750, and 695 cm^{-1}. The ultraviolet absorption maxima in ethanol were at $\lambda_{max}^{ethanol}$ 250 mμ (ε 1550), 255 (1580), 261 (1410), 267 (1080), and 275 (470). The nmr spectrum is shown in Table I.

Anal. Calcd for $C_{29}H_{24}S$: C, 86.10; H, 5.98. Found: C, 86.13; H, 6.12.

Thermoreaction.—A solution of 2 g of thiobenzophenone and 1.94 g of 1,4-diphenylbutadiene in 10 ml of benzene was heated at 100° for 95 hr. The reaction mixture was worked up as described above to yield 210 mg (5.1%) of the colorless prisms. It was identified as IV by the spectral data and mixture melting point.

1:1 Addition of Thiobenzophenone to 1,3-Cyclooctadiene. Photoreaction.—A mixture of 2 g of thiobenzophenone and 2.2 g of 1,3-cyclooctadiene was irradiated at room temperature. In this case, 82 hr were required for complete disappearance of the blue color of the mixture. The same procedure described above was followed to give 1.27 g (41%) of the colorless needles (from acetone–water), mp 110.5°. The structure of this compound was proved to be V by the following spectral data and elemental analysis. The infrared spectrum (KBr pellet) showed strong bands at 2925, 2850, 1630, 1490, 1440, 760, and 700 cm^{-1}. The nmr spectrum is shown in Table I.

Anal. Calcd for $C_{21}H_{22}S$: C, 82.45; H, 7.55. Found: C, 82.33; H, 7.25.

It was found that 1,3-cyclooctadiene did not react with thiobenzophenone by heating at 100°.

Oxidation of V with Peracetic Acid.—A mixture of 200 mg of V, 3 ml of acetic acid, and 2 ml of 30% aqueous hydrogen peroxide in 20 ml of acetone was left standing for 40 hr at room temperature. After decomposing the excess hydrogen peroxide with a small amount of manganese dioxide, the filtrate was evaporated to yield a solid substance. It was recrystallized from acetone–water to give 80 mg of colorless fine needles, mp 147–148°. The infrared spectrum (KBr pellet) showed strong bands at 2925, 2850, 1445, 1305, 1145, and 700 cm^{-1}. The nmr spectrum was shown in Table I.

Anal. Calcd for $C_{21}H_{22}SO_2$: C, 74.53; H, 6.55. Found: C, 74.16; H, 6.46.

Registry No.—I, 15052-31-0; II, 15052-32-1; III, 15052-33-2; IV, 15052-34-3; V, 15052-35-4; VII, 15052-36-5; thiobenzophenone, 1450-31-3.

Reaction of Bromine with Hindered Olefinic Bonds

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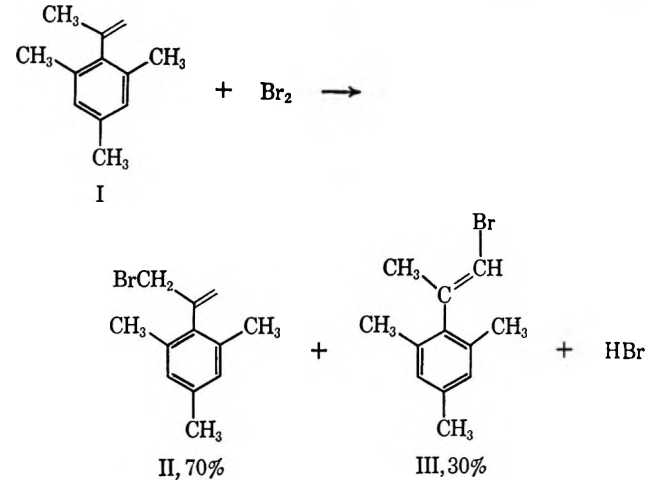
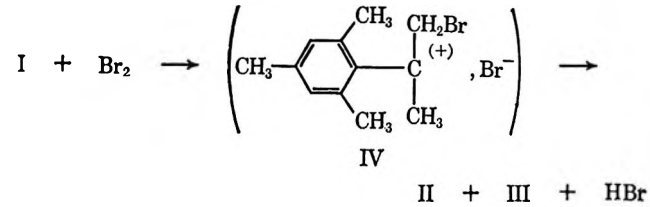
Bromine has been reported to react in an unexpected manner with α,*o*,*o*,*p*-tetramethylstyrene (I) yielding, rather than the expected addition product, hydrogen bromide and some unspecified substitution product.[2] We have reinvestigated this reaction to determine the structure of the substitution product and a possible mechanism for this anomalous reaction of bromine with an unsaturated linkage.

Mixing bromine with I in carbon tetrachloride at 0° results in immediate loss of the bromine color and evolution of hydrogen bromide. Gas chromatographic analysis of the reaction mixture showed that two bromination products in a ratio of about 7:3 were formed. Nmr analysis of the distilled mixture of substitution products indicated the predominant isomer to be α-bromomethyl-*o*,*o*,*p*-trimethylstyrene (II) and the other β-bromo-α,*o*,*o*,*p*-tetramethylstyrene (III). Passing a stream of nitrogen containing bromine vapor



into a pentane solution of I at −78° resulted in formation of a bright yellow solid, the color of which was distinctly different from the reddish brown color of solid molecular bromine in pentane at the same temperature. No evolution of hydrogen bromide occurred, but when the mixture was warmed to room temperature, the yellow solid disappeared and hydrogen bromide, II, and III were produced. Addition of a small amount of 95% ethanol to the yellow mixture produced in the reaction of I with bromine in pentane at −78° resulted in formation of a red alcoholic solution which separated from the pentane. This red solution was neutral at −78° but on warming became acidic and the red color disappeared. Gas chromatographic analysis of the resulting colorless alcoholic solution showed the presence of II and III and a trace of I. Gas chromatographic analysis of the pentane solution from which the yellow solid had been removed by the alcohol showed only traces of II and III but considerable amounts of unreacted I.

These observations are consistent with the formation of the carbonium ion–bromide ion pair IV rather than the covalent dibromide as the reaction product



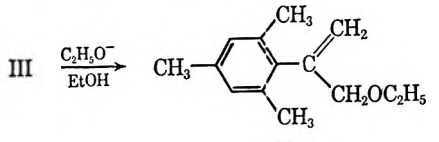
(1) National Institutes of Health Predoctoral Fellow, 1966–1967.

(2) M. S. Newman and N. C. Deno, *J. Amer. Chem. Soc.*, **73**, 3644 (1951); H. C. Brown and M. Grayson, *ibid.*, **75**, 20 (1953).

of I with bromine. At room temperature, the carbonium ion loses a proton readily yielding II and III, but at −78° in pentane the insoluble ion pair remains intact. The ion pair is apparently soluble in ethanol, producing a polar solution that is not miscible in pentane nor does it dissolve appreciable amounts of I. However, at room temperature, the carbonium ion is not stable in solution and decomposes, yielding a proton and the substitution products II and III.

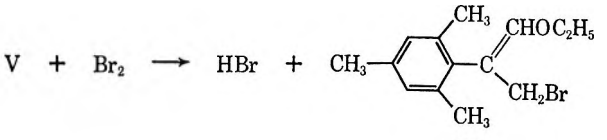
The reluctance of the ion pair to form the covalent dibromide is probably due to the steric difficulties encountered in formation of an sp^3 hybridized carbon in a benzylic position flanked by two *o*-methyl groups. This same sort of steric problem is encountered in addition reactions to carbonyl functions bonded to an aromatic ring and flanked by two *o*-methyl groups.[3] Free-radical additions of bromotrichloromethane and *n*-butanethiol to I do not take place, presumably because formation of the addition product requires an sp^3 hybridized carbon in the benzylic position.[4] Brown and Grayson suggested that hydrogen chloride and I formed an ion pair rather than the Markownikof addition product[2] which would also have an sp^3 hybridized carbon in the benzylic position.

Refluxing a mixture of II and III in ethanol with sodium ethoxide converts the allylic bromide II into 2-mesityl-3-ethoxyl-1-propene (V), whereas the vinyl



V

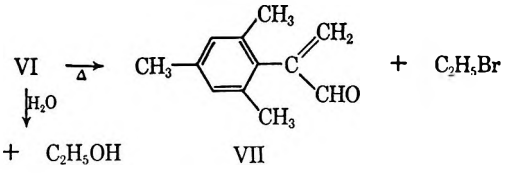
bromide III does not react and can be separated from the ether by distillation. Reaction of V with bromine in carbon tetrachloride at room temperature produced hydrogen bromide and the single substitution product, 1-ethoxy-2-mesityl-3-bromo-1-propene (VI), which we were unable to isolate but identified by its nmr spectrum. Passing bromide vapor in a stream of nitrogen into a solution of V in pentane at −78° resulted in



VI

formation of a bright yellow insoluble material which behaved similarly to the product formed from I and bromine at −78°. The material decomposed into hydrogen bromide and VI only when warmed to room temperature and was soluble in 95% ethanol forming a yellow solution that was not miscible in pentane. The course of reaction of V with bromine appears, as expected, very similar to that of I except that the ion pair fragments to produce only a single substitution product, namely, the vinyl ether VI.

Attempts to isolate VI by distillation resulted in pyrolysis of the vinyl ether, yielding 2-mesitylpropenal (VII) and ethyl bromide. Mixing water with a carbon tetrachloride solution of VI also converted this compound into the aldehyde VII. The precise course of these reactions was not investigated, al-



though it is interesting to note that decomposition of the vinyl ether in both cases resulted in loss of the bromine moiety, producing the less hindered unsaturated aldehyde.

Experimental Section

Reaction of I with Bromine at 0°.—A solution consisting of 2.9 g (0.018 mol) of bromine in 5 ml of carbon tetrachloride was added slowly to a solution of I (3.0 g, 0.019 mol) in 10 ml of carbon tetrachloride cooled in an ice bath and protected from light. Immediate evolution of hydrogen bromide and loss of the bromine color was noted. Gas chromatographic analysis of the reaction mixture (6 ft × ⅛ in. column packed with 10% SE-30 on Chromosorb W) indicated the presence of two substitution products with relative peak areas of 7:3. The reaction mixture was washed with water, sodium bicarbonate solution, and finally with water. After drying with $MgSO_4$, the carbon tetrachloride and unreacted I were removed by distillation. Vacuum distillation (90–100° at 0.03 mm) of the residue yielded 1.6 g of a mixture of α-bromomethyl-*o,o,p*-trimethylstyrene (II) (nmr 2.25, 4.05, 5.10, 5.65, and 6.80 ppm) and β-bromo-α,*o,o,p*-tetramethylstyrene (III) (nmr 1.98, 2.23, 5.90, and 6.80 ppm). The nmr signal integrations indicated II to be the predominant isomer.

Reaction of I with Bromine at −78°.—A solution of I (1 g, 0.006 mol) in 10 ml of pentane was cooled in a Dry Ice–acetone bath. A stream of nitrogen containing bromine vapor was bubbled through the pentane solution producing a bright yellow solid. There was no evidence of hydrogen bromide being formed either during the introduction of the bromine or as long as the mixture was maintained at −78°. However, upon warming the mixture to room temperature, the yellow solid disappeared and hydrogen bromide was evolved. Gas chromatographic analysis of the resulting colorless pentane solution indicated the presence of II and III.

Addition of 1 ml of 95% ethanol to a pentane mixture containing the yellow solid produced by reaction of bromine with I at −78° resulted in removal of the yellow solid from the pentane and formation of a red solution that was insoluble in the pentane. This solid was neutral at −78° but on warming to room temperature became acidic and colorless. Gas chromatographic analysis of the alcoholic solution after reaching room temperature and becoming colorless showed the presence of both II and III and only a trace of I. The pentane solution from which the yellow solid had been removed by the alcohol contained only traces of II and III but most of the unreacted I.

2-Mesityl-3-ethoxy-1-propene.—A mixture of II and III (1.6 g, in a ratio of 7:3) was allowed to reflux for 12 hr in a solution of sodium ethoxide in ethanol prepared from 2.3 g (0.10 mol) of sodium in 30 ml of absolute ethanol. The resulting mixture was allowed to stand for an additional 12 hr and then washed twice with water, dried with $MgSO_4$, and distilled. The first fraction was 2-mesityl-3-ethoxy-1-propene (0.77 g, 80% of theory): bp 113–116° (4.5 mm); $n^{20}D$ 1.5153; nmr (ppm), 1.20 (triplet, 3 H), 2.20 (9 H), 3.45 (quartet, 2 H), 3.85 (2 H), 4.80 (1 H), 5.50 (1 H), 6.75 (2 H).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.89. Found: C, 81.87; H, 10.06.

The second fraction was II (0.45 g): bp 80–96° (0.05 mm); $n^{20}D$ 1.5560; nmr (ppm), 1.98 (3 H), 2.20 (9 H), 5.90 (1 H), 6.80 (2 H).

Anal. Calcd for $C_{12}H_{15}Br$: C, 60.26; H, 6.32; Br, 33.41. Found: C, 60.16; H, 6.24; Br, 33.50.

Reaction of 1-Ethoxy-2-mesityl-1-propene (V) with Bromine.—Addition at 0° of a solution of bromine (0.6 g, 0.0037 mol)

(3) V. Meyer, *Ber.*, **27**, 510 (1894); V. Meyer and J. J. Sudborough, *ibid.*, **27**, 3146 (1894); M. S. Newman, *J. Amer. Chem. Soc.*, **63**, 2431 (1941); W. Reeve and E. L. Compere, Jr., *ibid.*, **83**, 2755 (1961); W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, **26**, 2306 (1960).

(4) E. S. Huyser and L. Kim, *J. Org. Chem.*, **33**, 94 (1968).

in 5 ml of carbon tetrachloride to a solution of V (0.5 g, 0.0025 mol) in 4 ml of carbon tetrachloride resulted in immediate reaction of the bromine and evolution of hydrogen bromide. The carbon tetrachloride was removed under vacuum and the resulting residue examined. The infrared spectrum showed no alcohol or carbonyl absorptions. The nmr spectrum (1.20 triplet, 2.10, 2.20, 2.30, 4.2, 6.0, and 6.75 ppm) of the material is consistent with the structure of 1-ethoxy-2-mesityl-3-bromo-1-propene (VI). Pyrolysis of this material at 80–100° at reduced pressure (18 mm) resulted in formation of ethyl bromide (collected in a Dry Ice trap and identified by its gc retention time) and 2-mesitylpropenal (VII) which was isolated as the 2,4-dinitrophenylhydrazone, mp 204–205°.

Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.93; H, 5.29; N, 15.65.

Treatment of a carbon tetrachloride solution of VI, prepared by reaction of 0.5 g (0.0025 mol) of bromine with 0.34 g (0.0025 mol) of V in 10 ml of carbon tetrachloride at 0°, with water produced a water layer containing ethanol (identified by its gc retention time and nmr analysis of the aqueous solution). Distillation of the carbon tetrachloride solution produced 0.25 g (57% of theory) of 2-mesitylpropenal, bp 96–98° (0.03 mm).

Introduction of bromine vapor carried in a stream of nitrogen into a pentane solution of V at −78° resulted in formation of an insoluble yellow material. When a portion of this mixture was allowed to warm to room temperature, the yellow solid disappeared and hydrogen bromide was evolved. Treatment of another portion of the pentane mixture with 95% ethanol at −78° resulted in removal of the yellow solid from the pentane and formation of a yellow alcoholic solution that was not miscible with pentane.

Registry No.—Bromine, 7726-95-6; II, 15135-12-3; III, 15135-13-4; V, 15135-14-5; VI, 15135-15-6; VII, 15135-16-7; VII 2,4-dinitrophenylhydrazone, 15135-17-8.

Synthesis of 2,6-Dialkylphenyl 4-Nitrophenyl Ethers from Highly Hindered Phenols[1a]

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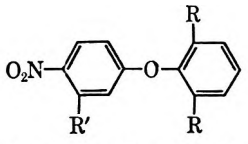
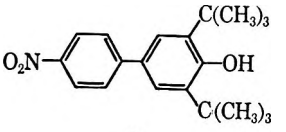
As intermediates in the preparation of a series of 3,5-dialkyl and 3,5,3′-trialkyl analogs of the thyroid hormones, the synthesis of a series of 2,6-dialkylphenyl 4-nitrophenyl ethers was desirable.



R=Me, *i*-Pr, *sec*-Bu, *t*-Bu; R′=H, Me

Our attempts to prepare these compounds from 2,6-dialkyl phenols by established methods[2–4] were unsuccessful, as might be expected from the highly hindered nature of the phenols. However, it was found that most of the required ethers (**1**–**6**, Table I) could be prepared in surprisingly good yield by condensation of 2,6-dialkyl phenols with *p*-chloronitrobenzene or 5-chloro-2-nitrotoluene in the presence of potassium or sodium hydroxide and dimethyl sulfoxide. From the reaction between 2,6-di-*t*-butylphenol and *p*-chloronitrobenzene, the isomeric biphenyl analog 2,6-di-*t*-butyl-4-(*p*-nitrophenyl)phenol (**7**) was isolated instead of the expected diphenyl ether.



7

Compound **7** retained the phenolic group as indicated by the infrared spectrum showing an OH band at 3600 cm^{-1} and the nmr spectrum integrating for one proton less than expected in the aromatic region, but giving a broad signal integrating for one hydroxyl proton at δ 5.5. The ultraviolet absorption maximum of **7** occurs at 346 mμ (ϵ 15,100) compared to maxima of 296–302 mμ (ϵ 6000–15,000) for the diphenyl ethers.

It has been shown previously[5–7] that the use of dimethyl sulfoxide as a reaction solvent can often enhance yields of compounds produced by nucleophilic attack. The synthesis of diphenyl ethers from *unhindered* phenols and 2,4-dinitrofluorobenzene[7] or *o*-chloronitrobenzene[8] using dimethyl sulfoxide has been reported. Condensation of the *hindered* 2,6-dimethylphenol with 2,6-dimethyl-4-bromoanisole to form 2,6-dimethylphenyl 3,5-dimethyl-4-methoxyphenyl ether by fusion of the reactants in the presence of a copper catalyst has also been reported.[9,10] However, this is, to our knowledge, the first time that synthesis of diphenyl ethers from phenols possessing two *ortho* alkyl substituents larger than methyl groups has been accomplished. The method has proved of unique value in establishing a synthetic route to thyroxine analogs possessing large alkyl groups on the inner ring.[11]

Experimental Section[12]

2,6-Dialkylphenyl 4-Nitrophenyl Ethers (1–4).—A mixture of the 2,6-dialkylphenol (0.12 mole), *p*-chloronitrobenzene (0.10 mole), potassium or sodium hydroxide (0.10 mole), and dimethyl sulfoxide (150 ml) was heated at 90° with stirring for 24 hr. The resultant dark green solution was poured into dilute hydrochloric acid (present to prevent emulsion forma-

(1) (a) This investigation was supported in part by Public Health Service Research Grant AM-04223 from the National Institute of Arthritis and Metabolic Diseases. (b) To whom inquiries concerning this paper should be addressed.

(2) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 445.

(3) C. M. Buess, T. Giudici, N. Kharasch, W. King, D. D. Lawson, and N. N. Saha, *J. Med. Chem.*, **8**, 469 (1965).

(4) F. Ullman and P. Sponagel, *Ber.*, **38**, 2211 (1905).

(5) C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).

(6) L. Friedman and H. Schechter, *ibid.*, **25**, 877 (1960).

(7) J. Murto, *Suomen Kemistilehti*, **38B**, 49 (1965); *cf. Quart. Rept. Sulfur Chem.*, **1**, 39 (1966).

(8) J. Schmutz, F. Künzler, F. Hunziker, and A. Bürki, *Helv. Chim. Acta*, **48**, 336 (1965).

(9) T. C. Bruice N. Kharasch, and R. J. Winzler, *J. Org. Chem.*, **18**, 83 (1953).

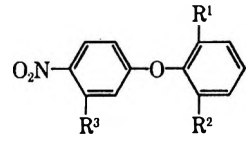
(10) H.-J. Bielig and G. Lützel, *Ann. Chem.*, **608**, 140 (1957).

(11) E. C. Jorgensen and J. Wright, submitted for publication.

(12) Melting points were determined with a Thomas–Hoover apparatus fitted with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-8 instrument. Microanalyses were performed by the Microanalytical Laboratory, University of California at Berkeley, Berkeley, Calif. Nmr spectra were obtained in $CDCl_3$ on a Varian A-60 instrument using tetramethylsilane as an internal standard. Ultraviolet spectra were determined in 95% ethanol, using a Beckman DB-G instrument.

TABLE I

2,6-DIALKYLPHENYL 4-NITROPHENYL ETHERS



No.	R¹	R²	R³	Mp, °C or bp (mm)	Yield, %	λmax, mμ (ε)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	Me	Me	H	61–62	82	300 (15,300)	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	69.29	5.43	5.98
2	*i*-Pr	*i*-Pr	H	92–93	75	300 (13,200)	$C_{18}H_{21}NO_3$	72.21	7.07	4.68	72.11	6.81	4.61
3	*sec*-Bu	*sec*-Bu	H	170 (5)	70	300 (15,300)	$C_{20}H_{25}NO_3$	73.36	7.70	4.28	73.38	7.70	4.42
4	Me	*t*-Bu	H	96	20	302 (12,000)	$C_{17}H_{19}NO_3$	71.56	6.71	4.91	71.70	6.61	5.15
5	*i*-Pr	*i*-Pr	Me	90–91	60	296 (6,000)	$C_{19}H_{23}NO_3$	72.82	7.40	4.47	73.06	7.26	4.59
6	*sec*-Bu	*sec*-Bu	Me	63–64	62	296 (7,500)	$C_{21}H_{27}NO_3$	73.87	7.97	4.10	74.11	7.65	4.12

tion) and extracted with chloroform.[13] The chloroform layer was washed twice with dilute hydrochloric acid and twice with water. After drying, the chloroform was removed under reduced pressure and the residue distilled under vacuum, the fraction distilling above 160° (5 mm) being collected. The resultant pale yellow oil was crystallized from ethanol.

5-Chloro-2-nitrotoluene was prepared by a modification of the method of Wibaut.[14] Fuming nitric acid (200 g, *d* 1.52) was added dropwise with stirring during 90 min to *m*-chlorotoluene (50 g), maintaining the temperature below 5°. After stirring for a further 2 hr at 0°, the mixture was refrigerated overnight, then poured onto crushed ice. The precipitated oil was extraced with ether and washed four times with 10% sodium bicarbonate solution and twice with water. After drying ($CaCl_2$), the ether was removed under reduced pressure to give 60 g of nitrated product. The 5-chloro-2-nitrotoluene predominated in the first yellow fractions obtained by elution from an acid-washed alumina column with 6% benzene in petroleum ether (bp 40–60°). The crude isomeric 3-chloro-4-nitrotoluene was present in later fractions. The 5-chloro-2-nitrotoluene obtained in this manner (40 g) contained a small proportion of *m*-chlorotoluene as indicated by thin layer chromatography and nmr spectroscopy, but could be used as such for the diphenyl ether condensation reaction. For analytical purposes a pure sample was obtained by crystallization from ethanol at low temperature: mp 24° (lit.[14] mp 24.9°).

Anal. Calcd for $C_7H_6ClNO_2$: C, 48.97; H, 3.49; N, 8.16. Found: C, 49.00; H, 3.50; N, 7.99.

2,6-Dialkylphenyl 3-methyl-4-nitrophenyl ethers (5, 6) were prepared in the same manner as **1–4**, substituting 5-chloro-2-nitrotoluene for the *p*-chloronitrobenzene. Both were isolated as crystalline solids from ethanol, following vacuum distillation.

2,6-Di-*t*-butyl-4-(*p*-nitrophenyl)phenol (7).—A mixture of 2,6-di-*t*-butylphenol (24.7 g, 0.12 mole), *p*-chloronitrobenzene (15.7 g, 0.10 mole), potassium hydroxide (5.6 g, 0.10 mole), and dimethyl sulfoxide (150 ml) was heated at 90° with stirring for 24 hr. The resulting dark blue solution was poured into dilute hydrochloric acid and extracted with chloroform. After drying, the chloroform was removed under reduced pressure and the dark oil remaining was crystallized three times from ethanol to yield (68%) the biphenyl analog **7**: mp 155–156°; $\lambda_{max}^{C_2H_5OH}$ 346 mμ (ε 15,100).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.70; H, 7.52; N, 4.55.

Registry No.—**1**, 15158-13-1; **2**, 15158-14-2; **3**, 15138-26-8; **4**, 15138-27-9; **5**, 15138-28-0; **6**, 15138-29-1; **7**, 15138-30-4.

Acknowledgment.—The authors are indebted to Mr. A. Ishimoto for the preparation of 5-chloro-2-nitrotoluene.

(13) 2,6-Diisopropylphenyl 4-nitrophenyl ether solidified when the reaction mixture was poured into water. The precipitate was crystallized from ethanol.

(14) W. P. Wibaut, *Rec. Trav. Chim. Pays-Bas*, **32**, 288 (1913).

The Reaction of Tetrakis(dimethylamino)-titanium with Tetramethyloxamide

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Received August 14, 1967

It has been reported that titanium tetramides aminate carboxylic acid derivatives, forming vinylidene diamines or *gem*-triamines.[1,2] From consideration of these results it would be predicted that oxalic acid derivatives would be converted by titanium amides into hexaminoethanes, presently an unknown class of compound. We have now found this not to be the case; instead, carbon–carbon bond cleavage accompanies amination in the oxalates.

Tetrakis(dimethylamino)titanium (**1**) reacts with 2 moles of tetramethyloxamide[3] (**2**) very slowly at room temperature and more rapidly at 80°, either neat or in solution (ether, benzene, or cyclohexane–dioxane) to form 2 moles of tetramethylurea (**3**), 1 mole of tris(dimethylamino)methane[2] (**4**), and a deep red, ill-defined substance containing complexed titanium. However, when **1** and **2** are allowed to react in the presence of excess dimethylamine, the stoichiometry given in eq 1 is observed. Titanium dioxide precipitates under these conditions.

$$Ti(NMe_2)_4 + 2(Me_2NCO)_2 \xrightarrow{Me_2NH} TiO_2 + 2(Me_2N)_2CO + 2(Me_2N)_3CH \quad (1)$$

When the course of the reaction is followed by nmr spectroscopy, a resonance not attributable to any of the reactants or products appears as the reactants begin to disappear, and then disappears after the reactants are used up and products appear. This resonance is presumed to be due to the presence of an intermediate in the amination reaction; its chemical shift (τ 7.60 in ether) is consistent with a structure containing two or more hindered dimethylamino

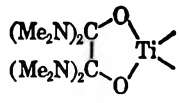
(1) H. Weingarten and W. A. White, *J. Amer. Chem. Soc.*, **88**, 850 (1966).

(2) H. Weingarten and W. A. White, *J. Org. Chem.*, **31**, 2874 (1966).

(3) Other oxalic acid derivatives would be converted into this amide by **1** before further reaction took place.[2]

groups on a single carbon atom [*cf.* $C(NMe_2)_4$, τ 7.4,[4] $HC(NMe_2)_3$, 7.7[2]].

It is reasonable to postulate that the reaction proceeds *via* initial coordination of **2** with **1**, possibly followed by transfer of two dimethylamino ligands from titanium to carbon to form an intermediate 1,1,2,2-tetrakis(dimethylamino)-1,2-ethanediolato complex (**5**). This complex can then slowly undergo



5

C–C and Ti–O bond scission (perhaps by displacement) with expulsion of **3**, followed by rapid proton abstraction from **2** or dimethylamine (or perhaps solvent) to form a complex containing the group $(Me_2N)_2CH$–O–Ti. Transfer of a dimethylamide from Ti to C then gives **4**.

With dimethylamine as the proton source, the species remaining after displacement of **4** will be formally $TiO(NMe_2)_2$ which can continue the reaction either by disproportionation[5] into **1** and TiO_2 or by itself. However, if **2** (or solvent) is the proton source, only one dimethylamide then remains per titanium atom, and this one dimethylamide will be sufficient only to effect the transformation of **2** into **3**, leaving behind the complex species containing titanium, oxygen, carbon, and (from their color) nitrogen which are observed.

There is not enough evidence available to suggest whether the failure to form an hexaminoethane is the result of inherent lability of that product or the result of steric, electronic, or other factors operating in the amination reaction, but it is clear that the result sets one limit on the scope of this very useful, novel reaction.

Experimental Section

Tetramethyloxamide and tetrakis(dimethylamino)titanium were prepared by W. A. White by standard methods.[2,6] Benzene solvent (Mallinckrodt AR) was distilled from calcium hydride, and ether and dioxane (both Mallinckrodt AR) from potassium–benzophenone ketyl, all in a nitrogen atmosphere. Cyclohexane from Matheson was distilled from concentrated sulfuric acid and washed over "activity I" neutral alumina. Dimethylamine was Eastman "White Label," used as received.

Nmr spectra were obtained using either a Varian A-60 or A-56/60 spectrometer with tetramethylsilane (TMS) as internal standard. Infrared spectra were obtained on neat films using a Beckman IR-4 spectrophotometer.[6]

All transfers of reagents were carried out in an efficient, nitrogen-filled drybox.

Nmr scale reactions were carried out by making up separate solutions of the reactants to known concentrations (w/v) and then mixing the appropriate quantities of the standard solutions. Relative concentrations were checked by integration of nmr spectra. In this fashion reactions of initial relative concentrations of 4:1, 2:1, and 1:1 oxamide–Ti were followed in benzene solvent. (Total reaction time was 4 days at 80°.)

Larger scale reactions were carried out by mixing appropriate quantities (0.01 mole of limiting reagent) of the reagents, adding solvent, and heating at reflux until the reaction was complete. (The reactions were monitored by nmr.) In this fashion 2.5:1 oxamide–Ti reactions were carried out in cyclohexane–dioxane (24 hr at 90°) and ether–dimethylamine (almost complete in 16 days at *ca.* 25°). The products were isolated by stripping off solvent and distilling at reduced pressure.

Tetramethylurea (**3**) was identified by its nmr and infrared spectra. The triaminomethane (**4**) was identified by its characteristic nmr spectrum[2] and the superposability of the infrared spectra of an authentic mixture of **3** and **4** with that exhibited by a mixture of the two obtained by distillation of one reaction mixture.

Registry No.—**1**, 3275-24-9; **2**, 1608-14-6.

(4) H. Weingarten and W. A. White, *J. Amer. Chem. Soc.*, **88**, 2885 (1966).

(5) H. Weingarten and J. R. Van Wazer, *ibid.*, **87**, 724 (1965).

(6) We wish to thank Mr. W. A. White for the preparation of these compounds and Mrs. N. K. Edelman for the measurement of spectra.

The Reaction of Unsaturated Ketones with Polynitro Addends

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There has been relatively little work published on the reactions of divinyl ketone (I) despite its position as the simplest compound containing the dienone system. In a recent paper, deJongh and Winberg[1] described the use of I in the synthesis of dispiro ketones, Arbuzov, Klimov, and Korolev[2] have prepared the interesting compound bis(5-norbornen-2-yl) ketone by a Diels–Alder reaction of divinyl ketone with cyclopentadiene, and Nazarov and coworkers have studied divinyl ketone and its derivatives as synthetic intermediates.[3]

Because of the potential of I as an acceptor molecule in Michael reactions, the available preparative methods were examined. Divinyl ketone has been prepared by the dehydrochlorination of di(β-chloroethyl) ketone.[4] by the thermal decomposition of di(β-methoxy) ketone,[5] by the oxidation of divinylcarbinol,[6] and by the thermal decomposition of the dihydrochloride salt of 1,5-bis(diethylamino)-3-pentanone.[7] The yields of pure ketone from all of these methods in this investigation were erratic and in general rather poor, ranging from about 5 to 25%. Since there is some evidence that the low yields may be due to the further reaction of divinyl ketone as it is formed,[6] attention was then directed toward the synthesis of ketals of I. The ketals should be stable to basic reaction conditions and to storage and yet should be a ready source of the unsaturated ketone.

The method of Garbisch for the preparation of cyclic dienone ketals[8] proved to be an easy and reliable method for the synthesis of 2,2-divinyl-1,3-dioxolane *via* bromination in ether of 2,2-diethyl-1,3-dioxolane (80% yield) followed by dehydrobromination with alcoholic caustic (60% yield). The ketal, as expected, was stable and could be readily hydrolyzed with dilute acid as required.

(1) H. A. P. deJongh and H. Winberg, *Tetrahedron*, **20**, 2553 (1964).

(2) Y. A. Arbuzov, W. M. Klimov, and S. M. Korolev, *Zh. Obshch. Khim.*, **32**, 3681 (1962).

(3) See I. N. Nazarov and S. I. Zav'yalov, *ibid.*, **23**, 1703 (1953), for pertinent references.

(4) J. Nelles, U. S. Patent 2,105,792 (January 18, 1938).

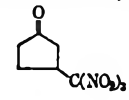
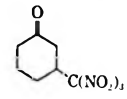
(5) I. N. Nazarov and I. V. Torgov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 419 (1946).

(6) S. F. Reed, *J. Org. Chem.*, **27**, 4116 (1962).

(7) G. S. Mironov, M. I. Farberov, and I. M. Orlova, *Zh. Obshch. Khim.*, **33**, 1512 (1963).

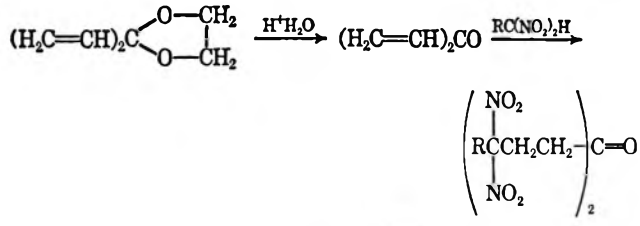
(8) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2019 (1965).

TABLE I
PROPERTIES OF POLYNITRO ADDUCTS OF UNSATURATED KETONES

Addend	Product[e]	Yield,[a] %	Mp, °C	Infrared maximum,[c] cm^{-1} -C=O	Infrared maximum,[c] cm^{-1} -NO$_2$	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
$(NO_2)_3CH$	$[(NO_2)_3CCH_2CH_2]_2C{=}O$[d]	70	121–122	1730	1594, 1355	21.88	2.10	21.88	22.25	2.26	21.86
$(NO_2)_2FCH$	$[(NO_2)_2FCCH_2CH_2]_2C{=}O$	51	77–78	1732	1595, 1317	25.45	2.42	16.97	25.85	2.42	16.69
$CH_3CH_2(NO_2)_2CH$	$[CH_3CH_2C(NO_2)_2CH_2]_2C{=}O$	70	97–98	1730	1565, 1372	37.71	5.14	16.00	37.99	4.99	16.02
$N{\equiv}C(NO_2)_2CH$	$[N{\equiv}C{\cdot}C(NO_2)_2CH_2CH_2]_2C{=}O$	25	104–105	1732	1600, 1297	31.39	2.32	24.41	...	...	23.79
$(NO_2)_2ClCH$	$[ClC(NO_2)_2CH_2CH_2]_2C{=}O$	...	86–87	1728	1586, 1305	23.14	2.20	15.42	23.11	2.23	15.14
$(NO_2)_3CH$		66	70	1733	1572, 1283	30.90	3.00	18.02	31.02	3.42	17.95
$(NO_2)_3CH$		87	53	1686[b]	1550,[b] 1281[b]	33.60	3.64	17.01	33.94	3.49	17.07

[a] Based upon unsaturated ketal. [b] Potassium bromide pellet. [c] Infrared data were obtained in methylene chloride solutions unless otherwise noted. [d] M. E. Hill, D. L. Ross, and C. L. Coon (personal communication, Stanford Research Institute) first prepared this compound by the addition of nitroform to divinyl ketone. [e] Respective registry no.: 15353-11-4, 15353-12-5, 15353-13-6, 15353-14-7, 15353-15-8, 15353-16-9, 15353-17-0.

For the present purpose, a prehydrolysis was not necessary. The slow addition of the acidic polynitro addend to an aqueous methanol solution of 2,2-divinyl-1,3-dioxolane gave good yields of the respective diadducts.



R = F, Cl, $-NO_2$, $-C{\equiv}N$, Et

The order of addition is important since the yields of the diadduct were markedly lower when the ketal was added to the addend solution, possibly because of the reaction of the polynitro carbanions with intermediate carbonium ions formed during the hydrolysis of the ketal.

The diadduct is apparently the main addition product of the reaction since the attempted preparation of the monoadduct of nitroform with the ketal led only to 1,1,1,7,7,7-hexanitro-4-heptanone, whatever the ratio of reactants. Presumably the inductive effect of the trinitromethyl group increases the rate of addition of the second group. Some credence is given to this viewpoint by a comparison of the carbonyl stretching frequencies for 2-pentanone (1717 cm^{-1}) and for 5,5,5-trinitro-2-pentanone (1736 cm^{-1}) in carbon tetrachloride.

The method was extended to the synthesis of 3-trinitromethylcyclohexanone and 3-trinitromethylcyclopentanone by the reaction of nitroform with 2-cyclohexenone ethylene ketal[8] and 2-cyclopentenone ethylene ketal.[8] An 87% yield of the cyclohexenone adduct was obtained by the addition of nitroform to an aqueous methanol solution of the ketal. For reverse addition the yield was lowered to 55%. However, a 64% yield of 3-trinitromethylcyclopentanone was obtained by the addition of the ketal to a solution of nitroform, while the reverse addition gave a comparable yield of 66%. In this case the rate of hydrolysis of the ketal is faster than the rate of formation of side products. This result is in keeping with the concept of *I* strain[9] wherein nonbonded interactions are relieved through the hydrolysis of the cyclopentanone ketal.

The compounds which were synthesized in this study and their properties are presented in Table I. No attempts were made to optimize the yields, which ranged from 25 to 87%. The method of preparation, while of limited general applicability, should be of value for preparing adducts of other reactive unsaturated ketones.

Experimental Section

Caution! Reasonable care and precautions should be taken when handling polynitro compounds. One attempted reaction of nitroform with a solution of impure divinyl ketone resulted in an explosion at refrigerator temperature.

2,2-Divinyl-1,3-dioxolane.—A solution of 2,2-bis(1-bromoethyl)1,3-dioxolane[10] (70.0 g, 0.243 mole) and 60.0 g (1.5 moles) of sodium hydroxide in 500 ml of methanol was refluxed for 72 hr. After cooling, the solution was poured into 1 l. of water saturated with sodium chloride which was then extracted with three 100-ml portions of pentane. After drying the combined extracts, the pentane was removed under reduced pressure. Distillation of the residue gave 18.4 g (60%) of 2,2-divinyl-1,3-dioxolane: bp 60° (43 mm); n^{24}D 1.4228. The nmr (CCl_4) spectrum showed a complex multiplet centered at 5.5 ppm (vinyl protons) and a sharp singlet at 3.9 ppm (ethylene protons). The integration ratio was 6:4. The purity of the ketal was judged to be 99+% by gas chromatographic analysis.

Example of the Method for Preparation of Divinyl Ketone Adducts.—A solution of nitroform (9.06 g, 0.06 mole) in 5 ml of 50% aqueous methanol was added dropwise to an agitated solution of 2,2-divinyl-1,3-dioxolane (3.78 g, 0.03 mole) in 30 ml of 50% aqueous methanol. After stirring overnight, the crude orange product was isolated by filtration and recrystallized from ethanol to give 8.05 g (70%) of diadduct, mp 121–122°.

3-Trinitromethylcyclohexanone.—A solution of nitroform (6.0 g, 0.04 mole) in 10 ml of 50% aqueous methanol was added dropwise to a stirred solution of 2-cyclohexenone ethylene ketal (6.0 g, 0.04 mole) in 50 ml of 50% aqueous methanol. The mixture was agitated for 3 hr at room temperature. The lower yellow oily layer was then extracted with methylene chloride. The methylene chloride extracts were washed with water and dried. Evaporation of the solvent under reduced pressure yielded 8.0 g of a crude light yellow oil. Crystallization from hexane gave a white crystalline product in 87% yield: mp 53°;

(9) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 265.

(10) The dibromo compound was prepared in 80% yield by bromination of an etheral solution of 2,2-diethyl-1,3-dioxolane following the general directions of Garbisch.[8]

nmr δ CCl_4 3.50 (1 H, broad methine multiplet), 1.8–2.7 (8 H, complex multiplet for the ring methylene protons).

3-Trinitromethylcyclopentanone.—A solution of 2-cyclopentenone ethylene ketal (5.0 g, 0.04 mole) in 10 ml of 50% aqueous methanol was added to a solution of nitroform (6.0 g, 0.04 mole) in 50 ml of 50% aqueous methanol. The title compound was isolated and purified in the same manner as described for 3-trinitromethylcyclohexanone. The yield was 64%: mp 70°: nmr δ CCl_4, 3.9 (1 H, broad methine multiplet), 2.5 (6 H, multiplet for the ring protons).

Registry No.—2,2-Divinyl-1,3-dioxolane, 15353-18-1.

Acknowledgment.—This work was supported by the Naval Ordnance Systems Command, Task Assignment ORD-033-101/067-1/F009-06-01.

Electron-Impact Fragmentations of $\Delta^{1(7)}$-Menthenone-2 and $\Delta^{8(9)}$-Menthenone-2

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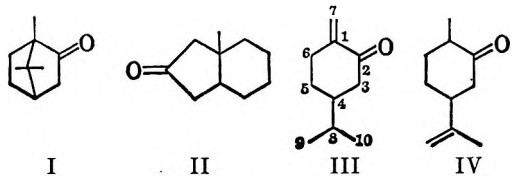
Details of the behavior of camphor (I) upon electron impact have been reported by Weinberg and Djerassi.[1] They have observed that (1) all of the major peaks in the mass spectrum of camphor are due to hydrocarbon species and the carbonyl group does not compete effectively with the hydrocarbon framework in directing the fragmentation of this molecule; (2) camphor and its isomer, *trans*-8-methylhydrindan-2-one (II), display very similar mass spectra, the principal difference residing only in the relative intensity of certain peaks; and (3) many of the fission reactions are best rationalized by postulating migrations of double bonds, alkyl groups, or hydrogen.



I II III IV

In connection with our pyrolysis study,[2] mass spectra of two further isomers of camphor, $\Delta^{1(7)}$-menthenone-2 (III) and $\Delta^{8(9)}$-menthenone-2 (IV) were obtained, which are reproduced in Figures 1 and 2, respectively.[3] Although the mass spectral peak positions of these compounds are generally similar to those of camphor, detailed study using deuterium-labeling and high-resolution techniques shows that much difference exists among the electron-impact fragmentation reactions of these compounds.

(1) D. S. Weinberg and C. Djerassi, *J. Org. Chem.*, **31**, 115 (1966).

(2) T. Sato, K. Murata, A. Nishimura, T. Tsuchiya, and N. Wasada, *Tetrahedron*, **23**, 1791 (1967).

(3) The mass spectra were determined on a CEC 21-103C mass spectrometer, the electron energy being 70 eV.

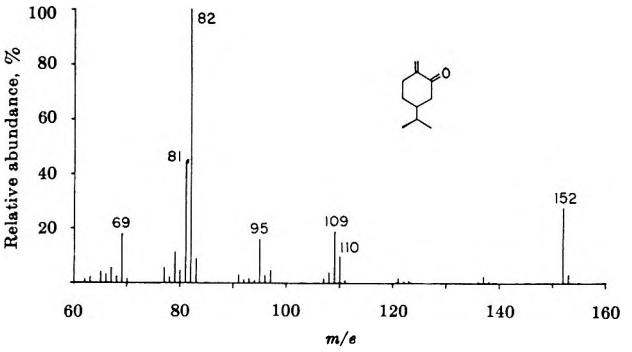


Figure 1.—Mass spectrum of $\Delta^{1(7)}$-methenone-2 (III).

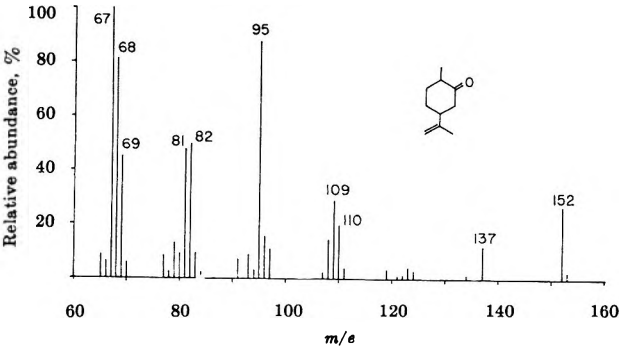


Figure 2.—Mass spectrum of $\Delta^{8(9)}$-methenone-2 (IV).

The principal mass spectral peaks (elemental compositions) of III determined by high-resolution measurement[4] are listed in Table I. High-resolution measurement was also carried out with III-3,3-d_2 and peaks were correlated to those of the nondeuterated analog. Unlike the case with camphor, most of the peaks are found to be doublets—a hydrocarbon ion peak and an oxygen-containing ion peak. It might be possible to write fragmentation mechanisms from these data, but there is not sufficient evidence to exclude alternatives explicitly and we avoid giving fragmentation mechanism in unwarranted detail.

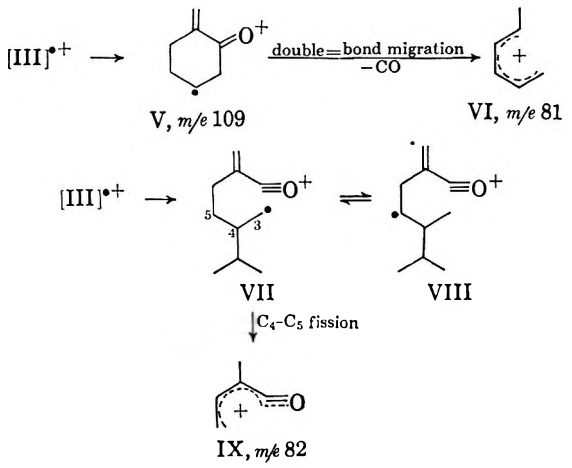
TABLE I[a,b]
PRINCIPAL MASS SPECTRAL PEAKS OF III AND THEIR DEUTERIUM SHIFTS IN THE 3,3-d_2 ANALOG

Elemental compositions	
III	III-3,3-d_2
C_8H_{14} (110)	C_8H_{14} (110)
$C_7H_{10}O$ (110)	$C_7H_8D_2O$ (112)
C_8H_{13} (109)	$C_8H_{11}D_2$ (111)
C_7H_9O (109)	$C_7H_7D_2O$ (111)
C_7H_{11} (95)	C_7H_{11} (95)
C_6H_7O (95)	$C_6H_5D_2O$ (97)
C_5H_6O (82)	C_5H_6O (82), C_5H_5DO (83), $C_5H_4D_2O$ (84)
C_6H_9 (81)	$C_6H_7D_2$ (83)
C_5H_9 (69)	C_5H_9 (69)
C_4H_5O (69)	C_4H_5O (69)

[a] High-resolution mass spectra were recorded on a photographic plate and the peak intensities were not determined quantitatively. It is definitely shown, however, that the elemental compositions and their deuterium shifts shown in the table constitute the major portions of the spectra. [b] Figures in the parentheses designate *m/e*.

(4) The mass spectra were determined on a CEC 21-110B mass spectrometer, the electron energy being 70 eV.

SCHEME I



The mechanism (V → VI, Scheme I) is substantiated by a metastable ion at m/e 60.3 ($81^2/109$ = 60.2). In support of this mechanism, the peak shifts to m/e 62.3 in the spectrum of III-3,3-d_2 ($83^2/111$ = 62.2).

It is notable that $C_5H_6O^+$ (m/e 82) ion splits into a triplet upon deuteration. A rapid radical migration (VII ⇌ VIII, Scheme I) is proposed by which an equilibrium between the hydrogen on C_3 and C_5 is attained prior to the C_4–C_5 bond fission in VII. This justifies the observation that ion IX gives rise to three peaks at m/e 82, 83, and 84 in the spectrum of d_2 species. Similar effects of equilibrium of hydrogen migration are observed in the spectrum of IV (*vide infra*).

High-resolution measurements[4] were carried out on IV and IV-3,3-d_2. Each of the elemental compositions in the spectrum of IV is correlated to that of deuterated analog in Table II. It is noted that several peaks

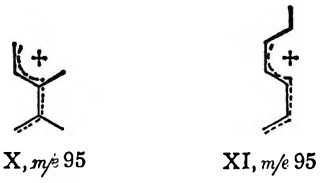
TABLE II[a]

PRINCIPAL MASS SPECTRAL PEAKS OF IV AND THEIR DEUTERIUM SHIFTS IN THE 3,3-d_2 ANALOG

Elemental compositions	
IV	IV-3,3-d_2
$C_9H_{12}O$ (137)	$C_9H_{11}D_2O$ (139)
C_8H_{14} (110)	C_8H_{14} (110)
$C_7H_{10}O$ (110)	$C_7H_8D_2O$ (112)
C_8H_{13} (109)	C_8H_{13} (109), $C_8H_{11}D_2$ (111)
C_7H_9O (109)	C_7H_8DO (110), $C_7H_7D_2O$ (111)
C_8H_{12} (108)	C_8H_{12} (108)
C_7H_{11} (95)	C_7H_{11} (95), $C_7H_9D_2$ (97)
C_6H_7O (95)	C_6H_7O (95), C_6H_6DO (96), $C_6H_5D_2O$ (97)
C_6H_{10} (82)	$C_6H_8D_2$ (84)
C_5H_6O (82)	C_5H_6O (82)
C_6H_9 (81)	C_6H_9 (81), C_6H_8D (82), C_6HD_2 (83)
C_5H_9 (69)	$C_5H_7D_2$ (71)
C_4H_5O (69)	C_4H_5O (69)
C_5H_8 (68)	C_5H_8 (68), C_5H_7D (69), $C_5H_6D_2$ (70)
C_5H_7 (67)	C_5H_7 (67), C_5H_6D (68), $C_5H_5D_2$ (69)

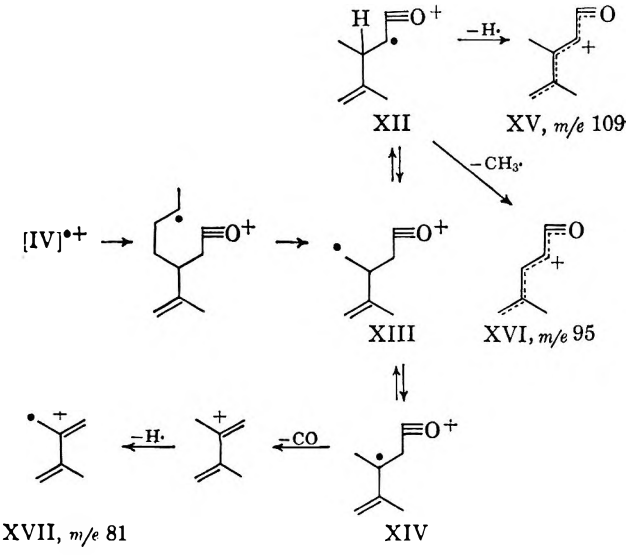
[a] See footnotes in Table I.

in the spectrum of IV split into doublets or triplets upon deuteration. Two postulations are set forward in order to rationalize the results. First, it is



proposed that some ions are not due to single species. For example, both X and XI are proposed for the ion $C_7H_{11}^+$ (m/e 95). The former will shift to m/e 97 while the latter will remain at m/e 95 upon deuteration. Second, an equilibrium among C_3, C_4, and C_5 hydrogen (XII ⇌ XIII ⇌ XIV) prior to the loss of methyl or hydrogen from XII or carbon monoxide from XIV is proposed (Scheme II). This justifies the

SCHEME II



observations that (1) ion XV (m/e 109) gives rise to two peaks at m/e 110 and 111, (2) ion XVI (m/e 95) gives rise to three peaks at m/e 95, 96, and 97, and (3) ion XVII (m/e 81) gives rise to two peaks at m/e 82 and 83 in the spectrum of d_2 species. The splitting of the ions $C_5H_8^+$ (m/e 68) and $C_5H_7^+$ (m/e 67) upon deuteration is rationalized by the postulation of similar equilibrium of hydrogen migration.

In conclusion, it was found that these relatively simple monocyclic ketones undergo quite complicated fragmentation and the fragmentation would involve the double bond and radical migrations. It was also found that while all of the major peaks in the mass spectrum of camphor were due to hydrocarbon species, those of III and IV were due to hydrocarbon and oxygen-containing species. This implies that III and IV, which are the pyrolysis products of camphor, are not concerned to any extent in the electron-impact fragmentation of camphor.

Registry No.—III, 15297-07-1; III-3,3-d_2, 15297-08-2; IV, 5948-04-9; IV-3,3-d_2, 15297-10-6.

Acknowledgment.—The authors are indebted to the Asahi Glass Foundation for financial support.

Efforts toward the Synthesis of Aliphatic Iodonium Salts[1]

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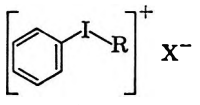
Received September 5, 1967

Although diaryliodonium salts have been known for almost 74 years,[2] salts in which one or both of the ligands are not aromatic are quite rare. Some years ago, Lachman tried unsuccessfully to prepare phenylethyliodonium chloride from diethylzinc and iodobenzene dichloride.[3] Neilands and coworkers have prepared some interesting iodonium betaines derived from the enolate anions of dimedone, methyl acetoacetate, 5-phenyl-1,3-cyclohexanedione, and dibenzoylmethane.[4] Recently, Beringer and Galton have synthesized some acetylenic iodonium salts by the reaction between a lithium acetylide and iodobenzene dichloride.[5]

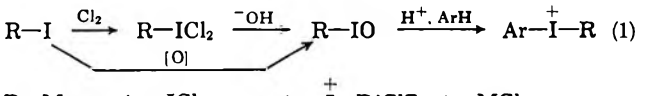
Our incentive to synthesize iodonium salts (I) where R is not aromatic was derived from a study of the mechanism of hydrolysis of diaryliodonium salts



I

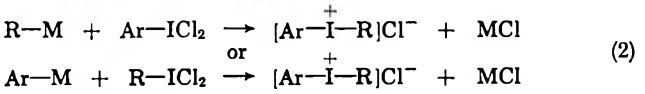
possessing weakly nucleophilic anions.[6] We report here the results of some attempts to prepare partially aliphatic iodonium salts in which the central iodine atom possesses an alicyclic group (R) of types known to be sluggish in both SN1 and SN2 reactions. It was hoped thereby to achieve a measure of kinetic stability toward nucleophilic reagents. The choices of R included cyclopropyl, 7,7-dimethyl-1-norbornyl,[7] and 9-triptycyl[7] radicals.

Two general synthetic approaches were considered: coupling between an appropriate iodoso derivative and an aromatic hydrocarbon[8] (eq 1) and coupling between an appropriate organometallic reagent and an iodo dichloride (eq 2).[9] For the first method, the



$$R\text{—}I \xrightarrow{Cl_2} R\text{—}ICl_2 \xrightarrow{^-OH} R\text{—}IO \xrightarrow{H^+,\ ArH} Ar\text{—}\overset{+}{I}\text{—}R \quad (1)$$

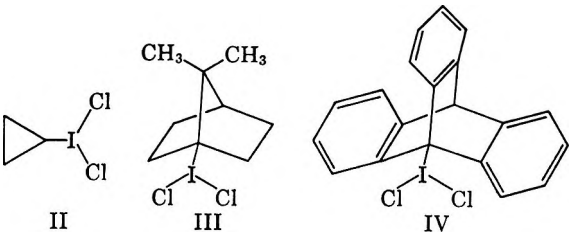
(O)



$$R\text{—}M + Ar\text{—}ICl_2 \longrightarrow [Ar\text{—}\overset{+}{I}\text{—}R]Cl^- + MCl$$
$$\text{or} \qquad (2)$$
$$Ar\text{—}M + R\text{—}ICl_2 \longrightarrow [Ar\text{—}\overset{+}{I}\text{—}R]Cl^- + MCl$$

requisite iodocyclopropane was obtained in 38% yield by treatment of the diacyl peroxide with iodine. A modified Hunsdiecker reaction[10] performed on apocamphane-1-carboxylic acid gave a 52% yield of 1-iodoapocamphane. A convenient synthesis of 9-iodotriptycene was achieved by means of a photochemical iodinative decarboxylation of triptoic acid.[11]

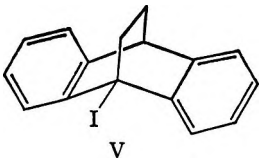
Treatment of iodocyclopropane and 1-iodoapocamphane with chlorine at low temperature gave what appeared to be the expected iodo dichlorides (II and III). These substances were much less stable than corresponding aromatic iodo dichlorides, and had to be stored below 0°.[12] It was not possible to obtain dichloride IV from 9-iodotriptycene, presumably because



II III IV

of steric crowding about the iodine. Dichlorides II and III reacted vigorously with cold, aqueous base[13] with formation of considerable amounts of elemental iodine, but no iodoso derivative could be isolated. Exner, who recently was able to convert a series of iodomethylsulfones to their respective dichlorides, found that these substances also did not hydrolyze to the expected iodoso derivatives.[14] The only reported nonaromatic iodoso compounds are those derived from 1,2-diiodoethylene and 1-chloro-2-iodoethylene (geometry not specified).[15] It is possible that conjugation with a double bond or with an aromatic ring is essential to the stability of the I–O bond.[2b]

In view of the failure of 9-iodotriptycene to add chlorine, 9,10-dihydro-9,10-ethano-9-iodoanthracene (V) was prepared in 63% yield by the modified Hunsdiecker reaction on the carboxylic acid. Treatment of V with chlorine at −25°, however, failed to produce the iodo dichloride.



V

Diaryliodonium salts may also be prepared by *in situ* oxidation of the appropriate iodide to the iodoso derivative in the presence of an aromatic hydrocarbon.[16] In the present cases, this reaction was unsuccessful. For example, starting material was recovered when oxidation was attempted on 9-iodotriptycene with either ammonium persulfate or peracetic acid as the oxidant.

(1) Supported by the National Science Foundation.

(2) (a) See C. Hartman and V. Meyer, *Ber. Deutsch. Chem. Ges.*, **27**, 426 (1894). (b) For a recent review of organic polyvalent iodine compounds, see D. F. Banks, *Chem. Rev.*, **66**, 243 (1966).

(3) A. Lachman, *Amer. Chem. J.*, **18**, 374 (1896).

(4) O. Neilands and G. Vanags, *Proc. Acad. Sci., USSR*, **129**, 983 (1959); **131**, 425 (1960); **141**, 1232 (1961); O. Neilands and B. Karele, *J. Org. Chem., USSR*, **2**, 491 (1966).

(5) F. M. Beringer and S. A. Galton, *J. Org. Chem.*, 30, 1930 (1965).

(6) M. C. Caserio, D. L. Glusker, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 336 (1959).

(7) (a) D. E. Applequist and J. D. Roberts, *Chem. Rev.*, **54**, 1065 (1954); (b) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 178.

(8) F. M. Beringer, *et al.*, *J. Amer. Chem. Soc.*, **75**, 2705 (1953); **81**, 342 (1959).

(9) (a) F. M. Beringer, J. W. Dehn, Jr., and M. Winicov, *J. Amer. Chem. Soc.*, **82**, 2948 (1960); (b) A. N. Nesmeyanov, "Selected Works in Organic Chemistry," The Macmillan Co., New York, N. Y., 1963, p 744.

(10) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

(11) D. H. R. Barton and E. P. Serebryakov, *Proc. Chem. Soc.*, 309 (1962); D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, *J. Chem. Soc.*, 2438 (1965).

(12) Iodomethane dichloride is reported to decompose above −28°; J. Thiele and W. Peter, *Ber. Deutsch. Chem. Ges.*, **38**, 2842 (1905).

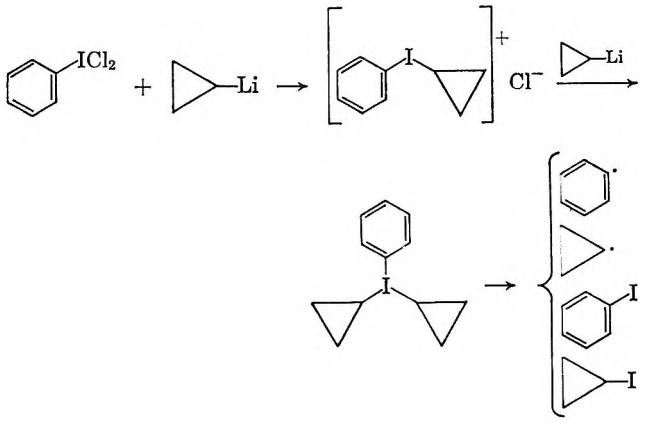
(13) H. J. Lucas, E. R. Kennedy, and M. W. Formo, *Org. Syn.*, **22**, 70 1942).

(14) O. Exner, *Collect. Czech. Chem. Commun.*, 24, 3562 (1959).

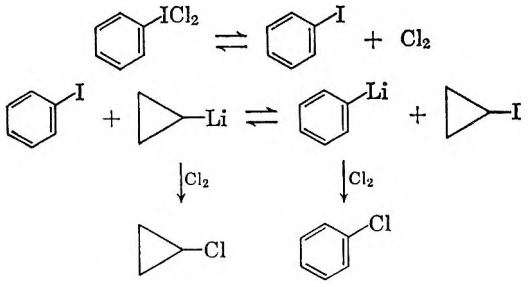
(15) C. Willgerodt, "Die organischen Verbindungen mit mehrwertigem Jod," F. Enke Verlag, Stuttgart, Ger., 1914, pp 250–251.

(16) F. M. Beringer, *et al.*, *J. Amer. Chem. Soc.*, **81**, 342 (1959).

The second general method involves organolithium reagents, but when either iodocyclopropane dichloride (II) or 1-(dichloroiodo)apocamphane (III) was treated with phenyllithium in ether at −75°, or when cyclopropyllithium was similarly treated with iodobenzene dichloride, no iodonium salt could be isolated. Vapor phase chromatographic examination of the etherates generally showed that mixtures of halides were present. Thus, starting with cyclopropyllithium and iodobenzene dichloride, chlorocyclopropane, iodocyclopropane, chlorobenzene, and iodobenzene were all present. The presence of these four constituents could be taken as presumptive evidence for the transient formation of cyclopropylphenyliodonium chloride which subsequently is converted to an unstable trisubstituted iodine that decomposes to phenyl and cyclopropyl radicals.[9a]



However, none of the expected phenylcyclopropane was formed. An alternative explanation for the various products is dissociation of iodobenzene dichloride to chlorine and iodobenzene followed by a series of halogen-metal exchanges.



Addition of benzyne to 9-bromoanthracene gave 9-bromotriptycene in 30–44% yield. Triptycyllithium was then prepared at −70° in ether–benzene and treated with iodobenzene dichloride. No triptycyliodonium salt could be isolated although a small amount of diphenyliodonium salt was isolated, indicative of a halogen–metal exchange followed by coupling of two benzene moieties.

The failure to obtain either aliphatic iodoso derivatives or aliphatic iodonium salts by conventional means may reflect an inherent reactivity or thermodynamic instability of these systems that is not obvious in the aromatic series. Some other possible lines of approach such as electrochemical means,[17] a carbonium ion salt with an appropriate iodide, decomposition of a bridgehead diazonium salt in the presence of an aromatic iodide,[18] etc., were not investigated.

(17) L. L. Miller and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **89**, 593 (1967).

Experimental Section

Iodocyclopropane.—Cyclopropanecarboxylic acid was converted to the acid chloride, which was treated with a urea–hydrogen peroxide complex[19] to give dicyclopropanoyl peroxide. To a suspension of 50.8 g (0.200 mole) of powdered iodine in 20 ml of bromobenzene at 105° was added slowly a solution of 22.5 g (0.132 mole) of dicyclopropanoyl peroxide in 80 ml of bromobenzene. Gas evolution was complete after 3 hr. The mixture was then diluted with 100 ml of pentane, treated successively with sodium bisulfite and sodium carbonate solutions, and dried. Distillation through a spinning-band column gave 17.0 g (38%) of liquid: bp 97–98° (lit.[20] 92–93°); δ ($CHCl_3$) 1.0 (multiplet, 4 H), 2.3 (multiplet, 1 H).

1-Iodoapocamphane.—Camphor-10-sulfonic acid was converted in two steps to ketopinic acid.[21] The Huang–Minlon modification of Wolff–Kishner reduction of this acid proceeded in 80% yield to give apocamphane-1-carboxylic acid. A mixture of 18.3 g (0.080 mole) of red mercuric oxide and 200 ml of cyclohexane was stirred and heated under reflux while 25.9 g (0.154 mole) of apocamphane-1-carboxylic acid in 175 ml of cyclohexane was added dropwise. The apparatus was then covered with toweling and 40.0 g (0.158 mole) of iodine added over 1.5 hr. After being heated under reflux for 3.5 hr more, the suspension was filtered, the filtrate shaken successively with sodium bisulfite and 2 *M* sodium hydroxide solutions, and dried. Evaporation of the solvent gave 23.3 g of crude material which was chromatographed on neutral alumina (pentane as eluent) to give 20.0 g (52%) of white solid: mp 129–131° (lit.[11] 130–132°); ν ($CHCl_3$) 2935, 2850, 1465, 1380, 1255, 965, 905, 880 cm^{-1}; δ ($CHCl_3$) 1.0 (s, 6 H), 1.1–2.2 (complex, 9 H).

9-Iodotriptycene.—Triptoic acid was available either by the addition of benzyne to methyl 9-anthroate followed by saponification or commercially from the Eastman Co. To a stirred and refluxed suspension of 6.7 g (0.0225 mole) of triptoic acid and 30.0 g (0.0677 mole) of lead tetraacetate in 300 ml of dry benzene there was added in portions a 0.408 *M* solution of iodine in benzene. As each portion was added, the flask was irradiated with 100-w tungsten lamp. Addition was stopped when a purple color persisted (*ca.* 145 ml, 0.059 mole). After being heated under reflux for another 1.5 hr, the suspension was filtered, the filtrate washed with sodium bisulfite and sodium hydroxide solutions and water and brine, then dried. Evaporation of the solvent left 2.29 g of a solid which was sublimed to give 1.97 g (23%) of white material: mp 259–265° (lit.[22] 262–265°); ν ($CHCl_3$) 3045, 2975, 1610, 1450 (doublet), 1285, 1145, 1035, 920, 830 cm^{-1}; δ ($CDCl_3$) 5.4 (s, 1 H), 6.8–7.1 (complex, 6 H), 7.2–7.4 (complex, 3 H), 7.5–7.9 (complex, 3 H).

Anal. Calcd for $C_{20}H_{13}I$ (380.0): C, 63.16; H, 3.45; I, 33.39. Found: C, 63.29; H, 3.49; I, 33.50.

9,10-Dihydro-9,10-ethano-9-iodoanthracene (V).—The modified Hunsdiecker reaction previously described for the preparation of 1-iodoapocamphane was applied to 6.0 g (0.024 mole) of 9,10-dihydro-9,10-ethanoanthracene-9-carboxylic acid.[23] There resulted 5.0 g (63%) of white solid: mp 136–138°; ν ($CHCl_3$) 3040, 2985, 2925, 1605, 1450, 1290, 1140 (doublet), 1035, 915, 820 cm^{-1}; δ ($CDCl_3$) 1.4–1.9 and 2.1–2.5 (complex, 4 H), 4.2 (t, J = 2.6 Hz, 1 H), 6.9–7.2 (complex, 6 H), 7.5–7.8 (complex, 2 H).

Anal. Calcd for $C_{16}H_{13}I$ (332.0): C, 57.83; H, 3.95; I, 38.22. Found: C, 57.66; H, 3.97; I, 38.19.

Chlorination of 1-Iodoapocamphane.—The following procedure is illustrative of conditions used in the chlorination experiments. A solution of 13 g (0.052 mole) of 1-iodoapocamphane in 45 ml of dry chloroform was stirred and cooled to −20°. Chlorine, scrubbed by passage through two towers of concentrated sulfuric acid and passage through glass wool, was admitted for 1.5 hours.

(18) L. Mascarelli, *Atti. Linc.*, **16** (II), 582 (1907).

(19) C-S. Lu, E. W. Hughes, and P. A. Giguere, *J. Amer. Chem. Soc.*, **63**, 1507 (1941).

(20) D. E. Applequist and D. F. O'Brien, *ibid.*, **85**, 743 (1963).

(21) P. D. Bartlett and L. H. Knox, *ibid.*, **61**, 3184 (1939); *Org. Syn.*, **45**, 14, 55 (1965).

(22) P. D. Bartlett and F. D. Greene, *J. Amer. Chem. Soc.*, **76**, 1088 (1954).

(23) The authors are indebted to Professor J. S. Meek for a generous sample of this acid.

The precipitated brick-orange dichloride (III) was removed by filtration and transferred quickly to a container for immediate storage in a refrigerator; the yield was 13–16 g (78–95%). At room temperature, spontaneous evolution of chlorine from the solid occurred. When a chloroform solution of the dichloride is allowed to sit exposed to the air at room temperature for a day, starting material can be recovered in good yield.

Attempted Hydrolysis of 1-(Dichloroiodo)apocamphane.—Approximately 1.2 g (3.7 mmoles) of 1-(dichloroiodo)apocamphane (III) was placed in a mortar at −5°, covered with 2 g of anhydrous sodium carbonate, and then ground with a pestle. With trituration there was added 0.5 ml of 5 *M* sodium hydroxide; a black paste resulted. When additional 2.5 ml of base was added, the color of the suspension changed to white. Water (20 ml) was added and grinding continued until all solid matter had gone into solution. Tests for iodide and chloride ions were positive; when the solution was extracted with ether and the ether evaporated, no residue of iodoso compound was obtained. The fate of the carbon skeleton was not pursued further.

9-Bromotriptycene.—Benzyne, generated by the method of Friedman and Logullo[24] from 3.7 g (0.026 mole) of anthranilic acid and 3.5 g (0.030 mole) of isoamyl nitrite, was added to 6.2 g (0.024 mole) of 9-bromoanthracene in 80 ml of methylene chloride. A chromatographic separation yielded 3.5 g (44%) of crude, yellow product which was recrystallized from methylcyclohexane to give nearly white crystals: mp 250–254° (lit.[25] 246–248°); ν ($CHCl_3$) 3045, 2980, 1605, 1450 (doublet), 1285, 1155, 1035, 935, 840 (doublet) cm^{-1}.

Anal. Calcd for $C_{20}H_{13}Br$ (333.0): C, 72.07; H, 3.94; Br, 23.99. Found: C, 72.30; H, 4.00; Br, 23.88.

Iodobenzene Dichloride and Triptycyllithium.—A solution of 4.00 g (12 mmole) of 9-bromotriptycene in a mixture of 95 ml of benzene and 225 ml of ether was cooled to −50°. Over a period of 0.75 hr there was added with stirring under argon 9.5 ml (15.2 mmole) of 1.6 *M* *n*-butyllithium in hexane. The mixture was stirred for 0.5 hr at −50°, then for 1 hr at −70° and 3.25 g (11.8 mmole) of iodobenzene dichloride was added portionwise. The resulting mixture was stirred at −70° for 10 hr and then the reaction flask was allowed to stand in a refrigerator for 2 days. A suspended white solid (0.47 g) which was removed by filtration and washed with water proved to be 9-bromotriptycene, mp 253–255°. Addition of potassium iodide solution to the above aqueous filtrate precipitated 0.1 g of diphenyliodonium iodide, mp 178°, and nmr spectrum identical with that of an authentic sample. The ethereal residue which contained chlorobenzene and iodobenzene in roughly equal amounts on evaporation gave 2.1 g of a mixture of 9-bromotriptycene and 9-iodotriptycene. No unreacted iodobenzene dichloride could be isolated.

Registry No.—1-Iodoapocamphane, 933-27-7; 9-iodotriptycene, 15364-53-1; V, 15364-54-2; 9-bromotriptycene, 15364-55-3.

(24) L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963).
(25) P. D. Bartlett, *et al.*, *ibid.*, **72**, 1003 (1950).

The Synthesis of Chlorobenzene-d_5 in a Radiofrequency Discharge

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Studies conducted in this laboratory dealing with the reactions of halobenzenes in an electrodeless radiofrequency (RF) discharge required the use of isotopically pure chlorobenzene-d_5. This material is not available commercially and a survey of the literature failed to uncover a method for its preparation. The synthesis of bromobenzene-d_5 has, however, been reported[1,2] and this material is commercially available[3] in 99.5% isotopic purity. Hence, a method for efficiently converting bromobenzene-d_5 into chlorobenzene-d_5 would be desirable.

Walling and Miller[4] had converted bromobenzene into chlorobenzene by photolytic chlorination, and it seemed that this procedure might be suitable for the synthesis of chlorobenzene-d_5. However, the original procedure afforded low yields of chlorobenzene based on the amount of bromobenzene reacted. In an attempt to maximize the conversion of bromobenzene into chlorobenzene by this reaction, a wide range of chlorine to bromobenzene ratios were investigated in this laboratory. Repeated attempts to obtain chlorobenzene by this route afforded a maximum of 20% conversion based on the amount of bromobenzene used.

Work performed elsewhere,[5] as well as in this laboratory, has demonstrated that aromatic carbon–halogen bonds can be broken with facility in an electrodeless RF discharge. Thus, it seemed reasonable that bromobenzene might be efficiently converted to chlorobenzene if it were passed through an RF discharge in the presence of chlorine. An attempt to effect this conversion by passing an equal mole ratio of chlorine gas and bromobenzene vapor through a 28-Mc electrodeless discharge afforded an approximately 1:1 mixture of chlorobenzene and bromobenzene together with trace amounts of benzene and higher boiling materials. The recovered products represented about 87% of the bromobenzene exposed to the discharge; the remainder undergoes complex competing reactions to give polymeric products and noncondensable gases. The over-all yield of chlorobenzene, based on the amount of bromobenzene reacted, is therefore approximately 45%.

The maximum conversion to chlorobenzene seems to occur with a 1:1 mole ratio of bromobenzene to chlorine. An investigation disclosed that higher chlorine–bromobenzene ratios resulted in the formation of a greater proportion of nonrecoverable products and a sharply increased percentage of benzene in the recovered material. For example, when a 7:1 ratio of chlorine to bromobenzene was used, only 43% of the reacted bromobenzene was converted to condensable materials; the remainder reacted to form polymeric materials and noncondensable gases. The condensable product was found to be a mixture of chlorobenzene and bromobenzene, together with a substantial amount of benzene. The over-all yield of chlorobenzene, based on the amount of bromobenzene reacted, was greatly reduced. These data are summarized in Table I.

Experiments in which bromobenzene-d_5 was used and the product mixture separated by preparative gas chromatography afforded chlorobenzene which was shown to be fully deuterated by mass spectrometry. Additionally, the recovered bromobenzene and benzene were also found to be fully deuterated.

The mechanism by which the presence of excess chlorine results in the formation of increased amounts

(1) R. I. Akawie, U. S. Atomic Commission NAA-SR-3043 (1958); see *Chem. Abstr.*, **53**, 11,295*d* (1959).
(2) B. Bak, J. N. Schoolery, and Y. A. Williams, *J. Mol. Spectr.*, **22**, 525 (1958).
(3) Stohler Isotope Chemicals, Rutherford, N. J. 07070.
(4) B. Miller and C. Walling, *J. Amer. Chem. Soc.*, **79**, 4187 (1957).
(5) J. K. Stille and C. E. Rix, *J. Org. Chem.*, **31**, 1591 (1966).

TABLE I
PRODUCTS FORMED FROM CHLORINE AND BROMOBENZENE IN A RADIOFREQUENCY DISCHARGE

Mole ratio of Cl_2–C_6H_5Br	% composition of material condensed at −78° [a] C_6H_5Br	C_6H_5Cl	C_6H_6	Higher boiling products
1:1	50	49	1	0.5
7:1	44	33	23	Trace

[a] Normalized to exclude polymeric deposits and noncondensable gases.

of benzene remains obscure at present. However, a free-radical process in which chlorine atoms abstract hydrogen from the aromatic ring to form HCl, which subsequently undergoes hydrogen abstraction by phenyl radicals to form benzene, seems likely. Further work is planned to investigate this possibility.

Experimental Section

A Heathkit Model TX-1 transmitter operating at a frequency of 28 Mc and an output of 100 w was used to supply power to the discharge tube. Power was coupled into the discharge tube, an 18-mm o.d. Pyrex tube, by an externally wound copper helix 2 cm in diameter and 11 cm long. The discharge tube wall temperature normally was approximately 30°.

In operation, the system was evacuated to <0.01 torr and then back filled with bromobenzene vapor and chlorine gas which were introduced through an inlet manifold-mixing chamber. The total pressure was adjusted to approximately 0.3 torr. Bromobenzene was bled through the discharge at a rate of 0.004 to 0.006 mole per hour and chlorine vapor was introduced at whatever rate was required to give the desired mole ratio.

Both analytical and preparative gas chromatography was conducted using SE-30 columns. The deuterium content of the discharge products was measured by mass spectrometry.

Bromobenzene-d_5 of 99.5% isotopic purity was obtained from Stohler Isotope Chemicals. Reagent grade chlorine was obtained from the Matheson Co.

Registry No.—Chlorobenzene-d_5, 3114-55-4.

Acknowledgment.—We wish to thank the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Mass spectral determinations were made by Dr. K. V. Krishnamurty and Mr. Gary Hermann.

A Convenient Procedure for the Preparation of Low-Boiling Alcohols and Amines *via* Lithium Aluminum Hydride and Deuteride Reduction

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In order to facilitate the elucidation of the mechanisms of aprotic and protic diazotizations of aliphatic amines, it was necessary to prepare a series of deuterated amines and alcohols. The syntheses usually involved a $LiAlH_4$ or $LiAlD_4$ reduction of either a nitrile, acid, or ester. Since the products of these reductions were low boiling and water soluble, isolation procedures usually recommended[1] were generally unsatisfactory. A procedure was developed which is efficient and convenient and is based on the use of high-boiling ether solvents as the reaction medium and high-boiling ether alcohols as product liberating reagents and isolation of product by distillation directly from the reaction mixture, a technique that heretofore has only been used in the preparation of labeled alcohols in a few isolated cases.[2-6] The scope and limitations of this technique were examined in detail and are reported herein.

The technique was used successfully to prepare labeled and unlabeled amines and alcohols with boiling points up to 117° in yields (isolated) ranging from 50 to 90%. Larger scale reductions (1–2 moles of oxidant) generally gave better yields (80–90%), especially in the case of the low molecular weight amines.

The use of this technique for the preparation and isolation of amines has not been previously reported. It is more convenient and efficient than the classical methods of product work-up and isolation from complex hydride reductions.[1]

All of the reductions listed in Table I were conducted in diethylene glycol diethyl ether. This solvent is usually satisfactory, however, some reductive cleavage[7] occurs yielding ethanol, which can be an annoying product contaminant. This was first suspected in the reduction of 2,2,2-d_3-acetic acid, since the deuterium content of the ethyl alcohol obtained was approximately 6%-d_0, 2%-d_2, and 92%-d_3. This was verified when the reduction of propionic acid was conducted in diethylene glycol diethyl ether. The propanol obtained contained 4% ethanol. However, other solvents, such as diethylene glycol dibutyl ether or diglyme,[8] can be used when necessary to avoid this problem.

Several limitations exist in the choice of the quenching alcohols. High boiling alcohols, such as octyl alcohol, are not satisfactory since insoluble soaps are formed which completely frustrate work-up. 1,2-Diols, *e.g.*, ethylene glycol, form insoluble gelatinous precipitates which effectively prevent complete hydride decomposition and product isolation. Monoalkyl ethers of ethylene and diethylene glycol, *e.g.*, *n*-butoxyethanol and diethylene glycol monoethyl ether, were found to be the most suitable.

Experimental Section

General Reaction Procedure.—The nitrile, ester, or acid (1 mol) was added dropwise (0.5–1 hr) at 5–70° (external cool-

(1) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948); *ibid.*, **69**, 1197 (1947).

(2) For example, reduction of carbon dioxide[3] and acetic-1-C^{14} acid[4] with $LiAlH_4$ was carried out in diethylene glycol diethyl ether and after addition of diethylene glycol monobutyl ether the alcohols (methanol and ethanol-1-C^{14}) were distilled out from the reaction mixture. Similarly ethanol[5] was prepared *via* $LiAlH_4$ reduction of acetic acid followed by quenching with β-phenoxyethanol and 1,1-d_2-propanol[6] by reduction of phenyl propionate in triglyme (triethylene glycol dimethyl ether) followed by addition of benzyl alcohol.

(3) R. F. Nystrom, W. H. Yanko, and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 441 (1948).

(4) R. Ostwald, P. T. Adams, and B. M. Tolberts, *ibid.*, **74**, 2425 (1952).

(5) J. D. Cox and H. S. Turner, *J. Chem. Soc.*, 3176 (1950).

(6) R. L. Baird and A. A. Aboderin, *J. Amer. Chem. Soc.*, **86**, 252 (1964).

(7) Cleavage of ethers by $LiAlH_4$ has also been observed by others. *Cf.* ref 3 and 4 and J. D. Cox, H. S. Turner, and R. J. Warne, *J. Chem. Soc.*, 3167 (1950).

(8) These solvents are partially cleaved to butanol and methanol, respectively.

TABLE I
ISOLATED YIELDS OF AMINES AND ALCOHOLS

Reactant	Moles	Reductant[a]	Product	% yield
CD_3CO_2D	1.0	$LiAlH_4$	CD_3CH_2OH	80–90[b]
$CH_3CH_2CO_2H$	0.1	$LiAlH_4$	$CH_3CH_2CH_2OH$	85[c]
$CH_3CD_2CO_2H$	0.26	$LiAlH_4$	$CH_3CD_2CH_2OH$	76
CH_3CD_2CN	0.11	$LiAlH_4$	$CH_3CD_2CH_2NH_2$	55
CD_3CH_2CN	0.64	$LiAlH_4$	$CD_3CH_2CH_2NH_2$	50
$(CH_3)_2CHCN$	0.12	$LiAlD_4$	$(CH_3)_2CHCD_2NH_2$	83
$(CH_3)_2CDCO_2CH_2CH_2OC_4H_9$	1.2	$LiAlH_4$	$(CH_3)_2CDCH_2OH$	78
$(CD_3)_2CDCN$	0.1	$LiAlH_4$	$(CD_3)_2CD—CH_2NH_2$	81
$CH_3CH_2CH_2CN$	0.24	$LiAlD_4$	$CH_3CH_2CH_2CD_2NH_2$	67
$CH_3CH_2CD_2CN$	0.11	$LiAlH_4$	$CH_3CH_2CD_2CH_2NH_2$	86
$CH_3CD_2CH_2CN$	0.09	$LiAlH_4$	$CH_3CD_2CH_2CH_2NH_2$	76
$CD_3CH_2CH_2CN$	0.13	$LiAlH_4$	$CD_3CH_2CH_2CH_2NH_2$	82
	1.0	$LiAlH_4$		75

[a] All reductions were effected in diethylene glycol diethyl ether and quenched with butoxyethanol or diethylene glycol monoethyl ether. [b] Contaminated with CH_3CH_2OH. [c] Contaminated with ~5% CH_3CH_2OH.

ing) to a stirred mixture of lithium aluminum hydride (or deuteride) (1 mole)[9] in diethylene glycol diethyl ether[10] (500 ml). The mixture was then heated for 1 hr at 100°. Hydrolysis with *n*-butoxyethanyl alcohol (360 g, 3 mol) was effected at 0–10°. A short distilling column was inserted and the product directly distilled.[11] The product was usually of sufficient purity for use in further chemical transformations. Further purification was accomplished by redistillation or in the case of amines, the amine hydrochloride was prepared.

Registry No.—Lithium aluminum hydride, 1302-30-3; lithium aluminum deuteride, 14128-54-2.

Acknowledgment.—The authors are grateful for financial support from the National Science Foundation (Grant No. GP-3976).

(9) In all cases, reduction of nitriles, acids, or esters, 1 mole of complex hydride was used per mole of oxidant.

(10) The diethylene glycol diethyl ether was distilled over calcium hydride or preferably lithium aluminum hydride.

(11) This distillation requires elevated pot temperatures, probably as a result of hydrogen bonding of the product with the monoalkyl glycol ether or Lewis acid–base complexing with the complex metal alcoholate. It is recommended that a portion of material be collected above the boiling point of product (glpc check) and that this be redistilled in order to obtain the maximum yield.

Anomalies in the Acetylation of *o*- and *p*-Xylenes[1]

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In the course of another investigation it became necessary to prepare 3,4-dimethylacetophenone (**1**). The material prepared from the aluminum chloride-catalyzed reaction of acetic anhydride and *o*-xylene following the standard procedure[2,3] was unexpectedly found (*via* glpc analysis)[4] to be a two-component mixture of 3,4-dimethylacetophenone (**1**, 52%) and 2,4-dimethylacetophenone (**2**, 48%).

Acetyl chloride in various solvents has also been widely used to effect acetylation of aromatic hydrocarbons.[5] The general procedure[6] for acetylation using acetyl chloride is the addition of an equimolar mixture of acetyl chloride–aromatic hydrocarbon to a stirred mixture of 1 mol of aluminum chloride in carbon disulfide. Ferric chloride has also been used as the catalyst in this method.[7] In the acetic anhydride procedure,[2,3] the anhydride (1 mol) is added dropwise to a stirred mixture of the aromatic hydrocarbon (1.25 mol) and aluminum chloride (2.8 mol) in carbon disulfide. Another useful technique introduced by Baddeley[8] and later used extensively by Brown[9] for acetylation of the methylbenzenes involves the addition of a homogenous solution of a 1:1 molar complex of acetyl chloride–aluminum chloride in ethylene chloride to a solution of the aromatic hydrocarbon (1 mol) in ethylene chloride. Since 2,4-dimethylacetophenone (**2**) was a major product from the reaction of acetic anhydride with *o*-xylene, it was felt that this reaction should be investigated to determine its origin and that a general survey of acetylation procedures would be useful. The results of this investigation are presented in Table I.

The unexpected product **2** which occurs both from acetic anhydride acetylation (acetic anhydride addition) of *o*-xylene or *p*-xylene is not a result of isomerization of the acetophenones, but it does arise by prior isomerization of the *o*- or *p*-xylenes to *m*-xylene presumably through the more stable σ-complex of *m*-xylene.[10] This was demonstrated by running a series of reactions in which the acetic anhydride was present in catalytic amounts (Table II). Little or no 2,4-dimethylaceto-

(1) Financial support (Grant No. 1348-AL) from the Petroleum Research Fund is gratefully acknowledged.

(2) (a) C. R. Noller and R. Adams, *J. Amer. Chem. Soc.*, **46**, 1889 (1924); (b) R. Adams and C. R. Noller in "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 109.

(3) In fact 3,4-dimethylacetophenone was previously prepared by this method. *Cf.* W. P. Campbell and M. D. Soffer, *J. Amer. Chem. Soc.*, **64**, 417 (1942).

(4) The mixture could also be separated by fractional distillation. *Cf.* Experimental Section.

(5) P. H. Gore in "Friedel-Crafts and Related Reactions," Vol. III, Part 1, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter XXXI.

(6) (a) C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 3. (b) A. Claus and R. Wollner, *Ber.*, **18**, 1856 (1885).

(7) (a) W. H. Perkin, Jr., and J. F. S. Stone, *J. Chem. Soc.*, **127**, 2275 (1925); (b) C. S. Marvel, J. H. Saunders, and C. G. Overberger, *J. Amer. Chem. Soc.*, **68**, 1085 (1946).

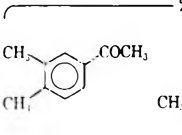
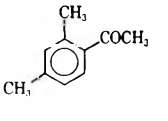
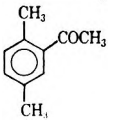
(8) G. Baddeley, *J. Chem. Soc., Suppl. 1*, S99 (1949).

(9) (a) H. C. Brown, G. Marino, and L. M. Stock, *J. Amer. Chem. Soc.*, **81**, 3310 (1959); (b) G. Marino and H. C. Brown, *ibid.*, **81**, 5929 (1959).

(10) (a) D. A. McCaulay, B. H. Shoemaker, and A. P. Lien, *Ind. Eng. Chem.*, **42**, 2103 (1950); (b) H. C. Brown and J. D. Brady, *J. Amer. Chem. Soc.*, **74**, 3570 (1952).

TABLE I

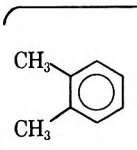
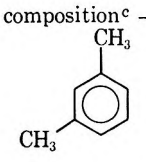
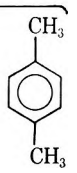
ACETYLATION OF *o*-, *m*-, AND *p*-XYLENES. EVALUATION OF REACTION TECHNIQUES

Run	Reagent added[a]	Moles $Me_2C_6H_4$	Moles Ac_2O	Moles AcCl	Moles $AlCl_3$	Solvent (ml)	Addn time, hr	Reflux time, hr	Yield, %[b]	% composition 		
1	Ac_2O	*o*- 2.0	2.2		5.4	CS_2 (1150)	2.25	2.5	81[c]	52	48	
2	Ac_2O	*o*- 0.125	0.1		0.28	CS_2 (50)	0.5	1.0	96	88	12	
3	*o*-$Me_2C_6H_4$	*o*- 0.125	0.1		0.28	CS_2 (50)	0.5	1.0	89	98	2	
4	$AlCl_3$	*o*- 0.125	0.1		0.28	CS_2 (50)	0.5	1.0	71	99	1	
5	AcCl	*o*- 0.125		0.1	0.12	CS_2 (50)	0.5	1.0	99	94	6	
6	*o*-$Me_2C_6H_4$	*o*- 0.125		0.1	0.12	CS_2 (50)	0.5	1.0	94	100		
7	AcCl-$AlCl_3$[d]	*o*- 1.0		1.0	1.0	EC[e] (750)	3.0		94[c]	100		
8	*o*-$Me_2C_6H_4$	*o*- 0.125		0.1	0.1	EC[e] (100)	0.5		99	100		
9	Ac_2O	*p*- 0.125	0.1		0.28	CS_2 (50)	0.5	1.0	99		31	69
10	*p*-$Me_2C_6H_4$	*p*- 0.125	0.1		0.28	CS_2 (50)	0.5	1.0	91			100
11	Ac_2O	*m*- 0.125	0.1		0.28	CS_2 (50)	0.5	1.0	86		100	
12	*m*-$Me_2C_6H_4$	*m*- 0.125	0.1		0.28	CS_2 (50)	0.5	1.0	90		100	
13	Ac_2O	Tech.[f] 0.125	0.1		0.28	CS_2 (50)	0.5	1.0	96	16	76	8
14	Ac_2O	Tech.[f] 2.0	2.2		5.4	CS_2 (1150)	4.0	2.0	82[c]	9	91	

[a] Added to a stirred mixture of the other reagents. [b] Glpc yield as determined by internal standard technique (4-methylacetophenone). [c] Isolated yield. [d] Homogeneous solution of complex in 500 ml of ethylene chloride. [e] EC = ethylene chloride. [f] Technical xylene (52%, *m*-; 38%, *o*-; 10%, *p*-).

TABLE II

ALUMINUM CHLORIDE-CATALYZED ISOMERIZATION OF THE XYLENES IN CARBON DISULFIDE[a,b]

$Me_2C_6H_4$	% composition[c] 		
ortho	77	23	
meta		98	2
para		27	73

[a] Reaction conditions were 0.125 mol of xylene, 0.28 mol of $AlCl_3$, and one drop of Ac_2O as a cocatalyst in 50 ml of CS_2 at reflux for 1.5 hr. [b] Reaction mixture is heterogeneous. [c] Glpc analyzed on 10 ft × 1/8 in. 5% Morflex 530-5% Bentone 34 on Chromosorb W 60–80.

phenone was formed from *o*- or *p*-xylene when the acetylation with acetic anhydride was carried out by addition of the hydrocarbon or aluminum chloride to the reaction mixture.

Prior isomerization of the xylene is time dependent. Thus, *o*-xylene is isomerized to the extent of 48% when the addition time of acetic anhydride was 2.25 hr (Table I, run 1, 2.0-mol scale) but only to 12% when the addition time was 0.5 hr (run 2, 0.1-mol scale).

The results are even more surprising since it has been shown that *o*-xylene is acetylated more rapidly than *m*-xylene (2.6 times faster in nitromethane).[11] The formation of a mixture of ketones is best explained by the occurrence of two competitive processes: (1) direct acetylation of unrearranged xylene to give the desired product and (2) isomerization to give the more stable *m*-xylene which is then acetylated.

This was dramatically demonstrated in the acetic anhydride acetylation of commercial xylene. All three dimethylacetophenones were produced when the addition time was only 0.5 hr (Table I, run 13); however, when the addition time was 4 hr (run 14), essentially only 2,4-dimethylacetophenone was formed.

(11) G. A. Olah, M. E. Moffatt, S. J. Kuhn, and B. H. Hardie, *J. Amer. Chem. Soc.*, **86**, 2198 (1964). These relative rates may not be applicable to reactions in carbon disulfide.

From the standpoint of laboratory convenience acetyl chloride is preferred over acetic anhydride since less aluminum chloride is required and the work-up is somewhat simpler. Isomerically pure dimethylacetophenones are only obtained when (1) acetyl chloride (or anhydride)–aluminum chloride mixture (soluble in ethylene chloride) is added to the xylene in ethylene chloride, (2) aluminum chloride is added to a mixture of acetyl chloride (or anhydride) and xylene in carbon dioxide or ethylene chloride, or (3) when there is an addition of the xylene to a mixture of aluminum chloride and acetyl chloride (or anhydride) in carbon disulfide.

Experimental Section

Infrared and nmr spectra were obtained on a Beckman IR8 spectrophotometer and a Varian A-60 spectrometer, respectively. All chemical shifts are reported in parts per million (ppm) on the δ scale relative to an internal standard of tetramethylsilane. Gas chromatographic data were obtained on a Varian-Aerograph Hy-Fi III Model 1200 using a 15 ft × 1/8 in. 5% silicone grease on Chromosorb G 60–80 column. The relative retention times of the acetophenones under conditions of column temperature (150°), injection temperature (230°), detector temperature (270°) and nitrogen (15 psi tank pressure), and hydrogen (5 psi tank pressure) pressure were as follows: 4-methylacetophenone (20.0 min), 1.00; 2,5-dimethylacetophenone, 1.24; 2,4-dimethylacetophenone, 1.32; and 3,4-dimethylacetophenone, 1.77.

Procedure.—The procedure followed for the carbon disulfide runs was basically that described in "Organic Syntheses."[12] The addend (see Table I) was added dropwise at such a rate that caused gentle refluxing of the carbon disulfide. The mixtures were analyzed by glpc with 4-methylacetophenone as an internal standard.

The components from run 1 (Table I) were separated by preparative glpc (6 ft × 0.25 in. 15% Apiezon L 5% Bentone 34 on Chromosorb P 60–80) and by fractional distillation (18-in. spinning-band column) to give 2,4-dimethylacetophenone, bp 92° (5.5 mm) [lit.[7b] 92–94° (5 mm)], and 3,4-dimethylacetophenone, bp 103° (5.5 mm) [lit.[7b] 95–97° (4 mm)]. The spectral data on these components agreed with that reported below. The identity of 2,4-dimethylacetophenone was further confirmed by oxidation[12] to 2,4-dimethylbenzoic acid, mp 124–126° (lit.[13] 126–127°); the amide derivation[14] had mp 179–180° (lit.[13] 179–181°).

(12) *Cf.* M. S. Newman and H. L. Holmes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 428.

(13) "Dictionary of Organic Compounds," Vol. II, I. Heilbron, Ed., Oxford University Press, New York, N. Y., 1965, p 1149.

(14) *Cf.* R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley and Sons, Inc., New York, N. Y., 1964, p 235.

For the ethylene chloride run[8,9] a 1:1 complex of aluminum chloride (133 g, 1.0 mol) and acetyl chloride (78.5 g, 1.0 mol) was prepared in 500 ml of ethylene chloride. This solution was added dropwise over 3 hr to a mechanically stirred solution of *o*-xylene (106 g, 1.0 mol) and 750 ml of ethylene chloride in a 3-l., three-necked flask. The reaction mixture was hydrolyzed by pouring it onto a slurry of ice–concentrated hydrochloric acid. The layers were separated. The organic layer was washed with water, 5% sodium bicarbonate solution, and water before being dried over calcium chloride. Rotary evaporation left 140 g (94%) of 3,4-dimethylacetophenone (essentially 100% pure by glpc), bp 100° (5 mm) and n^{20}D 1.5385 [lit.[7b] bp 95–97° (4 mm), n^{20}D 1.5381].

Ir and nmr analyses were run on the crude reaction products from the runs where glpc showed the presence of only one component. In this manner the products from runs 6, 10, and 11 (Table I) were positively identified as 3,4-dimethylacetophenone, 2,5-dimethylacetophenone, and 2,4-dimethylacetophenone, respectively. The nmr of 3,4-dimethylacetophenone showed a singlet at δ 2.28 (6 H), aromatic methyls; a singlet at 2.44 (3 H), acetyl methyl; a doublet at 7.10 (J = 7.5 cps, 1 H), aromatic hydrogen in the 5 position; a doublet at 7.61 (J = 7.5 cps); and an overlapping singlet at 7.64 (2 H) assigned to the aromatic hydrogen in the 6 position and the aromatic hydrogen in the 2 position, respectively. The nmr of 2,5-dimethylacetophenone showed a singlet at δ 2.22 (3 H), aromatic methyl in the 5 position; a broadened singlet at 2.38 (6 H), aromatic methyl in the 2 position and acetyl methyl; a singlet at 6.99 (2 H), aromatic hydrogens in the 3 and 4 positions; and a singlet at 7.37 (1 H), aromatic hydrogen in the 6 position. The nmr of 2.4-dimethylacetophenone showed a singlet at δ 2.25 (3 H), aromatic methyl in the 4 position, a singlet at 2.40 (3 H), aromatic methyl in the 2 position; a singlet at 2.46 (3 H), acetyl methyl; a broad band at 6.98 (2 H), aromatic hydrogens in the 3 and 5 positions, and a doublet at 7.57 (J = 7.5 cps, 1 H), aromatic hydrogen in the 6 position.

Registry No.—*o*-Xylene, 95-47-6; *n*-xylene, 108-38-3; *p*-xylene, 106-42-3; 3,4-dimethylacetophenone (1), 3637-01-2; 2,4-dimethylacetophenone (2), 89-74-7; 2,5-dimethylacetophenone, 2142-73-6.

A Facile and Economic Synthesis of Ethanol-OD[1]

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The use of large quantities of deuterium-labeled solvents is often precluded due to economic considerations. In some of our studies we required large quantities of ethanol-OD of high isotopic purity and thus were forced to find a low-cost procedure for its preparation. Previously, the most attractive procedure employed the acid-catalyzed deuterolysis of tetraethylorthocarbonate.[3] The current prohibitively high cost of tetraethylorthocarbonate, and the fact that only 2 moles of product are produced per mole of starting material, precluded the use of this material. Triethylorthocarbonate[4] and diethyl oxalate[5] have been used as starting materials; however, the costs are somewhat greater, and the utilization of starting material is poorer. Aluminum ethoxide[6] has also been employed as a starting material giving excellent yields of product. Aluminum ethoxide is quite expensive; however, it can be synthesized separately.[7] Several exchange procedures have been reported but none are suitable for the preparation of high isotopic purity ethanol-OD.

We have found that the uncatalyzed deuterolysis of tetraethylorthosilicate, followed by distillation of the ethanol-OD from the residual silicon dioxide under reduced pressure, produces 90% yields (based on the availability of all four ethoxyl groups) of ethanol-OD of very high isotopic (no O–H detectable by nmr) and chemical purity (>99.7%). The reaction may be carried out on a multiple mole basis. The cost of the ethanol-OD prepared by this procedure is roughly five cents per gram (based on the cost of the chemicals used) and is *considerably* cheaper than presently commercially available ethanol-OD of lower isotopic purity.

Although we have not extended this procedure to other alkanols-OD, a number of tetraalkylorthosilicates are available thus potentially providing sources of alkanols-OD considerably below current commercial prices.

Experimental Section

Preparation of Ethanol-OD.—The following procedure is typical although the quantities may be increased or decreased. A mixture of 104.2 g (0.5 mole) of tetraethylorthosilicate (Aldrich Chemical Co.) and 40 g (2 moles) of deuterium oxide (99.8%, Diaprep Inc.) is stirred in a stoppered distillation flask at room temperature until a viscous, miscible mixture is obtained (approximately 24 hr). The distillation flask is attached to a distillation head and condenser and subjected to distillation at 2 mm, collecting the product in a flask immersed in a Dry Ice–acetone bath, until no further product is produced. The ethanol-OD (90% average yield) displayed practically no O–H absorption in the infrared spectrum and no detectable OH in the nmr (<0.5%). The gas–liquid partition chromatogram indicated the presence of 0.2% D_2O, the remainder being C_2H_5OD.

Registry No.—Ethanol-OD, 925-93-9.

(1) Supported by the Petroleum Research Fund of the American Chemical Society, Grant 1225-A1, 3.

(2) Alfred P. Sloan Research Fellow, 1967–1969.

(3) J. D. Roberts, C. M. Regan, and Inka Allen, *J. Amer. Chem. Soc.*, **74**, 3679 (1952); D. S. Tarbell and W. E. Lovett, *ibid.*, **78**, 2259 (1956).

(4) V. J. Shiner, Jr., and M. L. Smith, *ibid.*, **83**, 593 (1961).

(5) C. Párkányi and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 2491 (1963).

(6) W. R. Vaughan, M. V. Andersen, Jr., H. S. Blanchard, D. I. McCane, and W. L. Meyer, *J. Org. Chem.*, **20**, 819 (1955).

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N.Y., 1943, p 599.

The Preparation of Fluorodinitroacetonitrile and Fluorodinitroacetamide[1]

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Chlorination of the dinitroacetonitrile anion was found to produce the chloro derivative $ClC(NO_2)_2CN$ in moderate yield.[2] Therefore, it was of interest to determine the course of reaction upon fluorination in aqueous media since it has been suggested that fluorina-

(1) This work was carried out under the sponsorship of the U. S. Army Missile Command, Redstone Arsenal, Alabama under Contract DA-021 ORD-11878 (Z) Mod. No. 7.

(2) C. O. Parker, *et al.*, *Tetrahedron*, **17**, 89 (1962).

tion in this media is predominantly electrophilic in nature.[3] Accordingly, aqueous fluorination of sodium dinitroacetonitrile produced fluorodinitroacetonitrile in moderate yield. The reaction proceeded smoothly

$$NaC(NO_2)_2CN + F_2 \longrightarrow FC(NO_2)_2CN + NaF$$

even with fluorine concentrations as high as 50 vol %. The product was removed from the aqueous mixture by an additional helium purge. Pure fluorodinitroacetonitrile is a colorless liquid with bp 74° and fp −13°. The composition of the compound was established by elemental analysis. Table I presents the characteristic

TABLE I
INFRARED SPECTRUM OF $FC(NO_2)_2CN$[a]

Absorption bands, μ
4.40 (m sharp)
6.12 (v s)
7.47 (wk sh)
7.74 (s)
9.20 (m s)
11.83 (m s sharp)
12.59 (s)

[a] Abbreviations are m = medium, v = very, wk = weak, sh = shoulder, and s = strong.

infrared absorption bands. The F^{19} nmr spectrum of $FC(NO_2)_2CN$ consists of a singlet at +91.4 ppm *vs.* CCl_3F).

Variation of the fluorine concentration, the reaction temperature and the ratio of reactants employed did not increase the yield of product above 30–35%. Increasing the concentration of $NaC(NO_2)_2CN$ in the reaction mixture resulted in the isolation of substantial amounts of acetonitrile upon fluorination. The formation of acetonitrile is probably a result of attack by the fluorine on oxygen or nitrogen to form unstable intermediates which would hydrolyse in the aqueous media. Possible hydrolysis products such as fluorine nitrate, and nitrate ion, were also found. The amount of acetonitrile in the fluorination product could be suppressed by use of dilute reaction mixtures containing as little as 3% $NaC(NO_2)_2CN$. Another reason for the moderate yield of product was the hydrolysis of $FC(NO_2)_2CN$ to fluorodinitroacetamide.

$$FC(NO_2)_2CN + H_2O \longrightarrow FC(NO_2)_2CONH_2$$

Fluorodinitroacetamide was obtained in quantitative yield by adding the stoichiometric amount of water to a HCl-saturated ether solution of fluorodinitroacetonitrile. The product was isolated by evaporation at 0° and extraction with methylene chloride. Fluorodinitroacetamide formed white feathery crystals, mp 32°. The infrared spectrum of $FC(NO_2)_2CONH_2$ contained peaks not present in the spectrum of the nitrile at 2.90 and 5.75 μ. The compound is soluble in water and attempts to isolate an alkali metal salt of the amide were not successful.

Experimental Section

Materials.—Sodium dinitroacetonitrile was prepared by the literature method.[4] The fluorine was obtained from General Chemical Co. and was used after it was passed through a NaF scrubber.

Fluorodinitroacetonitrile.—A solution of 10 g (65 mmoles) sodium dinitroacetonitrile in 300 ml of water was placed in a 500-ml, four-necked flask equipped with a magnetic stirrer, thermometer, and two gas inlet tubes. After cooling to 0°, a stream of 25% fluorine in helium was introduced at a rate of 1. l./hr. The temperature was maintained at 0° and the fluorination product was swept out of the reaction mixture by an additional stream of helium which was introduced through a gas dispersion tube. The off-gas was passed through four traps at −78° and then vented in order to avoid collecting fluorine nitrate which was sometimes formed. The fluorination was continued until the yellow color in the cyanodinitromethide ion faded away. In order to achieve complete removal of the product from the solution, the helium sweep was maintained for another hour. The combined fractions of all four −78° traps were dried over Drierite and condensed into a −30° trap. Fluorodinitroacetonitrile (2.6 g), mp −13°, was obtained in a 29% yield. Its vapor pressure at 25° was 65 mm.

Anal. Calcd for $C_3FN_3O_4$: C, 16.11; N, 28.19. Found: C, 16.16; N, 28.10.

Fluorodinitroacetamide.—Fluorodinitroacetonitrile (3 g, 20 mmoles) was condensed into a mixture of 30 ml of ether and 0.4 ml of water which had been saturated with hydrogen chloride. The hydrolysis proceeded smoothly on thawing. After standing for 1 hr at room temperature all volatile material was pulled off, keeping the reaction flask in a bath of 20°. The remaining semisolid was dissolved in 15–20 ml of methylene chloride and shaken over BaO to remove excess hydrogen chloride. Crystallization of the product took place when the solution was cooled slowly to −70°. The hygroscopic fluorodinitroacetamide was obtained in a 96% yield. It melted at 32° after sublimation under high vacuum.

Anal. Calcd for $C_2H_2FN_3O_5$: C, 14.38; H, 1.20; N, 25.15. Found: C, 14.91; H, 1.01; N, 24.87.

Registry No.—Fluorodinitroacetonitrile, 15562-09-1; fluorodinitroacetamide, 15562-10-4.

(3) V. Grakauskas, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 23M.
(4) C. O. Parker, *et al.*, *Tetrahedron*, **17**, 79 (1962).

The Reaction of Asparagine, Glutamine, and Derivatives with Phosgene

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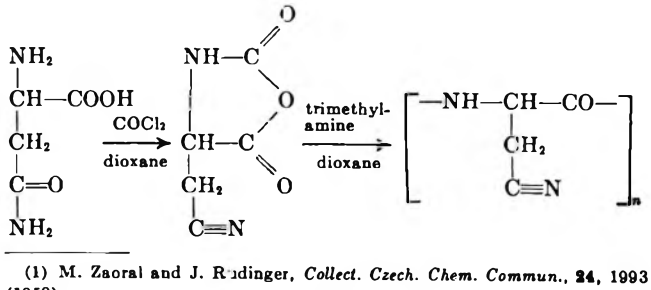
Several methods exist for the conversion of asparagine and glutamine derivatives into their corresponding nitriles.[1-4] An easy and convenient agent for the dehydration of these amino acids has now been found to be phosgene in dioxane. This reaction was discovered subsequent to the attempted preparation of the N-carboxy anhydride of asparagine by the usual procedure of passing phosgene through a dioxane sus-



(1) M. Zaoral and J. Rudinger, *Collect. Czech. Chem. Commun.*, **24**, 1993 (1959).
(2) C. Ressler and H. Ratzkin, *J. Org. Chem.*, **26**, 3356 (1961).
(3) B. Liberek, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, **10**, 227 (1962).
(4) B. Liberek, Cz. Buczel, and Z. Gnyonka, *Tetrahedron*, **22**, 2303 (1966).

pension of the amino acid. When the resulting anhydride was polymerized, the polymer isolated was poly-β-cyano-L-alanine, as shown by infrared absorption at 2235 cm^{-1} (C≡N stretching).

In order to investigate this dehydration reaction further, we treated N^{α}-carbobenzoxy-L-asparagine with phosgene in dioxane. The product, which was isolated in 81% yield, was identical with authentic N^{α}-carbobenzoxy-β-cyano-L-alanine.[1,3] Hydrogenation of this material with palladium catalyst produced α,γ-diaminobutyric acid as confirmed by paper chromatography.

The dehydration reaction with L-glutamine and N^{α}-carbobenzoxy-L-glutamine gave lower yields. The resulting carbobenzoxy-γ-cyano-α-aminobutyric acid separated as an oil.[2] Hydrogenation led to ornithine and traces of proline which were identified by paper chromatography.

This convenient dehydration, which is free of side reactions, suggests various applications, for instance, for the synthesis of the neurotoxic amino acid β-cyano-L-alanine[5,6] and of asparaginyl and glutaminyl peptides.[7]

Experimental Section

All melting points are uncorrected. Prior to analysis the polymers were dried at 105° and the other compounds at 50° *in vacuo* over phosphorus pentoxide.

β-Cyano-N-carboxy-L-alanine Anhydride (I).—Dry phosgene was passed for 3 hr through a suspension of 13 g of asparagine (0.1 mole) in anhydrous dioxane at 60°. Excess phosgene was removed from the solution by a stream of dry nitrogen, and the solvent was distilled *in vacuo* at 45°; the crystalline residue was dissolved in ethyl acetate. The anhydride, which crystallized on the addition of petroleum ether (60–70°), was collected and washed with petroleum ether, and recrystallized from ethyl acetate–petroleum ether. The infrared spectrum showed an absorption peak for nitrile at 2235 cm^{-1}. The yield was 10.2 g (60%), mp 75° dec.

Anal. Calcd for $C_5H_4N_2O_3$: C, 42.86; H, 2.88; N, 20.00. Found: C, 42.59; H, 3.00; N, 19.81.

γ-Cyano-N-carboxy-L-butyric Anhydride.—This compound was prepared in the same manner by passing phosgene through a glutamine suspension and was recrystallized from ethyl acetate–petroleum ether. The infrared spectrum showed an absorption peak for nitrile at 2235 cm^{-1}. The yield was 42%, mp 90–92°.

Anal. Calcd for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.76; H, 3.96; N, 18.16.

Poly-β-cyano-L-alanine.—β-Cyano-N-carboxy-L-alanine anhydride (19 g) was dissolved in dry dioxane (500 ml) and triethylamine (0.1 ml) was added. Polymerization proceeded at room temperature (magnetic stirring) with evolution of carbon dioxide. After 48 hr the product was filtered and washed with dioxane and ether. The infrared spectrum showed an absorption peak for nitrile at 2235 cm^{-1}. The yield was 10 g. The polymer is insoluble in the common solvents, dimethylformamide, water, acetic acid, ethanol, and sodium bicarbonate.

Anal. Calcd for $(C_4H_4N_2O \cdot {}^1/_4H_2O)_n$: C, 47.76; H, 4.22; N, 27.86. Found: C, 48.18; H, 4.15; N, 27.22.

A sample of the poly-β-cyano-L-alanine was hydrolyzed in 6 *N* hydrochloric acid for 24 hr at 105°, and chromatographed in *n*-butyl alcohol–glacial acetic acid–water (25:6:25 v/v). Only one spot, identical with authentic aspartic acid, was detected with ninhydrin on the paper chromatogram.

N-Carbobenzoxy-β-cyano-L-alanine.—Dry phosgene was passed for 1 hr at room temperature through a solution of carbobenzoxy-L-asparagine (13.2 g) in anhydrous dioxane, and the reaction mixture left for 2 hr at room temperature. The excess of phosgene was removed by a stream of nitrogen and most of the solvent was distilled off *in vacuo* at 45°. Upon the addition of 1 *N* hydrochloric acid, the residue crystallized and was recrystallized from ethylene chloride. The infrared spectrum showed an absorption peak for nitrile at 2235 cm^{-1}. The yield was 10 g (81%), mp 131–134°, $[\alpha]^{25}D$ −19.0 (*c* 1.25 methanol) (lit.[6] mp 128°, $[\alpha]^{21}D$ −18.6 (*c* 1.28, methanol); lit.[4] mp 133–134°, $[\alpha]^{21}D$ −19 (*c* 1.26, methanol).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.15; H, 5.05; N, 11.29.

Hydrogenation of this compound with palladium on charcoal under acidic conditions produced α,γ-diaminobutyric acid, as indicated by paper chromatography with an authentic sample of α,γ-diaminobutyric acid.

N-Carbobenzoxy-γ-cyano-α-amino-L-butyric acid.—The reaction was carried out and the product treated as described for the preparation of N-carbobenzoxy-β-cyano-L-alanine. On acidification, a thick oil was obtained which was extracted in ethyl acetate, dried over sodium sulfate and concentrated to dryness under reduced pressure. The infrared spectrum of this oil showed an absorption peak for nitrile at 2235 cm^{-1}. The yield was 75%.

Anal. Calcd for $C_{13}H_{14}N_2O_4$: N, 10.68. Found: N, 10.35.

Hydrogenation of this compound with palladium on charcoal under acidic conditions led to ornithine and proline as established by paper chromatography with authentic samples of ornithine and proline.

Registry No.—Asparagine, 70-47-3; glutamine, 56-85-9; phosgene, 75-44-5; I, 15275-68-0; γ-cyano-N-carboxy-L-butyric anhydride, 15231-19-3; N-carbobenzoxy-β-cyano-L-alanine, 3309-41-9; N-carbobenzoxy-γ-cyano-α-amino-L-butyric acid, 15231-21-7.

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(6) B. Tschiersch, *Tetrahedron Letters*, **747** (1964).
(7) B. Liberek, *Chem. Ind.* (London), 987 (1961).

Studies in the Xanthone Series. IX.[1] The Mechanism of the *para* Claisen Rearrangement of 1-(3,3-Dimethylallyloxy)-3,5,6-trimethoxyxanthone

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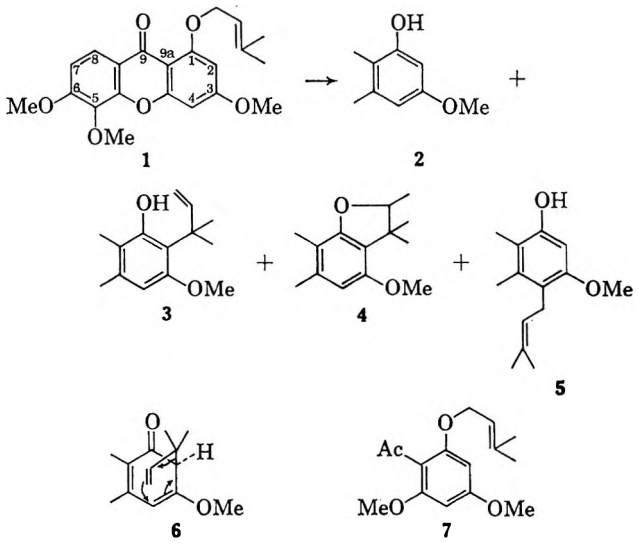
In a previous publication,[2] we reported that a Claisen rearrangement of 1-(3,3-dimethylallyloxy)-3,5,6-trimethoxyxanthone (**1**) gave four products, **2**, **3**, **4**, and **5**.[3] It was suggested[2] that the main product, **5**, formed by migration of the 3,3-dimethylallyl group to the *para* position, results from a Claisen rearrangement

(1) Part VIII: A. Jefferson and F. Scheinmann, *J. Chem. Soc., Sect. C*, 175 (1966).
(2) E. D. Burling, A. Jefferson, and F. Scheinmann, *Tetrahedron*, **21**, 2653 (1965).
(3) 2,4-Di-(3,3-dimethylallyl)-1-hydroxy-3,5,6-trimethoxyxanthone was also isolated in one experiment.[2] It was suspected that this product arose from rearrangement of an impurity in **1** since analogous migrations gave no diallylation: see (a) H. D. Locksley, I. Moore, and F. Scheinmann, *J. Chem. Soc., Sect. C*, 2265 (1966); (b) F. Scheinmann and H. Suschitzky, *Tetrahedron*, **7**, 31 (1959); (c) reference 4. Thus if 1-hydroxy-3,5,6-trimethoxyxanthone **2** reacts as an ambident anion (N. Kornblum, P. J. Berrigan, and W. J. le Noble, *J. Amer. Chem. Soc.*, **85**, 1141 (1963)) allylation at C-2 and then oxygen will yield 2-(3,3-dimethylallyl)-1-(3,3-dimethylallyloxy)-3,5,6-trimethoxyxanthone as an impurity in **1**. Mass spectral examination showed that with some ether samples the impurity arising from concurrent O- and C-isoprenylation was indicated as a small peak at *m/e* 438 with respect to the molecular ion peak at *m/e* 370 due to the ether **1**. Both molecular ions lost a fragment of 55 mass units consistent with loss of C_4H_7 from a 3,3-dimethylallyl ether or side chain. The radioactive ether **1** used for the mechanism studies was free from this and other impurities as shown by mass spectral and chromatographic evidence.

to C-2 followed by Cope-type rearrangement to C-4. From the work of Schmid, *et al.*, it is clear that for a hindered *o*-dienone such as **6**, steric inhibition of enolization can allow a Cope-type rearrangement to become a competitive reaction,[4] but in our case experimental support was required for the intramolecular pathway.[5]

A crossing experiment was thus carried out with a mixture of the xanthone ether **1** containing a ^{14}C-labeled dimethylallyl group and inactive 2-(3,3-dimethylallyloxy)-4,6-dimethoxyacetophenone (**7**). Both ethers had previously been shown to give *para* rearrangement products[2] at similar rates by thin layer chromatography experiments.

A convenient radiochemical synthesis of the 3,3-dimethylallyl-3,3-dimethyl-$^{14}C_2$ bromide was devised starting from acetone, and then reaction with 1-hydroxy-



3,5,6-trimethoxyxanthone **2** gave the active 3,3-dimethylallyl-3,3-dimethyl-$^{14}C_2$ ether **1**. Acetone-1,3-$^{14}C_2$[6] was reacted with lithium acetylide–ethylenediamine complex in dimethyl sulfoxide to give 3-methyl-1-butyn-3-ol-4,3-methyl-$^{14}C_2$.[7] Reduction of this ethynyl carbinol with a Lindlar catalyst[8] gave 3-methyl-1-buten-3-ol-4,3-methyl-$^{14}C_2$ which was converted into 3,3-dimethylallyl-3,3-dimethyl-$^{14}C_2$ bromide by hydrogen bromide.[9] After rearrangement of the mixture (**7** and radioactive **1**), the products were separated by thin layer chromatography and the specific activities of the starting xanthone ether **1** and the *para* Claisen product **5** were compared. Both xanthones (**1** and **5**) had virtually the same specific activity thus demonstrating that the *para* Claisen rearrangement must proceed largely by an intramolecular pathway.

Experimental Section

Synthesis of Labeled 3,3-Dimethylallyl Bromide 3-Methyl-1-butyn-3-ol-4,3-methyl-$^{14}C_2$.[7]—Acetylene was passed into a suspension of lithium acetylide–ethylenediamine complex (9.2 g) in dimethyl sulfoxide (50 ml) with stirring at room temperature. The gas flow was stopped and acetone-1,3-$^{14}C_2$[6] (5.8 g) was added over 30 min, and then the mixture was cooled to 0°, acidified to pH 7 with 2 *N* hydrochloric acid, and extracted with ether. The ethereal layer was washed with water and dried and the solvent removed to yield a residue which was distilled to give radioactive 3-methyl-1-butyn-3-ol (2 g, 24%), bp 101–103° (1 atm) (lit.[10] bp 103–104°).

3-Methyl-1-buten-3-ol-4,3-methyl-$^{14}C_2$.—This compound was prepared in 64% yield by the method described for the inactive product,[8] bp 98° (1 atm) (lit.[8] bp 97–98° (750 mm), 87%).

3,3-Dimethylallyl-3,3-$^{14}C_2$ Bromide.—A solution of 45% w/v hydrogen bromide in acetic acid (12 ml) was added to the radioactive 2-methyl-1-buten-3-ol (5 g) with stirring at 10°. After standing for 15 min, the mixture was poured into water and then extracted with ether. The ethereal layer was washed with water and dried ($CaCl_2$) and the solvent removed to leave a residue which was fractionally distilled to give the radioactive 3,3-dimethylallyl bromide (4 g, 46%), bp 35° (12 mm) (lit.[11] bp 26–33° (12 mm)). The distillate was stored over anhydrous potassium carbonate.

The radioactive xanthone ether **1** and the phloroacetophenone ether **7** were prepared following the procedures described in an earlier paper.[2]

Counting Experiments.—The determination of the specific activity for the compounds **1** and **5** was carried out using a Nuclear Chicago liquid scintillation system 725. The instrument was calibrated by the balance point method to carry out channels ratio measurements on the isotope ^{14}C.[12] Additions of nonradioactive forms of **1** and **5** were made to ^{14}C-hexadecane standards in PPO/POPOP scintillator solutions. The quenching caused by these compounds could be interpreted by reference to a standard quench correction curve. This standard curve was obtained from a set of quenched standards as supplied by the Nuclear Chicago Corp. Accurately weighed samples of active **1** and **5** were dissolved in 1 ml of dioxane, and to these solutions was added 5 ml of PPO/POPOP scintillator. Small weights of sample (0.6 mg) were used to avoid color quenching. The activity of the scintillator solutions were determined and specific activities calculated. Duplicate results showed that the compounds **1** and **5** were of identical specific activity within the limits of experimental error (Table I).

TABLE I

	1	**5**
Measured activity, cpm	53.51	51.71
Background blank of 1 ml of dioxane and 5 ml of scintillator, cpm (with vial correction)	27.13	27.13
Corrected activity, cpm	26.48	24.58
Channels ratio	55.10	56.81
Efficiency (from quench correction curve), %	79	77.5
True count, dpm	33.52	31.72
Weight of compound $\times 10^{-4}$, g	6.4	6.0
Specific activity, dpm/g	52,380	52,870
% specific activity of **5**/specific activity of **1**	101%	
Estimated errors		
(1) Statistical counting error		1%
(2) Weighing errors		2%
(3) Interpolation error in quench correction curve (±1% variation in counting efficiency)		3%

The counting experiments were duplicated and the results were shown to be in agreement.

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Amino Acids and Peptides. XVI.[1] Synthesis of a Tetrapeptide Sequence (A_9–A_{12}) of Glucagon

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Protected peptides corresponding to the A_9–A_{12} sequence of the hyperglycemic hormone glucagon[2] have been elaborated recently by several investigators. The first synthesis gave the tripeptide N-benzyloxycarbonyl-L-asparaginyl-L-tyrosyl-L-serine methyl ester, prepared by a coupling between N-benzyloxycarbonyl-L-asparagine *p*-nitrophenyl ester and L-tyrosyl-L-serine methyl ester.[3] The second preparation yielded N-trifluoroacetyl-β-*t*-butyl-L-aspartyl-L-tyrosyl-L-serine hydrazide, formed by joining N-trifluoroacetyl-β-*t*-butyl-L-aspartic acid with either O-benzyl-L-tyrosyl-O-benzyl-L-serine benzyloxycarbonylhydrazide or L-tyrosyl-O-benzyl-L-serine benzyloxycarbonylhydrazide.[4] Later, N-benzyloxycarbonyl-β-*t*-butyl-L-aspartyl-L-tyrosyl-L-serine methyl ester was made from N-benzyloxycarbonyl-β-*t*-butyl-L-aspartic acid and L-tyrosyl-L-serine methyl ester by a mixed anhydride procedure,[5] while the tetrapeptide under discussion was incorporated into a longer fragment by stepwise addition of individual amino acids from the carboxyl end.[6]

In continuation of earlier work, there is described here the formation of a protected A_9–A_{12} peptide and other related compounds. The procedure began with N^{ϵ}-benzylidene-L-lysine[7] (I), which on treatment with benzyl chloroformate and sodium hydroxide afforded both N^{ϵ}-benzyloxycarbonyl-L-lysine[8-11] (II) and N^{α}-benzyloxycarbonyl-L-lysine[7,10-12] (III). Reaction of compound III with *t*-butyl azidoformate[13] in the presence of dicyclohexylamine[14] led to N-benzyloxycarbonyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine dicyclohexylammonium salt[12,15-17] (IV). Alternatively, III was esterified with thionyl chloride and methanol to obtain syrupy N-benzyloxycarbonyl-L-lysine methyl ester hydrochloride[7] (V), which was converted by *t*-butyl azidoformate[13] into N-benzyloxycarbonyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester[16-19] (VI). Removal of the benzyloxycarbonyl group of compound VI by hydrogenation in acetic acid formed crystalline N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester hydroacetate[16,17] (VII). A 2-ethyl-5-phenylisoxazolium 3′-sulfonate[20,21] coupling between the amine VII and N-benzyloxycarbonyl-L-serine (VIII) yielded N-benzyloxycarbonyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester (IX). The dipeptide IX on hydrogenation in acetic acid afforded the corresponding amine hydroacetate (X); addition of N-benzyloxycarbonyl-O-benzyl-L-tyrosine *p*-nitrophenyl ester[22] (XI) formed amorphous N-benzyloxycarbonyl-O-benzyl-L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester (XII). The combination of N,O-dibenzyloxycarbonyl-L-tyrosine 2,4,5-trichlorophenyl ester[23] (XIII) and the amine X produced impure N,O-dibenzyloxycarbonyl-L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester (XIV). A third approach to this tripeptide sequence involved an azide synthesis[24,25] between N-benzyloxycarbonyl-L-tyrosyl-L-serine hydrazide (XVI) and the amine X affording N-benzyloxycarbonyl-L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester (XVIII). The hydrazide XVI was prepared from N-benzyloxycarbonyl-L-tyrosyl-L-serine methyl ester[26,27] (XV) in the usual manner, and from N,O-dibenzyloxycarbonyl-L-tyrosyl-L-serine methyl ester (XVII) by warming with excess hydrazine. The latter reaction is the second example of the removal of an O-benzyloxycarbonyl blocking group by hydrazine.[23]

Catalytic reduction in acetic acid of the tripeptide XVIII afforded L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester hydroacetate (XIX), which was coupled to N-benzyloxycarbonyl-β-*t*-butyl-L-aspartate α-2,4,5-trichlorophenyl ester[23] (XX) or the corresponding α-*p*-nitrophenyl ester[28-30] (XXI) to form the desired N-benzyloxycarbonyl-β-*t*-butyl-L-aspartyl-L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester (XXII). Reaction of compound XXII with hydrazine led to N-benzyloxycarbonyl-β-*t*-butyl-L-aspartyl-L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-

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lysine hydrazide (XXIII), an intermediate desired for future work in this series. Lastly, mention is made of N-benzyloxycarbonyl-L-tyrosyl-L-serylglycine methyl ester (XXIV), a compound prepared for the comparison of two azide coupling procedures.

Experimental Section[31]

N^{ϵ}-Benzylidene-L-lysine (I).—This compound was obtained by the addition of benzaldehyde to a chilled solution of L-lysine monohydrochloride in dilute lithium hydroxide (40.1 g, 68%), mp 205–207° (lit.[7] mp 206–208° dec).

N^{ϵ}-Benzyloxycarbonyl-L-lysine (II) and N^{α}-Benzyloxycarbonyl-L-lysine (III).—Chilled (0°) solutions of sodium hydroxide (1 *N*, 150 ml) and benzyl chloroformate (17 ml) were added in two portions within a brief period (5 min) to a cold (−1°), vigorously stirred solution of N^{ϵ}-benzylidene-L-lysine (23.4 g, 0.10 mole) in sodium hydroxide (1 *N*, 100 ml). Lower temperatures do not aid the reaction due to freezing of the sodium hydroxide solution at −2 to −3° and the conversion of the basic N^{ϵ}-benzylidene-L-lysine solution into a turgid mass below −5°. Stirring was continued for a short interval (0°, 10 min; room temperature, 10 min), after which concentrated hydrochloric acid (25 ml) was added, and the mixture was heated (50°, 5 min) and extracted with two 100-ml portions of ether. The water layer was adjusted to pH 6.2 and filtered to remove N^{ϵ}-benzyloxycarbonyl-L-lysine: mp *ca.* 235°; $[\alpha]^{25}D$ +14.0° (*c* 2.86, water containing 2 equiv of hydrochloric acid) [lit.[8–10] mp *ca.* 255, 262°; $[\alpha]D$ +14.4° (*c* 1.6, water containing 2 equiv of hydrochloric acid), $[\alpha]^{20}D$ +14.0° (*c* 0.5 *N* hydrochloric acid)]; ν_{max} 3330 (NH), 3030 (OH), 2935 (CH), 1687 (C=O), 1270 (CO), and 735 and 695 (Ph) cm^{-1}; λ_{max} 247, 252, 257, 264, and 267 mμ (ϵ 178, 223, 272, 237, and 172).

The remaining water solution was concentrated *in vacuo* (100 ml) and allowed to stand in the cold room to deposit slowly solid N-benzyloxycarbonyl-L-lysine, recrystallized from water (14.5 g, 52%): 230–233°; $[\alpha]^{22}D$ −10.3° (*c* 5.04, 0.2 *N* hydrochloric acid) [lit.[7,10,12] mp 235–237, 227–228°; $[\alpha]^{25}D$ −12.2° (*c* 5.6, 0.2 *N* hydrochloric acid), $[\alpha]^{20}D$ −7.3° (*c* 5, 0.5 *N* hydrochloric acid), $[\alpha]^{20}D$ −13.7° (*c* 2, 0.2 *N* hydrochloric acid)]; ν_{max} 3315 (NH), 3030 (OH), 2935 (CH), 1727 (C=O), 1242 (CO), and 740 and 698 (Ph) cm^{-1}; λ_{max} 247, 252, 258, 264, and 268 mμ (ϵ 143, 195, 247, 215, and 154).

N-Benzyloxycarbonyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine Dicyclohexylammonium Salt (IV).—Treatment of N-benzyloxycarbonyl-L-lysine with *t*-butyl azidoformate gave white needles of N-benzyloxycarbonyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine dicyclohexylammonium salt: mp 150–153°; $[\alpha]^{26}D$ +5.0° (*c* 1.00, methanol) [lit.[12,15,16] mp 156–157, 154–157, 153–155°; $[\alpha]^{20}D$ +7.82° (*c* 1, ethanol), $[\alpha]^{23}D$ +4.95° (*c* 1, dimethylformamide), $[\alpha]^{26}D$ +5.5° (*c* 4.6, methanol)]; ν_{max} 3380 broad (OH), 2925 (CH), 1690 broad (C=O), 1390 and 1360 (*t*-butyl), 1245 (CO), and 695 (Ph) cm^{-1}; λ_{max} 247, 252, 258, 262, 264, and 267 mμ (ϵ 153, 206, 252, 196, 216 and 154).

Anal. Calcd for $C_{31}H_{51}N_3O_6$ (561.7); C, 66.28; H, 9.15; N, 7.48. Found: C, 66.13; H, 9.11; N, 7.43.

N-Benzyloxycarbonyl-L-lysine Methyl Ester Hydrochloride (V).—Esterification of N-benzyloxycarbonyl-L-lysine with a mixture of thionyl chloride and methanol produced a syrup, which resisted crystallization by a variety of techniques.

N-Benzyloxycarbonyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine Methyl Ester (VI).—The product from the foregoing preparation was reacted with *t*-butyl azidoformate to yield colorless needles of N-benzyloxycarbonyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester: mp 62–63°; $[\alpha]^{28}D$ −10.0° (*c* 1.0, acetone); R_f 0.79 [lit.[16,18,19] mp 62–63, 57°; $[\alpha]^{26}D$ −9.3° (*c* 2.05, acetone), $[\alpha]^{26}D$ −10.6° (*c* 1.90, acetone)]; ν_{max} 3350 (NH), 2950 (CH), 1720 very broad (C=O), 1375 and 1350 (*t*-butyl), 1170 (CO), and 697 (Ph) cm^{-1}; λ_{max} 247, 252, 257, 261, 264, and 267 mμ (ϵ 141, 204, 230, 183, 193, and 135).

N^{ϵ}-*t*-Butyloxycarbonyl-L-lysine Methyl Ester Hydroacetate (VII).—Hydrogenolysis of N-benzyloxycarbonyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester in methanol with 1 equivalent of acetic acid formed needles of N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester hydroacetate: mp 78–79°; $[\alpha]^{27}D$ +15.3° (*c* 1.0, methanol) [lit.[16] mp 78–79°; $[\alpha]^{26}D$ +17.0° (c 2.1, methanol)]; R_f 0.24; ν_{max} 3380 (NH), 2970 (CH), 1720 very broad (C=O), 1390 and 1365 (*t*-butyl), and 1180 (CO) cm^{-1}; no selective absorption occurred in the ultraviolet region.

Anal. Calcd for $C_{14}H_{28}N_2O_6$ (320.4): C, 52.48; H, 8.81; N, 8.74. Found: C, 52.53; H, 8.79; N, 8.98.

N-Benzyloxycarbonyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine Methyl Ester (IX).—Triethylamine (1.39 ml, 0.010 mole) was added to a stirred suspension of N-benzyloxycarbonyl-L-serine (2.39 g, 0.010 mole) and 2-ethyl-5-phenylisoxazolium 3′-sulfonate (2.53 g, 0.010 mole) in acetonitrile (50 ml) at 0°. After 18 hr at 0°, there was added to the almost clear mixture a solution of N^{ϵ}-*t*-butoxycarbonyl-L-lysine methyl ester hydroacetate (3.20 g, 0.010 mole) and triethylamine (1.39 ml, 0.010 mole) in acetonitrile (50 ml) at 0°. The reaction was stirred at 0° for 24 hr, after which evaporation of the solvent yielded an oil that was distributed between ethyl acetate and water. The organic phase was washed with 0.5 *M* aqueous citric acid, water, saturated sodium bicarbonate solution, and brine, dried and taken to dryness. The residue was dissolved in ether and on standing at room temperature furnished white needles of N-benzyloxycarbonyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester (2.35 g, 49%): mp 106.5–107.5°; $[\alpha]^{26}D$ −11.2° (*c* 1.0, methanol); R_f 0.64; ν_{max} 3330 broad (OH), 2940 (CH), 1753, 1720, and 1710 (C=O), 1685 (urethane), 1645 (amide I), 1535 (amide II), 1392 and 1367 (*t*-butyl), 1250 broad (CO), and 697 (Ph) cm^{-1}; λ_{max} 247, 252, 257, 261, 264, and 267 mμ (ϵ 117, 158, 206, 154, 168, and 108).

Anal. Calcd for $C_{23}H_{35}N_3O_8$ (481.5): C, 57.37; H, 7.33; N, 8.73. Found: C, 57.36; H, 7.34; N, 8.96.

If the initial reaction mixture was allowed to warm to room temperature, a clear solution of the "Woodward" intermediate resulted after *ca.* 30 min. From this point onward, when the solution was maintained at 0° and the experiment executed in a manner identical with the above description, thin layer chromatography showed the final oil to be composed of two components (R_f 0.46 and 0.66), and the yield of pure dipeptide was low (17%).

L-Seryl-N^{ϵ}-butyloxycarbonyl-L-lysine Methyl Ester Hydroacetate (X).—A solution of N-benzyloxycarbonyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester (0.963 g, 0.002 mole) in methanol (10 ml) was hydrogenolyzed during 2 hr in the presence of 10% palladium on carbon (0.045 g) and acetic acid (0.13 ml, 0.0022 mole). The reaction mixture was filtered and the solvent evaporated to leave a clear oil, R_f 0.10.

N-Benzyloxycarbonyl-O-benzyl-L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine Methyl Ester (XII).—The aforementioned product was swirled with a solution of N-benzyloxycarbonyl-O-benzyl-L-tyrosine *p*-nitrophenyl ester (1.053 g, 0.002 mole) in chloroform (20 ml). After 48 hr, the solution was evaporated to dryness and the residue dissolved in ethyl acetate and washed with 0.5 *M* aqueous citric acid, saturated sodium bicarbonate solution, and brine. The dried solution was concentrated to a small volume and ether added to the opalescent point. On standing at room temperature, a gel deposited, which was collected, washed with ether, and dried. Reprecipitation from ethyl acetate–ether and drying furnished N-benzyloxycarbonyl-O-benzyl-L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester as an amorphous white powder (0.861 g, 59%): mp 118–120°; $[\alpha]^{26}D$ −8.4° (*c* 1.0, methanol; R_f 0.70; ν_{max} 3350 very broad (OH), 2930 (CH), 1690 very broad (C=O) and urethane), 1520 (amide II), 1392 and 1367 (*t*-butyl), 1245 (CO), and 695 (Ph) cm^{-1}; λ_{max} 227, 252, 258, 264, 267, 276, and 283 mμ (ϵ 16,000, 698, 970, 1210, 1350, 1600, and 1360).

Anal. Calcd for $C_{39}H_{50}N_4O_{10}$ (734.9): C, 63.75; H, 6.86; N, 7.62. Found: C, 63.75; H, 7.00; N, 7.74.

N,O-Dibenzyloxycarbonyl-L-tyrosyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine Methyl Ester (XIV).—To an ethyl acetate (5 ml) solution of L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine methyl ester hydroacetate, freshly prepared by the hydrogenation of N-benzyloxycarbonyl-L-seryl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine-methyl ester (0.159 g, 0.00033 mole), was added N,O-dibenzyl-

(31) Melting points are uncorrected. Microanalyses were provided by Messrs. Erich H. Meier and J. Consul, Microanalytical Laboratory, Stanford University. The optical rotation, infrared (potassium bromide), and ultraviolet (95% ethanol) measurements were obtained by Mrs. L. D. Carroll. Thin layer chromatography employed silica gel G (freshly activated) as the support, methanol–chloroform (1:9) for development, and iodine for visualization. Evaporations were performed under reduced pressure (water pump) in a rotatory evaporator at minimum temperature, while high-boiling solvents were removed at vacuum pressure (0.2–0.5 mm). Magnesium sulfate was used for drying purposes. Acetonitrile and dimethylformamide were spectroscopic quality; other solvents were reagent grade and light petroleum had bp 30–60°.

oxycarbonyl-L-tyrosine 2,4,5-trichlorophenyl ester (0.207 g, 0.00033 mole) in ethyl acetate (2 ml), followed by triethylamine (0.00033 mole). After 48 hr at room temperature, the reaction mixture was diluted with ethyl acetate (15 ml) and washed with 0.5 *M* aqueous citric acid, saturated sodium bicarbonate solution, and brine. The dried solution was evaporated to a small bulk and diisopropyl ether added to the opalescence point. On standing at room temperature, a gel separated, which was washed with diisopropyl ether and dried to give N,O-dibenzyloxycarbonyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester as an amorphous powder (0.172 g): mp 116–118°; R_f 0.75. No further work was done to characterize this product.

N-Benzyloxycarbonyl-L-tyrosyl-L-serine Methyl Ester (XV).—Dicyclohexylcarbodiimide (1.236 g, 0.0061 mole) was added to a solution of N-benzyloxycarbonyl-L-tyrosine[32] [1.576 g, 0.005 mole; mp 101–101°; $[\alpha]^{26}D$ +43.3° (*c* 2.01, chloroform)], L-serine methyl ester hydrochloride (0.776 g, 0.005 mole), and triethylamine (0.70 ml, 0.005 mole) in acetonitrile–dioxane (1:1, 50 ml) held at 0°. The usual work-up procedure led to N-benzyloxycarbonyl-L-tyrosyl-L-serine methyl ester (1.638 g, 79%): mp 151–152°; $[\alpha]^{25.5}D$ −3.3° (*c* 0.98, methanol) [lit.[26,27] mp 152°, 156–158°; $[\alpha]^{23}D$ −3.1° (*c* 2.2, methanol), $[\alpha]^{22}D$ −2.8° (*c* 2, methanol); ν_{max} 3340 very broad (OH), 1695 very broad (C=O and urethane), 1515 (amide II), 1240 very broad (OH), and 697 (Ph) cm^{-1}; λ_{max} 226, 252, 258, 264, 267, 277, and 284 mμ (ε 7760, 350, 535, 782, 986, 1380, and 1130).

Anal. Calcd for $C_{21}H_{24}N_2O_7$ (416.4): C, 60.57; H, 5.81; N, 6.73. Found: C, 60.55; H, 5.79; N, 6.88.

N,O-Dibenzyloxycarbonyl-L-tyrosyl-L-serine Methyl Ester (XVII).—A hot solution of L-serine methyl ester hydrochloride (4.655 g, 0.030 mole) in dimethylformamide (20 ml) was added to a solution of triethylamine (4.17 ml, 0.030 mole) in acetonitrile (100 ml) held at −20° (acetone–Dry Ice bath). While the temperature was maintained, N,O-dibenzyloxycarbonyl-L-tyrosine (13.49 g, 0.030 mole) was added, with the aid of a powder funnel and a little acetonitrile, followed by dicyclohexylcarbodiimide (6.49 g, 0.0315 mole). After 2 hr at 0°, the mixture was allowed to warm to room temperature and stirred overnight. After filtration from the precipitated dicyclohexylurea, the solvent was removed and the oily residue was redissolved in dichloromethane and washed with 0.5 *M* aqueous citric acid, saturated sodium bicarbonate solution, and brine. Evaporation of the dried organic phase furnished a white solid, which was crystallized from methanol to yield needles of N,O-dibenzyloxycarbonyl-L-tyrosyl-L-serine methyl ester (13.41 g, 81%): mp 176–177°; $[\alpha]^{22}D$ −4.2° (*c* 0.962, dimethylformamide); R_f 0.66; ν_{max} 3400 very broad (OH), 2950 (CH), 1750 (C=O), 1680 very broad (C=O and urethane), 1530 (amide II), 1265 (CO), and 696 (Ph) cm^{-1}; λ_{max} 252, 257, 262, 264, and 268 mμ (ε 525, 642, 613, 619, and 452).

Anal. Calcd for $C_{29}H_{30}N_2O_8$ (534.6): C, 65.16; H, 5.66; N, 5.24. Found: C, 65.17; H, 5.59; N, 5.55.

N-Benzyloxycarbonyl-L-tyrosyl-L-serine Hydrazide (XVI). A. From N-Benzyloxycarbonyl-L-tyrosyl-L-serine Methyl Ester.—A solution of N-benzyloxycarbonyl-L-tyrosyl-L-serine methyl ester (0.833 g, 0.002 mole) and 95% hydrazine (0.334 ml, 0.010 mole) in methanol (10 ml) on standing at room temperature for 48 hr formed white needles of N-benzyloxycarbonyl-L-tyrosyl-L-serine hydrazide (0.762 g, 91%): mp 226–227°; $[\alpha]^{21.5}D$ −4.9° (*c* 1.0, dimethylformamide), $[\alpha]^{26}D$ −20.9° (*c* 1.05, 1 *N* hydrochloric acid); ν_{max} 3400 very broad (OH), 3395 (NH), 2950 (CH), 1660 very broad (C=O) and urethane), 1515 (amide II), 1240 broad (CO), and 697 (Ph) cm^{-1}; λ_{max} 225, 252, 258, 264, 267, 277, and 283 mμ (ε 9860, 391, 576, 845, 1070, 1460, and 1190).

Anal. Calcd for $C_{20}H_{24}N_4O_6$ (416.4): C, 57.69; H, 5.81; N, 13.45. Found: C, 57.34; H, 6.00; N, 13.70.

B. From N,O-Dibenzyloxycarbonyl-L-tyrosyl-L-serine Methyl Ester.—N,O-Dibenzyloxycarbonyl-L-tyrosyl-L-serine methyl ester (5.506 g, 0.010 mole) was treated with hydrazine (3.34 ml, 0.100 mole) in methanol (70 ml) under reflux for 30 min and the reaction mixture left to crystallize at room temperature. Recrystallization of the product from methanol furnished N-benzyloxycarbonyl-L-tyrosyl-L-serine hydrazide (2.750 g, 66%), identical in all respects with the material from **A**.

N-Benzyloxycarbonyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine Methyl Ester (XVIII).—N-Benzyloxycarbonyl-L-tyrosyl-L-serine hydrazide (1.249 g, 0.003 mole) was dissolved in dimethylformamide (9 ml) by warming and the solution cooled to −40° (acetone–Dry Ice bath). Hydrochloric acid (1.86 *N*) in tetrahydrofuran (6.45 ml, 0.012 mol of hydrochloric acid) was then added, followed by *n*-butyl nitrite (0.41 ml, 0.0036 mole). After 30 min at −40°, triethylamine (1.67 ml, 0.012 mole) was added, and then a solution of N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester hydroacetate (1.057 g, 0.0033 mole) and triethylamine (0.46 ml, 0.0033 mole) in dimethylformamide (9 ml) at −20°. The final reaction mixture was left at 0° in the cold room for 48 hr.

Removal of the solvent left a residue, which was distributed between ethyl acetate and water. The organic phase was washed with 0.5 *M* aqueous citric acid, saturated sodium bicarbonate solution, and brine, and the dried solution evaporated, and the residue redissolved in tetrahydrofuran. The addition of light petroleum gave a gel, which was collected and washed with light petroleum. Reprecipitation of this product followed by washing and drying yielded N-benzyloxycarbonyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester (1.358 g, 70%): mp 116–118°; $[\alpha]^{25}D$ −8.3° (*c* 0.96, methanol), $[\alpha]^{27}D$ −6.2° (*c* 0.96, dimethylformamide); R_f 0.77; ν_{max} 3320 very broad (OH), 2950 broad (CH), 1680 very broad (C=O and urethane), 1515 (amide II), 1392 and 1365 (*t*-butyl), 1250 broad (CO) and 698 (Ph) cm^{-1}; λ_{max} 226, 253, 258, 264, 268, 277, and 283 mμ (ε 9670, 428, 668, 960, 1230, 1650, and 1410).

Anal. Calcd for $C_{32}H_{44}N_4O_{10}$ (644.7): C, 59.62; H, 6.88; N, 8.69. Found: C, 59.72; H, 6.98; N, 8.60.

L-Tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine Methyl Ester Hydroacetate (XIX).—N-Benzyloxycarbonyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester (1.289 g, 0.002 mole) was hydrogenated in methanol (20 ml) in the presence of 10% palladium-on-carbon catalyst (0.050 g) and acetic acid (0.12 ml, 0.002 mole). After removal of the catalyst, the solvent was evaporated to leave an oil, which was obtained as a gel from hot ethyl acetate–ether. Washing with ether and drying furnished L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester hydroacetate as a white powder (0.927 g, 81%): mp 103–105°; $[\alpha]^{24.5}D$ −5.1° (*c* 0.98, methanol); ν_{max} 3320 very broad (OH), 2950 broad (CH), 1670 very broad (C=O and urethane), 1510 (amide II), 1395 and 1363 (*t*-butyl), and 1250 broad (CO) cm^{-1}.

Anal. Calcd for $C_{26}H_{42}N_4O_{10}$ (570.6): C, 54.73; H, 7.42; N, 9.82. Found: C, 54.80; H, 7.31; N, 9.97.

N-Benzyloxycarbonyl-β-*t*-butyl-L-aspartyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine Methyl Ester (XXII). A. By Use of L-Tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine Methyl Ester Hydroacetate and N-Benzyloxycarbonyl-β-*t*-butyl-L-aspartate α-2,4,5-Trichlorophenyl Ester.—A dimethylformamide (15 ml) solution of L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester hydroacetate, freshly prepared by the hydrogenation of N-benzyloxycarbonyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester (1.928 g, 0.003 mole), was treated with N-benzyloxycarbonyl-β-*t*-butyl-L-aspartate α-2,4,5-trichlorophenyl ester[28] (1.508 g, 0.003 mole). After 48 hr, the solvent was evaporated and the residue redissolved in ethyl acetate and washed with 0.5 *M* aqueous citric acid, saturated sodium bicarbonate solution, and brine. On concentrating to a small volume and keeping at 0° for 24 hr, the dried ethyl acetate solution deposited a gel, which was collected with the aid of ether. Rewashing with ether and drying afforded N-benzyloxycarbonyl-β-*t*-butyl-L-aspartyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester as an amorphous, white powder (1.740 g, 71%): mp 94–96°; $[\alpha]^{27}D$ −26.1° (*c* 1.0, methanol); R_f 0.43; ν_{max} 3345 very broad (OH), 2975 (CH), 1700 very broad (C=O and urethane), 1510 (amide II), 1390 and 1365 (*t*-butyl), 1248 broad (CO) and 697 (Ph) cm^{-1}; λ_{max} 226, 252, 258, 264, 267, 277, and 283 mμ (ε 9560, 400, 615, 885, 1110, 1585, and 1345).

Anal. Calcd for $C_{40}H_{57}N_5O_{13}$ (815.9): C, 58.88; H, 7.04; N, 8.58. Found: C, 58.93; H, 7.16; N, 8.73.

B. The tetrapeptide was alternatively prepared from N-benzyloxycarbonyl-β-*t*-butyl-L-aspartate *p*-nitrophenyl ester and L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester hydroacetate (68%).

N-Benzyloxycarbonyl-β-*t*-butyl-L-aspartyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine Hydrazide (XXIII).—A solution of N-benzyloxycarbonyl-β-*t*-butyl-L-aspartyl-L-tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine methyl ester (0.816 g, 0.001 mole) and 95% hydrazine (0.17 ml, 0.005 mole) in methanol (15 ml) on standing at room temperature for 20 hr produced microcrystalline white needles, which were collected, washed with methanol, and dried to yield N-benzyloxycarbonyl-β-*t*-butyl-L-aspartyl-L-

(32) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine hydrazide (0.585 g, 72%): mp 186–188°; R_f 0.16.

Anal. Calcd for $C_{39}H_{57}N_7O_{12}$ (815.9): C, 57.41; H, 7.04; N, 12.02. Found: C, 57.17; H, 7.34; N, 12.17.

A number of attempts to secure pure tetrapeptide hydrazide from slightly impure tetrapeptide ester were unsuccessful; the tetrapeptide hydrazide was invariably obtained as a gel.

N-Benzyloxycarbonyl-L-tyrosyl-L-serylglycine Methyl Ester (XXIV).—A solution of sodium nitrite (0.210 g, 0.00305 mole) in water (3 ml) was added to a solution of N-benzyloxycarbonyl-L-tyrosyl-L-serine hydrazide (1.249 g, 0.003 mole) in acetic acid (18 ml), 2 *N* hydrochloric acid (12 ml), and water (10 ml) maintained at 0°. The resulting azide was precipitated with sodium chloride and extracted into three 10-ml portions of cold ethyl acetate. The combined extracts were washed free of acid with saturated sodium bicarbonate solution and dried (the drying agent was not removed until the coupling reaction was complete). A solution of glycine methyl ester, previously prepared by dissolving glycine methyl ester hydrochloride (0.414 g, 0.0033 mole) in dimethylformamide (30 ml) with warming, rapidly cooling the solution to 0°, and immediately adding triethylamine (0.46 ml, 0.0033 mole), was poured into the ethyl acetate solution of the azide. After 48 hr at 0°, the mixture was filtered, and the solvents evaporated, and the residue dissolved in the minimum amount of hot 50% aqueous methanol. On cooling, the solution deposited almost colorless needles of N-benzyloxycarbonyl-L-tyrosyl-L-serylglycine methyl ester (1.005 g, 71%): mp 204–206°; $[\alpha]^{27}D$ −7.0° (*c* 1.0, dimethylformamide); R_f 0.19; ν_{max} 3400 very broad (OH), 2950 (CH), 1745 (methyl C=O), 1689 (urethane C=O), 1642 (amide I), 1512 (amide II), 1230 broad (OH), and 698 (Ph) cm^{-1}; λ_{max} 226, 257, 264, 268, 274, 277, and 284 mμ (ε 9760, 688, 1000, 1330, 1650, 1790, and 1380).

Anal. Calcd for $C_{23}H_{27}N_3O_8$ (473.5): C, 58.35; H, 5.75; N, 8.87. Found: C, 58.52; H, 5.69; N, 9.03.

The tripeptide was alternatively prepared by use of *t*-butyl nitrite, N-benzyloxycarbonyl-L-tyrosyl-L-serine hydrazide and glycine methyl ester hydrochloride (74%).

Registry No.—II, 1155-64-2; III, 2212-75-1; IV, 2212-76-2; VI, 2389-49-3; VII, 3252-80-0; IX, 3236-14-4; XII, 15376-59-7; XIV, 15523-36-1; XV, 15364-45-1; XVI, 2480-91-3; XVII, 15364-47-3; XVIII, 15364-48-4; XIX, 15523-37-2; XXII, 15364-49-5; XXIII, 15364-50-8; XXIV, 15364-51-9.

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Derivatives of Morphine. V.[1] The Structure of Anhydrometathebainol

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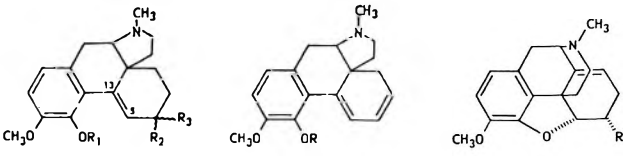
During their investigation of metathebainone (I), Small and Meitzner[2] described the preparation of "anhydrometathebainol" by dehydration of metathebainol (II) with ethanolic KOH at 160°. The authors were not able to assign a structure to the product, although they considered formula III, resulting from straightforward dehydration of II. However, they discarded III on the grounds that the dihydro derivative, obtained by catalytic hydrogenation,[3] seemed to be different from dihydrodesoxymetacodeine, the product of Wolff–Kishner reduction of I. The latter was assumed to be V and should hence be identical with dihydro-III. On this basis they concluded that "the formation of anhydrometathebainol has involved a deeper-seated structural change then mere dehydration."



I, R_1=H; R_2R_3=O
II, R_1=R_2=H; R_3=OH
IV, R_1=Ac; R_2=OAc; R_3=H
V, R_1=R_2=R_3=H
VI, R_1=Ac; R_2=R_3=H

III, R=H
VII, R=Ac

VIII, R=OH
IX, R=H

We were interested in the possibility of such a rearrangement and have reinvestigated this work in order to establish the structures of anhydrometathebainol and of the related dihydro derivatives. Metathebainol (II) was prepared either by catalytic hydrogenation[2] or, more conveniently, by borohydride reduction of metathebainone (I). In our hands the former procedure was erratic and gave mixtures, possibly containing products of hydrogenolysis which were not further investigated. Borohydride reduction resulted in a mixture of epimers which could be used directly for the subsequent step. The same crystalline diacetate (IV) was obtained from both preparations.

Dehydration of metathebainol by the method of Small and Meitzner[2] or by a slightly modified procedure gave crude anhydrometathebainol which could not be purified by crystallization. The melting points of this and of the other free phenols in this series were low and indefinite due to variable solvation and were therefore not suitable for characterization. Acetylation of anhydrometathebainol furnished the acetate, which could be purified readily and was identical with an authentic specimen.[2] The nmr spectrum showed a complex multiplet (3 H) in the olefinic region (δ 5.5–6.3), which was resolved into three distinct multiplets (one proton each), centered at δ 6.1, 5.92, and 5.67, on a 100-Mc instrument. The long-wavelength band in the uv region (see Experimental Section) showed a bathochromic shift (~18 mμ) with respect to metathebainol diacetate (IV) and to dihydroanhydrometathebainol acetate (see below). The strong negative circular dichroism ($\Delta\epsilon_{286-288}$ −11.3) and optical rotatory dispersion (complex negative effect, first extremum at 313 mμ, [Φ] −19,700°) are compatible with the presence of an inherently dissymmetric chromophore such as the nonplanar phenylbutadiene system. The above evidence is consistent with structure III for anhydrometathebainol which is further corroborated by the study of the dihydro derivative.

Catalytic hydrogenation of anhydrometathebainol acetate resulted in the uptake of 1 mol of hydrogen. The dihydro derivative was found to be identical with the product obtained on acetylation of dihydrodeoxymetacodeine (V), prepared[2] by Wolff–Kishner reduction of I. The structure of this was confirmed by spectroscopic data (see Experimental Section), which are consistent with VI. Of particular interest in the nmr

(1) Part IV: U. Weiss and S. J. Daum, *J. Med. Chem.*, **8**, 123 (1965).
(2) L. F. Small and E. Meitzner, *J. Amer. Chem. Soc.*, **55**, 4602 (1933).
(3) Throughout the metathebainone series, $\Delta^{5(12)}$ is relatively inert to catalytic hydrogenation.

spectrum is the resemblance of the olefinic region (triplet due to one proton centered at δ 6.0 for V and 5.8 for VI) to that of neopine (VIII) (triplet, δ 5.5; actually, the X part of a deceptively simple ABX system[4]) and deoxycodeine D (IX)[5] (triplet, δ 5.65).

It is thus clear that anhydrometathebainol possesses the expected structure III and that the earlier observations on the nonidentity of dihydroanhydrometathebainol and dihydrodesoxymetacodeine were erroneous.

Experimental Section

Melting points were determined on a Kofler block. Ultraviolet spectra were determined in ethanol on a Cary 14 spectrophotometer, infrared spectra in chloroform solution on a Beckman IR7 spectrophotometer, and nmr spectra in deuteriochloroform on a Varian A60 or HA100 instrument. The optical rotatory dispersion was measured on a Cary 60 spectropolarimeter, the circular dichroism on the Jouan dichrograph of the University of Strasbourg.

Metathebainol (II). A. Metathebainone (2.99 g) dissolved in a minimum of ethanol was treated with 0.1 *N* HCl (100 ml) and Adams catalyst (50 mg). The mixture was hydrogenated at 46 psi for 18 hr, filtered, basified with ammonia and extracted with chloroform. Evaporation of the extracts afforded an oil which crystallized on contact with methanol. Crystallization from methanol afforded metathebainol (1.93 g, 64%), mp 76–80° (lit.[2] mp 87–88° for chloroform solvate, 92–93° for methanol solvate); no carbonyl stretching appeared in the infrared spectrum. In another experiment, hydrogenation was continued for 12 hr and gave crystalline metathebainol, contaminated with starting material, in 27% yield.

B. Metathebainone (3.0 g) in ethanol (35 ml) was treated with sodium borohydride (1.75 g) portionwise with stirring for 30 min. Stirring was continued for 6 hr, acetone was added to decompose excess borohydride, the solution was poured into water, acidified with acetic acid, and basified with ammonia. Extraction with chloroform afforded an oil (2.97 g) which did not crystallize, but was sufficiently pure for the next step. Its infrared spectrum was essentially identical with that of the product from the previous preparation.

Metathebainol diacetate (IV) was prepared from metathebainol by the method of Small and Meitzner:[2] mp 137–138° (lit.[2] mp 140°); λ_{max} 291, 242, 214 mμ (ϵ 2900, 11,000, 27,200).

Anhydrometathebainol (III).—The base was prepared by the method of Small and Meitzner.[2] Alternatively, II (1.0 g) and potassium hydroxide (0.25 g) in ethylene glycol (6.5 ml) were heated at 160° for 4 hr. The reaction mixture was worked up in the usual way, affording III as a crystalline solid (0.27 g) after crystallization from methanol, indefinite mp 70–100° (lit.[2] mp 106–107°). Thin layer chromatography on silica gel using cyclohexane–diethylamine (9:1) as eluent showed the presence of some impurities. Purification of the product by preparative thin layer chromatography in the same solvent system gave a sample mp 112–115° (softens at 70°) after crystallization from methanol.

Acetylanhydrometathebainol (VII) could not be prepared by the published method.[2] It was obtained by acetylation of crude III with pyridine–acetic anhydride at room temperature for 5 days. It had mp 174–176° after crystallization from methanol (lit.[2] mp 166°); uv bands were at λ_{max} 307 mμ (ϵ 13,800), 245 (infl) (46,000), 225 (infl) (11,300), 211 (20,000). Circular dichroism showed a broad, evidently complex, negative band, between ~240 and 340 mμ, with maximum, $\Delta\epsilon$ −11.3, at 281–288 mμ. Optical rotatory dispersion in methanol (*c* 0.04) showed $[\Phi]_{325}$ −18,100° (sh), $[\Phi]_{313}$ −19,700°, $[\Phi]_{297}$ ±0°, $[\Phi]_{\sim 270-260}$ +38,000°, $[\Phi]_{248}$ +45,900° $[\Phi]_{230}$ +3600°, $[\Phi]_{220}$ *ca.* +17,000°. The identity with an authentic sample prepared by Small and Meitzner was established by mixture melting point determination and comparison of infrared spectra.

Acetyldihydroanhydrometathebainol (VI).—A solution of VII (0.425 g) in ethanol (20 ml) was shaken in an atmosphere of hydrogen in the presence of Adams catalyst (50 mg). Hydrogen uptake (35 ml; theoretical uptake for 1 mol = 32 ml) was complete in less than 1 hr. The solution was filtered and the filtrate was evaporated to dryness. The residual solid (0.44 g) was crystallized three times from hexane and had mp 115.5–116°. The solution of the compound in concentrated hydrochloric acid does not show the blue halochromism of II, III, and IV even on heating. Uv absorptions were at λ_{max} 288 mμ (ϵ 4000), 243 (10,400), 215 (29,900).

Anal. Calcd for $C_{20}H_{25}NO_3$; C, 73.24; H, 7.66; N, 4.17%. Found: C, 73.37; H, 7.70; N, 4.28%.

Wolff–Kishner Reduction of Metathebainone.—The preparation was carried out by the method of Small and Meitzner,[2] affording a crystalline solid, mp 51–69° (lit.[2] mp 72°), which rapidly darkened on exposure to air. It could be purified by preparative thin layer chromatography on silica gel using cyclohexane–diethylamine (9:1) as eluent and had mp 40–70° after crystallization from methanol. On standing over calcium chloride the solvent-free base was obtained as a glass. Acetylation with acetic anhydride in pyridine at room temperature for 2 days afforded the acetyl derivative, mp 114–115°, after crystallization from hexane. It was identical in every respect (mixture melting point determination and infrared spectrum) with VII.

Registry No.—III, 15448-36-9; VI, 15448-37-0; VII, 15448-38-1; morphine, 57-27-2.

Acknowledgment.—We are indebted to Drs. E. L. May and L. J. Sargent of this institute for kindly supplying a sample of acetylanhydrometathebainol originally prepared by Small and Meitzner, to Dr. E. Lustig, of the Food and Drug Administration, Washington, D. C., for measurement of the 100-Mc spectrum, to Mrs. K. Warren, National Heart Institute, for measurement of infrared spectra, and to Professor Guy Ourisson, Strasbourg, for measurement of the circular dichroism.

(4) T. Rull, *Bull. Soc. Chim. Fr.*, 586 (1963).

(5) U. Weiss, unpublished results.

Synthesis of Murrayanine[1]

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Received September 7, 1967

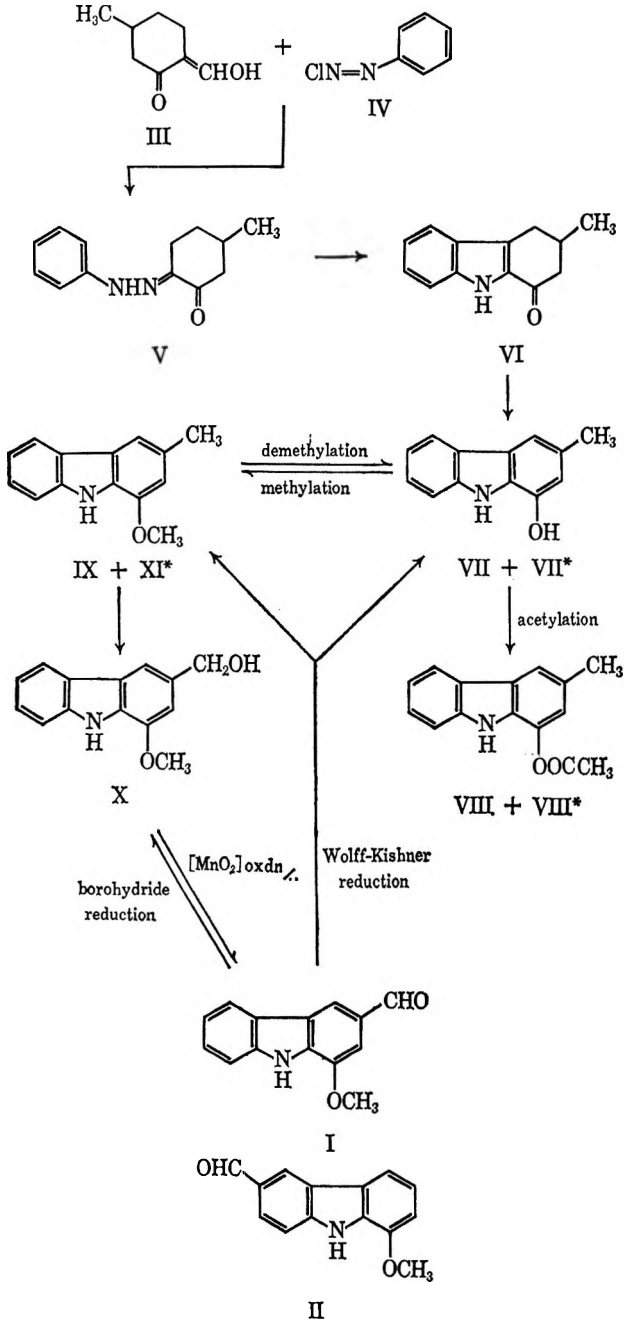
In a previous communication, the structure of murrayanine, $C_{14}H_{11}NO_2$, mp 168°, a simple carbazole derivative isolated from the stem bark of *Murraya koenigii* Spreng., was proposed as 1-methoxy-3-formylcarbazole (I) by Chakraborty, Barman, and Bose.[2a] From the spectral evidences (uv, ir, nmr) and the results of reactions, it was shown that murrayanine could be formulated either as 1-methoxy-3-formylcarbazole (I) or as 1-methoxy-6-formylcarbazole (II). The assignment of the formyl group at position 3 of the carbazole nucleus was made on the basis of nmr data of murrayanine. We, therefore, sought a confirmation of the previously proposed structure by synthesis. The present report relates to the synthesis of murrayanine and the preparation of compounds (VII and VIII) from natural murrayanine. The intermediate

(1) When this synthesis was complete we received a personal communication from Dr. D. J. Crum informing us that he has also synthesized murrayanine. Since then we came across his communication (*Chem. Commun.*, 417, 1966) which shows that his method and approach are different from ours. A short communication on our results appeared in *Sci. Cult.* (Calcutta), **32**, 590 (1966). The paper was presented at the Joint Convention of the Chemical Research Committee, C. S. I. R., and the Society of Biological Chemists of India, held at Delhi on Dec 25–27, 1966.

(2) (a) D. P. Chakraborty, B. K. Barman, and P. K. Bose, *Tetrahedron*, **21**, 681 (1965); (b) B. H. Brown and P. G. Philpott, *J. Chem. Soc.*, 7185 (1965), and references therein.

compounds (VII–X) obtained during synthesis have also been derived from natural murrayanine.

Recent reports[2b] show that the Japp–Klingemann reaction provides a convenient method for the synthesis of the hydrazones required for indole synthesis by the Fischer method. The hydrazone necessary for the present synthesis was obtained by the condensation of 2-hydroxymethylene-5-methylcyclohexanone (III) with phenyldiazonium chloride (IV) under Japp–Klingemann condition.[3] The resulting 4-methylcyclohexane-1,2-dione-1-phenylhydrazone (V), was cyclized to 1-oxo-3-methyl-1,2,3,4-tetrahydrocarbazole (VI), using a mixture of acetic acid and concentrated hydrochloric acid as the condensing agent. The dehydrogenation of 1-oxo-3-methyl-1,2,3,4-tetrahydrocarbazole (VI) with



* Derived from murrayanine.

(3) D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *Chem. Ind.* (London), 1684 (1966).

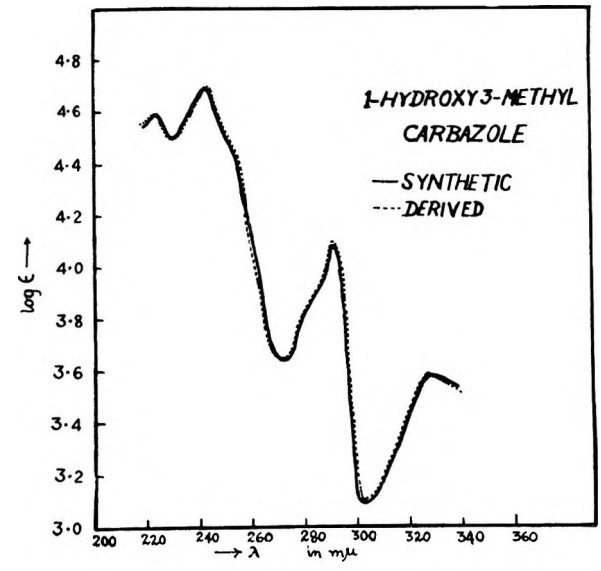


Figure 1.

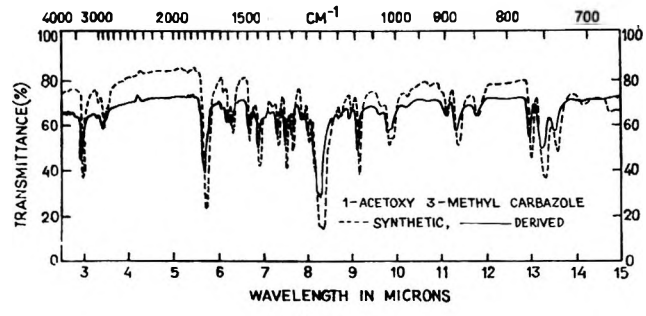


Figure 2.

Pd–C (10%)[4,5] in a sealed tube under evacuated condition instead of chloranil[6,7] furnished 1-hydroxy-3-methylcarbazole (VIII). This was found to be identical (melting point, mixture melting point, and superimposible uv spectrum, Figure 1) with the phenol (VII-derived) obtained by demethylation of the Wolff–Kishner reduction product (IX-derived) of murrayanine.

The phenol (VII-derived) was also obtained from the alkaline fraction of the Wolff–Kishner reduction product of murrayanine. 1-Acetoxy-3-methylcarbazole (VIII), obtained by acetylation of phenol VII with pyridine and acetic anhydride, was identical with the phenol acetate derived from murrayanine (melting point, mixture melting point, and superimposible ir spectrum, Figure 2). Phenol VII on methylation with diazomethane in the presence of methanol furnished 1-methoxy-3-methylcarbazole (IX) identical with the Wolff–Kishner reduction product of murrayanine (IX-derived). This eventually confirms the structure of the Wolff–Kishner reduction product of murrayanine as 1-methoxy-3-methylcarbazole. The conversion of 1-methoxy-3-methylcarbazole into 1-methoxy-3-formylcarbazole would now accomplish the desired synthesis of murrayanine. For this purpose, compound IX was brominated with N-bromosuccinimide[8] in the pres-

(4) J. A. Cummins and M. L. Tomlinson, *J. Chem. Soc.*, 3475 (1955).
(5) R. H. Shapiro in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p 371.
(6) N. Campbell and B. M. Barclay, *Chem. Rev.*, **40**, 359 (1947).
(7) G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.*, 700 (1951).
(8) H. Schmidt and P. Karrer, *Helv. Chim. Acta.*, **29**, 573 (1946).

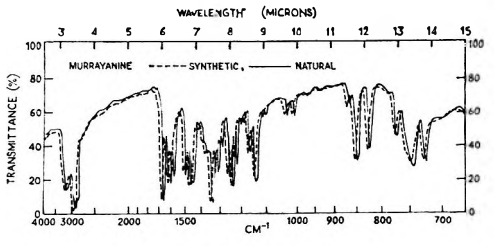


Figure 3.

ence of traces of benzoyl peroxide and the resulting 1-methoxy-3-bromomethylcarbazole was hydrolyzed *in situ* with caustic potash to 1-methoxy-3-hydroxymethylcarbazole (X). Compound X was found to be identical with the borohydride reduction product of murrayanine reported previously[1] (mp and mmp 127°). The benzylic alcohol X was oxidized with manganese dioxide[9] in carbon tetrachloride to 1-methoxy-3-formylcarbazole (I-synthetic), which was found to be identical with natural murrayanine in all respects (melting point, mixture melting point, uv spectrum, and superimposible ir spectrum, Figure 3).

Experimental Section

All melting points were determined on a Kofler block. The alumina used was of Brockmann grade as prepared by Sarabhai-Merck Co. of India. Petroleum ether refers to the fraction boiling between 40 and 60°.

4-Methylcyclohexane-1,2-dione 1-Phenylhydrazone (V).—2-Hydroxymethylene-5-methylcyclohexanone[3] (3.5 g) in methanol (36 ml) was added to an aqueous solution of sodium acetate (5.5 g in 19 ml of water). To this solution was added a solution of phenyl diazonium-chloride (prepared from 2.7 g of aniline) during 25 min under mechanical agitation when the crystals of 4-methylcyclohexane-1,2-dione 1-phenylhydrazone was obtained. On recrystallization from ethanol the compound V, mp 209°, was obtained in 75% yield.

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.36; H, 7.19; N, 13.08.

1-Oxo-3-methyl-1,2,3,4-tetrahydrocarbazole (VI).—4-Methylcyclohexane-1,2-dione 1-phenylhydrazone (2.4 g) was boiled with glacial acetic acid (19 ml) and concentrated hydrochloric acid (4.5 ml) for 5 min and then diluted with ice water (70 ml). The solid obtained was filtered, washed with water, dried, and crystallized from benzene when colorless needles, mp 197°, of VI were obtained in 77% yield: $\lambda_{max}^{ethanol}$ 237 mμ (log ε 4.26) and 308 mμ (log ε 4.36); ν_{max}^{KBr} 3257 (-NH-), 1639 (carbonyl), 1562 and 1527 (aromatic system), 1379 (C-methyl) and 925, 869, and 813 cm^{-1} (substituted benzene ring).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.38; H, 6.58; N, 7.03. Found: C, 78.29; H, 6.78; N, 6.92.

1-Hydroxy-3-methylcarbazole (VII).—1-Oxo-3-methyl-1,2,3,4-tetrahydrocarbazole (1.5 g) was dehydrogenated with Pd-C (10%, 0.75 g) at 250–270° for 4 hr in a sealed, evacuated tube in the presence of dry alcohol (0.5 ml). The reaction product was cooled and filtered. The semisolid mass left after the removal of the solvent from the filtrate was dissolved in ether from which the phenolic fraction was separated by extraction with aqueous sodium hydroxide solution (5%). The alkaline solution was acidified with 10% hydrochloric acid and was extracted with ether. On removal of ether and chromatography over silica gel (10 g) a pale brown crystalline product, mp 155–156°, was obtained from the benzene eluent. On recrystallization from benzene–petroleum ether, almost colorless needles, mp 158°, were obtained in 45% yield: $\lambda_{max}^{ethanol}$ 224 mμ (log ε 4.59), 242 (4.69), 292 (4.09), and 330 (3.58); ν_{max}^{KBr} 3400 (-NH-), 3279 (hump, bonded hydroxyl), 1613 and 1587 (aromatic system), 1389 (C-methyl), and 980 and 854 cm^{-1} (substituted aromatic ring).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.01; H, 5.72; N, 6.80.

(9) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

1-Acetoxy-3-methylcarbazole (VIII).—A solution of 1-hydroxy-3-methylcarbazole (300 mg) in pyridine (1 ml) after heating with acetic anhydride (1 ml) on a water bath for 1 hr was poured into ice water from which the acetate separated. It was filtered. The crude acetate on repeated crystallization from benzene–petroleum ether mixture gave 260 mg of colorless needles: mp 154°; $\lambda_{max}^{ethanol}$ 238 mμ (log ε 4.62), 248 (4.40), 257 (4.15), 292 (4.12) and 328 (3.38); ν_{max}^{KBr} 3400 (-NH-), 1762 (acetoxy), 1626, and 1587 (aromatic system), 1370 (C-methyl) and 900 and 885 cm^{-1} (substituted benzene ring).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.50; H, 5.33; N, 6.05.

1-Hydroxy-3-methylcarbazole from Murrayanine (VII-Derived). A.—Murrayanine on Wolff–Kishner reduction furnished a neutral oily product as reported previously.[1] The alkaline aqueous fraction of the Wolff–Kishner reduction product furnished on acidification a solid, mp 140–145°. This product, on chromatography over silica gel and subsequent crystallization from benzene–petroleum ether, furnished almost colorless needles, mp 158°. This was found to be identical with 1-hydroxy-3-methylcarbazole by mmp 158° and a superimposible uv spectrum (Figure 1).

B.—The Wolff–Kishner reduction product of murrayanine (200 mg) was demethylated with HBr (48%; 1 ml) and glacial acetic acid (2.8 ml). The demethylated product on chromatography through silica gel and on crystallization from benzene–petroleum ether mixture melted at 158° (100 mg) alone or when mixed with 1-hydroxy-3-methylcarbazole (VII). The uv spectrum of the demethylated product was superimposible with that of 1-hydroxy-3-methylcarbazole.

1-Acetoxy-3-methylcarbazole Derived from Murrayanine (VIII-Derived).—The phenol derived from murrayanine was acetylated as was the synthetic phenol (VII) to an acetate which had a melting point and mixture melting point (154°) identical with the synthetic sample. The ir spectra of the synthetic 1-acetoxy-3-methylcarbazole (VIII) and that of the phenol acetate derived from murrayanine were superimposible (Figure 2).

1-Methoxy-3-methylcarbazole (IX).—1-Hydroxy-3-methylcarbazole (350 mg) in methanol (25 ml) was treated with an ethereal solution of diazomethane and kept overnight in a refrigerator. After removal of the solvent, an oily product was obtained. This on distillation at 125–130° (0.05 mm) yielded a colorless oil (280 mg). This was found to be identical, by paper chromatography and uv spectral measurements, with the Wolff–Kishner reduction product of murrayanine (R_f 0.73, alcohol–water–acetic acid, 27:21:2): $\lambda_{max}^{ethanol}$ 226 mμ (log ε 4.4), 243 (4.5), 252 (4.4 hump), 281 (3.7), 290 (3.8) and 330 (3.5).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.73; H, 6.28; N, 6.56.

1-Methoxy-3-hydroxymethylcarbazole (X).—To a cold solution of 1-methoxy-3-methylcarbazole (400 mg) in carbon tetrachloride (50 ml) were added N-bromosuccinimide (338 mg) and a trace amount of benzoyl peroxide. The mixture was kept at room temperature for 4 hr and then refluxed for 15 min. The reaction mixture was then filtered and the residue obtained after removal of the solvent was hydrolyzed with 5% alcoholic KOH (10 ml). The hydrolyzed product was taken up with ether and the brownish semisolid mass obtained after working up the ether extract was chromatographed over alumina (8 g). A solid product, mp 119–121°, was obtained from benzene–ether (1:1) eluent. This product on repeated recrystallization from benzene–petroleum ether yielded 40 mg of a colorless product, mp 127°, identical with the sodium borohydride reduction product of murrayanine (X): mp, mmp 127°; $\lambda_{max}^{ethanol}$ 225 mμ (log ε 4.40), 242 (4.57), 252 (4.50), 2.90 (3.96) and 330 (3.55).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.90; H, 5.87; N, 6.10.

1-Methoxy-3-formylcarbazole (I-Synthetic).—To a solution of 1-methoxy-3-hydroxymethylcarbazole (100 mg) in dry CCl_4 (50 ml) was added active MnO_2 (1 g). The mixture was stirred for 6 hr and then filtered. The filtrate on removal of the solvent gave an oily product. This was dissolved in minimum amount of benzene and chromatographed over alumina (5 g). Several fractions collected with benzene as eluent gave on removal of the solvent a colorless solid, mp 160–162°. This was further purified by sublimation at 160° (0.05 mm) and subsequent crystallization from benzene–petroleum ether mixture when colorless needles (50 mg) were obtained. The compound melted at 168° alone or when mixed with natural murrayanine: $\lambda_{max}^{ethanol}$ 238 mμ (log ε 4.45), 247 (4.30), 274 (4.58), 289 (4.55) and 335 (4.15); ν_{max}^{Nujol}

3150 (-NH-), 1660 (aromatic aldehyde), 1620, 1600, 1575 (aromatic residue), and 850, 824, 773, 745, and 725 cm^{-1} (substituted benzene derivatives).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.35; H, 4.70; N, 6.00.

Registry No.—I, 723-97-7; V, 15562-11-5; VI, 14961-29-6; VII, 14960-81-7; VIII, 14961-28-5; IX, 4532-33-6; X, 3909-78-2.

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Intramolecular Diels–Alder Reactions. V. Synthesis of Dehydro-β-peltatin Methyl Ether[1a]

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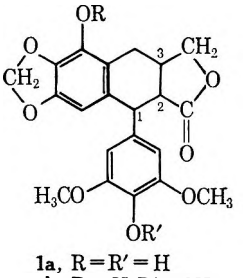
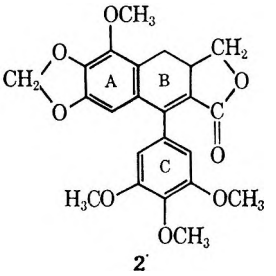
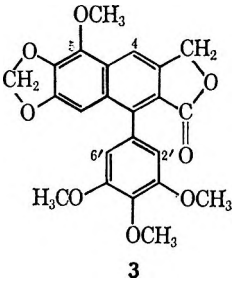
During the period 1947–1953, Hartwell, *et al.*,[2] reported the isolation from podophyllin of the tumor-necrotizing agents α- and β-peltatin and structural investigations on them. The structures proposed (**1a** and **1b**, respectively) were based on (1) oxidative degradations, (2) analogy of spectral characteristics and chemical transformations with those found in the podophyllotoxin system, and (3) conversion of both peltatins into the same permethyl ether (**1c**). These studies clearly established the carbon skeleton of the peltatins and the locations of the phenolic, methoxy, and methylenedioxy substituents thereon. The stereochemistries at C-1, C-2, and C-3[3] as well as the orientation of the lactone ring (*i.e.*, as shown, or alternatively with the carbonyl and methylene moieties reversed) were still open to question. The research presented here serves to establish unequivocally the orientation of the lactone ring.



1a, R = R′ = H
b, R = H, R′ = CH_3
c, R = R′ = CH_3



2



3

The ethyl ester of *trans*-2-methoxy-3,4-methylenedioxycinnamic acid (of established isomeric structure)[4] was reduced by means of lithium aluminum hydride to *trans*-2-methoxy-3,4-methylenedioxycinnamyl alcohol. The crude, open-chain ester formed from this alcohol and 3,4,5-trimethoxyphenylpropiolyl chloride was cyclized by means of refluxing acetic anhydride to a single product, **2**. Dehydrogenation of **2** by means of Pd–C in cymene or by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene afforded **3**, identical with the product obtained from dehydrogenation of β-peltatin-B methyl ether **1c** (derived directly from podophyllin). The identity of these products assures that cyclization of the open-chain ester did occur into ring A (where only a single position for cyclization was available) rather than into ring C and, thus, establishes the orientation of the lactone ring as that shown in formulas **1**–**3**. Cyclization into ring A is consistent with expectations for an intramolecular Diels–Alder reaction and with previous results on other *trans*-cinnamyl phenylpropiolates which reacted under similar conditions.[5,6]

It might be noted that the nmr signal for the proton on C-4 in the 1-phenylnaphthalene lignan lactone **3** falls at δ 8.17. The appearance of this singlet at such a low field is ascribed to the deshielding influence of the *peri* methoxy group at C-5. Dudek[7] has observed similar downfield shifts of signals for *peri* protons in naphthalenes which bear an OH, OCH_3, or NH_2 substituent in an α position. In an earlier paper[6] the presence or absence of a singlet at $\delta > 8.0$ was of diagnostic pertinence to the direction of cyclization in the intramolecular Diels–Alder reaction. In those examples, however, one was concerned only with the respective presence or absence of an aromatic hydrogen atom in a position *ortho* to the carbonyl group of the lactonic moiety. In no case was it possible to obtain a cyclized product bearing a methoxy or methylenedioxy group in a position *peri* to an aromatic hydrogen atom. In the present case, on the other hand, either direction of cyclization should give a product with a low-field singlet in its spectrum.

(1) (a) This investigation was supported by Research Grant No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. (b) Research Associate, 1966–1967.

(2) (a) J. L. Hartwell, *J. Amer. Chem. Soc.*, **69**, 2918 (1947); (b) J. L. Hartwell and W. E. Detty, *ibid.*, **70**, 2833 (1948); (c) *ibid.*, **72**, 246 (1950); (d) J. L. Hartwell, A. W. Schrecker, and G. Y. Greenberg, *ibid.*, **74**, 6285 (1952); (e) A. W. Schrecker and J. L. Hartwell, *ibid.*, **75**, 5924 (1953).

(3) The numbering used in this paper is consistent with *Chemical Abstracts* practice but does not follow that used by Hartwell, *et al.*,[2] and by some other workers in the lignan field.

(4) See the Experimental Section for evidence on aspects of both positional and geometric isomerism in this starting material.

(5) L. H. Klemm, D. H. Lee, K. W. Gopinath, and C. E. Klopfenstein, *J. Org. Chem.*, **31**, 2376 (1966). *Cf.* L. H. Klemm and K. W. Gopinath, *J. Heterocycl. Chem.*, **2**, 225 (1965).

(6) L. H. Klemm, K. W. Gopinath, D. H. Lee, F. W. Kelly, E. Trod, and T. M. McGuire, *Tetrahedron*, **22**, 1797 (1966).

(7) G. O. Dudek, *Spectrochim. Acta*, **19**, 691 (1963).

Experimental Section[8]

o-Vanillin was converted into 3-methoxycatechol by Dakin oxidation[9] and then to 1-methoxy-2,3-methylenedioxybenzene.[10] This ether was formylated to a mixture of isomers, which were separated chromatographically.[11] The isomer[12] of melting point 103–104° was condensed with malonic acid to give *trans*-2-methoxy-3,4-methylenedioxycinnamic acid.[13]

Ethyl *trans*-2-Methoxy-3,4-methylenedioxycinnamate.—A mixture of 6 g of the preceding 2-methoxy-3,4-methylenedioxycinnamic acid, 200 ml of absolute ethanol, and 2 ml of sulfuric acid was refluxed for 12 hr, evaporated to 130 ml, and treated with a cold solution of 5 g of sodium bicarbonate in 1.5 l. of water. The refrigerated mixture depcsited a solid which was recrystallized from methanol to give 5.1 g (76%) of prisms: mp 61–62°;[14] $\nu_{max}^{CHCl_3}$ 1720 (ester C=O), 935 (OCH_2O),[15] 985 cm^{-1} (*trans* CH=CH).[16] The nmr spectrum (CCl_4) showed a triplet at δ 1.29 (J = 7 cps, 3 H, CH_3 of ethyl group), a singlet at 4.03 (3 H, CH_3O group) which overlaps the upfield signal of a quartet at 4.17 (J = 7 cps, 2 H, CH_2 of ethyl group), a singlet at 5.93 (2 H, OCH_2O group), a doublet at 6.26 (J = 16 cps, 1 H, vinylic proton α to ester group), doublets at 6.46 and 7.00 (J = 7.6 cps, 1 H each, aromatic protons), and a doublet at 7.72 (J = 16 cps, 1 H; vinylic proton β to ester group).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.47; H, 5.50.

***trans*-2-Methoxy-3,4-methylenedioxycinnamyl Alcohol.**—To a cold (−10°), stirred suspension of 1.5 g (40 mmol) of lithium aluminum hydride in 75 ml of anhydrous ether was added dropwise a solution of 5 g (20 mmol) of the preceding ester in 150 ml of ether. The reaction mixture was stirred at the same temperature for 3 hr longer and then treated first with ethyl acetate and then with water. The residue from evaporation of the water-washed, dried organic phase was chromatographed on 80 g of Woelm neutral alumina. The first fraction of effluent (eluent benzene) was discarded. Elution with 400 ml of 2% methanol in chloroform gave 2.5 g (60%) of colorless liquid; infrared bands were $\nu_{max}^{CHCl_3}$ 3570 (OH) and 935 cm^{-1} (OCH_2O). The nmr spectrum ($CDCl_3$) showed a broad singlet at δ 3.23 (probably OH group), a singlet at 3.94 (3 H, CH_3O group), a doublet at 4.23 (J = 5.5 cps, CH_2 of CH_2OH group), a singlet at 5.86 (2 H, OCH_2O group), and a complex multiplet at 6.0–7.0 (4 H, aromatic plus vinylic protons).

The **3,5-dinitrobenzoate**[17] derivative of the carbinol formed bright orange needles from chloroform–ethanol, mp 160.5–162°.

Anal. Calcd for $C_{18}H_{14}N_2O_9$: C, 53.73; H, 3.51; N, 6.96. Found: C, 53.87; H, 3.59; N, 7.20.

1-(3,4,5-Trimethoxyphenyl)-3-hydroxymethyl-5-methoxy-6,7-methylenedioxy-3,4-dihydro-2-naphthoic Acid Lactone (2).—A mixture of 1.18 g (5 mmol) of 3,4,5-trimethoxyphenylpropiolic acid,[16] 2.5 ml of fresh reagent-grade thionyl chloride, and 15 ml of anhydrous benzene was refluxed for 45 min. Excess thionyl chloride was removed by repetitive distillation *in vacuo* with benzene. To the residue was added a solution of 1.04 g (5 mmol) of the preceding carbinol in 27 ml of benzene and 1.5 ml of pyridine. The mixture was refluxed for 4 hr, cooled, washed,[18] and evaporated to give 2 g of crude ***trans*-2-methoxy-3,4-methylenedioxycinnamyl 3,4,5-trimethoxyphenylpropiolate** as a viscous brown liquid; infrared bands were $\nu_{max}^{CHCl_3}$ 2240 (C≡C), 1710 (ester C=O), 935 cm^{-1} (OCH_2O). The nmr spectrum ($CDCl_3$) showed singlets at δ 3.81, 3.84 (broad), and 3.97 (CH_3O groups), a singlet at 5.88 (OCH_2O group), and a complex multiplet at 5.7–7.2 (vinylic and aromatic protons).

A solution of this crude ester in 25 ml of acetic anhydride was refluxed for 4.5 hr and evaporated *in vacuo* to leave a solid which was triturated with ether and recrystallized, first from chloroform–cyclohexane (yield 400 mg) and then repeatedly (with use of activated charcoal one time) from acetone–ethanol to give lactone **2** as cream-colored needles: mp 251–252°; $\nu_{max}^{CHCl_3}$ 1750 (α,β-unsaturated-γ-lactone), 940 cm^{-1} (OCH_2O). The nmr spectrum ($CDCl_3$) showed singlets at δ 3.83 (6 H, presumably CH_3O groups at C-3′ and C-5′), 3.91 and 4.02 (3 H each, CH_3O groups) which overlap complex absorption in the region of 2.2–4.9 (aliphatic protons), as well as at 5.96 (2 H, OCH_2O group), 6.29 (1 H, aromatic proton at C-8), and 6.51 (2 H, aromatic protons at C-2′ and C-6′).

Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.59; H, 5.19.

Dehydro-β-peltatin Methyl Ether (3). A. From 2.—A mixture of 250 mg of preceding lactone, 0.5 g of 30% palladium on carbon, and 12 ml of *p*-cymene was refluxed for 18 hr in an atmosphere of nitrogen. Crystallization from chloroform–cyclohexane of the residue obtained from filtration and evaporation of the reaction mixture gave 150 mg (60%) of flakes of **3**: mp 266–268°; $\nu_{max}^{CHCl_3}$ 1755 (lactone C=O), 945 cm^{-1} (OCH_2O); $\lambda_{max}^{100\%\ EtOH}$ 263 mμ (log ϵ 4.62), 320 (3.92), 355 shoulder (3.61) [lit.[2e] mp 271–272°; $\lambda_{max}^{95\%\ EtOH}$ 264 mμ (log ϵ 4.71), 318 (3.92), 356 (3.65)]. The nmr spectrum ($CDCl_3$) showed singlets at δ 3.83 (6 H, presumably CH_3O groups at C-3′ and C-5′), 3.97 and 4.21 (3 H each, CH_3O groups), 5.38 (broadened somewhat, 2 H, CH_2 of lactone group), 6.06 (2 H, OCH_2O), 6.56 (2 H, aromatic protons at C-2′ and C-6′), 6.88 (1 H, aromatic proton at C-8), and 8.17 (broad, 1 H, aromatic proton at C-4).

A solution of 32 mg of lactone **2** and 68 mg of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 20 ml of benzene was refluxed for 3 hr. Elution chromatography of the cooled solution by means of Woelm neutral alumina and chloroform gave 21 mg (55%) of **3**, identical with the product obtained from dehydrogenation with palladium–charcoal.

B. From β-Peltatin-B Methyl Ether.—A solution of 0.21 g of β-peltatin-B methyl ether[19] and 0.91 g of DDQ in 50 ml of benzene was refluxed for 6 hr and processed as in the preceding paragraph. Crystallization of the chromatographic product from chloroform–cyclohexane afforded 0.15 g (72%)[20] of **3**, mp 265–267°, identical with the product from part A as based on mixture melting point, as well as infrared, ultraviolet, and nmr spectra.

Registry No.—**2**, 15619-23-5; **3**, 15656-72-1; $C_{13}H_{14}O_5$, 15619-24-6; *trans*-2-methoxy-3,4-methylenedioxycinnamyl alcohol, 15619-25-7; $C_{18}H_{14}N_2O_9$, 15619-26-8; *trans*-2-methoxy-3,4-methylenedioxycinnamyl 3,4,5-trimethoxyphenylpropiolates, 15619-27-9.

(8) Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Ultraviolet spectra were obtained by means of a Cary Model 15 spectrophotometer, infrared spectra by means of a Beckman IR-5 spectrophotometer, and nmr spectra by means of a Varian Associates A-60 instrument and using tetramethylsilane as an internal standard.

(9) A. R. Surrey, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 759.

(10) K. N. Campbell, P. F. Hopper, and B. K. Campbell, *J. Org. Chem.*, **16**, 1736 (1951).

(11) A. F. Wagner, E. Walton, A. N. Wilson, J. O. Rodin, F. W. Holly, N. G. Brink, and K. Folkers, *J. Amer. Chem. Soc.*, **81**, 4983 (1959).

(12) This isomer was identified as croweacic aldehyde by Wagner, *et al.*,[11] and by W. B. Brownell and A. W. Weston [*ibid.*, **73**, 4971 (1951)]. The structure of croweacic aldehyde was established as 2-methoxy-3,4-methylenedioxybenzaldehyde by A. R. Penfold, G. R. Ramage, and J. L. Simonsen [*J. Chem. Soc.*, 756 (1938)].

(13) Penfold, *et al.*,[12] described this product as the "β-form" of 2-methoxy-3,4-methylenedioxycinnamic acid. Their observations indicate that the "β-form" has the *trans* configuration, expected for the product from the Doebner modification of the Knoevenagel reaction on an aromatic aldehyde. See J. R. Johnson in "Organic Reactions," Vol. I, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1942, p 210; H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 225; J. J. Bloomfield and R. Fuchs, *J. Org. Chem.*, **26**, 2991 (1961). An infrared absorption band at 985 cm^{-1} and the coupling constant of J = 16 cps for the vinylic protons in our ethyl ester are also consistent with the *trans* configuration (*vide infra*). *Cf.* A. J. Speziale and C. C. Tung, *ibid.*, **28**, 1353 (1963).

(14) After drying for 48 hr *in vacuo* at room temperature. A sample dried for 2 hr in air melted at 51–52°.

(15) An absorption band at 935 cm^{-1} is also found for methylenedioxybenzene in chloroform.

(16) L. H. Klemm, K. W. Gopinath, G. C. Karaboyas, G. L. Capp, and D. H. Lee, *Tetrahedron*, **20**, 871 (1964).

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, New York, N. Y., 1956, p 212.

(18) In the previous manner.[16]

(19) Derived by methylation[2d] of β-peltatin, isolated in our laboratory from Podophyllin, N. F. (Merck) by Mrs. B. Haxby according to the chromatographic procedure of Hartwell and Detty.[2c]

(20) Schrecker and Hartwell[2e] reported a yield of 17% for this dehydrogenation process when palladium–charcoal plus benzoquinone in diphenyl ether was used.

Quantitative Studies in Stereochemistry. Photochemistry. IV. The Ratios of Diastereomeric Pinacols Formed in the Ultraviolet-Promoted Bimolecular Reduction of Acetophenone-[7-^{14}C] in Amine Media

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Previous reports from this laboratory have dealt with the stereochemical consequences of photopinacolizing acetophenone or benzaldehyde in neutral–acidic[1a] and in strongly alkaline media,[1b] as well as the results from a number of *para*-substituted acetophenones.[1c] The present note further extends the study to an examination of the ratios of *dl*- to *meso*-acetophenone pinacols observed when amines are employed as the solvent/donor.

The use of amines in the photopinacolization of benzophenones has been examined by Cohen and coworkers,[2] and by Davidson.[3] These investigators established that amines can serve as hydrogen donors, occasionally more satisfactorily than their carbinol counterparts. The present study would appear to be the first to examine acetophenone for corresponding reactivity. This was deemed desirable in view of the fact that acetophenone and benzophenone display strikingly different chemical behavior upon irradiation in strongly alkaline media.[1b] This is also the first report concerning the effects of amines upon the ratio of diastereomers produced in a reaction of this type.

Five amines, selected for their diversity, were utilized in isotope dilution experiments. The results are tabulated in Table I. All amines examined proved to be satisfactory hydrogen donors but inferior to 2-propanol in this respect. Certain selected values from earlier studies in other solvent/donors are included in the table for evaluative comparisons.

TABLE I

PHOTOPINACOLIZATION OF ACETOPHENONE-[7-^{14}C]

Run	Solvent/donor	Time, hr	Pinacol yield,[a] %	Ratio *dl*/*meso*
1[b]	2-Propanol (0.01 *N* potassium 2-propoxide)	18	56.4	2.98
2[b]	50% aqueous 2-propanol	18	94.6	1.31
3[c]	2-Propanol	18	100	1.09
4[b]	Cyclohexane	72	33.5	1.03
5	Tri-*n*-propylamine	42	58.4	1.02
6	Piperidine	18	81.9	0.95
7	Di-*n*-butylamine	42	82.1	0.93
8	Isopropyl amine	18	79.6	0.90
9	DABCO[d]	42	21.4	0.81

[a] Based on starting ketone. [b] From ref 1b. [c] From ref 1a. [d] Diazabicyclooctane (triethylenediamine), 5 g in 15 ml of C_6H_6.

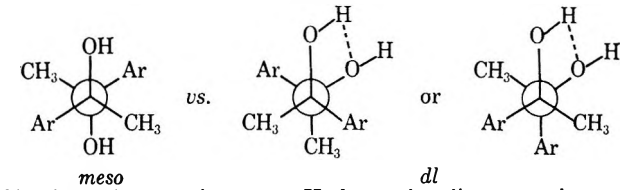
(1) (a) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **31**, 3755 (1966); (b) J. H. Stocker and D. H. Kern, *ibid.*, **33**, 291 (1968); (c) J. H. Stocker, D. H. Kern, and R. Jenevein, *ibid.*, **33**, 412 (1968).

(2) (a) S. G. Cohen and J. I. Cohen, *J. Amer. Chem. Soc.*, **89**, 164 (1967); (b) S. G. Cohen and R. J. Baumgarten, *ibid.*, **87**, 2996 (1965).

(3) R. S. Davidson, *Chem. Commun.*, 575 (1966).

An explanation of the stereochemistry observed in alcoholic media has been previously proposed.[4] It was suggested that interspecies hydrogen bonding between radicals about to dimerize, in competition with simple steric control, played a role in determining the resultant ratio of diastereomeric pinacols as illustrated in Scheme I.

SCHEME I



meso — Simple steric control

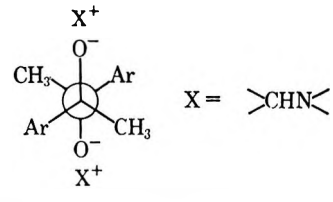
dl — Hydrogen bonding control

The stereochemistry observed with the use of amines cannot be due to the basicity of the amines, since alkaline solutions increase the *dl* to *meso* ratio (run 1).[4] Similarly, a consideration of solvent polarity will not account for the data. Solvents ranging from cyclohexane to aqueous alcohol all yield the *dl*-pinacol as the preponderant diastereomer (runs 2, 3, 4). The *meso*-pinacol predominates only in amine solution.

This anomalous behavior in the presence of amines may be ascribable to a difference in the mode of hydrogen transfer. It has been established that in alcoholic media a hydrogen atom is abstracted from the carbinol donor by the triplet ketone.[5] Cohen,[2a] however, has suggested that the corresponding amine reactions may proceed by an initial electron transfer from the nitrogen atom of the amine to the triplet ketone, with a subsequent proton transfer and electron redistribution, according to the sequence

$$>\ddot{C}H\ddot{N}< + \overset{\bullet}{O}{=}C< \longrightarrow >CH\overset{\bullet}{\underset{+}{N}}< + \underset{-}{O}{-}\dot{C}< \longrightarrow >\dot{C}{-}\ddot{N}< + HO{-}\dot{C}<$$

We would like to suggest that if the polar intermediates above exist in the form of an ion pair and are sufficiently long lived, dimerization may take place between two such species. Hydrogen bonding during the dimerization step would not be expected to play a significant role in this case. The sterically most favorable resulting structure would then be



Protonation of the above would yield the *meso*-pinacol. A relatively small contribution from this pathway would account for the lower *dl*/*meso* ratios observed when amines are used as solvent/donors.

From the limited number of amines examined, there would appear to be a qualitative correlation between the base strength and steric availability of the electron pair, and the observed stereochemistry.

(4) For a detailed discussion of the photopinacolization of acetophenone in acidic and basic media, see ref 1b.

(5) J. N. Pitts, Jr., R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald, and R. B. Martin, *J. Amer. Chem. Soc.*, **81**, 1068 (1959).

Experimental Section

The source or synthesis of the acetophenone-[7-^{14}C], *meso*- and *dl*-acetophenone pinacols, as well as the apparatus and general procedure employed, has been previously described.[1a,b] The several amines examined were of the highest research grades obtainable and further purified by traditional techniques where deemed necessary. All reaction mixtures involved 1 g of ketone and 10 ml of amine excepting run 9 as noted in the Table I compilation footnotes.

Registry No.—Acetophenone-[7-^{14}C], 5821-66-9.

Acknowledgment.—Financial assistance from the U. S. Atomic Energy Commission under Contract No. AT-(40-1)-2833(ORO-2833-15) is gratefully acknowledged.

Quantitative Studies in Stereochemistry. Photochemistry. V. The Ratio of Diastereomeric Pinacols Formed in the Ultraviolet-Promoted Bimolecular Reduction of Deoxybenzoin

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As part of a broad program designed to study the stereochemistry of the photopinacolization process, reports from this laboratory have described the ratio of diastereomeric pinacols formed from acetophenone[1,2] and various *para*-substituted acetophenones.[3] The present report describes a quantitative measurement by nmr techniques of the amounts of the two pinacols formed when an α-substituted acetophenone, deoxybenzoin, is photopinacolized in 2-propanol in both acidic and basic media. Formal assignment of diastereomeric identity of the pinacols is also made.

In compiling all pertinent literature data, it was noted that previous reports of the predominant diastereomer formed when deoxybenzoin was photopinacolized were in conflict with each other. Thus, Bergmann and Hershberg[4] reported obtaining the higher melting α pinacol (mp 214°) in 80% yield; "no trace of the β form was detected." On the other hand, Crawford and coworkers[5] have reported a 97% yield of a pinacol with a melting point of 172°, corresponding to the lower melting β isomer.[6] By implication, each of the above reactions proceeded in a highly stereoselective manner but with stereochemically different results.

The pure pinacols utilized in the present study were synthesized photochemically. The nmr of each showed a quartet for the nonequivalent benzylic protons, an hydroxylic proton, and a complex phenyl signal. The spectra were sufficiently different so as to provide a convenient means of distinguishing the two pinacols, independently and in mixtures. Consequently, the crude reaction mixture was analyzed by nmr, and the amounts of each isomer as well as residual ketone were obtained. In neutral or slightly acidic 2-propanol, high yields of 1,2,3,4 tetraphenyl-2,3-butanediol result. From 0.5 g of deoxybenzoin, an 82% yield of pinacol was obtained with 16% unreacted starting material after 4 hr of irradiation. From 1.0 g of deoxybenzoin, a quantitative yield of pinacol was obtained after 12 hr. The ratio of β-to α-pinacol was 1.15 ± 0.05. In basic solution, 0.5 g of ketone yielded 75% pinacol after 12 hr, with 22% recovered deoxybenzoin, and a β to α ratio of 3.0 ± 0.1.

By analogy to a number of other pinacols, the *meso* structure was assigned to the diastereomer with the hydroxylic proton at higher field strength[7] (α-pinacol). Correspondingly, the β-pinacol is the *dl* isomer. Thus, the *dl*-pinacol predominates in both acidic and basic 2-propanol. These results are analogous to those obtained for acetophenone, which yields *dl* to *meso* ratios of 1.10 and 2.85 in acid and base, respectively.[2]

It must be concluded that both of the previous reports[4,5] are incorrect and the reaction proceeds, as do the comparable acetophenone photopinacolizations, with a rather low stereoselectivity.

Experimental Section

Deoxybenzoin, mp 54–56°, was obtained from Matheson Coleman and Bell and used as received. The 2-propanol was standard reagent grade and used without further purification. The general procedure[3] and photochemical apparatus[1] have been described; F8T5(BLB) bulbs (3500 Å peak) and Pyrex glass were used exclusively. All runs were made with a ketone concentration of 5%. The alkaline solutions were 50% aqueous 2-propanol, 0.2 *N* with respect to KOH. Melting points were determined on a Kofler hot stage and are uncorrected.

meso-**1,2,3,4-Tetraphenyl-2,3-butanediol** (α-**Pinacol**).—The suspension resulting from the irradiation of 1 g of deoxybenzoin in acidic 2-propanol was filtered, and the white needles were recrystallized from heptane to yield 380 mg of pinacol: mp 213–214°; nmr, phenyl, τ 2.80 (multiplet, 20 H); benzylic, 6.68 (quartet, 4 H), J_{AB} = 14 cps, $\Delta\nu_{AB}$ = 43 cps; hydroxylic, 7.90 (singlet, 2 H).

dl-**1,2,3,4-Tetraphenyl-2,3-butanediol** (α-**Pinacol**).—The mother liquor from the above was concentrated and crystallized from heptane to yield 350 mg of pinacol: mp 171–172°; nmr, phenyl, τ 2.80 (multiplet, 20 H); benzylic, 6.75 (quartet, 4 H), J_{AB} = 14 cps, $\Delta\nu_{AB}$ = 28 cps; hydroxylic, 7.51 (singlet, 2 H).

Registry No.—Deoxybenzoin, 451-40-1.

Acknowledgments.—Financial support of this research under Atomic Energy Commission Contract No. AT-(40-1)-2833 (ORD-2833-18) is gratefully acknowledged. The nmr instrument employed, an A-60 (Varian Corp.), was awarded Louisiana State University in New Orleans by the National Science Foundation under GP-3674.

(1) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **31**, 3755 (1966).
(2) J. H. Stocker and D. H. Kern, *ibid.*, **33**, 291 (1968).
(3) J. H. Stocker, D. H. Kern, and R. M. Jenevein, *ibid.*, **33**, 412 (1968).
(4) F. Bermann and Y. Hirshberg, *J. Amer. Chem. Soc.*, **65**, 1429 (1943).
(5) H. M. Crawford, M. E. Seager, and F. E. Warneke, *ibid.*, **64**, 2862 (1942).
(6) The two diastereomers of deoxybenzoin pinacol, 1,2,3,4-tetraphenyl-2,3-butanediol, are both known and have most frequently been prepared by the Grignard reaction or by the reduction of deoxybenzoin, or benzoin. E. J. Chu and J. Chu [*J. Chin. Chem. Soc.* (Taipei), **10**, 14 (1943)] record several pertinent references; they observed a melting point of 208–209° for the α and 172° for the β pinacol. Beilsteins Handbuch, [F. Richer, Ed., (Vol. VI, 4th ed, 2nd Suppl., Springer-Verlag, Berlin, 1944, p 1059)] lists 215–216° and 172–173° for the α and β forms, respectively. The corresponding figures from the present study (see Experimental Section) are 213–214° and 171–172°.
(7) This method of assignment has been previously employed: J. H. Stocker, *J. Amer. Chem. Soc.*, **88**, 2878 (1966). See also ref 3.

The Photolysis of a 5-Oxo Steroid Derivative

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The ultraviolet irradiation of 17-oxo steroids in organic solvents is known to invert the configuration of the C-13 angular methyl group, giving rise to the corresponding lumi steroids in which rings C and D are *cis* fused.[2] In this connection, we were interested in the possibility that irradiation of the 5-oxoandrostane derivative I might yield the corresponding C-10 epimer II.

The synthesis of I was accomplished readily by utilizing 11β-hydroxytestosterone 17-acetate[3] as starting material. Ozonolysis of the latter compound gave the keto acid IIIa as an amorphous solid[4] which was characterized by conversion into its methyl ester IIIb and the corresponding 17β-hydroxy derivatives IIIc and IIId. Compound IIIa gave the lactone I by heating in benzene with *p*-toluenesulfonic acid or by heating with acetic anhydride containing a trace of sodium acetate.[5] Hydrolysis of the lactone I also gave IIIc, which was identical with the acid obtained by hydrolysis of IIIa.

The major product isolated from the irradiation of I in aqueous dioxane was the acid Va, which was characterized as its methyl ester Vb. The latter compound was converted into the diacid VIa and the dimethyl ester VIb. Irradiation of I in *t*-butyl alcohol gave the *t*-butyl ester Vc, which on hydrolysis also gave the diacid VIa.

Quinkert and coworkers[6] and recently Meinwald and Schneider[7] have demonstrated that prolonged ultraviolet irradiation of nonconjugated ketones gives rise to carboxylic acids or carboxylic acid derivatives *via* ketene intermediates. Similarly, the intermediate ketene IV seems likely as the primary product of the photolysis of I.

Experimental Section[8]

11β,17β-Dihydroxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid 17-Acetate (IIIa) and Methyl Ester (IIIb).—A solution of 5.0 g (0.0144 mol) of 11β-hydroxytestosterone 17-acetate,[3] 6 ml of glacial acetic acid, and 114 ml of ethyl acetate was ozonized in a bath of Dry Ice and acetone for 16 min (Welsbach T-23 Laboratory Ozonator, pressure 8.0 psi, rotameter float 0.08 S. C. F. M.). The resulting yellow solution was flushed at −78° with oxygen for 5 min and with nitrogen for 25 min. The solution was then treated at 0° with 100 ml of glacial acetic acid, 20 ml of water, and 8 ml of 30% hydrogen peroxide. The colorless solution was allowed to stand at 5° overnight and was then concentrated under reduced pressure to a total weight of 15.8 g, the water bath being kept at 40–50°. The residue was distributed between 200 ml of benzene and 350 ml of a 7% sodium carbonate solution by shaking for 15 min. The benzene layer was then extracted with two 100-ml portions of 10% sodium carbonate solution. The combined sodium carbonate extracts were poured into an excess of ice-cold 6 *N* hydrochloric acid solution and the resulting mixture was extracted with ethyl acetate. These extracts were dried and evaporated to give 4.95 g (94%) of crude IIIa which could not be crystallized: $\nu_{max}^{CHCl_3}$ 3615, 1710, 1255, and 1045 cm^{-1}; ν_{max} (piperidine–chloroform) 3620, 1730, 1705, 1625, 1565, 1495, 1480, 1257, and 1045 cm^{-1}.

In another experiment on the same scale, the final ethyl acetate extracts were concentrated to a total weight of 6.64 g. This residue (containing some acetic acid), dissolved in 20 ml of methanol, was treated at 0° with an excess of diazomethane in ether. The solvents were evaporated and the residue was chromatographed on 100 g of silica gel. The ethyl acetate–benzene (10:90) fraction was crystallized from ether–hexane to yield 3.68 g of methyl ester IIIb, mp 107–108°. Several recrystallizations from the same solvent system gave the analytical sample: mp 108–109°; $[\alpha]^{25}D$ +47.0° (*c* 1.0 in ethanol); $\nu_{max}^{CHCl_3}$ 3620, 1735, 1710, 1255, and 1045 cm^{-1}; nmr ($CDCl_3$), δ 1.10 (18-CH_3), 1.37 (19-CH_3), 2.03 ($OCOCH_3$), and 3.66 ($COOCH_3$).

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.56; H, 8.20.

11β,17β-Dihydroxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid ε-Lactone 17-Acetate (I). A.—A solution of 7.89 g of the crude keto acid IIIa and 430 mg of *p*-toluenesulfonic acid monohydrate in 630 ml of benzene was heated under reflux for 1.5 hr (Dean–Stark apparatus). The resulting solution was extracted once with dilute sodium bicarbonate solution, once with water, dried, and evaporated to give 6.27 g of crude I. Column chromatography on 65 g of silica gel and elution with ethyl acetate–benzene (10:90) gave a fraction which was crystallized from ethyl

(1) (a) F. Hoffmann-La Roche & Co., AG, Basel, Switzerland; (b) to whom enquiries may be addressed.

(2) (a) A. Butenandt, A. Wolff, and P. Karlson, *Ber.*, **74**, 1308 (1941); (b) A. Butenandt, W. Friedrich, and L. Poschmann, *ibid.*, **75**, 1931 (1942); (c) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **34**, 2053 (1951); (d) J. P. L. Bots, *Rec. Trav. Chim. Pays-Bas*, **77**, 1010 (1958); (e) H. Wehrli and K. Schaffner, *Helv. Chim. Acta*, **45**, 385 (1962).

(3) (a) M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.*, **75**, 5927 (1953); (b) O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(4) The ozonolysis of the 17-propionate has been described by E. Caspi, W. Schmid, and B. T. Khan, *J. Org. Chem.*, **26**, 3898 (1961).

(5) E. Caspi, B. T. Khan, and W. Schmid, *ibid.*, **26**, 3894 (1961).

(6) G. Quinkert, *Angew. Chem., Intern. Ed. Engl.*, **4**, 211 (1965).

(7) J. Meinwald and R. A. Schneider, *J. Amer. Chem. Soc.*, **87**, 5218 (1965).

(8) Melting points were determined in a capillary tube and are corrected. The infrared spectra were recorded on a Beckman IR 9 spectrophotometer and the nmr spectra on a Varian A-60 instrument using tetramethylsilane as an internal reference standard. The organic solutions were dried over anhydrous sodium sulfate. Column chromatography was carried out on 0.2–0.5-mm silica gel manufactured by E. Merck AG, Darmstadt.

acetate–hexane to yield 4.1 g of lactone I, mp 245–246° (under vacuum). Recrystallization from the same solvent gave the analytical sample: mp 245.5–246.5° (under vacuum); $[\alpha]^{26}D$ −26.4° (*c* 1.0 in dioxane); $\nu_{max}^{CHCl_3}$ 1720, 1250, and 1040 cm^{-1}; nmr ($CDCl_3$), δ 1.02 (18-CH_3), 1.35 (19-CH_3), and 2.05 ($OCOCH_3$).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.93; H, 8.02.

B.—The crude acid IIIa (9.9 g) and 2.25 g of fused sodium acetate were heated under reflux in 900 ml of acetic anhydride for 2 hr (nitrogen atmosphere). The solution was then filtered from undissolved sodium acetate and was concentrated under reduced pressure. The residue was dissolved in methylene chloride and this solution was washed with dilute sodium bicarbonate solution, water, dried, and evaporated. The residue was chromatographed on 200 g of silica gel. Elution with ethyl acetate–benzene (10:90) and crystallization from ethyl acetate–hexane gave 2.9 g of crude lactone I, mp 232–237°. Further crystallization yielded 1.87 g of the pure compound, mp 245–246° (under vacuum), identical with the product obtained by method A.

11β,17β-Dihydroxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid (IIIc). A. From I.—The lactone I (250 mg) was hydrolyzed by heating under reflux for 10 min with a solution of 250 mg of potassium hydroxide, 0.25 ml of water, and 5 ml of methanol. The reaction mixture was then evaporated under reduced pressure and the residue was dissolved in water. The resulting solution was acidified at 0° with dilute hydrochloric acid solution. The precipitate was filtered, washed with water, and dried, yielding 198 mg (85%) of keto acid IIIc, mp 224.5–226° dec. Several recrystallizations from aqueous acetone gave the analytical sample: mp 225–226° dec; $[\alpha]^{26}D$ +69.9° (*c* 1.1 in ethanol); ν_{max}^{KBr} 3535, 3380, 1690, 1240, and 1050 cm^{-1}; ν_{max} (piperidine–chloroform) 3620, 1705, 1625, 1565, and 1400 cm^{-1}; nmr (dimethylformamide-d_7), δ 1.05 (18-CH_3), 1.37 (19-CH_3).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.58; H, 8.78.

B. From IIIa.—In a similar manner the crude acetate IIIa (4.26 g) was hydrolyzed by heating under reflux for 10 min with a solution of 4.6 g of potassium hydroxide, 5 ml of water, and 50 ml of methanol. The reaction mixture was then evaporated and the residue was dissolved in 20 ml of water. This solution was acidified at 0° with dilute hydrochloric acid solution. After standing in the refrigerator overnight, the resulting precipitate was filtered, washed with cold water, and recrystallized twice from aqueous acetone (charcoal) yielding 2.26 g of keto acid IIIc, mp 224–225° dec, identical with the sample obtained by hydrolysis of the lactone I.

11β,17β-Dihydroxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid Methyl Ester (IIId).—Treatment of IIIc (0.75 g) with diazomethane in methanol–ether, followed by crystallization from ethyl acetate–hexane, gave 0.43 g of the methyl ester IIId, melting at 93.5–96°, resolidifying at 98°, and remelting at 121.5–122°; $[\alpha]^{26}D$ +66.6° (*c* 1.0 in ethanol); $\nu_{max}^{CHCl_3}$ 3620, 1730, and 1708 cm^{-1}; nmr ($CDCl_3$), δ 1.07 (18-CH_3), 1.38 (19-CH_3), and 3.70 ($COOCH_3$).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.43; H, 8.74.

Irradiation of I in Aqueous Dioxane. Preparation of 9β-Acetoxydodecahydro-5,9aβ-dimethyl-2-oxo-2H-indeno[5,6-*b*]oxepine-6α-propionic Acid (Va) and Methyl Ester (Vb).—A solution of 2.57 g (7.38 mmol) of I in 200 ml of dioxane and 10 ml of water was irradiated (Corex filter) for 7.5 hr at 25–30°.[9] After evaporation of the solvents the residue was dissolved in benzene. The acidic reaction products were extracted by shaking this solution three times with 60-ml portions of 10% sodium carbonate solution. (Thin layer chromatography indicated the presence of some I and several other products in the resulting benzene layer.) The sodium carbonate extracts were combined and acidified at 0° with dilute hydrochloric acid solution. The resulting precipitate was filtered, washed with water, and dried to give 1.08 g of crude acid Va. Crystallization from aqueous acetone gave 0.761 g of Va, mp 108–111°. Several recrystallizations from ethyl acetate gave the analytical sample: mp 100–101° dec; $[\alpha]^{26}D$ −30.6° (*c* 0.8 in dioxane); $\nu_{max}^{CHCl_3}$ 1725, 1265, 1160, and 1034 cm^{-1}; ν_{max} (piperidine–chloroform) 1725, 1625, 1565, 1385, 1265, 1160, and 1030 cm^{-1}; nmr ($CDCl_3$), δ 1.08 (9a-CH_3), 1.12 (doublet, 5-CH_3), and 2.05 ($OCOCH_3$).

Anal. Calcd for $C_{20}H_{30}$: C, 65.55; H, 8.25. Found: C, 65.49; H, 8.36.

The crude acid Va (1.95 g) was treated with excess diazomethane, followed by column chromatography of the product on silica gel. The product was eluted with ethyl acetate–benzene (15:85) and was crystallized several times from ether–hexane to give 0.76 g of the methyl ester Vb: mp 112–112.5°; $[\alpha]^{25}D$ −27.1° (*c* 0.9 in dioxane); $\nu_{max}^{CHCl_3}$ 1730, 1260, 1160, and 1030 cm^{-1}; nmr ($CDCl_3$), δ 1.08 (9a-CH_3), 1.10 (doublet, J = 7 cps, 5-CH_3), 2.02 ($OCOCH_3$), and 3.70 ($COOCH_3$).

Anal. Calcd for $C_{21}H_{32}O_6O_6$: C, 66.30; H, 8.48. Found: C, 66.23; H, 8.66.

Irradiation of I in *t*-Butyl Alcohol. Preparation of 9β-Acetoxydodecahydro-5,9aβ-dimethyl-2-oxo-2H-indeno[5,6-*b*]oxepine-6α-propionic Acid *t*-Butyl Ester (Vc).—A solution of 3.32 g (9.55 mmol) of I in 310 ml of *t*-butyl alcohol was irradiated (Corex filter) for 7 hr at 50–60° and for an additional 3 hr at 30–40°.[9] After evaporation of the solvent the residue was chromatographed on 100 g of silica gel. Elution with ethyl acetate–benzene (4:96) gave Vc along with a small amount of a less polar by-product. The latter compound was removed readily by one recrystallization from ether–hexane to give 0.85 g of *t*-butyl ester Vc, mp 125–126°. (Further elution with ethyl acetate–benzene (8:92) gave an additional 1.45 g of Vc containing a trace of a more polar by-product which could not be removed by crystallization from ether–hexane.) Crystallization of the 0.85 g sample from ether–hexane gave the analytical sample: mp 129–130°; $[\alpha]^{26}D$ −24.1° (*c* 0.8 in dioxane); $\nu_{max}^{CHCl_3}$ 1725, 1370, 1260, and 1150 cm^{-1}; nmr ($CDCl_3$), δ 1.08 (9a-CH_3), 1.10 (doublet, J = 7 cps, 5-CH_3), 1.45 ($COOC(CH_3)_3$), and 2.03 ($OCOCH_3$).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 67.96; H, 9.00.

***trans*-4α-(2-Carboxyethyl)hexahydro-1β,6β-dihydroxy-γ,7aβ-dimethylindan-5β-butyric Acid (VIa). A. From Vb.**—A solution of Vb (200 mg), 300 mg of potassium hydroxide, 0.3 ml of water, and 5 ml of methanol was heated under reflux for 20 min. The reaction mixture was then evaporated and the residue was dissolved in water. The aqueous solution was acidified with dilute hydrochloric acid solution and was extracted four times with ethyl acetate. The dried extracts were evaporated and the residue was crystallized twice from acetone–ether to give 103 mg (57%) of the dicarboxylic acid VIa, mp 187.5–188° dec; $[\alpha]^{26}D$ +57.0° (*c* 1.0 in ethanol). Crystallization from the same solvent mixture gave the analytical sample: mp 189.5–190° dec; $[\alpha]^{25}D$ +58.0° (*c* 1.0 in ethanol); neutralization equivalent 167; ν_{max}^{KBr} 3540, 3450, 1715, 1465, 1420, 1285, 1270, 1200, 1185, and 1030 cm^{-1}; ν_{max} (piperidine–chloroform) 1630, 1570, 1400, and 1390 cm^{-1}; nmr (dimethylformamide-d_7), δ 1.00 (7a-CH_3), 1.02 (doublet, γ-CH_3).

Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 63.39; H, 9.03.

B. From Vc.—A solution of 0.20 g of Vc, 0.4 g of potassium hydroxide, 0.40 ml of water, and 4.0 ml of methanol was heated under reflux for 5 hr. Working up as described for the hydrolysis of Vb gave 0.094 g (58%) of the dicarboxylic acid VIa, mp 188.5–189° dec, $[\alpha]^{26}D$ +58.7° (*c* 1.0 in ethanol), identical with the product obtained by hydrolysis of Vb.

***trans*-4α-(2-Carboxyethyl)hexahydro-1β,6β-dihydroxy-γ,7aβ-dimethylindan-5β-butyric Acid Dimethyl Ester VIb.**—The dicarboxylic acid VIa (1.70 g) was treated with an excess of diazomethane in ether. Several recrystallizations from acetone–hexane gave 1.05 g of the dimethyl ester VIb: mp 117.5–118.5°; $[\alpha]^{25}D$ +53.4° (*c* 1.0 in ethanol); $\nu_{max}^{CHCl_3}$ 3620, 1730, 1460, 1440, 1260, 1175, and 1020 cm^{-1}; nmr ($CDCl_3$), δ 1.00 (7a-CH_3), 1.02 (doublet, γ-CH_3), and 3.68 ($COOCH_3$).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.50; H, 9.01.

Registry No.—I, 15983-73-0; IIIa, 15983-71-8; IIIb, 15983-72-9; IIIc, 15983-69-4; IIId, 15983-70-7; Va, 15983-82-1; Vb, 15983-83-2; Vc, 16031-71-3; VIa, 15983-84-3; VIb, 15983-85-4.

(9) Irradiations were carried out using a Hanovia 200-W high pressure mercury vapor lamp. The lamp was placed in a water-cooled quartz immersion well, which was in turn fitted inside a water-jacketed Pyrex reaction vessel of slightly larger diameter. The reaction mixture was flushed with nitrogen for 30 min prior to irradiation which was then carried out with magnetic stirring under a slow stream of nitrogen. The dioxane and *t*-butyl alcohol were purified by distillation over sodium.

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses, and to Mr. S. Traiman and Dr. E. Billeter for the infrared and nmr spectra, respectively. We are also indebted to Mr. C. Angevine and Mrs. A. Kahn for technical assistance.

Preparation of 1-Deuteriobenzaldehydes by Lithium Aluminum Deuteride Reduction of N-*t*-Butylbenzamides

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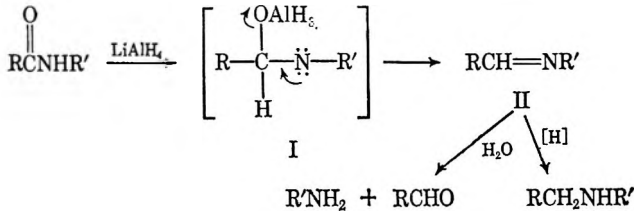
The normal product resulting from the treatment of an amide with lithium aluminum hydride is the corresponding amine.[2] However, numerous investigators have reported the concomitant formation of significant amounts of aldehyde[3] and alcohols[4] under the reaction conditions. Often the formation of aldehydes becomes the major course of the reaction.[5-7] This is readily understandable if one views the reaction as proceeding by the addition of the hydride reagent to the amide carbonyl group to give a derivative of a geminal amino alcohol (I). Elimination from this intermediate yields an aldimine (II) which on hydrolysis affords the aldehyde or, on further reduction, produces the amine.



The need for 1-deuteriobenzaldehydes in connection with other work led us to investigate procedures for the preparation of labeled aldehydes from amides. The recognized[8] sensitivity of hydride reductions to steric factors suggested the possibility that the reduction could be arrested at the aldimine stage if the effective hydride source (I) and the intermediate (II) contained sufficiently bulky substituents close to the reaction site. The lithium aluminum deuteride reduction of N-*t*-butylbenzamides proved to be a convenient route to the desired 1-deuteriobenzaldehydes. The necessary amides were readily prepared by the reaction of the corresponding acid chlorides with *t*-butylamine.

Optimum yields of aldehyde were obtained when equimolar amounts of lithium aluminum deuteride and amide in ether solution were heated under reflux for 15 hr. The use of a lower ratio of deuteride to amide resulted in the recovery of much unconverted amide, while increased reaction time appears to have a negligible, if any, effect on the yields. Increasing the molar ratio of deuteride to amide to 1.5 causes the complete reduction of the imine to the corresponding N-*t*-butylbenzylamine and no aldehyde is obtained when the reduction product is treated with 5% HCl.

Several methods[9] are available for the preparation of benzaldehyde-1-*d*. The method described in the present work has been successfully applied to the synthesis of the following 1-deuteriobenzaldehydes with the indicated yields: anisaldehyde (57%), *p*-tolualdehyde (58%), and benzaldehyde (33%). The convenience of this method compares favorably with the alternate procedures.

Experimental Section[10]

The following procedure is typical.

N-*t*-butylanisamide.—To a cooled, stirred solution of *t*-butylamine (16.4 g, 0.22 mol) in 60 ml of ether was added a solution of anisoyl chloride (17.1 g, 0.10 mol) in 60 ml of ether over a period of 2 hr. The precipitated amine hydrochloride was removed by filtration and the ethereal solution containing the amide was washed with water and dried over anhydrous sodium sulfate. Removal of the ether gave 19.2 g of crude material which was recrystallized from hexane–chloroform to afford 12.6 g (60%) of N-*t*-butylanisamide, mp 116–117°.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.41; H, 8.18; N, 6.85.

N-Anisylidene-*t*-butylamine.—To a stirred slurry of lithium aluminum deuteride (1.26 g, 0.030 mol) in 100 ml of anhydrous ether was added a solution of N-*t*-butylanisamide (5.18 g, 0.025 mol) in 150 ml of anhydrous ether over a 30-min period. The reaction mixture was heated under reflux for 15 hr after which the reaction was quenched by the cautious addition of 5 ml of water followed by 3 ml of 10% sodium hydroxide. The ether layer was concentrated on a rotary evaporator to give 4.78 g of a colorless oil. The nmr spectrum of the oil indicated its composition to be 90% aldimine (CH_3 singlet, 1.28 ppm), 5% unreacted amide (CH_3 singlet, 1.46 ppm), and 5% amine (CH_3 singlet, 1.16 ppm).

Anisaldehyde-1-*d*.—The crude aldimine (4.78 g) obtained from the lithium aluminum deuteride reduction was stirred at 70° with 60 ml of 5% hydrochloric acid for 30 min. The imine hydrochloride which precipitated initially was gradually converted to an insoluble oil. The reaction mixture was cooled to room temperature and extracted with 75 ml of ether. The ether extract was washed with 5% sodium hydroxide, followed by water, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to give 2.43 g (71%) of a colorless oil. The nmr spectrum showed this material to be essentially pure anisaldehyde-1-*d*. Distillation gave a colorless oil (1.96 g, 57%), bp 76° (0.6 mm). The infrared spectrum showed a C–D stretching doublet at 2050 and 2100 cm^{-1} and no aldehyde proton could be detected by nmr analysis.

Registry No.—Lithium aluminum deuteride, 14128-54-2.

Acknowledgment.—This work was supported in part by grants from The City College Research Committee, The City University of New York, and the National Science Foundation Undergraduate Research Participation Program.

(1) Participant in National Science Foundation Undergraduate Research Program, Summer 1967.

(2) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p 544.

(3) D. R. Husted and A. H. Ahlbrecht, *J. Amer. Chem. Soc.*, **74**, 5422 (1952).

(4) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

(5) F. Weygand and R. Mitgau, *Chem. Ber.*, **88**, 301 (1955).

(6) H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **83**, 4549 (1961).

(7) H. A. Staab and H. Braunling, *Ann.*, **654**, 119 (1962).

(8) F. Weygand and D. Tietjen, *Chem. Ber.*, **84**, 625 (1951).

(9) For leading references, see D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966); R. A. Olofson and D. M. Zimmerman, *J. Amer. Chem. Soc.*, **89**, 5057 (1967).

(10) Melting points are corrected and boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord Model 137 infrared spectophotometer. Nmr spectra were determined with a Varian Associates A-60 spectrometer and absorptions are reported in parts per million (ppm) relative to tetramethylsilane for 15% solutions in deuteriochloroform.

A Simple Thiol Synthesis

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The reaction of organic halides with sodium trithiocarbonate has been widely used for the preparation of disubstituted trithiocarbonates.[1] During a recent investigation of the chemistry of dialkyl trithiocarbonates, we found alkyl mono- and dihalides, upon treatment with sodium trithiocarbonate, could easily be converted into the corresponding mono- or dimercaptan.[2] The reaction is rapid, simple to conduct, and affords the thiol in good yield.

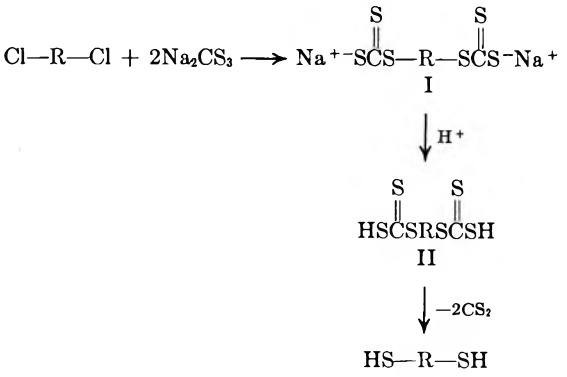
Thus, addition of 1.0 mol of dichlorodiethyl ether (I, R = $CH_2CH_2OCH_2CH_2$) to 2.0 mol of aqueous sodium trithiocarbonate at 40° resulted in a slightly exothermic reaction. The reaction mixture was heated to 60° for 2 hr; however, we have found the reaction to be quite rapid and essentially completed after 15–30 min. Similarly, reaction temperatures of 40–70° had no noticeable effect on the yield. Extraction of the basic reaction mixture permitted the removal of the nonacidic by-product, namely, thioxane (10–15%). Acidification was understandably exothermic liberating carbon disulfide and β,β'-dimercaptodiethyl ether.

The results of this simple one-step thiol synthesis are summarized in Table I. Yields are based on product isolation; the products were identified by physical constants and infrared and pmr spectroscopy.

We postulate the reaction proceeding through the sodium salt of the monoalkyl trithiocarbonic acid (I) which, upon acidification, yields the monoalkyltrithiocarbonate (II). The monoalkyltrithiocarbonate, being unstable,[3] decomposes spontaneously to liberate the mercaptan and carbon disulfide.

An alternate mechanism, such as the acid hydrolysis of either the cyclic or polymeric dialkyl trithiocarbonate,[1] may be excluded since the trithiocarbonate should be extractable from the basic reaction mixture. Similarly, the lack of carbon disulfide generation during the reaction permits the exclusion of mercaptide formation. Additional evidence for our mechanism was obtained by pmr spectroscopy. The pmr spectra of the aqueous basic reaction mixture (after solvent extraction) and an authentic sample of I, prepared from the dimercaptan, sodium hydroxide, and carbon disulfide, exhibited an identical complex multiplet.[4] This information along with Hantzsch's observation that II is less stable than I has prompted us to favor the sequence outlined in Scheme I.

SCHEME I



Experimental Section

All boiling points are uncorrected. All infrared spectra were recorded with a Perkin-Elmer Infracord spectrophotometer. Pmr spectra were determined at 27° (probe temperature) with a Varian Associates Model A-60A spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the τ scale in parts per million (ppm) relative to TMS (τ 10.00). For each compound, chemical shifts cited are the centers of the multiplets. Numbers in parentheses refer to the multiplicity of the observed resonance. An F & M Scientific Corporation Model 810 and an Aerograph Model 350 chromatograph were used for glpc analyses.

Reagents.—The reagents were all obtained from commercial sources and used without further purification.

Preparation of Aqueous Sodium Trithiocarbonate.—Sodium sulfide (1030 g, 4.3 mol) was dissolved in 500 ml of water at 30°. To this solution was added 356 g (4.7 mol) of carbon disulfide. The reaction mixture was warmed to 40° and allowed to stir for 6 hr. The excess carbon disulfide was removed by evaporation at reduced pressure; the resulting deep red liquid was diluted to 2 l. to afford an ~33% solution.

General Procedure.—The halide was added dropwise to the aqueous sodium trithiocarbonate at 25°. The reaction mixture was heated at 60° for 1–5 hr. During the reaction essentially no carbon disulfide formation was observed. The basic reaction mixture was extracted with ether to remove any unreacted starting material or other nonacidic products. Acidification of the aqueous layer with sulfuric acid resulted in carbon disulfide generation and recovery (90%). The acidic aqueous medium was extracted three times with ether; the combined ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure to yield the dimercaptan.

1,4-Butanedithiol.—To 350 ml (0.75 mol) of aqueous sodium trithiocarbonate at 25° was added 31.8 g (0.25 mol) of 1,4-dichlorobutane in 25 min. The reaction mixture was heated to 60° and allowed to stir at 60° for 5 hr. Isolation of the product by the general procedure described above afforded 18.7 g (61%) of 1,4-butanedithiol: bp 65–68° (13 mm) (lit.[5] bp 75–76° (11 mm)); infrared spectrum, 2548 cm^{-1}; pmr spectrum (CS_2 solution), τ 8.67 (S–H, 3), 8.28 (CH_2–C, 2 × 3), 7.43 (CH_2–S,C).

Anal. Calcd for $C_4H_{10}S_2$: S, 52.5; SH, 54.0; mol wt, 122. Found: S, 52.3; SH, 53.4; mol wt, 120 (osmometer).

β,β'-Dimercaptodiethyl Ether.—To 350 ml (0.75 mol) of aqueous sodium trithiocarbonate at 40° was added 36 g (0.25 mol) of dichlorodiethyl ether in 30 min. The reaction mixture was heated to 60° and allowed to stir at 60° for 2 hr. Isolation of the product by the general procedure described above followed by distillation afforded 23.0 g (66%) of β,β'-dimercaptodiethyl ether: bp 83–85° (9 mm) (lit.[6] bp 90° (10 mm)); infrared spectrum, 2550 cm^{-1}; pmr spectrum (CS_2 solution), τ 8.48 (S–H, 3), 7.40 (CH_2–S, 2 × 3), 6.47 (CH_2–O, 3). The infrared spectrum and glpc retention time were identical with an authentic sample.

Triglycol Dimercaptan.—To 400 ml (0.86 mol) of aqueous sodium trithiocarbonate at 25° was added 56 g (0.3 mol) of triglycol dichloride in 15 min. The reaction mixture was heated to 60° and allowed to stir at 60° for 5 hr. The product was isolated as described above to afford 42.0 g (77%) of triglycol di-

(1) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1958.

(2) After the completion of our work a patent appeared describing similar results: Belgium Patent 668,364 (Dec 16, 1965) to Dr. Speiss G.m.b.H.; *Chem. Abstr.* **65**, 5418 (1966).

(3) A. Hantzsch and W. Bucerius, *Ber.*, **59**, 793 (1926). Hantzsch observed that ethyl trithiocarbonate decomposed easily whereas its salt, $C_2H_5SCS_2^-M^+$, was quite stable.

(4) A multiplet at τ 8.5–9.0 relative to acetone (internal standard) was observed for I (R = $CH_2CH_2OCH_2CH_2$–).

(5) G. Schwarzenback and A. Epprecht, *Helv. Chim. Acta*, **19**, 169 (1934); *Chem. Abstr.*, **30**, 4074 (1936).

(6) H. Rheinboldt, E. Giesbrecht, and S. Mathias, *Univ. Sao Paulo, Fac. Filosof., Cienc. Letras, Botan.*, Bol. No. 129, 133 (1951); *Chem. Abstr.*, **46**, 7554 (1952).

TABLE I

REACTION OF HALIDES WITH SODIUM TRITHIOCARBONATE

Halide	Reaction conditions	Product	Yield,[a] %
$ClCH_2CH_2CH_2CH_2Cl$	5 hr at 60°	$HSCH_2CH_2CH_2CH_2SH$	61
$ClCH_2CH_2OCH_2CH_2Cl$	2 hr at 60°	$HSCH_2CH_2OCH_2CH_2SH$	66
$ClCH_2CH_2OCH_2CH_2OCH_2CH_2Cl$	5 hr at 60°	$HSCH_2CH_2OCH_2CH_2OCH_2CH_2SH$	77
$C_6H_5CH_2Cl$	1 hr at 60°	$C_6H_5CH_2SH$	25

[a] No attempt was made to optimize yields.

mercaptan: bp 86° (0.4 mm) (lit.[7] bp 125–131° (5 mm)); infrared spectrum, 2557 cm^{-1}; pmr spectrum (neat), τ 8.08 (S–H, 3), 7.33 (CH_2–S, 2 × 3), 6.43 (CH_2–O, 3). The infrared spectrum was identical with an authentic sample.

Benzyl Mercaptan.—To 135 ml (0.3 mol) of aqueous sodium trithiocarbonate at 25° was added 25.2 g (0.2 mol) of benzyl chloride in 21 min. The reaction mixture was warmed to 60° and allowed to stir at 60° for 1 hr. Isolation of the product as described in the general procedure afforded 6.2 g (25%) of benzyl mercaptan: bp 88–89° (11 mm) (lit.[8] bp 100° (22 mm)); infrared spectrum, 2560 cm^{-1}; pmr spectrum (CS_2 solution), τ 8.43 (S–H, 3), 6.48 (CH_2–S, 2), 2.88 (C_6H_5, 1). This material was identical in all respects with an authentic sample.

Registry No.—1,4-Butanedithiol, 1191-08-8; β,β′-dimercaptodiethyl ether, 2150-02-9; triglycol dimercaptan, 14970-87-7; benzyl mercaptan, 100-53-8.

Acknowledgments.—The authors are grateful to Mr. J. Lake for his able technical assistance and to Mr. R. Pearce for obtaining the nmr spectra.

(7) J. R. Dann, P. P. Chiesa, and J. W. Gates, Jr., *J. Org. Chem.*, **26**, 1991 (1961).

(8) J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, 579 (1950); *Chem. Abstr.* **44**, 6810 (1950).

The Reaction of Lead Tetraacetate with Malonic Acid

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Since the effect of malonic acid on lead tetraacetate (LTA) decomposition was first reported,[3] it has generally been assumed that the source of this effect is due to the methylene hydrogens of malonic acid. This assumption, which was not tested, received support from the success of methylmalonic acid and ethyl acetoacetate and the failure of dimethylmalonic acid in effecting methylation of aromatic compounds.[3]

We have found, however, that malonic acid is not attacked by LTA except by carboxylate exchange to yield an insoluble mixed salt which decomposes much more readily than does LTA itself.

Our interest in this interaction arose because of the possibility that malonic acid might give rise to a methylenelike species through oxidative bisdecarboxylation similar to that observed with 1,2-dicarboxylic acids.[4] Since the fate of the malonic acid in Fieser's work was not determined, such a process could have occurred to an appreciable extent without being detected.

Whereas LTA and malonic acid separately do not evolve gas in pyridine at room temperature, a mixture of the two yields 0.6 ± 0.2 mol of CO_2 per mole of LTA in less than 2 hr. The amount of CO_2 remains essentially constant over a range of LTA–malonic acid mole ratios of 0.2 to 1.0. Before gas evolution begins, a precipitate forms. A similar result is obtained in benzene except that decomposition occurs at an appreciable rate only at reflux. The precipitate can be collected; heating it produces the same results, with insoluble material remining after gas evolution is complete. Both precipitates have been analyzed (Table I);

TABLE I

PRECIPITATES FORMED FROM LTA AND VARIOUS ACIDS

Acid	% Pb	Acetate/acid	Moles of CO_2/mole of Pb	Half-life, hr[a]
Malonic[b]	45.4	3.5	0.5	1.4
Malonic[c]	57.2	1.2		
Succinic[b]	37.5	1.6	1.25	1.6
Dimethylmalonic[b]	37.4	2.2	0.6	1.0

[a] Time required for half of the total CO_2 to be evolved in refluxing benzene. [b] Precipitate before heating. [c] Precipitate obtained after CO_2 evolution was complete.

clearly, the percentage of malonate increases during decomposition. The data in Table I are not intended to correspond to molecular formulas; the precipitates are probably polymeric.[5] Heating the filtrate produces no gas evolution, thus ruling out formation of acetyl peroxide in the exchange process.[6] From 80 to 90% of the original malonic acid routinely has been accounted for in the final precipitate, and the acid has been recovered and positively identified.

Attempts were made to detect methylene formation by inclusion of cyclohexene under a variety of reaction conditions. Both cyclohexene and norcarane react with LTA, but at a rate slower than does malonic acid.[7] No materials could be detected which implied formation and further reaction of norcarane.

In pyridine, a 15% yield of picolines, based on CO_2 evolution, is obtained. The ratio of 2- to 3- and 4-picolines is approximately 2:1, which corresponds to the ratio reported for free-radical attack.[8] Electrophilic substitution proceeds almost entirely in the 3

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(2) NDEA Fellow, 1963–1966.

(3) L. F. Fieser and F. C. Chang, *J. Amer. Chem. Soc.*, **64**, 2043 (1942).

(4) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).

(5) L. C. Willemsens and G. J. M. van der Kerk, "Investigations in the Field of Organolead Chemistry," International Lead Zinc Research Organization, Inc., New York, N. Y., 1965, p 78.

(6) M. S. Kharasch, H. N. Friedlander, and W. H. Urry, *J. Org. Chem.*, **16**, 533 (1951).

(7) S. Moon, *ibid.*, **29**, 3456 (1964); R. J. Ouellette, A. South, Jr., and D. L. Shaw, *J. Amer. Chem. Soc.*, **87**, 2602 (1965).

(8) R. A. Abramovitch and J. G. Saha, *Advan. Heterocyclic Chem.*, **6**, 229 (1966).

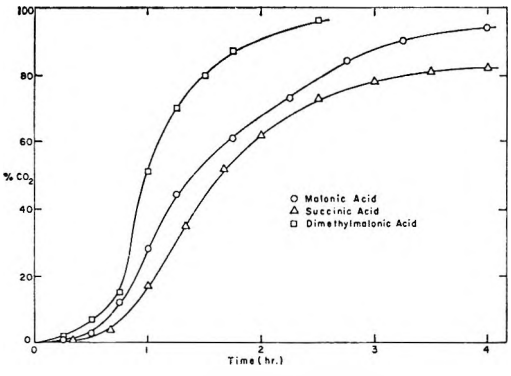

Figure 1.—CO_2 evolution at 80° in benzene from mixed salts of LTA and dicarboxylic acids.

position,[8] whereas methylene insertion produces only 2-picoline.[9] This in fact offers a convenient test for the nature of an attacking reagent, when suitable, since analysis can easily be made by vpc. Methylene diacetate is also produced, in less than 1% yield. This could have resulted from the malonic acid,[10] but has been found in decompositions of LTA alone.[6] One other unidentified product was detected in trace amounts; it is probably an α-acetoxypicoline.[11] Polymeric materials similar to those obtained by Bartlett and Gortler from peroxy derivatives of malonic acid[12] could not be detected.

Contrary to Kochi's results with pentanoic acids,[13] the rate of total gas evolution is unaffected by oxygen or copper salts.

Dimethylmalonic and succinic acids were briefly examined for comparison. They both behave similarly, as shown in Table I. The relative rates of decomposition in refluxing benzene (Figure 1) parallel increased bulk at the α carbon of the acid, indicating a steric basis for promotion of the decomposition. However, this conclusion must be tempered by the fact that these acids are involved in the decomposition itself, in contrast to malonic acid.[3,4,10] This difference is evident in the increased yield of gas from the succinic acid precipitate. Also, work-up of the final mixture from decomposition of the dimethylmalonic acid precipitate afforded a small amount of sweet-smelling oil, probably 2,2-diacetoxypropane.[10] Neither of these decompositions produced well-defined precipitates which could be analyzed meaningfully.

The absence of oxygen inhibition, combined with the isomer distribution of the picolines produced in pyridine, thus point to a nonchain, free-radical decomposition of the mixed salt. Its insolubility precludes any significant attack by radicals in a potential chain-propagating step. In pyridine, exchange is apparently possible to yield pyridine-containing complexes which are even more labile than are the simple mixed salts. Therefore, whereas ethyl acetoacetate and other nonacidic materials may promote methylation by LTA because of the reactivity of an activated methylene group, the behavior of malonic acid must be attributed only to its ability to form a less stable, mixed salt. Other dicarboxylic acids act similarly; the mode of decomposition, however, depends on the acid employed.

(9) R. Daniels and O. L. Salerni, *Proc. Chem. Soc.*, 286 (1960).
(10) J. J. Tufariello and W. J. Kissel, *Tetrahedron Lett.*, 6145 (1966).
(11) L. F. Fieser, R. C. Clapp, and W. H. Daudt, *J. Amer. Chem. Soc.*, **64**, 2052 (1942).
(12) P. D. Bartlett and L. B. Gortler, *ibid.*, **85**, 1864 (1963).
(13) J. K. Kochi, *ibid.*, **87**, 3609 (1965).

Experimental Section

Lead tetraacetate moist with acetic acid was placed in a tared flask which was then evacuated to a constant weight. Solvent was drawn into the flask instead of air until the LTA was covered, thus greatly reducing the sensitivity of dry LTA to atmospheric moisture. Pyridine reacts with LTA with evolution of heat to form a Pb(IV) complex. When it was used, the contents were allowed to return to room temperature. The flask was then opened to dry air or nitrogen and attached by means of Gooch tubing to a flask containing a known amount of solid acid. The other attachment was through a condenser either to a gas buret (total gas) or to a series of cold traps and weighed Ascarite tubes (CO_2). The whole apparatus was flushed with nitrogen before the acid was added; when measuring CO_2, the flow was continued throughout the run. The effect of oxygen was determined by measuring the rate of gas evolution after addition of a known amount of oxygen through a rubber septum. In some experiments, cuprous chloride was added during the run. No change in the rate of gas evolution was noted in either case.

In some experiments, the precipitate was collected in a drybox and dried to constant weight in a vacuum desiccator. It was used by adding it as quickly as possible to benzene at reflux temperature, care being taken to avoid excessive foaming.

Products were analyzed by vpc as individual fractions after fractional distillation of the filtered reaction mixture. Diphenyl ether was added to ensure complete distillation of picolines.

Precipitates were analyzed for lead by EDTA titration at pH 10, using Eriochrome T indicator,[14] after digestion in hot nitric acid. The acetate to acid ratios were determined by nmr analyses of centrifuged water solutions obtained by treating the precipitates with excess sulfide ion.

Registry No.—Lead tetracetate, 546-67-8; malonic acid, 141-82-2; succinic acid, 110-15-6; dimethylmalonic acid, 595-46-0.

(14) H. Flaschka, A. J. Barnard, Jr., and W. C. Broad, *Chemist-Analyst*, **47**, 52 (1958).

1,3-Bis(*m*-bromophenyl)- and 1,3-Bis(*p*-chlorophenyl)disiloxane

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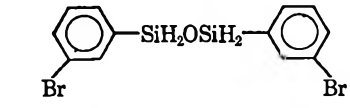
We wish to report the synthesis of 1,3-bis(*m*-bromophenyl)disiloxane (1) and 1,3-bis(*p*-chlorophenyl)disiloxane (2) and an unusual redistribution reaction



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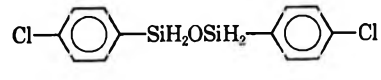

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which accompanies their hydrolysis. Only five 1,3-dialkyldisiloxanes[1,2] and one diaryldisiloxane, 1,3-

(1) H. H. Anderson and A. Hendifar, *J. Amer. Chem. Soc.*, **81**, 1027 (1959); H. H. Anderson, *ibid.*, **81**, 4785 (1959); H. H. Anderson, *ibid.*, **82**, 1323 (1960); H. H. Anderson and L. R. Grebe, *J. Org. Chem.*, **26**, 2006 (1961).
(2) R. Müller, R. Köhne, and S. Sliwinski, *J. Prakt. Chem.*, **11**, 336 (1960).

diphenyldisiloxane,[3] have been previously reported. Their hydrolytic behavior has not been studied.

The two disiloxanes were synthesized by the route used by Harvey, Nebergall, and Peake[3] for 1,3-diphenyldisiloxane with critical modifications in procedure to compensate for the greater reactivity of the halophenyl compounds. Reduction of *p*-chlorophenyl- and *m*-bromophenyltrichlorosilane with lithium aluminum hydride proceeded smoothy, as reported for phenyltrichlorosilane,[3] to give excellent yields of *p*-chlorophenylsilane[4,5] and the previously unknown *m*-bromophenylsilane. Molecular weight determinations in acetone and benzene indicated *p*-chlorophenylsilane to be dimeric; however, the infrared and nmr spectra, both neat and in benzene solution, showed no abnormalities and were analogous to the spectra of *m*-bromophenylsilane which gave the expected value for molecular weight.

The conversion of *m*-bromophenyl- and *p*-chlorophenylsilane into the corresponding halophenylbromosilanes was accomplished by bubbling hydrogen bromide gas into an ethereal solution of the halophenylsilane at room temperature.[3,6] Under these conditions, phenylsilane itself was converted into phenylbromosilane in almost quantitative yield with no evidence of further reaction of the product with hydrogen bromide after several hours. In contrast, vapor phase chromatograms of the reaction mixtures resulting from both *m*-bromophenyl- and *p*-chlorophenylsilane showed two higher boiling products in addition to the desired halophenylbromosilanes. Presumably, these were the halophenyldibromo- and -tribromosilanes formed by attack of hydrogen bromide on the initially formed product. In the case of *m*-bromophenylsilane, *m*-bromophenyldibromosilane was isolated by distillation and identified by elemental analysis; the suspected *m*-bromophenyltribromosilane was too thermally unstable to survive distillation. Acceptable yields of the desired halophenylbromosilanes were obtained by carefully monitoring the course of the reaction by gas chromatography and immediately distilling the reaction mixture when the optimum yield was reached.

Addition of ethereal solutions of the halophenylbromosilanes to ice, followed by immediate separation of the ether layer and distillation, afforded 1,3-bis(*m*-bromophenyl)disiloxane (1) and 1,3-bis(*p*-chlorophenyl)-disiloxane (2) in yields of 74 and 86%, respectively. As a consequence of the electron-withdrawing halogen substituents,[7] the bis(halophenyl)disiloxanes undergo facile hydrolysis. In contrast to 1,3-diphenyldisiloxane, which is not noticeably attacked in moist ether containing calcium sulfate,[8] 1,3-bis(*m*-bromophenyl)- and 1,3-bis(*p*-chlorophenyl)disiloxane evolved hydrogen under these conditions and were consumed within 4 and 12 hr, respectively. With potassium carbonate in place of calcium sulfate, hydrolysis of the disiloxanes was complete within 10–15 min.

Hydrolysis, to give a siloxane polymer, was accompanied by partial rearrangement to the corresponding halophenylsilane. The latter, formed in 23–27% yield based on halophenyl groups, were isolated from the calcium sulfate-catalyzed reaction by distillation and shown to be identical with authentic samples by refractive index, nuclear magnetic resonance and infrared spectroscopy, and vapor phase chromatographic retention time. The viscous polymer produced by calcium sulfate-catalyzed hydrolysis of 1,3-bis(*p*-chlorophenyl)disiloxane was not well characterized, although the presence of unhydrolyzed silicon–hydrogen bonds was indicated by infrared spectroscopy and by evolution of hydrogen upon treatment with sodium hydroxide. The resinous polymer obtained by hydrolysis in the presence of potassium carbonate, on the other hand, analyzed correctly for the fully hydrolyzed, cross-linked polymer, $(ClC_6H_4SiO_{1.5})_x$.

The rearrangement of the disiloxanes to halophenylsilanes apparently accompanies hydrolysis, since no rearrangement occurred with calcium sulfate or potassium carbonate in the absence of water. Furthermore, both hydrolysis and rearrangement proceeded in the absence of calcium sulfate or potassium carbonate in homogeneous water–tetrahydrofuran solution. It was also shown that the halophenylsilanes hydrolyze under the same conditions as the corresponding disiloxanes, but at a much slower rate.

Formation of the halophenylsilanes can be explained only by a redistribution of silicon–oxygen and silicon–hydrogen bonds. We know of only one other example of such a redistribution taking place under such mild conditions, that being with disiloxane itself, which has been reported to give monosilane upon hydrolysis,[9,10] or monosilane and a solid residue upon storage at room temperature for long periods.[11] The mechanism of these redistributions is unknown.[11]

Experimental Section[12]

Materials.—Tetrachlorosilane (Peninsular Chem-Research, Inc.) was redistilled before use, bp 57° (745 mm). *p*-Chlorophenyltrichlorosilane (Peninsular Chem-Research, Inc.) was used as received, 93% purity by gas chromatography. *m*-Dibromobenzene (Eastman Organic Chemicals), >97% pure by gas chromatography, was used as received.

***m*-Bromophenyltrichlorosilane.**[13]—*m*-Bromophenylmagnesium bromide was prepared from 29 g (1.2 g-atoms) of magnesium turnings and 236 g (1.0 mol) of *m*-dibromobenzene in 550 ml of ether. The resulting solution was diluted with 300 ml of ether and then added dropwise over a 3-hr period to a solution of 680 g (4.0 mol) of tetrachlorosilane in 1000 ml of ether while maintaining the mixture at 5–10° by means of an ice bath. The mixture then was allowed to warm to room temperature and stand overnight. The mixture was filtered in an atmosphere of dry nitrogen and the filter cake washed with ether. The combined filtrate was stripped of solvent and then distilled to obtain 112.3 g (39%) of *m*-bromophenyltrichlorosilane, bp 64–83° (0.20–0.35 mm).

Anal. Calcd for $C_6H_4BrCl_3Si$: C, 24.81; H, 1.39; Br, 27.51; Cl, 36.62; Si, 9.67; mol wt, 291. Found: C, 24.55; H, 1.38; Br, 27.76; Cl, 36.30; Si, 9.66; mol wt, 283.

(3) M. C. Harvey, W. H. Nebergall, and J. S. Peake, *J. Amer. Chem. Soc.*, **79**, 1437 (1957).

(4) V. O. Reikhfeld, *Zh. Obshch. Khim.*, **31**, 1576 (1961).

(5) A. M. Coleman and H. Freiser, *J. Amer. Chem. Soc.*, **83**, 4127 (1961).

(6) W. S. Miller, J. S. Peake, and W. H. Nebergall, *ibid.*, **79**, 5604 (1957).

(7) C. Eaborn, "Organosilicon Compounds," Butterworth and Co., Ltd., London, 1960, pp 200–207.

(8) As Drierite, W. A. Hammond Drierite Co., Zenia, Ohio.

(9) A. Stock and C. Somieski, *Ber.*, **56**, 132 (1923).

(10) These reactions are probably analogous to the sodium alkoxide-catalyzed redistribution of organoalkoxysilicon hydrides; ref 7, p 213.

(11) E. A. V. Ebsworth, "Volatile Silicon Compounds," The Macmillan Co., New York, N. Y., 1963, pp 32–33.

(12) Boiling points are uncorrected. Infrared spectra were recorded both neat and in carbon disulfide on a Beckman IR-5 spectrophotometer. Nmr spectra were recorded in carbon tetrachloride on a Varian A-60 instrument using tetramethylsilane (δ 0) as an internal standard.

(13) E. J. Pepe, U. S. Patent 2,975,204 (Mar 14, 1961); *Chem. Abstr.*, **55**, 15,417 (1961). See, however, A. D. Petrov, M. I. Batuev, V. A. Ponomorenko, A. D. Snegova, A. D. Matveeva, and B. A. Sokolov, *Zh. Obshch. Khim.*, **27**, 2057 (1957).

Crude bis(*m*-bromopheryl)dichlorosilane, 35.9 g (17%), was obtained as a higher boiling fraction, bp 149–150° (0.12 mm); the crude product contained approximately 20% of close-boiling impurities which could not be removed by fractional distillation.

m-Bromophenylsilane.—*m*-Bromophenyltrichlorosilane, 273.2 g (0.94 mol), in 175 ml of ether was added dropwise to 37.0 g (0.97 mol) of lithium aluminum hydride in 750 ml of ether at 10–15°. The mixture was allowed to warm to room temperature and stand overnight. Hydrolysis of the salts was effected by the addition of ice followed by 500 ml of cold 5% sulfuric acid. The ether layer was washed free of acid with cold water, separated and dried over anhydrous calcium sulfate.[8] The ether was removed by distillation and the residual oil fractionally distilled to obtain 123.1 g (70%) of *m*-bromophenylsilane, bp 88.5° (29 mm), $n^{25}D$ 1.5652. Vapor phase chromatography indicated a purity of >99.5%. However, the material fumed in moist air and gave an immediate strong acid test with moist indicator paper indicating the presence of traces of acid impurities.

Characteristic bands in the infrared spectrum were noted at 3100, 2170, (Si–H),[14] 2000–1650, 1600–1480, 1390 (Ar–Si),[14,15] 1075, 995, and 920 (–SiH_3)[15] cm^{-1}.

The nmr spectrum showed a singlet at δ −4.17 (Si–H; Si^{29} satellites at −2.46 and −6.96, J_{SiH} = 203 cps) and a multiplet centered at −7.32 (aromatic protons) in the ratio of 3.00:4.15.

Anal. Calcd for C_6H_7BrSi: C, 38.51; H, 3.77; Br, 42.71; Si, 15.01; mol wt, 187. Found: C, 38.72; H, 3.72; Br, 42.50; Si, 15.18; mol wt, 190.

p-Chlorophenylsilane.[4,5]—The lithium aluminum hydride reduction of 429 g (2.0 mol) of *p*-chlorophenyltrichlorosilane was carried out as described above for *m*-bromophenyltrichlorosilane. Distillation afforded 256.6 g (90%) of *p*-chlorophenylsilane, bp 75–77° (40 mm), $n^{25}D$ 1.5357 (lit.[5] bp 76° (53 mm), $n^{25}D$ 1.5354). Vapor phase chromatography indicated a purity of at least 99.5%, although moist indicator paper showed an immediate acid reaction when exposed to an atmosphere of *p*-chlorophenylsilane suggesting the presence of traces of acid impurities.

The infrared spectrum exhibited characteristic bands at 3100–3025, 2170 (Si–H),[14] 2000–1700, 1580–1490, 1390 (Ar–Si),[14,15] 920 (–SiH_3),[16] and 818 (*para* substituted) cm^{-1}.

The nmr spectrum had a singlet at δ −4.16 (–SiH_3; Si^{29} satellites, J_{Si-H} = 202 cps) and a multiplet centered at −7.32 (aromatic protons, A_2B_2 symmetry) in the ratio of 3:4.

Anal. Calcd for C_6H_7ClSi: C, 50.51; H, 4.95; Cl, 24.85; Si, 19.69; mol wt, 143. Found: C, 50.42; H, 5.00; Cl, 24.47; Si, 19.83; mol wt, 288, 280 (osmometric in benzene and acetone, respectively).

m-Bromophenylbromosilane.—Anhydrous hydrogen bromide gas was bubbled through a solution of 80.9 g (0.43 mol) of *m*-bromophenylsilane in 550 ml of ether for 6 hr at 15–20°. The course of the reaction was followed by gas chromatography and the reaction was stopped when only a trace of starting material remained. The ether and hydrogen bromide were immediately stripped at reduced pressure and the product distilled to obtain 83.6 g (73%) of crude product, bp 56–60° (0.20 mm). Redistillation gave 67.1 g (59%) of *m*-bromophenylbromosilane, bp 38–39° (0.06 mm).

Anal. Calcd for $C_6H_6Br_2Si$: C, 27.09; H, 2.27; Br, 60.08; Si, 10.56. Found: C, 26.99; H, 2.36; Br, 60.04; Si, 10.79.

When the reaction mixture, saturated with hydrogen bromide, was not worked up immediately, but was allowed to stand overnight, the yield of *m*-bromophenylbromosilane fell to 30%. The remainder of the product consisted of *m*-bromophenyldibromosilane, bp 66° (0.15 mm), isolated in 8% yield by distillation, as well as a higher boiling material which decomposed upon attempted distillation.

Anal. Calcd for $C_6H_5Br_3Si$: C, 20.89; H, 1.46; Br, 69.50; Si, 8.14. Found: C, 20.69; H, 1.60; Br, 69.60; Si, 7.97.

p-Chlorophenylbromosilane.—Anhydrous hydrogen bromide was bubbled through a solution of 107 g (0.75 mol) of *p*-chlorophenylsilane in 750 ml of dry ether for 6 hr at 10–20°. The course of the reaction was followed by gas chromatography and gas introduction was stopped when only a trace of starting material remained. Ether and hydrogen bromide were removed as rapidly as possible at reduced pressure in the cold and the residual oil was distilled to obtain 133.6 g (80%) of *p*-chlorophenylbromosilane, bp 46–50° (0.4–0.6 mm), $n^{25}D$ 1.5356.

Anal. Calcd for $C_6H_6BrClSi$: C, 32.52; H, 2.73; Br, 36.06; Cl, 16.00; Si, 12.66. Found: C, 32.37; H, 2.60; Br, 35.82; Cl, 16.05; Si, 12.49.

When the reaction mixture was not worked up immediately, but was allowed to stand in contact with hydrogen bromide, the yield of *p*-chlorophenylbromosilane dropped and two higher boiling materials appeared in the gas chromatogram of the reaction mixture. The higher boiling products could not be isolated by distillation in sufficient quantity and purity to permit an accurate analysis.

1,3-Bis(*m*-bromophenyl)disiloxane (1).—A solution of 67 g (0.30 mol) of *m*-bromophenylbromosilane in 200 ml of ether was shaken with ice, the ether layer immediately separated, and the ether was removed at reduced pressure. The residual oil was distilled[17] to obtain 33.8 g (74%) of 1,3-bis(*m*-bromophenyl)-disiloxane: bp 121–122° (0.05 mm); $n^{25}D$ 1.5916; d_{20} 1.5262. Vapor phase chromatography indicated the purity to be 97%.

The infrared spectrum showed absorbance at 3050, 2175 (Si–H),[14] 2000–1700, 1570–1470, 1400 (Ar–Si),[14,15] 1130–1075 and 950 (Si–O–Si),[18] 920 and 870 (–SiH_2),[16] and 780 cm^{-1}.

The nmr spectrum exhibited a singlet at δ −5.08 (–SiH_2–, Si^{29} satellites, J_{Si-H} = 225 cps) and a multiplet centered at −7.39 (aromatic protons) in the ratio of 1:2, respectively.

Anal. Calcd for $C_{12}H_{12}Br_2Si_2O$: C, 37.12; H, 3.12; Br, 41.17; Si, 14.47; mol wt, 388. Found: C, 37.12; H, 3.27; Br, 41.33; Si, 14.70; mol wt, 398.

1,3-Bis(*p*-chlorophenyl)disiloxane (2).—A solution of 111.6 g (0.50 mol) of *p*-chlorophenylbromosilane in 325 ml of ether was shaken with 200 g of ice. The ether layer was immediately separated, the ether removed at reduced pressure, and the residue distilled to obtain 64.5 g (86%) of 1,3-bis(*p*-chlorophenyl)disiloxane: bp 117–115° (0.30–0.25 mm); $n^{25}D$ 1.5632; d_{20} 1.2033. Vapor phase chromatography indicated a purity of 97%.

The infrared spectrum had absorbances at 3100–3050, 2175 (Si–H),[14] 2000–1750, 1600–1500, 1400 (Ar–Si),[14,15] 1090 (Si–O–Si),[18] 1022 (*para*-substituted), 955 and 850 (–SiH_2),[16] and 815 cm^{-1} (*para*-substituted).

The nmr spectrum had a singlet at δ −5.08 (Si–H; Si^{29} satellites, J_{Si-H} = 222 cps) and a multiplet centered at −7.38 (aromatic protons, A_2B_2 symmetry); the ratio of silane to aromatic protons was 1:2.

Anal. Calcd for $C_{12}H_{12}Cl_2Si_2O$: C, 48.16; H, 4.04; Cl, 23.69; Si, 18.77; mol wt, 299. Found: C, 48.09; H, 4.22; Cl, 23.48; Si, 18.71; mol wt, 306.

Hydrolytic Redistribution of Bis(halophenyl)disiloxanes.—The hydrolysis of *m*-bromophenylbromosilane and *p*-chlorophenylbromosilane was carried out on a 0.2-mol scale as described above and the ethereal solutions were allowed to stand over calcium sulfate[8] (1–2 g) for 24 hr. The calcium sulfate was removed by filtration, the ether was removed by distillation, and the oily residues were vacuum distilled to obtain 8.6 g (0.046 mol) of *m*-bromophenylsilane and 7.9 g (0.055 mol) of *p*-chlorophenylsilane, respectively. The products were identified by comparison of their refractive indices, nmr and infrared spectra, and vapor phase chromatographic retention times with those of authentic samples. The distillation residues consisted of clear, tacky, rubbery material which liberated hydrogen when treated with aqueous potassium hydroxide.

Test tube experiments (1 g of the disiloxane, 2 ml of ether, 0.5 g of calcium sulfate[8] or potassium carbonate, and 0.5 ml of water) were monitored by vapor phase chromatography. These showed that the disappearance of 1,3-bis-(*p*-chlorophenyl)disiloxane was complete in 10–15 min with potassium carbonate and in 12 hr with calcium sulfate. With 1,3-bis(*m*-bromophenyl)disiloxane, disappearance of the disiloxane was complete in 10–15 min with potassium carbonate and in 4 hr with calcium sulfate. Evolution of hydrogen, confirmed by mass spectrometric analysis, and formation of the corresponding halophenylsilanes paralleled the disappearance of the disiloxane.

The hydrolysate from the calcium sulfate-catalyzed hydrolysis of 1,3-bis(*p*-chlorophenyl)disiloxane was heated to 195° (0.3 mm) to drive off volatiles, leaving a clear, viscous material. The infrared spectrum showed characteristic absorption for Si–H at 2175 and Si–O–Si at 1088 cm^{-1}.

(14) M. C. Harvey, W. H. Nebergall, and J. S. Peake, *J. Amer. Chem. Soc.*, **76**, 4555 (1954).

(15) C. W. Young, P. C. Servais, C. C. Currie, and M. J. Hunter, *ibid.*, **70**, 3758 (1948).

(16) H. E. Opitz, J. S. Peake, and W. H. Nebergall, *ibid.*, **78**, 292 (1956).

(17) Pot residues were spontaneously flammable in air at room temperature.

(18) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 124 (1949).

Anal. Calcd for $(ClC_6H_4SiHO)_x$: C, 46.00; H, 3.22; Cl, 22.64; Si, 17.93. Found: C, 43.12; H, 3.25; Cl, 22.33; Si, 18.80.

The brittle resin from the potassium carbonate-catalyzed hydrolysis of 1,3-bis(*p*-chlorophenyl)disiloxane was triturated with ether and dried.

Anal. Calcd for $(ClC_6H_4SiO_{1.5})_x$: C, 44.04; H, 2.46; Cl, 21.66; Si, 17.17. Found: C, 43.81; H, 2.50; Cl, 20.97; Si, 17.07.

In the absence of water and using freshly dried samples of calcium sulfate and potassium carbonate, gas evolution was initially slow and stopped within 1 hr; only traces of halophenylsilane could be detected by vapor phase chromatography. Conversely, although 1,3-bis(*m*-bromophenyl)disiloxane gave no detectable reaction with water in the absence of calcium sulfate or potassium carbonate within 18 hr at room temperature, addition of sufficient tetrahydrofuran to give a homogeneous solution resulted in hydrogen evolution, formation of *m*-bromophenylsilane, and complete disappearance of the disiloxane in 3 days.

Similar experiments demonstrated that hydrolysis of *p*-chlorophenyl- and *m*-bromophenylsilane takes place at a much slower rate than with the disiloxanes. For example, 5–7 days were required for the complete disappearance of *m*-bromophenylsilane in the presence of calcium sulfate and water; only a trace of 1,3-bis(*m*-bromophenyl)disiloxane could be detected at any time in the mixture.

Registry No.—1, 15894-12-9; 2, 15894-13-0; *m*-bromophenyltrichlorosilane, 15894-14-1; bis(*m*-bromophenyl)dichlorosilane, 15894-15-2; *m*-bromophenylsilane, 15894-16-3; *p*-chlorophenylsilane, 3724-36-5; *m*-bromophenylbromosilane, 15894-18-5; *p*-chlorophenylbromosilane, 15894-19-6; *m*-bromophenyldibromosilane, 15894-20-9.

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Cyclic Ethylene Ketals of Chlorinated Cage Ketones. An Improved Synthesis of Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-one[1]

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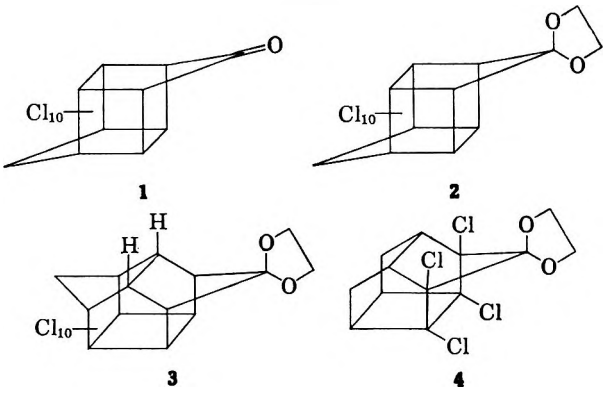
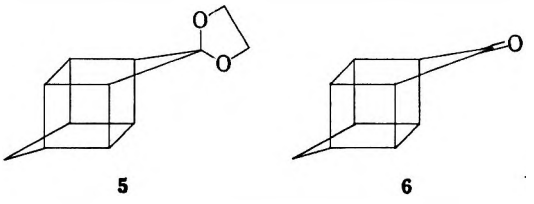
Ketalization is a valuable means for protecting ketone groups while other chemical transformations are carried out. However, conventional methods of ketal formation are not applicable to the highly electrophilic ketone (1), a strained chlorinated cage derivative. Thus Griffin and Price[2] found that 1 gave only hemiketals when treated with either ethyl orthoformate or ethylene glycol under the usual conditions for acid-catalyzed ketalization. These observations were explained by the destabilization, through angle strain and inductive effects, of the carbonium intermediate presumably involved in acid-catalyzed ketalization; it may be assumed that other strained α-halogenated ketones would be similarly resistant to normal ketalization procedures. Griffin and Price were able to make some full ketals of 1 by treating the hemiketals with diazomethane. The success of this process depends on the stability and acidic character of the hemiketals of ketones of this type. We reasoned that these properties would enable us to prepare the cyclic ethylene ketals through base-catalyzed cyclization of the hemiketals formed by addition of a 2-haloethanol to the electrophilic carbonyl group. This approach has been used to prepare cyclic ketals of perfluoroacetone and related compounds.[3]

We found that 1 or its hydrate (which is presumably in equilibrium with a small concentration of the free ketone) reacted with 2-chloro- or 2-bromoethanol to give a hemiketal which, with triethylamine or aqueous sodium hydroxide, cyclized to the ketal 2 (Chart I). No cyclic ketal could be detected before treatment with base. The procedures given in the Experimental Section for the synthesis of 2 were selected from numerous preparative runs in which various combinations of the haloethanol and base components with either the ketone or its hydrate were successfully employed. The generality of the method was shown by preparing the ketals 3 and 4 from the corresponding ketones.

CHART I



Compound 2 was dehalogenated with lithium and *t*-butyl alcohol[4] to give 5. Although there was extensive ring cleavage with formation of unsaturated byproducts, a modest yield of 5 was readily isolated. Acid hydrolysis of 5 gave the ketone 6, the structure of which was confirmed by Wolff–Kishner reduction to the corresponding hydrocarbon. Although no strict comparison



under controlled conditions was made, the dechlorination of 2 appears to proceed more smoothly than that of the corresponding dimethyl ketal.[2] The sequence described here thus constitutes an improved route to the ketone 6.

Experimental Section[5]

Decachloropentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-one, Cyclic Ethylene Ketal (2). Method A.—A mixture of 4.91 g (0.01

(1) A portion of this work has appeared as a preliminary communication: R. J. Stedman, L. D. Davis, and L. S. Miller, *Tetrahedron Lett.*, 4915 (1967).

(2) G. W. Griffin and A. K. Price, *J. Org. Chem.*, **29**, 3192 (1964).

(3) H. E. Simmons and D. W. Wiley, *J. Amer. Chem. Soc.*, **82**, 2288 (1960).

(4) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind.* (London), 405 (1960).

(5) Corrected capillary melting points are reported. Infrared spectra were run in mull with a Perkin-Elmer Infracord; nmr spectra were run with a Varian A-60 spectrometer, at 5% concentration when solubility permitted, with TMS as internal standard.

mol) of 1 (prepared by vacuum sublimation of the hydrate) and 5 ml of 2-bromoethanol was stirred for 45 min at room temperature and then for 15 min at 50°. The clear viscous solution, which showed no carbonyl absorption in the infrared region, was treated with 2.1 ml (0.015 mol) of triethylamine. The temperature rose to *ca.* 60° and a solid was deposited. After 30 min the mixture was added with stirring to 100 ml of 2.5 *N* NaOH and 50 ml of ethanol. The insoluble material was collected and amounted to 5.26 g (99%) of 2. After recrystallization from ethanol it shrank from 300°, and darkened but did not melt at 350°; no infrared absorption in the OH or C=O stretching regions; nmr signal ($CDCl_3$) at δ 4.27 (sharp singlet).

Anal. Calcd for $C_{12}H_4Cl_{10}O_2$: C, 26.95; H, 0.75. Found: C, 27.22; H, 0.75.

Method B.—A mixture of 10.16 g (0.02 mol) of 1 hydrate and 25 ml of 2-chloroethanol was stirred for 24 hr at room temperature. The solid slowly dissolved during this time. The mixture was cooled in ice and treated with 8.5 ml (0.06 mol) of triethylamine. There was a vigorous exothermic reaction and a solid was deposited. After stirring for 2 hr at room temperature the mixture was added to alkali as in method A. The insoluble product amounted to 9.97 g (93%) of 2. This material was suitable for dechlorination.

1,3,5,7,8,9,10,11,12,12-Decachlorohexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-4-one, Cyclic Ethylene Ketal (3).—A 450-mg (0.871-mmol) sample of the parent ketone[6] was mixed with 0.2 ml of 2-bromoethanol. The ketone dissolved in a few minutes to give a viscous solution which showed no carbonyl absorption in the infrared region. After 30 min the reaction mixture was added to 9 ml of 2.5 *N* NaOH and 1.5 ml of ethanol to precipitate 280 mg (57%) of 3, mp 180–184° (lit.[6] mp 186–188°; mixture melting point undepressed).

2,3,5,6-Tetrachloropentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-4-one, Cyclic Ethylene Ketal (4).—From 1.0 g (3.36 mmol) of the ketone[7] and 1.5 ml of 2-bromoethanol, under the conditions used in the preparation of 3, was obtained 0.82 g (72%) of the ketal 4, mp 216–220° (lit.[7] mp 219–221°; mixture melting point undepressed).

Pentacyclo[5.3.0.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$]decan-5-one, Cyclic Ethylene Ketal (5).—To a solution of 55 g (0.103 mol) of 2 in 850 ml of dry tetrahydrofuran, contained in a 5-l. flask with a very efficient condenser, were added 193 ml (2.06 mol) of dry *t*-butyl alcohol and 28.6 g (4.12 g-atoms) of lithium wire, cut into small pieces. The reaction mixture was kept under nitrogen. A very vigorous reaction began after a few minutes and was moderated by cooling as necessary. When it subsided somewhat, heat was supplied to maintain the reflux for a further 1 hr. The reaction mixture was poured onto ice and the product was extracted into 1:1 benzene–ether. The extracts were washed with water and evaporated to leave a dark oil. Glpc[8] showed this to consist of the product (60%) with a major impurity (20%) having a longer retention time and several minor faster moving components. The crude mixture was taken up in 300 ml of acetone, heated to reflux, and treated portionwise with 60 g of finely powdered potassium permanganate. A strong permanganate color persisted in the solution after refluxing for 30 min.[9] The solution was filtered and the filtrate was heated with sufficient methanol to discharge the permanganate color. Filtration and evaporation gave a colorless oil which was partitioned between benzene–ether and dilute Na_2CO_3. The organic phase was washed with water and evaporated to leave 7.0 g of a light yellow oil, 96% pure by glpc, which was distilled at 0.06 mm from a bath at 135° (substantial viscous residue) to give 5.4 g (28%) of 5, largely crystalline at room temperature and showing no impurities by glpc. This was recrystallized from methanol at −30° and sublimed (65°, 18 mm) to give the pure ketal: mp 32.5–34°; very strong infrared absorption at 9.02 μ (COC);[10] nmr signals (CCl_4) at δ 1.37 (2 H partly resolved triplet, cage CH_2), 2.42, 2.61, and (2.89 2 H, 4 H, and 2 H, respectively, broad singlets, methine CH), and 3.73 (4 H singlet, OCH_2CH_2O).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.50; H, 7.32.

Pentacyclo[5.3.0.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$]decan-5-one (6).—A 5.85-g sample of 5 (not distilled, 96% by glpc) was refluxed for 6 hr with 60 ml each of benzene and 3 *N* HCl. The aqueous phase was withdrawn and replaced with fresh acid and the mixture was refluxed for a further 4 hr. The benzene layer was separated, washed with water, and evaporated to a partially crystalline residue. This was distilled (sausage flask) at 22 mm with a bath temperature of 165°. The largely crystalline distillate was warmed with 7 ml of pentane and cooled to −30° to yield 1.86 g (15% from 2) of 6, mp 125–126°. Recrystallization from pentane raised the melting point to 127–128° (lit. mp 123°[2] and 120–122°[11]): infrared absorption, complex band centered at 5.75 μ (C=O); nmr signals (CCl_4) at δ 1.42 (2 H partly resolved triplet, CH_2), and at 2.58, 2.76, and 3.33 (2 H, 4 H, and 2 H, respectively, broad singlets, methine CH).

Wolff–Kishner reduction of 6 under conditions employed for an isomeric ketone[12] gave pentacyclo[5.30.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$]decane, mp 126–127° (sealed capillary, uncorrected, lit.[12] mp 125–127°). Ketalization with 2,2-dimethoxypropane and methanolic HCl gave the oily dimethyl ketal. The nmr spectra of both the hydrocarbon[12] and the dimethyl ketal[2] were identical with those reported in the literature.

Registry No.—2, 15650-61-0; 5, 15745-98-9; 6, 15745-99-0.

Acknowledgments.—We wish to thank Dr. J. R. E. Hoover for his interest and encouragement during the course of this work. We are indebted to Miss M. A. Carroll and her staff for the elemental analyses and to Mr. R. J. Warren and his associates for the nmr spectra.

(6) R. J. Stedman and L. S. Miller, *J. Org. Chem.*, **32**, 35 (1967).

(7) R. J. Stedman, L. S. Miller, and J. R. E. Hoover, *Tetrahedron Letters*, 2721 (1966).

(8) Column packed with 5% SE-30 silicone gum rubber on 60–80 mesh Chromosorb W.

(9) In some cases, part of the permanganate formed a cake at the bottom of the flask and did not react. If this occurred, more permanganate was added to complete oxidation of the unsaturated components.

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 116.

(11) W. G. Dauben and D. L. Whalen, *J. Amer. Chem. Soc.*, **88**, 4739 (1966).

(12) W. L. Dilling, H. P. Braendlin, and E. T. McBee, *Tetrahedron*, **23**, 1211 (1967).

The Stereochemistry of the Addition of Cobalt Hydrocarbonyl to 1,2-Diphenylcyclobutene-1

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Since the discovery[1] that hydrogen tetracarbonylcobaltate(−I), $HCo(CO)_4$ (commonly called cobalt hydrocarbonyl), is the active form of the catalyst in the oxo reaction, many studies have been reported in which this compound has been used in the stoichiometric hydroformylation of olefins. However, despite the theoretical and commercial importance of the reaction, neither the kinetics nor the stereochemistry of the stoichiometric reaction has been completely established. In one of the few stereochemical studies[2] of the catalytic high pressure oxo reaction, 3,4-di-O-acetyl-D-xylal was shown to yield a product corresponding to *cis* addition of $HCo(CO)_4$. In a related reaction, cyclohexene oxide

(1) M. Orchin, L. Kirch, and I. Goldfarb, *J. Amer. Chem. Soc.*, **78**, 5450 (1956).

(2) A. Rosenthal and D. Abson, *Can. J. Chem.*, **42**, 1811 (1964).

has been shown[3] to react with $HCo(CO)_4$ to give, after methanolysis of an acylcobalt intermediate, a *trans*-hydroxy ester. A more detailed study[4] of the same reaction showed that one of the major products was a hydroformylated dimer with all-*trans* stereochemistry.

Part of the difficulty of establishing the stereochemistry is the fact that the reaction of $HCo(CO)_4$ with olefins leads to extensive isomerization as well as to mixed products.[5]

During the past few years, we have been investigating substrates which may minimize some of the difficulties commonly encountered in attempts to establish the stereochemistry of the $HCo(CO)_4$ olefin addition. 1,2-Diphenylcyclobutene-1 appeared to be a particularly useful substrate because phenyl-conjugated olefins react with $HCo(CO)_4$ to give hydrogenated products[6,7] and the two possible stereoisomeric 1,2-diphenylcyclobutanes are known.[8]

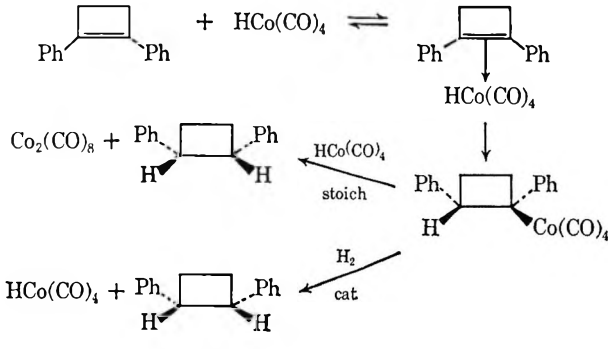
The reaction of 1,2-diphenylcyclobutene-1 with excess cobalt hydrocarbonyl in hexane at room temperature under 1 atm of carbon monoxide gave about 30% conversion into 1,2-diphenylcyclobutanes consisting of less than 4% *trans*- and about 96% *cis*-1,2-diphenylcyclobutane.

1,2-Diphenylcyclobutene was also hydrogenated by subjecting it to high pressure oxo conditions. Nmr and vpc analyses showed complete conversion into the cyclobutanes consisting of 10% *trans* and 90% *cis* isomer.

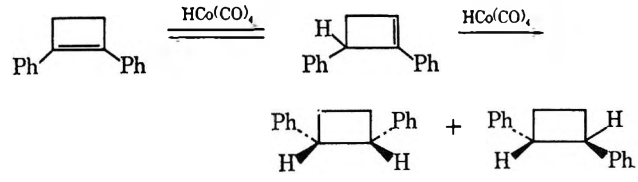
An authentic sample of *cis*-1,2-diphenylcyclobutane, subjected to the same reaction conditions under which hydrogenation of 1,2-diphenylcyclobutene occurred, showed no isomerization to the *trans* isomer either under room or high pressure conditions.

The predominant formation of the *cis* isomer is most easily explained by the reaction sequence involving an alkylcobalt tetracarbonyl[9] as an intermediate (Chart I).

CHART I



The formation of small amounts of the *trans* isomer may be explained by the isomerization of 1,2-diphenylcyclobutene by cobalt hydrocarbonyl[10] and subsequent *cis* addition of cobalt hydrocarbonyl to the isomeric diphenylcyclobutene. The *cis* addition to the isomerized diphenylcyclobutene can occur from either the top or the bottom, leading to *cis* and *trans* products.



Experimental Section

Melting points were taken on a Fisher-Johns block and are uncorrected. Nmr spectra were taken on a Varian A-60 spectrometer and ir spectra on a Perkin-Elmer Infracord 337. Vpc data were obtained on an F & M 700 gas chromatograph (10% Apiezon L on firebrick column, 5 ft × 0.25 in, 230°, flow rate 98 cc/min, 40 psi, chart paper speed 1.1 cm/min).

1,2-Diphenylcyclobutene-1 and authentic samples of *cis*- and *trans*-1,2-diphenylcyclobutane were prepared by known methods.[8]

Stoichiometric Reaction of Cobalt Hydrocarbonyl with 1,2-Diphenylcyclobutene-1.—An excess (4.65 mmol) of a 0.39 *M* hexane solution of cobalt hydrocarbonyl was added in three portions over a period of 3 days to 0.30 g (1.45 mmol) of 1,2-diphenylcyclobutene in 15 ml of hexane. The reaction was run in a serum-stoppered flask under an atmosphere of CO. After 3 days, the reaction was quenched with 0.1 *N* NaOH solution, and then the aqueous layer was syringed off and 3 ml of dimethylformamide was added to destroy the dicobalt octacarbonyl. The mixture was stirred overnight, washed with water three times, and the hexane layer was dried over magnesium sulfate and then evaporated to dryness. The nmr[8] of a $DCCl_3$ solution of the residue showed clearly that the two major components of the reaction mixture were *cis*-1,2-diphenylcyclobutane and unchanged 1,2-diphenylcyclobutene-1 and that about a 30% conversion into 1,2-diphenylcyclobutane had occurred. Vpc analysis showed three components, eluted at 7, 9, and 16 cm relative to chloroform, which was used as the solvent. Authentic samples of *cis*- and *trans*-1,2-diphenylcyclobutane and 1,2-diphenylcyclobutene-1 were eluted at 7, 9, and 16 cm, respectively. By using a 20% Apiezon L column at 230° (other conditions the same), the resolution between the *cis*- and *trans*-diphenylcyclobutanes was increased and peak integration showed less than 4% *trans*.

Catalytic Hydrogenation of 1,2-Diphenylcyclobutene.—Solutions of 0.54 g (2.59 mmol) 1,2-diphenylcyclobutene-1 in 30 ml of hexane and 0.34 g (0.99 mmol) of dicobalt octacarbonyl in 35 ml of hexane were introduced into a 300-ml Magnadrive autoclave. The autoclave was pressured with 1500 psi each CO and H_2 at room temperature, heated to 110° for 2 hr (3750 psi) and cooled gradually to room temperature. The reaction mixture was worked up in the same manner as the room temperature reaction. The nmr analysis showed complete reaction and vpc analysis indicated about 10% *trans*- and the rest *cis*-1,2-diphenylcyclobutane. For further identification, a small amount of pure *cis* isomer was crystallized from ethanol (mp 38–39° (lit.[8] mp 38–39°)). The same distribution of isomers was obtained with methanol as a solvent.

Attempted Isomerization of *cis*-1,2-Diphenylcyclobutane.—*cis*-1,2-Diphenylcyclobutane was subjected to conditions identical with the room temperature and autoclave reactions and no *trans*-1,2-diphenylcyclobutane could be detected by vpc analysis in either case.

Registry No.—1,2-Diphenylcyclobutene-1, 3306-02-3.

Acknowledgment.—The authors are grateful to the donors of the Petroleum Research Fund administered by the American Chemical Society for partial support of this work.

(3) R. F. Heck, *J. Amer. Chem. Soc.*, **85**, 1460 (1963).
(4) L. Roos, R. W. Goetz, and M. Orchin, *J. Org. Chem.*, **30**, 3023 (1965).
(5) G. L. Karapinka and M. Orchin, *ibid.*, **26**, 4187 (1961).
(6) I. Wender and M. Orchin, Bureau of Mines Report of Investigations, 1948, p 4270.
(7) M. Orchin in "Advances in Catalysis," Vol. 5, W. G. Frankenburg, V. I. Komarewsky, and E. K. Rideal, Ed., Academic Press Inc., New York, N. Y., 1953, p 385.
(8) R. M. Dodson and A. G. Zielske, *J. Org. Chem.*, **32**, 28 (1967).
(9) R. F. Heck and D. S. Breslow, *Chem. Ind.* (London), **17**, 467 (1960).
(10) M. Orchin in "Advances in Catalysis," Vol. 16, D. D. Eley, H. Pines, and P. B. Weisz, Ed., Academic Press Inc., New York, N. Y., 1966, p 21.

Stereoselective Electrochemical Reduction of Geminal Dihalocyclopropanes

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Received September 19, 1967

A recent study[1] of the stereochemistry of electrochemical reduction of optically active 1-bromo-2,2-diphenylcyclopropylcarboxylic acid and derivatives of the acid demonstrated a stereochemical spectrum ranging from 56% inversion to 38% retention of configuration. The data were interpreted in terms of a competition between protonation of a carbanion-electrode complex from the rear and protonation of the carbanion in solution. The present report demonstrates both stereochemical discrimination by the electrode between two possible sites for electroreduction and a solvent effect upon stereoselectivity of the reduction; the data are summarized in Table I.

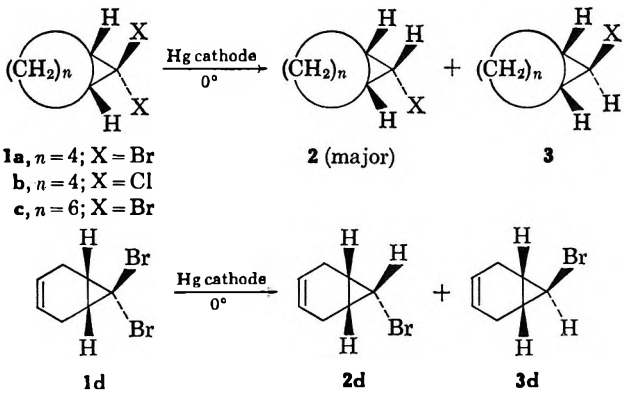
TABLE I
STEREOCHEMISTRY IN CONTROLLED POTENTIAL ELECTROLYSIS OF DIHALOCYCLOPROPANES

Expt	Substrate	Solvent	Relative % of products[c] 2	3
1	1a	100% DMF[a]	61	39
2	1a	96% DMF–4% H_2O	75	25
3	1a	100% CH_3OH	66	34
4	1a	95% CH_3OH–5% H_2O	73	27
5	1a	95% CH_3OH–5% HCl[b]	78	22
6	1a	90% CH_3OH–10% H_2O	84	16
7	1a	100% HOAc	80	20
8	1b	100% DMF	81	19
9	1b	96% DMF–4% H_2O	84	16
10	1b	100% CH_3OH	95	5
11	1b	95% CH_3OH–5% HCl	100	0
12	1b	33% HMPA[d]–67% EtOH	100	0
13	1c	100% CH_3OH	100	0
14	1c	95% CH_3OH–5% HCl	100	0
15	1d	100% CH_3OH	73	27
16	1d	90% CH_3OH–10% H_2O	91	9

[a] DMF = dimethylformamide. [b] 95% methanol–5% concentrated aqueous hydrochloric acid. [c] Precision of results ±3% after a minimum of five integrations per sample. [d] HMPA = hexamethyl phosphoramide.

The major product in all electrochemical reductions of geminal dihalocyclopropanes **1a–d** is the *cis* isomer **2**, and in solvents of higher water content the proportion of **2** is increased (*e.g.*, expt 1 and 2 or 3 and 4). Because of limited solubility of the geminal dihalides in more highly aqueous solvents, a wide range of solvent compositions was not investigated. In view of this and the fact that the solvents differ in a number of properties, including proton-donating ability and dielectric constant, detailed discussion of trends would be speculative. The synthetic advantage in increasing the stereoselectivity by use of a more highly aqueous solvent is apparent, however (*cf.* expt 15 and 16).

(1) R. Annino, R. E. Erickson, K. Michalovic, and B. McKay, *J. Amer. Chem. Soc.*, **88**, 4424 (1966).



1a, $n = 4$; X = Br
b, $n = 4$; X = Cl
c, $n = 6$; X = Br

2 (major) **3**

1d **2d** **3d**

In terms of a mechanistic scheme previously advanced by Annino, *et al.*,[1] for electrochemical reductions of monohalocyclopropanes, there are two alternate explanations for the stereoselective formation of the *less stable* isomers **2a–d**. Either the "outside" halogen (*cis* to the two hydrogens at the ring junction) is reduced with retention of configuration, or the "inside" halogen is reduced, with inversion of configuration. We prefer the first course, for the following reasons. Assuming a substrate-electrode geometry in which the carbon–halogen bond is either parallel to the electrode surface or in which the bromine is nearest the electrode,[1,2] steric repulsions are far greater in the transition state for reduction of the "inside" halogen. If, then, reduction of the "outside" halogen is involved, it is necessary to postulate that the initially formed halocyclopropyl carbanion must diffuse into solution and be protonated before it can lose much, or any, of its configuration. Experiment 12 is consistent with this interpretation. Sternberg, *et al.*,[3] have demonstrated that the solvent system 33 mol % hexamethylphosphoramide (HMPA)–67% EtOH provides an effectively *aprotic* region at the electrode surface, presumably because of preferential adsorption of the highly polar HMPA. Even though the carbanion in expt 12 must move away from the electrode, therefore, to seek a proton, the stereochemistry of reduction is the same as in the other runs. Reduction of the "inner" halogen would require subsesequent isomerization to a less stable anion before protonation.

Experimental Section[4]

Dihalocyclopropanes (1a–d) were prepared according to published procedures.[5–7]

General.—Electrolyses were carried out in a divided cell of conventional design[1] equipped with platinum gauze anode and magnetically stirred mercury pool cathode and immersed in an ice bath. The reference electrode was a silver wire immersed in saturated aqueous potassium chloride in a Fisher Remote Reference Junction and positioned 1 mm from the cathode surface. Cathode potentials were controlled by a solid-state potentiostat to be described elsewhere.

(2) J. W. Sease, P. Chang, and J. L. Groth, *ibid.*, **86**, 3154 (1964).

(3) H. W. Sternberg, R. E. Markby, I. Wender, and D. M. Mohilner, *ibid.*, **89**, 186 (1967).

(4) Nmr spectra were measured on a Varian A-60A spectrometer. Solvents were reagent grade used without further purification. Vapor phase chromatography (vpc) was carried out on a Varian Aerograph Model P-3 instrument using 10% Carbowax on Fluoropak.

(5) D. Seyferth, J. M. Burlitch, and J. K. Heeren, *J. Org. Chem.*, **27**, 1491 (1962).

(6) W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **76**, 6164 (1954).

(7) S. Winstein and J. Sonnenberg, *ibid.*, **83**, 3235 (1961).

(8) L. Meites in "Technique of Organic Chemistry," Vol. 1, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 3297.

Electrolyses.—A 1 *M* solution of lithium chloride (50 ml) in the appropriate solvent was placed in the cathode compartment; the anolyte was identical, but also contained 5 ml of 95% hydrazine. The solvent was purified by pre-electrolysis in a nitrogen stream for 30 min at a cathode potential of −1.1 V *vs.* Ag–AgCl for **1a**, **c**, and **d**, and −2.0 V for **1b**. The dihalide (5–7 mmol) was added and electrolysis was allowed to proceed until current had decayed to background. The catholyte was poured into water, extracted with pentane, washed with water, and dried over magnesium sulfate. The pentane was carefully distilled; the **2**–**3** mixtures were analyzed by nmr spectroscopy by the method of Seyferth, *et al.*[9] Results generally agreed with results of independent vpc analyses. Yields of halocyclopropanes were in the range 80–90%.

Registry No.—**1a**, 15649-61-3; **1b**, 15649-62-4; **1c**, 15649-58-8; **1d**, 15834-79-4.

Acknowledgment.—Financial support by the Petroleum Research Fund is gratefully acknowledged.

(9) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963).

Ethyl (Dimethylsulfuranylidene)acetate. II. Reactions with α,β-Unsaturated Esters in Ethanol Solutions

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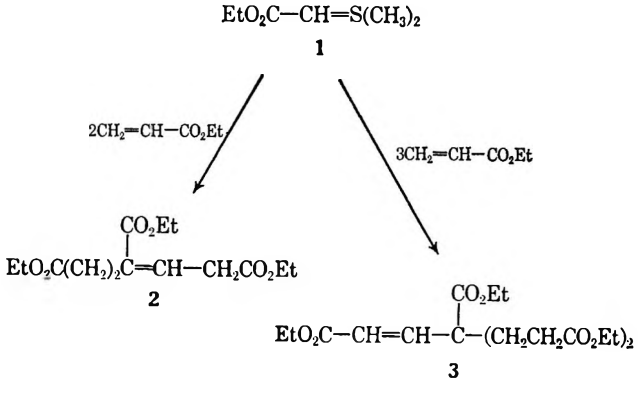
The general reaction between ethyl (dimethylsulfuranylidene)acetate (EDSA, **1**) and α,β-unsaturated compounds in aprotic solvents to produce substituted cyclopropanes was recently reported.[1] We now report that reaction of EDSA with certain α,β-unsaturated esters in ethanol solution leads not to cyclopropanes but rather to open-chain products of varying complexity.

Results and Discussion

Reaction of EDSA with 4 molar equiv of ethyl acrylate in ethanol at 30–35° afforded a 69% yield (based on EDSA) of triethyl 2-pentene-1,3,5-tricarboxylate (**2**) along with a 20% yield of triethyl 3-(2-ethoxycarbonylethyl)-1-pentene-1,3,5-tricarboxylate (**3**). Tetraester



3 was subsequently prepared in 40% yield as the sole product obtained from ethyl acrylate and EDSA when the latter was generated slowly *in situ* by reaction of carbethoxymethyl dimethylsulfonium bromide with anhydrous potassium carbonate.

$$EtO_2C{-}CH_2\overset{+}{S}(CH_3)_2Br^- + 3CH_2{=}CH{-}CO_2Et \xrightarrow{K_2CO_3} \mathbf{3}$$

Ethyl crotonate and EDSA afforded a 75% yield of diethyl 3-methylglutaconate (**4**) as a 50:50 mixture of *cis–trans* isomers while EDSA and diethyl fumarate gave triethyl aconitate (**5**) in 87% yield as a 70:30 mixture of *trans–cis* isomers.

$$\mathbf{1} + CH_3CH{=}CHCO_2Et \longrightarrow EtO_2C{-}CH{=}\overset{CH_3}{\overset{|}{C}}{-}CH_2CO_2Et \quad \mathbf{4}$$

$$\mathbf{1} + EtO_2CCH{=}CHCO_2Et \longrightarrow EtO_2C{-}CH{=}\overset{CO_2Et}{\overset{|}{C}}{-}CH_2CO_2Et \quad \mathbf{5}$$

Compound **2** was identified by elemental and nmr analyses and by hydrogenation followed by saponification to the known 1,3,5-pentanetricarboxylic acid. Structure **3** was assigned on the basis of elemental and nmr analyses. Saponification of **4** gave the known 3-methylglutaconic acid as a mixture of *cis–trans* isomers, and **5** was identified by comparison with an authentic sample of triethyl aconitate.

The formation of **2** has been rationalized according to Scheme I.

SCHEME I[a]

$$\mathbf{1} + CH_2{=}CH{-}Z \longrightarrow Z{-}\underset{\overset{|}{{}^+S(CH_3)_2}}{CH}{-}CH_2{-}\bar{C}H{-}Z \quad \mathbf{A}$$

$$\mathbf{A} \xrightarrow[\text{(ylide formation)}]{H^+\text{ shift}} Z{-}\bar{C}{-}(CH_2)_2Z \xrightarrow{CH_2{=}CH{-}Z} Z{-}\underset{\overset{|}{{}^+S(CH_3)_2}}{\overset{(CH_2)_2Z}{\overset{|}{C}}}{-}CH_2{-}\bar{C}H{-}Z \xrightarrow[-(CH_3)_2S]{H^+\text{ shift}} \mathbf{2}$$

[a] Z = CO_2Et

Compound **3** can be visualized as being formed *via* intermediates A and B by Michael reaction of the latter with 2 mol of ethyl acrylate.

$$\mathbf{A} \xrightarrow[-(CH_3)_2S]{H^+\text{ shift}} Z{-}CH{=}\underset{\mathbf{B}}{CH{-}CH_2{-}Z} \xrightarrow{2CH_2{=}CH{-}Z} \mathbf{3}$$

The conversions of ethyl crotonate into **4** and diethyl fumarate into **5** are believed to occur by the same mechanism.

$$\mathbf{1} \xrightarrow{RCH{=}CHZ} \left[Z{-}\underset{\overset{|}{{}^+S(CH_3)_2}}{CH}{-}\underset{\overset{|}{R}}{CH}{-}\bar{C}H{-}Z \right] \xrightarrow[-(CH_3)_2S]{H^+\text{ shift}} Z{-}CH{=}\overset{R}{\overset{|}{C}}{-}CH_2{-}Z$$

4, R = CH_3
5, R = CO_2Et

Experimental Section[2]

Reaction of EDSA with Ethyl Acrylate.—To a solution of 20.0 g (0.20 mol) of ethyl acrylate in 50 ml of absolute ethanol was

(1) G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967).

(2) Melting points are corrected; boiling points are uncorrected. Nmr spectra were obtained in $CDCl_3$ with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Glpc analyses were done with an F & M Model 720 instrument using a column packed with 5% of XF-1150 on Chromosorb W.

added a solution of 7.4 g (0.05 mol) of EDSA[1] in 25 ml of ethanol. Ice cooling was needed to hold the temperature at 30–35°.

After an overnight stand at 25°, the mixture was flashed into a Dry Ice cooled trap at 5 mm and 25°. Glpc analysis of the volatiles indicated the presence of 0.048 mol of dimethyl sulfide and 0.080 mol of ethyl acrylate.

Distillation of the residue gave 9.8 g (69%) of triethyl 2-pentene-1,3,5-tricarboxylate, bp 106–109° (<1 mm) and $n^{25}D$ 1.4553, and 4.1 g of residue (21% yield calculated as **3**).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.7; H, 7.7. Found: C, 58.7; H, 7.8.

The nmr spectrum showed multiplets at δ 1.3 (9 H, $-CO_2CCH_3$), 2.0–2.7 (4 H, $C{=}C(CH_2)_2COOR$), and 3.9–4.4 (6 H, CO_2-CH_2–), a triplet at 7.0 (1 H, -CH=CCOOR), and a doublet at 3.4 (2 H, $-C{=}CCH_2COOR$).

Distillation of the residue gave material with bp 170–175° (<1 mm) in good recovery. It was shown by infrared analysis to be identical with compound **3** prepared below.

2-Pentene-1,3,5-tricarboxylic Acid.—A solution of 8.0 g (0.028 mol) of triester in 50 ml of concentrated hydrochloric acid was warmed on the steam bath for 4 hr and then allowed to stand overnight. Filtration of the resulting precipitate gave 3.4 g, mp 181–182°; concentration of the filtrate followed by crystallization from acetone gave another 0.5 g, mp 178–180° (70% combined yield). Recrystallization of the two crops gave product with mp 181–182°.

Anal. Calcd for $C_8H_{10}O_6$: C, 47.5; H, 5.0. Found: C, 47.8; H, 5.1.

The nmr spectrum showed a multiplet at δ 2.0–2.7 (4 H, $C{=}C(CH_2)_2COO$–), a doublet at 3.3 (2 H, $-O_2CCH_2C{=}C$–), a triplet at 6.9 (1 H; –CH=C–), and a singlet at 11.1 (3 H, -COOH).

Hydrogenation of the unsaturated acid was carried out in a Parr hydrogenator using 5% palladium-on-carbon catalyst, ethyl alcohol as solvent, and a pressure of 40 psi. One molar equivalent of hydrogen was absorbed in 0.5 hr to give 1,3,5-pentanetricarboxylic acid, mp 112–114°. A mixture melting point with an authentic sample (mp 113–115°)[3] was not depressed. The infrared spectra were identical.

Reaction of Carbethoxymethyl Dimethylsulfonium Bromide with Potassium Carbonate and Ethyl Acrylate.—A mixture of 22.9 g (0.10 mol) of sulfonium bromide,[1] 30.0 g of ethyl acrylate, 21 g of anhydrous potassium carbonate, and 100 ml of absolute ethanol was allowed to stir for 18 hr at 25°.

Filtration followed by Claisen distillation gave 15.3 g (40% yield) of relatively pure product, bp 174–187° (<1 mm) and $n^{25}D$ 1.4605. Redistillation through a small Vigreux column gave analytically pure triethyl 3-(2-ethoxycarbonylethyl)-1-pentene-1,3,5-tricarboxylate: bp 203–206° (1 mm), $n^{25}D$ 1.4616.

Anal. Calcd for $C_{19}H_{30}O_8$: C, 59.1; H, 7.8; mol wt, 386. Found: C, 59.4; H, 7.9; mol wt, 395 ± 12 (ebullioscopic, benzene).

The nmr showed multiplets at δ 1.3 (12 H, RCO_2CCH_3), 1.8–2.8 (8 H, $-CH_2$–), and 4.2 (8 H, RCO_2CH_2–) and doublets at 6.0 (1 H, $RO_2CCH{=}C$) and 7.1 (1 H, $RO_2C{-}C{=}CH$–).

Reaction of EDSA with Ethyl Crotonate.—A mixture of 11.4 g (0.10 mol) of ethyl crotonate, 7.4 g of EDSA (0.05 mol), and 50 ml of ethanol was held at room temperature for 4 days and then heated under reflux for 1 hr.

Claisen distillation gave 7.5 g (75%) of diethyl 3-methylglutaconate, bp 65–66° (<1 mm), $n^{25}D$ 1.4488 (lit.[4] *cis*, bp 131° (9 mm), $n^{20}He$ 1.452; *trans*, bp 127° (12 mm), $n^{20}He$ 1.452).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 59.9; H, 8.1.

Nmr analysis indicated an approximately 1:1 mixture of *cis* and *trans* isomers showing a triplet at δ 1.2 (6 H, RCO_2CCH_3), two doublets at 2.0 and 2.2 (3 H, $C{=}C{-}CH_3$), two singlets at 3.2 and 3.7 (2 H, $C{=}C{-}CH_2{-}COOR$), a quartet at 4.2 (4 H, RCO_2CH_2–), and a multiplet at 5.8 (1 H, $-HC{=}C$–).

Saponification by aqueous ethanolic sodium hydroxide gave an 86% yield of isomers, mp 95–110°. Recrystallization from benzene afforded a mixture with constant mp 111–115°.[5]

Anal. Calcd for $C_6H_8O_4$: C, 50.0; H, 5.6; neut equiv, 72. Found: C, 50.3; H, 5.7; neut equiv, 72.

(3) R. P. Mariella, R. Clutter, and H. G. Ebner, *J. Org. Chem.*, **20**, 1702 (1955).

(4) "Dictionary of Organic Compounds," Vol. 4, Oxford University Press, New York, N. Y., 1965, p 2311.

(5) For a discussion of these *cis* and *trans* isomers, see L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, 198 (1958).

Nmr analysis indicated an approximately 2:1 ratio of *cis–trans* isomers ($COOH{-}CH_2COOH$): a pair of doublets at δ 2.0 and 2.2 (3 H, $C{=}C{-}CH_3$), a doublet at 3.3 (J = 1–2 cps), and a singlet at 3.7 in the ratio of 2:1 (2 H, $-C{=}C{-}CH_2{-}COO$–), a singlet at 4.7 (2 H, -COOH), and a multiplet at 5.9 (1 H, $-CH{=}C$–).

Triethyl Aconitate.—The reaction was carried out as above using 34.4 g (0.20 mol) of diethyl fumarate and 14.8 g (0.10 mol) of EDSA in 75 ml of ethanol.

After 18 hr the mixture was Claisen distilled to give 17.1 g (0.10 mol) of recovered diethyl fumarate, bp 60–70° (<1 mm), and 22.5 g (87%) of triethyl aconitate, bp 97–99° (<1 mm), $n^{25}D$ 1.4515 (lit.[6] bp 165° (12 mm), $n^{20}D$ 1.4556).

Glpc analysis indicated a 70:30 mixture of *trans–cis* isomers.[7] The early emerging peak was confirmed as the *trans* isomer by saponifying and then reesterifying Pfizer technical grade triethyl aconitate (all *trans*). The Pfizer triester and the 70:30 mixture showed nearly identical infrared spectra.

An nmr analysis was carried out on the 70:30 product showing multiplets at δ 1.3 (9 H, RCO_2CCH_3) and 4.2 (6 H, RCO_2CH_2–) and singlets at 3.9 (2 H, $-C{=}CCH_2{-}CO_2R$) and 6.9 (1 H, $RO_2CH{=}C$–). A minor multiplet at 2.5 indicated the presence of a small amount of impurity. The latter was not resolved by glpc analysis.

Registry No.—**1**, 5697-31-4; **2**, 15649-51-1; $C_8H_{10}O_6$, 15717-32-5; **3**, 15649-53-3; **4** (*cis*), 15649-54-4; **4** (*trans*), 1466-21-3; $C_6H_8O_4$ (*cis*), 15649-56-6; $C_6H_8O_4$ (*trans*), 372-42-9.

(6) Reference 4, Vol. 1, p 33.

(7) J. Casanova, Jr., and D. A. Rutolo, Jr. (*Chem. Commun.*, 1224 (1967)) have reported the formation of *trans*-trimethyl aconitate from the reaction of methyl (dimethylsulfuranylidene)acetate with dimethyl fumarate in methanol solution.

Ethyl (Dimethylsulfuranylidene)acetate. III. Reaction with α-Bromo Acrylic Compounds

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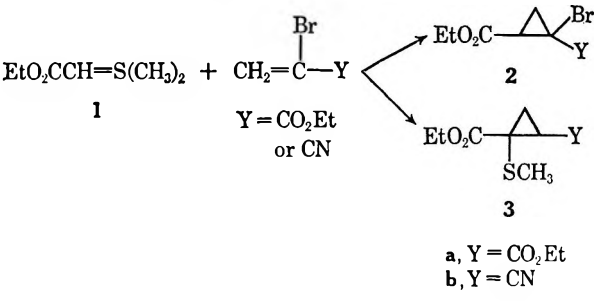
Received October 17, 1967

Earlier reports have described the synthesis[1] of ethyl (dimethylsulfuranylidene)acetate (**1**, EDSA), its reaction with α,β-unsaturated compounds in aprotic solvents to produce cyclopropanes,[1] and its reaction with α,β-unsaturated esters in ethanol solution to give esters of acyclic polybasic acids.[2]

The reactions of EDSA with 2-bromoacrylonitrile and ethyl 2-bromoacrylate were carried out with the expectation that bromocyclopropanes **2** might be produced.



Whereas **2a** was indeed produced (36% yield) from the reaction of EDSA with ethyl 2-bromoacrylate at room temperature *in benzene solution*, very little was

(1) G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967).

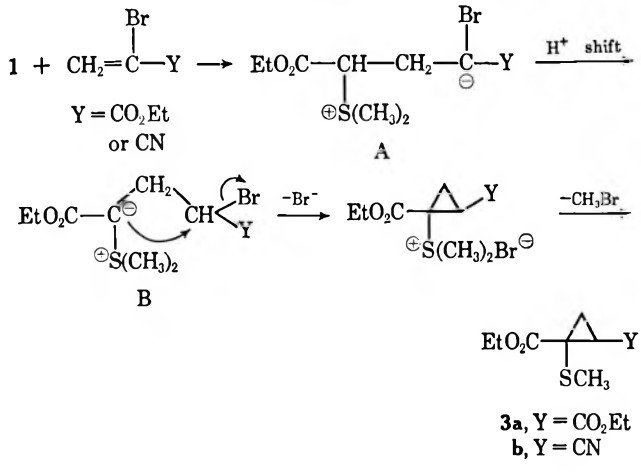
(2) G. B. Payne, *ibid.*, **33**, 1284 (1968).

formed using acetone as solvent. In the latter case, the predominant product (52% yield) was the methylthio compound **3a** (a 25% yield of **3a** was also observed in the reaction carried out in benzene).

Interestingly, very little **2b** appeared to be formed from EDSA and 2-bromoacrylonitrile irrespective of the solvent used. Thus, with acetone the yield of **3b** was 50% based on EDSA, whereas with benzene **3b** and **2b**[3] were obtained in 29 and 6% yields, respectively.

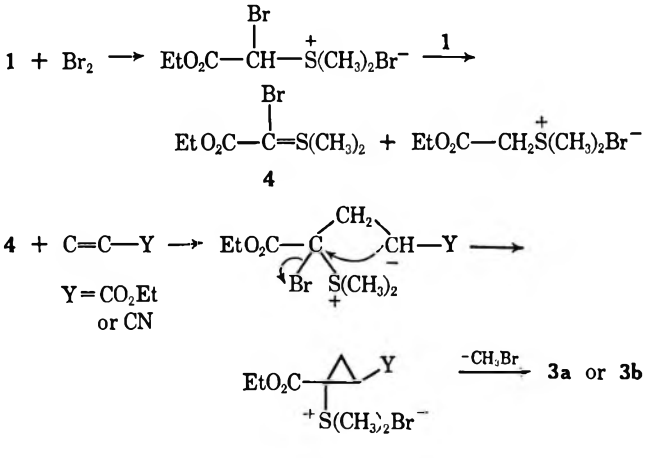
The formation of **3a** and **3b** has been rationalized according to Scheme I. The relatively polar solvent acetone apparently facilitates the prototropic shift to produce new ylide B at the expense of direct ring closure of A to give **2**.

SCHEME I



Structures **3a** and **3b** were assigned on the basis of elemental, infrared, and nmr analyses and subsequently confirmed by alternate syntheses according to Scheme II.

SCHEME II



Bromo ylide **4**[4] was prepared *in situ* by adding 1 molar equiv of bromine to 2 of EDSA in chloroform at ice temperature. On completion of the addition, the cold mixture was treated immediately[5] with either ethyl acrylate or acrylonitrile to give **3a** and **3b** in 59 and 80% yields, respectively. Compound **3b** was again formed as virtually the sole product, whereas **2a** was obtained as a by-product to **3a** in 7% yield. The preferential displacement of bromide ion relative to dimethyl sulfide observed in the present study is in accord with earlier work.[6]

(3) An analytical sample of this minor component was not secured; its identification must therefore be considered tentative.

(4) See K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **31**, 1689 (1966), for a discussion of the reactions of bromine and iodine with some resonance-stabilized sulfonium ylides.

(5) Infrared analysis of a chloroform solution of the bromo ylide indicated it to have a half-life of less than 1 hr at room temperature.

Experimental Section[7]

Ethyl 2-Bromoacrylate and 2-Bromoacrylonitrile.—To 26 g (0.10 mol) of ethyl 2,3-dibromopropionate (Columbia Organic Chemicals) held in a 200-ml distillation flask was added 13 g (0.10 mol) of quinoline. The mixture was allowed to warm to about 75–80° for 10 min and then vacuum distilled from the quinoline salt. The yield of ethyl 2-bromoacrylate, bp 50–60° (10 mm) and n^{25}D 1.4710, was 16 g (90%). Redistillation from hydroquinone at 10 mm gave purified ester, bp 50–53° and n^{25}D 1.4672 (lit.[8] bp 76–77° (33 mm), n^{25}D 1.4678), in 70% yield over-all.

Application of the above procedure to 2,3-dibromopropionitrile (Columbia) gave 2-bromoacrylonitrile, bp 40–45° (40 mm), n^{25}D 1.4717 (lit.[9] bp 116° (740 mm)), in 84% yield. It was used immediately without further purification.

Reaction of EDSA with 2-Bromoacrylonitrile.—To a stirred solution of 14.8 g (0.10 mol) of EDSA in 100 ml of dry acetone was added dropwise at 30–35° over 0.5 hr a solution of 13.2 g (0.10 mol) of 2-bromoacrylonitrile in 50 ml of acetone. The mixture was stirred 3 hr longer and allowed to stand overnight.

Filtration gave 1.3 g (5%) of carbethoxymethyl dimethylsulfonium bromide, mp and mmp 80–82° dec. Vacuum concentration of the filtrate followed by Claisen distillation gave 9.4 g (50% yield) of a mixture of *cis*- and *trans*-ethyl 2-cyano-1-methylthiocyclopropanecarboxylate, bp 88–93° (<1 mm). The purity (two isomers) was 95% by glpc analysis.

Redistillation using a 0.7 × 50 cm glass spiral packed column gave the two isomers with bp 97–98° (1 mm), n^{25}D 1.4901. The relative amounts were 25:75, early to late emerging peaks.[10]

Anal. Calcd for $C_8H_{11}O_2NS$: C, 51.7; H, 6.0; S, 17.3. Found: C, 51.4; H, 6.0; S, 16.6.

The infrared spectrum showed significant bands at 5.83, 7.92, 8.90, and 10.0 μ. Nmr analysis showed triplets at δ 1.4 (3 H, CO_2CCH_3) and 2.6 (1 H, C–C–CHCN), a multiplet at 1.8 (2 H, cyclopropyl protons), a singlet at 2.4 (3 H, SCH_3), and a quartet at 4.2 (2 H, CO_2CH_2).

Reaction of EDSA with Ethyl 2-Bromoacrylate.—To a stirred solution of 35.8 g (0.20 mol) of ethyl 2-bromoacrylate in 100 ml of dry acetone was added dropwise at 25–30° over 0.5 hr a solution of 14.8 g of EDSA (0.10 mol) in 50 ml of acetone.

After stirring for 3 hr and then standing overnight, the mixture was filtered, concentrated, and Claisen distilled to give 15.4 g of product with bp 75–88° (0.2 mm). By glpc analysis the material contained 12.2 g (53% yield) of diethyl 1-methylthio-1,2-cyclopropanedicarboxylate and 0.8 g (3% yield) of diethyl 1-bromo-1,2-cyclopropanedicarboxylate.

Redistillation through the packed column gave analytically pure methylthio compound, bp 87–90° (<1 mm), n^{25}D 1.4754, as a single isomer by glpc.

Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.7; H, 6.9; S, 13.8. Found: C, 51.8; H, 6.9; S, 13.6.

The infrared spectrum showed significant bands at 5.81, 7.95, 8.45, 8.88, 9.70, and 11.6 μ. Nmr analysis showed triplets at δ 1.3 (6 H, CO_2CCH_3) and 2.7 (1 H, C–C–CHCOOR), a multiplet at 1.7 (2 H, cyclopropyl protons), a singlet at 2.2 (3 H, SCH_3), and a quartet at 4.2 (4 H, CO_2CH_3).

(6) See J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p 167.

(7) Boiling points are uncorrected. Nmr spectra were obtained in $CDCl_3$ with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Glpc analyses were done on an F & M Model 720 instrument using a 10-ft column packed with 5% of X-1150 on Chromosorb W.

(8) "Dictionary of Organic Compounds," J. R. A. Pollock and R. Stevens' Ed., Oxford University Press, New York, N. Y., 1965, Vol. 1, p 417.

(9) H. Brintzinger and A. Scholz, *Chem. Ber.*, **83**, 141 (1950).

(10) The two isomers could not be separated by glpc trapping; no attempt was made to determine the stereochemistry of any of the products obtained in this study.

The reaction was repeated using *benzene* in place of acetone. Claisen distillation gave 15.5 g of mixture, bp 82–87° (<1 mm). Glpc analysis indicated the presence of 38% of diethyl 1-methylthio-1,2-cyclopropanedicarboxylate (25% yield based on EDSA) and 62% of diethyl 1-bromo-1,2-cyclopropanedicarboxylate (36% yield). The latter was isolated by glpc trapping as a single isomer.

Anal. Calcd for $C_9H_{13}O_4Br$: C, 40.8; H, 4.9. Found: C, 40.9; H, 5.2.

Significant bands in the infrared were located at 5.83, 7.94, 8.44, and 8.89 μ. Nmr analysis showed triplets at δ 1.3 (6 H, CO_2CCH_3) and 2.6 (1 H, C-C-CHCOOR), a doublet at 1.9 (2 H, cyclopropyl protons), and a quartet at 4.2 (4 H, CO_2CH_2).

Reaction of Acrylonitrile with the Bromo Ylide from EDSA.—To a stirred solution of 14.8 g (0.10 mol) of EDSA in 100 ml of chloroform was added dropwise at 5–10° a solution of 8.0 g (0.05 mol) of bromine in 25 ml of chloroform. There was then added immediately 5.3 g (0.10 mol) of acrylonitrile and the mixture was allowed to warm slowly to room temperature over 18 hr.

After vacuum concentration at 25°, the residue was treated with acetone and filtered to give 8.5 g (74% yield) of carbethoxymethyl dimethylsulfonium bromide, mp and mmp 80–82° dec. The filtrate was reconcentrated and then Claisen distilled to give 7.4 g (80% yield) of ethyl 2-cyano-1-methylthiocyclopropanecarboxylate, bp 80–85° (<1 mm), as a 38:62 mixture of isomers. The purity was 99% (two isomers) and the product was shown to be the same (except for slight variation in ratio of isomers) as that prepared from EDSA and 2-bromoacrylonitrile by glpc, infrared, and nmr comparisons.

Reaction of Ethyl Acrylate with the Bromo Ylide from EDSA.—The above reaction was repeated, substituting 10.0 g (0.10 mol) of ethyl acrylate for acrylonitrile. Claisen distillation gave 9.0 g, bp 55–80° (<1 mm). Glpc analysis indicated the presence of 76% by weight of diethyl 1-methylthio-1,2-cyclopropanedicarboxylate and 11% of diethyl 1-bromo-1,2-cyclopropanedicarboxylate. These compounds correspond to yields of 59 and 7%, respectively, based on EDSA.

Glpc trapping gave a pure sample of the methylthio compound; its infrared spectrum was identical with that of the product prepared from EDSA and ethyl 2-bromoacrylate.

Registry No.—**1**, 5697-31-4; **2a**, 15619-29-1; **3a**, 15619-30-4; **3b**, 15619-31-5.

Hydrogenation of β-Amino-α,β-Unsaturated Esters[1]

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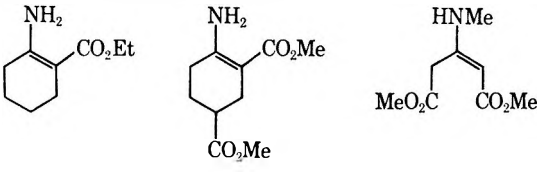
Received September 22, 1967

The hydrogenation of the double bond of most enol derivatives of β-dicarbonyl compounds (vinylogous carboxylic acid derivatives) generally takes place readily at low temperatures and pressures using a palladium catalyst.[3,4] However, hydrogenolysis is favored by more drastic conditions as well as by the use of platinum catalysts.[3–5] Overreduction of β-amino-α,β-unsaturated ketones (vinylogous amides) is observed under all conditions.[6]

From the limited amount of data reported on the hydrogenation of β-amino-α,β-unsaturated esters (vinylogous urethans), it is apparent that these compounds are more difficult to hydrogenate than are the other vinylogous carboxylic acid derivatives[7a] and, if care is not taken, extensive hydrogenolysis can take place.[7b] It has recently been shown by Liska,[8] however, that saturation of the double bond of 3,4,5,6-tetrahydroanthranilic ester (**1**) could be accomplished by the use of rhodium on alumina at 85° and 500 psi.

Our interest in this problem was aroused when it was found that under these conditions methyl 4-carbomethoxy-3,4,5,6-tetrahydroanthranilate (**2**) was completely inert to hydrogenation. This difficulty observed in the hydrogenation of the 4-carboxy compound **2** coincides with the lack of reactivity reported for the hydrogenation of the double bond of 3-cyclohexene carboxaldehydes.[9] Whereas it was apparent that more drastic conditions would be required for the hydrogenation of **2**, it was also necessary that they be chosen so as to minimize hydrogenolysis.



1 **2** **3**

Thus, in order to find the optimum conditions for the hydrogenation not only of **2**, but also of other vinylogous urethans, a thorough study of the reaction was made. Compounds **1** and **2** and dimethyl β-methylaminoglutaconate (**3**) were hydrogenated under a variety of conditions. It is interesting to note that with platinum oxide in glacial acetic acid the β-keto ester from which the vinylogous urethan was formed was the only isolable product. Since the solvent was carefully dried before use it is quite probable that this "hydrolysis" occurred by way of a Michael addition of the solvent to the unsaturated ester followed by elimination of the amine group and then hydrolysis of the resulting enol derivative during work-up. The use of the Liska[8] conditions gave satisfactory results in the hydrogenation of **3** as well as **1**.

However, with a 5% palladium-on-charcoal catalyst at 85° and 1000–1500 psi excellent yields of the saturated amino esters were obtained. With **2**, which was resistant to hydrogenation under practically all other conditions, the saturated product was obtained in 80–90% yield by this procedure. Since these conditions did give such superior results, their use is recommended for the hydrogenation of all vinylogous urethans. Temperature control in this reaction is critical, however, since at room temperature no reaction occurred and at higher temperatures (120°) extensive deamination was observed.

(1) Supported by Grants NH-10107 from the National Institutes of Health and 2474 from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgement is made of this support.

(2) NDEA Predoctoral Fellow, 1965–present.

(3) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965.

(4) P. N. Rylander and S. Starrick, *Engelhard Ind. Tech. Bull.*, **7**, 106 (1966).

(5) Pl. A. Plattner, A. Fürst, and J. Hellerbach, *Helv. Chim. Acta*, **30**, 100 (1947); B. D. Astill and V. Boekelheide, *J. Amer. Chem. Soc.*, **77**, 4079 (1955); R. H. Baker and P. C. Weiss, *ibid.*, **66**, 343 (1944).

(6) C. P. Rader, G. E. Wicks, R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

(7) (a) B. R. Baker, R. E. Schaub, M. V. Querry, and J. H. Williams, *ibid.*, **17**, 97 (1952); (b) R. H. Baker and A. H. Schlesinger, *J. Amer. Chem. Soc.*, **68**, 2009 (1946).

(8) K. J. Liska, *J. Pharm. Sci.*, **53**, 1427 (1964).

(9) I. N. Nazarov, G. P. Kugatova, and G. A. Laumenskas, *Zh. Obshch. Khim.*, **27**, 2450 (1957); H. E. Hennis and W. B. Trapp, *J. Org. Chem.*, **26**, 4678 (1961).

Experimental Section[10,11]

Ethyl 3,4,5,6-tetrahydroanthranilate (1) was prepared following the procedure of Prelog and Geyer,[12] mp 73–74.5 (lit.[12] mp 72–73.5). The product amino ester from the hydrogenation was isolated as the HCl salt, mp 128–129° (lit.[8] mp 131–133°).

Methyl 4-carbomethoxy-3,4,5,6-tetrahydroanthranilate (2) was prepared in quantitative yield from 2,4-dicarbomethoxycyclohexanone[13] by the procedure described by Becker,[14] mp 58–60.5° (hexane–benzene–ether, 10:1:1).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.22; H, 7.22; N, 6.74.

Dimethyl β-N-Methylamino Glutaconate (3).—In a three-necked flask equipped with a gas inlet tube, mechanical stirrer, and a Dean–Stark water separator was placed 17.4 g (0.1 mol) of dimethyl acetone–dicarboxylate dissolved in 250 ml of dry benzene. The solution was heated to 60–70° and methylamine gas was bubbled in slowly. The temperature of the reaction mixture was kept between 70–75° and the gas flow continued until the theoretical amount of water was trapped in the water separator. The benzene was removed under reduced pressure giving a viscous oil which slowly crystallized. After washing thoroughly with anhydrous ether 14 g of white crystals, mp 83–90°, was obtained. Repeated recrystallization from ether gave a mixture of *cis* and *trans* isomers, mp 92–99°.

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.18; H, 6.86; N, 7.49.

The product amino diester, dimethyl β-N-methyl glutarate, was purified as its 3,5-dinitrobenzamide, mp 86–88° (pentane–chloroform).

Anal. Calcd for $C_{15}H_{17}N_3O_9$: C, 46.98; H, 4.47; N, 10.97. Found: C, 47.07; H, 4.67; N, 11.01.

Recommended Procedure for the Hydrogenation of Vinylogous Urethans. The Hydrogenation of 2.—To 8 g of 5% palladium on charcoal was added, carefully, 35 ml of dry dioxane so that the catalyst was thoroughly moistened with the solvent. To this paste was added, carefully, 65 ml of absolute methanol. (Direct addition of methanol to a dry hydrogenation catalyst can result in severe fires.[3]) This mixture was poured into the hydrogenation apparatus and 12.5 g of the vinylogous urethan 2 in 125 ml of methanol added. The hydrogenation was run for 18–24 hr at 85° and 1000–1500 psi. After this time the reaction mixture was cooled, the catalyst filtered off, and the solvent removed under reduced pressure at 30–35°. The cloudy residue was taken up in ether and filtered. Evaporation of the ether from the filtrate gave 11.25 g (90%) of the product amino diester as a colorless oil. The 3,5-dinitrobenzamide had mp 175–176° (ether–methanol).

Anal. Calcd for $C_{17}H_{19}N_3O_9$: C, 49.88; H, 4.68; N, 10.26. Found: C, 49.77; H, 4.93; N, 9.99.

Registry No.—2, 15649-59-9; 3,5-dinitrobenzamide of hydrogenated 2, 15649-60-2; 3 (*cis*), 15649-63-5; 3,5-dinitrobenzamide of hydrogenated 3, 15717-42-7; 3 (*trans*), 15983-53-6.

(10) Infrared spectra were recorded on a Beckman IR-10 spectrophotometer. The extent of hydrogenation was determined in some cases by product isolation and in others it was estimated by observing the decrease in adsorption at 1655 ($NH_2C{=}CC(=O)OR$) and at 1620 cm^{-1} (C=C)[11] and the corresponding increase in adsorption at 1730 ($CH_2(O{=})COR$) as well as by tlc.

(11) F. Korte and K. Trautner, *Chem. Ber.*, **95**, 295 (1962).

(12) V. Prelog and U. Geyer, *Helv. Chim. Acta*, **28**, 1677 (1945).

(13) H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 912 (1946).

(14) H. G. O. Becker, *J. Prakt. Chem.*, **12**, 294 (1961).

Synthesis of *exo,exo*-5,6-Dideuterio-*syn*-7-acetoxynorbornene and *exo,exo*-5,6-Dideuterio-2-norbornene

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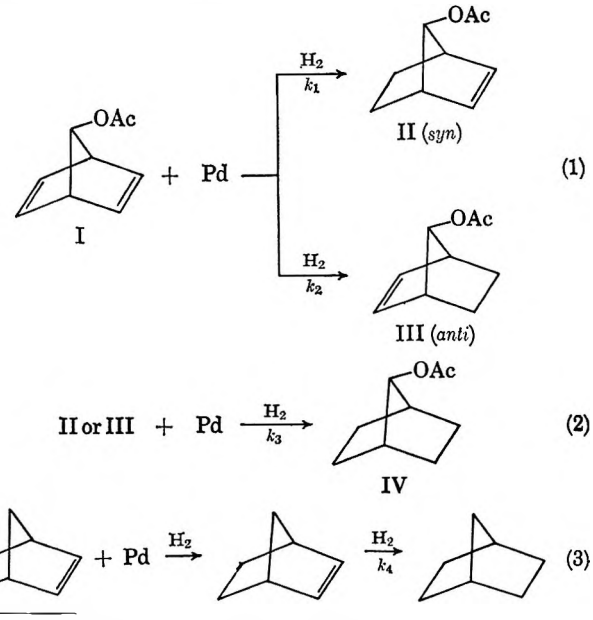
Received August 16, 1967

In a previous publication in which the synthesis of *syn*-7-acetoxynorbornene (II) by the platinum-catalyzed reduction of 7-acetoxynorbornadiene (I) was described, the isolated yield of *syn*-acetate was reported to be 22%.[1] During a subsequent study of reductions in the 7-substituted norbornadienyl system and the effect of various transition metal catalysts,[2] 7-acetoxynorbornadiene was hydrogenated over a palladium catalyst in the presence of an equal molar amount of norbornadiene.[3] The utilization of this technique increased the yield of *syn*-7-acetoxynorbornene (II) to ~40% (~70% by glpc). When deuterium was substituted for hydrogen in this reduction, a comparable yield of *exo,exo*-5,6-dideuterio-*syn*-7-acetoxynorbornene was realized. Furthermore, this method has led to a procedure for achieving the deuterium reduction of norbornadiene to *exo,exo*-5,6-dideuterionorbornene (V) with high selectivity and conversion. These useful synthetic procedures are presented in detail in the Experimental Section of this Note.

The significantly increased yield of the *syn*-acetate (II) is attributed to two factors that operate in this reduction. One of these is the preferential reduction of the less sterically hindered *anti* double bond of the dienyl acetate (I). The other is the competitive hydrogenation on the catalyst surface of the various diolefinic and monoolefinic species present in the reaction mixture. The relative amounts of the various reduction products as a function of per cent reduction are illustrated by Figure 1. It is apparent that norbornadiene is rapidly reduced to norbornene while the reduction of dienyl acetate (I) to the isomeric *syn*- (II) and *anti*-acetates (III) proceeds at a somewhat slower rate. The norbornene produced, however, which reduces more slowly than the dienyl acetate (I), is reduced more rapidly than either the *syn* (II) or the *anti* (III) isomer. This rate differential effectively suppresses the subsequent conversion of II and III to saturated acetate product (IV). The data of Figure 1 may be rationalized by consideration of eq 1–3. The



(1) B. Franzus, W. C. Baird, Jr., E. I. Snyder, and J. H. Surridge, *J. Org. Chem.*, **32**, 2845 (1967).

(2) The results of this work will be fully described in forthcoming publications.

(3) This experiment was performed at the suggestion of Professor H. C. Brown in order to investigate several anomalies that had been observed regarding the stereochemistry of these reductions.[2] The synthetic utility of this reduction was not anticipated.

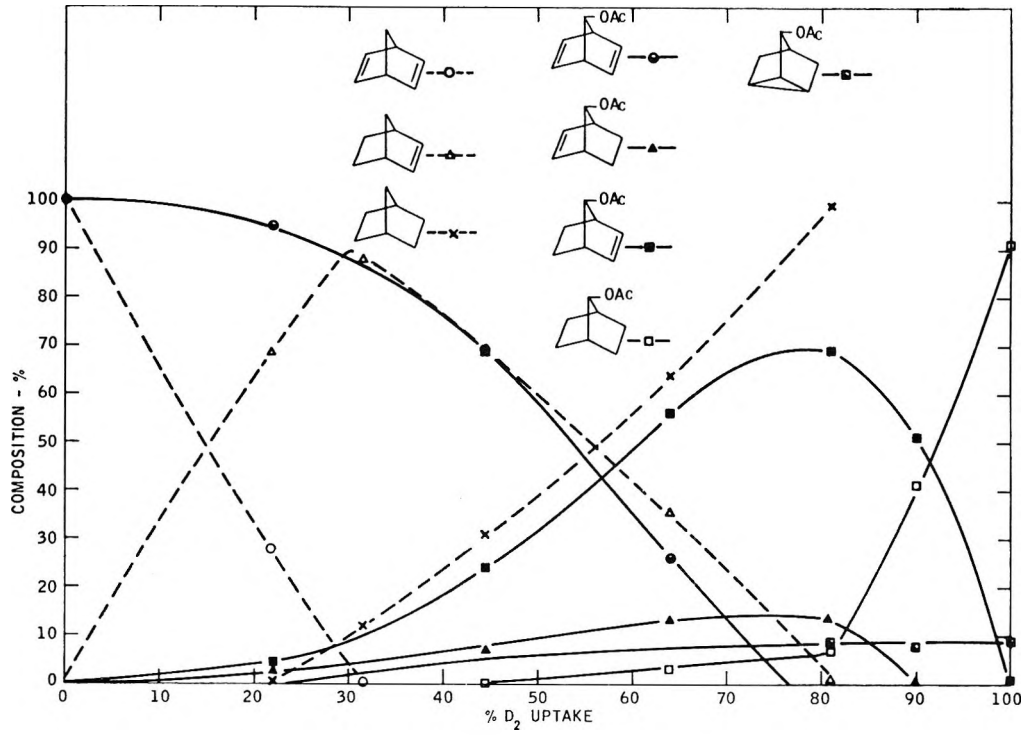
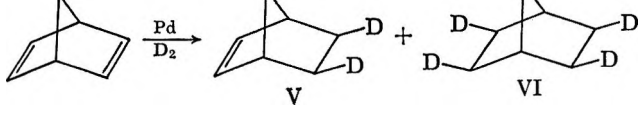


Figure 1.—Competitive reduction of norbornadiene and 7-acetoxynorbornadiene.

yields of II and III are obviously optimized when reaction 3 is faster than reaction 2 but slower than reaction 1 ($k_3 < k_4 < k_1$ or k_2). For purposes of synthesizing *syn*-7-acetoxynorbornene (II) or *exo,exo*-5,6-dideuterio-*syn*-7-acetoxynorbornene, one can take advantage of these rate differentials by stopping the reduction at the point where 7-acetoxynorbornadiene is no longer present. At this stage of the reduction the amount of II present as a percentage of all acetates is 63–73% (by glpc analysis); the amount of III present is 7–17%. In order to achieve this degree of selectivity it is necessary to use an initial norbornadiene to catalyst mole ratio of at least 25:1 when norbornadiene and dienyl acetate are present in equimolar amounts. Lower norbornadiene to catalyst ratios produce significantly smaller amounts of II and larger amounts of III. Furthermore, selectivity to the *syn* isomer (II) cannot be realized by substituting norbornene for norbornadiene or by using a platinum catalyst. However, the course of the reduction is not dependent on reducing the palladium catalyst with hydrogen (deuterium) before exposing it to the diolefins.

During this study it was noted that high yields of norbornene could be obtained by the hydrogenation of norbornadiene over a prereduced palladium catalyst. If deuterium were substituted for hydrogen, this method would afford a convenient synthesis of *exo,exo*-5,6-dideuterionorbornene (V). A typical reduction gave (by glpc analysis) 91.7% V, 5.9% *exo,exo,exo,exo*-2,3,5,6-tetradeuterionorbornane (VI), and 2.4% unreacted norbornadiene. The isolated yield of dideuterionorbornene amounted to ~50%. If a nonprereduced palladium catalyst was employed, the selectivity to V diminished to ~70%. Reductions performed over platinum catalysts were totally nonselective; typical reactions gave 37.6% V, 30.2% VI, and 32.2% unreacted norbornadiene.



V VI

Experimental Section

7-Acetoxynorbornadiene was purchased from Frinton Laboratories, Vineland, N. J., and was used without further purification. Norbornadiene and palladium on powdered charcoal were obtained from Matheson Coleman and Bell.

Analytical glpc was performed with a Perkin-Elmer Model 154-D vapor fractometer. The 7-acetoxy compounds were analyzed on a 2 m × 0.25 in. column packed with 30% FFAP (Varian Aerograph) on acid-washed Chromosorb W at 136° with a 100 ml/min helium flow. The norbornyl hydrocarbons were analyzed on a 2 m × 0.25 in. Perkin-Elmer "U" (squalane) column at 100° with a 95 ml/min helium flow. Varian Aerograph Autoprep Model A-700 was used for the preparative scale glpc.

Nmr spectra were determined with a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Mass spectral data were determined with the Esso Chemical Physics mass spectrometer using both chemical ionization[4] and electron-impact techniques.

Competitive Reduction of Norbornadiene and 7-Acetoxynorbornadiene.—For purposes of following the changes in composition of a reduction mixture, 0.301 g of 10% palladium on powdered charcoal in 5 ml of methanol was saturated with deuterium in a gas buret apparatus at atmospheric pressure. Into this slurry 5 ml of a methanol solution of 0.889 g (5.92 mmol) of 7-acetoxynorbornadiene (I) and 0.647 g (7.04 mmol) of norbornadiene were injected with a syringe. Periodically 0.1-ml samples were withdrawn from the reduction mixture and were analyzed by glpc. When 487 ml (21.8 mmol at STP) of D_2 had been consumed, the gas uptake ceased. Glpc analysis at this point showed no unsaturated compounds remaining. The results of this experiment are plotted in Figure 1 where the y axis is the per cent of each compound present when the acetate esters and the hydrocarbons are each considered separately to be 100%.

Preparation of *exo,exo*-5,6-Dideuterio-*syn*-7-acetoxynorbornene (II).—In 20 ml of methanol 0.486 g of 10% palladium on powdered charcoal was saturated with 5.1 ml of deuterium. Into this slurry was injected a mixture of 2.40 g (16.0 mmol) of 7-acetoxynorbornadiene (I) and 1.52 g (16.5 mmol) of norborna-

(4) M. S. B. Munson and F. H. Field, *J. Amer. Chem. Soc.*, **88**, 2621 (1966).

diene. This mixture was reduced with 1130 ml (46.3 mmol at STP) of deuterium or 71% of the amount required for complete reduction. Glpc analysis showed the acetate composition to be 72.4% *syn*-7-acetoxynorbornene (II), 12.9% *anti*-7-acetoxynorbornene (III), 7.2% 7-acetoxynorbornane (IV), and 7.5% 3-acetoxynortricyclene.[5] Isolation of II was accomplished *via* the silver nitrate technique previously described[1] and gave 1.08 g (41%) which by glpc analysis was 93% II, 5% III, and 2% an unidentified impurity. *syn*-7-Acetoxynorbornene[6] (II) has previously been identified. The nmr spectra (in $CDCl_3$) of *exo,exo*-5,6-dideuterio-*syn*-7-acetoxynorbornene (II) exhibits the characteristic "doublet of triplets" for vinyl hydrogens (δ 6.05, area 2) typical of *syn* compounds,[6-9] bridge hydrogen (multiplet, δ 5.05, area 1), bridgehead hydrogens (multiplet, δ 3.1, area 2), $OC(=O)CH_3$ hydrogens (singlet, δ 2.05, area 3), and *endo* hydrogens (singlet, δ 1.05, area 1.8). The nmr spectrum also shows *exo* hydrogens (multiplet, δ 2.28, area 0.2). The small amount of *exo* hydrogen arises from both incomplete deuteration (see mass spectral data) and some *endo* addition.[2] The mass spectral data (*via* the chemical ionization technique[4]) were obtained by Dr. Frank H. Field of these laboratories; the data showed that compound II was about 90% d_2 and 10% d_1.

Preparation of *exo,exo*-5,6-Dideuterio-2-norbornene (V).—In 15 ml of methanol 0.325 g of 10% palladium on powdered charcoal was saturated with 4.8 ml of deuterium. Into this mixture was injected 2.93 g (31.9 mmol) of norbornadiene which was partially reduced with 802 ml (32.8 mmol at STP) of deuterium. Glpc analysis of this mixture showed 86% norbornene, 7% norbornadiene, and 7% norbornane. The reduction mixture was filtered, added to 30 ml of H_2O, and extracted three times with 15-ml portions of pentane. The combined pentane extracts were dried over anhydrous $MgSO_4$ and reduced in volume to 3 ml by atmospheric distillation on a Todd fractionation assembly equipped with a Monel spiral column. Injections of 0.28 ml of the concentrated solution were chromatographed on a 20 ft × $^3/_8$ in. column packed with 30% silicone SE-30 on 60/80 Chromosorb P at 110° with 80 ml/min helium flow. Norbornene had a retention time of 12 min from air and was collected in Dry Ice–isopropyl alcohol cooled traps, giving 1.48 g (46%) which by glpc analysis was 95% norbornene and 5% of an unidentified impurity. The nmr spectrum of compound V has previously been described.[10] Mass spectra of compound V by the chemical ionization method[4] indicates 5% d_1 and 95% d_2. By electron impact compound V analyzes 99% d_2 and 1% d_1.

Registry No.—II(5,6-dideuterio), 15649-38-4; V, 3675-40-9.

Acknowledgment.—The authors are indebted to Dr. Frank H. Field for his aid in obtaining and interpreting the mass spectral data.

(5) Identified by comparison with an authentic compound: L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Amer. Chem. Soc.*, **78**, 2819 (1956).
(6) E. I. Snyder and B. Franzus, *ibid.*, **86**, 1166 (1964).
(7) G. Haywood-Farmer, R. E. Pincock, and J. I. Wells, *Tetrahedron*, **22**, 2007 (1966).
(8) H. Tanida and Y. Hata, *J. Org. Chem.*, **30**, 977 (1965).
(9) H. Tanida, T. Tsuji, and T. Irie, *ibid.*, **31**, 3941 (1966).
(10) W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *J. Amer. Chem. Soc.*, **89**, 410 (1967).

Base-Catalyzed Elimination Reactions of Substituted 2-(4-Pyridyl)ethylamines

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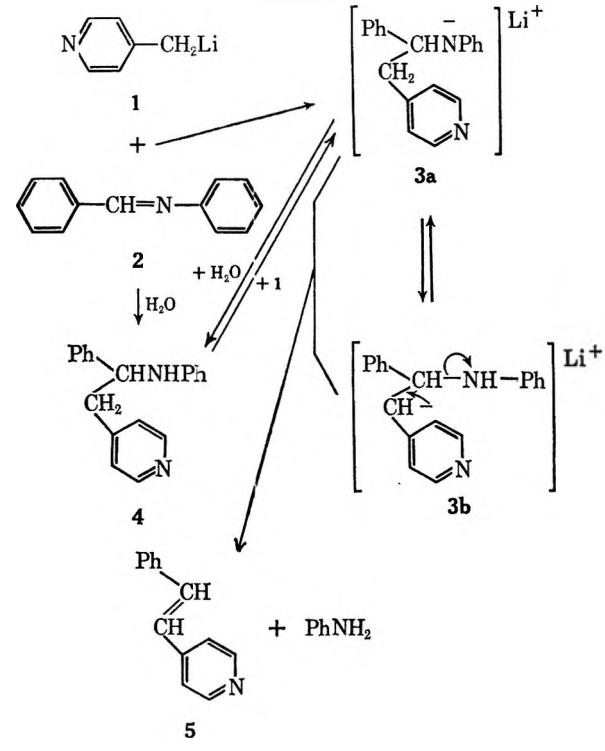
Our interest in the synthesis of compounds derived from 4-picolyllithium[1] led us to synthesize some N,1-diphenyl-2-(4-pyridyl)ethylamines. These compounds were prepared by treating arylideneanilines with 4-picolyllithium (**1**). During the course of this work we observed two elimination reactions (Scheme I). When a solution of benzylideneaniline (**2**) was

SCHEME I



treated at low temperature with **1**, rapid hydrolytic work-up afforded the desired pyridylethylamine **4** in excellent yield.[2,3]

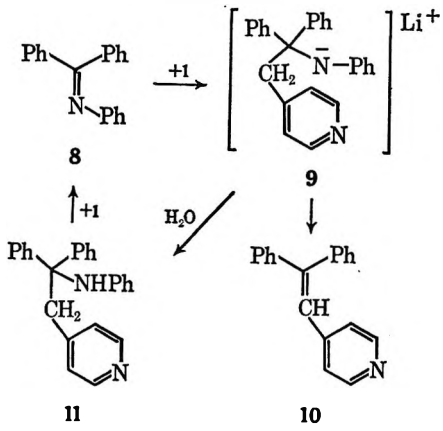
If, however, the reaction mixture was heated or allowed to stir at room temperature for a prolonged time, only the stilbazole (**5**) was isolated. That compound **4** was an intermediate in the formation of **5** could be demonstrated by treating a solution of **4** with either **1** or phenyllithium and warming the reaction mixture. Again, aniline was eliminated and **5** was the isolated product. A plausible mechanism for the elimination of aniline would involve a shift of the negative charge from the initial anion **3a** to give the carbanion **3b**.[4] Either of these intermediates could readily rearrange as shown to form **5** with the expulsion of the aniline anion.

In an attempt to find evidence for the existence of the carbanion **3b**, the reaction mixture was allowed to stand at room temperature until visual estimation of a thin layer chromatogram indicated that the product **5** was present in about 30% yield. At this time the reaction mixture was quenched with deuterium oxide. An examination of the nmr spectrum of the product **4** showed the deuterium to be located only on the nitrogen. Thus, the proposed carbanion **3b** is either very short-lived and undergoes immediate elimination to give **5** or compound **5** is formed directly from the anion **3a** *via* a concerted elimination.

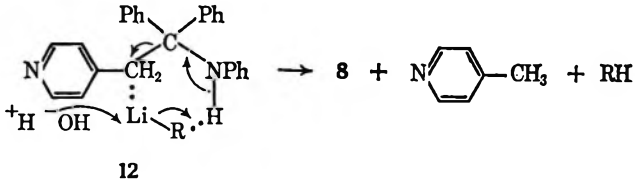
(1) (a) R. I. Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **31**, 2415 (1966); (b) M. E. Derieg, B. Brust, and R. I. Fryer, *J. Heterocycl. Chem.*, **3**, 165 (1966).
(2) The structure of compound **4** was confirmed by an independent synthesis described in the Experimental Section.
(3) F. F. Shuman and E. D. Amstutz, *Rec. Trav. Chim.*, **84**, 441 (1965).
(4) H.-D. Becker, *J. Org. Chem.*, **29**, 2891 (1964).

The same reaction sequence was next carried out on compound **8** (Scheme II) and the initial results were in agreement with those observed for the previous sequence in that rapid work-up of the reaction mixture gave **11** while prolonged standing gave the analogous phenylstilbazole **10**. The structure of **10** was confirmed by an

SCHEME II



independent synthesis involving the dehydration of 1,1-diphenyl-2-(4-pyridyl)ethanol which in turn was prepared from benzophenone by treatment with **1**. The mechanism of the formation of **10** from **8** presumably would be analogous to the sequence **3a,b** to **5**. However, when compound **11** was treated with **1** or with phenyllithium, picoline was eliminated on hydrolysis giving the Schiff base **8** in very high yield instead of the expected stilbazole **10**. Therefore, in this reaction, neither **9** nor the corresponding carbanion could be an intermediate since the product would then be compound **10**. The failure of **11** to react with either sodium hydride or lithium hydride in tetrahydrofuran further demonstrates the difficulty of the deprotonation of **11** to **9** in a nonaqueous system. The possibility of a retro-aldol type of reaction can also be discounted since the expected products, *i.e.*, compounds **8** and **1**, would then recombine to yield **9** and ultimately either **11** and/or **10**. One explanation for the elimination of picoline could be that a stable complex,[5] such as **12**, is initially formed and that upon the addition of water it is decomposed into **8**, picoline, and RH.



Experimental Section

All melting points were determined microscopically on a hot stage and are corrected. Spectra were obtained for all compounds and were compared in order to confirm or exclude the expected structural changes. Tetrahydrofuran (THF) was dried over Woelm grade I neutral alumina.

1-Anilino-1-phenyl-2-(4-pyridyl)ethane (4).—A mixture of 19.7 g (0.1 mol) of 4-phenacylpyridine,[1a] an excess of aniline (0.25 mol), 100 ml of pyridine, 100 ml of benzene, and 15 ml of concentrated hydrochloric acid was heated under reflux for 48 hr using a Dean–Stark trap to remove water. The reaction mixture was cooled and filtered to give 25.5 g (82.8%) of 4-(β-phenyliminophenethyl)pyridine hydrochloride. Recrystallization from ethanol gave the analytically pure compound as yellow prisms, mp 261–271°.

Anal. Calcd for $C_{19}H_{16}N_2 \cdot HCl$: C, 73.90; H, 5.55; Cl, 11.48. Found: C, 74.02; H, 5.89; Cl, 11.56.

A solution of 15 g of 4-(β-phenyliminophenethyl)pyridine hydrochloride (48.5 mmol) in 200 ml of ethanol and 5 ml of concentrated ammonium hydroxide was treated with 7.0 g of sodium borohydride. The reaction mixture was diluted with water, cooled, and filtered to give 11.65 g (87.5%) of **4**, mp 115–118°. Recrystallizations from a mixture of methylene chloride and hexane gave the pure material as colorless plates, mp 118–119°.

Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61; N, 10.21. Found: C, 82.98; H, 6.63; N, 10.39.

The dihydrochloride of **4** was prepared from an ethereal solution of **4** and dry hydrogen chloride. Recrystallizations from a mixture of methanol and ether gave colorless plates, mp 182–186°.

Anal. Calcd for $C_{19}H_{18}N_2 \cdot 2HCl$: C, 65.71; H, 5.80; Cl, 20.42. Found: C, 65.69; H, 5.71; Cl, 20.18.

Reaction of Benzylideneaniline (2) with 4-Picolyllithium (1).—A solution of 49.5 g (0.5 mol) of **1**[1a] in 300 ml of THF, under dry nitrogen and at −25°, was stirred during the dropwise addition (20 min) of a solution of 88 g (0.49 mol) of **2** in 240 ml of THF. Stirring was continued for 30 min and the reaction was quenched by the addition of 150 ml of water. The reaction mixture was extracted with 6 *N* hydrochloric acid; the acid layer was washed with ether and poured into an excess of ammonium hydroxide and ice. A yellow gum formed and slowly solidified. The solid was removed by filtration and was washed well with water giving, after air drying, 108.1 g of crude **4**.

When the reaction was performed on a 0.1-mol scale (18 g of **2**) at room temperature and allowed to stir overnight, work-up as described above afforded 6.5 g (36%) of 4-stilbazole (**5**). Recrystallizations from dilute acetone gave the pure product, mp 131.5–132° (lit.[6] mp 131°). By heating the reaction mixture at reflux for 2.5 hr the yield of **5** was increased from 36% to approximately 65%.

1,1-Diphenyl-2-(4-pyridyl)ethylene (10).—A solution of 10 g of 1,1-diphenyl-2-(4-pyridyl)ethanol[7] (36.4 mmol) in 50 ml of 70% H_2SO_4 was stirred and heated at 75° for 22 hr. The reaction mixture was treated with ice, made basic with ammonium hydroxide, and extracted with methylene chloride. The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was crystallized from hexane to give 7.6 g (81.4%) of **10**. Recrystallizations from a mixture of methylene chloride and hexane gave the analytical sample as colorless prisms, mp 74–76°.

Anal. Calcd for $C_{19}H_{15}N$: C, 88.68; H, 5.88. Found: C, 88.71; H, 5.91.

Reaction of N-Benzohydrylideneaniline (8) with 1.—A solution of 9.9 g (0.1 mol) of **1** in 200 ml of THF at −30° was stirred under dry nitrogen during the dropwise addition (30 min) of a solution of 25.7 g (0.1 mol) of **8** in 200 ml of THF. Stirring was continued for 30 min at −30° when the reaction was quenched with 60 ml of water. The reaction mixture was worked up as described for the isolation of compound **4** to give 24.8 g (70.6%) of 1-anilino-1,1-diphenyl-2-(4-pyridyl)ethane (**11**). Recrystallizations from methylene chloride gave an analytically pure sample as colorless prisms, mp 234–236°.

Anal. Calcd for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.99; H, 6.45; N, 7.79.

The salt was prepared by treating a solution of **11** in chloroform with dry hydrogen chloride. Recrystallizations from a mixture of ethanol and ether gave the hydrochloride as yellow plates, mp 199–201°.

Anal. Calcd for $C_{25}H_{22}N_2 \cdot HCl$: C, 77.60; H, 5.99; Cl, 9.16. Found: C, 77.76; H, 5.90; Cl, 9.25.

When the reaction mixture (36.4 g of **8**, 0.14 mol) was heated under reflux for 18 hr, the usual work-up yielded an oil which was separated from the aqueous phase by ether extraction. The organic phase was washed with water, dried over magnesium sulfate, and evaporated to give an oily residue which was then extracted with petroleum ether (bp 30–60°). Removal of the

(5) This is compatible with the observations that the addition of the organometallic compound to **11** results in a black solution and **8** could not be detected in the reaction mixture until the addition of water.

(6) E. A. Wagstaff, *J. Chem. Soc.*, 276 (1934).

(7) H. B. Wright, D. A. Dunnigan, and U. Biermacher, *J. Med. Chem.*, **7**, 113 (1964).

solvent and recrystallization from dilute acetone gave 9.15 g (25.6%) of pure 10, mp 74–76°. The combined mother liquors contained 8, 10, and 11 in approximately equal amounts as seen by visual estimation on a thin layer chromatogram.

Reaction of 11 with 1.—A solution 3.5 g (10 mmol) of 11 in 50 ml of THF was treated with a solution of 10 mmol of 1 in 50 ml of THF and the resulting black solution was stirred under dry nitrogen overnight at room temperature. The reaction mixture was then poured over ice and 2.5 g (97.4%) of yellow crystalline 8, devoid of 11 and 10 (mp 109–113°, lit.[3] 115–116°), was removed by filtration. The same result was obtained when the reaction mixture was heated under reflux and also when phenyllithium was substituted for 1 in the reaction.

Registry No.—4-(β-Phenylmonophenethyl)pyridine hydrochloride, 15813-15-7; 4, 15856-53-8; 4 2HCl, 15813-16-8; 10, 15814-97-8; 11, 15814-98-9; 11 HCl, 15813-17-9.

Acknowledgment.—We are indebted to Dr. A. Steyermark and his staff for the microanalyses and to Mr. S. Traiman for the determination of infrared spectra.

The Chlorination of Diethyl Acetylenedicarboxylate with Ferric Chloride

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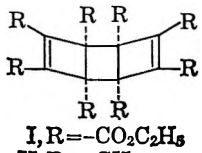
We recently became interested in the synthesis of *syn*-octacarbethoxytricyclo[4.2.0.0^{2,5}]octadiene (I) in connection with some photochemical studies. Since the aluminum chloride catalyzed tetramerization of 2-butyne to the octamethyl derivative II had been reported,[1] it was felt that a similar Lewis acid catalyzed



I, R=$-CO_2C_2H_5$
II, R=$-CH_3$

reaction of diethyl acetylenedicarboxylate (III) should lead to the desired tetramer (I). To avoid the possibility of undesirable side reactions between aluminum chloride and the diester,[2] ferric chloride was chosen as the Lewis acid. Instead of producing I, however, ferric chloride served as a stereospecific chlorinating agent to yield diethyl dichlorofumarate (IV).

When a solution of III in cyclohexane was added to a stirred suspension of anhydrous ferric chloride in the same solvent, a viscous, amorphous complex which adhered to the walls of the flask was formed. Complex formation could be monitored by gas chromatography of the supernatant liquid, and appeared to be essentially complete after 1.5 hr. Continued stirring of the reaction mixture, followed by hydrolysis, produced a mixture of starting material and one major volatile product. That this product was not the expected tetramer (I) was demonstrated by its mass spectrum, which displayed a peak for the molecular ion at 239.9947, and suggested the formula $C_8H_{10}O_4Cl_2$. This formula was confirmed by combustion analysis and additional molecular weight data. The nmr spectrum exhibited *only* the characteristic signals for the grouping $-OCH_2CH_3$. Only two structures accommodated this data, diethyl dichloromaleate and diethyl dichlorofumarate (IV). Unequivocal proof that the product was not the maleate derivative was obtained by comparison of its glpc retention time with that of authentic diethyl dichloromaleate, prepared from the commercially available dichloromaleic anhydride. Earlier workers[3] had demonstrated that the acid-catalyzed esterification of this anhydride proceeds without isomerization. In addition, the well-defined separation of the two isomeric esters on gas chromatography gave assurance of the stereospecificity of the chlorination.

The chlorination of benzene derivatives,[4] alcohols,[5] and esters[5] by ferric chloride have been reported. Since there appeared to be no previous reports of chlorination of acetylenic compounds by ferric chloride,[6] however, a cursory investigation of the reaction mechanism was made. The dependence of the yield of diethyl dichlorofumarate (IV) upon reaction parameters is summarized in Table I.

TABLE I

Reaction time, hr	Moles of $FeCl_3$/mole of III	% yield of IV
1.5	8.71	4.3
17	2.03	7.7
17	4.13	20.5
16	8.42	19.7
45	9.76	30.4

The physical state of the intermediate complex makes extreme emphasis upon the effect of varying the $FeCl_3$/III ratio on the yield of IV unjustifiable. It is not inconceivable that a significant amount of ferric chloride became occluded in the sticky complex during the early stages of the reaction, and was thereby effectively removed from the reaction media.

From the low yield of IV after a reaction time of 1.5 hr (complex formation complete), it was inferred that chlorination was not simply a result of the hydrolysis of the complex. This experiment also demonstrated that chlorination occurred more slowly than complex formation, a hypothesis which was substantiated by the dependence of the yield of IV on reaction time. Finally, when diphenylacetylene was treated with ferric chloride for 22 hr, no reaction occurred. Thus it appeared that the carbethoxy groups were involved in the chlorination reaction.

(1) H. M. Rosenberg and E. C. Eimutis, *Can. J. Chem.*, **45**, 2263 (1967).
(2) A. F. Dobryanskiĭ and Yu. I. Kornilova, *Sb. Statei Obsch. Khim. Akad. Nauk SSSR*, **1**, 320 (1953); *Chem. Abstr.*, **49**, 867*d* (1955).
(3) N. R. Eldred and D. M. Yound, *J. Amer. Chem. Soc.*, **75**, 4338 (1953).
(4) P. Kovacic and N. O. Brace, *ibid.*, **76**, 5491 (1954).
(5) M. Dangyan, *J. Gen. Chem. USSR*, **8**, 1780 (1938); *Chem. Abstr.*, **33**, 4957 (1939).
(6) For a recent review of additions to acetylenes, see E. Winterfeldt, *Angew. Chem. Intern. Ed. Engl.*, **6** (5); 423 (1967). See also F. Behlmann, *Angew. Chem.*, **69** (3), 82 (1957), and G. Chavanne, *Bull. Soc. Chem. Belges*, **26**, 287 (1912).

The initial complex probably results from coordination of ferric chloride at each of the carbonyl oxygens.[7] It would be reasonable to expect the complexed carbonyl groups to assume the *anti* conformation with respect to each other. Chlorine transfer in this conformation from the complexed Lewis acids to the neighboring acetylenic carbons would then yield the observed product.

Experimental Section

The diethyl acetylenedicarboxylate used in this study was purchased from Farchan Research Laboratories (Wickliffe, Ohio) and was used without further purification. The sublimed anhydrous ferric chloride powder and the cyclohexane were Matheson Coleman and Bell analytical reagent grade. Gas chromatography was performed on a Barber–Coleman Model 5000 gas chromatograph with 6 ft × 0.25 in. 10% SE30 on 60–80 Chromosorb W columns. The check for volatile products was carried out by programming column temperature from 100–270°, while the quantitative gas chromatography was done isothermally at 125° using hexamethylbenzene as a standard.

Reaction of Diethyl Acetylenedicarboxylate with Ferric Chloride. General Procedure.—To a stirred suspension of 1.6260 g (9.41 mmol) of anhydrous ferric chloride in 10 ml of cyclohexane was added dropwise over 35 min a solution of 0.790 g (4.64 mmol) of diethyl acetylenedicarboxylate in 10 ml of cyclohexane. After stirring for 17 hr, the cyclohexane solution was decanted onto 10 g of ice. The residue in the reaction flask was dissolved in ice water and added to the cyclohexane above. The organic layer was separated and saved and the aqueous layer extracted once with 30 ml of cyclohexane. The combined organic layers were dried over anhydrous magnesium sulfate, the dessicant removed by filtration, and the filtrate concentrated to a volume of *ca.* 10 ml on a rotary evaporater without the application of heat. Hexamethylbenzene (0.1280 g) was added and the composition of the solution was found by quantitative gas chromatography to be 0.086 g of IV (7.7%) and 0.56 g of III. A pure sample of IV was obtained by preparative gas chromatography using a 5 ft × $^3/_8$ in. 5% SE 30 on 60–80 Chromosorb W at 100°. The analytical sample had $n^{25}D$ 1.4672.

Anal. Calcd for $C_8H_{10}Cl_2O_4$: C, 39.84; H, 4.18; Cl, 29.42; mol wt, 241. Found: C, 39.75; 39.85; H, 4.03, 4.14; Cl, 29.25; 29.28; mol wt, 246 (osmometry).

Diethyl Dichloromaleate.—A solution of 5.2 g of dichloromaleic anhydride (0.031 mol) and 0.2 g of *p*-toluensulfonic acid in 300 ml of absolute ethanol and 150 ml of anhydrous benzene was refluxed for 12 days, using a Dean–Stark moisture trap to periodically remove 20-ml portions of the condensate. The product was worked up in the usual manner to give diethyl dichloromaleate as a clear colorless liquid, bp 70–72° (0.1 mm), which was homogeneous to vapor phase chromatography.

Registry No.—Diethyl acetylenedicarboxylate (III), 762-21-0; ferric chloride, 7705-68-0; diethyl dichlorofumarate (IV), 15649-40-8; diethyl dichloromaleate, 15649-41-9.

(7) M. Zackrisson and I. Lindqvist, *J. Inorg. Nucl. Chem.*, **17**, 69 (1961).

Reaction of Nitro Alcohols with Sulfur Tetrafluoride[1]

KURT BAUM

Contribution No. 278 from the Aerojet-General Corporation, Von Karman Center, Azusa, California

Received October 16, 1967

No general method is available for the synthesis of β-halo derivatives of polynitroalkanes. The preparation of 2,2,2-trinitrochloroethane and 2,2-dinitrochloropropane from mixed acetals of the corresponding alcohols and phosphorous pentachloride has been reported.[2] Sulfuryl chloride[3] has been used to convert 2,2-dinitropropanol and 2,2-dinitropropanediol into the chloro derivatives and thionyl chloride[4] was used similarly with these alcohols and with 2,2,2-trinitroethanol. Attempts to prepare 2,2,2-trinitrobromoethane from the alcohol were unsuccessful using a variety of brominating agents.[4] The nitration of 2,3-dibromopropene has been reported to give 1,2-dibromo-1,1-dinitroethane, 1,1-dinitro-2-bromoethane, and 2-nitro-2,3-dibromopropanoic acid.[5] The β-iodo and -fluoro derivatives of polynitro compounds have not been reported.

Hydroxy groups have been replaced with fluorine by the reagent, sulfur tetrafluoride, but the reaction was not used as a preparative method for simple fluoroalkanes.[6] The reactivity of hydroxylic compounds with sulfur tetrafluoride was reported to be a function of the acidity of the hydroxyl groups. Moderate yields of fluorinated products were obtained with acidic hydroxy groups such as in tropolones, but with aliphatic alcohols ethers were major by-products. Nitro groups would, therefore, be expected to enhance the reactivity of alcohols toward sulfur tetrafluoride.

It was found that 2,2,2-trinitroethanol could be converted into 2,2,2-trinitrofluoroethane at ambient temperature in 63% yield in 4 days. 2,2-Dinitropropanol and 2,2-dinitro-1,3-propanediol were less reactive, and were converted into 2,2-dinitrofluoropropane and 2,2-dinitro-1,3-difluoropropane at 85–90°, with a 46% yield after 20 hr of reaction time for the former and a 62% yield after 8 hr for the latter. Attempts to prepare 2-methyl-2-nitrofluoropropane from 2-methyl-2-nitropropanol were unsuccessful. After a reaction period of 8 hr at 110°, only starting material and a trace of material with carbonyl absorption in its infrared spectrum were found.

$$(NO_2)_3CCH_2OH \xrightarrow{SF_4} (NO_2)_3CCH_2F$$

$$CH_3C(NO_2)_2CH_2OH \xrightarrow{SF_4} CH_3C(NO_2)_2CH_2F$$

$$HOCH_2C(NO_2)_2CH_2OH \xrightarrow{SF_4} FCH_2C(NO_2)_2CH_2F$$

The nmr spectra of the latter two products showed long-range H–F coupling of 2–2.5 cps through four bonds. The nmr and ir spectra are described in the Experimental Section.

Experimental Section

2,2,2-Trinitrofluoroethane.—Sulfur tetrafluoride (103 ml at −78°) was condensed into an evacuated 300-ml stainless steel bomb containing 100 g (0.55 mol) of trinitroethanol, and the mixture was allowed to stand at ambient temperature for 4 days. The bomb was then vented through an aqueous alkali trap. The residue was dissolved in 300 ml of methylene chloride, and the solution was washed six times with 50-ml portions of water.

(1) Supported by the Office of Naval Research.

(2) S. S. Novikov and G. A. Shvekgheimer, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2026 (1960).

(3) L. W. Kissinger, T. M. Benziger, H. E. Ungnade, and R. K. Rohner, *J. Org. Chem.*, **28**, 2491 (1963).

(4) F. B. Borghardt, A. K. Seeler, and P. Noble, Jr., *J. Org. Chem.*, **31**, 2806(1966).

(5) A. D. Nikolaeva, E. V. Redkina, and G. Kamai, *Tr. Kazansk. Khim. Tekhnol. Inst.*, **23**, 243 (1957); *Chem. Abstr.*, **52**, 8937 (1957).

(6) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960).

The solvent was removed by distillation, and the residue was sublimed onto a −78° cold finger condenser at 0.1 mm to give 64 g (63% yield) of 2,2,2-trinitrofluoroethane, mp 34–35°.

Anal. Calcd for $C_2H_2N_3O_6F$: C, 13.10; H, 1.10; N, 22.95; F, 10.38. Found: C, 13.12; H, 1.11; N, 23.22; F, 10.39.

The infrared spectrum in carbon tetrachloride consisted of the following peaks: 3.38 (w), 3.43 (w), 3.52 (w), 6.30 (s), 7.0 (w), 7.79 (s), 7.93 (m), 9.20 (m), 9.8 (m), 10.15 (m), 11.40 (w), and 11.75 μ (w).

2,2-Dinitrofluoropropane.—Sulfur tetrafluoride (20 ml at −78°) was condensed into an evacuated 75-ml stainless steel bomb containing 15 g (0.10 mol) of 2,2-dinitropropanol. The bomb was heated remotely for 20 hr at 85–90° and was then cooled to room temperature. The above procedure resulted in the isolation of 7.0 g (46% yield), mp 62–63°, with a crystalline phase change at 50°.

Anal. Calcd for $C_3H_5N_2O_4F$: C, 23.68; H, 3.29; N, 18.43; F, 12.50. Found: C, 23.67; H, 3.29; N, 18.43; F, 11.80.

The infrared spectrum of a carbon tetrachloride solution consisted of peaks at 3.50 (w), 6.40 (s), 6.90 (m), 6.96 (m), 7.18 (m), 7.30 (w), 7.40 (w), 7.60 (s), 7.90 (w), 8.10 (w), 8.65 (w), 8.90 (w), 9.49 (s), 11.5–11.65 (doublet, m), and 11.85 μ (m).

The proton nmr spectrum consisted of a methylene doublet at δ 5.12 (J = 46 cps) and a methyl doublet at 2.25 (J = 2 cps). The only[19] nmr signal was a triplet at ϕ 230.3 (J = 45 cps).

2,2-Dinitro-1,3-difluoropropane.—Sulfur tetrafluoride (20 ml at −78°) and 2,2-dinitro-1,3-propanediol (10 g, 0.060 mol) were allowed to react 8 hr at 85–90° by the above procedure to give 6.3 g (62% yield) of 2,2-dinitro-1,3-difluoropropane, mp 54°.

Anal. Calcd for $C_3H_4N_2O_4F_2$: C, 21.17; H, 2.35; N, 16.47; F, 22.35. Found: C, 21.07; H, 2.07; N, 16.19; F, 22.24.

The infrared spectrum of a solution in carbon tetrachloride contained peaks at 3.40 (w), 3.50 (e), 6.39 (s), 6.90 (m), 7.44 (m), 7.65 (s), 7.95 (w), 8.30 (w), 9.25 (m), 9.50 (s), 9.60 (s), 11.45 (w), and 11.84 μ (m).

The proton nmr spectrum consisted of a doublet of doublets at δ 5.32 (J = 46 and 2.5 cps) and the fluorine nmr spectrum consisted of a triplet at ϕ 235.0 (J = 45 cps).

Registry No.—2,2,2-Trinitrofluoroethane, 15892-91-8; 2,2-dinitrofluoropropane, 15892-92-9; 2,2-dinitro-1,3-difluoropropane, 15892-93-0; sulfur tetrafluoride, 7783-60-0.

Acknowledgment.—The author is indebted to Mr. K. Inouye for elemental analysis and to Mr. L. A. Maucieri for the nmr spectral determinations.

The Oxidation of Azines with Lead Tetraacetate. II[1]

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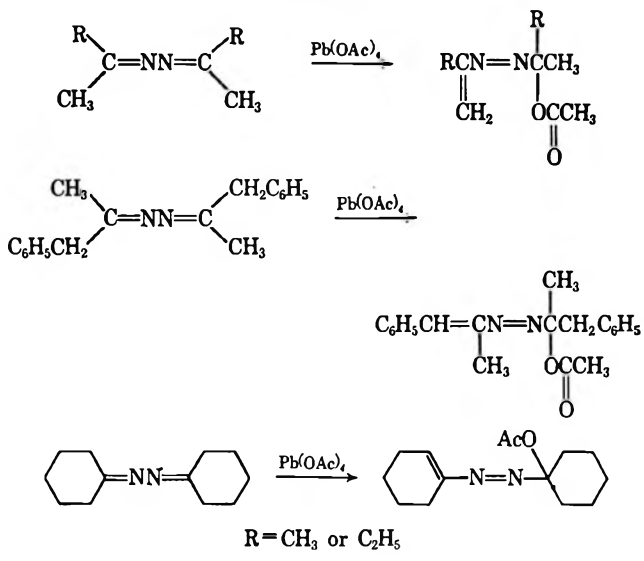
Received November 2, 1967

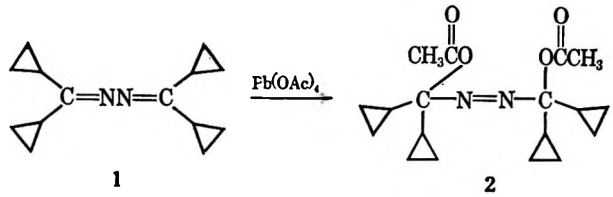
It was reported earlier[2] that the oxidation of ketazines with lead tetraacetate afforded α,β-unsaturated azoacetates in 40–70% yield (Scheme I). It was also noted that these products arose *via* abstraction of one of the active hydrogens on an α-carbon atom followed by conjugate addition of an acetate moiety. It was therefore of interest to investigate the oxidation of ketazines which possessed only less active hydrogens on the α-carbon atom in an attempt to form α,α'-diacetoxyazo compounds. Such compounds would resemble the α,α'-dichloroazo compounds prepared by Goldschmidt and Acksteiner.[3]

SCHEME I



R = CH_3 or C_2H_5

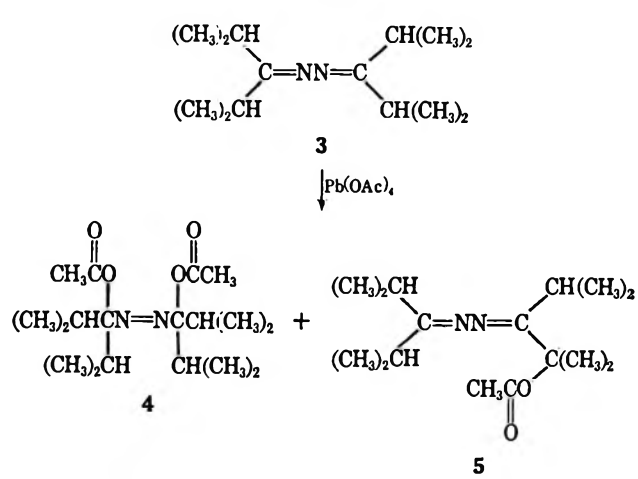
The first case to be investigated was that of dicyclopropylketazine (**1**). It was found that oxidation of this azine with lead tetraacetate in refluxing benzene afforded the bisacetoxyazo compound (**2**) in 42% yield. The structure of **2** was clearly defined by its infrared, ultraviolet, and nmr spectra and by its elemental analysis.



1 **2**

The oxidation of diisopropylketazine with lead tetraacetate was then studied. In this case it was found that oxidation gave rise to a mixture of products: the bisacetoxyazo compound (**4**) in 36% yield and the α-acetoxyazine (**5**) in 16% yield (Scheme II). Again the structures of **4** and **5** were established by infrared, ultraviolet, and nmr spectroscopy and microanalysis.

SCHEME II



3

4 **5**

(1) This investigation was supported by Public Health Service Research Grant AI-02923 from the National Institute of Allergy and Infectious Diseases.

(2) B. T. Gillis and M. P. LaMontagne, *J. Org. Chem.*, **32**, 3318 (1967).

(3) S. Goldschmidt and B. Acksteiner, *Ann.*, **618**, 173 (1958).

Benzophenone azine was found not to react with lead tetraacetate under the conditions used in the previous cases. Starting material was quantitatively recovered in all attempted oxidations even though all the lead tetraacetate had been consumed. It is believed that at 80° the lead tetraacetate would form radicals which could decompose if they did not react with the azine. No obvious reason suggests itself for the lack of reaction of benzophenone azine with lead tetraacetate other than the disruption of the conjugated system.

It is believed that the oxidation of azines **1** and **3** with lead tetraacetate proceed *via* a free-radical mechanism. First, no reaction occurs with either azine **1** or **3** at room temperature but the reaction does proceed nicely at 80°; secondly, the formation of the α-acetoxyazine **5** is consistent with a free-radical mechanism since abstraction of the tertiary hydrogen atom would give rise to a rather stable free radical. Such a type reaction would not likely occur in the case of dicyclopropylketazine. It should also be noted that no allylic acetate was isolated in the oxidation of azine **1**. It was also noted that the oxidations of these azines required somewhat more than 1 equiv of lead tetraacetate indicating that some decomposition of the oxidant probably occurs during the course of the reaction.

Experimental Section[4]

Oxidation of Dicyclopropylketazine (1) with Lead Tetraacetate.—To a solution of 20.0 g (0.092 mol) of dicyclopropylketazine[5] in 300 ml of reagent grade benzene was added 85 g (0.163 mol) of lead tetraacetate (85% active). The reaction mixture was heated to reflux for 24 hr. The lead diacetate was then filtered and the excess lead tetraacetate was destroyed by addition of water. The solution was washed several times with water and saturated sodium bicarbonate solution. The benzene solution was then dried over anhydrous sodium sulfate and the solvent was removed with the aid of an aspirator. The residual oil was allowed to sit in the refrigerator overnight. The crystals which formed were washed with cold ethanol to give 12.0 g (42%) of **2**, mp 83–84°. An analytical sample of **2** was prepared by recrystallization from a minimal amount of hot 95% ethanol. The ultraviolet spectrum of **2** had λ_{max}^{EtOH} 360 mμ (ε 34).[6] The infrared spectrum of **2** had strong acetate peaks at 1750 and 1250 cm^{-1} but no azine band at 1610 cm^{-1}. The nmr spectrum of **2** had a sharp singlet at 2.0 ppm, a multiplet of peaks at 1.65–1.20 ppm, and a multiplet at 0.9–0.3 ppm. The relative intensities were 6:4:16, respectively.

Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.47; H, 7.82; N, 8.46.

Oxidation of Diisopropylketazine (3) with Lead Tetraacetate.—To a solution of 20.0 g (0.09 mol) of diisopropylketazine[7] in 300 ml of reagent grade benzene was added 84 g (0.16 mol) of lead tetraacetate (85% active). The solution was heated to reflux for 24 hr. Work-up similar to that previously described afforded a residual liquid which upon cooling in the refrigerator overnight gave 11.0 g (36%) of the bisacetoxyazo compound (**4**), mp 100–101.5°. An analytical sample of **4** was obtained by recrystallization from hot 95% ethanol. The ultraviolet spectrum of **4** had λ_{max}^{EtOH} 355 mμ (ε 21).[6] Its infrared spectrum had strong acetate peaks at 1750 and 1240 cm^{-1} and no azine peak at 1625 cm^{-1}. The nmr spectrum had a septet at 3.1–2.4 ppm, a singlet at 2.05 ppm, and two distorted doublets at 1.3–0.8 ppm. The relative intensities were 4:6:24, respectively.

Anal. Calcd for $C_{18}H_{34}N_2O_4$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.26; H, 10.14; N, 8.36.

Distillation of the mother liquor obtained in the filtration of **4** afforded 4.1 g (16%) of a yellow liquid (**5**), bp 82–84° (0.25 mm). The infrared spectrum of α-acetoxydiisopropylketazine (**5**) had strong acetate peaks at 1750 and 1245 cm^{-1} in addition to an azine band at 1625 cm^{-1}. The nmr spectrum showed two septets at 3.5–2.4 ppm (due to the two conformations of the azine), an acetate singlet at 2.0 ppm, and a multiplet of peaks at 1.6–0.9 ppm. The relative intensities were 4:3:24, respectively.

Anal. Calcd for $C_{16}H_{30}N_2O_2$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.19; H, 10.90; N, 10.13.

Oxidation of Benzophenone Azine with Lead Tetraacetate.—To a solution of 10.0 g (0.028 mol) of benzophenone azine in 250 ml of reagent grade benzene was added 14.6 g (0.028 mol) of lead tetraacetate (85% active). The reaction mixture was heated to reflux for 24 hr. A test for lead tetraacetate was weakly positive. Work-up similar to that previously described afforded 9.8 g (98%) of a yellow solid whose infrared spectrum and melting point were identical with that of benzophenone azine.

Registry No.—Lead tetraacetate, 546-67-8; **1**, 15813-18-0; **2**, 15813-21-5; **3**, 15813-19-1; **4**, 15813-20-4; 5, 15856-54-9.

Acknowledgment.—The authors wish to acknowledge the assistance of the National Science Foundation in providing for departmental use a Cary 14 spectrophotometer, upon which the ultraviolet spectra contained herein were obtained.

(4) Boiling points and melting points are uncorrected. Microanalyses were performed by A. Bernhardt, Mülheim, Germany, and H. Galbraith, Knoxville, Tenn. The spectra were measured on a Cary Model 14 ultraviolet-visible spectrophotometer and a Perkin-Elmer Model 137 double-beam infrared spectrophotometer. The nmr spectra were measured on a Varian Model A-60 spectrophotometer at 60 MHz with tetramethylsilane as an internal standard.

(5) H. Hart and O. E. Curtis, Jr., *J. Amer. Chem. Soc.*, **78**, 112 (1956).

(6) D. C. Iffland, L. Salisbury, and W. R. Schafer, *ibid.*, **83**, 747 (1961).

(7) A. Maihle, *Bull. Soc. Chim. Fr.*, **27**, 541 (1920).

The Hydrolysis of Some Sodium N-Substituted Sulfamates in Aqueous Perchloric Acid[1]

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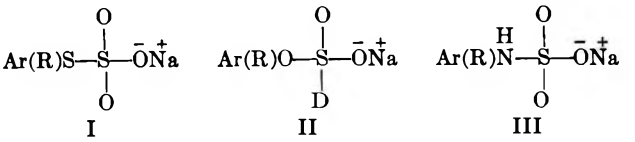
Received October 17, 1967

Recently, Kice *et al*,[2] reported that sodium S-alkyl and S-aryl thiosulfates (I) hydrolyze at similar rates in aqueous acid. In contrast, sodium aryl sulfates (II) hydrolyze much faster than sodium alkyl sulfates.[3] This difference has been attributed to increased delocalization of electrons on oxygen into the aryl π system in the transition state for hydrolysis of II compared to its ground state.[4] This effect is presumably absent in hydrolysis of compounds of type I. We wish to report kinetic results that we have obtained on the hydrolysis of the corresponding nitrogen system, the sodium N-substituted sulfamates (III).



I II III

(1) Taken in part from the M.S. Thesis of M. D. Bentley, Auburn University, Auburn, Ala., 1965.

(2) J. L. Kice, J. M. Anderson, and N. E. Pawlowski, *J. Amer. Chem. Soc.*, **88**, 5245 (1966).

(3) S. Burnstein and S. Liberman, *ibid.*, **80**, 5235 (1958).

(4) J. L. Kice and J. M. Anderson, *ibid.*, **88**, 5242 (1966).

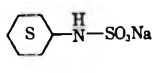
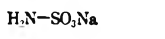
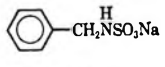
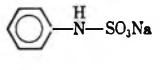
The mechanism of hydrolysis of sulfamic acid proposed by previous workers[5,6] involves rate-determining cleavage of the N–S bond without participation of water (A-1 mechanism). Hydrolysis of the N-substituted sulfamates in aqueous acid by a similar mechanism would then be analogous to the established mechanism[4] for hydrolysis of substituted sulfates and thiosulfates (I and II). On this basis, one might predict that since nitrogen and oxygen are both in period II of the periodic table the reactivity pattern of the sulfamates would more closely resemble that of compounds of type II than type I. This is borne out in the results presented in Table I. The 3100-fold acceleration of sodium N-phenylsulfamate compared with its saturated analog, sodium N-cyclohexylsulfamate, implies a substantial delocalization increase in the transition state for hydrolysis of the former. This is also reflected in the lower (5–6 kcal/mol) activation energy of the aryl sulfamate compared to the alkyl derivatives. The rate acceleration of the sulfamates might be compared with the 500-fold acceleration of $C_6H_5O\bar{S}O_3\overset{+}{N}a$ relative to $CH_3O\bar{S}O_3\overset{+}{N}a$ reported by Kice.[4]

$$\overset{+}{H} + H_2N\bar{S}O_3 \rightleftharpoons H_3\overset{+}{N}-\bar{S}O_3 \xrightarrow{\text{slow}}$$

$$NH_3 + SO_3 \xrightarrow[\text{fast}]{H_2O} \overset{+}{N}H_4 + H\bar{S}O_4$$

TABLE I

HYDROLYSIS RATES OF SODIUM N-SUBSTITUTED SULFAMATES IN AQUEOUS PERCHLORIC ACID

Structure	Temp, °C	k, sec^{-1}	k (rel) 99.96°	E_a, kcal/mol
	89.98	7.44×10^{-6}		
	99.96	2.56×10^{-5}		
	109.75	7.53×10^{-5}	1	32.4
	69.85	9.25×10^{-6}		
	80.01	3.42×10^{-5}		
	89.98	1.20×10^{-4}	13[a]	31.5
	80.01	1.24×10^{-5}		
	89.98	4.56×10^{-5}		
	99.96	1.20×10^{-4}	5	30.8
	30.61	2.65×10^{-5}		
	39.23	8.22×10^{-5}		
	48.97	2.94×10^{-4}	3100[a]	25.8

[a] From extrapolated rate data.

The relative reactivity of sodium sulfamate and the sodium N-alkylsulfamates appears to be in the order expected on the basis of inductive stabilization of the N–S bond. Indeed, the σ^* values[7] for these substituents are linearly related to the corresponding log k value ($\rho^* = 3.5$), although any argument based on those several values is obviously tenuous.

Experimental Section

Sodium sulfamate was prepared by NaOH neutralization of recrystallized sulfamic acid.

Sodium N-cyclohexylsulfamate (Abbott, Food Grade) was recrystallized first from dilute aqueous NaOH, then from ethanol–water.

Sodium N-benzylsulfamate and sodium N-phenylsulfamate were prepared by the method of Audrieth and Sveda[8] from the corresponding amines and chlorosulfonic acid. The preparation of sodium N-benzylsulfamate is presented below as an example.

Sodium N-Benzylsulfamate.—To 65.5 ml (0.6 mol) of benzylamine (Eastman, Practical Grade) dissolved in 250 ml of chloroform was added 13.2 ml (0.2 mol) of chlorosulfonic acid (Eastman, Practical) with stirring over a period of 1.5 hr at 0°. The resulting suspension of white solid was suction filtered and the insoluble material dissolved in 20 g (0.5 mol) of sodium hydroxide in 100 ml of water. After evaporation, the resulting sodium N-benzylsulfamate was thrice recrystallized from 75% ethanol to yield 6.50 g of pure material.

Anal. Calcd for $C_7H_8NSO_3Na$: S, 15.33. Found: S, 15.21.

Kinetic Procedures.—All kinetic runs were made in duplicate with solutions of 0.02 *M* sulfamate in 1.41 *M* perchloric acid which was prepared by dilution of 60% perchloric acid (J. T. Baker, Reagent Grade). The reactions were followed by titration of sulfate in aliquots of the reaction mixture using the titrimetric method of Archer.[9] All runs were made using the usual sealed ampoule technique except those on sodium N-phenylsulfamate which were conducted in a volumetric flask from which aliquots were removed. All were thermostated to ±0.05° using an oil bath in conjunction with a Sargent Thermonitor temperature control system.

Registry No.—Perchloric acid, 7601-90-3; sodium N-cyclohexylsulfamate, 139-05-9; sodium sulfamate, 13845-18-6; sodium N-benzylsulfamate, 15790-83-7; sodium N-phenylsulfamate, 15790-84-8.

Acknowledgments.—The authors thank Dr. C. G. Venier for helpful discussions and R. Jay Murray for least-squares treatment of the kinetic data. They also express appreciation to the Royal Crown Cola Co., Columbus, Ga., for their generous contribution of several starting materials.

(5) J. P. Candlin and R. G. Wilkens, *J. Chem. Soc.*, 4236 (1960).
(6) B. E. Fleischfresser and I. Lauder, *Aust. J. Chem.*, **15**, 242 (1962).
(7) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co. New York, N. Y., 1962, p 87.
(8) L. F. Audrieth and M. Sveda, *J. Org. Chem.*, **9**, 89 (1944).
(9) E. E. Archer, *Analyst*, **82**, 208 (1957).

Dihydroacridizinium Salts[1]

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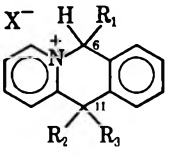
Reduction of acridizinium compounds both catalytically[2,3] and by means of sodium borohydride[3] has been previously described. In both cases reduction occurred in the quinolizinium portion of the molecule to produce benzoquinolizidines. It appeared to be of interest to study reduction under different conditions to determine whether a product could be obtained in which reduction was less complete. When a 10% Pd–C catalyst was substituted for the platinum oxide[2,3] previously employed, absorption of hydrogen at atmospheric pressure by acridizinium bromide decreased sharply after the consumption of 1 molar equiv. The colorless product which showed no significant ultraviolet absorption above 262 mμ was assigned the structure of 6,11-dihydroacridizinium (1) bromide. Acridizinium salts with substituents at the 6 and 11

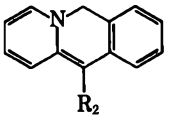
(1) This research was supported by a grant (CA-05509) from the National Cancer Institute of the National Institutes of Health.
(2) C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.*, **77**, 4812 (1955).
(3) C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **25**, 294 (1960).

TABLE I

NMR DATA FOR 6,11-DIHYDROACRIDIZINIUM SALTS (1–7) AND ACRIDIZINES (8–9)



1–7

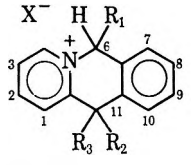


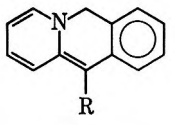
8–9

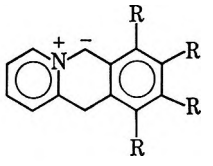
Compd	R_1	R_2	R_3	Solvent	Chemical shifts, (δ multiplicity and area) 6	11	Other nonaromatic
					Salts		
1	Me	H	H	D_2O	6.02 (s, two)	4.77 (s, two)	
2	H	H	Me	D_2O	6.02 (q, two)	4.72 (q, one)	1.93 (d, three)
3	Me	H	H	TFA[a]	6.04 (q, one)	4.60 (s, two)	1.86 (d, three)
5	H	H	$PhCH_2$	TFA	5.17 (q, two)	4.92 (t, one)	3.28 (d, two)
6	H	Me	$PhCH_2$	TFA	5.11 (q, two)		2.13 (s, three), 3.19 (s, two)
7	H	Me	Me	TFA	5.90 (s, two)		1.88 (s, six)
					Acridizines		
8		H		C[b]	5.20 (s, two)	c	
9		CH_3		C	5.05 (s, two)		2.43 (s, three)

[a] Trifluoroacetic acid. [b] Deuteriochloroform. [c] The proton at C-11 gives a signal indistinguishable from that of aromatic protons.

positions[4,5] were subjected to reduction over a palladium catalyst and likewise afforded 6,11-dihydro derivatives (2–5).







1, $R_1 = R_2 = R_3 = H$
2, $R_2 = R_2 = H$; $R_3 = Me$
3, $R_1 = Me$; $R_2 = R_3 = H$
4, $R_1 = R_2 = H$; $R_3 = Ph$
5, $R_1 = R_2 = H$; $R_3 = PhCH_2$
6, $R_1 = H$; $R_2 = Me$; $R_3 = PhCH_2$
7, $R_1 = H$; $R_2 = R_3 = Me$

8, R = H (not isolated)
9, R = CH_3

10, R = H
11, R = Cl

The nmr spectrum of 6,11-dihydroacridizinium (1) bromide in deuterium oxide showed two-proton singlets at δ 6.02, and 4.77, assigned to the methylene protons at the 6 and 11 positions, respectively. One would expect that it would be the methylene group adjacent to the positive charge on nitrogen which would be the more strongly deshielded, and examination of the nmr spectra of the 6-methyl- and 11-methyl-6,11-dihydroacridizinium salts (3 and 2, respectively) confirms this hypothesis (Table I).

Of the two types of methylene protons present in the dihydro compound (1) the *less* deshielded undergoes deuterium–hydrogen exchange more rapidly. When the salt 1 stands in neutral deuterium oxide nmr shows that 50% of the C-11 hydrogens have exchanged after 11 days while no exchange of the C-6 protons is perceptible during this period.

Since 1 resembles a 2-picolinium salt, several attempts were made to condense it with benzaldehyde in the presence of base (piperidine)[6] and acetic anhydride,[7] and under neutral conditions (sealed tube). No condensation product could be isolated, however.

An aqueous solution of 1, on treatment with aqueous sodium hydroxide, immediately yielded a bright red precipitate. No solvent was found for the recrystallization of the precipitate, and further reactions were carried out on material that was simply washed with water. The action of base on 11-methyl-6,11-dihydroacridizinium (2) bromide afforded a purple compound with the composition to be expected if the salt had lost the elements of hydrogen bromide. The choice between the 6H-acridizine structure 8 and that of the betaine (10) can be made on the basis of nmr (Table I). It is quite clear from a comparison of the spectra of the two bases that the methylene group at C_6 is intact, hence the possibility of the betaine structure (10) can be eliminated. The tetrachlorobetaine 11 has been proposed[8] as the product of the reaction of sodium methoxide with 3,4,5,6-tetrachloro-*o*-xylylene-α,α′-dipyridinium dibromide. On the basis of our evidence the correct structure would be 7,8,9,10-tetrachloro-6H-acridizine, analogous to 8. Addition of acid to acridizine afforded the expected dihydroacridizinium salt (1).

Since structure 8 is that of an anhydro base, the possibility that it might undergo alkylation reactions[9] was investigated. Addition of the red compound (8) to excess benzyl bromide yielded a tarry substance, which on treatment with perchloric acid yielded a crystalline product. The nmr spectrum (Table I) indicated that benzylation took place at the 11 position to give 11-benzyl-6,11-dihydroacridizinium (5) perchlorate. An independent preparation of 5 by reduction of 11-benzylacridizinium perchlorate (prepared by a standard method for preparation of acridizinium salts)[4b] confirmed the structure of the benzylation product.

(4) (a) C. K. Bradsher and T. W. G. Solomons, *J. Amer. Chem. Soc.*, **81**, 2550 (1959); (b) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).

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(6) (a) W. H. Mills and W. J. Pope, *J. Chem. Soc.*, **121**, 946 (1922); (b) A. P. Phillips, *J. Org. Chem.*, **12**, 333 (1947).

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(9) (a) O. Mumm, *Ann.*, **443**, 272 (1925); (b) W. H. Mills and R. Raper, *J. Chem. Soc.*, **127**, 2466 (1925); (c) E. E. P. Hamilton and R. Robinson, *ibid.*, **109**, 1029 (1916); (d) R. Robinson and J. E. Saxton, *ibid.*, 976 (1952); (e) J. W. Armit and R. Robinson, *ibid.*, **121**, 827 (1922); (f) D. O. Holland and J. H. C. Naylor, *ibid.*, 1657 (1955).

TABLE II

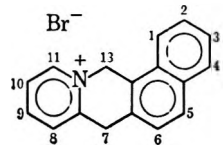
6,11-DIHYDROACRIDIZINIUM SALTS BY CATALYTIC REDUCTION

Compd	R_1	R_2	R_3	X	Yield,[a] %	Mp, °C	λ_{max},[b] mμ (log ε)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	H	H	H	Br[c]	57	188.5–192	262 (3.71)	$C_{13}H_{12}BrN$	59.56	4.61	5.34	59.42	4.56	5.37
	H	H	H	ClO_4[d]		218–223		$C_{13}H_{12}ClNO_4$	55.43	4.29	4.97	55.43	4.30	4.92
2	H	H	CH_3	Br[e]	53	205–210		$C_{14}H_{14}BrN$	60.88	5.11	5.07	60.75	5.19	4.81
	H	H	CH_3	ClO_4[e]		177–179	264 (3.79)	$C_{14}H_{14}ClNO_4$	56.86	4.77	4.74	56.74	4.74	4.59
3	CH_3	H	H	ClO_4[e,f]	27	148–154	265 (3.75)	$C_{14}H_{14}ClNO_4$	56.86	4.77	4.74	56.90	4.88	4.87
4	H	H	C_6H_5	Br[g]	49	192–197		$C_{19}H_{16}BrN \cdot {}^1/_4H_2O$	66.58	4.85	4.08	66.55	4.81	3.87
	H	H	C_6H_5	ClO_4[h]		163–165	267 (3.78)	$C_{19}H_{16}ClNO_4$	63.78	4.51	3.92	63.88	4.62	3.92
5	H	H	$C_6H_5CH_2$	Br[g,i]		123.5–127		$C_{20}H_{18}BrN \cdot H_2O$	64.87	5.44	3.78	64.79	5.40	3.70
	H	H	$C_6H_5CH_2$	ClO_4[a]	7	165–167	267 (3.78)	$C_{20}H_{18}ClNO_4$	64.60	4.88	3.77	64.40	4.88	3.93

[a] Obtained by reduction of the corresponding acridizinium compound. [b] Determined in 95% ethanol. [c] Recrystallized from methanol–ethyl acetate. [d] Recrystallized from methanol. [e] Recrystallized from water. [f] Reduction carried out on bromide, but product isolated as perchlorate. [g] Recrystallized from absolute ethanol–ethyl acetate. [h] Recrystallized from absolute ethanol. [i] Obtained from the perchlorate by ion exchange.

Benzylation of 11-methyl-6H-acridizine (9) occurs more readily (50% yield) than it does for parent compound 8, and likewise occurs at position 11 affording 6. Methylation of 9 yielding 7 has likewise been accomplished. Methylation of the parent acridizine (8) appeared to give an inseparable mixture.

The selective reduction was extended to benz[*h*]-acridizinium bromide[10] which absorbed 1 mol of



12

hydrogen to afford what uv and nmr evidence indicate to be the 7,13-dihydro derivative (12).

Experimental Section

Analyses were carried out by Janssen Pharmaceutica, Beerse, Belgium, except as noted. The melting points were determined in capillary tubes using the Laboratory Devices Mel-Temp apparatus and are uncorrected. The ultraviolet absorption spectra were measured in 95% ethanol using a Beckman Model DB spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 nmr spectrophotometer using tetramethylsilane as a standard. Infrared spectra were obtained on a Perkin-Elmer 137 Infracord spectrophotometer using potassium bromide pellets.

Hydrogenation of Acridizinium Salts. 6,11-Dihydroacridizinium (1) Bromide.—To a suspension of 9.75 g of acridizinium bromide in 75 ml of 95% ethanol, was added 2.5 g of 10% palladium on charcoal. Themi xture was stirred under 1 atm of hydrogen. After *ca.* 20 min, 975 ml (theoretical, 925 ml) of hydrogen had been absorbed and the rate of hydrogen absorption decreased sharply. The solution was filtered and concentrated and the residual oil crystallized by addition of acetone. Recrystallization from methanol–ethyl acetate afforded 5.60 g (57%) of colorless hygroscopic crystals, mp 187–192°. The results of this and related experiments are summarized in Table II. In some of the reduction experiments there was no noticeable change in rate of hydrogenation and the experiment was simply discontinued after slightly more than 1 molar equiv had been absorbed.

11-Benzyl-6,11-dihydroacridizinium (5) Perchlorate by Alkylation.—To a solution of 2 g of 6,11-dihydroacridizinium bromide in 40 ml of water, 8 ml of 5% sodium hydroxide was added. The red precipitate which formed was collected, washed with large amounts of water, and allowed to remain on the reaction filter (with air passing through) until dry to yield 1.30 g (94%). The crude acridizine did not have a melting point, but darkened above 60°, and turned from red to yellow-brown simply on standing; the λ_{max} signals were at 238 mμ (log ε 3.98), 259 sh (3.91), 412 (3.47). This crude acridizine did not give satisfactory elemental analyses, but was pure enough for the alkylation experiment.

A suspension of 1.53 g of the crude acridizine (8) in 10 ml of ice cold benzyl chloride was swirled until the solid become dark and tarry. The supernatant liquid was decanted and the tarry mass dissolved in a few milliliters of ethanol. A few drops of 25% perchloric acid was added and the mixture allowed to stand for 1 week. The resulting crystals were recrystallized from ethanol. A further precipitate from the decanted benzyl chloride was purified in the same way affording a total yield of 0.73 g (21%).

This material had the identical infrared absorption spectrum and did not depress the melting point of the benzyldihydroacridizinium perchlorate obtained *via* reduction of the 11-benzylacridizinium salt (Table II).

11-Methylacridizine (9).—This compound was prepared in the same manner as acridizine (8) except that 2%, rather than 5%, sodium hydroxide solution was used. The purple product appeared to be less stable than 8 immediately after filtration and inadequate washing with water resulted in rapid decomposition. From 0.50 g of 11-methyl-6,11-dihydroacridizinium bromide 0.26 g (74%) of 9 was obtained. No solvent was found from which it could be recrystallized. The analytical sample was prepared from very pure starting material, was washed well with water, and was analyzed[11] as soon as it was dry; the λ_{max} signals were at 243 mμ (log ε 4.31), 240 (4.29), 363 (3.64), 382 (3.68), 402 (3.56).

Anal. Calcd for $C_{14}H_{13}N \cdot {}^1/_2H_2O$: C, 82.32; H, 6.90; N, 6.86. Found: C, 82.54; H, 6.69; N, 6.66.

11-Benzyl-11-methyl-6,11-dihydroacridizinium (6) Bromide.—Powdered 11-methylacridizine (0.6 g) was added with swirling to 3 ml of ice-cold benzyl bromide. A white precipitate formed which was collected by filtration and washed with acetone. After one recrystallization from methanol–ethyl acetate there was obtained 0.52 g (50%) of colorless crystals, mp 220.5–222°. The analytical sample melted at 223–225°, λ_{max} 266 mμ (log ε 3.77).

Anal. Calcd for $C_{21}H_{20}BrN$: C, 68.86; H, 5.50; N, 3.82. Found: C, 68.90; H, 5.55; N, 3.71.

11,11-Dimethyl-6,11-dihydroacridizinium (7) Perchlorate.—Powdered 11-methylacridizine (9, 0.68 g) was added with swirling to 3 ml of methyl iodide over a period of 3 min. The precipitate (0.41 g) which formed was collected by filtration and washed with acetone. The crude product was converted into the perchlorate salt by dissolving in water and treating with silver nitrate solution, then hydrobromic acid (to remove excess silver ion), and finally with excess perchloric acid. On cooling, 0.17 g (17%) of crystals formed, mp 192–195°. An analytical sample, mp 196–197°, was obtained by recrystallization from water, λ_{max}, 264 mμ (log ε 3.78).

Anal. Calcd for $C_{15}H_{16}ClNO_4$: C, 58.16; H, 5.21; N, 4.57. Found: C, 58.40; H, 5.25; N, 4.52.

11-Benzylacridizinium Perchlorate.—A mixture containing 8 g (0.04 mol) of 2-pyridyl benzyl ketone, 8 g (0.12 mol) of ethylene glycol, 3.2 g of *p*-toluenesulfonic acid, and 160 ml of benzene was heated under reflux for 72 hr in an apparatus provided with

(10) C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.*, **78**, 2459 (1956).

(11) Analysis was by Triangle Chemical Laboratories, Chapel Hill, N. C.

a modified Dean–Stark water separator. The mixture was poured into 10% sodium carbonate solution and the benzene layer separated. The aqueous layer was extracted several times with benzene. The combined benzene layers were washed with water and dried over sodium sulfate. The solvent was removed leaving 6.5 g of oil, presumably 2-(2-benzyl[1.3]dioxolan-2-yl)pyridine. To the crude product was added 4.3 g of benzyl bromide and 2 ml of tetramethylenesulfone. The mixture was kept at 50° for 4 days and the resulting viscous oil was washed with ethyl acetate and placed in 110 g of polyphosphoric acid. The mixture was heated at 115° for 12 hr, then poured on 110 g of ice. When the ice had melted, 100 ml of water was added and the mixture was heated on a steam bath for 4 hr. The solution was treated with charcoal and after cooling 25% perchloric acid was added until precipitation was complete. The gray-green precipitate was collected and recrystallized (charcoal) twice from absolute ethanol to yield 0.66 (5%) of yellow-green crystals, mp 215–223°. An analytical sample melted at 218–223°; the λ_{max} signals were at 242 mμ (log ε 4.45), 250 (4.46), 366 (3.82), 382 (3.83), 404 (3.78).

Anal. Calcd for $C_{20}H_{16}ClNO_4$: C, 64.95; H, 4.36; N, 3.79. Found: C, 64.86; H, 4.41; N, 3.90.

7,13-Dihydrobenz[*h*]acridizinium (12) Bromide.—The reduction of benz[*h*]acridizinium bromide[10] was carried out in 37% yield essentially as in the hydrogenation of acridizinium bromide. The product was colorless: mp 240–258°; λ_{max} 267 mμ (log ε 4.04); nmr (D_2O), δ 4.28 (S, 2, CH_2, C-7), 5.40 (S, 2, CH_2, C-13).

Anal. Calcd for $C_{17}H_{14}BrN$: C, 65.40; H, 4.52; N, 4.49. Found: C, 65.12; H, 4.50; N, 4.44.

The perchlorate had mp 167.5–171°.

Anal. Calcd for $C_{17}H_{14}ClNO_4$: C, 61.54; H, 4.25; N, 4.22. Found: C, 61.31; H, 4.19; N, 4.19.

Registry No.—**1**, X = Br, 15757-24-1; **1**, X = ClO_4, 15815-87-9; **2**, X = Br, 15757-25-2; **2**, X = ClO_4, 15815-88-0; **3**, X = ClO_4, 15815-89-1; **4**, X = Br, 15757-26-3; **4**, X = ClO_4, 15815-90-4; **5**, X = Br, 15757-27-4; **5**, X = ClO_4, 15892-89-4; **6**, X = Br, 15757-28-5; **7**, X = ClO_4, 15815-91-5; **8**, 260-61-7; **9**, 15815-92-6; **12**, X = Br, 15757-29-6; **12**, X = ClO_4, 15815-93-7; 11-benzylacridizinium perchlorate, 15815-94-8.

Acknowledgment.—We wish to thank Dr. Alan Fozard for the suggestion of this problem as well as for helpful discussions during the course of the work.

Alkylation of Alkali Metal Salts of Pyrrole with Allyl and *n*-Propyl Tosylate

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In the course of a study of the factors affecting the position of alkylation of ambident anions, the reaction of alkali metal salts of pyrrole with allyl tosylate was investigated to evaluate the effectiveness of the latter as an alkylating agent.

The product of this reaction was a mixture of the isomeric allylpyrroles and higher boiling compounds which are presumed to be diallylpyrroles. In general, the composition of the product paralleled the one observed earlier in the reaction of alkali metal salts of pyrrole with allyl bromide.[1] In the present work, however, the N/C alkylation ratios, expressed in terms of the relative percentages of 1-, 2-, and 3-allylpyrrole, were considerably higher (Table I). It should be noted that the actual amount of carbon alkylation is higher than these numbers indicate, because of the further reaction of part of the initially formed 2- and 3-allylpyrrole to yield diallylpyrroles.[1,2] Nonetheless, there is a significant difference in selectivity between the two alkylating reagents allyl tosylate and allyl bromide.

TABLE I

REACTIONS OF PYRROLYLMETAL SALTS WITH ALLYL TOSYLATE AND ALLYL BROMIDE AT 65°

		Relative %					
		1-Allyl-pyrrole		2-Allyl-pyrrole		3-Allyl-pyrrole	
Cation	Solvent	*a*	*b*	*a*	*b*	*a*	*b*
K^+	Dimethyl sulfoxide	99	89	0.50	8.0	0.50	3.0
K^+	Tetrahydrofuran	86	80	11	18	3.0	2.0
K^+	Benzene	66	14	25	80	9.0	6.0
Na^+	Tetrahydrofuran	30	19	54	77	16	4.0
Na^+	Tetrahydrofuran (inverse addition)	72	36	22	58	6.0	6.0
Li^+	Tetrahydrofuran	24	1.0	59	90	17	9.0

[a] Reaction with allyl tosylate. [b] Reaction with allyl bromide (see ref 1 and 11).

The effect of the leaving group on the position of alkylation of ambident anions has been studied in relatively few cases and seems to vary. Thus, a change in the leaving group from Cl^- to Br^- to I^- has been reported to have no effect on product composition in the reaction of the sodium salt of 2,6-dimethylphenol with allyl and benzyl halides.[3] Similarly, no effect has been observed in the reaction of the lithium salt of 2-nitropropane with benzyl halides in dimethylformamide.[4] On the other hand, the same change in the leaving group has been found to decrease the yield of O-alkylated product in the reaction of the potassium, or sodium salt of ethyl acetoacetate with alkyl halides in dimethylformamide,[5] or dimethyl sulfoxide,[6] and in the reaction of the sodium salt of 2-carbethoxycoumaran-3-one with benzyl and *m*-nitrobenzyl halides in dimethylformamide.[7] In the same way, a change from Br^- to I^- causes a decrease in N alkylation in the reaction of the sodium salt of indole with alkyl halides.[2]

Tables I and II show that a change to more polar solvents increased the N/C alkylation ratio in the reaction of pyrrolylpotassium with allyl tosylate. This trend is in agreement with previous observations that aprotic solvents of higher ability to solvate cations favor

TABLE II

EFFECT OF TEMPERATURE ON THE REACTION OF PYRROLYLPOTASSIUM WITH ALLYL TOSYLATE

		Relative %		
Solvent	Temp, °C	1-Allyl-pyrrole	2-Allyl-pyrrole	3-Allyl-pyrrole
Dioxane	50	82	13	5.0
Dioxane	75	86	11	3.0
Dioxane	100	89	9.0	2.0
Toluene	50	47	37	16
Toluene	75	53	33	14
Toluene	100	62	25	13

(1) C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **84**, 43 (1962).

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(4) N. Kornblum, P. Pink, and K. V. Yorka, *ibid.*, **83**, 2779 (1961).

(5) G. Brieger and W. M. Pelletier, *Tetrahedron Lett.*, 3555 (1965).

(6) W. J. LeNoble and J. E. Puerta, *ibid.*, 1087 (1966).

(7) N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Amer. Chem. Soc.*, **88**, 5660 (1966).

substitution at the more electronegative atom of the ambident anion.[1-3,8,9]

In the case of pyrrolylsodium, which is readily soluble in tetrahydrofuran, slow addition of a solution of the salt to a solution of the alkylating agent (inverse addition) increased markedly the relative amount of N-alkylated product in the present reaction with allyl tosylate, just as in the previously reported reaction with allyl bromide.[1]

When reactions were run in the same solvent (Table I, tetrahydrofuran), the position of substitution of the pyrrolyl anion was affected by the nature of the cation, in agreement with the findings that in aprotic solvents of low dielectric constant the proportion of alkylation at the more electronegative atom of the ambident anion increases as the cation is changed from Li^+ to Na^+ to K^+.[1,3,8,9] In this connection the fact should be noted that pyrrolylmagnesium halides are alkylated almost exclusively on carbon.[10]

Table II shows that in the treatment of pyrrolylpotassium with allyl tosylate an increase in the reaction temperature caused a small (dioxane) to moderate (toluene) increase of the relative percentage of N alkylation. The effect of temperature on the position of alkylation of ambident anions is not uniform. There was no clear-cut effect in the reaction of pyrrolylpotassium with allyl bromide,[11] but increased C alkylation was observed at a higher temperature with crotyl and benzyl halides.[1] A temperature increase has been reported to favor O alkylation of sodio-2-carbethoxycyclanones with isopropyl iodide in dimethyl sulfoxide,[12] O alkylation of ethyl acetoacetate with *n*-butyl chloride, and potassium carbonate in dimethyl sulfoxide, but C alkylation when the last reaction is run in N-methylpyrrolidine.[5]

The higher relative percentage of N-alkylated product generally obtained when *n*-propyl tosylate was substituted for allyl tosylate as the alkylating agent (Table III) is consistent with the greater selectivity of saturated alkyl halides, compared with allyl halides, in alkylating pyrrolylmetal salts[1] and indolylsodium[2] predominantly on the nitrogen atom, and salts of phenols,[3] or ethyl acetoacetate[6] predominantly on the oxygen atom. The effect of the cation on product composition is again significant in this case (Table III), as in the case with allyl tosylate (Table I).

TABLE III

REACTIONS OF PYRROLYLMETAL SALTS WITH *n*-PROPYL TOSYLATE AT 65°

Cation	Solvent	Relative %: 1-*n*-Propylpyrrole	2-*n*-Propylpyrrole	3-*n*-Propylpyrrole
K^+	Tetrahydrofuran	97	2.5	0.50
K^+	Benzene	95	4.0	1.0
Na^+	Tetrahydrofuran	65	32	3.0
Li^+	Tetrahydrofuran	25	70	5.0

(8) D. Y. Curtin and D. H. Dybvig, *J. Amer. Chem. Soc.*, **84**, 225 (1962).
(9) N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85**, 1148 (1963).
(10) (a) P. S. Skell and G. P. Bean, *ibid.*, **84**, 4655 (1962); (b) C. E. Griffin and R. Obrycki, *J. Org. Chem.*, **29**, 3090 (1964); (c) A. J. Castro, J. F. Deck, N. C. Ling, J. P. Marsh, Jr., and G. E. Means, *ibid.*, **30**, 344 (1965).
(11) E. P. Papadopoulos, Ph.D. Thesis, University of Kansas, Lawrence, Kan., 1961; *Dissertation Abstr.*, **22**, 3858 (1962).
(12) S. J. Rhoads and R. W. Hasbrouck, *Tetrahedron*, **22**, 3557 (1966).

Experimental Section

The reactions were run under nitrogen at 65° for 8 hr, and the products were analyzed by gas–liquid partition chromatography. A 275-cm column packed with Chromosorb W 60/80, containing 20% silicone oil was used in a model 154 Perkin-Elmer vapor fractometer with helium as the carrier gas. Bromobenzene was the internal standard, and the peak areas were measured with a planimeter.

Procedure.—To a solution of 0.25 mol of pyrrole in 100 ml of dry solvent,[13] 0.20 g-atom of potassium[14] was added and the mixture was refluxed with stirring until completion of the reaction. After addition of 100 ml of solvent, the temperature was adjusted to the desired value, and 0.20 mol of the alkyl tosylate,[15] dissolved in 100 ml of solvent, was added dropwise over a period of 1 hr.[16] The reaction mixture was stirred at constant temperature for a further 8 hr; then it was cooled to room temperature and filtered. After the solid material had been washed with ether, it was dissolved in 100 ml of water, and the aqueous solution was extracted with ether. The combined filtrate, ether washings, and extracts were then dried over anhydrous magnesium sulfate. After removal of the solvents by distillation under reduced pressure, the residue was analyzed by gas–liquid partition chromatography.

Registry No.—Allyl tosylate, 4873-09-0; *n*-propyl tosylate, 599-91-7; pyrrolylpotassium, 16199-06-7.

Acknowledgments.—We gratefully acknowledge the support of this work by a grant from the Arts and Sciences Research Committee of the American University of Beirut. We also thank Professor C. H. Issidorides for his help with the manuscript.

(13) For the reactions run in dimethyl sulfoxide, pyrrolylpotassium was prepared in tetrahydrofuran. This solvent was subsequently removed by distillation under reduced pressure and replaced by dimethyl sulfoxide.
(14) Sodium hydride and lithium hydride were used for the preparation of the corresponding salts of pyrrole.
(15) Z. Foldi, *Chem. Ber.*, **53**, 1836 (1920).
(16) In the inverse addition reaction, a solution of 0.20 mol of pyrrolylsodium in 200 ml of tetrahydrofuran was added dropwise, over a period of 4 hr, to 0.20 mol of allyl tosylate dissolved in 100 ml of tetrahydrofuran, at 65°.

The Benzene–Resorcinol–Phthaleinanhydride of v. Pechmann

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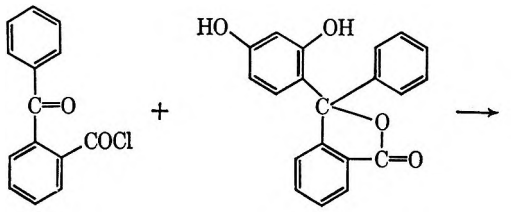
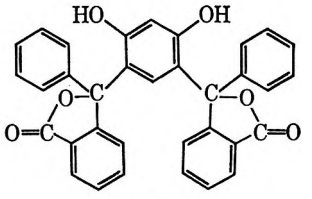
On heating *o*-benzoylbenzoic acid with resorcinol in sulfuric–acetic acid, v. Pechmann[1] obtained a compound of unestablished structure which he named benzene–resorcinol–phthaleinanhydride. This same compound (I) also resulted from the reaction of *o*-benzoylbenzoic acid with resorcinol in the presence of anhydrous zinc chloride.[2]

In this Note it is shown that I can also be obtained in high yields from 2 mol of *o*-benzoylbenzoyl chloride (II) and 1 mol of resorcinol by the method of Blicke[3] and in 94% yield and high purity in the reaction of equimolar quantities of II with 3-phenyl-3-(2,4-dihydroxyphenyl)-phthalide (III).

(1) H. v. Pechmann, *Ber.*, **14**, 1862 (1881).
(2) M. H. Hubacher, *J. Org. Chem.*, **23**, 1400 (1958).
(3) F. F. Blicke and R. D. Swishers, *J. Amer. Chem. Soc.*, **56**, 923 (1934).



II III



I

On caustic fusion of I, 2,4-dihydroxybenzophenone, benzoic acid, and 4,6-dihydroxyisophthalic acid were obtained. Thus the structure of I is undoubtedly that of 4,6-bis(3-phenylphthalidyl)resorcinol, belonging to a class of compounds for which the name of diphthalein is suggested.

Orndorff and Murray[4] obtained two phthaleins in the reaction of 2-(4-hydroxybenzoyl)benzoic acid with resorcinol, which they believed to be isomers. Two phthaleins were also obtained in this laboratory from II and hydroquinone and from II and pyrogallol. It is quite possible that on reinvestigation one of each pair of compounds will be found to be a diphthalein.

Experimental Section[5]

Preparation of I. A. From II and Resorcinol.—To a solution of II, prepared from 45.2 g of *o*-benzoylbenzoic acid and 30 g of thionyl chloride, in 250 ml of benzene was added 11.0 g of powdered resorcinol. The suspension was heated to 80–85° for 4 hr. A fine, gray precipitate formed with the evolution of HCl. The mixture was filtered the next day and the cake washed with 50 ml of benzene and with six portions of 60 ml of ethanol, leaving 40.5–43.1 g (77–82%) of I, mp 278–290°.

B. From II and III.—To II, prepared from 22.6 g of *o*-benzoylbenzoic acid and 15 g of thionyl chloride, in 170 ml of benzene, was added 31.8 g of III,[2] mp 199–200°. The mixture was slowly heated to 80°, yielding 49.4 g (94%) of I, mp 290–292°.

I (1 g) required 650 ml of acetic acid or 2 l. of ethanol for recrystallization. The crystals from acetic acid sintered with gas evolution at 227–235°, solidified, and remelted at 292–294°.

Crystals from acetic acid, dried at 20–25°, were analyzed. *Anal.* Calcd for $C_{34}H_{22}O_6 \cdot CH_3COOH \cdot H_2O$: C, 71.46; H, 4.67. Found: C, 71.26; H, 5.03.

After being dried under vacuum at 230–235°, I was again analyzed. *Anal.* Calcd for $C_{34}H_{22}O_6$: C, 77.56; H, 4.21. Found: C, 77.20; H, 4.14.

A solution of 16 mg of I in 50 ml of 0.1 *N* sodium hydroxide is of strong reddish orange color.

Alkaline Degradation of I. A.—A solution of 10 g of I in 30 ml of 2.5 *N* sodium hydroxide was kept for 3 weeks over nitrogen, then acidified, yielding 5.19 g of *o*-benzoylbenzoic acid and 1.3 g of resorcinol.

B.—A solution of 10 g of I in 100 ml of 0.1 *N* sodium hydroxide was refluxed for 30 min, yielding 5.9 g of *o*-benzoylbenzoic acid and 1.1 g of resorcinol.

C.—I (10 g) was added to 50 g of molten potassium hydroxide at 240–245°. The melt was stirred for 10 min, then cooled, and dissolved in water. The solution yielded 4.77 g of benzoic acid, 0.67 g of 2,4-dihydroxybenzophenone (mp 142–143°), and two nonsublimable acids, which were separated from each other by fractional crystallization from 50% acetic acid. One melted at 236.2–237.3° dec and the other at 298–300° dec. The latter proved to be 4,6-dihydroxyisophthalic acid, which when treated with diazomethane yielded the dimethyl 4,6-dimethoxyisophthalate, mp 145.0–147.5°, after sublimation under high vacuum and subsequent crystallization from methanol, and did not depress the melting point of authentic dimethyl 4,6-dimethoxyisophthalate,[6] mp 147.8–148.3°.

Diacetyl Derivative of I.—A mixture of 2.63 g of I, 10 ml of acetic acid, 5 ml of acetic anhydride, and 1 drop of concentrated sulfuric acid was refluxed for 1 hr. The mixture was poured on ice and the precipitate crystallized from ethanol (1 g in 100 ml). This diacetyl derivative melted at 253.0–256.3° (lit.[1] mp 245°). *Anal.* Calcd for $C_{38}H_{26}O_8$: C, 74.74; H, 4.29; mol wt, 611; $2CH_3CO$, 14.1. Found: C, 74.64; H, 4.24; mol wt, 606 ± 28 (Rast); CH_3CO, 13.8 (lit.[1] C, 74.9, H, 4.3).

Dr. David N. Kendall reported on the infrared spectrum of compound I, scanned as Nujol and hexachlorobutadiene mulls: "An absorption band is observed at 893 cm^{-1}, which is believed to arise from 1,2,4,5-tetrasubstituted benzene. Monosubstituted benzene absorptions are present at 695 and 749 cm^{-1} and *ortho*-disubstituted benzene absorption at 765 cm^{-1}. Compound I shows ketone carbonyl absorption of a γ-lactone with α,β-unsaturation at 1721 cm^{-1}; aromatic hydroxyl at 3205, 1383, and 1292 cm^{-1}; aromatic C=C at 1610, 1597, 1517, and 1490 cm^{-1}; and C–O–C of the C–O–C=O grouping at 1259 cm^{-1}. The infrared spectra of I and the known compound III are very similar in the 5000–1250-cm^{-1} region."

Registry No.—I, 15791-04-5.

(4) W. R. Orndorff and R. R. Murray, *J. Amer. Chem. Soc.*, **39**, 683 (1917).
(5) All melting points are corrected.
(6) F. v. Hemmelmayr, *Monatsh. Chem.*, **38**, 87 (1917); E. Spaeth, *et al.*, *Ber.*, **64**, 2211 (1931).

The Acetate-Catalyzed Enolization of 2-Butanone

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Recently, several papers have appeared on the relative rates of enolization at the two sites of simple unsymmetrical ketones, studied by deuterium exchange and nmr techniques.[1-8] Generally, the results obtained by different workers are in agreement, but our results[1] and those of Rappe,[4,5] on the enolization of 2-butanone differ in two important respects. We find that the relative rates for base-catalyzed enolization at the methylene and α-methyl positions are *different* for different bases and that the rate of exchange in the absence of catalyst is negligible. Rappe finds the relative rates *the same* for different bases and an appreciable rate for the so-called uncatalyzed reaction. Because of this, we have recently studied the uncatalyzed and acetate-catalyzed reactions again and have redetermined the acetate catalysis constants using the buffer method suggested by Bell.[9] Our previous method involved the extraction of catalytic constants for acetate from over-all rate data by an extrapolation technique.[1]

(1) (a) J. Warkentin and O. S. Tee, *Chem. Commun.*, **7**, 190 (1966); (b) J. Warkentin and O. S. Tee, *J. Amer. Chem. Soc.*, **88**, 5540 (1966).
(2) C. Rappe, *Acta. Chem. Scand.*, **20**, 376 (1966).
(3) C. Rappe, *ibid.*, **20**, 1721 (1966).
(4) C. Rappe, *ibid.*, **20**, 2236 (1966).
(5) C. Rappe, *ibid.*, **20**, 2305 (1966).
(6) C. Rappe, *ibid.*, **21**, 857 (1967).
(7) A. A. Bothner-By and Colette Sun, *J. Org. Chem.*, **32**, 492 (1966).
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(9) R. P. Bell and P. Jones, *J. Chem. Soc.*, 88 (1953).

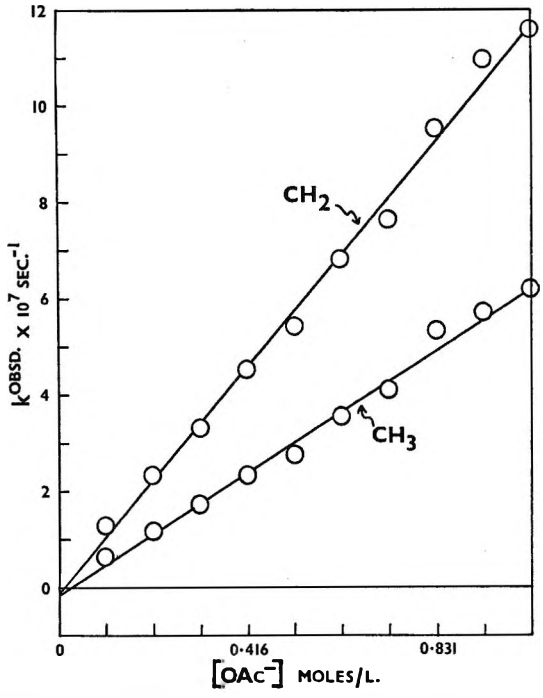

Figure 1.—Plot of observed pseudo-first-order rate constants against acetate concentration for H–D exchange of 2-butanone; buffer ratio 0.0936.

The observed rate constant for reaction in acetate buffers can be represented as a sum of terms (eq 1).

$$k^{obsd} = k_o + k_{D_3O^+}[D_3O^+] + k_{OD^-}[OD^-] + k_A[DOAc] + k_p[OAc^-] + k_p[DOAc][OAc^-] \quad (1)$$

In a buffer solution, the pD and hence $[D_3O^+]$ and $[OD^-]$ remain constant upon dilution. Consequently, as [DOAc] and $[OAc^-]$ are varied at constant buffer ratio, the first three terms in eq 1 remain constant. Writing r = buffer ratio = $[DOAc]/[OAc^-]$, and assuming k_p to be small[9] in comparison with k_A and k_B, eq 1 reduces to eq 2.

$$k^{obsd} = k' + (k_A r + k_B)[OAc^-] \quad (2)$$

If k_p is negligible, as assumed, a plot of k^{obsd} *vs.* $[OAc^-]$ will be linear, with slope $(k_A r + k_B)$ and intercept k'. The acetic acid concentration was kept low to emphasize the base-catalyzed reaction, and, because k_A is smaller than k_B,[8] the important contributor to the slope was expected to be k_B. However, both k_A and k_B can be obtained in principle by varying the buffer ratio r, and this was done. If k_p is not negligible, relative to the other terms, curved plots should result.

Our results, obtained as described in the Experimental Section, are given in Table I, and k^{obsd} *vs.* $[OAc^-]$ for one buffer ratio is plotted in Figure 1.

The catalytic constants for acetate at 54.8°, obtained from the slopes of the graphs, are given in Table II.

The errors involved in kinetic measurements by nmr are not low. In common with Bothner-By and Sun[7] we found individual integrations varying by as much as 10%, and as the integral areas decrease the error in them increases. Nevertheless, we feel that we can draw the following conclusions with a high degree of confidence.

1. The plots are straight lines. Therefore, there is no detectable contribution from the product term $[OAc^-][DOAc]$.

Table I

Pseudo-First-Order Rate Constants for H–D Exchange of 2-Butanone in Deuterium Oxide Acetate Buffer at 54.8°

Buffer ratio, HA/A$^-$	Acetate concn, *M*	$k^{obsd} \times 10^7$ sec^{-1} CH$_2$	CH$_3$
0.0936	1.039	11.60 ± 0.29	6.22 ± 0.09
0.0936	0.935	10.97 ± 0.30	5.74 ± 0.11
0.0936	0.831	9.54 ± 0.20	5.37 ± 0.11
0.0936	0.727	7.67 ± 0.19	4.10 ± 0.05
0.0936	0.623	6.82 ± 0.15	3.55 ± 0.06
0.0936	0.520	5.46 ± 0.10	2.78 ± 0.04
0.0936	0.416	4.58 ± 0.11	2.36 ± 0.03
0.0936	0.312	3.31 ± 0.08	1.72 ± 0.02
0.0936	0.208	2.37 ± 0.07	1.20 ± 0.02
0.0936	0.104	1.31 ± 0.07	0.65 ± 0.04
0.0469	1.039	11.52 ± 0.35	6.09 ± 0.14
0.0469	0.935	9.53 ± 0.18	5.19 ± 0.10
0.0469	0.831	11.03 ± 0.33	4.79 ± 0.14
0.0469	0.727	9.35 ± 0.61	4.27 ± 0.15
0.0469	0.623	6.56 ± 0.18	3.57 ± 0.05
0.0469	0.520	5.97 ± 0.60	3.47 ± 0.10
0.0469	0.416	4.23 ± 0.11	2.20 ± 0.03
0.0469	0.312	3.37 ± 0.09	1.76 ± 0.03
0.0469	0.208	2.15 ± 0.08	1.23 ± 0.02
0.0469	0.104	1.31 ± 0.18	0.36 ± 0.15

Table II

Acetate Catalysis Constants k_B, at 54.8°, for the H–D Exchange of 2-Butanone

	$k_B \times 10^7$ l. m^{-1} sec^{-1} CH$_2$[a]	CH$_3$[a]	Ratio k_{CH_2}/k_{CH_3}[a]	$2k_{CH_2}/3k_{CH_3}$[b]
Buffer ratio 0.0936	11.40 ± 0.31	6.19 ± 0.22	1.84 ± 0.12	1.23 ± 0.08
Buffer ratio 0.0469	11.54 ± 0.88	5.88 ± 0.23	1.96 ± 0.23	1.31 ± 0.15
Average	11.47 ± 0.59	6.03 ± 0.22	1.90 ± 0.17	1.27 ± 0.11
Previous results[c]	11.8 ± 0.5	5.47 ± 0.70	2.16 ± 0.36	1.44 ± 0.24

[a] Reactivity is defined on the *per hydrogen* basis, as was done previously.[1] [b] Relative reactivity on the *per group* basis. These ratios are labeled K_D by Rappe.[4] [c] See ref 1.

2. Within the limits of experimental error the plots go through the origin. Therefore, under our conditions, catalysis by D_2O, D_3O^+, or OD^- is not detectable relative to catalysis by OAc^-.

3. The catalytic constants for acetate at 54.8° are the same, within the limits of experimental error, as those previously obtained by our extrapolation technique[1] (see Table II).

4. The results for the two buffer ratios are the same, within the limits of error (Table II). This means that catalysis by acetic acid (the term k_A[DOAc]) is negligible relative to acetate catalysis and that the slopes of the graphs (Figure 1) may be taken to represent acetate catalysis alone.

For comparison purposes, the ratio k_{CH_2}/k_{CH_3} for deuterioxide catalysis was also measured at 54.8°. Two measurements gave for k_{CH_2}/k_{CH_3} 0.88 ± 0.05 and 0.84 ± 0.08. These values are very different from the rate ratio for acetate catalysis (1.9) measured at the same temperature. Also, on comparison with the value of about 1.0 previously obtained for catalysis by OD^- at 0°, it appears that the activation energy for exchange at the methyl group exceeds that for exchange at the methylene group, at least for deuterioxide catalysis. Work is currently under way to obtain activation parameters for both processes accurately.

In order to try to obtain values for the rate constants of the uncatalyzed reaction, a sample of 2-butanone in

0.1 M NaCl–D_2O was maintained at 54.8° and integrated with the others. After 2 months no sign of exchange was observed—the nmr peaks were still sharp and unsplit,[10,11] and the integral values were unchanged from the original. We were, therefore, unable to obtain rate constants for the uncatalyzed reaction. This contrasts with Rappe's findings,[4,5] which were that, after "several months" at 30°, exchange could be observed. After 2 months at nearly double this temperature we could observe none. This finding is in accord with our previous estimate[1] that the uncatalyzed reaction would contribute 1% or less to the total reaction at 60°, with acetate concentrations in D_2O of 0.1 M or more. In support also is Hine's recent estimate[8] that the uncatalyzed deuteration of methoxyacetone would contribute a maximum value of 0.2% of the total to base-catalyzed reaction rates, under a wide variety of conditions. It is likely that a high rate of "uncatalyzed exchange," where observed, is really the result of catalysis by unrecognized impurities.

We believe that this work firmly establishes the dependence of relative catalytic constants (k_{CH_2}/k_{CH_3}), for deuterium exchange into 2-butanone, on the nature of the catalyzing base. Such dependence was to be expected, since enolization is closely analogous to bimolecular elimination, in which product ratios depend on the base employed.[12] The relative importance of the steric requirements of the base and of its strength is not completely understood at this time.[12]

Experimental Section

Reagent grade chemicals were used; acetic acid and 2-butanone being redistilled before use. Sodium acetate was dried at 160° to obtain the anhydrous material. D_2O was used as supplied by the Columbia Organic Chemicals Co. Stock reagent solutions, made up gravimetrically, were two sodium acetate–acetic acid buffer solutions in D_2O, with buffer ratios of 0.0936 and 0.0469; the acetate concentration in each case being about 1.1 M. Aliquots of these solutions were then diluted with a solution of sodium chloride in D_2O of equivalent molarity. By this procedure ten solutions with acetate concentrations varying between about 1.1 and 0.11 M, at a constant buffer ratio of 0.0936 and a constant ionic strength of about 1, were obtained, as well as ten similar solutions at a buffer ratio of 0.0469. Addition of 0.1 ml of 2-butanone to 1 ml of the above solutions resulted in a 2-butanone concentration of 1.18 M, an ionic strength of 1.04, and the acetate concentrations shown in Table I. After mixing, the solutions were sealed into standard nmr tubes which had been cleaned with chromic acid, thoroughly rinsed, and dried.

Samples were immersed in a thermostat at 54.8°, together with a sample containing 2-butanone and 1.04 M sodium chloride, but no acetate. Integrations were performed every 1 or 2 days as necessary, after quenching exchange by chilling the tube with ice. Reaction outside the bath was negligible, and time outside the bath was not counted.

Exchange was followed to at least one half-life by integrating the signals from the 1 and 3 positions, using the β-methyl group as internal standard, on a Varian A-60 instrument.[1,11] Each sample was integrated six times and an average was taken.

The integral from the β-methyl group was taken as internal standard and the areas for the 1 and 3 positions were converted into the average number of hydrogen atoms per molecule remaining at these positions. On plotting the logarithms of these numbers against time, good straight lines were obtained even for exchanges followed to over two half-lives. Each graph contained at least 15 points. A linear least-squares program for the IBM 7040 computer was used to obtain pseudo-first-order rate constants and their standard deviations, and, from these figures, acetate catalysis constants.

For the study of deuterioxide catalysis at 54.8°, a deuterioxide concentration of 1.962×10^{-3} M was used. The probe temperature was set, using the variable-temperature controller, at 54.8 ± 0.5°, and the deuterioxide solution was equilibrated to that temperature by leaving it in the probe for a few minutes. Butanone at the same temperature was then added, after which the tube was shaken and replaced in the probe. Integrations were performed every 150 sec over a 90-min period, which was about one half-life under the reaction conditions. The signal from the nonexchanging β-methyl group was used to normalize integrals (I_t) as described above, and best fits to the equation $\log I_t = k^{obsd}t/2.303$ were computed.

Registry No.—2-Butanone, 78-93-3.

Acknowledgment.—The authors are grateful to the National Research Council of Canada for financial support.

(10) Splitting of the nmr peaks was taken to be a more reliable indication of initial deuterium substitution than change in the integral values. See ref 11 for splitting patterns resulting from varying amounts of substitution.

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Conformational Analysis of the Carbon–Oxygen Bond of Alcohols Using J_{HCOH}

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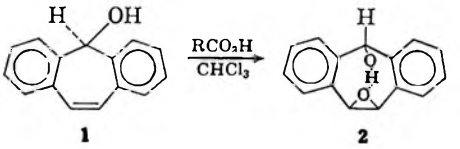
Since the report that J_{HCOH}[1] can often be determined in DMSO solution[2], several papers[3–6] have appeared in which a conformational dependence is invoked for J_{HCOH} similar *in qualitative form* to that observed for J_{HCCH}.[7,8] Unfortunately, it is difficult to restrict rotation about the C–O bond of an alcohol, so that values of J^{trans}_{HCOH} and J^{cis}_{HCOH} have not been available, thus precluding corroboration and quantitative application of this potentially useful conformational probe. We have, quite fortuitously,[9] synthesized an alcohol in which the pertinent rotation is restricted by strong internal hydrogen bond formation and from which a value can be obtained for J^{trans}_{HCOH}.

Epoxidation of **1** by *m*-chloroperbenzoic acid yields **2**; the nmr ($CDCl_3$) spectrum showed signals at τ



1 **2**

2.75 (m, 8 H, aromatics), 4.65 (d, 1 H, J = 12.5 cps, carbinol methine), 5.20 (d, 1 H, J = 12.5 cps, hydroxyl), 5.59 (s, 2 H, methines adjacent to epoxide function). The infrared spectrum has a single,

(1) *I.e.*, the nmr coupling constant of a hydroxyl proton with a vicinal carbinol proton.

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(4) J. J. Uebel and H. W. Goodwin, *J. Org. Chem.*, **31**, 2040 (1966).

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(6) R. J. Ouelette, D. L. Marks and D. Miller *ibid.*, **89**, 913 (1967).

(7) M. Karplus *ibid.*, **85**, 2870 (1963).

(8) Similar conformational dependencies have been found for $J_{^{13}CCCH}$ (G. J. Karabatsos, C. E. Orzech, Jr., and N. Hsi, *ibid.*, **88**, 1817 (1966)) and J_{HCCF} (K. L. Williamson, Y. Li, F. H. Hall, and S. Swager, *ibid.*, **88**, 5679 (1966)).

(9) N. L. Bauld and Y. S. Rim, *ibid.*, **89**, 179 (1967).

somewhat broad, hydroxyl stretch at ν ($CHCl_3$) 3440 cm^{-1} which is unaffected by dilution (no free -OH from 15–1%). Clearly, **2** is exclusively internally hydrogen bonded and must have the assigned *cis* structure. The strength of the hydrogen bond is such that it resists rapid proton exchange in $CDCl_3$, so that J_{HCOH} is observable (12.5 cps). This value is also obtained in CCl_4 and is unaffected by dilution (15–5% $CDCl_3$) or temperature (−60° to ambient). Even DMSO only slightly disrupts the bond. In this solvent J_{HCOH} = 10.7 cps. The addition of several drops of water still does not affect the hydroxyl doublet, but addition of a few drops of acid does eliminate it.

The coupling constants obtained here are more than twice as large as any we have noted in the literature (3.5–5.7 cps[3-6]). It is therefore suggested, and models support this suggestion, that the internal hydrogen bond of **2** effectively locks the O–H bond into a conformation *trans* (ϕ = 180°) to the carbinol methine C–H bond and that, accordingly, J^{trans}_{HCOH} = 12–13 cps.

In contrast to **2**, **1** has J_{HCOH} (DMSO) = 4 cps (no splitting observed in $CDCl_3$). This is a typical HCOH splitting and indicates that the large splitting found for **2** is unrelated to the electronegativity of the adjacent phenyl rings.

The value of J^{trans}_{HCOH} found here is in the range observed for J^{trans}_{HCCH} (sp^3 carbon) (10.5–12.4 cps[10]). The "free rotation" value of J_{HCOH} (3.5–5.7 cps) is apparently a little smaller than that of J_{HCCH} (6–8 cps). It therefore appears that J_{HCOH} (ϕ) and J_{HCCH} (ϕ) are quantitatively comparable.

Registry No.—**1**, 15591-50-1; **2**, 15591-51-2.

Acknowledgment.—We thank the National Science Foundation and the Welch Foundation for support of this work.

(10) A. A. Bothner-by, "Advances in Magnetic Resonances," Vol. I, Academic Press Inc., New York, N. Y., 1965, p 203.

The Preparation and Reactions of Some Stable Dibenzotropylium and Dihydrodibenzotropylium Ions

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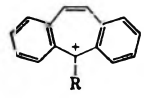
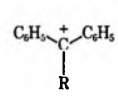
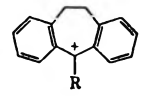
Received August 31, 1967

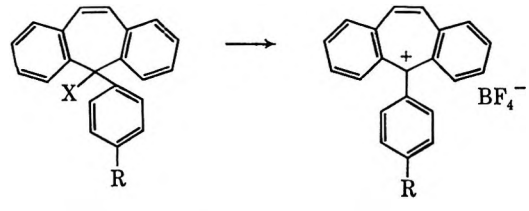
The stability of the dibenzotropylium and some 5-aryldibenzotropylium ions has been determined by measurement of their pK_{R^+} values[1-3] (Table I). These results are noteworthy because the phenyl- and *p*-methoxyphenyl-substituted compounds were less stable than the unsubstituted one. Examination of the pK_{R^+} values of the di- and triphenylmethyl series (Table I) would have predicted the order of stability to be *p*-methoxyphenyl > phenyl > unsubstituted in the dibenzotropylium series. These unexpected results were attributed to steric inhibition of resonance. The dihydrodibenzotropylium ions exhibited the expected order of stability (Table I), the only discrepancy being the large difference in pK_{R^+} between the unsubstituted ion and the diphenylmethyl ion. The values reported in Table I for the dibenzo- and dihydrodibenzotropylium ions have been confirmed in our work.

TABLE I[a]
pK_{A^+} VALUES

R			
H	−3.7	−13.3	−8.0
C_6H_5	−5.8	−6.6	−7.0
	−5.7[b]		−6.7[b]
p-$MeOC_6H_4$	−6.1	−3.4	−4.5

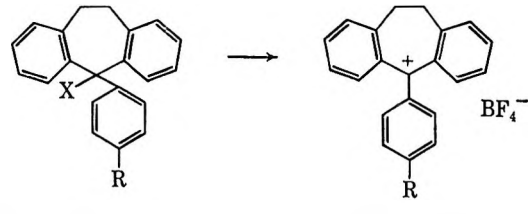
[a] See ref 1. [b] See ref 3.

The purpose of this investigation was to examine the possibility of preparing stable ions of the dibenzotropylium (**2**) and dihydrodibenzotropylium (**4**) types, and study their chemical properties. The ions chosen for examination were those having the *p*-methoxyphenyl (**2a** and **4a**) and *p*-dialkylaminophenyl group (**2b**, **2c**, and **4b**).



1a, R = OMe; X = OH
b, R = NMe_2; X = OH
c, R = OMe; X = H
d, R = OH; X = H
e, R = NMe_2; X = H

2a, R = OMe
b, R = NMe_2
c, R = NEt_2



3a, R = OMe; X = OH
b, R = NMe_2; X = OH
c, R = OMe; X = H
d, R = OH; X = H
e, R = NMe_2; X = H

4a, R = OMe
b, R = NMe_2

The *p*-methoxyphenyldibenzotropylium ion **2a** was isolated as the black fluoroborate in good yield from the corresponding alcohol **1a**, upon treatment with fluoroboric acid. Although it can be stored unchanged in the cold, it is rapidly converted back into the alcohol by atomospheric moisture. Sodium borohydride reduction of **2a** gave ether **1c**, which was identical with material prepared from the *p*-hydroxy compound **1d**. When treated with cycloheptatriene, compound **2a** abstracted a hydride ion and gave the tropylium ion (86%), as would be predicted from the pK_{R^+} values (Table I) of the two ions (tropylium ion pK_{R^+} = +9.9).[4]

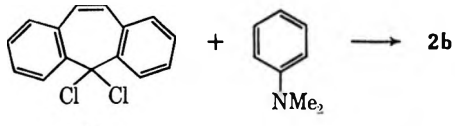
(1) G. Berti and A. DaSettimo, *Ann. Chim.*, **49**, 1237 (1959).
(2) G. Berti, *J. Org. Chem.*, **22**, 230 (1957).
(3) P. Rumpf and R. Reynaud, *Bull. Soc. Chim. Fr.*, **1964**, 558.
(4) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 365.

TABLE II
EXPERIMENTAL DATA FOR NEW COMPOUNDS

Compd	Mp, °C	Yield, %	Recrystn solvent	Molecular formula	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
1b	169–170	28	Ethanol	$C_{23}H_{21}NO$	84.5	6.4	4.3	84.2	6.3	4.3
3b	149–150	79	Ethanol	$C_{23}H_{23}NO$	84.0	7.1	4.3	84.3	7.1	4.3
2a	206 dec	90	None	$C_{22}H_{17}BF_4O$	68.8	4.5		68.4	4.7	
2b	241–242	95	Ethyl acetate–nitromethane	$C_{23}H_{20}BF_4N$	69.5	5.1	3.5	69.4	4.9	3.3
2c	241–243	12	Ethyl acetate–acetonitrile	$C_{25}H_{24}BF_4N$	70.5	5.7	3.3	70.5	5.9	3.6
4a	172–173	90	None	$C_{22}H_{19}BF_4O$	68.4	5.0		68.1	5.1	
4b	255–257	95	Ethyl acetate–nitromethane	$C_{23}H_{22}BF_4N$	69.1	5.6	3.5	69.3	5.7	3.4
1c	138–139	71	Ethanol	$C_{22}H_{18}O$	88.6	6.1		88.3	6.1	
1e	141–142	55	Ethanol	$C_{23}H_{21}N$	88.6	6.8	4.5	88.4	6.7	4.5
3c	103–104	80	Ethanol	$C_{22}H_{20}O$	88.0	6.7		88.3	6.9	
3e	101–102	32	Ethanol	$C_{23}H_{23}N$	88.2	7.4	4.5	87.9	7.3	4.5
3d	154–155	44	Methylcyclohexane	$C_{21}H_{18}O$	88.0	6.3		87.8	6.4	

The yellow dihydro ion **4a** was obtained as the fluoroborate in an analogous manner from alcohol **3a**. It is slowly converted by moisture or aqueous acetonitrile back into the alcohol, and is reduced to ether **3c** by sodium borohydride. This ether was identical with material prepared by methylation of phenol **3d**. Dihydro ion **4a** also afforded the tropylium ion (86%) when treated with cycloheptatriene.

Attention was next turned to the more electron-donating dialkylamino substituent, in the hope of obtaining more stable compounds. A variety of methods were examined for the preparation of the dimethylamino compound **2b**. Treatment of alcohol **1b** with fluoroboric acid gave the expected product in good yield. A second successful method of preparation was condensation of N,N-dimethylaniline with dichloride **5**. The observation that the methoxyl



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group of compound **2a** can be displaced by dimethylamine afforded still a third method, although the yield was low. When diethylamine was used in this procedure, the diethylamino compound **2c** was obtained. The structure of **2b** was established by reduction to amine **1e**, which was prepared independently by condensation of 5-chloro-5H-dibenzo[*a*,*d*]cycloheptene with N,N-dimethylaniline.

The stability of the *p*-alkylaminophenyl compounds **2b** and **2c** is noteworthy, and unexpected from the trend found in Table I. They are quite stable to atmospheric moisture, and the orange color of the ions in acetonitrile persists for days. Since they do not abstract a hydride ion from cycloheptatriene, their pK_{R^+} values must be greater than that of the tropylium ion (+9.9). This stability must mean that the 5-phenyl group can be forced to be nearly coplanar with the dibenzotropylium system by a sufficiently strong electron-donating group, thus overcoming the proposed[1] steric hindrance.

The dihydro system is also markedly stabilized by a *p*-dimethylaminophenyl group. Treatment of alcohol **3b** with fluoroboric acid gave compound **4b**, which is stable to moisture and unreactive toward cycloheptatriene. Its pK_{R^+} value is thus greater than +9.9. Reduction of **4b** with sodium borohydride gave amine **3e**, prepared independently from 5-chloro-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene and N,N-dimethylaniline.

Experimental Section[5]

Preparation of Alcohols.—Compounds **1a** and **3a** were prepared as described,[1] and new alcohols **1b** and **3b** (Table II) were prepared in a similar manner.

Preparation of Carbonium Ion Salts.—The procedure used was that of Dauben, *et al.*,[6] on 0.01 mol of the alcohol (**1a**, **1b**, **3a**, and **3b**). The product was precipitated from solution with ether.

A second method of preparation was by alkylation with dichloride **5**.[7] A mixture of 13 g (0.050 mol) of dichloride **5**, 12 g (0.10 mol) of N,N-dimethylaniline, and 50 ml of 1,2-dimethoxyethane was allowed to stand for 1 hr. The solvent was removed and the residue dissolved in 3% hydrochloric acid. Addition of excess 48% fluoroboric acid caused an oil to separate, which was dissolved in a minimum of propionic anhydride. Addition of ether gave red solid **2b** which was recrystallized from ethyl acetate–nitromethane (8.0 g, 42%).

A third method was displacement of a methoxyl group. A solution of 3.8 g (0.010 mol) of compound **2a** in 10 ml of acetonitrile was treated with diethylamine dropwise until the color disappeared. A 100-ml portion of ether was added and, upon cooling, 1.4 g of solid separated. After recrystallization from acetonitrile–ethyl acetate, 0.5 g (12%) of **2c** was obtained, mp 241–243°.

The use of dimethylamine gave 0.22 g (5%) of compound **2b**.

Reduction of Carbonium Ion Salts.—A 1.0-g portion of the salt was added to a solution of 0.5 g of sodium borohydride in 10 ml of diglyme. The color of the ion disappeared, water was added in excess, and the precipitate was recrystallized from ethanol. Mixture melting points with the materials prepared as described below were not depressed.

Alternate Preparation of Ethers 1c and 3c.—Phenol **1d** was prepared as described,[8] and phenol **3d**, mp 154–155°, was prepared in a similar manner with 5-chloro-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene[9] (44%). Methylation of phenol **1d** with sodium hydride and dimethylsulfate gave ether **1c** (53%), and similar treatment of phenol **3d** gave ether **3c** (73%).

Alternate Preparation of Amines 1e and 3e.—A solution of 1 g of 5-chloro-5H-dibenzo[*a*,*d*]cycloheptene[8] and 2 g of N,N-dimethylaniline in 30 ml of benzene was heated at reflux for 30 min. The solvent was removed and the residue was washed with dilute sodium hydroxide solution before extraction into methylene chloride. The solid obtained upon removal of the solvent was recrystallized from ethanol to give amine **1e** (66%).

Amine **3e** was prepared similarly (53%) from 5-chloro-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene.[9]

Nmr Spectra.—The spectra of compounds **1a–e** contained singlet peaks for the vinyl protons at δ 6.65–6.72 ppm; the tertiary CH peak appeared at 5.25 and 5.30, respectively, in **1c** and

(5) All melting points are uncorrected. The nmr spectra were measured on a Varian Model A-60 instrument in deuteriochloroform.

(6) H. J. Dauben, Jr., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).

(7) J. J. Looker, *ibid.*, **31**, 3599 (1966).

(8) G. Berti, *Gazz. Chim. Ital.*, **87**, 293 (1957).

(9) Aldrich Chemical Co., Milwaukee, Wis.

1e. In the tropylium salts 2a–c, the vinyl proton peaks were merged with the aryl protons. In the dihydro alcohols 3a–b, the $-CH_2CH_2-$ protons were present as multiplets at δ 2.75 and 2.87, respectively; this peak appeared at 2.8–2.9 in 3c–e, and as a singlet at 3.15–3.20 in 4a–b. Signals for aryl protons and alkyl substituents appeared at the expected positions.

Registry No.—1b, 5371-47-1; 1c, 15735-61-2; 1e, 15856-55-0; 2a, 15722-31-3; 2b, 15722-32-4; 2c, 15722-33-5; 3b, 5371-46-0; 3c, 15735-63-4; 3d, 15735-64-5; 3e, 4821-67-4; 4a, 15722-34-6; 4b, 15722-35-7.

Indolothiapyrylium Compounds. IV. Indolo[3,2-c]thiapyrylium Perchlorate[1,2]

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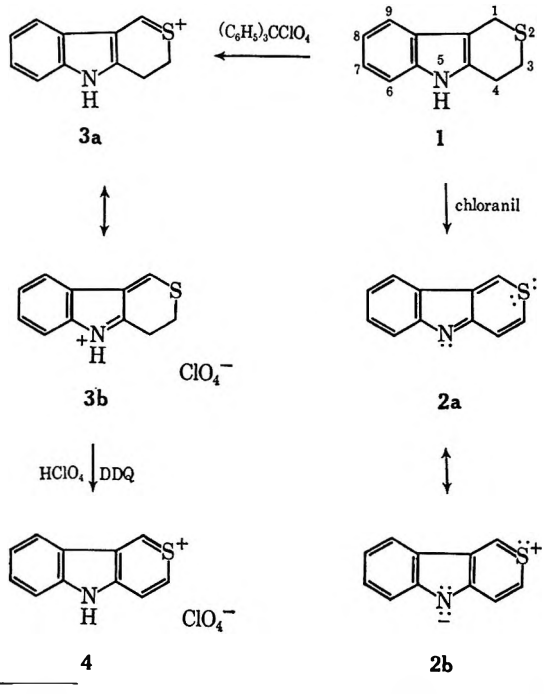
Received October 4, 1967

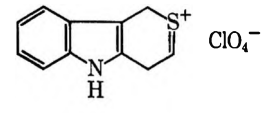
In a recent article,[2] we reported that 1,3,4,5-tetrahydrothiapyrano[4,3-*b*]indole (1) and several of its substituted analogs were readily dehydrogenated with chloranil or dicyanodichloroquinone (DDQ) to yield the corresponding thiapyrano[4,3-*b*]indoles (*e.g.*, 2 from 1), which represent a new class of pseudoazulenes having pronounced thiapyrylium-like character of the sulfur-containing ring (*cf.* canonical form 2b). Although the parent thiapyranoindole (2), at 10^{-4} *M* concentration in 95% ethanol, could be titrated spectrophotometrically with ethanolic hydrogen chloride to give the conjugate cation, repeated attempts to prepare indolothiapyrylium salts (4) by direct interaction of 2 with acids gave tars which were exceedingly difficult to purify. We now wish to report the isolation of indolo[3,2-*c*]thiapyrylium perchlorate (4),[4] prepared by the alternative route shown in formulas 1 → 3 → 4.



3a 1 3b 2a 4 2b

1,3,4,5-Tetrahydrothiapyrano[4,3-*b*]indole (1)[2,5] reacted with an equimolar portion of trityl perchlorate[6] in refluxing glacial acetic acid to give a 94% yield of 3,4-dihydroindolo[3,2-*c*]thiapyrylium perchlorate (3), and the same product was obtained in only slightly reduced yield (84%) when a 100% excess of trityl perchlorate was used. This orange crystalline compound (3) exhibited an intense visible absorption at 414 mμ (log ε 4.20) attributable to the chromophore $-\overset{+}{N}H=C-C=C-S- \longleftrightarrow -NH-C=C-C=\overset{+}{S}-$ (*cf.* 3a ⟷ 3b), and lying in the same range (400–420 mμ) as the long wavelength absorption of the thiapyrano[4,3-*b*]indoles (2)[2] and the benz[*b*]indolo[2,3-*d*]-thiapyrylium perchlorates.[7]

The nmr spectrum of 3 (*cf.* Experimental Section) was also consistent with the assigned structure in which H-1 appeared as a singlet resonance band at very low field (δ 9.48) as expected[7,8] for a proton adjacent to a thionium sulfur. The observation that both the low-field proton of the $-CH=\overset{+}{S}-$ group and the four methylene protons (δ 3.65) appeared as singlets ruled out the possibility of the alternate structure (5) in which the $-\overset{+}{S}=CH-CH_2-$ group should exhibit an AX_2 splitting pattern.[9]



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Dehydrogenation of 3 with dicyanodichloroquinone in acetic acid containing perchloric acid afforded a 33% yield of indolo[3,2-*c*]thiapyrylium perchlorate (4), a stable green-yellow salt, which was also stable in glacial acetic acid solution and recrystallized well from this solvent. In acetonitrile, containing excess perchloric acid to suppress dissociation[10] of the cation, this salt (4) exhibited an ultraviolet-visible spectrum essentially identical with that previously illustrated[2] for the same cation produced from 2 with ethanolic hydrogen chloride at spectrophotometric concentration.

The nmr spectrum of 4 (*cf.* Experimental Section) showed well-defined absorptions of three unusually deshielded protons assignable to H-1, -3, and -4. As in the case of other polynuclear thiapyrylium compounds[8] the two most deshielded protons (H-1 and -3) are associated with positions of unusually low electron density and exhibit characteristic splitting[8] (J_{13} = 3.0 cps) through the thionium sulfur. The HMO electron density pat-

(1) Abstracted in part from the Ph.D. Thesis of C. J. Ohnmacht, Lehigh University, 1966.

(2) Part III: T. E. Young, C. J. Ohnmacht, and C. R. Hamel, *J. Org. Chem.*, **32**, 3622 (1967).

(3) Warner-Lambert Research Fellow, 1965–1966.

(4) For consistency with the recommended name of the free base (2) *viz.*, thiapyrano[4,3-*b*]indole, the name of the cation (4) should be thiapyrano-[4,3-*b*]indolium. However, the alternate name indolo[3,2-*c*]thiapyrylium appears to be more accurately descriptive of the structure of cation 4, and is therefore preferred.

(5) G. M. Bennet and W. B. Waddington, *J. Chem. Soc.*, 2829 (1929).

(6) K. A. Hoffman and H. Kirmreuther, *Ber.*, **42**, 4865 (1909).

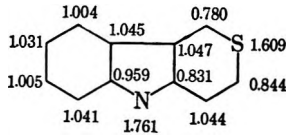
(7) T. E. Young and P. H. Scott, *J. Org. Chem.*, **30**, 3613 (1965).

(8) T. E. Young and C. J. Ohnmacht, *ibid.*, **32**, 1558 (1967).

(9) J. D. Roberts, "An Introduction to the Analysis of Spin–Spin Splitting in High Resolution Nuclear Magnetic Resonance Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, p 64.

(10) As previously discussed in detail[2] the cation of 4 dissociates to the free base (2) in nonacidic solvents, and in 95% ethanol solution exhibits an apparent pK_a = 5.2 at 25°.

tern (summarized on formula 6)[11-13] further shows that the positive charge distribution is +0.391 on sulfur and +0.239 on nitrogen with the remaining charge distributed dominantly on the carbons of the sulfur-containing ring. The corroborative agreement of the charge density calculation with the observed nmr spectrum clearly characterizes this moiety as an indolo[3,2-*c*]-thiapyrylium cation.



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Experimental Section[14]

3,4-Dihydroindolo[3,2-*c*]thiapyrylium Perchlorate (3).—In a three-necked flask equipped with a magnetic stirrer was placed 6.70 g (0.0354 mol) of 1,3,4,5-tetrahydrothiapyrano[4,3-*b*]-indole,[2,5] and 100 ml of glacial acetic acid, and the mixture was heated to 90° under a flow of dry nitrogen. Trityl perchlorate,[6] (12.0 g, 0.0351 mol) was then added slowly from a small erlenmeyer flask attached to the reaction flask with a piece of Gooch tubing. When all of the trityl perchlorate had been added, the solution temperature was held at 90° for 10 min, then refluxed for 10 min, the solution being deep orange at this point. The solution was then allowed to cool to room temperature with stirring as orange crystals separated. After standing at room temperature for 2 hr, the crystals were collected by filtration, washed with glacial acetic acid, then washed with ether, and air dried to give 9.56 g (94% yield) of orange crystals, mp 164–169° dec. Three recrystallizations from glacial acetic acid gave analytically pure **3**, mp 175–177° dec.

Anal. Calcd for $C_{11}H_{10}ClNO_4S$: C, 45.92; H, 3.50; N, 4.87; S, 11.14. Found: C, 46.11; H, 3.30; N, 4.80; S, 11.06.

Ultraviolet-visible spectrum gave $\lambda_{max}^{1\%\ HClO_4\ in\ MeCN}$ 257 mμ (log ε 4.15), 263 (4.10) sh, 294 (3.63), 414 (4.20).

The nmr spectrum in deuteriotrifluoroacetic acid showed H-1 at δ 9.48 (singlet integrating for one proton) and the methylene protons, H-3 and H-4, as a singlet at 3.65 (integration for four protons). The N–H and remaining aromatic protons at H-6, -7, -8, and -9 appeared as a low lying multiplet at δ 7.83 (one proton, not specifically assignable) and an intense multiplet at 7.58 (integration for four protons).

Indolo[3,2-*c*]thiapyrylium Perchlorate (4).—A stirred solution of 2.02 g (7.0 mmol) of **3**, 1.59 g (7.0 mmol) of 2,3-dichloro-5,6-dicyanoquinone, 1 ml of 70% perchloric acid, and 50 ml of glacial acetic acid was refluxed for 2 hr during which the solution became dark red. The mixture was then allowed to cool to room temperature, and the green-brown crystals which had formed were collected by filtration, washed with dry ether, and dried *in vacuo* over potassium hydroxide. The yield was 1.10 g of crude product, mp 158–165°. Recrystallization from acetic acid yielded 0.65 g (33%) of olive-drab crystals, mp 200–203° dec, with shrinking at 192°. Three more recrystallizations from acetic acid yielded analytically pure **4** as green-yellow crystals, mp 217–220° dec.

Anal. Calcd for $C_{11}H_8ClNO_4S$: C, 46.24; H, 2.82; S, 11.22. Found: C, 46.24; H, 3.09; S, 11.24.

Ultraviolet-visible spectrum showed $\lambda_{max}^{1\%\ HClO_4\ in\ MeCN}$ 240 mμ (log ε 4.04), 267 (4.41) sh, 277 (4.47), 297 (4.17) sh, 330 (3.69), 359 (3.60).

The nmr spectrum in deuteriotrifluoroacetic acid showed H-1 at δ 10.13 (doublet, J_{13} = 3.0 cps), H-3 at 9.16 (quartet, J_{13} = 3.0 cps, J_{34} = 9.5 cps), and H-4 at 8.85 (doublet, J_{34} = 9.5 cps), each integrating for one proton. The N–H and remaining aromatic protons at H-6, -7, -8, and -9 appeared as a doublet (J = 7.5 cps, integration for one proton) at δ 8.43 (not explicitly assignable) and an unresolved multiplet centered at 7.77 (integration for four protons).

Registry No.—**3**, 15816-29-2; **4**, 15816-28-1.

Acknowledgments.—We are grateful to the Warner-Lambert Research Institute for support of this work and to the National Science Foundation for a grant to purchase the nmr spectrometer.

(11) The electron densities of cation **4** were derived from Hückel molecular orbital calculations performed as previously described[2] using the parameters $\alpha_N = \alpha + 2\beta$ and $\beta_{CN} = \beta$ for pyridinium nitrogen[12] and $\alpha_S = \alpha + \beta$ and $\beta_{CS} = 0.6\beta$ for the sulfur atom.[13]

(12) R. Zahradník and J. Koutecký, *Advan. Heterocycl. Chem.*, **5**, 72 (1965).

(13) R. Zahradník, *ibid.*, **5**, 1 (1965).

(14) Melting points were determined on a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.) and are corrected. Ultraviolet-visible spectra were recorded on a Beckman DK-2A spectrophotometer. Nmr spectra were determined on a Varian A-60 instrument using tetramethylsilane as an internal standard. Analyses were performed by Dr. V. B. Fish of Lehigh University and by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Reinvestigation of the Orientation of Halogen Substitution in Imidazoles by Nuclear Magnetic Resonance Spectroscopy[1a]

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The chemistry of imidazole and the position of halogen substitution under different conditions of reaction have been studied in detail but hitherto the interpretation of some of the observations has proved difficult.[2] Pauly and his coworkers[3] iodinated imidazole and 4(5)-methylimidazole in alkaline conditions and concluded that the monoiodinated products obtained either by direct iodination or by deiodination were the C-2-substituted products. The diiodoimidazoles obtained either in alkaline media[3a] or at pH 7[4] were considered to be 2,4(5) substituted. It has also been shown that in alkaline media diazo coupling to imidazole occurs at the C-2 position.[5] Bromination of N-methylimidazole with cyanogen bromide also led to the exclusive formation of 2-bromoimidazole.[6] Monobromo and dibromo products obtained by bromination of 4(5)-methylimidazole[7] and imidazole in chloroform and by debromination of the fully halogenated derivatives were shown to be 4- and 5-substituted compounds.[8,9] Nitration and sulfonation in

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(2) (a) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, p 192; (b) K. Schofield, *Quart. Rev.* (London), **4**, 382 (1350); (c) K. Hofmann, "Imidazole and its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1953, pp 111–124; (d) E. S. Schipper and A. R. Day, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., p 194; (e) R. D. Brown, "Current Trends in Heterocyclic Chemistry," A. Albert, G. M. Badger, and C. W. Shoppee, Ed., Academic Press Inc., New York, N. Y., 1958, p 13; (f) J. H. Ridd, "Physical Methods in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, pp 109–160.

(3) (a) H. Pauly and K. Gundermann, *Ber.*, **41**, 3999 (1908); (b) H. Pauly, *ibid.*, **43**, 2243 (1910); (c) H. Pauly and E. Arauner, *J. Prakt. Chem.*, **118**, 33 (1928).

(4) J. H. Ridd, *J. Chem. Soc.*, **1955**, 1238.

(5) R. G. Fargher and F. L. Pyman, *ibid.*, **115**, 217 (1919).

(6) W. J. Langenbeck, *J. Prakt. Chem.*, (2) **119**, 77 (1928).

(7) F. L. Pyman, *J. Chem. Soc.*, **97**, 1815 (1910).

(8) F. L. Pyman and G. M. Timmis, *ibid.*, **123**, 494 (1923).

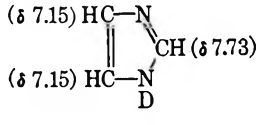
(9) I. E. Balaban and F. L. Pyman, *ibid.*, **121**, 947 (1922).

strong acid solutions also led to the exclusive formation of 4(5)-substituted products.[5,9] Studies of the deuteration[10] of imidazole indicated that a 4,5-disubstituted product was formed in neutral D_2O and the 2-deuterioimidazole was formed in alkaline D_2O solutions.

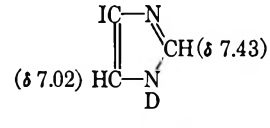
The monoiodo product obtained by iodination of histidine, considered to be 2-iodohistidine by Brunings,[11] has been shown by the present authors[12] by chemical reactions and nuclear magnetic resonance (nmr) spectroscopy to be 4(5)-iodohistidine. The same results were obtained by Holloway, *et al.*,[13] and Aonuma.[14] The 2-iodoimidazole reported by Pauly and Arauner[3c] was also demonstrated to be 4(5)-iodoimidazole by our studies.[12] Pauly and Arauner relied on the previously determined location of bromo substituents in the imidazole ring[8,9] in their identification of the iodo derivatives. Thus, the reported location of the bromine atoms is also open to question. The present study was undertaken to establish the configuration of bromo- and iodo-substituted derivatives of imidazole and 4(5)-methylimidazole.

Results and Discussion

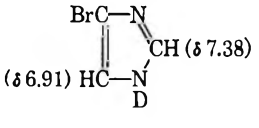
In the imidazole spectrum (A), the band at δ 7.15, which has twice the intensity of that at 7.73, clearly identifies the chemical shifts of the two symmetrical hydrogens attached to the C-4 and C-5 positions. We have shown[12] that the presence of the two bands of equal intensity at δ 7.02 and 7.43 in the spectrum of the monoiodoimidazole (B) proves that the isomer is 4(5)-iodoimidazole. The spectrum of the monobromoimidazole (C) shows two bands of equal intensity at δ 6.91 and 7.38 and confirms the identification by Balaban and Pyman[9] that the isomer is 4(5)-bromoimidazole since only this isomer could show two such bands.



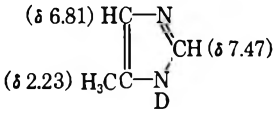
A



B



C



D

Preparation of the diiodoimidazoles by iodination of imidazole in alkaline media, at pH 7, and by the reduction of triiodoimidazoles with sodium sulfite yielded the same isomer. The nmr spectrum of each of the three isomers has a single band at δ 7.47. Since the position of this band is the same as the unequivocally identified C-2 hydrogen of 4(5)-iodoimidazole (B), it is assigned to the hydrogen at the C-2 position. These spectra confirm that the isomers formed in all the three different experimental conditions are only 4,5-diiodoimidazoles. The spectrum of dibromoimidazole shows a single band at δ 7.35 occupying the same position as the proton signal of the C-2 hydrogen of 4(5)-bromoimidazole (C). Hence, this spectrum confirms the identification by Balaban and Pyman[9] that the compound is 4,5-dibromoimidazole.

The nmr spectrum of 4(5)-methylimidazole shows two bands of equal intensity at δ 6.81 and 7.47 representing the hydrogen atoms at C-5(4) and C-2, respectively. A band at δ 2.23 is due to protons of the methyl group. The spectra of both monoiodo-4(5)-methylimidazole and monobromo-4(5)-methylimidazole show one single peak at δ 7.38 and 7.27, respectively. The band corresponding to the hydrogen atom at C-5(4) in 4(5)-methylimidazole is absent from both spectra. Pauly and Arauner[3c] considered the iodo derivative as C-2 substituted, but the spectrum shows that the compound is 4(5)-iodo-5(4)-methylimidazole. The result also establishes the conclusion of Pyman and Timmis[8] that the bromo derivative is 4(5)-bromo-5(4)-methylimidazole.

The present studies prove that during the iodination of imidazole in alkali or at pH 7 the initial attack occurs at the C-4(5) position of the imidazole ring rather than at the C-2 position. The sulfite reduction of both triiodo- and tribromoimidazole has been demonstrated to yield the corresponding 4(5)-mono- and 4,5-dihalogenated products. These results disprove the idea that the iodine substituent in the imidazole ring at the C-2 position is less reactive toward sulfite than is bromine.[2c,3c] The establishment of the configurations of these halogenoimidazoles indicates that the electrophilic substitution of bromine and iodine in the imidazole ring either in alkaline or neutral media (pH 7) preferentially occurs at the 4(5) position as with nitration and sulfonation.[5,9]

Since it now appears that electrophilic substitution occurs at the 4(5) position, we considered it important to investigate the reported electrophilic substitution into the 2 position by diazonium salts.[5] The monoazo derivative obtained by coupling 5-diazo-1H-tetrazole with imidazole was used in this study. The nmr spectrum of this compound shows a single band at δ 7.56. The tetrazole has no unexchangeable hydrogens and the spectrum should show only the chemical shifts of the hydrogens in the imidazole ring. The single peak in the spectrum indicates that either the compound is monosubstituted at the C-2 position or it is disubstituted at the C-2 and C-4(5) or at the C-4,5 positions. The chemical analysis of the compound indicates that it is monosubstituted and the absorption maximum at 376 mμ in bicarbonate buffer, pH 8.8, also confirms that it is monosubstituted, since monoazohistidine has a maximal absorption at 360 and the bisazo compound at 480 mμ.[15,16] Though there is a downfield shift of the proton signals at C-4,5 to δ 7.56 for this compound, the identification of the compound as a monosubstituted product establishes that it is C-2 substituted. This result also confirms[5] that the substitution in the imidazole occurs initially at the C-2 position during diazo-

(10) R. J. Gillespie, A. Grimison, J. H. Ridd, and R. F. M. White, *J. Chem. Soc.*, 3228 (1958).

(11) K. J. Brunings, *J. Amer. Chem. Soc.*, **69**, 205 (1947).

(12) H. B. Bensusan and M. S. R. Naidu, *Biochemistry*, **6**, 12 (1967).

(13) C. T. Holloway, R. P. M. Bond, I. G. Knight, and R. B. Beechey, *Biochemistry*, **6**, 19 (1967).

(14) S. Aonuma, Osaka University, Osaka, Japan, personal communication, 1967.

(15) B. N. Ames and H. K. Mitchell, *J. Amer. Chem. Soc.*, **74**, 252 (1952).

(16) M. Sokolovsky and B. L. Vallee, *Biochemistry*, **5**, 3574 (1966).

nium coupling in alkaline media. Although this is also an electrophilic substitution, this result is not contradictory since apparently the initial attack occurs at the nitrogen of the ring.[15]

Experimental Section

The nmr spectra were determined with a Varian Associates A-60 spectrometer with the samples dissolved in 1 *N* NaOD solution. Chemical shifts (δ) are given in parts per million relative to the internal reference, the sodium salt of 3-trimethylsilyl-1-propane sulfonic acid. Infrared spectra were obtained with the Beckman IR-8 spectrophotometer. Ultraviolet absorption spectra were measured with the Perkin-Elmer Model 202 spectrophotometer. All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Samples for analysis were dried under vacuum over phosphorus pentoxide at 62° for 12–18 hr and the elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Imidazole, obtained from Aldrich Chemical Co., Inc., was recrystallized from benzene (mp 89°).

4(5)-Iodoimidazole was prepared according to our procedure[12] by deiodinating triiodoimidazole with sodium sulfite, mp 137–138° (lit.[3a] 136°).

4(5)-Bromoimidazole was prepared by reducing tribromoimidazole with sodium sulfite in aqueous solution according to the method of Balaban and Pyman.[9] The compound was recrystallized from a mixture of chloroform and petroleum ether to give colorless leaflets, mp 130–131° (lit.[9] 131°).

Anal. Calcd for $C_3H_3N_2Br$: C, 24.51; H, 2.06; N, 19.06; Br, 54.38. Found: C, 24.59; H, 2.02; N, 18.90; Br, 54.32.

4,5-Diiodoimidazole was prepared in alkaline solution by iodinating imidazole with an equimolar amount of iodine. The imidazole (2 g, 29 mmol) was dissolved in 600 ml of 0.04 *N* sodium hydroxide. About 150 ml of pure hexane was added and the flask chilled to 0°. Iodine (7.44 g, 29 mmol) in 600 ml of hexane was added dropwise with vigorous stirring. Simultaneously, 600 ml of 0.2 *N* sodium hydroxide was added dropwise to prevent any precipitation of the reaction product. The addition took about 2 hr and the temperature of the reaction mixture rose to 10°. The reaction mixture was neutralized to pH 7 and left overnight in the refrigerator. The colorless, crystalline material which separated out was collected (3.4 g). The filtrate on evaporation gave 0.4 g of additional material. Recrystallization from dilute alcohol gave colorless, granular crystals, mp 197–198° (lit.[3a] 180°).

Anal. Calcd for $C_3H_2N_2I_2$: C, 11.30; H, 0.63; N, 8.76; I, 79.34. Found: C, 11.42; H, 0.71; N, 8.77; I, 79.40.

4,5-Diiodoimidazole was also prepared by iodinating imidazole at pH 7 according to Ridd[4] and by the removal of a single iodine from triiodoimidazole by refluxing with an equimolar amount of sodium sulfite, according to Brunings.[11] The products from these two preparations showed no depression of melting point with the analyzed preparation described above. The infrared spectra of the three diiodo compounds were identical.

4,5-Dibromoimidazole was prepared according to the procedure of Balaban and Pyman[9] by reducing tribromoimidazole with sodium sulfite in aqueous solution. The compound recrystallized from dilute ethanol and dilute acetic acid appeared as colorless, needle-shaped crystals, mp 229–230° (lit.[9] 225°).

Anal. Calcd for $C_3H_2N_2Br_2$: C, 15.95; H, 0.90; N, 12.41; Br, 70.80. Found: C, 16.12; H, 1.04; N, 12.44; Br, 70.86.

4(5)-Methylimidazole was prepared according to the procedure of Yabuta and Kambe.[17] The vacuum-distilled product has been further purified according to the procedure of Koessler and Hanke.[18] Fine, colorless, crystalline material, mp 56° (lit.[19] 56–56.5°).

Anal. Calcd for $C_4H_6N_2$: C, 58.51; H, 7.37; N, 34.13. Found: C, 58.28; H, 7.52; N, 33.90.

4(5)-Iodo-5(4)-methylimidazole was prepared by iodinating 4(5)-methylimidazole in 0.04 *N* NaOH with a 0.5 *M* amount of iodine and isolating the product from the solution at pH 7.4. Recrystallization from hot water gave colorless crystals, mp 176–177° (lit.[3c] 171°).

Anal. Calcd for $C_4H_5N_2I$: C, 23.10; H, 2.42; N, 13.47; I, 61.01. Found: C, 22.44; H, 2.13; N, 13.25; I, 62.09.

4(5)-Bromo-5(4)-Methylimidazole was prepared according to the procedure of Pyman.[7] The compound, recrystallized from ethyl acetate–*n*-hexane, gave fine, silky needles, mp 154–155° (lit.[7] 155°).

Anal. Calcd for $C_4H_6N_2Br$: C, 29.85; H, 3.13; N, 17.41; Br, 49.65. Found: C, 29.46; H, 3.08; N, 16.41; Br, 51.00.

2-(5-Tetrazolylazo)imidazole was prepared by the slow addition of 5-diazo-1-H-tetrazole (prepared from 2.6 g of 5-amino-1-H-tetrazole[16]) to a solution of 3.4 g of imidazole in 100 ml of 6% sodium carbonate at 0° with stirring. The dark orange material which separated was found to be the bisazo derivative with a maximal absorption at 475 mμ. The filtrate on concentration under vacuum yielded some bisazo derivative and then appreciable amounts of a crystalline, orange-yellow material. The orange-yellow material was recrystallized twice from water to yield light orange-yellow globules (3.5 g) which decomposed explosively at 240°. The absorption spectrum of the product in bicarbonate buffer, pH 8.8, showed a sharp absorption band at 376 mμ, indicating that it is a monoazo compound.

Anal. Calcd for $C_4H_4N_8 \cdot 2H_2O$: C, 24.00; H, 4.00; N, 56.00. Found: C, 24.34; H, 3.14; N, 57.39.

Registry No.—4(5)-Bromoimidazole, 6967-66-2; 4(5)-methylimidazole, 872-33-3; 4(5)-iodo-4(5)-methylimidazole, 15813-07-7; 4(5)-bromo-4(5)-methylimidazole, 15813-08-8; 4,5-diiodoimidazole, 15813-09-9; 2(5-tetrazolylazo)imidazole, 15813-10-2; 4,5-dibromoimidazole, 4150-74-5.

(17) Y. Yabuta and K. Kambe, *Bull. Agr. Chem. Soc. Jap.*, **4**, 74 (1928); *Chem Abstr.*, **24**, 3509 (1930).

(18) K. K. Koessler and M. T. Hanke, *J. Biol. Chem.*, **39**, 497 (1919).

(19) A. Windaus and F. Knoop, *Ber.*, **38**, 1166 (1905).

Configuration of the Asparaginyl and Aspartyl Residues of Bacitracin[1a]

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Recently this laboratory reported a micromethod for identifying residues of asparagine and glutamine in *endo* position in peptides.[2] In this method, the peptide amides are dehydrated with ethylene chlorophosphite to the corresponding β-cyanoalanyl and γ-aminobutyryl derivatives, which are reduced with sodium–methanol–ammonia, then hydrolyzed to the easily recognizable 2,4-diaminobutyric acid (2,4-DAB) and ornithine. In a limited number of model compounds, residues of isoasparagine and isoglutamine were partly converted into β-alanine and γ-aminobutyric acid by reductive fission of the intermediate α-aminonitrile derivatives.[2,3]

When the dehydration–reduction procedure was applied to commerical bacitracin, approximately 0.7 mol of 2,4-DAB formed per mole of leucine or lysine, which identified the amide-bearing group as

(1) (a) This work was aided by Grant NB-04316 from U. S. Public Health Service and by Muscular Dystrophy Associations of America. (b) Recipient of a general research support summer fellowship, 1966.

(2) C. Ressler and D. V. Kashelikar, *J. Amer. Chem. Soc.*, **88**, 2025 (1966).

(3) Recently this technique proved useful in identifying, for the first time in a natural product, isoglutamine and isoasparagine residues as constituents of the cell wall peptidoglycans of certain bacteria: E. Muñoz, J.-M. Ghuysen, M. Leyh-Bouille, J.-F. Petit, H. Heymann, E. Bricas, and P. Lefrancier, *Biochemistry*, **5**, 3748 (1966); D. Jarvis and J. L. Strominger, *ibid.*, **6**, 2591 (1967); J.-M. Ghuysen, E. Bricas, M. Leyh-Bouille, M. Lache, and G. D. Shockman, *ibid.*, **6**, 2607 (1967).

an asparaginyl rather than an isoasparaginyl residue.[4a] The single amide-bearing group of bacitracin has continued to evoke interest since 2 mol of aspartic acid are derived from the antibiotic, one of L, the other of D configuration,[5] and a definite assignment of these to the asparaginyl and aspartyl residues has not been made. It was known that L-aspartic acid was derived from the residue adjacent to the lysine residue, whereas the aspartic acid more easily liberated on partial acid hydrolysis had the D configuration.[5b,c] Results of lithium borohydride reduction of esterified bacitracin A and commercial bacitracin indicated that the residue giving rise to D-aspartic acid had a free β-carboxyl group.[6] The asparaginyl residue was thereby inferred to have the L-configuration.[2]

The validity of this inference now has been examined by applying the dehydration–reduction technique to commercial bacitracin on a millimole scale, isolating the formed 2,4-DAB, and determining its optical configuration.

After dehydration–reduction, the treated bacitracin was freed of salts with a cation-exchange resin and hydrolyzed in acid. The 2,4-DAB was purified by chromatography on the automatic amino acid analyzer[7] in a slightly modified system that separated it well from lysine, ornithine, and the other amino acids present in the hydrolysate. Buffer salts were removed from the eluent with a column of Dowex 50W resin. The 2,4-DAB was purified further by paper electrophoresis, then converted into the crystalline monohydrochloride which was recrystallized. This isolated material had the same infrared spectrum and the same behavior on chromatography and cochromatography on the amino acid analyzer and on paper electrophoresis at several different pH conditions as the authentic amino acid. Although slightly lower in magnitude, its optical rotation agreed in sign with that of reference L-2,4-DAB monohydrochloride. This confirms the L configuration of the asparaginyl residue of bacitracin and implies that the aspartyl residue has the D configuration. As concluded earlier,[2] of the structures for bacitracin suggested by the studies of Abraham and Craig and their coworkers,[5c,6] the various findings on amide and carboxyl groups appear to favor that one which contains an ϵ-(D-aspartyl-L-asparaginyl)-L-lysine sequence[4b] within a cyclopeptide moiety of seven rather than six amino acid residues.

Experimental Section[8]

Bacitracin (1 mmol) was heated with ethylene chlorophosphite (47 ml) in triethyl phosphite (160 ml) at 97–100° for 24 hr, as described previously for a microscale.[2] The dehydrated peptide in liquid ammonia (700 ml) and methanol (21 ml) was treated with sodium (8.1 g) in portions, after which ammonium chloride (16 g) was added. To the residue left after evaporation of ammonia and methanol were added 17 ml of 2 *N* HCl and 50 ml of warm water. The tan solid was filtered off and hydrolyzed in 20 ml of 6 *N* HCl. The aqueous filtrate at pH 2 was applied to a column (36 × 4 cm) of AG 50W-X2 (H^+ cycle) resin. This was washed with water until the effluent was chloride free, then eluted with 3 *N* NH_3. Ninhydrin-positive basic fractions were concentrated to dryness and hydrolyzed in 50 ml of 6 *N* HCl. The two hydrolysates were taken to dryness. The residues were dissolved in a minimum volume of water and, in batches of 18 μmol each of 2,4-DAB, applied at pH 2 to the 50-cm resin column (newly regenerated) of the amino acid analyzer. The material was chromatographed in system C[8] at a flow rate of 0.5 ml/min. At an effluent volume of 50 ml, 1-ml fractions were collected with a fraction collector and analyzed with ninhydrin.[9] The 2,4-DAB was eluted at 167–179 ml and was well separated from the preceding peak containing ornithine and lysine at 145–160 ml. Ten such runs afforded 127 μmol of 2,4-DAB. The eluate was freed of most of the salts with a column (26 × 1.7 cm) of Dowex 50W-X8 (H^+ cycle) resin,[10] and the material was eluted with 6 *N* NH_3 in the manner already described. Fractions appearing 8–16 ml after the breakthrough of base yielded 72 mg of solid containing 21% 2,4-DAB (125 μmol). This was electrophoresed in portions as a band on paper in pyridinium acetate buffer, pH 5.6.[8] The 2,4-DAB was located with ninhydrin and eluted with water; the eluate was then taken to dryness. The material was precipitated from aqueous solution at pH 5 with ethanol. The solid was dried and extracted into a small volume of water. The solution had 22 mg of solid containing 37% 2,4-DAB (69 μmol). To it was added 0.3 ml of 2 *N* HCl. It was then taken to dryness, and the residue was dissolved in water and adjusted to pH 5 with dilute pyridine. Crystallization was initiated from several drops of aqueous solution by addition of hot ethanol to give 7.5 mg of 2,4-DAB of 76% purity. Recrystallization from the same solvent gave 4.8 mg of light colored prisms of 2,4-DAB monohydrochloride of 98% purity on amino acid analysis in system B. On cochromatography with the authentic material on the analyzer in system A, a single peak emerged with 95% recovery. The material traveled as a single spot with the mobility of authentic 2,4-DAB when electrophoresed on paper in formate–acetate buffer, pH 1.8; pyridinium acetate buffer, pH 4.0 and 5.6; and sodium barbital buffer, pH 8.5. It had $[\alpha]^{25}D$ +21.6° (*c* 0.3, 5 *N* HCl); reference L-2,4-DAB·HCl had $[\alpha]^{25}D$ +24.2° (*c* 0.4) (lit.[11] $[\alpha]^{25}D$ +24.2° (*c* 2)).

Registry No—L-2,4-DAB, 1758-80-1; L-2,4-DAB monohydrochloride, 15765-10-3.

Acknowledgments.—We thank Drs. A. Spector and L.-K. Li of Columbia University College of Physicians and Surgeons for use of their polarimeter.

(4) (a) In view of the presence of ϵ-(aminosuccinyl)lysine in partial acid hydrolysates of bacitracin A [D. L. Swallow and E. P. Abraham, *Biochem. J.*, **70**, 364 (1958); see also ref 5c], carbobenzoxy-L-aminosuccinimide was also subjected to dehydration, reduction, and hydrolysis, but formation of 2,4-DAB was not detected. (b) ϵ-(Aminosuccinyl)lysine is thus derived originally from the ϵ-(L-asparaginyl)-L-lysine sequence in the antibiotic, although ϵ-(α-L-aspartyl)-L-lysine and ϵ-(β-L-aspartyl)-L-lysine are capable of cyclizing to this succinimide derivative (see reference cited in 4a).

(5) (a) L. C. Craig, W. Hausmann, and J. R. Weisiger, *J. Biol. Chem.*, **199**, 865 (1952); (b) I. M. Lockhart and E. P. Abraham, *Biochem. J.*, **62**, 645 (1956); (c) for a review, see E. P. Abraham, "Biochemistry of Some Peptide and Steroid Antibiotics," John Wiley and Sons, Inc., New York, N. Y., 1957.

(6) D. L. Swallow and E. P. Abraham, *Biochem. J.*, **72**, 326 (1959).

(7) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

(8) Bacitracin was the commercial preparation described previously.[2] Ethylene chlorophosphite was a gift of Hooker Chemical Co., Niagara Falls, N. Y. Dowex 50W-X8 and AG 50W-X2 cation-exchange resins (both 100–200 mesh) were obtained from Bio-Rad Laboratories, Richmond, Calif., and Calbiochem, Los Angeles, Calif. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Optical rotations were measured in a Perkin-Elmer Model 141 photoelectric polarimeter read against air. Amino acid analyses were obtained on the Beckman-Spinco Model 120 automatic amino acid analyzer with sulfonated styrene–8% divinylbenzene copolymer resin. Complete analyses of basic amino acids in hydrolysates of treated bacitracin were made on the 50-cm column, Type 50A resin, 25–31 μ, 0.38 *N* sodium citrate buffer, at pH 4.25 and 50°[2] (system A). Routine determinations of 2,4-DAB in isolates were done on the 15-cm column, Type 15A resin, 19–25 μ, with 0.35 *N* sodium citrate buffer, at pH 5.28 and 50°[7] (system B). Preparative chromatography was on the 50-cm column, Type 50A resin, with the latter buffer at pH 5.28 and 50° (system C). Preparative paper electrophoresis was carried out on 10-cm-wide strips of Whatman No. 3MM paper at 9 V/cm for 3.5 hr. Acid hydrolyses were carried out in 6 *N* HCl under nitrogen in an oil bath at 120° for 16 hr.

(9) S. Moore and W. H. Stein, *J. Biol. Chem.*, **211**, 907 (1954).

(10) The resin was regenerated as described [S. Moore and W. H. Stein, *ibid.*, **192**, 663 (1951)], then converted with HCl into H^+ cycle and washed free of acid before use.

(11) S.-C. J. Fu, K. R. Rao, S. M. Birnbaum, and J. P. Greenstein, *ibid.*, **199**, 207 (1952).

The Preparation of Spiro[2.5]octan-6-one. Catalytic Hydrogenation of a Vinylcyclopropane

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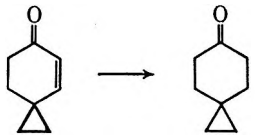
In connection with other work, we required a sample of the unknown spiro ketone **2**. The preparation of **2** appeared to be straightforward, involving reduction of the unsaturated spiro ketone **1** available from the procedure of Fassnacht and Nelson.[2] Preliminary experiments indicated, however, that even under very mild conditions of catalytic hydrogenation, considerable cleavage of the cyclopropane ring accompanied double-bond reduction. Since the hydrogenolysis product



1 **2**

proved difficult to separate from **2**, various conditions were examined to effect the desired reduction; some of the results are shown in Table I.

TABLE I

REDUCTION OF SPIRO[2.5]OCT-4-EN-6-ONE (**1**) AT 25° [a]

Catalyst	Solvent	% **2**	% 4-ethylcyclohexanone (**4**)
5% Pd/C	50% aqueous EtOH	23	77
5% Pd/C	Absolute EtOH	43	57
5% Pd/C	THF	47	53
5% Pd/C	Hexane	68	32
5% Pd/C	94% aqueous EtOH 0.12 *N* NaOH	60	40
5% Pd/C	85% aqueous EtOH 0.01 *N* NaOH	84	16
PtO_2	THF	91	9
Raney Ni[b]	THF	100	0

[a] Reductions were carried out at a constant pressure of 1 atm (H_2 plus solvent vapor pressure) and were carried to completion. Weight ratios of ketone to catalyst were in most cases about 20:1; reaction times ranged from 13 to 63 min. For reduction using Raney Ni, the ketone to catalyst ratio was 4.5:1, and reaction time was 175 min. [b] W-2.

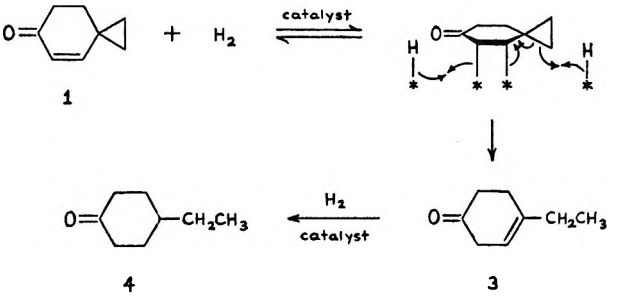
Hydrogenolyses of vinyl-substituted cyclopropane derivatives have often been observed,[3] but relatively little work has been directed toward selective reduction of the double bond. Exceptions are found in the work of Slabey and Wise,[3b] who reported such selectivity in the high-pressure reduction of isopropenylcyclopropane using Ba–Cu–CrO catalyst; considerable hydrogenolysis occurred, however, when the double bond was more highly substituted. The use of mercury-poisoned Raney nickel, first reported by Corner and Pease in 1945,[4] seemed more promising for the present purpose. The catalyst did indeed prove effective in preventing hydrogenolysis of **1**, although hydrogenation to **2** proceeded very slowly. However, unpoisoned Raney nickel was found to be equally effective. This result was unexpected since Raney nickel has been found to cause the hydrogenolysis of vinylcyclopropanes under comparable conditions.[3c,5] The only complication (which also occurred with poisoned Raney nickel) was a relatively slow reduction of the product, **2**, to the corresponding alcohol. Hydrogenation using Raney nickel was examined in various solvents; production of the alcohol was found to be slowest, relative to hydrogenation of the double bond, when tetrahydrofuran was used. This combination of catalyst and solvent is therefore considered optimal for preparation of the title spiro ketone.

The hydrogenolysis of **1** observed with palladium or platinum catalysts (Table I) gave 4-ethylcyclohexanone as the only cleavage product, with no trace of 4,4-dimethylcyclohexanone being found (vpc); spiro[2.5]-octane itself is catalytically reduced to 1,1-dimethylcyclohexane.[6]

Cleavage of the bond adjacent to the point of substitution is the usual mode of hydrogenolysis of vinylcyclopropanes,[3] and is thought to result from initial adsorption at the double bond, followed by migration of the point of adsorption to the three-membered ring.[3a]

Interestingly, in several runs stopped short of completion (using catalysts which gave hydrogenolysis), an intermediate was found which proved to be 4-ethyl-3-cyclohexenone (**3**), demonstrating that under these conditions the complete reduction does not occur in a single step. A possible mechanism involving **3** is outlined in Scheme I (arrows represent movements of single electrons).

SCHEME I



1 **4** **3**

Experimental Section

2-(4-Methoxyphenyl)ethanol.—A solution of 150 g (0.90 mol) of *p*-methoxyphenylacetic acid in 350 ml of tetrahydrofuran (THF) was added to a stirred solution of 35 g (0.92 mol) of lithium aluminum hydride in 650 ml of THF under nitrogen over a period of 1.5 hr. After stirring at room temperature for 5 hr, the thick slurry evolved heat and became less viscous; stirring was continued for an additional 5 hr. The excess hydride was decomposed with 15 ml of ethyl acetate, after which 750 ml of 6 *N* sulfuric acid was added. Several hours of stirring led to a clear two-phase system. The aqueous phase was extracted with THF, and the combined THF solutions were washed with 5% base and saturated salt solution, then dried with anhydrous potassium carbon-

(1) N D E A Title IV Predoctoral Fellow, 1964–1967.

(2) J. H. Fassnacht and N. A. Nelson, *J. Org. Chem.*, **27**, 1885 (1962).

(3) (a) J. Newham, *Chem. Rev.*, **63**, 123 (1963); (b) V. A. Slabey and P. H. Wise, *J. Amer. Chem. Soc.*, **74**, 3887 (1952); (c) R. Van Volkenburgh, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *ibid.*, **71**, 172 (1949); (d) M. Hanack, H. J. Schneider, and H. Schneider-Bernlöhr, *Tetrahedron*, **23**, 2195 (1967).

(4) E. S. Corner and R. N. Pease, *Ind. Eng. Chem., Anal. Ed.*, **17**, 564 (1945).

(5) R. Van Volkenburgh, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, **71**, 3595 (1949).

(6) R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *ibid.*, **70**, 946 (1948).

ate. Solvent was removed by distillation (last traces at 1 mm) to give a residue of 108 g (0.71 mol, 79%) of light yellow oil, initial bp 101° (0.8 mm),[7] which was used without further purification. The nmr and ir spectra of this material indicated that it contained no appreciable impurities.

The general procedure of Fassnacht and Nelson[2] was used for the preparation of **1**, with modifications to accommodate a larger scale reaction. As these modifications led to improved yields, they are presented below.

2-(2,5-Dihydro-4-methoxyphenyl)ethanol.—To a stirred solution of 304 g (2.0 mol) of 2-(4-methoxyphenyl)ethanol and 450 g of methanol in 2.5 l. of liquid ammonia, 75 g (10.8 g-atoms) of lithium was added at a rate sufficient to maintain reflux and a blue color in solution. An additional 160 g of methanol and 15 g (2.2 g-atoms) of lithium were added alternately in portions. Treatment as previously described[2] followed by rotary evaporation gave a light orange residue weighing 298 g (1.94 mol, 97%). Nmr and ir analyses indicated that this material was substantially pure and free from starting alcohol; it was used without further purification. Attempted distillation[2] on this scale led to extensive decomposition.

4-(2-Hydroxyethyl)-3-cyclohexenone.—A solution of 285 g (1.85 mol) of 2-(2,5-dihydro-4-methoxyphenyl)ethanol, 1 l. of THF, 550 ml of water, and 55 ml of concentrated sulfuric acid was stirred for 1.5 hr at 25°. A mixture of 300 g of ice and 300 ml of 6 *N* sodium hydroxide was then added with stirring, after which the solution was saturated with salt. The aqueous layer was separated, extracted with THF, and the combined organic phases washed and dried as described previously.[2] Solvent and residual water were removed by rotary evaporation at 40–50°, to give 241 g (1.72 mol, 93%) of product. The nmr spectrum of this material showed no appreciable differences from that of a sample collected by vpc (5 ft × 0.25 in. 20% SF-96 on Chromosorb W, 158°), and it was used without further purification.

The tosylate of this alcohol was prepared in the usual manner in pyridine solution, yielding 319 g of viscous oil. Nmr analysis indicated a purity of >80%, and no further purification was attempted.

Spiro[2.5]oct-4-en-6-one.—To a stirred solution, under nitrogen, of 98.0 g (0.33 mol) of the crude tosylate in 3.3 l. of anhydrous dioxane (distilled from sodium metal after 20-hr reflux), 10 drops of anhydrous *t*-butyl alcohol were added, followed by 12.9 g (0.54 mol) of sodium hydride. The mixture was then stirred at high speed while it was heated to reflux for 11 hr, allowed to cool to room temperature, and treated with 1 l. of saturated ammonium chloride solution. The aqueous layer was separated and extracted with ether, and the combined organic phases were dried with anhydrous magnesium sulfate. Solvents were removed by distillation through a 2-ft Vigreux column (final bp 101°). The residue was distilled through a short Vigreux column, giving 22.4 g of material of bp 69–73° (3 mm). Gas chromatography (20 ft × 0.25 in. 15% Carbowax 6000 on Chromosorb W, 175°) showed this material to contain impurities with retention times (RT) of 40, 42, and 73 relative to the major product of RT 100. Since previous experiments had shown that the impurities of RT 40 and 42 would be difficult to separate from the saturated spiro ketone, the mixture was redistilled through a spinning-band column to give 14.0 g of material containing 96% RT 100 and 4% RT 73, bp 86–87° (8 mm). The nmr spectrum of pure RT 100, obtained in the final distillation fractions, demonstrated it to be the compound previously described.[3] The ir spectrum (CCl_4) had characteristic bands[8] at 860 (s), 910, 935, 970, 1010, 1035 (w), 1055 (w), 1120, 1190, 1615, 1680 (vs), and 3070 cm^{-1}.

Spiro[2.5]octan-6-one.—The 14.0 g of material described above was dissolved in 200 ml of THF and hydrogenated over 1.5 g of W-2 grade Raney nickel in a Parr apparatus at room temperature and 10–50 psig. Contamination of the mixture by THF-soluble compounds in the stopper was eliminated by inserting a tight-fitting Teflon disk between stopper and solution. The pressure was carefully monitored and the hydrogenation stopped when the theoretical hydrogen uptake had been achieved. The time required was 7 hr. After filtration of the solution, traces of remaining catalyst were collected on a magnetic stirring bar. Solvent was removed by distillation through a 2-ft Vigreux column at atmospheric pressure, and the residue was distilled through a spinning-band column to give 11.1 g (0.09 mol, 81%) of 99.5% pure spiro[2.5]octan-6-one, bp 93.5° (33 mm). The characteristic bands[8] in the ir spectrum (CCl_4) occurred at 880 (w), 920 (w), 1010, 1045 (w), 1140, 1715 (s), and 3065 cm^{-1}; the nmr spectrum (CCl_4) had bands at δ[9] 0.47 (s, 4 H), 1.63 (t, J = 6.5 cps, 4 H), and 2.32 (t, J = 6.5 cps, 4 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.0; H, 9.8.

Identification of the Intermediate (3).—Small-scale hydrogenations (Table II), duplicating conditions given in Table I, were stopped prior to completion and analyzed by vpc on the Carbowax column described above. In every case, a broad peak was observed which was not present in mixtures from hydrogenations carried to completion. This peak was collected and found by its nmr spectrum to consist of approximately equal parts of **3** and 4-ethyl-2-cyclohexenone (**5**). Reinjection of the mixture into the gas chromatograph caused further isomerization, greatly increasing the percentage of **5**. Attempted purification by vpc of the product of an independent synthesis of **3** (described below) also produced a mixture of **3** and **5**. These data suggest that the actual hydrogenation intermediate, before partial isomerization to **5** on the vpc column, is compound **3**.

TABLE II

PARTIAL REDUCTION OF SPIRO[2.5]OCT-4-EN-6-ONE

Catalyst	Solvent	Percentage of total products 2	4	3	% starting material consumed
5% Pd/C	THF	50	35	15	57
5% Pd/C	THF	47	26	27	32
5% Pd/C	Absolute EtOH	38	42	20	54

4-Ethyl-3-cyclohexenone (3).—A small sample of the *p*-toluenesulfonate of 4-(2-hydroxyethyl)-3-cyclohexenone was reduced with lithium aluminum hydride in ether. After removal of the ether, the product was oxidized by the Jones procedure.[10]

Registry No.—2, 15811-21-9.

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