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LITHIUM ALUMINUM HYDRIDE REDUCTION OF
SUBSTITUTED 4-HYDROXYPHENACYL HALIDES

by

Richard Volkert Flor VI

1972

A dissertation submitted to the Graduate Faculty in Chemistry
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy, The City University of New York.

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Dedication

The greatest pleasure in my years at City College was the experience of teaching several undergraduate classes. From them I learned much and shall remember in particular the general chemistry classes as our finest moment. To them in particular this is dedicated, for many reasons, not the least of which was their interest in my own progress in higher education.

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In Gratitude, Fall 1971

Richard

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The undergraduate students who participated in various phases of research related to the whole of this thesis development are especially to be commended for dedication and effort for which I owe them much: Elizabeth Moy Chan, Vincent Phillip Gullo, William Christopher Hollinsed, Elaine Jessen, and Bess Bryna Kupfer. Miguel Mieles is due a special thanks for having taken all of the infrared spectra.

I wish to express my gratitude to the American Chemical Society/Petroleum Research Fund for a Graduate Fellow Grant (GF #573).

I am deeply grateful to Janet Dell for typing this thesis--far above the call of blood and family.

Abstract

The LiAlH_4 reduction in ether of a series of 3',5'-symmetrically substituted-4'-hydroxy-2-bromoacetophenones was studied. In general, two principal products were obtained, a primary alcohol and an alkane, and two minor products. As the 3',5' substituents were increased in size from hydrogen to methyl, ethyl, isopropyl, tert.-butyl the percent of primary alcohol product increased. The respective percentages were ca. 0%, 34%, 47%, 63%, ca. 90%. The percent alkane declined correspondingly: ca. 90%, 63%, 44%, 28%, ca. 0%. Reduction with LiAlD_4 established that the aryl ring had migrated from carbon-1 to carbon-2 to yield the general structure $\text{ArCH}_2\text{CD}_2\text{OH}$, and established that the alkane product had the general structure $\text{ArCD}_2\text{CH}_2\text{D}$, i.e., no aryl ring migration had occurred. The principal minor products were the alkyl bromide, which LiAlD_4 reduction established as having the general structure $\text{ArCD}_2\text{CH}_2\text{Br}$, and a dimeric ether, $\text{ArCH}_2\text{CD}_2\text{OCD}(\text{CH}_2\text{D})\text{Ar}$. The reduction of these compounds required about 10 min in refluxing ether.

Substitution of chlorine for bromine in three of the acetophenones studied (3',5' = methyl, ethyl, isopropyl) resulted in a marked increase in primary alcohol product to ca. 64%, 54%, 78%, respectively, and a sharp drop in alkane product. The alkyl chloride product, $\text{ArCH}_2\text{CH}_2\text{Cl}$, increased considerably to 11 - 17% of the total, and the dimeric product remained about constant. Substitution of halogens,

Cl or Br, in the 3',5' positions effectively stopped production of the primary alcohol, leading instead to alkane and a benzylic alcohol product, of the general structure $\text{ArCH}(\text{OH})\text{CH}_3$. However, these were much slower reductions than the previous ones, and required ca. 900 min to completely reduce the halohydrins formed in the initial reduction. Substitution of alkyl or phenyl groups on the 2-carbon of the bromoketones of the alkylphenols shortened the reduction time to ca. 4 - 6 min and led to ca. 95 - 100% production of the respective primary alcohols, $\text{ArCR}_1\text{R}_2\text{CH}_2\text{OH}$. This appears to require aryl ring migration from carbon-1 to carbon-2, as before. This substitution at carbon-2 involved hydrogen, methyl; methyl, methyl; hydrogen, phenyl; hydrogen, ethyl for two series of structures: where the 3',5' substituent was methyl or tert.-butyl. In addition, substitution of a methyl on carbon-2 where the 3',5' substituent was Cl, and the displaced halogen was bromine, produced ca. 50% primary alcohol and 50% benzylic alcohol upon prolonged refluxing.

A mechanism is proposed to account for these results. It involves the generation of a halohydrin dianion, from the reaction of the phenol hydrogen and reduction of the carbonyl group. The halohydrin undergoes competing processes: the halogen can be displaced from carbon-2, leading to benzylic alcohol (which was observed as a product in the cases where the 3',5' substituent was a halogen), or an alkane, from the relatively rapid hydrogenolysis of the C-O bond, or oxyaryl ring migration occurs. The oxyaryl ring

migration is thought to involve initial closure, with bromine displacement, to a spirocyclopropanol, followed by opening to an aldehyde and reduction to the primary alcohol. The alkyl halide product appears to arise from hydrogenolysis of the C-O bond of the halohydrin before either of the major reactions occur. The dimer appears to involve attack of initially formed primary alcohol during the cleavage of the C-O bond. The oxyaryl ring migration is favored by substitution upon carbon-2, and/or larger 3',5' substituents. It was possible to independently prepare the halohydrin, $\text{ArCH(OH)CH}_2\text{Br}$, where the 3',5' substituent was isopropyl and reduce it with an excess of LiAlH_4 . The result was a satisfactory reproduction of the product distribution as was obtained from the reduction of the parent 2-bromoketone.

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Statement of the Problem

Nomenclature

Statement of the Problem.

The dissertation research presented here is concerned with the lithium aluminum hydride reduction of a series of 2-haloketones. The structure of these haloketones contains as recurring units certain phenol rings, and also a limited number of common structures for the aliphatic portion of the ketone. The syntheses leading to the 2-haloketones and the nature of the products of reduction lends this series of compounds to a systematized nomenclature.

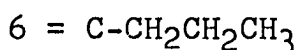
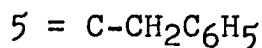
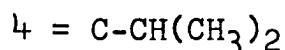
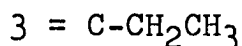
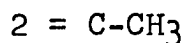
Nomenclature.

(A) The following phenols are designated by capital Roman numerals.

- I = phenol.
- II = 2,6-dimethylphenol.
- III = 2,6-diethylphenol.
- IV = 2,6-diisopropylphenol.
- V = 2,6-di-tert.-butylphenol.
- VI = 2,6-dichlorophenol.
- VII = 2,6-dibromophenol.
- VIII = 2,6-diiodophenol.

The prefix MeO- designates the methyl ether of the phenol, or a derivative thereof.

(B) Subscripts refer to the group attached to the phenol. If the group is bonded to the phenol oxygen, the Roman numeral is primed. If the group is bonded para to the phenol OH, the Roman numeral is unprimed.



(C) The subscripts have small letters that define the functionality involved.

a = Ketone. E.g. 2a = COCH_3 .

b = 2-bromoketone. E.g. 2b = COCH_2Br . (Bromine is understood to be the halogen. If chlorine or iodine is the halogen, it is indicated thus: b-Cl or b-I.)

c = primary alcohol from reduction and rearrangement. E.g. 2c = $\text{CH}_2\text{CH}_2\text{OH}$.

d = alkane from the reduction and hydrogenolysis of the carbonyl group. E.g. 2d = CH_2CH_3 .

e = bromohydrin. E.g. 2e = $\text{CH(OH)CH}_2\text{Br}$. (e-Cl is the chlorohydrin; e-I is the iodohydrin.)

f = benzylic alcohol from reduction of the ketone. E.g. 2f = CH(OH)CH_3 .

g = symmetrical dimeric ether. E.g. 2g = $(\text{ArCH}_2\text{-CH}_2)_2\text{O}$.

h = unsymmetrical dimeric ether. E.g. $2h = \text{ArCH}_2\text{CH}_2\text{OCH}(\text{CH}_3)\text{Ar}$.

i = spiro-cyclopropanol.

j = spiro-cyclopropanone.

k = epoxide. E.g. $2k = \text{ArCH} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{CH}_2 \end{array}$.

l = quinone-methide, as anion from epoxide opening.

m = alcohol precursor of the unsymmetrical ether, h.

n = unsymmetrical benzylic ether, terminal alkane.

o = unsymmetrical benzylic ether, terminal alcohol.

p = 2-bromoalkane from the hydrogenolysis of the ketone. E.g. $2p = \text{CH}_2\text{CH}_2\text{Br}$. (p-Cl is the chloroalkane, p-I is the iodoalkane.)

q = the bromo precursor of h. E.g. $2q = \text{ArCH}_2\text{CH}_2\text{OCH}(\text{CH}_2\text{Br})\text{Ar}$. (q-Cl is the chloro precursor of h, etc.)

r = alcohol from oxygen-shift to carbon-2 during reduction.

s = spiro-cyclopropane.

t = aldehyde precursor of the primary alcohol from rearrangement.

(D) No distinction is made in the nomenclature between deuterium and hydrogen labelled compounds. The text and diagrams will show the difference. E.g. $\text{II}_{2c} = \text{ArCH}_2\text{CD}_2\text{OH}$ or $\text{ArCH}_2\text{CH}_2\text{OH}$ depending upon whether the reduction was with lithium aluminum deuteride or hydride.

Hypothetical Flow Sheet to Illustrate Nomenclature.

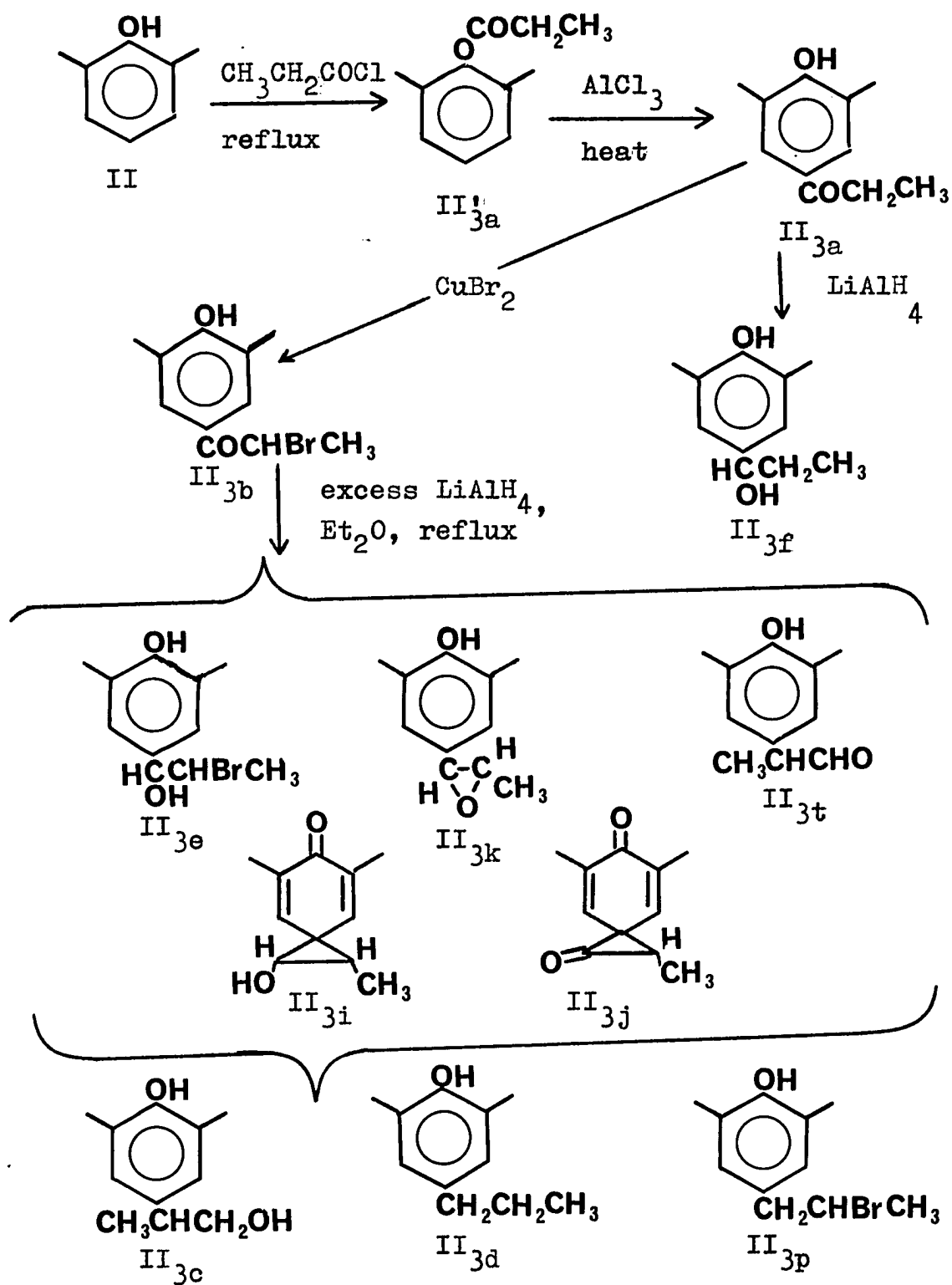
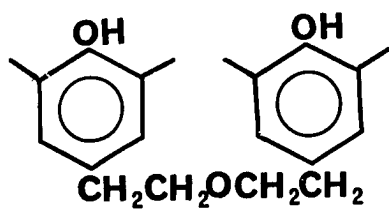
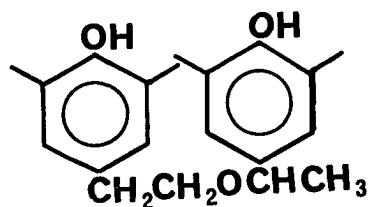


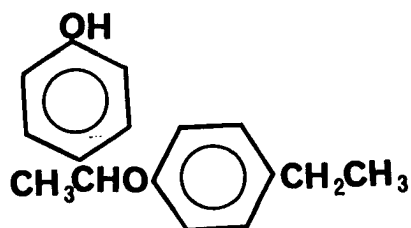
Illustration of Less Frequent Products.



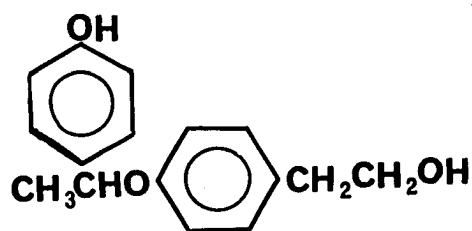
II_{2g}



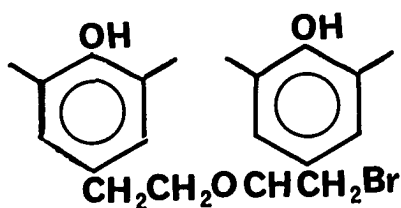
II_{2h}



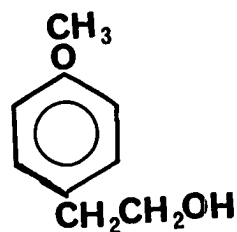
I_{2n}



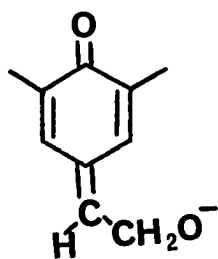
I_{2o}



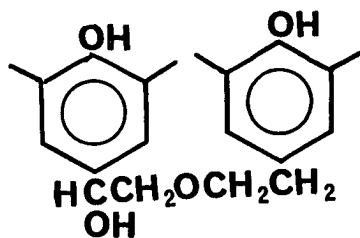
II_{2q}



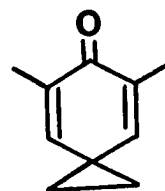
MeO-II_{2c}



II₂₁



II_{2m}



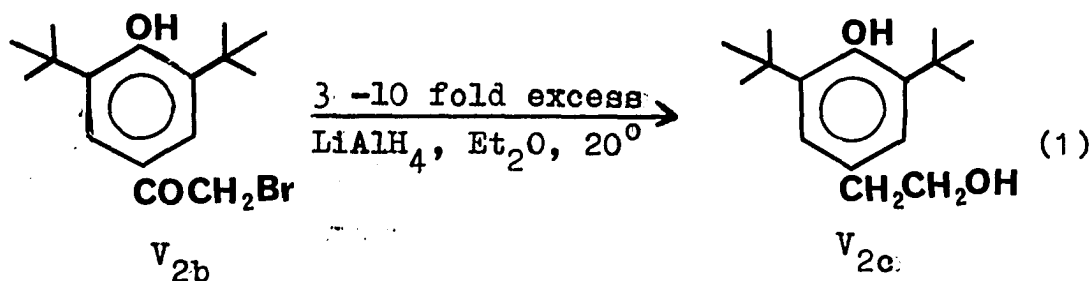
II_{2s}

Introduction

Scope of Dissertation Research

Introduction

A report appeared by V. V. Ershov and coworkers¹ concerning the reduction of 2-bromo-3',5'-di-tert.-butyl-4'-hydroxyacetophenone (V_{2b}), which evidently involved some sort of structural rearrangement, as shown in Eq 1:

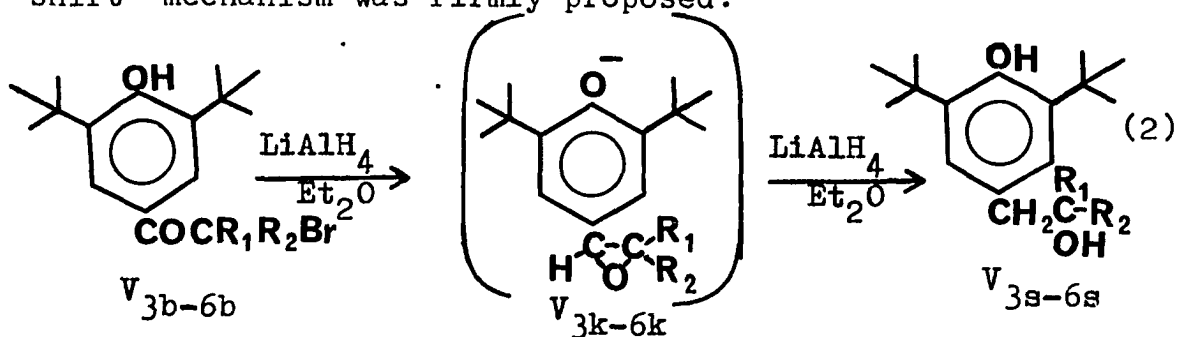


These authors implied that the carbonyl oxygen had shifted position during the course of the reduction. Their report prompted a deceptively simple question: had the oxygen shifted, did the aromatic ring shift during the reduction, or did both rearrangement paths occur? While that problem was pondered in these laboratories (and our earlier work indicated that Ershov's group was incorrect at least as far as the mechanism of Eq 1 was concerned) the Russian workers published a second study² which considerably extended the

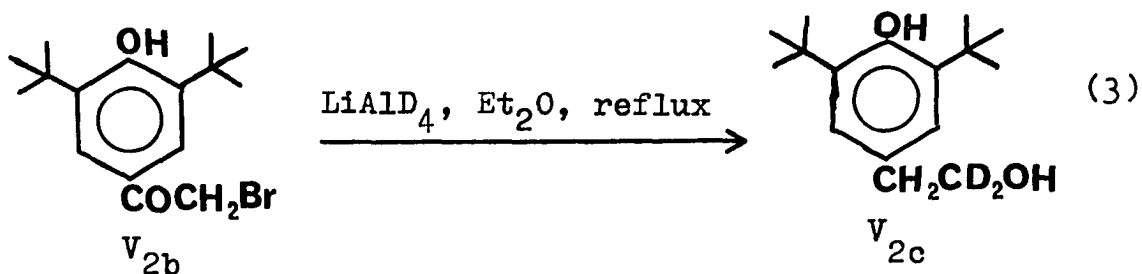
(1) V.V. Ershov, A.A. Volod'kin, and N.V. Portnykh, Bul. Acad. Sci. USSR, 1632 (1966).

(2) A.A. Volod'kin, N.V. Portnykh, and V.V. Ershov, ibid., 1352 (1967).

list of substrates subjected to the reduction. This time they stated that the mechanism of the reduction involved an epoxide intermediate which underwent "abnormal" opening to the products V_{3r-6r} as shown in Eq 2, i.e., the "oxygen-shift" mechanism was firmly proposed:



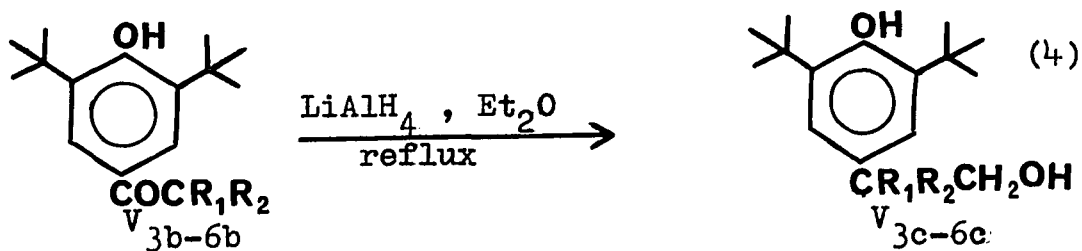
The first work from these laboratories to be published was addressed to the question of the "oxygen-shift" vs. "aryl-shift" mechanism³ and involved a deuterium labelling study with the results shown in Eq 3:



The incompatibility of the position of the label with the oxygen-shift mechanism will be described subsequently in Other Mechanisms: Epoxide Intermediates, p160 .

(3) L.H. Schwartz and R.V. Flor, Chem. Commun., 1129 (1968).

That left the second set of results² to be explained. Preliminary work in these laboratories was rather heavily weighted against the results proposed by Ershov's group in Eq 2, and compelled us to reinvestigate that work.⁴ Our results are shown in Eq 4:



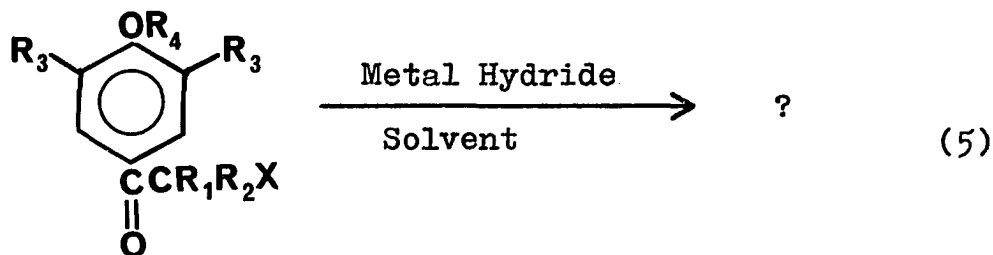
The dilemma was cleanly resolved, the structures proposed earlier,³ which reflected the oxygen-shift were in error, and the aryl-shift was in fact operating. (It should be noted that we did not duplicate two of the earlier cases:³ $\text{R}_1, \text{R}_2 = \text{H}, n\text{-propyl}$, and $\text{H}, \text{isobutyl}$. However, there is no obvious reason to suppose that the last two substitutions could alter the outcome of the reduction.) The results of these earlier reductions are gathered in Table VI, p 38.

Scope of the Dissertation Research

It was obvious that a rearrangement was occurring during the course of the LiAlH_4 reductions,¹⁻⁴ and the

(4) L.H. Schwartz and R.V. Flor, J. Org. Chem. 34, 1499 (1969).

problem was conceived in terms of a far more general system than the one which initiated the whole investigation. Consider the general structure and reaction conditions shown in Eq 5:



To reduce the problem to manageable proportions for a thesis dissertation, the following structural features were held constant: X= bromine, and R_4 = hydrogen. Given those conditions, the problem was: (a) What would be the effect on the reaction as the groups flanking the phenol H (R_3) were varied from hydrogen to methyl, ethyl, isopropyl, tert.-butyl? (b) What would be the effect on the reaction as the substitution on carbon-2 was changed from $\text{R}_1 = \text{R}_2 =$ hydrogen to alkyl groups? (c) Could a mechanism be proposed and tested satisfactorily that would account for the results of (a) and (b)?

For convenience, and to permit some relationships to be established and maintained with our and Ershov's earlier work,¹⁻⁴ it was decided to restrict the reducing agent, at least initially, to LiAlH_4 slurried in ethyl ether.

Immediate interest was directed toward extending beyond the confines of what was defined as the scope of the

dissertation in (a), (b), and (c), above, to further structural changes. The next priorities were to establish the effect of electronegative flanking groups ($R_3 = \text{Cl, Br, I}$) while the reducible group remained COCH_2Br . Then it was desired to establish the effect of changing the departing halogen from bromine to chlorine, and perhaps ultimately to fluorine and iodine.

Much further along in this area of research, the effect of other reducing agents (e.g., NaBH_4) and solvents other than ethyl ether are expected to be examined. There also remains the intriguing question of what happens when R_4 is no longer hydrogen, but an alkyl group, specifically methyl.

This dissertation describes the results of the investigations proposed as fundamental in (a) and (b) and such of the other work, currently underway, as is sufficiently complete to warrant inclusion. Finally, the whole of the work is presented in a unified mechanism as was sought in (c).

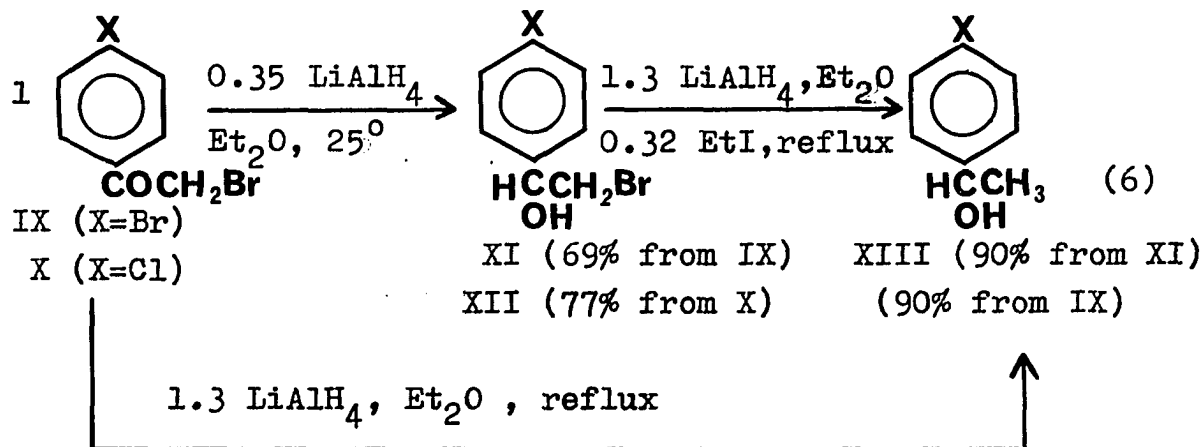
Background

Background

The literature concerning the use of lithium aluminum hydride and related complex metal hydrides as reducing agents is extensive. No effort to review the field is attempted here. Rather, a few papers are presented, illustrative of the general theme of the dissertation work, to provide a framework for subsequent discussion.

(A) Halohydrin Formation in Phenacyl Halide Systems.

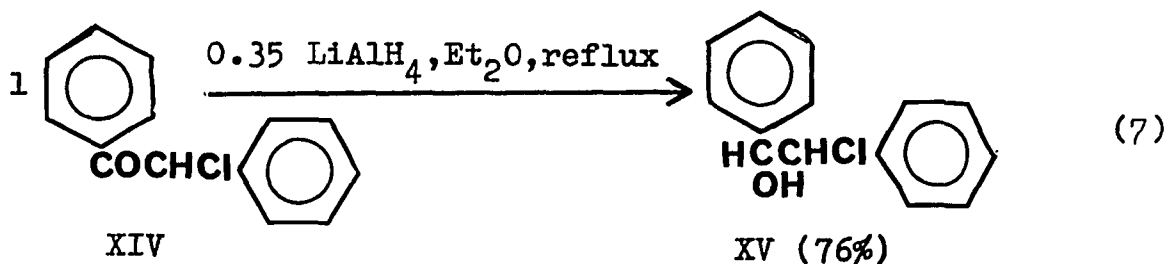
Early work by R. E. Lutz et al showed that phenacyl halides and desyl chloride (XIV) were smoothly reduced to halohydrins by LiAlH_4 in ether,⁵ as shown in Eqs 6 and 7:



What was noteworthy here was the smooth formation of the halohydrins, and the demonstration in one case, XI, that the

(5) R.E. Lutz, R.L. Wayland, Jr., and H.G. France, J. Amer. Chem. Soc., 72, 5511 (1950).

halohydrin was readily reduced to the benzylic alcohol, XIII. Also of interest, albeit not unexpected, was the observation that the benzylic alcohol, XIII, was the product, not the alkane from hydrogenolysis thereof. This would follow from the known resistance of benzylic alcohols to LiAlH_4 hydrogenolysis unless a para- OH or NH_2 is present. Similarly, desyl chloride (XIV) was reduced to its halohydrin (XV) in high yield (Eq 7):



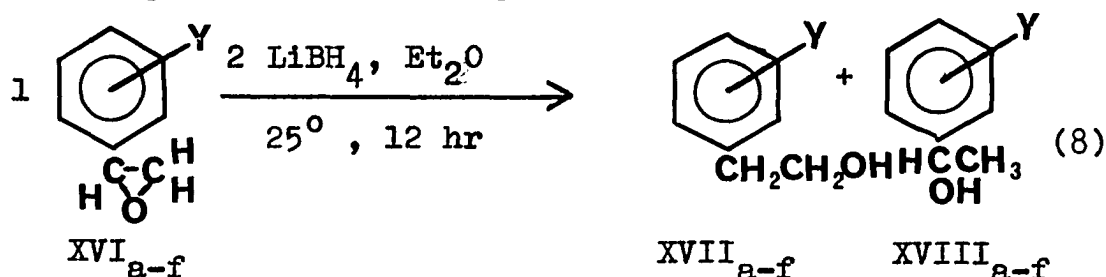
In conclusion, the standard reaction of a phenacyl bromide or chloride is reduction to a halohydrin, or benzylic alcohol, depending upon the amount of LiAlH_4 , and neither process occurs with aryl rearrangement. This stands in marked contrast with the results of this dissertation research, where aryl rearrangement is virtually the normal reaction.

(B) Complex Metal Hydride Reductions of Substituted Styrene Oxides.

The direction of epoxide ring opening in a variety of styrene oxides with LiBH_4 was investigated by R. Fuchs and G.J. Park^{6a,b} who established a clear relationship

-
- (6)(a) R. Fuchs, J. Amer. Chem. Soc., 78, 5612 (1956);
 (b) G.J. Park and R. Fuchs, J. Org. Chem., 21, 1513 (1956).

between the direction of epoxide ring opening and the electron-donating ability of the substituents on the aromatic ring as outlined in Eq 8:



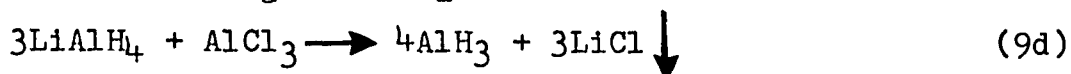
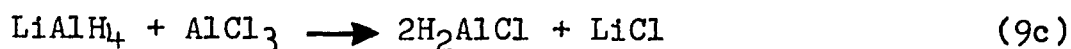
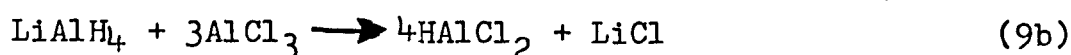
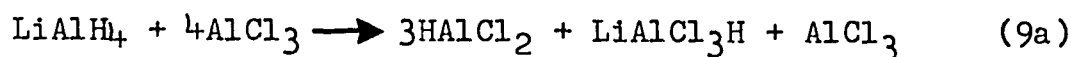
The results were: XVI_a (Y = para-CH₃O), 95% XVII_a; XVI_b (Y = para-CH₃), 68% XVII_b; XVI_c (Y = H), 26% XVII_c; XVI_d (Y = meta-CH₃O), 23% XVII_d; XVI_e (Y = para-Br), 16% XVII_e; XVI_f (Y = 3,4-di-chloro), 5% XVII_f. The balance of the product in all cases was the corresponding benzylic alcohol, XVIII. The experimental results were successfully fitted to a Hammett plot (σ) vs. log (percent of primary alcohol) product, with $\rho = -1.6$. The addition of 0.5 mol MgBr₂^{6b} raised the yield of primary alcohol to 84% (and 93% in a duplicate run) of the product for XVI_b. This demonstrated the effect of a Lewis acid in promoting formation of the primary alcohol product.

K. W. Trevoy and W. G. Brown⁷ found LiAlH₄ reduction of styrene oxide (XVI_c) in ether produced 95% of the benzylic alcohol, XVIII_c, and 5% of the primary alcohol, XVII_c.

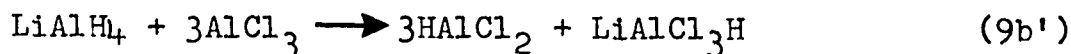
(7) K.W. Trevoy and W.G. Brown, J. Amer. Chem. Soc., 71, 1675 (1949).

(C) The Nature of $\text{LiAlH}_4\text{-AlX}_3$ Reagents and Their Effect Upon Reduction Mechanisms.

E. C. Ashby and J. Prather⁸ mixed cooled solutions (-10°) of LiAlH_4 and AlCl_3 , both in ether, followed by addition of Et_3N and filtration of the LiCl . They were able to establish the stoichiometry and elemental composition of the products as the Et_3N complexes. The pertinent equations, omitting the Et_3N , are 9 a - d:



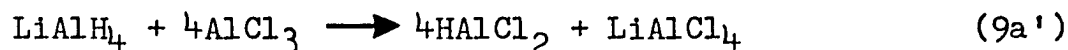
It should be noted that LiCl does not precipitate the reactions shown in Eq 9b and c until Et_3N is added. The LiCl solubility in ether is explicable if the complex formation is assumed, viz.:



The equations for the reactions with AlBr_3 and AlI_3 follow exactly. There is the trivial difference that LiBr and LiI are quite soluble in ether, necessitating concentration of the initial product and extraction of the

(8) E.C. Ashby and J. Prather, J. Amer. Chem. Soc., 88, 729 (1966).

hydrioaluminum halide with benzene. The reaction shown in Eq 9a was somewhat in doubt, because an alternative exists, Eq 9a':



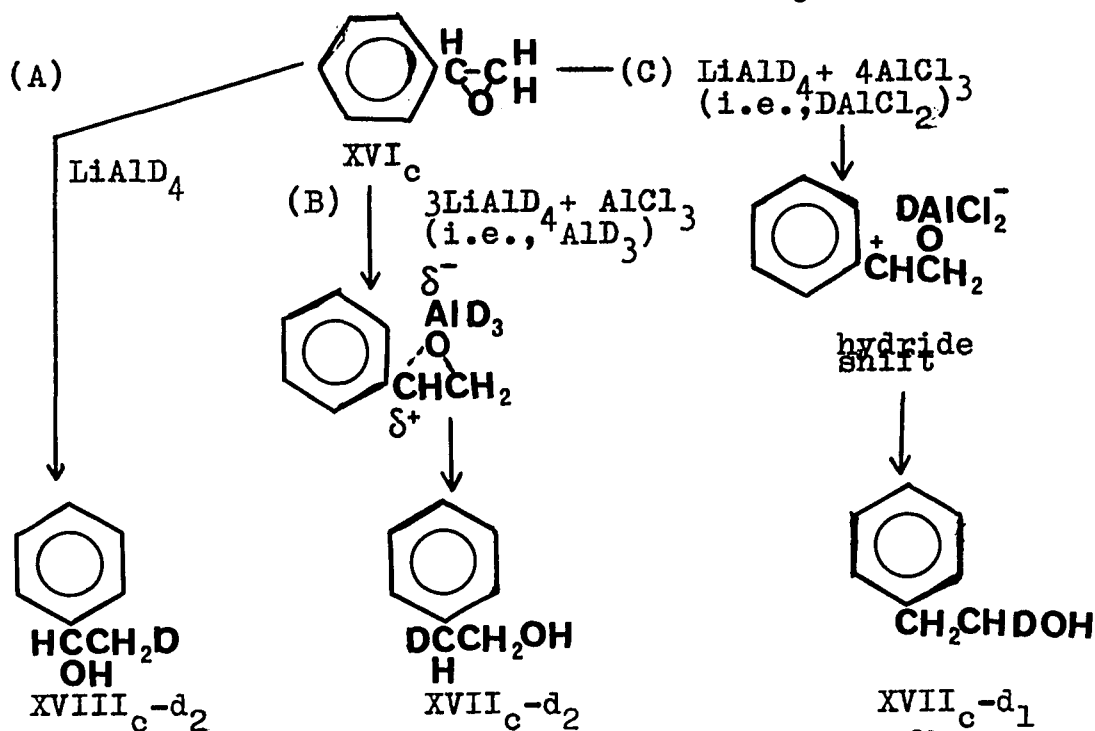
Eq 9a' could also occur--and explain the lack of precipitation of LiCl from the ether solutions; however, this was not as favored on chemical reaction grounds, as will be discussed presently.

Using these results, Ashby and Prather reinterpreted earlier work by E. L. Eliel and his coworkers^{9a,b} (Chart I), assuming that HALX_2 and AlX_3 will be of comparable strength as Lewis acids, but much stronger than AlH_3 . The explanation advanced concerning the paths followed (see Chart I) is relatively straightforward. (A) and (D) represent ordinary $\text{S}_{\text{N}}2$ attack at the least hindered site. (B) and (E) represent complexation of the epoxide by the effective reagent, AlD_3 or AlH_3 , causing partial opening of the epoxide ring by these weak Lewis acids, followed by immediate reduction of the more stable incipient carbonium ion. (C) and (F) represent complexation of the epoxide by the effective reagent, DAlCl_2 or HALCl_2 , causing opening of the epoxide ring by these Lewis acids, which are stronger than AlH_3 , but weaker reducing agents, followed by hydride or phenyl shifts,

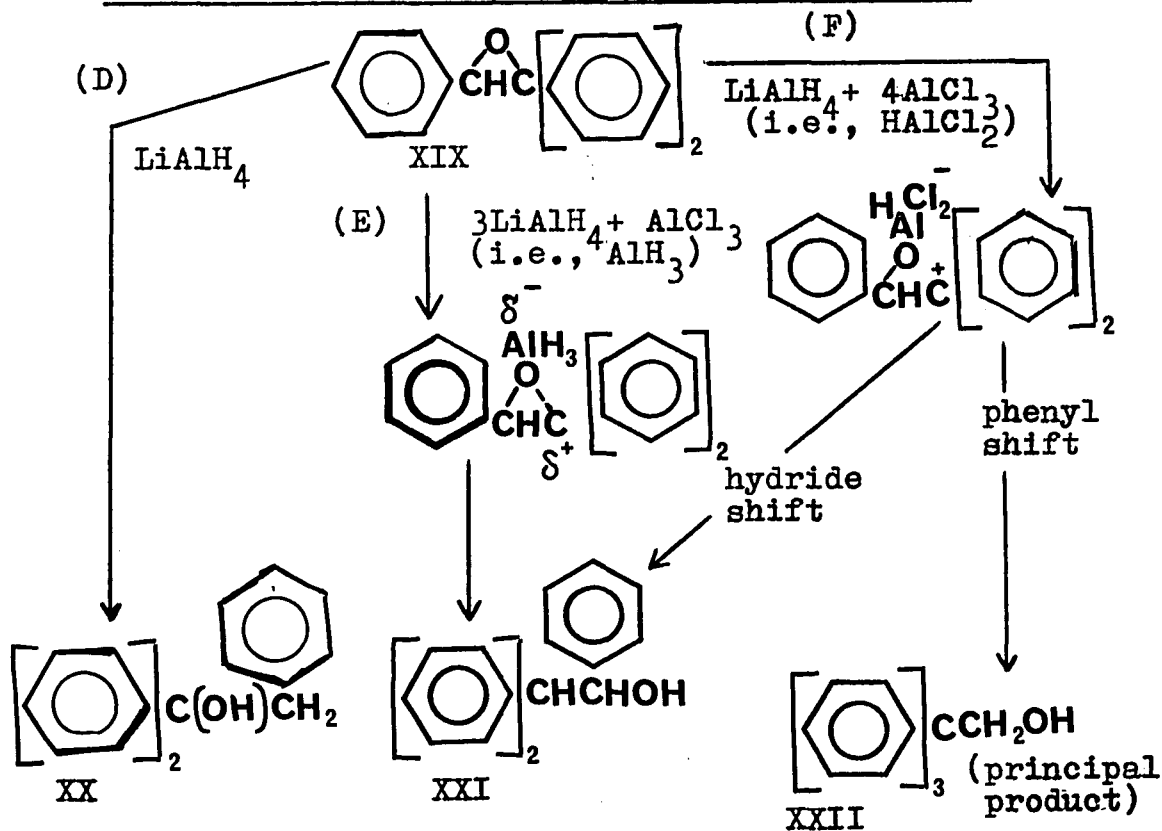
(9)(a) E.L. Eliel and D.W. Delmonte, J. Amer. Chem. Soc., 80, 1744 (1958); (b) M.N. Rerick and E.L. Eliel, ibid., 84, 2356 (1962).

Chart I⁸

The Reduction of Styrene Oxide (XVI_c)^{9a}



The Reduction of Triphenylstyrene oxide (XIX)^{9b}



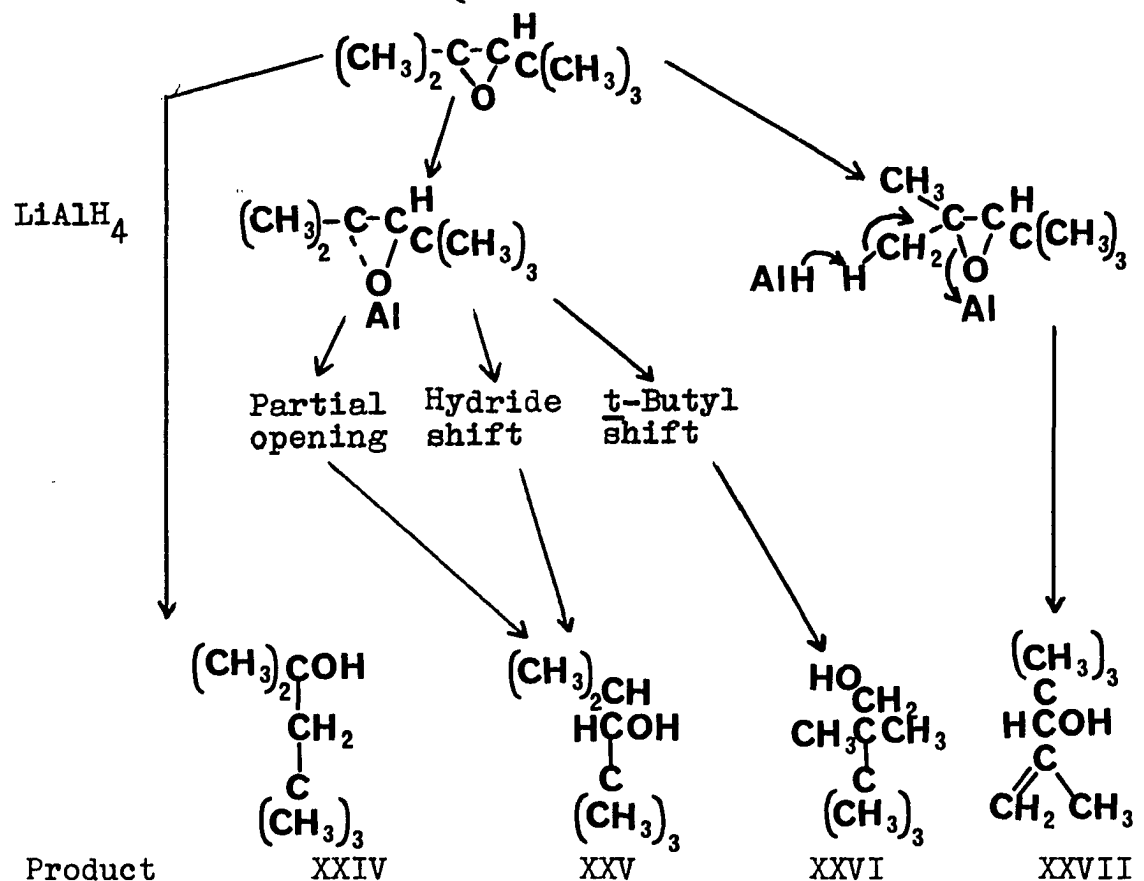
and reduction to the final products. (The intermolecular reductions have been omitted.)

Ashby and B. Cooke¹⁰ extended the work with mixed hydride reagents to β -diisobutylene oxide (XXIII) (Chart II) and reinforced the previous suggestions.⁸ The explanation follows the same course as described for Chart I. The effect of enhanced ring opened product--as reflected by the product from tert.-butyl migration (XXVI)--as the Lewis acidity rises (HAlI_2 to HAlCl_2) compared to the correspondingly weaker Lewis acids (H_2AlI to H_2AlCl) employed is especially striking. The authors also secured evidence that Eq 9a, p 17, was correct: the ratio of XXVI/XXV was 4.7 when $\text{LiAlH}_4 + 4\text{AlCl}_3$, the presumed generator of LiAlCl_3H , was used as opposed to a ratio of 7.2 when pure HAlCl_2 was used as the reducing agent. LiAlCl_3H should be a better hydride donor than HAlCl_2 in intermolecular $\text{S}_{\text{N}}2$ attack upon the HAlCl_2 --complexed epoxide (the intermolecular reductions have been omitted from Chart II). Hence the amount of XXV would be raised in the presence of LiAlCl_3H , producing the observed change in ratios. The extent of hydride shift to product XXV, vs. tert.-butyl shift was checked with 1 $\text{LiAlD}_4 + 3\text{AlCl}_3$ reduction. It was found by nmr spectral examination of XXV that ca. 7% of the postulated fully opened carbonium ion

(10) E.C. Ashby and B. Cooke, J. Amer. Chem. Soc., 90, 1625 (1968).

Chart II¹⁰

The Reduction of β -Diisobutylene Oxide (XXIII)^a



Reagent ^b	Yield, Percent of Total			
LiAlH_4^c	100	0	0	0
AlH_3	12	34	9	45
H_2AlCl	2	24	65	8
H_2AlBr	5	44	44	7
H_2AlI	0	33	35	32
HAlCl_2	1	16	75	8
HAlBr_2	1	19	65	15
HAlI_2	3	23	54	20

^a Three equivalents of hydride per mole of epoxide, 2 hr reaction at 25°. ^b Effective reagent in solution, e.g., $3\text{AlCl}_3 + 1 \text{LiAlH}_4$ is listed as AlH_3 , etc. ^c 24 hr reflux.

undergoes hydride shift to yield XXV and 93% undergoes tert.-butyl shift to yield XXVI. This agreed with earlier work by Eliel.¹¹

(D) Studies on the Reduction of Halogen and Epoxide Compounds.

A series of papers by Eliel and his coworkers provides much of the background for the mechanisms believed to be operative in this dissertation.

The pertinent work was initiated by the reduction of several 2-chloroacids and esters to produce alcohols.¹² It was suggested that chlorohydrins were intermediates in the reduction, accordingly a series of 2-chloroacids and esters were reduced with LiAlH_4 .¹³ It was established that 2-chlorohydrins could be produced in high yield by addition of a solution of LiAlH_4 to the substrate (inverse addition), or the substrates could be reduced largely to the alcohols by a sufficient excess of LiAlH_4 . It was also established that the ease of displacement of chlorine was primary chlorine

(11) E.L. Eliel and M.N. Rerick, J. Amer. Chem. Soc., 82, 1362 (1960).

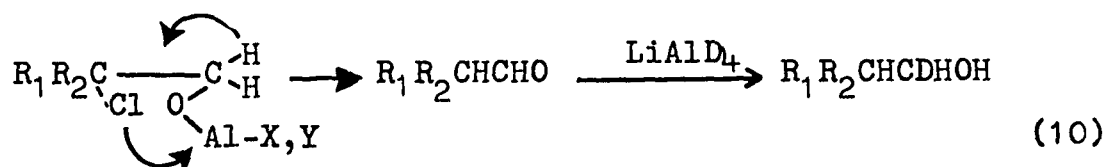
(12) E.L. Eliel and J.P. Freeman, J. Amer. Chem. Soc., 74, 928 (1952).

(13) E.L. Eliel, C. Herrmann, and J.P. Traxler, J. Amer. Chem. Soc., 78, 1193 (1956).

... > secondary chlorine < tertiary chlorine.

The observation that chlorine and bromine were readily displaced led to the suggestion that a cyclic transition state which involved interaction of the alkoxy bound aluminum with the adjacent halogen had occurred. This suggestion was advanced because the reduction of aliphatic chlorides by LiAlH_4 was known to be slow in refluxing ether.¹³

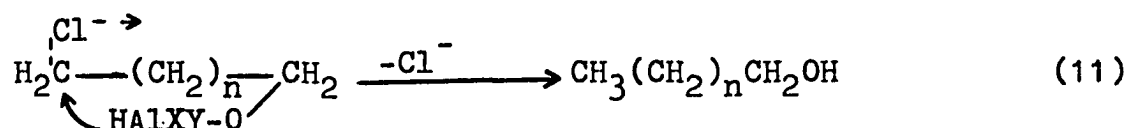
Reduction with LiAlD_4 of model vicinal halohydrins established:¹⁴ (a) the halogen could be directly displaced by D; (b) if displacement was hindered (e.g., a tertiary halide), the aluminum could assist the departure of the halogen by helping to pull it off via a cyclic transition state. This process allowed a hydride shift to occur. The addition of small amounts of hydroxylic materials to the LiAlH_4 in the reduction of a tertiary chlorohydrin increased the rate of conversion of that substrate to the alcohol. That observation suggested Lewis acid character was imparted to the partially decomposed LiAlH_4 . A cyclic transition state was proposed to account for the hydride shift, as shown in Eq 10:



(14) E.L. Eliel and T.J. Prosser, J. Amer. Chem. Soc., 78, 4045 (1956).

The Al was shown as bonded to X,Y rather than to AlD₃ to include the general cases where a hydroxylic solvent was added and X and Y could be O⁻ or RO⁻.

The direct displacement of halogen by Al-H via a cyclic transition state was tested by the reduction of a series of ω-chlorohydrins.¹⁵ The ease of displacement of the chlorine, to yield the alcohols, was rapid displacement if chlorine was in the 2 or 3 position, very slow if chlorine was in the 5 or 6 position, with the 4 position as an intermediate case. These results suggested that an alternate reaction operates if the halogen is readily susceptible to direct displacement by alkoxy bound Al-H, as shown in Eq 11:



The possible role of epoxides as intermediates in the reduction of halohydrins became important when phenyl substituted bromohydrins were reduced.^{9a} Those reductions gave products that required the epoxide ring to have opened "normally" (S_N2 attack by LiAlH₄ at the least hindered site) but also "abnormally" (e.g., the reverse direction of ring opening). Therefore, the reduction of epoxides was studied to determine whether they could be intermediates, especially

(15) E.L. Eliel and J.T. Traxler, J. Amer. Chem. Soc., 78, 4049 (1956).

in the benzylic and tertiary halohydrin reductions.¹⁶ It was established that hydride attack was at the least hindered site of the epoxide, as long as the reducing agent was LiAlH_4 . However, this mode of attack was effectively reversed when the reducing agent was $1 \text{ LiAlH}_4 + 4 \text{ AlCl}_3$. These results with LiAlH_4 and 3 or 4 AlCl_3 have been discussed, i.e., Eq 10 and 11, in the light of Ashby's work^{8,10}, see p 18. The addition of an epoxide pathway for the reduction of the highly substituted or benzylic halohydrins appeared warranted in addition to the two modes of attack via cyclic transition states.

(E) Some Other Rearrangements During LiAlH_4 Reductions.

(One). Double-Bond Participation During Reduction.

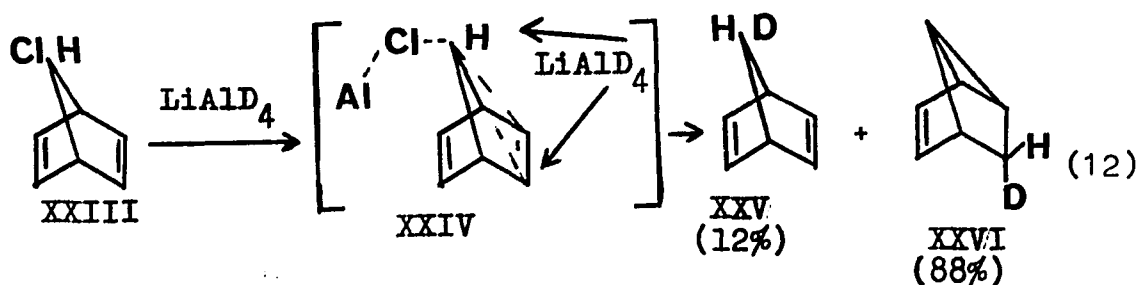
P. Story^{17,18} offered another example of the general theme that groups displaced only with difficulty, but adjacent to electron-donating centers, invite such assistance in their displacement. They reduced 7-chloronorbornadiene

(16) E.L. Eliel and M.N. Rerick, J. Amer. Chem. Soc., 82, 1362 (1960).

(17) P.R. Story, J. Amer. Chem. Soc., 83, 3347 (1961);

(18) P.R. Story and M. Saunders, ibid., 84, 4876 (1962).

(XXIII) as shown in Eq 12:

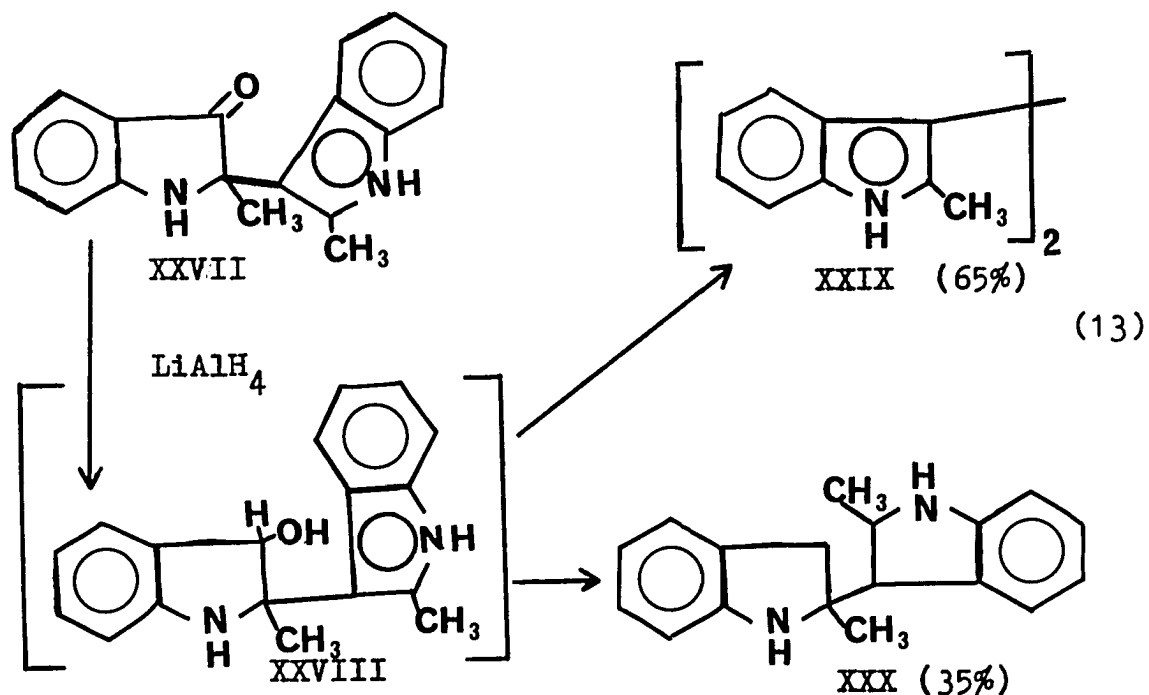


They obtained the alkene XXVI, labelled endo- as 88% of the product, with only 12% of the 7-deuterionorbornadiene (XXV). The bridged carbonium ion, XXIV, was advanced as the crucial intermediate structure. The Al was pictured as weakly pulling off the Cl, leading to prompt reduction of the carbonium ion, presumably before extensive charge separation occurred. The authors noted that addition of traces of water--as in Eliel's work¹⁴--generated the same products, but faster. Presumably a slightly stronger Lewis acid was generated thereby, which would account for those observations.

(Two). Rearrangements to Achieve Aromaticity.

B. Witkop and J. B. Patrick¹⁹ provided an early example of extensive participation of a neighboring group, resulting in an aromatic ring system as shown in Eq 13:

(19) B. Witkop and J.B. Patrick, J. Amer. Chem. Soc. 73, 713 (1951).



They reduced 2-methyl-2,3'-(2'-methylinidyl) indoxyl (XXVII) in an attempt to obtain the alcohol, XXVIII, but obtained 65% of 2-methyl-3,3'-(2'-methylinidyl) indole (XXIX) and 35% of 2-methyl-2,3'-(2'-methylinidyl) 2,3-dihydroindole (XXX). Presumably the desired alcohol, XXVIII, undergoes hydro-
genolysis to XXIX or rearrangement--probably as the carbon-
oxygen bond is being cleaved--to XXX.

Results and Discussion

Results and Discussion

(A) Results of the Lithium Aluminum Hydride Reductions.

In the following pages are presented the results of the reductions in tabular form. Examination of the tables reveals a variety of observations which require a suitable mechanistic explanation. They will be briefly summarized at this time: (a) The reduction of $I_{2b} - V_{2b}$, i.e., where the reducible group is $COCH_2Br$ and the 3',5' "flanking" groups are alkyl, shows a sharp decrease in alkane product as the series hydrogen (ca. 90%), methyl (63%), ethyl (44%), isopropyl (28%), tert.-butyl (ca. 0%) is ascended. Correspondingly, the primary alcohol product rises: ca. 0%, 34%, 47%, 63%, ca. 90%, respectively. Reduction with $LiAlD_4$ results in alkane labelled as $ArCD_2-CH_2D$, whereas the primary alcohol is labelled $ArCH_2CD_2OH$. (b) When the reducible group is $COCH_2Cl$ (i.e., $II_{2b}-Cl$), the amount of primary alcohol is markedly higher than for the corresponding bromine compounds, viz.: 64% vs. 34% from II_{2b} , 65% vs. 44% from III_{2b} , 78% vs. 63% from IV_{2b} . Accordingly, the alkane product is a lower percentage than from the bromoketones. In addition, the presence of other products (dimers and alkyl halide) totalling a few percent (ca. 3 - 10%) from the bromine compounds, increased for the chlorine analogs to ca. 15 - 20% of the total. (c) In the tert.-butyl series, V_{3b-6b} (see Table VI), the substitution

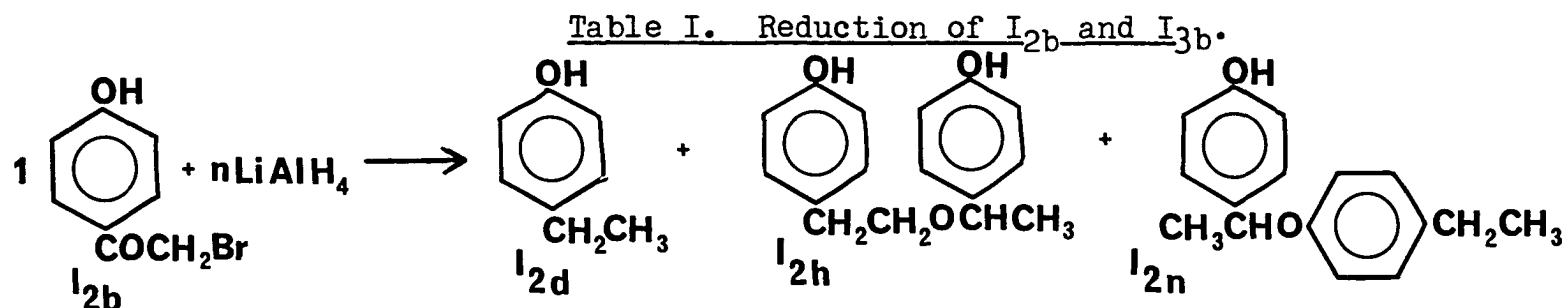
of $\text{COCR}_1\text{R}_2\text{Br}$ for COCH_2Br increased the yield of the primary alcohol product from 90% to effectively 100%. A more dramatic example of the effect of substitution on carbon-2 was provided in the series II_{3b-5b} (see Table III). There the primary alcohol product was increased to 95 - 97% of the total, from ca. 34% for the COCH_2Br group, II_{2b} . (d) In marked contrast to the alkyl flanking groups, substitution of chlorine or bromine in the 3',5' positions, as shown by the work of W. C. Hollinsed,²⁰ Table VII, p 39, results in the absence of primary alcohol product, and the appearance of benzylic alcohols as the major product. The alkane product continues to appear, but at a reduced level compared to the methyl flanking group (II_{2b}). (f) A final contrast to the results of (d) and (a - c) was provided by the work of E. M. Chan,²¹ Table VIII, p 41. There the flanking group was chlorine, as in (d), but the reducible group was COCHBrCH_3 , as in (c). The result was marked production of the bromohydrin. Under forcing conditions (extended reflux, considerable excess of LiAlH_4) the primary alcohol and benzylic alcohol were produced in roughly equal quantities, while the alkane appears not to have been produced.

(20) W.C. Hollinsed, The City College, many of whose unpublished observations are gathered in Table VII.

(21) E.M. Chan, The City College, many of whose unpublished observations are gathered in Table VIII.

It will be observed that other entries note different reflux times, amounts of LiAlH_4 , concentration of substrate, and a group of products, usually in minor amounts. These matters will be commented upon as required in the mechanism discussion.

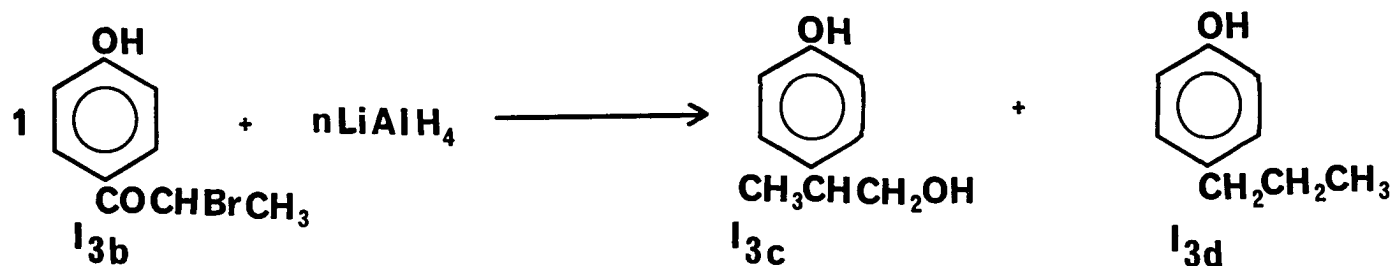
Quantitative chromatographic separation of the products in Tables VII²⁰ and VIII²¹ are currently underway.



Entry	Compd	Reflux, min	mol LAH	Percent Product Distribution (Molar Yield, %)		
1	I_{2b}	360	2.26	91	I_{2d} , 9	Unassigned (91.5%) ^a
2	I_{2b}	360	2.26	91	I_{2d} , 9	Unassigned (93.6%) ^a
3	I_{2b}	360	9.00 ^b	66.6	I_{2d} , 33.4	Unassigned (82.8%) ^a
4	I_{2b}	360	2.25	86.2	I_{2d} , 13.8	Unassigned (93.5%) ^a
5	I_{2b}	360	2.25	79.3	I_{2d} , 20.7	Unassigned (90.4%) ^a
1,2,5				(85.6	I_{2d} , 8.1 I_{2n} , 6.3 I_{2h} (59.3%))	^{c,d}

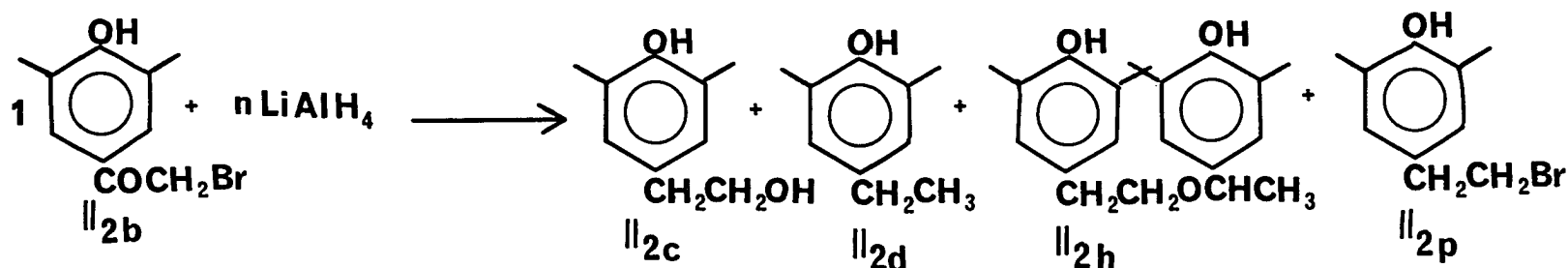
^a Analyses by nmr. ^b 0.0050 mol I_{2b} /200 ml ether, all others are 0.0100 mol/100 ml ether. ^c Dry column chromatography results. ^d Severe loss of I_{2d} via sublimation during work-up.

Table I (continued)



Entry	Compd	Reflux, min	mol LAH	Percent Product Distribution (Molar Yield, %)		
6	I _{3b}	360	2.25	80	I _{3c} , 20	Unassigned (86.4%) ^a
7	I _{3b}	360	2.25	80	I _{3c} , 20	Unassigned (92%) ^a
6,7				(84.5	I _{3c} , 12.2	Unassigned, 3.5 I _{3d} (77.5%)) ^c
8	I _{3b}	360	2.40	80	I _{3c} , 20	Unassigned (94.5%) ^a

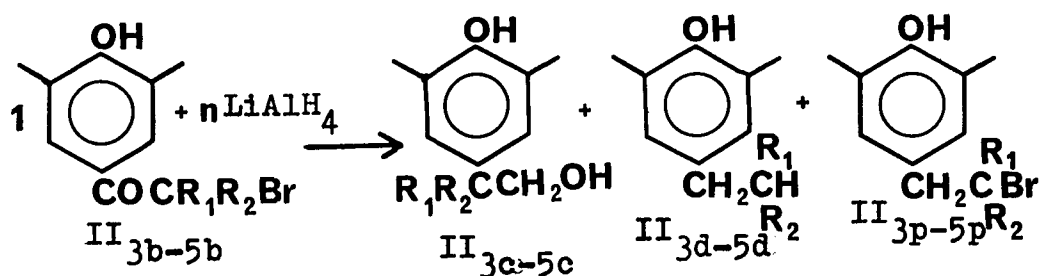
^a Analyses by nmr. ^b 0.0050 mol I_{2b}/200 ml ether, all others are 0.0100 mol/100 ml ether. ^c Dry column chromatography results. ^d Severe loss of I_{2d} via sublimation during work-up.

Table II. Reduction of II_{2b} and II_{2b}-Cl


Entry	Compd	Reflux, min	n, mol LAH	Percent Product Distribution (Molar Yield, %)			
1	II _{2b}	360	2.26	30.3 II _{2c} , 69.7 II _{2d}			(98.6%) ^a
2	II _{2b}	360	2.25	34.4 II _{2c} , 65.6 II _{2d}			(98.6%) ^a
1,2				(34.2 II _{2c} , 62.6 II _{2d} , 1.4 II _{2h} , 1.7 II _{2g} and II _{2p}			(79.5%) ^b
3	II _{2b}	360	9.00 ^c	36 II _{2c} , 64 II _{2d}			(92.2%) ^a
4	II _{2b}	360	2.96 ^d	32.6 II _{2c} , 67.4 II _{2d}			(96.5%) ^a
5	II _{2b}	360	2.96 ^d	36.2 II _{2c} , 63.8 II _{2d}			(96.5%) ^a
4,5				(32.4 II _{2c} , 63.9 II _{2d} , 1.5 II _{2h} , --II _{2g} , 2.2 II _{2p}			(81.0%) ^b
6	II _{2b} -Cl	360	2.25	ca 53.6 II _{2c} , 33.4 II _{2d}			(91.7%) ^a
7	II _{2b} -Cl	360	2.25	ca 51.8 II _{2c} , 34.3 II _{2d}			(91.6%) ^a
6,7				(64.0 II _{2c} , 15.8 II _{2d} , --II _{2h} , --II _{2g} , 17.1 II _{2p} -Cl, 3.2 II _{2q} -Cl			(78.3%) ^b

^a Analyses by nmr. ^b Dry column chromatography results. ^c 0.0050 mol II_{2b}/200 ml ether, all others are 0.0100 mol II_{2b}/100 ml ether. ^d LiAlD₄.

Table III. Reduction of II_{3b-5b}.

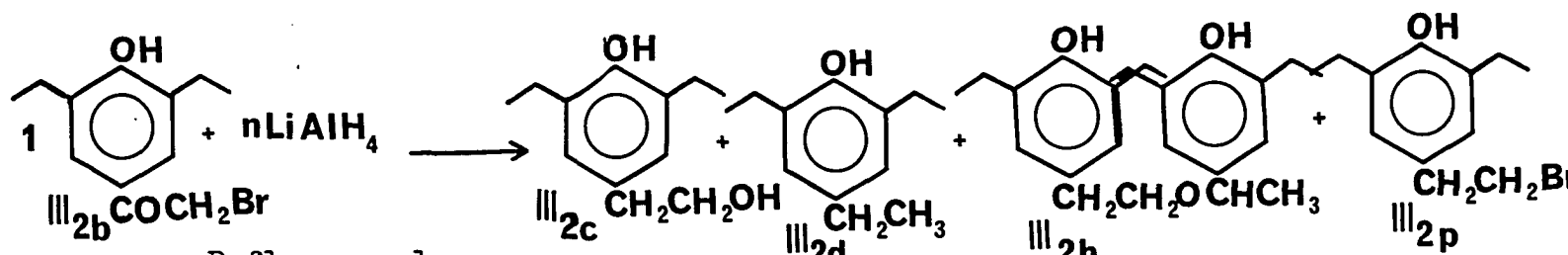


Entry	Compd	Reflux, min	mol LAH	Product Distribution (Molar Yld, %)	
1	II _{3b}	360	2.25	100 II _{3c}	(98.0%) <u>a</u> , <u>b</u>
2	II _{3b}	360	2.25	100 II _{3c}	(96.6%) <u>a</u> , <u>b</u>
3	II _{3b}	60	2.25	100 II _{3c}	(97.3%) <u>a</u> , <u>b</u>
4	II _{3b}	4	2.25	ca. 80-90 II _{3c}	(96%) <u>a</u> , <u>c</u>
5	II _{4b}	360	2.34	100 II _{4c}	(96.7%) <u>a</u> , <u>d</u>
6	II _{4b}	60	2.26	100 II _{4c}	(96.6%) <u>a</u> , <u>d</u>
7	II _{4b}	60	2.25	100 II _{4c}	(97.8%) <u>a</u> , <u>d</u>
8	II _{4b}	4	2.26	100 II _{4c}	(98.3%) <u>a</u> , <u>d</u>
9	II _{5b}	300	2.25	95 II _{5c} , 5 II _{5d}	(97.0) <u>a</u> , <u>e</u>
10	II _{5b}	60	2.25	95 II _{5c} , 5 II _{5d}	(99.5) <u>a</u> , <u>e</u>
11	II _{5b}	60	2.26	95 II _{5c} , 5 II _{5d}	(97.0) <u>a</u> , <u>e</u>
12	II _{5b}	4	2.25	95 II _{5c} , 5 II _{5d}	(99.1%) <u>a</u> , <u>e</u>

a Analyses by nmr. b Concentration of the product indicated perhaps 4% other material was present (e.g. II_{3p} or II_{3e}). c The reaction had reached at least 80% of completion, but the other components were unidentified.

d Concentration of the product indicated perhaps 2.9% other material was present (e.g. II_{4d}). e Other material was discernible in the crude product nmr spectrum, concentration of which indicated it to be 4.7% II_{5d}.

Table IV. Reduction of III_{2b} and III_{2b}-Cl

							
Entry	Compd	Reflux, min	mol LAH	Percent Product Distribution (Molar Yield, %) ^a			
1	III _{2b}	180	2.25	40	III _{2c} , 60	III _{2d}	(92.5%) ^a
2	III _{2b}	300	2.25	40.8	III _{2c} , 59.2	III _{2d}	(100%) ^a
3	III _{2b}	300	2.26	44.6	III _{2c} , 55.4	III _{2d}	(100%) ^a
2,3				(46.7	III _{2c} , 44.3	III _{2d} , 4.0 III _{2h} , 4.9 III _{2p}	(86.4%) ^b
4	III _{2b}	360	9.00 ^c	48	III _{2c} , 52	III _{2d}	(94.8%) ^a
5	III _{2b}	300	2.70 ^d	55.2	III _{2c} , 44.8	III _{2d}	(99.7%) ^a
6	III _{2b}	300	2.77 ^d	48.9	III _{2c} , 51.1	III _{2d}	(100%) ^a
5,6				(47.9	III _{2c} , 44.0	III _{2d} , 2.2 III _{2h} , 4.5 III _{2p}	(81.9%) ^b
7	III _{2b} -Cl	300	2.26	ca 75.6	III _{2c} , 24.4	III _{2d}	(94.5%) ^a
8	III _{2b} -Cl	300	2.25	ca 78.1	III _{2c} , 21.9	III _{2d}	(96.2%)
7,8				(64.8	III _{2c} , 13.4	III _{2d} , 4.4 III _{2h} , ^e 12.4 III _{2p} -Cl, 1.4 III _{2e} -Cl)) ^b	

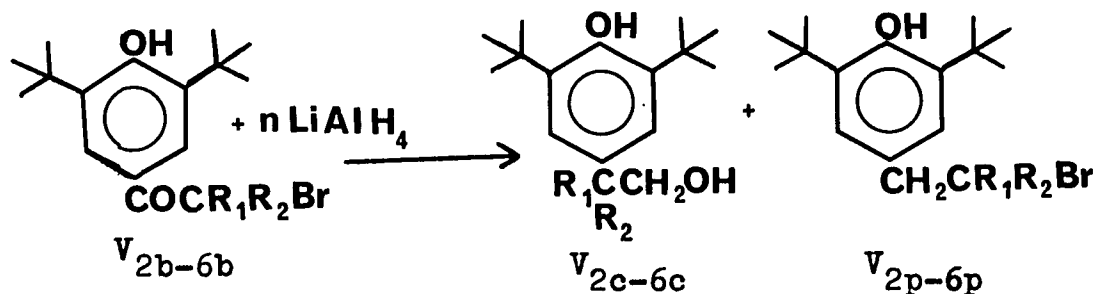
^a Analyses by nmr. ^b Dry column chromatography results. ^c 0.0050 mol III_{2b}/200 ml ether, all others are 0.0100 mol III_{2b}/100 ml ether. ^d LiAlD₄. ^e Mass spec shows trace of III_{2q}-Cl.

Table V. Reduction of IV_{2b} and IV_{2b}-Cl

Entry	Compd	Reflux, min	mol LAH	Percent Product Distribution (Molar Yield, %)			
1	IV _{2b}	180	2.26	66.7	IV _{2c} , 33.3	IV _{2d}	(98.6%) ^a
2	IV _{2b}	180	2.25 ^d	66.7	IV _{2c} , 33.3	IV _{2d}	(98.8%) ^a
3	IV _{2b}	360	9.00 ^c	65.5	IV _{2c} , 34.5	IV _{2d}	(97%) ^a
4	IV _{2b}	360	2.25	67	IV _{2c} , 33	IV _{2d}	(99.2%) ^a
5	IV _{2b}	360	2.27	64	IV _{2c} , 36	IV _{2d}	(99.0%)
4,5				(63.4	IV _{2c} , 28.2	IV _{2d} , 2.5 IV _{2h} , 5.6 IV _{2p} , 0.5 IV _{2a}	(87.0%) ^b
6	IV _{2b}	360	2.74 ^d	65.2	IV _{2c} , 34.8	IV _{2d}	(99.5%) ^a
7	IV _{2b}	360	2.80 ^d	65.2	IV _{2c} , 34.8	IV _{2d}	(100%) ^a
6,7				(63.4	IV _{2c} , 27.5	IV _{2d} , 3.7 IV _{2h} , 5.4 IV _{2p}	(89.2%) ^d
8	IV _{2b}	40	2.25	63	IV _{2c} , 37	IV _{2d}	(98.0%) ^a
9	IV _{2b}	10	2.26	65.1	IV _{2c} , 34.9	IV _{2d}	(100%) ^a
10	IV _{2b} -Cl	360	2.25	ca 79	IV _{2c} , 21	IV _{2d}	(98.1%) ^a
11	IV _{2b} -Cl	360	2.26	ca 79	IV _{2c} , 21	IV _{2d}	(98.1%) ^a
10,11				(77.6	IV _{2c} , 7.8	IV _{2d} , 2.3 IV _{2h} , 10.9 IV _{2p} -Cl, 0.1 IV _{2a} , 1.2 IV _{2e} -Cl	(86.3%) ^d

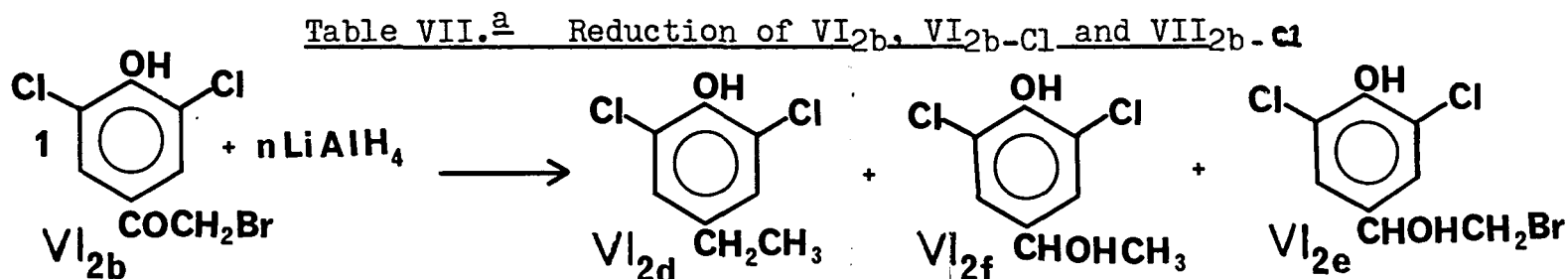
^a,^b,^c,^d: See Table IV, page 36.

Table VI
Reduction of V_{2b-6b}



Entry	Compd	Reflux, min	mol LAH	% Product Distribution (Molar Yield, %)	
				V _{2c}	V _{2p}
1	V _{2b}	180	2.25	90 V _{2c} , 10 V _{2p}	(97.5%) ^a
2	V _{2b}	270	4.84 ^b	90 V _{2c} , 10 V _{2p}	(93.5%) ^a
3	V _{3b}	180	2.40	100 V _{3c}	(98.9%) ^a
4	V _{3b}	180	2.16	100 V _{3c}	(89.4%) ^{a, c}
5	V _{3b}	4	2.25	100 V _{3c}	(95.8%) ^a
6	V _{4b}	180	2.25	100 V _{4c}	(81.0%) ^{a, c}
7	V _{4b}	180	2.25	100 V _{4c}	(98.1%) ^a
8	V _{4b}	30	2.34	100 V _{4c}	(100%) ^a
9	V _{4b}	4	2.26	100 V _{4c}	(98.3%) ^a
10	V _{5b}	180	2.28	100 V _{5c}	(88.6%) ^{a, c}
11	V _{5b}	180	2.25	100 V _{5c}	(96.8%) ^a
12	V _{5b}	4	2.36	100 V _{5c}	(98.3%) ^a
13	V _{6b}	180	2.25	100 V _{6c}	(92.6%) ^a
14	V _{6b}	180	2.25	100 V _{6c}	(98.1%) ^a

^a Analyses by nmr. ^b LiAlD₄. Product structure was ArCH₂CD₂OH for V_{2c}. ^c Spillage of crude product occurred.



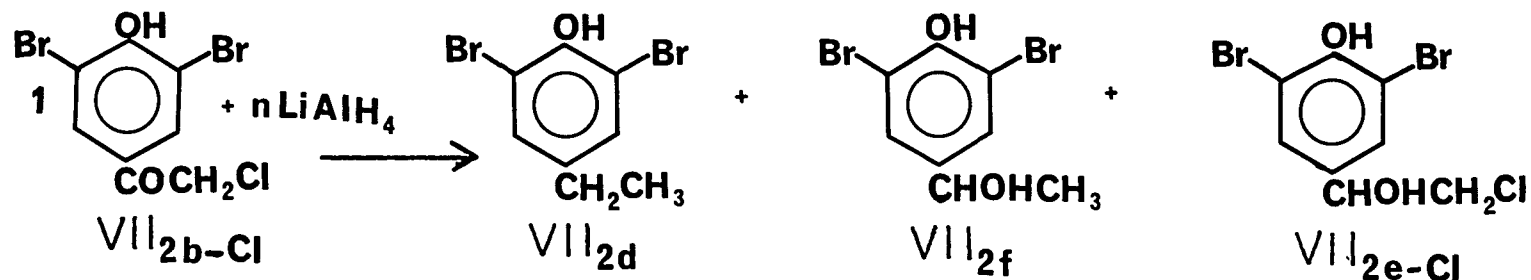
Entry	Compd.	Reflux, min	mol LAH	Percent Product Distribution (Molar Yield, %)		
				VI _{2f}	VI _{2d}	VI _{2e}
1	VI _{2b}	180	2.36	90.4	9.6	(76%) ^b
2	VI _{2b}	180	2.25	84.5	15.5	(95%) ^b
3	VI _{2b}	180	2.25	85.5	14.5	(95%)
4	VI _{2b}	30	2.25	85.0	5	10.0 (85%) ^b
5	VI _{2b} -Cl	1200	2.15	69.9	30.1	(98%) ^b
6	VI _{2b} -Cl	180	2.30	63.7	7.3	29.0 (87%) ^b
7	VI _{2b} -Cl	180	2.25	68.5	11.5	20.0 (88%) ^b
8	VI _{2b} -Cl	60	2.25	51.8	11.1	37.1 (90%) ^b

^a Unpublished observations of William Christopher Hollinsed, The City College.

^b Analyses by nmr.

Table VII.^a Reduction of VI_{2b}, VI_{2b-Cl} and VII_{2b-Cl}

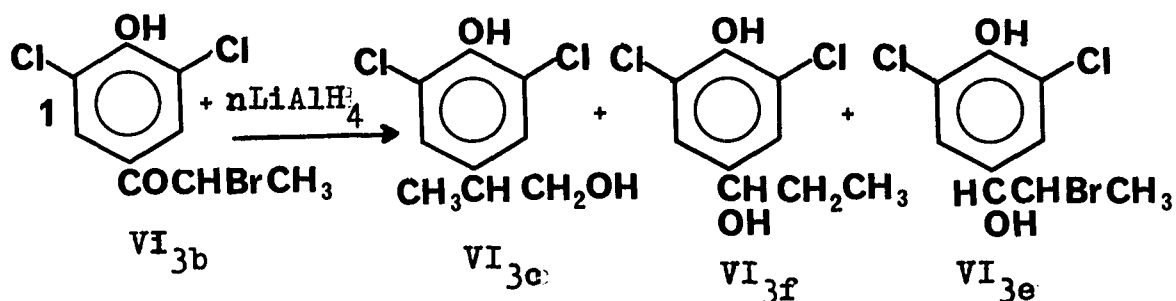
(Continued)



Entry	Compd	Reflux, min	mol LAH	Percent Product Distribution (Molar Yield, %)	
9	VII _{2b-Cl}	180	2.25	36.4 VII _{2f} , 6.8 VII _{2d} , 56.8 VII _{2e-Cl}	(75%) ^b

^a Unpublished observations of William Christopher Hollinsed, The City College.

^b Analyses by nmr.

Table VIII ^aReduction of VI_{3b}

Entry	Compd	Reflux, min	mol LAH	Percent Product Distribution
1	VI _{3b}	30	2.25	61 VI _{3e} , 39 Unassigned ^b
2	VI _{3b}	30	2.25	66 VI _{3e} , 34 Unassigned ^b
3	VI _{3b}	30	2.25	61 VI _{3e} , 39 Unassigned ^b
4	VI _{3b}	30	2.25	90 VI _{3e} , 10 Unassigned ^{b,c}
5	VI _{3b}	180	2.25	69 VI _{3e} , 31 VI _{3c} ^{b,d}
6	VI _{3b}	180	2.25	68 VI _{3e} , 22 VI _{3c} , 10 VI _{3f} ^b
7	VI _{3b}	180	9.00	4 VI _{3e} , 62 VI _{3c} , 34 VI _{3f} ^b
8	VI _{3b}	360	9.00	17 VI _{3e} , 50 VI _{3c} , 33 VI _{3f} ^b
9	VI _{3b}	900	9.00	-- VI _{3e} , 47 VI _{3c} , 53 VI _{3f} ^b
10	VI _{3b}	966	9.00	-- VI _{3e} , 57 VI _{3c} , 43 VI _{3f} ^b
11	VI _{3b}	1050	9.00	-- VI _{3e} , 50 VI _{3c} , 50 VI _{3f} ^b

^a Unpublished observations of Elizabeth Moy Chan, The City

College. ^b Analyses by nmr. ^c 0.0100 mol VI_{3b}/300 ml

of ether, all others are 0.0100 mol VI_{3b}/100 ml of ether.

^d Trace of VI_{3f}.

(B) Methods of Analysis and Proof of Structure.

Stability of Products to the Reaction Conditions.

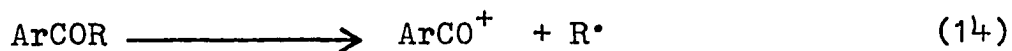
The methods of analysis and proof of structure for the various compounds, taken as classes of compounds, is discussed in sections 1 - 9. The method of determining product distribution is discussed in section 10. The stability of the products is discussed in section 11.

(1) The various phenol esters were known compounds with the exception of 2,6-dimethylphenyl 2-phenylacetate (II'_{5a}). The identities of the known esters were readily confirmed by their nmr and ir spectra, and comparison of physical constants with the literature values. The structure of II'_{5a} was confirmed by its nmr, ir and mass spectra as well as elemental analysis.

(2) The identities of the various ketones were similarly confirmed by comparison of their physical constants with the literature values. There were two exceptions: 3',5'-dimethyl-4'-hydroxy-2-phenylacetophenone (II_{5a}) and 3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2a}). The identity of these compounds were also confirmed by microanalysis. For all cases, the ir spectra confirmed that they were ketones, and the mass spectra confirmed the molecular weights.

The mass spectra of the thirteen ketones reported

in the Experimental Section, p 223, follow the expected pattern of cleavage:²²



In every case, the base peak had the m/e value of the ArCO^+ fragment.

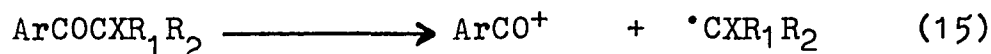
There were four cases where ambiguity existed in the interpretation of the mass spectra: II_{2a} - V_{2a} , i.e., where the aromatic ring is substituted by Me, Et, iso-Pr, or t-Bu, and the ketone fragment was COCH_3 . Of these cases, the latter two are more likely than the former to involve loss of methyl from the alkyl flanking groups on the ring.

(3) The structures of the haloketones were confirmed by microanalysis, except for the two cases, I_{2b} and I_{3b} , where the literature melting points were regarded as reliable. The nmr, ir and mass spectra were straightforward and all contribute to confirming the assigned structures. Many of the haloketones were known, which allowed comparison of melting points as well.

The mass spectra of the eighteen haloketones

(22) H.C. Hill, Introduction to Mass Spectroscopy, Heyden and Son, Ltd. (1966). Cf. Ch 3 p 45ff, and Ch 4, p 105ff.

reported in the Experimental Section (p 202) follow the expected pattern of cleavage:²²



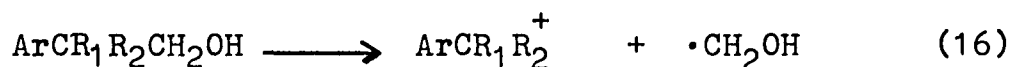
(4) The structures of the primary alcohols were indicated by their nmr spectra. Microanalyses were satisfactory for all compounds that were analyzed: the deuterated alcohols and I_3C were not analyzed. The structures of the deuterated alcohols were inferred from the method of synthesis: LiAlD_4 rather than LiAlH_4 was used as the reducing agent, and the products were separated by the same chromatographic techniques as used for the hydrogen compounds. The nmr spectra confirmed the site of the label as $\text{ArCH}_2\text{CD}_2\text{OH}$, exclusively. The ir spectra showed the expected C-D absorption bands at ca. $2100\text{--}2200\text{ cm}^{-1}$, a region where the corresponding hydrogen compounds lacked absorption.

Initially,⁴ the final confirmation that the rearranged alcohols were in fact primary alcohols was made by their nmr spectra in DMSO-d_6 . This follows from the work of O. L. Chapman and R. W. King,^{23a} and D. E. McGreer and M.M. Mocek^{23b} which showed that a CH_2OH group gave a triplet for the hydroxyl proton due to coupling with the methylene

(23)(a) O.L. Chapman and R.W. King, J. Amer. Chem. Soc., 86, 1256 (1964); (b) D.E. McGreer and M.M. Mocek, J. Chem. Ed., 40, 358 (1963).

protons in dimethylsulfoxide. This was done only for the series V_{2c}-6c. Thereafter, the nmr shifts of the RCH₂OH protons were firmly established, hence the other primary alcohols did not require DMSO-d₆ spectra.

The ir spectra provided additional evidence²⁴ for a primary alcohol function by the COH band at ca. 1050 cm⁻¹. The mass spectra of the sixteen primary alcohols reported in the Experimental Section (p 223), generally follow the expected pattern of cleavage:²²

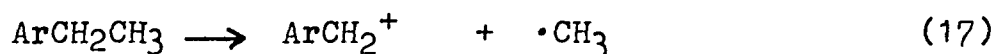


Fourteen of the primary alcohols exhibit this pattern exactly, yielding the ArCH₁R₂⁺ fragment as the base peak. Compound V_c (R₃ = t-Bu) gave equal base peaks from loss of CH₃ or CH₂OH. In the deuterated analog of V_{2c}, the base peak was due to loss of CH₃ with the peak due to loss of CD₂OH being 81% thereof. The mass spectra provided the final confirmation of the assigned structures for the deuterated alcohols II_{2c}-V_{2c}: the molecular weights were two mass units higher than the hydrogen analogs, whereas the base peak was the same (except for V_{2c}), which indicated the loss of CD₂OH vs. CH₂OH.

(24) K. Nakanishi, Infrared Absorption Spectroscopy, Holden-Day, Inc. (1962). Cf p 31.

(5) The structure of the alkanes was indicated by their nmr spectra. Microanalyses were satisfactory for compounds $\text{II}_{2\text{d}}$ - $\text{IV}_{2\text{d}}$. (There was no $\text{V}_{2\text{d}}$.) $\text{I}_{2\text{d}}$ and $\text{I}_{3\text{d}}$ (4-ethyl and 4-n-propylphenol, respectively) were compared directly to the nmr spectra of commercially available materials (Aldrich Chemical Co.). The nmr spectra indicated the position of the deuterium label to be $\text{ArCD}_2\text{CH}_2\text{D}$, exclusively. The ir spectra showed the expected C-D absorption bands at ca. $2100 - 2200 \text{ cm}^{-1}$, where the corresponding hydrogen analogs showed no absorption.

The eight mass spectra of alkanes reported in the Experimental Section (pp 197 and 223) largely exhibit the expected pattern of cleavage:²²



Six exhibit this pattern exactly, yielding the ArCH_2^+ or ArCD_2^+ fragment as the base peak. The parent ion was the base peak for $\text{I}_{2\text{d}}$, with the peak due to loss of methyl being 17% thereof. The base peak of the deuterated analog of $\text{IV}_{2\text{c}}$ was formed by loss of a CH_3 from one of the isopropyl groups, although loss of CH_2D was 40% thereof. However, in all cases the mass spectra confirm the deuterated alkanes as being three mass units higher than the corresponding hydrogen analogs.

(6) The structure of the halohydrins was based on the structure of chlorohydrin $\text{IV}_{2\text{e-Cl}}$. It was possible to

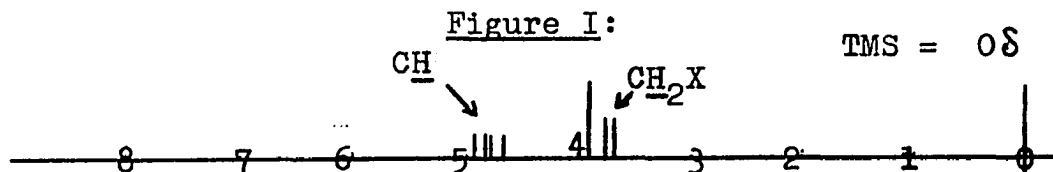
synthesize and recrystallize this compound and obtain a satisfactory microanalysis. The mass spectrum confirmed the molecular weight, and showed the loss of CH_2Cl to give ArCHOH^+ as the base peak. The ir spectrum suggested that the compound was a benzylic alcohol,²⁴ lacking in ketone absorption. The nmr spectrum of the $\text{ArCH(OH)CH}_2\text{Cl}$ protons were an ABX pattern, with chemical shifts of δ 4.70, 4.80, 4.82, 4.92 (1H,CH) and δ 3.58, 3.62, 3.70 (2H, CH_2Cl).

E. I. Snyder,²⁵ in a discussion of three-spin nmr spectra reported the critical shifts for styrene bromohydrin (XXXI) (in acetone) as δ 4.98 (1H,CH), δ 3.63 and 3.68 (2H, CH_2Br) with small coupling constants. He noted that the chemical shifts were somewhat different in CHCl_3 , and that the ABX pattern had collapsed altogether in benzene. Further, he observed that the general cases of $\text{C}_6\text{H}_5\text{CHXCH}_2\text{Y}$ had not given the anticipated clean ABX patterns. Consequently, it was necessary to establish the nmr pattern for the compounds in this work.

The conclusion arrived at from the nmr spectrum of chlorohydrin $\text{IV}_{2e-\text{Cl}}$ was that the ABX system of $\text{ArCH(OH)CH}_2\text{X}$ appeared as two doublets from the methine proton of unequal coupling appearing as four peaks, the center two being separated by ca. 1 Hz. The methylene protons (AB) appear as

(25) E.I. Snyder, J. Amer. Chem. Soc., 88, 1155(1966).

one large peak (integral 1H), and upfield two smaller peaks separated by ca. 1 Hz (integral 1 H). The pattern was essentially uniform for all of the halohydrins, $\text{ArCH(OH)CH}_2\text{X}$, of this dissertation and was unaffected by exchange with D_2O . This general pattern is shown in Figure I:



Synthesis of the bromohydrin, IV_{2e} , gave a product of apparently high purity (by nmr); however, it was not possible to recrystallize or further purify this compound, and no microanalysis was attempted. The structure proof rests upon the mass spectrum--which gave the correct parent ion peaks, and lost CH_2Br to yield ArCHOH^+ as the base peak, exactly as the chlorine analog did. The nmr spectrum exhibited a pattern similar to that of the chlorohydrin $\text{IV}_{2e-\text{Cl}}$: 4 peaks for the methine proton (δ 4.75, 4.85, 4.86, 4.96), 3 peaks for the methylene protons (δ 3.48, 3.52, 3.60) with the expected upfield shift (ca. 0.1 δ) for the AB protons due to the different halogen.

Additional support for the nmr spectrum as the basis for determining the presence of the halohydrin came

from the work of V. Gullo²⁶ who found the ABX pattern of the bromohydrin V_{2e} to be δ 4.74, 4.81, 4.85, 4.95 (1 H, CH), and δ 3.50, 3.52, 3.62 (2H, CH_2Br). That bromohydrin was prepared in exactly the manner of IV_{2e} (see Experimental Section, p 272), apparently in high purity (by nmr). As for the case of IV_{2e} , it was not possible to recrystallize or purify this compound further, therefore no microanalysis was attempted. However, the mass spectrum confirmed the molecular weight.

On the basis of the preceding evidence, it was possible to confirm the structures of the remaining halo-hydrins: $III_{2e}-Cl$, VI_{2e} , VI_{3e} , and $VII_{2e}-Cl$ on the basis of the nmr spectral pattern.

(7) Two of the benzylic alcohols, II_{2f} ($R_3 = Me$) and VI_{2f} ($R_3 = Cl$) were isolated, purified and gave satisfactory microanalyses. The ir spectra suggested that they were benzylic alcohols.²⁴ The mass spectra confirmed the molecular weights. Both compounds exhibited an $ArCHOH^+$ fragment as the base peak, due to loss of CH_3 .

(26) Unpublished observations of V.P. Gullo, The City College. In connection with another problem, Mr. Gullo had occasion to prepare several of the compounds in this work, and certain derivatives thereof, which had considerable significance for this work.

This evidence permitted the assignment of the benzylic protons in the nmr spectrum of ArCH(OH)CH_3 . The structure of the benzylic alcohol IV_{2f} ($\text{R}_3 = \text{iso-Pr}$) was inferred from its nmr spectrum which was similar to those of II_{2f} and VI_{2f} .

(8) The assignment of the structure of the dimers $\text{II}_{2h} - \text{IV}_{2h}$ rested in part on the preparation of two model compounds: 1-(3,5-diisopropyl-4-hydroxyphenyl)ethyl ethyl ether (XXXII) and 1-(3,5-dimethyl-4-hydroxyphenyl)ethyl ethyl ether (XXXIII), (see p281) whose structures are shown in Figure II:

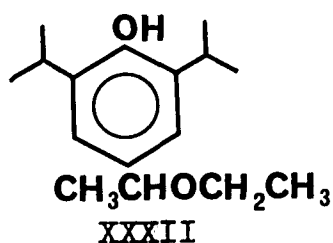
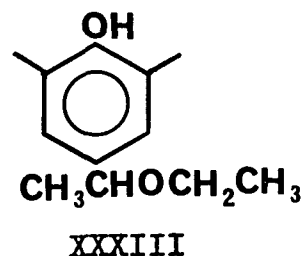


Figure II:



The structure of compound XXXII was assigned on the basis of a satisfactory microanalysis, supported by an appropriate parent ion in the mass spectrum, with peaks in the ir spectrum assignable to an ether linkage and an nmr spectrum consistent with the structure $\text{ArCH(CH}_3\text{)OCH}_2\text{CH}_3$. (Compound XXXIII was not isolated, however, the nmr spectrum of the crude reduction mixture matched the pattern of the significant protons in XXXII, which reinforced the original assignments.)

The ir spectrum of impure IV_{2h} suggested that the compound was an ether, and the m/e of the parent ion was

consistent with the molecular weight. The nmr spectrum of the compound showed similarities to those of XXXII and XXXIII and was consistent with the structure $\text{ArCH}(\text{CH}_3)\text{OCH}_2\text{-CH}_2\text{Ar}$. The other dimers, $\text{II}_{2\text{h}}$ and $\text{III}_{2\text{h}}$, were assigned the same structure on the basis of their very similar chemical shifts and coupling patterns to that of $\text{IV}_{2\text{h}}$. In addition, the structure of $\text{III}_{2\text{h}}$, from the reduction of $\text{III}_{2\text{b-Cl}}$, was confirmed by mass spectroscopy. The mass spectrum of the isolated sample of $\text{III}_{2\text{h}}$ showed the presence of $\text{III}_{2\text{q-Cl}}$. The latter had the correct molecular weight as well as the expected 3:1 Cl^{35} to Cl^{37} peak heights. The dimers from the LiAlD_4 reduction must have the structure $\text{ArCD}(\text{CH}_2\text{D})\text{OCD}_2\text{-CH}_2\text{Ar}$ on the basis of their nmr spectra.

(9) Quantitative column chromatography did not separate the alkyl halide from the alkane. The mixture is referred to as the alkane fraction. The structure of the alkyl halides was established on the basis of their nmr spectra as $\text{ArCH}_2\text{CH}_2\text{X}$. The reductions with LiAlD_4 afforded the deuterated analogs, the nmr spectra of which required the site of the label to be $\text{ArCD}_2\text{CH}_2\text{X}$, exclusively. The mass spectra of these compounds, as mixtures with the appropriate alkane, confirmed the molecular weights. Because the alkyl halides were not separated from the alkanes, it was essential that the isotope distribution be observed, 1:1 for Br^{79} to Br^{81} and 3:1 for Cl^{35} to Cl^{37} --and this was observed.

The nmr spectra of the alkane fraction from the LiAlH_4 reduction of the 2-bromoketones could not rule out the presence of the symmetrical dimers, $(\text{ArCH}_2\text{CH}_2)_2\text{O}$, because the chemical shifts and coupling patterns would be very similar to $\text{ArCH}_2\text{CH}_2\text{Br}$ for the two types of ethylene groups. However reduction of the 2-chloroketones gave alkane fractions where the other compound present in this fraction had the $\text{ArCH}_2\text{CH}_2\text{Cl}$ protons shifted downfield from the similar material from the 2-bromoketones. Therefore the other compound in the alkane fraction had to be the alkyl halide, $\text{ArCH}_2\text{CH}_2\text{X}$.

At that point, the symmetrical dimer could be present only in traces in the alkane fraction and it was detected only in the case of II_{2g} . The amount of II_{2g} was likely to be very small from the relative peak intensities found in the mass spectrum. Further, the deuterium labelled dimer should be $\text{ArCH}_2\text{CD}_2\text{OCH}_2\text{CD}_2\text{Ar}$ for mechanistic reasons to be discussed in Section H. That required a ArCH_2 peak in the deuterium compound at ca. δ 2.8. This was not observed for the III_{2d} and III_{2p} mixture, the IV_{2d} and IV_{2p} mixture, and only barely discernible for the II_{2d} , II_{2p} and II_{2g} mixture.

(10) The product distribution where mixtures were obtained, i.e., $\text{I}_{2b} - \text{V}_{2b}$ and $\text{II}_{2b-\text{Cl}} - \text{IV}_{2b-\text{Cl}}$, were initially determined by the nmr integration with the

hydroxyl protons present, followed by integration after D_2O exchange. The phenol H peaks were at ca. δ 5, while the ROH peaks were at ca. δ 2. Because the two types of hydroxyl protons were well separated in these mixtures, it was possible to use the $ArOH$ integral as a check on the total amount of products, while the ROH integral served as a check on the total amount of primary alcohol product--which was the overwhelmingly predominant source of ROH.

The two general bases of the calculation were the aromatic peaks and the RCH_2OH peaks. The integral of the aromatic peaks gave the total number of moles present. (This method counts dimeric products as two monomers.) From this number of moles was subtracted the number of moles of primary alcohol product indicated by the hydroxymethylene integral. The results were adjusted to the best fit, if necessary, by comparison with other parts of the spectrum known to be due to a single material--which was generally possible for the II_{2b} case--and cross-checked with the results indicated by the hydroxyl integrals. Then the remaining material was assigned as alkane product.

This procedure worked reasonably well as long as the primary alcohol and alkane were the vast majority of the product, i.e., over 90%. Under those circumstances, the error was effectively within 2%, which was as precise as the integrals were. It was essential that the nmr percentages be known accurately, because the chromatographic

separation did not return more than 90 wt% of the incoming material. Once separated, the major (alkane and primary alcohol) and minor (dimers, halohydrins and miscellaneous) products, percentages were recalculated to give the new molar distribution of products. When the percentages, before and after chromatography, agreed, there was no need to fear that selective losses of one or more products had occurred during chromatographic separation. For example, Tables II and IV, p 34 ff show ca. $\pm 3\%$ agreement by nmr and quantitative chromatography between the values obtained for the primary alcohols produced by the reduction of the bromoketones.

When the 2-chloroketones were reduced, the percent of unsymmetrical dimer and alkyl chloride rose considerably. Unfortunately, the CH_2X peaks of these products overlaps the upfield member of the $\text{ArCH}_2\text{CH}_2\text{OH}$ triplet, thereby raising the nmr percentages of the primary alcohols. The assigned percentages of the alkanes were automatically lowered thereby, but to an inaccurate figure because the side products could not be directly estimated. It was necessary to assume that the percentages indicated by chromatographic separation were correct. This assumption was considered reasonable, inasmuch as the agreement achieved in the cases of the 2-bromoketones was good, and the 2-chloroketones gave the same types of product, albeit in different distribution.

The reduction of I_{2b} was in a class by itself. It did not appear possible to duplicate the results of any given run, except by chance. Consideration of the problem, in retrospect, indicates that there was a possibility that the reduction was exceptionally sensitive to the rate of stirring while the $LiAlH_4$ was added. (Because the various entries were interspersed with reductions of the other compounds, which gave reproducible results, the possibility that any given can of ether or bottle of $LiAlH_4$ was the source of the difficulty was eliminated.) In any event, it was perfectly clear that this reduction mixture would remain intractable even if the results could be stabilized, because the principal product, the alkane, sublimed with great ease during the original workup, and also during the workup of the chromatography fractions. Therefore the percentage of alkane obtained was always lower than the true value. It is believed that the problem of selective loss of a product was confined to this particular case, and all the rest of the data may be considered quite reliable, However, the quantitative nature of the results for the case of I_{2b} should be regarded with reserve.

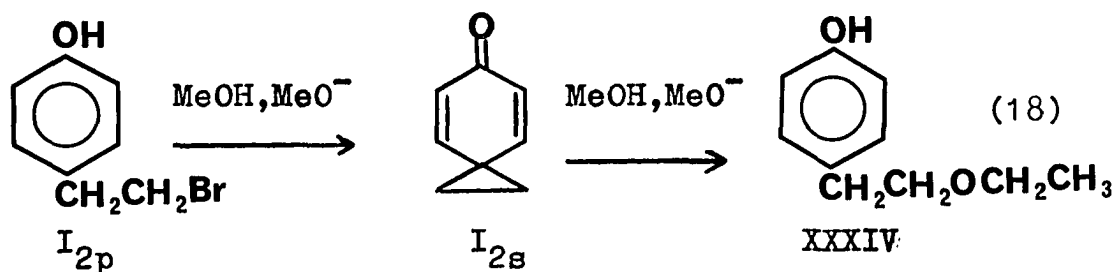
(11) The stability of the products to the reaction conditions was obviously a matter of great concern. For this purpose it is convenient to divide the products into two classes: the primary alcohols and alkanes, and the minor products--alkyl halides, unsymmetrical dimers,

halohydrins and miscellaneous other products.

N. G. Gaylord²⁷ in his compilation of the early work done with LiAlH_4 , and other metal hydrides, provided assurance that the alkane product was safe from further reduction inasmuch as it was the ultimate product of reduction.

The primary alcohol products present another problem altogether. An ordinary primary alcohol would be quite resistant to further reduction to the alkane²⁷ via hydrogenolysis of the C-O bond. However, these primary alcohols are a rather special case because they have an oxyaryl group on the 2-carbon, which could conceivably participate and facilitate the C-O hydrogenolysis.

R. Baird and S. Winstein²⁸ performed an early study of great interest in this connection as shown in Eq 18:

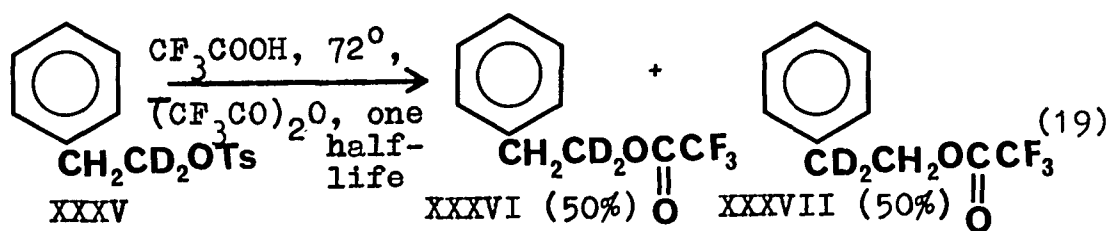


(27) N.G. Gaylord, Reduction with Complex Metal Hydrides, Interscience Publishers, Inc. (1956). Cf. Ch 6, 7, 11, 14 and 16.

(28) R. Baird and S. Winstein, J. Amer. Chem. Soc., 85, 567 (1963).

They isolated spiro(2,5)octa-1,4-diene-3-one (I_{2s}) and showed that it was the crucial intermediate. This work had disturbing implications for the stability of the primary alcohols produced in this study.

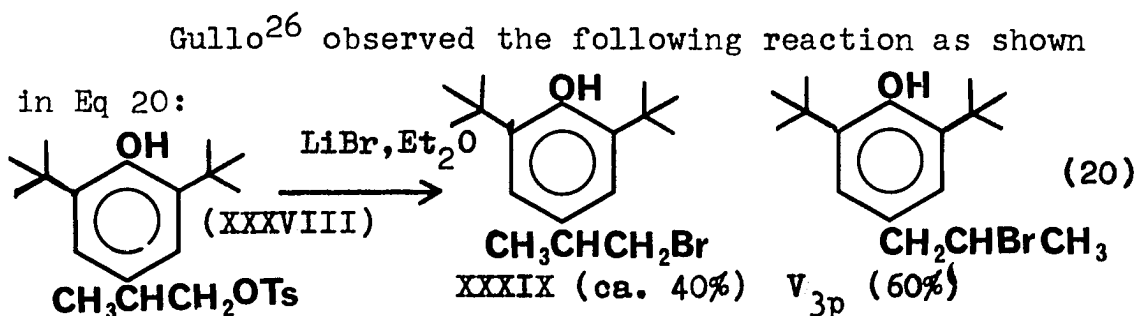
J. E. Nordlander and W. G. Deadman²⁹ can be considered to have brought D. J. Cram's suggestion^{30a,b} and S. Winstein's elaborate work on phenonium ion participation to some sort of climax as shown in Eq 19:



Their trifluoroacetytolysis may be regarded as having established that phenonium ions can intervene in solvolytic reactions. Even the recovered starting material of Eq 19, XXXV, showed 5% scrambling of the tosylate. That the phenyl ring itself, not a phenoxide ion, could intervene in the loss of X from $\text{ArCH}_2\text{CH}_2\text{X}$ was even more disturbing than Winstein's work.²⁸

(29) J.E. Nordlander and W.G. Deadman, J. Amer. Chem. Soc., 90, 1590 (1968).

(30)(a) D.J. Cram, ibid., 71, 3863 (1949);
 (b) D.J. Cram, ibid., 74, 2129 (1952).



Here a simple salt, LiBr, displaced a primary tosylate in ether, with rearrangement, in a compound directly related to the primary alcohols of this dissertation.

Our earliest work reported^{3,4} was done with the V_{2b-6b} series (see Table VI, p 38) with a reflux period of at least 180 min. This resulted in no significant amounts of alkane product. Four min reductions were performed much later, largely to obtain some idea of how fast the reaction occurred. Again, only primary alcohol product was obtained, these results establish the stability of the primary alcohols under the reaction conditions.

There remained the possibility that some special factor might have maintained the stability of the primary alcohols V_{2c}-V_{6c}. Therefore another example was tested: IV_{2b} was reduced for 180, 40 and 10 min as well as the usual 360 min period. The product distribution (see Table V, p 37) was within the usual limits of reproducibility. Therefore the primary alcohol was not reduced with the passage of time to alkane in that case either. As a final measure of assurance, II_{2b} was reduced for 60, 40, 20 and 10 min and gave the same percentages as obtained

for the 360 min run. (Those results were omitted from Table II.) Consequently, it was firmly established that the primary alcohol products were not converted to the alkanes within the maximum reduction time (360 min) employed in this work for I_{2b} - V_{2b} .

The alkyl halides were a special case, for they should undergo slow reduction to the alkane with the passage of time. Gaylord²⁷ supports this, and the work of Eliel¹³ indicates slow reduction for the $ArCH_2CH_2Cl$ group (ca. 1.3% hr). Consequently, the alkyl halides may be regarded as precursors of the alkanes, but fairly stable precursors within the reduction times employed here.

It would be anticipated²⁷ that the alkyl bromide, $ArCH_2CH_2Br$, would be reduced somewhat faster than the chloride. However, examination of the nmr spectrum of the crude product from the reduction of V_{2b} , which contained perhaps as much as 10% of the alkyl bromide, does not show clear signs of alkane from reduction of the alkyl bromide after 180 min of reflux. Consequently, the alkyl bromide can be regarded also as reasonably stable.

The symmetrical dimer, $(ArCH_2CH_2)_2O$, should be quite stable towards reductive cleavage in these systems as primary ethers normally are.²⁷ With the exception of II_{2g} , there was no other mass spectral evidence for this type of dimer. It does not appear tenable to propose that

these dimers were initially formed and rapidly cleaved. The nmr spectra of the products of reductions at short periods of time (ca. 10 min) do not exhibit significant peaks upfield of the $\text{RCH}_2\text{CH}_2\text{OH}$ triplet (for the bromoketones), where the corresponding peaks of the dimers would appear; see the alkyl halides and unsymmetrical dimers for their chemical shifts p 253; in sufficient quantity to seriously interfere with the integration procedure previously described in part (10). We should then be forced to the conclusion that the formation of these dimers (a) did not occur, or (b) occurred but the products were cleaved with astonishing rapidity. Conclusion (a) appears to be the more reasonable.

The unsymmetrical dimers, $\text{ArCH}_2\text{CH}_2\text{OCH}(\text{CH}_3)\text{Ar}$, should undergo slow cleavage to primary alcohol and alkane because they are benzylic ethers. That this cleavage was in fact very slow was demonstrated for the case of IV_{2h} , and will be discussed further in Section H, p 152.

The occasional appearance of the ketone (e.g., II_{2a} , IV_{2a}) as a product has to be accounted for. It was shown in this work that the ketone IV_{2a} was reduced within 10 min (see Experimental Section, p 249). This suggests the conclusion that the ketone did not exist as such in the reaction mixture. This matter will be discussed further in Section G, p 121.

Benzylic alcohols were not found among the products

for the series I_{2b} - V_{2b} and the chloroketones II_{2b-Cl} - IV_{2b-Cl} . It was expected²⁷ that benzylic alcohols with electron-donating substituents on the aromatic ring would be rapidly reduced to the alkane. For compounds within the scope of this dissertation, A. A. Volod'kin, V. V. Ershov, and N. V. Portnykh³¹ reduced the ketones V_{2a-6a} ($R_3 = t\text{-Bu}$) with $LiAlH_4$ in ether to the alkanes V_{2d-6d} in high yield under mild conditions. Ershov's group was forced to employ $NaBH_4$ ³² in order to secure the benzylic alcohols, and then only in low yield (ca. 50%), the other product was largely the alkane. This suggests that the benzylic alcohols may be regarded as precursors of the alkanes.

The obvious exception was where the flanking groups were halogens (Tables VII²⁰ and VIII²¹). There, the reduction proceeds smoothly to benzylic alcohols, but very slowly thereafter proceeds to the alkane. This is further documented in the Experimental Section, p200 and p283, where the preparation of VI_{2d} and VI_{2f} are given. Consequently the benzylic alcohols may be considered products of the reduction for those cases, Tables VII²⁰ and VIII.²¹

(31) A.A. Volod'kin, V.V. Ershov, and N.V. Portnykh, Bul. Acad. Sci., USSR, 384 (1967).

(32) A.A. Volod'kin, N.V. Portnykh, and V.V. Ershov, ibid., 223 (1968).

The last set of compounds to be considered are the halohydrins. In the series derived from the phenols I - V, they were rarely encountered. They were suspected to be precursors of the final products. Tables VII²⁰ and VIII,²¹ show that the halohydrins were produced in significant quantities. Examination of the entries where they were noted as products reveals that they were clearly precursors of benzylic alcohols and alkanes (for Table VII,²⁰ pp 39 and 40), and of the benzylic alcohol and primary alcohol (for Table VIII,²¹ p 41). For example, Entry 8 of Table VII²⁰ shows 37.1% of the chlorohydrin VI_{2e-Cl} after 60 min of reflux, but no chlorohydrin after 1200 min (Entry 5), only the final products--benzylic alcohol VI_{2f} and alkane VI_{2d} (R₃ = Cl).

(C) Presentation of the Alternative Mechanisms.

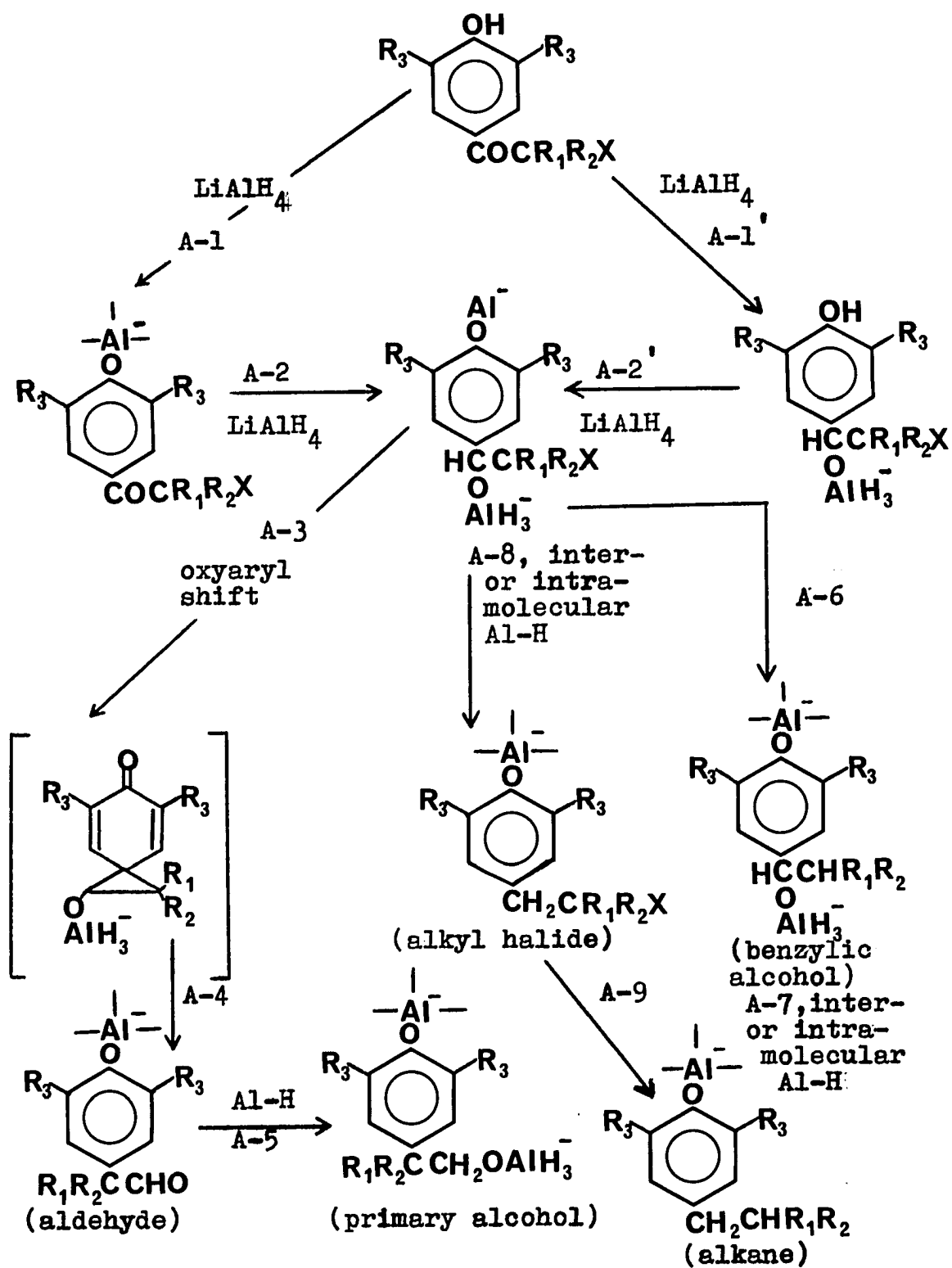
The two mechanisms that appeared to rationalize the experimental results of Tables I - VIII are presented here. They are shown in flow diagrams with the steps numbered. Only the most probable steps are given for each mechanism. The two mechanisms are very briefly compared in the following Section. Full discussion of the steps involved in the mechanism believed to be correct is deferred to Section G.

(One) Mechanism A. Product Formation Through a Halohydrin Intermediate.

The steps A-1 and A-2 or A-1' and A-2' both lead to the crucial halohydrin intermediate. For compounds where R₃ is small (H, Me, Et, iso-Pr), the dominant route is A-1, then A-2. For the bulky tert.-butyl, A-1' followed by A-2' is possibly the dominant route.

The halohydrin intermediate then can undergo three intramolecular modes of further reaction. Hydrogenolysis of the Al-O-C bond leads to alkyl halide, via A-8, which is very slowly converted to alkane via A-9. Displacement of the halogen by O-Al-H leads to the benzylic alcohol, via A-6, which suffers rapid hydrogenolysis to the alkane via A-7. Alternatively, the halogen is displaced with a concomitant closure to the spiro-cyclopropanol system via A-3. This intermediate (or transition state) rapidly opens (or continues) to the aldehyde, A-4. The aldehyde is

Mechanism A



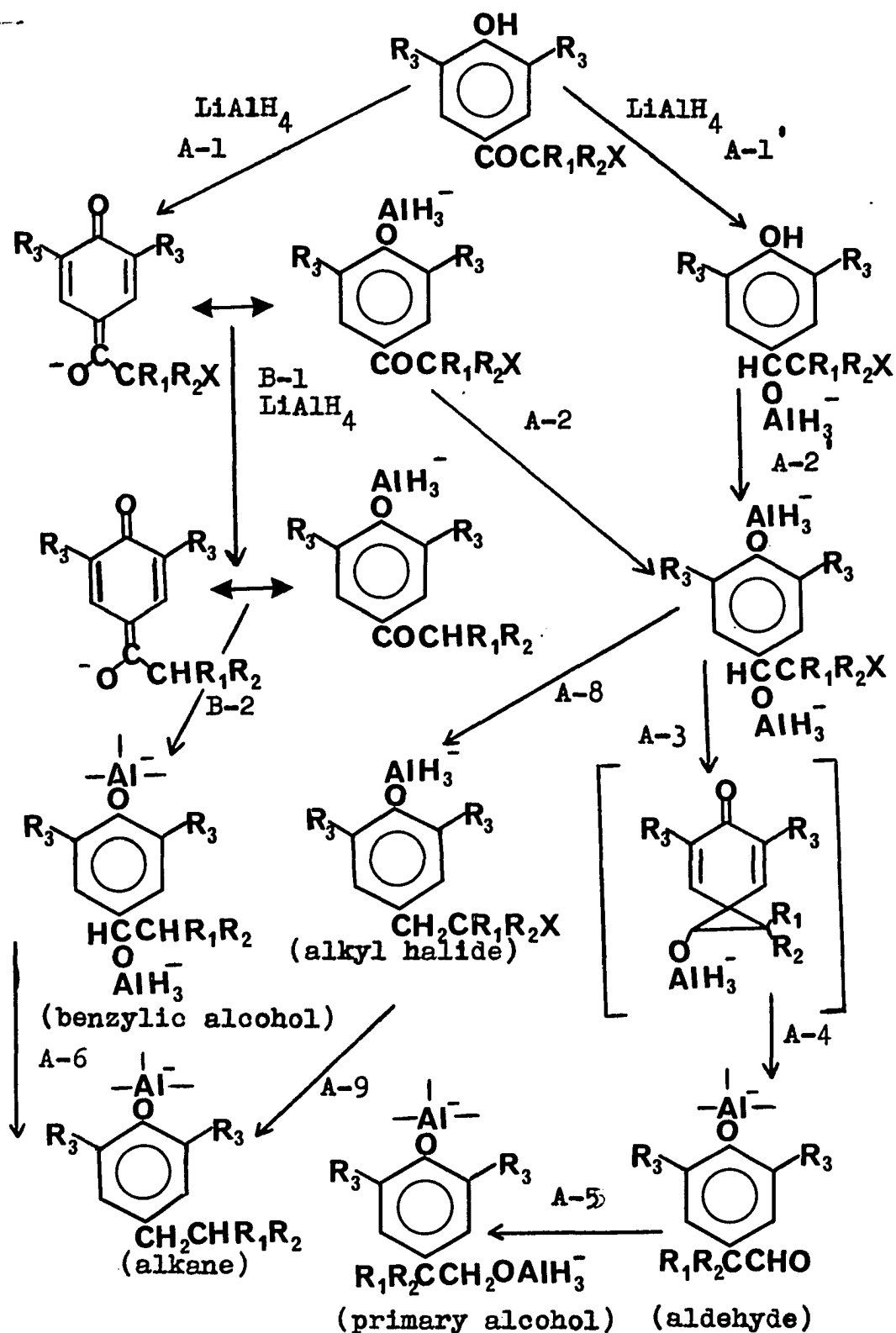
rapidly reduced to the primary alcohol in A-5--with the oxyaryl ring having migrated from carbon-1 to carbon-2.

(Two) Mechanism B. Determination of Product Distribution Prior to Halohydrin Formation.

Mechanism A and mechanism B share many common steps: to emphasize this, the steps in mechanism B are labelled as the similar steps in mechanism A. Where R_3 is small, e.g., H, Me, Et, the initial attack largely yields phenoxide ions via A-1. In mechanism B the phenoxide ions decrease the reactivity of the carbonyl function (as shown in the adjacent resonance structure) which allows displacement of the halogen via B-1 to occur (in preference to reduction of the carbonyl function via A-2), and ultimately yields the alkane product.

The alternate route in mechanism B is reduction of the carbonyl group via A-1', which is especially favored by bulky R_3 groups. These compounds suffer the loss of the phenol H via A-2' to generate the halohydrin (some of which may be formed via A-2). The halohydrin can undergo displacement of the halogen via steps A-3, 4, 5 to produce the primary alcohol--with the oxyaryl ring having migrated from carbon-1 to carbon-2. Alternately, the halohydrin could suffer C-O hydrogenolysis in A-8 to yield the alkyl halide, which in turn could be slowly reduced to alkane via A-9.

Mechanism B



(D) Comparison of the Two Mechanisms.

The major difference between the two mechanisms is that mechanism A predicts that the halohydrin is the source of all the observed products. Mechanism B predicts that the halohydrin is the precursor, in particular, of the primary alcohol, while the ketone generated in B-1 is the source of the alkane. It must be clearly understood that the restriction upon the ability of the halohydrin in mechanism B to produce alkane product is entirely a deliberate choice to emphasize a difference between mechanisms A and B. A priori, it remains perfectly plausible that a combination of mechanisms A and B could account for every product distribution encountered. The most obvious similarity between the mechanisms is that both invoke the formation of a spirocyclopropanol whose further reactions lead to the primary alcohol. Another similarity is that both mechanisms consider the halohydrin to be the source of the alkyl halide.

The mechanisms differ in the role of R_3 . Mechanism B assumes that R_3 determines the product distribution by its effect on the initial distribution of attack by the $LiAlH_4$. Mechanism A assumes that as R_3 becomes larger the $ArO-Al$ bond is weakened, thus diverting more of the halohydrin to the aryl migration pathway, to primary alcohol, and also increasing the $Al-O-C$ hydrogenolysis pathway, to alkyl halide. According to mechanism A, when R_3 is a halogen, the oxyaryl anion is stabilized, which disfavors

oxyaryl migration (A-3, 4,5). From the view of mechanism B, with R_3 a halogen, the acidity of the $ArOH$ rises, favoring A-1; thus alkane, and its benzylic alcohol precursor become the products.

The mechanisms differ in the reason for increased primary alcohol product when the displaced halogen is changed from Br to Cl. Mechanism A again assumes that the halohydrin is generated, however, the O-Al-H displacement of halogen in A-6 is apparently less favored than the aryl migration in A-3. Mechanism B ascribes the increase in primary alcohol product to electronic factors: the C-Cl bond is more polar than the C-Br bond, hence the adjacent carbonyl carbon might therefore be somewhat more positive than in the C-Br case. Thus Cl favors initial attack upon the carbonyl carbon, hence more halohydrin, which is the precursor of primary alcohol and alkyl halide.

Both mechanisms predict that substitution upon carbon-2 where either or both R_1 and R_2 are no longer H, makes displacement of the halogen, X, more difficult by S_N2 -type attack. Consequently, the reaction is channelled into A-3. A-2 serves as a shunt into the halohydrin in mechanism B, inasmuch as the resonance stabilization can be important only as long as B-2 is fast compared to A-2.

At this point, both mechanisms qualitatively account for the product distribution, and discussion of the reasons

for the steps will be deferred until more data are presented. Both mechanisms, if followed through with LiAlD_4 , predict the observed position of the deuterium label. Therefore, those studies cannot differentiate between the two mechanisms.

(E) Reduction with Limited Amounts of LiAlH_4 .

The Site of Initial Attack by the LiAlH_4 .

In an effort to obtain information about the site of initial attack of the LiAlH_4 , a study was performed by E. Jessen.³³ This involved three substrates: II_{2b} , IV_{2b} and V_{2b} ($\text{R}_3 = \text{Me}$, iso-Pr, and tert.-Bu, respectively) with different amounts of LiAlH_4 . The results are gathered in Table IX, p 72 .

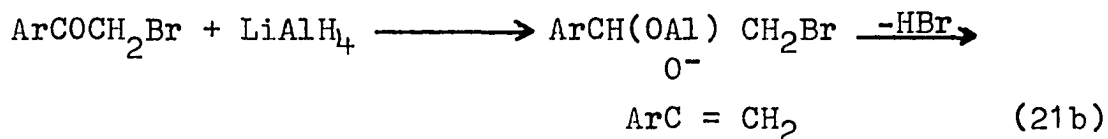
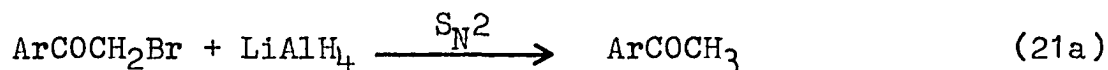
The results of the study were somewhat inconclusive but served to establish several points which may be summarized as: (a) The compound II_{2b} ($\text{R}_3 = \text{Me}$) appears to undergo preferential attack at the phenol H before the carbonyl was attacked (Entries 1, 2). As the amount of LiAlH_4 was increased (Entries 3 - 6), the consumption of hydride also increased. However the ratio of primary alcohol to alkane was consistently greater than unity,

(33) E. Jessen, The City College, many of whose unpublished observations are gathered in Table IX.

whereas the ordinary reduction with 2.25 mol LiAlH_4 gave 65% alkane and 35% primary alcohol--a complete reversal. (b) Compound IV_{2b} ($\text{R}_3 = \text{iso-Pr}$) appeared to behave in a manner similar to II_{2b} , rather than V_{2b} . That is, loss of the phenol H appeared to occur in preference to reduction of the carbonyl group. (c) Compound V_{2b} ($\text{R}_3 = \text{tert.-Bu}$) appeared to suffer reduction far more readily than II_{2b} for the same amount of LiAlH_4 (Cf. Entry 10 vs. 1 and 2; Entries 11 and 12 vs. 3 and 4). The material balance for all the reductions neglects the reaction of LiAlH_4 with the ArOH , and assumes that ketone arises from direct displacement of Br by H, i.e., via Eq 21a. Otherwise more hydride would have been consumed than was available for the reaction in some of the V_{2b} cases--which implies that the aromatic ring migrated without loss of the phenol H. This point will be discussed again in Section I, p 157.

The study confirmed the expectation that the initial attack was shifted from the phenol H to the carbonyl or the halogen as the flanking groups (R_3) increased in size. The discovery of ketone in the reduction of II_{2b} afforded support to mechanism B, but introduced a confusing note in examination of the reductions of V_{2b} ($\text{R}_3 = \text{t-Bu}$): ketone was found there also. This posed a considerable problem, inasmuch as ketone (if present in the reduction mixture as such, and not as the presumably less reducible ketolate anion) must be the precursor of alkane, and no alkane was

found in the reduction of V_{2b} with 2.25 LiAlH₄. Consequently, it became necessary to consider whether the reactions shown in Eq 21a or 21b were the source of the ketone:



Eq 21a has literature support insofar as it depicts nucleophilic substitution of the Br. A. Streitwieser, Jr.³⁴ gives several examples of the greatly enhanced rate of nucleophilic displacement of halogen with an adjacent carbonyl group. Indeed, it was this possibility that led to the construction of mechanism B. On the other hand, Eq 21b also has inferential support. It will be recalled that Eliel¹³ had isolated aldehydes in some 2-haloacid or ester reductions. There it was shown that the aldehyde did not exist as such in the reaction medium, but was present as the aldehyde enolate. Similarly, it is possible that our systems generate complex aluminum salts that eliminate HBr (as H₂ and Br⁻) to yield the ketolate anion. That anion would also resist further reduction, but revert to the

(34) A. Streitwieser, Jr., Solvolytic Displacement Reactions, McGraw-Hill, 1962. Cf. p 28 ff.

Table IX^a. The Reduction of II_{2b}, IV_{2b}, V_{2b} with Limited Amounts of LiAlH₄

$ \begin{array}{c} \text{R}_3 \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{N}_{2b} \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{COCH}_2\text{Br} \end{array} + n \text{LiAlH}_4 \longrightarrow \begin{array}{c} \text{R}_3 \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{N}_{2a} \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{COCH}_3 \end{array} + \begin{array}{c} \text{R}_3 \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{N}_{2c} \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{CH}_2\text{CH}_2\text{OH} \end{array} + \begin{array}{c} \text{R}_3 \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{N}_{2d} \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{CH}_2\text{CH}_3 \end{array} + \begin{array}{c} \text{R}_3 \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{N}_{2e} \text{---} \text{C}_6\text{H}_3 \text{---} \text{R}_3 \\ \\ \text{HCCH}_2\text{Br} \\ \\ \text{OH} \end{array} $									
Entry	Compd	$\frac{n, \text{mol}}{\text{LiAlH}_4}$	Percent Product Distribution ^b						Hydride Consumed ^f
1	II _{2b}	0.25	8 II _{2a}	92 II _{2b}					8 %
2	II _{2b}	0.25	6 II _{2a}	94 II _{2b}					6 %
3	II _{2b}	0.50	6 II _{2a}	71 II _{2b}	13 II _{2c}	10 II _{2d}			31 %
4 ^c	II _{2b}	0.50	7 II _{2a}	70 II _{2b}	14 II _{2c}	9 II _{2d}			31 %
5	II _{2b}	0.75	8 II _{2a}	48 II _{2b}	31 II _{2c}	13 II _{2d}			36.3%
6	II _{2b}	1.00	10 II _{2a}	27 II _{2b}	47 II _{2c}	16 II _{2d}			38 %
7	II _{2b}	2.25	-- II _{2a}	-- II _{2b}	41 II _{2c}	59 II _{2d}			28.8%
8	II _{2b}	2.25	-- II _{2a}	-- II _{2b}	35 II _{2c}	65 II _{2d}			29.4%
9 ^d	IV _{2b}	0.25	-- II _{2a}	81.4 IV _{2b}	18.6 Unidentified ^e				-
10	V _{2b}	0.25	10.5 V _{2a}	47 V _{2b}	10.5 V _{2c}	-- V _{2d}	32 V _{2e}		63.5%
11	V _{2b}	0.50	3.6 V _{2a}	23 V _{2b}	25 V _{2c}	-- V _{2d}	48 V _{2e}		50.8%
12	V _{2b}	0.50	7 V _{2a}	23 V _{2b}	28 V _{2c}	-- V _{2d}	42 V _{2e}		52.5%

^a Unpublished observations of E. Jessen, The City College. ^b Analyses by nmr.

^c 11 hr 8 min reflux period. ^d 20 min reflux period. ^e The material could not be positively identified, but was not any of the monomeric products, e.g. IV_{2a-f}.

^f Basis of calculation: no reaction with ArOH, 1H to produce ketone, or halohydrin, 2H to produce primary alcohol, 3H to produce alkane.

ketone upon treatment with water. The occurrence of ketone product will be discussed further in Section G, p 121.

The studies reported in Table IX³³ were not performed with concomitant measurement of hydrogen evolution, nor were the reaction mixtures treated with acetic anhydride to trap the ketolate anion as its acetate, as Eliel had done.¹³ Consequently, it is not possible to state whether Eq 21a or b (or both) was the source of the ketone.

The reduction of II_{2b} in Entries 3 - 6 of Table IX proved somewhat troubling. It was found that the primary alcohol product exceeded the alkane formed using 0.50 to 1.00 mol LiAlH₄. Apparently the paths leading to those two products are sensitive to the amount of LiAlH₄ present, and it is possible to rationalize this in terms of the selected mechanism. This matter will be discussed further in Section G, p 114.

(F) Determination of the Mechanism. Reduction of a Halohydrin.

The problem of deciding between mechanism A or B was approached from two sides. (A) The period of reduction was shortened for a selected bromoketone, IV_{2b} (R₃ = iso-Pr), in an effort to obtain bromohydrin and ketone in the very early stages of the reduction. This was done also with the parent ketone, IV_{2a}, to find out whether the ketone and the bromoketone were reduced at significantly different rates. (B) The bromohydrin IV_{2e} was prepared and reduced with more than the usual 2.25 mol of LiAlH₄, the products were separated and compared to those obtained from the reduction of the bromoketone IV_{2b}.

For the purpose of determining whether mechanism A or B was operative, it was necessary to carry out the proposed studies on a compound that gave significant amounts of both primary alcohol and alkane. That requirement excluded I_{2b} (R₃ = H) and V_{2b} (R₃ = t-Bu). Of the remaining three compounds, II_{2b} and IV_{2b} were the most accessible synthetically. The essential work was done with IV_{2b}. It was clear from the work of E. Jessen³³ (p 72) that the study would have to be performed with at least the usual 2.25 mol of LiAlH₄, as limited amounts did not resolve the problem. Mechanism A was established as correct, excluding Mechanism B.

The reduction of the ketone IV_{2b} (R₃ = iso-Pr) for 10 min in refluxing ether is reported in the Experimental Section, p 249. The reduction gave a complex mixture which was not characterized, but was subjected to rereduction with 2.25 mol LiAlH₄ for 24 hr (p 251). This second reduction did not produce the alkane, IV_{2d}, in amounts significantly greater than had been present after the initial 10 min reduction. These reductions used 2.25 mol LiAlH₄ whereas the alkane was synthesized by reduction with 3.0 mol LiAlH₄ (p 199). The difference in amount of LiAlH₄ was eliminated as the source of the difficulty when the ketone was reduced with 2.25 mol LiAlH₄ for 24 hr (p 250), and gave 91% alkane IV_{2d} and 9% benzylic alcohol IV_{2f}. This result was very similar to that obtained upon reduction of the ketone with 3.0 mol LiAlH₄.

Consequently, it was not possible to examine the reduction of the ketone IV_{2b} (R₃ = iso-Pr) in the first few minutes of the reaction. Apparently addition of water and subsequent work up of the reaction mixture yielded products of side reactions that did not yield the alkane IV_{2d} upon further treatment with LiAlH₄. The nature of these products is unclear, but the significance is obvious: this compound can not be investigated after only 10 min reduction nor for shorter periods of time by the methods employed.

Reduction of the bromoketone IV_{2b} for 4 min at ca. 0° is reported on p 253 . The result was a complex mixture, but no bromohydrin could be detected. (This is not quite the same thing as no bromohydrin was formed, because the bromohydrin could have been destroyed in the isolation procedure.)

Reduction of the bromoketone IV_{2b} for 3 min in refluxing ether is reported on p 254. About two-thirds of the product was primary alcohol IV_{2c} and alkane IV_{2d}, but neither ketone nor bromohydrin were evident. The remaining one-third was a complex mixture, but no carbonyl groups were left. (This last point is very evident in the nmr spectrum, for reduction of the carbonyl always caused an upfield shift of ca. 0.8 ppm of the aromatic protons.)

The bromoketone IV_{2b} was reduced for 2 min at ca. 10° (p 255). The products included the ketone (14.6%), starting material (6.7%), and only 21.6% of the primary alcohol and alkane products. The remaining 58.7% was a complex mixture very similar to what was obtained in the two previous reductions. Accordingly a portion of this crude product was rereduced with 2.25 mol LiAlH₄ for 20 min in refluxing ether. The new product was ca. 32% primary alcohol and alkane, but 68% could not be assigned.

These results appeared to be very similar to those obtained in the reduction of the ketone IV_{2b}, i.e.,

the reduction of the carbonyl occurred rapidly in refluxing ether, but the reaction could not be interrupted after only 3 min. If the reduction was interrupted by the addition of water and the usual work up, compounds were obtained that did not undergo further reduction to the usual products, the primary alcohol IV_{2c} and the alkane IV_{2d}. The appearance of the ketone IV_{2a} among the products of the 2 min reduction at 10° may be ascribed to other factors--specifically the temperature--which will be discussed in Section G, p 121. Very similar results were obtained in the reduction of II_{2b} (R₃ = Me) for 2 min in refluxing ether (p 234), viz. the carbonyl group was entirely reduced, the primary alcohol II_{2c} and alkane II_{2d} were present but the product mixture became a purple tar upon heating (67°) to remove the ether and evolved an acidic gas (HBr). We shall presently note that HBr evolution is a sign indicative of bromohydrin decomposition.

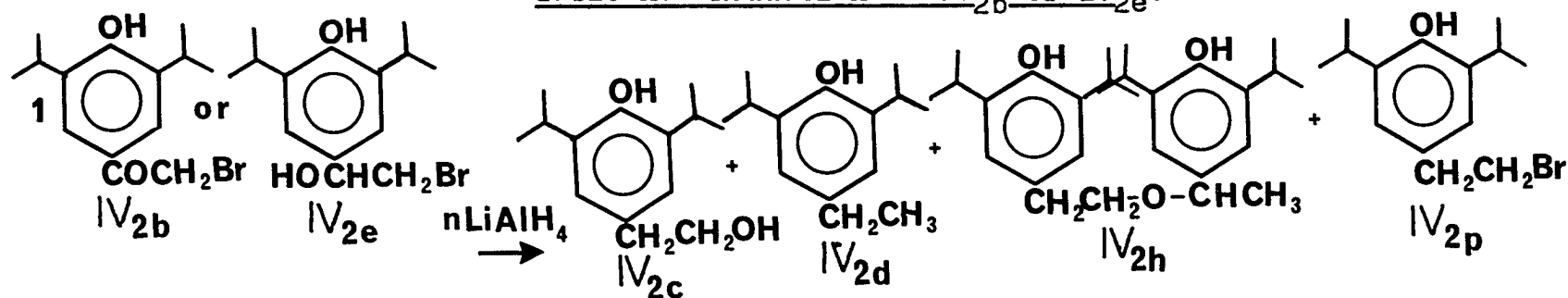
It is clear that reduction of the ketones or bromo-ketones (e.g. II_{2b} or IV_{2b}) cannot produce useful information under the desired conditions: a few min of reduction in refluxing ether with 2.25 mol LiAlH₄. One conclusion that could be drawn from these studies was that the reduction of the carbonyl group proceeded very rapidly, within the first 2 - 4 min, but that time was not sufficient to allow complete formation of the stable alkane and primary alcohol products. However it was shown that the

bromoketone IV_{2b} was completely reduced to final products in 10 min, whereas the ketone IV_{2a} was not.

The experiments leading to the successful preparation of the bromohydrin IV_{2e} (R₃ = iso-Pr) illuminated several points (see p 272): (a) it may be prepared very readily using NaBH₄/EtOH at -50°; (b) it is very unstable toward heating as it becomes a purple tar and evolves HBr, which partly explained the lack of success in isolating it from the LiAlH₄ reductions of ether solutions of IV_{2b}. (Those mixtures, from LiAlH₄ reduction, were heated during workup over 40°, see p 255, which was shown to destroy the bromohydrin.) Once obtained, the bromohydrin IV_{2e} was reduced with LiAlH₄ with the results listed in Table X. For convenience, several entries from Table V (Reduction of IV_{2b}) are included for direct comparison.

It should be noted that the reductions of the bromohydrin IV_{2e} (R₃ = iso-Pr) were performed with more LiAlH₄ and in more dilute solution than was the case for IV_{2b} (R₃ = iso-Pr). This was deliberately done to minimize formation of the dimer IV_{2h}. Examination of Entry 3 of Table X reveals that the use of more LiAlH₄ than the customary 2.25 mol and a higher dilution with ether did not affect the results (Cf. Entry 3 vs 1 and 2). Therefore it was anticipated that the bromohydrin reductions would be reasonably comparable to the bromoketone (IV_{2b}) reductions.

Table X. Reduction of IV_{2b} or IV_{2e}.



Entry	Compd	n, mol LiAlH ₄	Percent Product Distribution				(Molar Recovery)	
1 ^a	IV _{2b}	2.25	67	IV _{2c} , 33	IV _{2d}		(99.2%)	^b
2 ^a	IV _{2b}	2.27	64	IV _{2c} , 36	IV _{2d}		(99.0%)	^b
1,2			63.4	IV _{2c} , 28.2	IV _{2d} , 2.5	IV _{2h} , 5.6	IV _{2p} , 0.5	IV _{2a} (87.0%) ^c
3 ^a	IV _{2b}	9.00 ^d	65.5	IV _{2c} , 34.5	IV _{2d}			(97.0%) ^b
4 ^e	IV _{2e}	5.56 ^f	69	IV _{2c} , 31	IV _{2d}			(97.5%) ^b
			67.4	IV _{2c} , 20.2	IV _{2d} , 7.35	IV _{2h} , 5.06	IV _{2p} , -	IV _{2a} (84.0%) ^c
5 ^e	IV _{2e}	5.56 ^f	67	IV _{2c} , 33	IV _{2d}			(94.0%) ^b
			71.9	IV _{2c} , 18.8	IV _{2d} , 5.53	IV _{2h} , 3.77	IV _{2p} , -	IV _{2a} (92.2%) ^c
6 ^e	IV _{2e}	9.11 ^g	79.4	IV _{2c} , 20.6	IV _{2d}			(96.4%) ^b

^a 360 min reflux. ^b Analyses by nmr. ^c Dry column chromatography results.

^d 0.0050 mol IV_{2b}/200 ml ether. ^e 30 min reflux. ^f 0.0100 mol IV_{2e}/200 ml ether.

^g 0.0100 mol IV_{2e}/250 ml ether, required 5 min to reach reflux. Entries 1, 2 and 3 are taken from Table V.

Examination of the entries for the bromohydrin reduction (4 and 5) shows: (a) All four of the principal products were formed from the bromohydrin alone, i.e., the primary alcohol IV_{2c}, alkane IV_{2d}, dimer IV_{2h}, and the alkyl bromide IV_{2p}. (b) The agreement between the product distributions was good. The bromoketone IV_{2b} yields 63.4% IV_{2c} vs. 67.4, 71.9% from IV_{2e}; IV_{2b} yields 28.2% IV_{2d} vs. 20.8, 18.8% from IV_{2e}; IV_{2b} yields 2.5% IV_{2h} vs. 7.35, 5.53% from IV_{2e}; IV_{2b} yields 5.6% IV_{2p} vs. 5.06, 3.77% from IV_{2e}.

That the agreement was not perfect was partly due to the fact that reduction of the bromohydrin began in mideas res, which appears to encourage formation of the dimer IV_{2h}. There also appears to be a temperature effect operating. The reduction of the bromoketone caused the ether to boil within a minute or so, whereas reduction of the bromohydrin did not cause the ether to boil. In part this was due to the higher dilution employed for the bromohydrin, which necessitated the transfer of the flask fairly rapidly to a preheated bath (62°) to raise the temperature of the ether to 35°. In part this was due to the nature of the compounds. The highly exothermic reduction of the carbonyl cannot occur with the bromohydrin. The heat evolved in this initial reduction is available in the bromoketone reduction, which hastens the boiling of the ether.

There was no reason to assume that the temperature

dependence for formation of the primary alcohol and alkane would be the same, therefore the discrepancies are plausibly explained on that ground. There is further evidence for this, Entry 6, Table X: reduction of IV_{2e} with 9.11 mol $LiAlH_4$ in the ratio of 0.0100 mol IV_{2e} /250 ml ether produced 79.4% IV_{2c} and 20.6% IV_{2d} . In this case, the volume of ether involved, 750 ml, was so large that the system required ca. 5 min to reach reflux vs. the 2 - 3 min for Entries 4 and 5.

As a result of the experiments recorded in Table X, the bromohydrin (or chlorohydrin) was accepted as the source of all the observed products for the entire series of compounds studied. The extension of the results of IV_{2e} ($R_3 = \text{iso-Pr}$) actually only affected the cases where R_3 was H or an alkyl group. It will be recalled (see Tables VII,²⁰ pp 39 and 40, and VIII,²¹ p 41) that the halohydrin was indirectly observed to give the products where R_3 was Br or Cl. (Although the pure bromohydrins have not yet been reduced for those cases, the partial results make the outcome of those experiments a certainty.) Once the halohydrin was established as the crucial intermediate, leading to all of the products, mechanism A was established. Therefore it is now appropriate to discuss the reduction of the entire series of compounds in terms of mechanism A.

(G) Discussion of the Mechanism

(I.) Development of the Mechanism

Rigorous discussion of the intimate details of all the steps involved in the reductions of this dissertation is severely handicapped by the nature of the LiAlH_4 - Et_2O - substrate system. The substrates were perfectly soluble in the volume of ether employed, but the LiAlH_4 (or LiAlD_4) was added as a finely divided solid to the substrate solution. This invariably produced a voluminous precipitate within a minute or so after addition. The question of the physical state of the reactants arises immediately, but cannot be answered. There is no assurance that the reactions to be discussed actually occur in solution. The data do not demand that they occur only on the surface of the particles of LiAlH_4 . The addition of the LiAlH_4 as a finely divided solid immediately introduces the problem of temperature dependence--as was alluded to in the preceding section. The rate of dissolution of the LiAlH_4 should be dependent upon the particle size as well as the temperature. The rate at which the partially reduced substrate breaks free of the particle surface should be temperature dependent. Finally, the temperature dependence of formation of the various products is not likely to be identical.

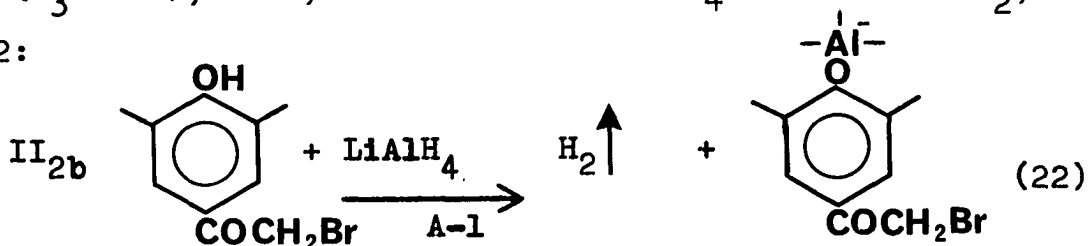
Kinetic studies were not performed. The only information that we have in this area is that the reactions proceeded within a few minutes to completion (for the

alkyl-phenol derivatives) which is inconveniently rapid for kinetic studies. The handicaps impose severe problems of proving various details of the mechanism. The solution which was adopted was to treat individual substrate molecules as if they were isolated in solution and treat the various reaction steps as if they were intramolecular, see p 111. (That this approach is commonly adopted does not by itself constitute justification for it.) The plausibility of each step (and assumption) is dealt with as the discussion proceeds.

The first assumption that requires justification is whether or not the substrate-- LiAlH_4 reactions can be treated as if they were reactions in a homogeneous solution. The interesting physical changes attendant upon addition of ca. 0.86g of LiAlH_4 to 100 ml of ether containing a few grams of substrate are described in the Experimental Section, p 223. The essential observation was the transformation of the initial solution into a gelatinous mass, which temporarily rendered the magnetic stirrer ineffective. This transformation typically occurred within 60 sec -- which is a period within which the reactions are known to have not reached completion. The finely divided nature of the gelatinous mass argues for a very rapid dispersal and solution of the LiAlH_4 particles, followed by precipitation from homogeneous solution. This suggests that the reactions were occurring, at least in part, in aggregates far smaller than would be the case if one chose to envision a single substrate molecule

undergoing complete reduction to a final product at the surface of a LiAlH_4 particle.

The first step of the reaction is illustrated for II_{2b} ($\text{R}_3 = \text{Me}$), i.e., reaction with LiAlH_4 to liberate H_2 , Eq 22:



(Although we shall follow the reaction by steps, it will be noted that the flow sheet is found on p 64.) The reaction of LiAlH_4 with alcohols and phenols to liberate H_2 is a simple acid-base reaction that was documented quite early. The reactions do differ in one aspect, as noted by Gaylord,²⁷ in that LiAlH_4 can proceed to $\text{Al}(\text{OR})_4^-$ with unhindered primary alcohols, but stops at $\text{HAL}(\text{OC}_6\text{H}_5)_3^-$ for phenol itself. Presumably the introduction of a fourth phenoxide would be sterically difficult.

For the compounds covered in this dissertation, the Al is assumed to be bound, more or less tightly to the oxy-aryl anion, in keeping with the above observation on phenol itself. An alternate view of the nature of the ArO^- and Al interaction, which leads to the same conclusions, is presented at the end of this discussion, see p 101. Clearly, increasing the size of the flanking groups (R_3) from H to tert.-butyl can only make the attachment of three such anions

to a single Al difficult to impossible. It remains possible that H_2AlOR , HAl(OR)_2 or $\text{H}_2\text{Al(OAr)}$ can also be coordinating ligands to the oxyaryl anion. The Al coordinated to the ArO^- will be left unspecified as to the other groups upon it. However, the use of 2.25 mol of LiAlH_4 per mole of substrate makes it mathematically possible for each substrate molecule to have two Al bound to it--one to the ArO^- , the other to the RO^- (from the carbonyl reduction).

The work of Jessen³³ which is found in Table IX,³³ p 72, Section E, indicates that the initial attack is directed to the ArOH for R_3 of increasing size up to isopropyl. With V_{2b} ($\text{R}_3 = \text{t-Bu}$), the evidence indicated that the alternative attack, A-1' (carbonyl reduction) followed by A-2' (removal of the phenol H) was the route to the halohydrin intermediate. Depending upon the basis of calculation and the question whether Eq 21a or 21b (see p 71) was the source of the ketone products (Section E), it was entirely possible that the tert.-butyl compounds (V_{2b-6b}) were reduced to the rearranged primary alcohols without the phenol H having been removed. The question of whether the tert.-butyl cases represent aryl migration with the phenol proton present or removed could not be answered directly.

The reduction of V_{3b} to the primary alcohol V_{3c} (see Table VI, p 38) had been established very early in this work as a rapid one: complete reduction was achieved in 4 min. Therefore it was used as the test of the entire

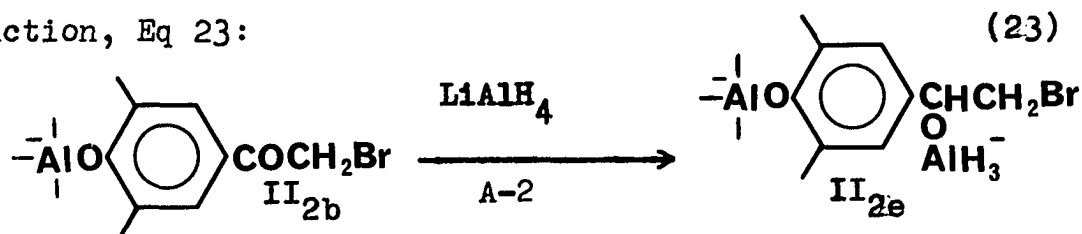
tert.-butyl (as R_3) series. The addition of 1 mol of this compound as a solid to 2.25 mol of $LiAlH_4$ slurried in ether (which reversed the ordinary procedure employed in this dissertation) was shown to produce the same product, V_{3c} , in 4 min and also evolved the correct amount (1 mol) of gas (presumably H_2) within 4 min of reaction. More importantly, 94% of the gas evolution occurred in the first 15 sec of reaction, see p 267. Unless it can be established that V_{3b} reacts to completion in much less than 15 sec (which is not easy to do) it remains a tenable assumption that the phenol H was removed prior to aryl migration for the cases where $LiAlH_4$ was in excess, i.e., Tables I - VI (p 32 ff.). The effect of this gas evolution study is to compress the time scale to the first 15 sec of reaction for the $R_3 = \text{tert.}$ -butyl compounds, but it does not answer the question whether the removal of the phenol H is necessary in these compounds for the oxyaryl migration to occur.

The cases where R_3 was a halogen, Cl or Br, (Tables VII,²⁰ pp39 and 40, and VIII,²¹ p 41) may be considered analogous to Me or Et respectively on steric grounds. (The van der Waals radii taken from Hine³⁵ are: Me, 2.0 Å; Cl, 1.8 Å; Br, 1.95 Å; I, 2.15 Å. The ethyl group is

(35) J. Hine, Physical Organic Chemistry, Second Edition, McGraw-Hill, 1962. Cf p. 28.

approximately the size of a Br.) Therefore, all compounds other than V_{2b-6b}, where R₃ is smaller than tert.-butyl, will be taken to have lost the phenol H in the first step.

The second step would be reduction of the carbonyl function, Eq 23:



This produces the dianion of the bromohydrin II_{2e} with an Al bonded to each of the oxygens. (It is assumed that the corresponding chloroketones, II_{2b-Cl} - IV_{2b-Cl} follow A-1 and A-2 to reach the respective chlorohydrins.) The other bromoketones referred to in this work are assumed to have arrived at this stage also via A-1, then A-2, with the exception of V_{2b-6b}, which perhaps arrived at this stage via A-1' then A-2'.

Because we cannot differentiate between Al or Li bound to the alkoxy group, for convenience in representation, we shall show this as ROAlH₃⁻. We shall briefly digress into two aspects that this Al-O bonding assumption generates: the milder reducing capacity of the H₃Al(OR) and the stability of this species towards disproportionation. First let us consider the growth of the use of LiAl(O-tert.-Bu)₃H, LiAl(OEt)₃H, and LiAl(OMe)₃H as reducing agents. Some of the early and systematic work in this area was

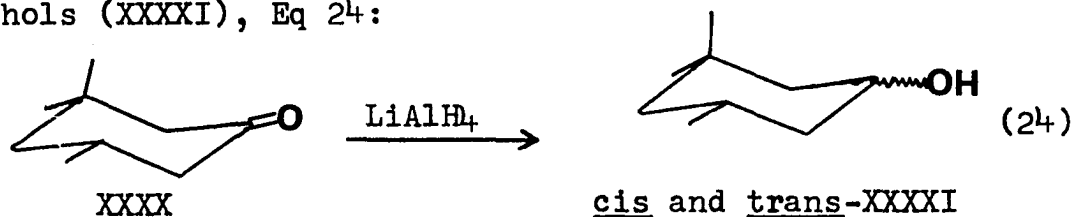
provided by H. C. Brown and his coworkers^{36a,b,c} which established the stoichiometry of the $\text{LiAl(OR)}_n\text{H}_{4-n}$ reagents,^{36a} and the generally milder reducing power of these reagents--initially directed toward aldehyde syntheses from nitriles^{36b} and amides.^{36c} Part of the motivation for the development of the milder alkoxy derivatives of LiAlH_4 was to obtain reagents, the reactions of which could be studied kinetically. As H. C. Brown noted^{36a} (and many others have before) LiAlH_4 reduces carbonyl groups so rapidly that kinetic studies are generally not attempted with that reagent. Brown also noted that secondary alcohols and acetone tend to disproportionate^{36a} to tetra-substituted aluminum alkoxides and LiAlH_4 . Our compounds upon reduction become secondary alcohols. If disproportionation led to tetra-substituted aluminum alkoxides, it is possible that further reactions would become much slower because they would require intermolecular transfer of a hydride.

Elie^{37a,b} studied the reduction of

(36)(a) H.C. Brown and C.J. Shoap, J. Amer. Chem. Soc., 88, 1079 (1964); (b) H.C. Brown and C.P. Garg, ibid., 88, 1085 (1964); (c) H.C. Brown and A. Tsukamoto, ibid., 88, 1089 (1964).

(37)(a) H. Haubenstock and E.L. Elie, J. Amer. Chem. Soc., 84, 2363 (1960); (b) Idem., ibid., 84, 2368 (1960).

3,3,5-trimethylcyclohexanone (XXXX) to the cis and trans alcohols (XXXXI), Eq 24:



It was found that the results of the reduction could be best explained^{37a} if LiAlH_4 was the hydride "carrier" and also rapid disproportionation to Al(OR)_4^- occurred to that AlH_4^- which had already reacted. This was invoked to explain the lack of steric effects when different secondary alkoxy derivatives of LiAlH_4 were utilized. Reduction of the same substrate^{37b} with NaBH_4 or KBH_4 required a different interpretation of the data: there the successive removal of H from BH_4^- produced a larger and more reactive reagent, but not the disproportionation which the LiAlH_4 reduction appears to undergo.

Examination of Eliel's work^{37a} discloses only two instances where the rate of addition of reagents was given (one of 15 min in THF, one of 60 min in Et_2O soln). Presumably these authors deliberately performed the reductions under conditions of thermodynamic control--to allow the postulated disproportionation to occur. In the alkylphenol (I - V) derivatives of this thesis, reduction was completed within 10 min (for X = Br), whereupon Eliel's 60 min addition would be very liesurely indeed. There is an additional point of greater significance: the addition of

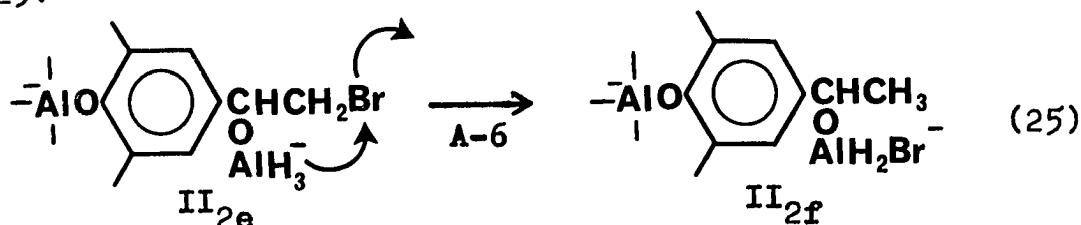
camphor (XXXXII) to LiAlH_4 gave more trans-XXXXI than LiAlH_4 did alone with XXXX, Eq 24. Eliel concluded that the bulky isobornyloxy anion (XXXXIII) was highly unlikely to be "zipped-down" to $\text{Al}(\text{OR}_4)^-$ due to the size of the alkoxy group.

An effort was made to examine the steric factors involved using Cortaulds space-filling models. We had no Al and were forced to employ tetrahedral carbon as a substitute. Given this limitation, and the danger of over-reliance upon models, certain things appeared evident. It was possible to place four isopropoxy groups about the central "Al." Both camphor (XXXXII) and II_{2e} appear to be quite able to add to an "Al" which had already one of those substrates upon it. Neither four isobornyloxy anions (XXXXIII), from camphor, nor four of II_{2e} could be placed about a single "Al." Three of either of those anions were rather crowded about a single "Al." To the extent that models may be relied upon, it would appear that our halo-hydrins, e.g. II_{2e} , resemble camphor rather more than they resemble acetone in their placement around Al. Therefore it would appear to be reasonable to suppose that one or perhaps two such groups would be attached to a given Al. However, it is more convenient to draw that Al as ROAlH_3^- , provided that it is clearly understood that $\text{ROAlH}_2(\text{OR})^-$, $\text{ROAlH}_2(\text{OAr})^-$, or $\text{ROAlH}(\text{OR})_2^-$ are not being excluded.

Further reactions which the bromohydrin II_{2e} may

undergo are competitive. (In the general case of the halo-hydrins, the further reactions also would be expected to be competitive.) To facilitate comparison of the product ratios as R_3 was varied while the reducible group remained COCH_2X the pertinent data of Tables I - VI are combined in Table XI, p 92 and recalculated as ratios (based on the alkane product) and the free energy differences, ΔG^* , for each pair of alkane and primary alcohol or alkyl halide products are also listed.

The ordinary reaction which the bromohydrin could undergo is A-6, displacement of the Br (or Cl) as shown in Eq 25:



This is the reaction found by Lutz⁵ which has already been reviewed in the Background, p 14,15. This displacement reaction would also hold for $R_3 = \text{Br}$ or Cl (Table VII). The transition state is none other than that of Eq 11 (p 24) based on Eliel's work. (It is not known what becomes of the Br^- after it is displaced, but it could bind to the Al (as shown) to maintain four-coordinate Al. This assumption is not essential to the Discussion.)

There is a minor divergence of the further reactions of the benzylic alcohol at this point. For the

Table XI ^a

(A) Comparison of the Amount of Alkane & Alkyl Halide Product

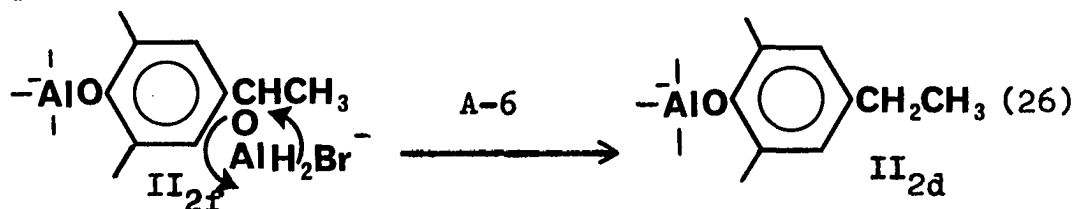
<u>Entry</u>	<u>Source Compd</u>	<u>% Alkyl Halide</u>	<u>% Alkane</u>	<u>Total, %</u>	<u>Ratio RX/RH</u>	<u>ΔG^*, ^c Cal/mol</u>
1	I _{2b}	<0.5 ^b	85.6	86.1	<.0058	> -3,140
2	II _{2b}	1.7	62.6	64.3	.0272	-2,200
3	II _{2b}	2.2	63.9	66.1	.0344	-2,050
4	II _{2b} -Cl	17.1	15.8	32.9	1.083	49
5	III _{2b}	4.9	44.3	49.2	.110	-1,350
6	III _{2b}	4.5	44.0	48.5	.102	-1,400
7	III _{2b} -Cl	12.4	13.4	25.8	.925	-50
8	IV _{2b}	5.6	28.2	33.8	.199	-1,100
9	IV _{2b}	5.4	27.5	32.9	.196	-1,020
10	IV _{2b} -Cl	10.9	7.8	18.7	1.40	208
11	V _{2b}	10	<0.5 ^b	10.5	>20	>1,850

(B) Comparison of the Amount of Alkane & Primary Alcohol Product

<u>Entry</u>	<u>Source Compd</u>	<u>%Primary Alcohol</u>	<u>% Alkane</u>	<u>Total, %</u>	<u>Ratio ROH/RH</u>	<u>ΔG^*, ^d Cal/mol</u>
1	I _{2b}	<0.5	85.6	86.1	<.0058	> -3,140
2	II _{2b}	34.2	62.6	96.8	.546	-390
3	II _{2b}	32.4	63.9	96.3	.506	-400
4	II _{2b} -Cl	64.0	15.8	79.8	4.05	864
5	III _{2b}	46.7	44.3	91.0	1.055	32.7
6	III _{2b}	47.9	44.0	91.9	1.09	53.2
7	III _{2b} -Cl	64.8	13.4	78.2	4.84	973
8	IV _{2b}	63.4	28.2	91.6	2.25	500
9	IV _{2b}	63.4	27.5	90.9	2.30	514
10	IV _{2b} -Cl	77.6	7.8	85.4	9.95	1,410
11	V _{2b}	90	<0.5 ^b	90.5	180	>3,200

^a Gathered from Tables I - VI. ^b Assumed value. Compound not detected by nmr. ^c $\Delta G^* = RT \ln(RX/RH)$. ^d $\Delta G^* = RT \ln(ROH/RH)$.

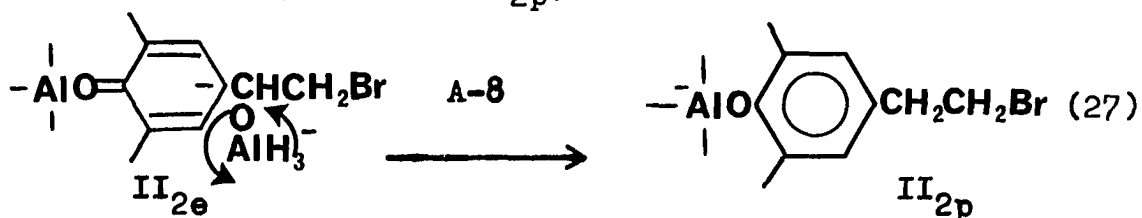
alkyl flanking groups (as R_3), step A-7 is rapid, as shown in Eq 26:



It has been noted already (see p 61) that the benzylic alcohols with alkyl groups as R_3 suffer rapid hydrogenolysis of the C-O bond. (For our purposes, it is immaterial whether this cleavage proceeds through the para-quinone-methide, or via intermolecular displacement, or as shown.) Where R_3 is a halogen, this hydrogenolysis is very slow as can be seen by inspection of Table VII,²⁰ p 39, where the benzylic alcohol is clearly a product. Further, it was found and noted in the Experimental Section (p 221) that the benzylic alcohol VI_{2f} ($R_3 = \text{Cl}$) was rather easy to obtain but the alkane VI_{2d} was quite difficult to obtain via hydrogenolysis of the starting ketone VI_{2a}.

It is convenient to take production of the alkane product as the standard reaction and compare the other reactions to it. This is what was done in Table XI. There are cautionary notes to bear in mind while inspecting Table XI: the extreme cases, I_{2b} and V_{2b}, represent arbitrary values. Neither alcohol nor alkyl halide were found among the products of I_{2b} by chromatography, so a minimum value (0.5%) was chosen. Similarly, for V_{2b} no alkane was detected by nmr spectral analysis, and a

maximum value of 0.5% was assumed. In general terms, it is evident that the rise of primary alcohol product is paralleled by a rise in alkyl halide product--but at a much lower level. This is believed to reflect the influence of a single driving force: the effectiveness with which the ArO^- is bound by Al. In general terms one can rationalize the rise in primary alcohol or alkyl halide product (at the expense of the alkane), because a less tightly bonded ArO^- effectively means a greater intensity of negative charge at the carbon para to it (the 1'-carbon). This is shown for step A-8, to produce the alkyl halide II_{2p} , in Eq 27:



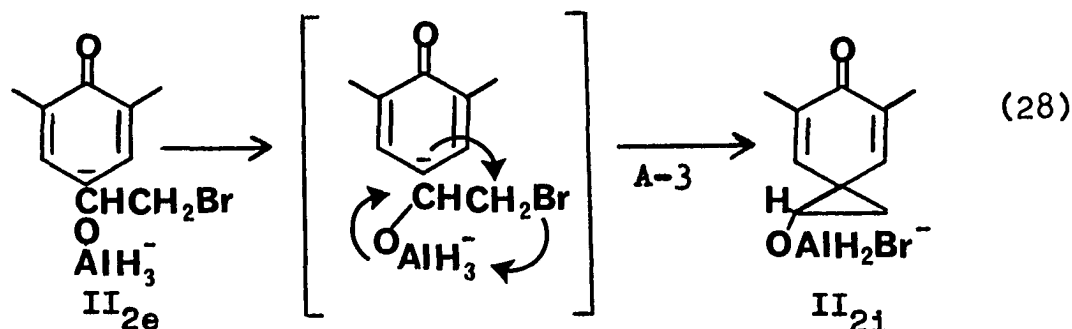
The quinoid resonance structure shown in Eq 27 has been added to emphasize the ability of the aromatic ring system to facilitate the C-O bond cleavage. Gaylord²⁷ has noted that benzylic alcohols are resistant to hydrogenolysis by LiAlH_4 unless an ortho or para OH or NH_2 group is present. In a recent paper, Cerny and Malek³⁸ describe the successful reduction and hydrogenolysis of the ArCH_2O in ortho and para-benzaldehyde (XXXXIV) to the cresols employing sodium-bis-(2-methoxyethoxy) aluminum hydride. (In this

(38) M. Cerny and J. Malek, Tet. Let., 22, 1739, (1969).

hydrogenolysis, even LiAlH_4 is not particularly effective.) These results lend support to the view that there is at least some $\text{S}_{\text{N}}1$ character in the transition state for the $\text{ArCH}_2\text{-O}$ hydrogenolysis--and this is what is emphasized in the quinone resonance structure for $\text{II}_{2\text{e}}$.

The further reaction of $\text{II}_{2\text{p}}$ with a source of H leading to reduction to the alkane, step A-9, appears to be quite slow and will not concern us further. The step may be assumed to be a bimolecular displacement on a primary halide. (This point has already been covered in Section B, p 59. It should be noted in this connection that it is not possible to invoke large quantities of alkyl bromide as an initial product which was fairly rapidly reduced to the alkane. For that concept to be valid, the reductions of $\text{IV}_{2\text{b}}$ and $\text{II}_{2\text{b}}$ should show considerable amounts of alkyl bromide at 10 min reduction vs. 360 min, and this was not found, see Table II, p 34, and Table V, p 37.

Perhaps the most interesting product is the primary alcohol, which is believed to arise via a cyclic transition state with removal of the Br, as shown in Eq 28:



The closure step is most easily visualized in the quinoid form. The closure step is a variation on Eq 10 (p 24) due to Eliel's work. Here, the oxyaryl ring is believed to be extensively involved in assisting in the C-Br bond breaking. Once this transition state is invoked, we have a conceptual basis for understanding the variation in products as the series $I_{2b} - V_{2b}$ is ascended. Substitution of CH_3 for H as the flanking group (R_3) apparently weakens the ArO-Al bond, for primary alcohol is suddenly a product. Weakening the ArO-Al bond has the effect of intensifying the negative charge on carbon-1' as shown in Eq 28--which was invoked to explain the formation of the supposed precursor of primary alcohol. It cannot be stated whether this effect is due only (partly?) to the size of methyl vs. H, or whether the inductive effect contributes also. Substitution of ethyl or isopropyl as R_3 involves entropy restrictions upon the alkyl groups, which in turn should progressively weaken the ArO-Al bond, leading to more primary alcohol and alkyl halide products. Finally, at $R_3 = \text{tert.}-\text{butyl}$, the effectiveness of the Al bonding to the ArO^- may collapse altogether. This could lead to total formation of the primary alcohol and alkyl halide products. It is not possible to separate the inductive from the steric factors by this analysis. However, it is possible to realize that they will operate in the same direction--to increase the primary alcohol product. It is also clear that the general trends will hold whether the ArOAl bonding is polar

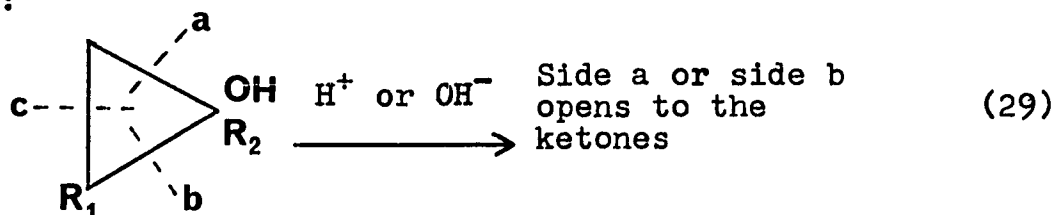
covalent or a tight ion pair--and we cannot decide between them.

It appears that the oxyaryl anion with the smallest ortho groups (i.e. $R_3 = H$) lead to phenoxy bonded side products, whereas the cases where $R_3 = Me$, or larger, do not. The most accessible ArO^- would be in I_{2b} and I_{3b} , for these have only ortho hydrogens to screen the ArO^- , and they were observed to give the most (and only cases) of those side products. Apparently, the AlH_3 or H_2AlOR etc. is sufficiently close to the ArO^- in all the other cases, and the alkyl flanking groups large enough, to block formation of dimers arising from ArO^- displacement of Br (or Cl).

Whether II_{2i} is a transition state or an intermediate cannot be stated with certainty. Nonetheless, it is useful to picture it an intermediate and enquire what reactions such a compound could be expected to undergo. It is also important to be able to rule out reactions that would lead to products which were not observed. Excluded is attack upon the carbonyl of II_{2i} , Eq 28, by $LiAlH_4$, AlH_3 or H_2AlOR etc. This attack is excluded on the basis of other work: Baird and Winstein²⁸ in their paper, cited on p 56, also reduced I_{2s} (from Eq 18) with $LiAlH_4$ to 4-ethylphenol (I_{2d}). Apparently opening of the cyclopropyl ring of I_{2s} takes precedence over reduction of the carbonyl group.

Ershov and his coworkers³⁹ reduced V_{2s} with $LiAlH_4$ and obtained V_{2d} --again the alkane product was obtained. These two examples span the least and most protected of the carbonyls ($R_3 = H$ or tert.-butyl), consequently it may be assumed that all cases in between are secure from reduction of the carbonyl group. For our compounds, there is the additional effect of the cyclopropyloxy group, which will be noted presently in Eq 31.

It is of particular interest to enquire what sort of reactions the cyclopropanol ring undergoes. C. H. DePuy⁴⁰ recently reviewed the direction of such ring openings, (Eq 29):



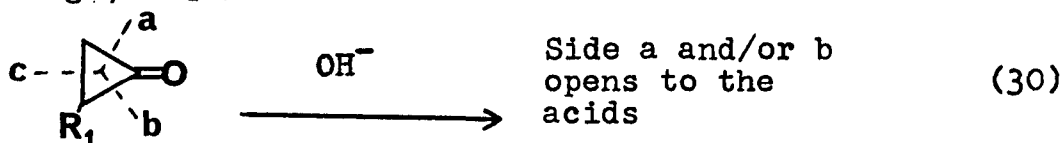
The important observation is that both sides a and b open under acid or base attack, but not side c. N. C. Turro⁴¹ recently reviewed the direction of cyclopropanone ring

(39) I.S. Belostotskaya, A.A. Volod'kin, and V.V. Ershov, Bul. Acad. Sci. USSR, 1033 (1967).

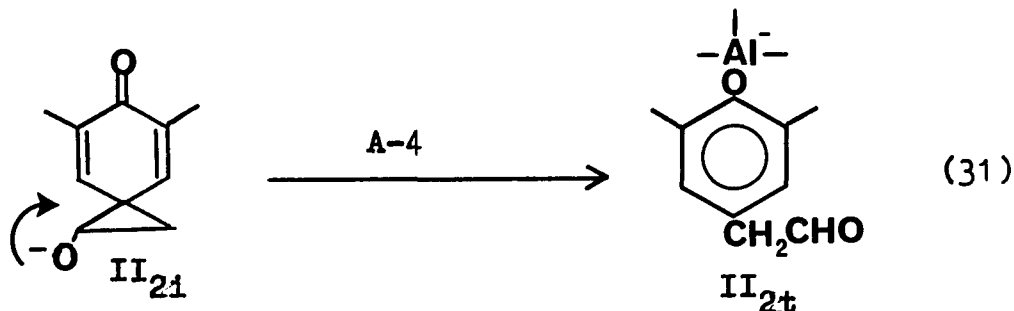
(40) C.H. DePuy, Acc. Chem. Res., 1, 33 (1968).

(41) N.J. Turro, ibid., 2, 25 (1969).

openings, (Eq 30):

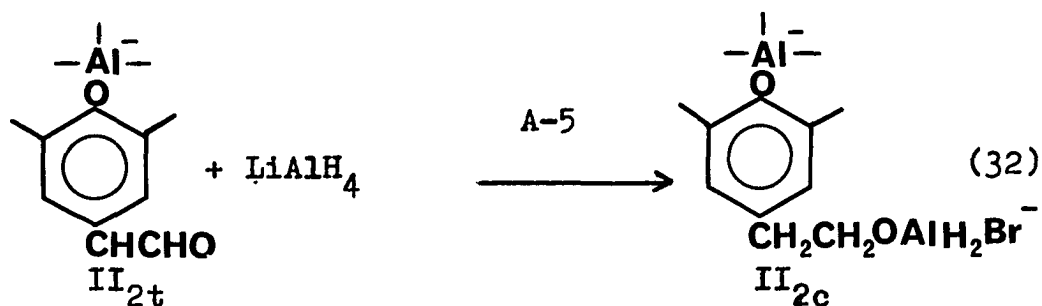


and noted that base attack opens sides a and/or b but not c. (However, side c will open under acid attack.) Examination of the proposed next step of reaction, A-4, as shown in Eq 31:



discloses that the proposed opening involves cleavage of side b of the cyclopropanol. Either side a or b could cleave, however, cleavage of side a does not restore the aromaticity of the ring whereas cleavage of side b does. This is consistent with DePuy's⁴⁰ work. We do not invoke cleavage of side c, although it would restore the aromaticity of the ring, and generate the benzylic alcohol II_{2f}, the precursor of alkane II_{2d}. DePuy showed base catalyzed (i.e. by O⁻) cleavage of cyclopropanols to be rapid, in our case this would suggest that cleavage of side b should take precedence over cleavage of side c.

The last step would be the reduction of the aldehyde II_{2t}, (Eq 32):



The postulated reduction of the aldehyde is unexceptional, and expected to occur very rapidly. That this opening to aldehyde (step A-4, Eq 31) followed by reduction is correct is indicated by the work of B. Kupfer.⁴² That work (which will be treated in Section I, p 156) involved reduction with $\text{LiAl}(\text{O}t\text{-Bu})_3\text{H}$ in limited amounts to produce considerable amounts of the halohydrin V_{2e} ($\text{R}_3 = t\text{-Bu}$) and also some V_{2t} . At this point, the aldehyde product V_{2t} is of major interest. It is easy to conceive that some aldehyde could survive in this case, because the reducing agent is relatively weak and was present in limited amount. Clearly, there would be no hope of finding such a readily reduced compound in Tables I - VI, where a considerable excess of a powerful reducing agent-- LiAlH_4 -- was employed.

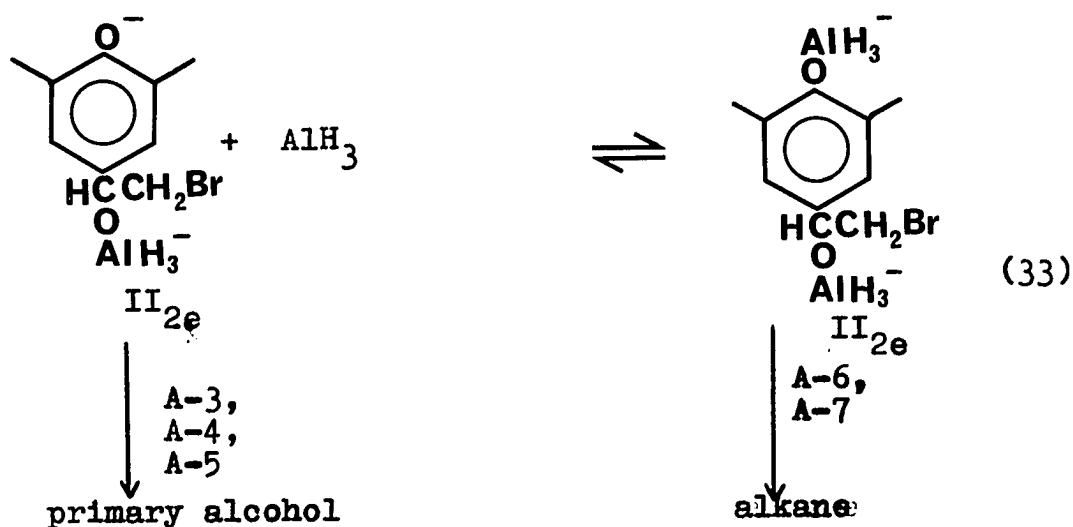
We will briefly summarize the high points of the preceding arguments at this time. Reaction of LiAlH_4 with phenolic H, ketones or aldehydes, and the ring opening of

(42) B.B. Kupfer, The City College, unpublished observations.

cyclopropyloxy anions are all known to be very rapid reactions. The only junction from which the products are assumed to be the result of competitive reactions is at the halohydrin stage. And in fact, it has been shown that the halohydrin IV_{2e} (R₃ = iso-Pr) gave rise to all of the products of the reduction of the bromoketone IV_{2b} (see Section F, p 80). The reactions of the halohydrin: A-3, or A-6, or A-8, p 64, are assumed to be the rate determining steps. This cannot be easily proved for the bromohydrins from phenols I - V, because they are too reactive to allow demonstration of their existence, let alone accumulation, in the early stages of the reduction with excess LiAlH₄. (What could be done is to demonstrate that the complete reduction of bromohydrin IV_{2e} proceeds at the same rate as complete reduction of bromoketone IV_{2b}.) A further assumption is the description of the pathway leading to alkane from the halohydrin as an entirely separate reaction from the one which leads to primary alcohol. This assumption is necessary to maintain a rationale for the decrease in alkane product as R₃ increases in size, as was noted in connection with Eq 30. (Of course this would cease to be an assumption if a typical spiro-cyclopropanol, e.g. IV_{2i} (R₃ = iso-Pr), could be prepared and found to yield only the primary alcohol, IV_{2c}, upon LiAlH₄ reduction.)

The reactions of the model compound, II_{2b} (R₃ = Me), have been drawn as ArOAl in Eq 22 - 32. An alternate

possibility could be that shown below in Eq 33:



The equilibrium shown in Eq 33 could be responsible for the product distribution. That fraction of the molecules which is present as ArO^- could react rapidly via Steps A-3, 4 to yield the primary alcohol II_{2c} . The oxyaryl ring migration could be rapid due to the negative charge on the phenol oxygen. The reduction of the negative charge intensity by ArO^- bonding to AlH_3 could reduce the tendency of the oxyaryl ring to migrate, thus allowing Steps A-6, 7 to occur, yielding the alkane II_{2d} . The equilibrium position could be expected to depend upon the size of the alkyl flanking groups (R_3). As the series $\text{R}_3 = \text{H}$ to t-Bu is ascended, the equilibrium position would be more likely to lie to the left in Eq 33, thus raising the yield of primary alcohol product--which is observed to be true. For compounds where R_3 is Br or Cl, the electronegativity of the halogens could effectively shift the equilibrium to

the right in Eq 33 by reducing the intensity of the negative charge on the phenol oxygen. This would lead to the observed benzylic alcohol and alkane products. This is the alternative view which was referred to on p 84.

We do not have experimental data to decide how tightly the ArO^- is bonded to the AlH_3 . We cannot state how rapid the equilibration of Eq 33 is, nor can we state whether such equilibration alone would account entirely for the observed product distribution: there remains the possibility that some of the ArOAlH_3^- might lead to primary alcohol. Consequently, we regard both representations as plausible. The one shown in Eq 22 - 32 was chosen because it is more convenient to draw such equations.

(A) The products of the reduction of VI_{2b} ($\text{R}_3 = \text{Cl}$) and VII_{2b} ($\text{R}_3 = \text{Br}$) should be biased towards alkane and benzylic alcohols, as compared to compounds where $\text{R}_3 =$ alkyl group. This was found to be the case, and no products of aryloxy rearrangement were found, see Table VII, pp 39,40. This is a reasonable extension of the results with the alkyl-phenol derivatives. Given the fact that $\text{R}_3 = \text{H}$ (I_{2b}) yields neither primary alcohol nor alkyl halide, then an electro-negative R_3 (Cl or Br) could be expected to inductively stabilize the ArO^- sufficiently to reduce the negative charge intensity on carbon-1'. The negative charge intensity on carbon-1' was invoked as the factor which led to hydrogenolysis, giving alkyl halide, or oxyaryl ring

migration, affording primary alcohol. It is then plausible that the first series of steps: A-1, A-2, p 64, should proceed for compounds VI_{2b} or VII_{2b} but A-3 and A-8 are disfavored for lack of sufficient negative charge intensity on carbon-1'. The only reaction which is not expected to be severely slowed down would be A-6--which leads to benzylic alcohol. Because these benzylic alcohols have halogens on the ring, they are resistant, but not impervious to hydrogenolysis, as was previously discussed on p61 .

Examination of Table VII (pp 39,40) discloses that the chlorohydrin VI_{2e-Cl} ($R_3 = Cl$) was present as 37% of the product after 60 min of reduction (Entry 8), but only 20 - 29% of the product after 180 min of reduction (Entries 6, 7), and was absent after 1200 min of reduction (Entry 5), leaving only benzylic alcohol VI_{2f} and alkane VI_{2d} as the products. The simplest conclusion is that extrapolation to the beginning of the reaction would yield chlorohydrin VI_{2e-Cl} as the first product. Therefore this reduction belongs within the scope of the mechanism because reduction proceeds through the halohydrin.

It will be noted that the percentage of alkane VI_{2d} ($R_3 = .Cl$) in Entry 5 reached 30% (after 1200 min) compared to 15% (after 180 min) in Entries 2 and 3 (from VI_{2b}). This reflects the slow hydrogenolysis of the benzylic alcohol VI_{2f} to the alkane VI_{2d} . The appearance of 57% chlorohydrin VII_{2b-Cl} ($R_3 = Cl$) after 180 min reaction (Entry 9) as

opposed to 20 - 29% chlorohydrin $\text{VI}_{2\text{b-Cl}}$ ($\text{R}_3 = \text{Br}$) after 180 min reaction (Entries 6,7) is troublesome--why should there be more chlorohydrin with $\text{R}_3 = \text{Br}$ than with $\text{R}_3 = \text{Cl}$? (However, the presence of such a large amount of chlorohydrin strongly suggests that the reduction of $\text{VII}_{2\text{b-Cl}}$ is also within the scope of the mechanism.)

Equally troublesome is the presence of 10% of bromohydrin $\text{VI}_{2\text{e}}$ after 30 min reaction (Entry 4)! The appearance of that bromohydrin is very unexpected and the experiment should be repeated. Given the considerable difficulties of synthesizing $\text{IV}_{2\text{e}}$ ($\text{R}_3 = \text{iso-Pr}$) ($\text{IV}_{2\text{e}}$ could not be synthesized with LiAlH_4 at 0° , and required NaBH_4 in EtOH at -50° , p 272), it was not expected that any of the bromohydrins, $\text{I}_{2\text{e}} - \text{VIII}_{2\text{e}}$, would be recovered from reduction with excess LiAlH_4 in refluxing ether. What is suggested is that we are encountering a solubility problem. Perhaps the halophenol derivatives, $\text{VI}_{2\text{b}}$, $\text{VI}_{2\text{b-Cl}}$, $\text{VII}_{2\text{b-Cl}}$, are rather less soluble as their halohydrin dianion-Al complexes than those from the alkylphenols. The expected reactions might not occur as rapidly if the complexes are bound into insoluble lumps. There are two slight indications which support this possibility: (a) The halophenol derivatives themselves were observed to be rather less soluble in ether than the alkylphenol derivatives. This was a qualitative observation, we never measured the solubilities. (b) On one occasion, Gullo²⁶

reduced 0.10 mol of V_{3b} ($R_3 = t\text{-Bu}$) with 0.225 mol LiAlH_4 in several hundred ml of ether and the mechanical stirrer failed very shortly after the LiAlH_4 was added. The initially formed paste fell to the bottom of the flask and remained a mass throughout 180 min of reflux. Cautious workup left no doubt that LiAlH_4 was present in vast excess at the end of the reduction. The principal product was the primary alcohol V_{3c} , as expected, but ca. 2% of the product was the halohydrin V_{3e} as determined by the nmr spectrum of the residue from recrystallization. Small scale reductions of V_{3b} with efficient stirring were observed (Table VI, p 38) to produce V_{3c} without a trace of the halohydrin V_{3e} , and in 4 min--not 180 min. If the possibility of solubility differences is not the cause of these observations, we are at a loss to explain what happened.

The effect of the size and electronegativity of the halogen has so far been ignored, and deliberately so. As will be seen presently, it is more convenient to introduce this factor during the discussion of part E, below.

(B) Whether the reduction of the chloroketones $\text{II}_{2b\text{-Cl}} - \text{IV}_{2b\text{-Cl}}$ ($R_3 = \text{Me, Et, iso-Pr}$) is properly within the scope of the mechanism could be handled rigorously or on the basis of indirect evidence. Rigorous proof would involve the synthesis of the chlorohydrin $\text{IV}_{2b\text{-Cl}}$ ($R_3 = \text{iso-Pr}$)

(which has already been achieved, see p 275), reduction of chlorohydrin IV_{2b-Cl} (which has not been done), and reduction of the chloroketone IV_{2b-Cl} with $LiAlD_4$ (which has been accomplished, but not brought to the point where the data are complete--preliminary observations, R.V. Flor). Then we would have an exact parallel to the work on the bromoketone IV_{2b} ($R_3 = \text{iso-Pr}$). It is not regarded as necessary to perform this full sequence upon the chloroketones II_{2b-Cl} and III_{2b-Cl} --one example should suffice.

Inasmuch as the rigorous proof has not been fully completed, it is necessary to rely upon indirect evidence. The indirect evidence supports the assumption that the reduction of the chloroketones $II_{2b-Cl} - IV_{2b-Cl}$ are within the scope of the mechanism. Examination of Table IV (p 36), Entries 7 and 8 shows the chlorohydrin III_{2e-Cl} ($R_3 = \text{Et}$) (1.4%) was isolated after 300 min reduction, and Table V (p 37), Entries 10 and 11 shows the chlorohydrin IV_{2e-Cl} ($R_3 = \text{iso-Pr}$) (1.2%) was isolated after 360 min reduction. As in the cases of halophenol derivatives, which were just discussed, the presence of chlorohydrin immediately raised the suspicion that the reduction proceeded through the chlorohydrin.

Further indirect evidence is presented in Table XII, p 110, which is a compilation of experimental attempts to produce the chlorohydrin IV_{2e-Cl} ($R_3 = \text{iso-Pr}$) via reduction with $LiAlH_4$. (See Experimental Section, p 274.)

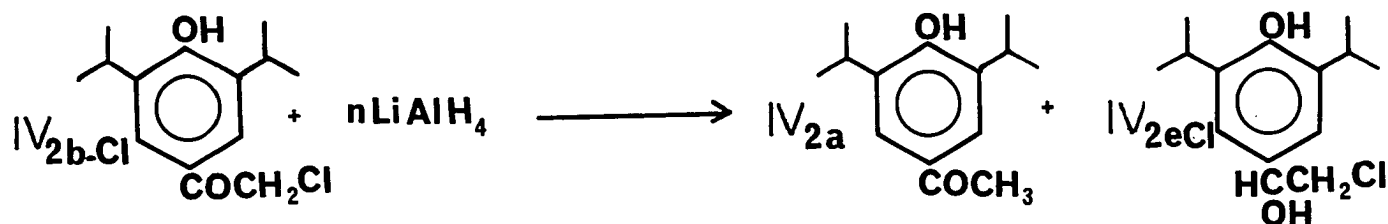
The results were not reproducible. It is apparent that it is possible to obtain essentially pure chlorohydrin in a cold solution, ca. 0° (Cf. Entries 2, 4 and 7) within 2 - 4 min. However, it is equally obvious from the other entries that LiAlH_4 reduction is not a reliable synthetic procedure for this compound. Entry 9 demonstrated that the primary alcohol IV_{2c} and alkane IV_{2d} can be produced at 23° along with (and presumably from) the chlorohydrin. Particularly amazing was the erratic appearance of ketone IV_{2a} , especially here, in the presence of a marked excess of LiAlH_4 . It was this finding in particular that prompted our introductory discourse to this Section on the problem of the physical state and temperature effects operating in these reductions. Again, it is not clear how the ketone is formed.

Further evidence exists that the reduction of the chloroketones is within the scope of the mechanism. Although the experimental work on the LiAlD_4 reduction of $\text{IV}_{2e}\text{-Cl}$ ($\text{R}_3 = \text{iso-Pr}$) is incomplete, that which has been accomplished shows the products of the reduction to have the deuterium in precisely the positions found in the similar reduction of bromoketone IV_{2b} . This work also shows ca. 20% (after 30 min) deuterated chlorohydrin $\text{IV}_{2e}\text{-Cl}$ which was reduced at a much slower rate than the bromohydrin IV_{2e} (Cf. Table X, p 79). The last piece of indirect evidence that the reduction of the chloroketones

II_{2b}-Cl - IV_{2b}-Cl is within the scope of the mechanism is that they produced the same products as the respective bromoketones, but in different proportions (Cf. Tables II, IV, V, p 3⁴ ff.).

The problem of why the product distributions differ for the reductions of the chloroketones and the bromoketones is a difficult one. The experimental results are collected and presented as product ratios in Table XI, p 92. The nature of the problem is rather simple: there are too many variables to consider at once. Presumably, the products of those reductions result from competition between Steps A-3 and A-6. However, a prediction about whether Step A-3 will predominate over Step A-6 in the reduction of the chloroketones vis-a-vis the bromoketones, thus leading to the observed higher yields of primary alcohols from the chloroketones, depends upon several factors. It would be necessary to be able to determine a priori that Al-H displacement on the C-Cl bond will be slower than Al-H displacement on the C-Br bond, which is probable, for Step A-6, while the cyclic transition state for Eq 28 (Step A-3) will be relatively faster for the Al-Cl interaction vis-a-vis the Al-Br interaction. The ratio of the changes in rates must favor Step A-3 over Step A-6 for the reduction of the chloroketones. However, this could not be predicted when we consider that four separate rates of reaction must be independently estimated

Table XII. Reduction of IV_{2b}-Cl with LiAlH₄



Entry	a, mol IV _{2b} -Cl	n, mol LiAlH ₄	Et ₂ O, ml	Time, min	Percent Product Distribution ^c			
1	.0100	.0226	250, ^a 100 ^b	4	20.6 IV _{2a} ,	4.4 IV _{2b} -Cl,	75 IV _{2e} -Cl	
2	.0200	.0450	380, 20	3	-- IV _{2a} ,	--	ca. 100 IV _{2e} -Cl	
3	.0200	.0450	380, 20	2	34.4 IV _{2a} ,	35.2 IV _{2b} -Cl,	30.2 IV _{2e} -Cl	
4	.0200	.0450	380, 20	3	-- IV _{2a} ,	--	ca. 100 IV _{2e} -Cl	
5	.0200	.0450	380, 20	3.5	10.5 IV _{2a} ,	--	89.5 IV _{2e} -Cl	
6	.0200	.0450	380, 20	3	30.8 IV _{2a} ,	3.8 IV _{2b} -Cl,	65.5 IV _{2e} -Cl	
7	.0100	.0225	190, 10	3	-- IV _{2a} ,	--	ca. 100 IV _{2e} -Cl	
8	.0200	.0200	380, 20	3	17.5 IV _{2a} ,	46.2 IV _{2b} -Cl,	36.4 IV _{2e} -Cl	
9 ^{d,e}	.0200	.0450	380, 20	3	-- IV _{2a} ,	--	95 IV _{2e} -Cl	
10 ^{f,g}	.0200	.0450	380, 20	3	4.4 IV _{2a} ,	--	73.7 IV _{2e} -Cl	

^a Ml of Et₂O in which IV_{2b}-Cl was dissolved, prior to LiAlH₄ addition. The soln was brought to ca. 0° unless otherwise specified. ^b Ml of Et₂O at room temp added to rinse in the LiAlH₄. ^c Analyses by nmr. ^d Soln at 23°. ^e 5% IV_{2c} + IV_{2d}. ^f Soln at 12 - 13°. Entries 1 - 8 were performed in an ice bath; 9 was performed in a room temp water bath; 10 was performed in a cold water bath, ca. 11°. ^g 22.7% IV_{2c} + IV_{2d}.

to obtain the desired rate ratios.

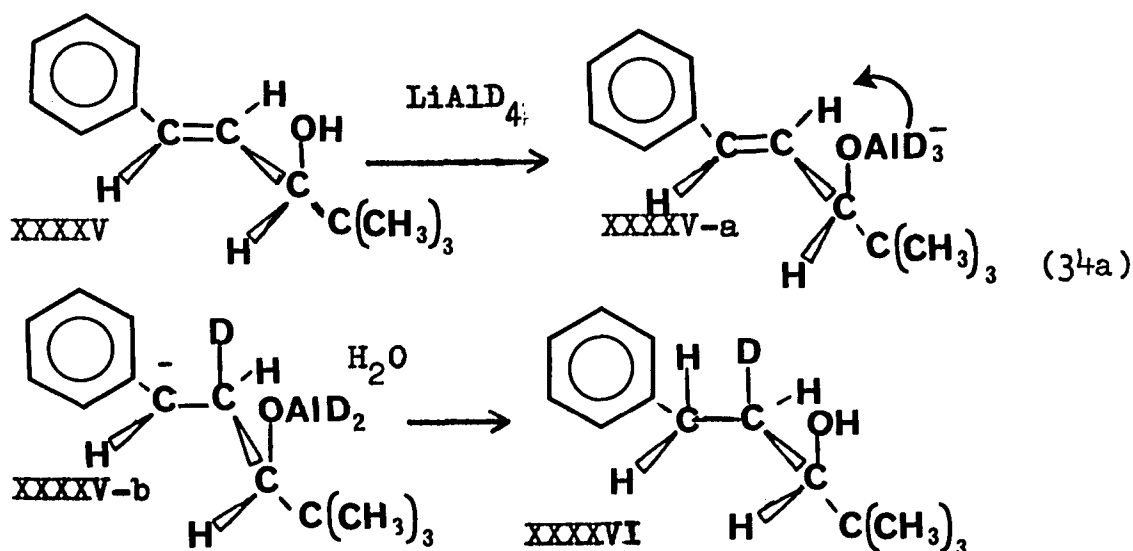
(C) The mechanism which is proposed treats nearly all the steps as intramolecular. For an overview of the situation it will be helpful to examine the flow sheet of the entire mechanism, p 64. This general flow sheet was proposed to account for the products of the reduction, the position of the deuterium label, and in a qualitative sense, to account for the rapidity of the reduction of the bromo-ketones of Tables I - VI (p 32 - 38). In this regard we drew heavily upon the work of Eliel and his coworkers, which was reviewed in Section D of the Background (p 22 - 25).

Eliel was confronted with similar problems of accounting for the products, the position of the deuterium label, and also qualitatively for the rate of the halo-hydrin reductions. To account for these results, he proposed what are the fundamental equations of this dissertation: Eq 10 (p 23) and Eq 11 (p 24). Both involve cyclic intramolecular transition states and they reappear in this dissertation as Steps A-3 (with oxyaryl ring migration vs. hydride migration in Eq 10), and A-6 (with displacement of halogen by hydride as in Eq 11).

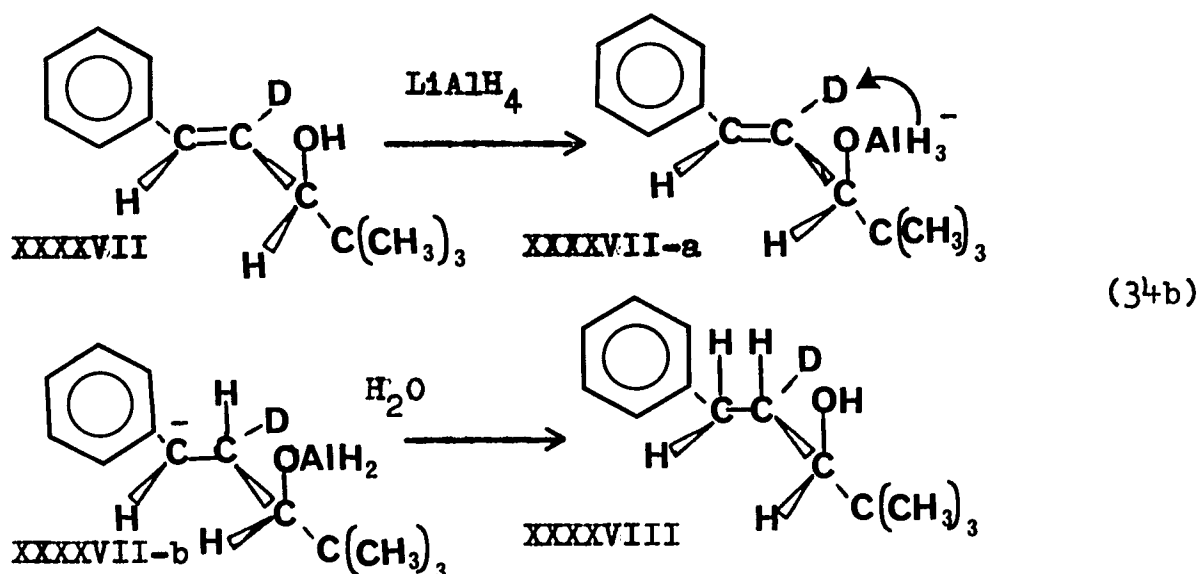
The formation of dimers is not covered here, nor mentioned in the mechanism, which deals only with the formation of monomeric products. The possible origin and

role of dimers will be discussed in Section H (p 146). The source of hydride that reduces the aldehyde in Step A-5 and the source of hydride that reduces alkyl halide to alkane in Step A-9 is no doubt intermolecular. The position of the deuterium label, and the structurally rearranged carbon-2 substituted primary alcohols, require Step A-3, which is necessarily intramolecular. However, we do not know if the spiro-cyclopropanol structure is an intermediate or a transition state. The hydrogenolysis of the C-O bond, Step A-7, could be either intra- or intermolecular.

In addition to Eliel's work which prepared the foundation for the concept of intramolecular alkoxy bound Al-H displacement of halogen as shown in Eq 11, or Step A-6, there is a recent study by W. T. Borden⁴³ which supports the stereochemical consequences of intramolecular Al-D or Al-H attack as shown in Eq 34 a, b:



(43) W.T. Borden, J. Amer. Chem. Soc., 92, 4898 (1970).

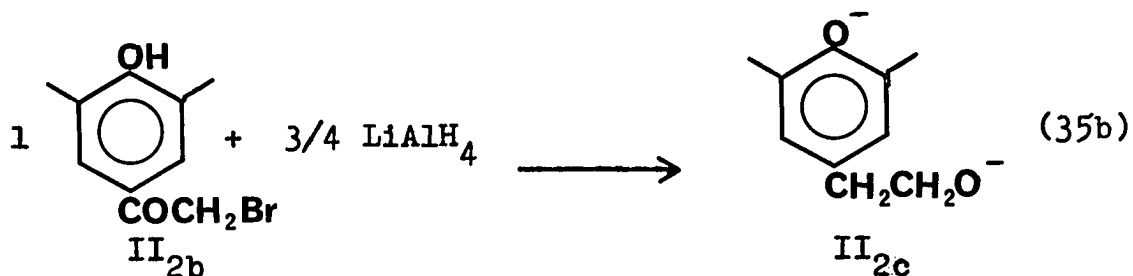
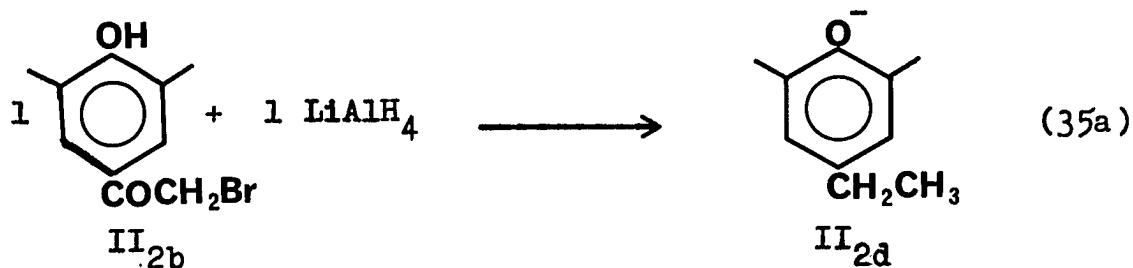


What is very significant here is that Borden's work involves compounds which are sufficiently far removed from ours and Eliel's that he added to the general process a clear cut case where intramolecular delivery of H or D by alkoxy bound Al-H or Al-D is required to explain the experimental results. This reinforces the tenability of our respective equations, Eliel's Eq 11 and our Step A-6.

It will be noted that Borden's work⁴³ excludes intermolecular attack by excess Al-H or Al-D. We cannot exclude intermolecular attack in Step A-6 as Borden's results enabled him to. We do have a series of results scattered throughout Tables I - V (p 32 - 37) where the amount of LiAlH_4 was 9.0 mol vs. the usual 2.25 mol (a fourfold increase in LiAlH_4) and the substrate was diluted fourfold with ether. The results were the same as the ordinary reductions, within experimental error. Although the LiAlH_4 was added here as a finely divided solid

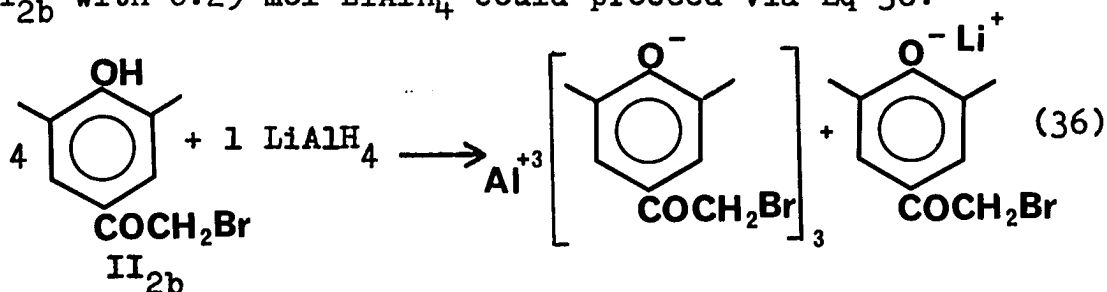
(a solution would have been better), it appeared to dissolve upon addition as rapidly as in the cases of less LiAlH_4 . It is possible that concentration and solubility factors combine in all the instances studied to produce no change in product ratios. However, it is at least as valid to suspect that the major processes--Steps A-3 and A-6, p 64, are intramolecular and hence not susceptible to reasonable changes in LiAlH_4 . (As long as there are at least two LiAlH_4 molecules available per substrate molecule--this point will emerge in (D), which follows presently.) If the process that leads to alkane, Step A-6, was sensitive to "unbound" LiAlH_4 , we would expect more alkane product to have been formed, and this is not so. Examination of Steps A-3 and A-6 makes it appear likely that A-6 should be more susceptible to increase with excess "unbound" LiAlH_4 --if it was not an intramolecular process. The nmr spectra of the product mixtures from reduction with the higher amount of LiAlH_4 also discloses a decrease in the quantity of side products--dimers, alkyl halides. However the decrease in alkyl halide, in particular, could be due to reduction by the excess LiAlH_4 .

(D) It is now appropriate to refer back to Table IX³³ of Section E (p 72) and attempt to fit the results of reduction with limited amounts of LiAlH_4 into the mechanism. It is useful to note the stoichiometry of the two principal products, shown in Eq 35a, b:

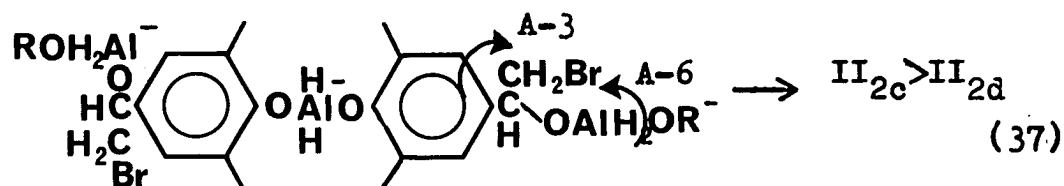


Eq 35a and 35b should be regarded as bookkeeping exercises, because they require total utilization of the available hydride, and maximum coordination of the Al. To emphasize the accounting aspect of these equations, the products are shown as the anions in solution, and no effort is made to allocate the Li or Al. It remains clear that any amount of LiAlH_4 below 1 mol is virtually certain to be a severe deficit of LiAlH_4 -- and the results in Table IX,³³ p 72, support that contention.

We shall discuss the results by compound, passing over the ketone products until the end of this discussion. Entries 1 - 8 deal with II_{2b} ($\text{R}_3 = \text{Me}$). The reaction of II_{2b} with 0.25 mol LiAlH_4 could proceed via Eq 36:



Eq 36 requires that LiAlH_4 behaves only as a base and also rests upon the assumption that three oxyaryl anions can coordinate around one Al. This assumption has already been considered to be not very likely for phenol derivatives with substituents other than hydrogen as the ortho flanking groups as was discussed in connection with Eq 22, p 84, of this Section. Similarly we have indicated in connection with Eq 23, p 87, that inspection of models suggests it is not realistic to expect more than two halohydrin oxygens (RO^-) to coordinate readily with a single Al. Obviously, fewer than two LiAlH_4 per mole of substrate require "doubling-up" of ArO^- and/or RO^- upon a single Al. An example of such doubling-up is shown in Eq 37:



The arrangement of anions about the Al is arbitrary in Eq 37. The implications of this sort of arrangement (or permutations, e.g., RO^- for ArO^- , etc.) led us to expect that the reductions of II_{2b} with a deficiency of LiAlH_4 , defined by the mechanism as less than two molecules of LiAlH_4 , would lead to more primary alcohol product II_{2c} relative to alkane product II_{2d} .

It was shown repeatedly (see Table II, p 34, in addition to Table IX,³³ p 72) that the alkane II_{2d} ($\text{R}_3 = \text{Me}$) is formed in roughly twice the amount of primary alcohol

II_{2c} when 2.25 mol of LiAlH₄ were employed. The reason the results of reduction with limited amounts of LiAlH₄ were anticipated was the expectation that two effects would operate and that they would operate in the same direction: (1) Addition of more ligands (other than hydride) to the Al which is coordinated to the ArO⁻ shown in Eq 37 could, because of increased steric hindrance, weaken the effectiveness of the ArOAl bond, leading to more oxyaryl ring migration-which is necessary to obtain primary alcohol. (That is shown in Eq 37 as the arrow marked A-3.) This factor is in keeping with the suggestion advanced for the relative importance of Eq 25 and 28 as the size of the ortho blocking groups are changed. (2) Addition of RO⁻ or ArO⁻ to the Al bound to the reduced carbonyl oxygen decreases the effectiveness of that Al as a hydride donor to displace Br--which is necessary to obtain alkane. (That is shown in Eq 37 as the arrow marked A-6.) This factor is in keeping with the work of H. C. Brown^{36a,b,c} which was previously mentioned in connection with Eq 23 of this Section. Eliel's work¹⁴ (see Section D of the Background) also suggests that doubling-up of alkoxy species on a given Al increases the Lewis acid character of that Al--which in our case would increase the relative importance of oxyaryl ring migration.

Compound IV_{2b} (R₃ = iso-Pr) appears only once as Entry 9 in Table IX,³³ p 72. A full study on the products

was not undertaken because this reduction was performed to determine if isopropyl groups were sufficiently "smaller" than tert.-butyl groups to determine where the initial attack is shifted from the phenol H to the carbonyl group. Compound IV_{2b} was not studied in a manner which would be useful for this discussion, so we shall pass over to the last case: V_{2b}.

Compound V_{2b} ($R_3 = \underline{t}\text{-Bu}$) was reduced also with a deficiency of LiAlH_4 and was expected to give considerable amounts of rearranged primary alcohol V_{2c} and bromohydrin V_{2e}, based on the work by B. Kupfer⁴² which showed the same sort of behavior with $\text{LiAl}(\text{O-}\underline{t}\text{-Bu})_3\text{H}$. (That work will be reviewed in Section I.) It is useful to recalculate the percent hydride consumed given in Table IX³³ on a different basis: assume all the ArOH is removed (1H). For the formation of products, assume that the following additional hydride is consumed: assume Eq 21b, p 71, is the source of ketone (2H), 1H is needed to produce the halohydrin, 2H for the primary alcohol, and extra 3H for the alkane product. This accounting leads to 1.68 mol H consumed vs. 2.00 mol H available (84%) for Entry 3; 1.69 mol H consumed vs. 2.00 mol H available (84.5%) for Entry 4; 1.74 mol H consumed vs. 1.00 mol H available (174%) for Entry 10; 2.05 mol H consumed vs. 2.00 mol H available (102%) for Entry 11; 2.12 mol H consumed vs. 2.00 mol H available (106%) for Entry 12.

These figures are revealing in several respects. Entries 3 and 4 are for II_{2b} ($\text{R}_3 = \text{Me}$) but represent 3 and 11 hr reflux periods, respectively. Obviously the 16% H that is not consumed in 3 hr remained inaccessible after 11 hr. On the other hand, Entries 10, 11 and 12 are for V_{2b} ($\text{R}_3 = \text{t-Bu}$) and show a more efficient hydride consumption. Entry 10 is excessively efficient--174% consumption of hydride--hence we conclude that the first assumption for the calculation is incorrect here. In the reduction of compound V_{2b} we cannot assume all the ArOH has reacted when we use a deficiency of hydride. (That in turn led to the ambiguity about ArOH migration for V_{2b} which has already been discussed in Section E, p 70.) The accounting for Entries 11 and 12 is close enough to 100% for these assumptions to be acceptable, were it not for the result of Entry 10--which causes doubt to remain that all the ArOH was removed for V_{2b} in those entries. These figures also provide a plausible clue why the reduction of II_{2b} differs so markedly from V_{2b} . If we invoke Al bonding to the ArO^- (as was done at the beginning of this Section), then II_{2b} can be bonded more tightly in an ArOAl specie than V_{2b} can, for steric reasons, as was mentioned earlier, p 96. It was suspected that Al bonding to the ArO^- of V_{2b} could prove ineffectual on steric grounds, see p 96, which would have the consequence that the AlH_3 would be free to react further. Possibly the Li cation serves directly as the counterion for V_{2b} , and possibly altering the migrating

tendency of the V ring, but we have no data for this effect. This would allow LiAlH_4 to reduce V_{2b} more extensively than it reduced II_{2b} (Cf. Entries 11, 12 vs. 3, 4 of Table IX³³).

Why the products of reduction of II_{2b} ($\text{R}_3 = \text{Me}$) and V_{2b} ($\text{R}_3 = \text{t-Bu}$) differ when a deficiency of LiAlH_4 was employed is a matter of conjecture. Whatever are the details of the bonding in solution, we cannot circumvent the known and demonstrated ease of reduction of the bromohydrins-- IV_{2e} ($\text{R}_3 = \text{iso-Pr}$) was discussed in Section F, and V_{2e} ($\text{R}_3 = \text{t-Bu}$) will be discussed in Section I. (The best characterized bromohydrin, IV_{2e} , was observed in the course of efforts to synthesize it to be very readily reduced by Al-H , and even NaBH_4 (in EtOH). We expect that the structurally similar V_{2e} if "free" should be rapidly reduced by an Al-H specie in solution.) This suggests that the bromohydrin V_{2e} is somehow shielded when a deficiency of LiAlH_4 is employed, or we would expect some further reduction. It is possible that the Al manages to coordinate 3RO^- about it to give a rather insoluble complex for V_{2e} , while the similar complex of II_{2e} is sufficiently soluble, or not formed fast enough, which allows its further reduction. It is possible, indeed likely, that the bromohydrin V_{2e} can be formed with the ArOH present, and the oxyaryl migration would not be expected to be as rapid as in the case where the H was lost to yield ArO^- . This would be one factor that could allow the isolation of V_{2e} . On

the other hand, the results in Table IX³³ for II_{2b} (R₃ = Me) make it evident that the ArOH is removed first, hence any bromohydrin II_{2e} would be likely to be present as the dianion and suffer rapid (relative to the ArOH form) rearrangement.

We shall cover the problem of ketone generation for the last time here. We do not know whether the reaction shown in Eq 21a or 21b, p 71, or both (or neither) are the source of this product (see p 71 of Section E). We do have two clearly defined sets of conditions where it will be among the products: (1) Ketone appears if the hydride source is in marked deficiency, regardless of hours of refluxing (Cf. Table IX,³³ p 72 of Section E with LiAlH₄, and Table XIV,⁴² p 158 of Section I with LiAl(O-t-Bu)₃H. (2) Ketone appears if the hydride source is a solid but the solution of substrate is cold (Cf. Table XII, p 110, with LiAlH₄), regardless of the excess of hydride. What should be done is to add acetic anhydride to the reaction mixtures for these two sets of conditions, as was previously suggested in connection with Eq 21a and 21b. Then we will have data, and at that time it should prove possible to offer something more than speculation whether the ketone does or does not arise via the halohydrin, whether this is or is not an intermolecular process, and even whether the different sets of conditions produce ketone by different routes.

(E) The presence of an alkyl or phenyl substituent on carbon-2 of the haloketones raises several questions:

- (a) What is the product distribution upon reduction?
(b) Can the product distribution be accounted for? (c)
What effects are possible when the reduction may proceed through diastereomers generated in the initial reduction to the halohydrin?

Alkyl or phenyl substitution on carbon-2 leads to increased production of rearranged primary alcohols for the alkylphenols II and V, and with technical reservations concerning the intrusion of side products (see p 124), also for I, i.e. the case of I_{3b} ($R_3 = H$). Our first work⁴ in this area was with the series of bromoketones V_{3b-6b} ($R_3 = t\text{-Bu}$). These reductions all led to the primary alcohols from rearrangement, V_{3c-6c} , as has already been noted in Eq 4 in the Introduction. It was also noted that this result was expected on the basis of our earliest work³ involving V_{2b} and $LiAlD_4$, which was described in Eq 3 of the Introduction. Inasmuch as we suspected from the reduction of V_{2b} ($R_3 = t\text{-Bu}$) that oxyaryl ring migration was the dominant characteristic imparted to the phenolic ring by the flanking tert.-butyl groups, it was hardly amazing that compounds V_{3b-6b} underwent apparently exclusive rearrangement upon reduction. However, that work was largely defensive: as we pointed out in the Introduction, we could not reconcile the mechanisms we were considering with the results of Ershov's work,² and therefore our work on those compounds could not be considered a reasonable

test of the mechanism at that time.

What was required was a series of compounds where the least substituted member ($\text{ArCOCBrR}_1\text{R}_2$; $\text{R}_1=\text{R}_2=\text{H}$) gave both alkane and primary alcohol products upon reduction. Consideration of the synthetic problems and nmr spectra that were expected, led us to choose the phenol II and to synthesize compounds II_{3b-5b} ($\text{R}_3 = \text{Me}$) in addition to II_{2b} , which had much earlier been achieved and reduced. The syntheses of these ketones were largely known and relatively easy as is noted in the Experimental Section, p 182. More important was the nmr spectrum that would result. It is obviously more desirable to have a singlet (from $\text{R}_3 = \text{Me}$) in the nmr spectrum, comparable to the singlet for compounds V_{2b-6b} (from $\text{R}_3 = \text{tert.}-\text{Butyl}$), rather than complicate the nmr spectrum needlessly with flanking ethyl or isopropyl groups. It was observed that reduction of compound V_{6b} yielded V_{6c} , apparently cleanly, but with an unattractive nmr spectrum (recall that the functionality in V_{6c} is $\text{ArCH}(\text{CH}_2\text{OH})\text{CH}_2\text{CH}_3$), therefore II_{6b} was not synthesized because it was unlikely to yield any more information than the reduction of V_{6b} had. The reduction of compounds II_{3b-5b} yielded ca. 95 - 97% of the primary alcohol from rearrangement vs. 34% from II_{2b} (see Tables II and III, p 34 ff.).

I_{2b} ($\text{R}_3 = \text{H}$) gave no primary alcohol I_{2c} , while I_{3b} gave ca. 84.5% primary alcohol I_{3c} , and ca. 3.5% alkane I_{3d} . Very clearly the primary alcohol is the dominant product

in the latter case. (The presence of 12.2% of unassigned material was the justification for the technical reservation about the series derived from phenol (I). We already knew that I_{2b} was prone to give products due to the intervention of the phenol oxygen in its reduction, and fully expected the phenol oxygen to continue to do so in the higher members of its series, e.g., I_{3b} . Examination of the nmr spectra of the unassigned fractions from the chromatographic separation of the products of the reduction of I_{3b} shows material that is virtually certain to have come from such oxygen intervention, i.e., dimers, perhaps trimers.)

Equally interesting was the behavior of VI_{3b} ($R_3 = Cl$) relative to VI_{2b} , which gave no primary alcohol upon reduction. (See Tables VII²⁰ and VIII,²¹ p 39 ff.) We noted somewhat earlier in this discussion, p102, that the presence of halogens on the aromatic ring was expected to lessen the tendency of oxyaryl ring migration for VI_{2b} and VII_{2b} , i.e., no primary alcohol might be formed. As noted in Table VIII,²¹ p 41, reduction of VI_{3b} ($R_3 = Cl$) yields ca. 50% primary alcohol VI_{3c} after extended refluxing and 50% benzylic alcohol VI_{3f} (the equivalent of alkane VI_{3d} if we view the benzylic alcohol as the precursor of the alkane). That reduction of VI_{3b} requires 900 - 1050 min of refluxing to reduce the last of the bromohydrin VI_{3e} , vs. ca. 4 - 10 min for the bromohydrins from the alkylphenols indicates that one must be very cautious in this

area because the relative insolubility of a species in ether may drastically reduce the rate of reaction.

The side products of the reduction of compounds II_{3b-5b} ($R_3 = \text{Me}$) appeared to be the alkyl bromide II_{3p} , the alkane II_{4d} , and the alkane II_{5d} . It should be noted that these side products were not isolated by chromatographic separation as was the case for the reductions of $\text{I}_{2b} - \text{IV}_{2b}$ ($R_3 = \text{H, Me, Et, iso-Pr}$). Rather, they were concentrated by repeated recrystallization of the primary alcohol. Thus, these materials were concentrated sufficiently to permit nmr spectral assignment of their structures. A similar effort to concentrate side products in the V_{3b-6b} ($R_3 = \text{t-Bu}$) reductions was not undertaken, in part because the nmr spectra of those crude products, V_{3c-6c} , appeared essentially free of anything else, and partly because we could infer small quantities of other materials from the nmr spectra of the II_{3b-5b} reduction mixtures. The alkyl bromide II_{3p} would probably arise in the usual manner, i.e., via Step A-8. However, it is not at all certain that any alkane II_{3d} , or the better established structures, II_{4d} , II_{5d} , arise solely (or at all) by the ordinary route, Steps A-6, A-7, p 64.

It is apparent from the enhanced yields of primary alcohols obtained in the reduction of the carbon-2 substituted bromoketones relative to $R_1 = R_2 = \text{H}$, that such substitution favors Step A-3, p 64. As was the case

in the chloroketone reductions, which were discussed on p 106, we are dealing with competing rates but cannot determine whether the increased yield of primary alcohol is due to a relative increase in the rate of Step A-3, and/or a decrease in the rate of Step A-6, to yield alkane. (For the moment, we shall assume that Step A-6, hydride displacement, remains the source of the alkane.) As far as Step A-6 is concerned, the available evidence is not unambiguous that alkyl substitution upon carbon-2 will enhance the rate of intramolecular displacement of halogen. Whether this ambiguity is due to steric effects in the transition state is not clear.

Winstein and Grunwald^{44a} investigated the rate of base catalyzed closure of chlorohydrins to epoxides (three-membered rings) as a function of the neighboring group (which would correspond to our oxyaryl ring on carbon-1) and the effect of substitution, especially by methyl groups, upon carbon-1 and carbon-2. They found that methyl and especially dimethyl substitution upon carbon-2 assists the epoxide closure by RO^- . Winstein and Grunwald also noted that a single methyl substituted upon the 3-carbon of 3-chloroacids increased the rate of base catalyzed

(44)(a) S. Winstein and E. Grunwald, J. Amer. Chem. Soc., 70, 828 (1948).

lactone formation by a factor of 5. Observe that this lactone closure involves a 4-membered transition state, and a final ring size of 4 members. It should be noted that this work involves 3 or 4-membered transition states, leading to 3 or 4-membered rings, with the reactions performed mostly in water, alcohols, dioxane or mixtures thereof.

Earlier work by G. Salomon^{44b} showed that methyl substitution upon carbon-1 or carbon-2 of 2-chloroethylamines increased the rate of ring closure: by a factor of 4 if the methyl was on carbon-2, but by a factor of 30 if the methyl was on carbon-1. However, phenyl substitution on carbon-2 increased the rate of ring closure by a factor of 800, whereas substitution on carbon-1 decreased the rate of cyclization to ca. 60% of the original rate for 2-chloroethylamine. Salomon also noted that the rate of imine cyclization drops in going from 3 to 4 members, rises sharply at the 5-membered ring, then declines as the imine ring size increases. Generally the rate of cyclization drops as the solvent system is made more nonpolar, especially as the water content of the solvent declines.

Particularly interesting is the work of H. Freundlich and G. Salomon,^{44c} especially on the 5-membered

(44)(b) G. Salomon, Helv. Chem. Acta., 16, 1361, (1933); (c) H. Freundlich and G. Salomon, Z. Phys. Chem., 166, 161 (1933).

cyclic imine. It was just noted that this is the fastest cyclization of the straight chain chloroalkylamines, however, substitution of a methyl on the 4-carbon (which bears the Cl) causes the rate of cyclization to drop by a factor of more than 22. This is an example where methyl substitution decreases the rate of displacement.

Considering systems more similar to ours, we have the work of Eliel and Traxler¹⁵ on the reduction of both the 3- and 2-chloroacids. The chloroacids are very rapidly reduced to the chlorohydrins, and the alkoxy-bound Al-H then determines the mode of halogen displacement. The 3-chloroacids are a fairly simple case to examine: no methyl substitution on the 3-carbon gave a 62% conversion to the alcohol via Cl displacement, one methyl substituted on the 3-carbon reduced the conversion to 21% alcohol, and two methyls substituted on the 3-carbon reduced the conversion to 6% alcohol. Some of the chlorine displacement may have occurred by intermolecular processes, however, it remains clear that this system--involving a formal six-membered transition state--does not behave as the three or four-membered transition states of Winstein and Grunwald^{44a} or Salomon,^{44b} because methyl substitution on carbon-3 decreases the rate of displacement.

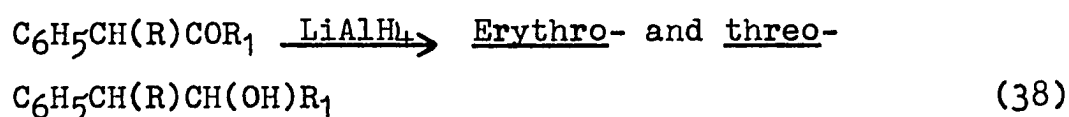
The compounds of immediate concern are the 2-chloroacids: the extent of conversion of the tertiary 2-chloroacid to alcohol was about 36-fold that of the

secondary 2-chloroacid for the same period of reflux. The primary 2-chloroacid was not as clear-cut a case due to experimental difficulties, but its conversion to alcohol appears to be in the range of 3 to 10-fold that of the secondary 2-chloroacid. Here we have a formal 5-membered transition state but a change in mechanism is occurring here: the primary and secondary 2-chloroacids (and chlorohydrins) undergo Al-H displacement of halogen via Eq 11, p 24, whereas the tertiary 2-chloroacids undergo the hydride shift of Eq 10, p 23. It is this change of mechanism that makes a direct comparison of the reduction of the 2-chloroacids to the 3-chloroacids insecure: the 2-chloroacids could be displaying the same decrease in ease of displacement of halogen as methyl substitution on the 2-carbon increases (except for the intervention of the hydride shift of Eq 10) as the 3-chloroacids do. However we cannot be certain of a parallel between the reactions of the 2- and 3-chloroacids because of the change in mechanism.

At the same time, alkyl or phenyl substitution upon carbon-2 should make the intramolecular concerted removal of halogen via Step A-3 somewhat easier because the carbon-2 can more readily accept some positive charge if carbon-2 is a secondary, tertiary, or benzylic carbon as opposed to being a primary carbon as in the reduction of compounds I_{2b} - VII_{2b}. This expectation is in keeping with the results of Winstein and Grunwald.^{44a}

The reason for the uncertainty about the origin of the alkane product lies in the stereochemistry of the reduction and the possibility of steric effects altering the previously proposed steps to the alkane: A-6, A-7, p 64 . Consideration of the general structure of the haloketones requires that they exist as a mixture of enantiomers for all cases where $R_1 \neq R_2$. For compounds I_{3b} ; $II_{3b,5b}$; $V_{3b,5b,6b}$; and VI_{3b} we have a mixture of enantiomers. The problem arises when we consider the next aspect which the existence of the enantiomeric bromoketones poses: reduction to the bromohydrin must give diastereomers, but in what ratios? At this important point the literature fails to enlighten us.

Quite a number of authors^{45a-d} have dealt with various aspects of this sort of reduction, or commented thereupon. Cram and Abd Elhafez^{45a} performed the basic work, as shown in Eq 38:



(45)(a) D.J. Cram and F.A. Abd Elhafez, J. Amer. Chem. Soc., 74, 4828 (1952); (b) H. Felkin, Compt. Rend., 231, 1316 (1950); (c) J.W. Cornforth, R.H. Cornforth, and K.K. Matthew, J. Chem. Soc., 112 (1959); (d) H.O. House, Modern Synthetic Reactions, W.A. Benjamin (1965).

For $R = \text{CH}_3$, $R_1 = \text{CH}_3$, the erythro-threo ratio was 1:2.5; for $R = \text{C}_2\text{H}_5$, $R_1 = \text{CH}_3$, the ratio was 1:3; for $R = \text{CH}_3$, $R_1 = \text{C}_6\text{H}_5$, the ratio was greater than 4:1. That work provided the basis for Cram's rules of asymmetric induction. The suggestion advanced to explain the results is that the reactive conformer of the ketone is the one with the carbonyl group least shielded from attack by the groups on the adjacent carbon. The carbonyl group is believed to be approximately anti to the largest group, and the preferred attack by LiAlH_4 occurs on the face of the carbonyl group shielded by the smaller of the two remaining groups. However, we have haloketones to consider, and the effect of the carbon-halogen dipole upon the most reactive conformer of the haloketone is open to question.

Lutz⁵ reported the reduction of desyl chloride (XIV) to give 100% erythro-chlorohydrin (XV) (see Eq 7, p 15). Felkin^{45b} reported desyl chloride (XIV) to give 50% erythro- and 50% threo-chlorohydrin (XV), and the Cornforths' in surveying their results^{45c} with Grignard additions to chloroketones concluded that the product of desyl chloride (XIV) reduction should be 100% threo-chlorohydrin (XV). This conclusion was arrived at by invoking the often cited analogy between the behavior of Grignard additions and LiAlH_4 reductions. House^{45d} supports the Cornforths' position on the matter of the dipole interaction requiring the Cl and CO to be anti. Then the

reactive conformer has CO and Cl anti, with the preferential attack determined by the size of the two other (alkyl or aryl) groups. However, it is not established that Br forces the reactive conformer to have the CO and Br anti by similar dipole-dipole repulsions. (Resonance charge transfer from the aryloxy anion to the carbonyl oxygen could force the Br and CO to be anti in our bromoketones.) This situation is clearly unsatisfactory for predictive purposes in our system. The only data we have are two small fragments: Gullo's²⁶ V_{3e} ($R_3 = t\text{-Bu}$) appears to be 50:50 of both diastereomers (by nmr), as does Chan's³¹ VI_{3e} . Too much must not be made of these observations because the alkyl groups involved were H and CH_3 in both cases, which is hardly comparable to H and C_6H_5 , e.g., for II_{5a} and V_{5e} , and therefore may not reflect the diastereomeric ratio in the latter cases. Furthermore, both pieces of work require resolution and independent reduction of those diastereomers.

Let us consider the problems which the stereochemistry of reduction generates. Consider the conformers shown in Chart III, p 135, for erythro- II_{5e} ($R_3 = \text{Me}$) and threo- II_{5e} . (Only one of each pair of diastereomers is shown.) We shall follow Eliel⁴⁶ and attempt to estimate

(46) E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, Inc. (1962) Cf. Ch. 6.

the preferred reactions based on the most favorable conformers as the first approximation. It appears that conformer X of the erythro-II_{5e} can account for the ca. 5% of the alkane II_{5d} which is formed, while conformer Y' of the threo-II_{5e} can account for the 95% primary alcohol II_{5c} which is formed. All that is required is that the initial reduction of bromoketones where $R_1 \neq R_2 \neq H$ yield ca. 95% threo isomer. This appears not unreasonable if the Cornforths^{45c} are correct, insofar as II_{5e} ($R_1 = H$, $R_2 = C_6H_5$) is concerned, but appears to be excessively skewed in favor of the threo isomer for II_{3e} ($R_1 = H$, $R_2 = CH_3$). (See Cram's^{45a} results, p 130.)

There are objections to explaining our results solely on conformational reactivity grounds. One objection is that this explanation ignores the effect of the Al-Br interaction. There exists a study by Curtin and Meislich⁴⁷ somewhat similar to ours, involving the reaction of silver salts and the Grignard reagent upon erythro- and threo-1-p-chlorophenyl-1,2-diphenyl-2-bromoethanol (II). The reactions are shown in Chart IV, p137 . (Only one diastereomer of each pair is shown in Chart IV.) The reaction with the silver salts proceeds in a manner which keeps the

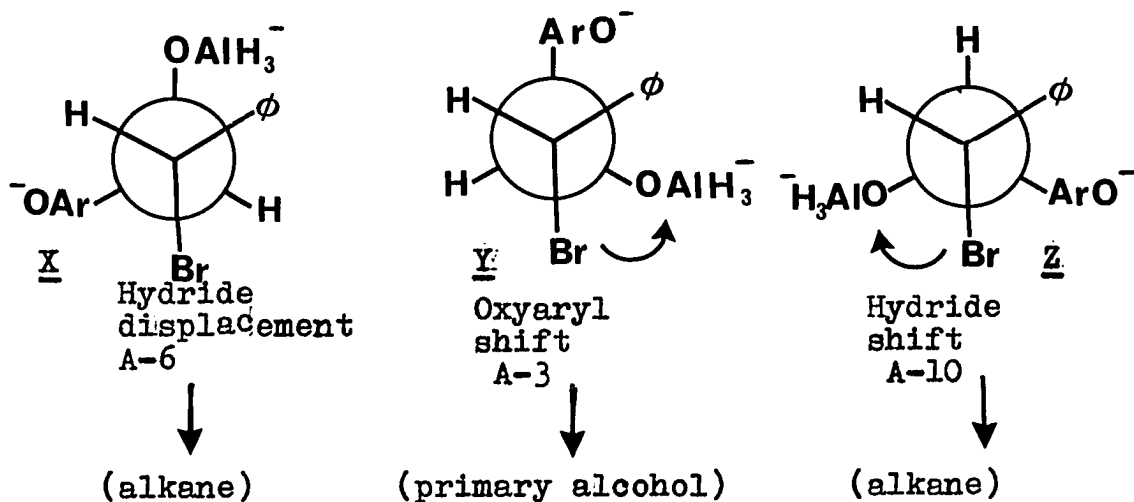
(47) D.Y. Curtin and E.K. Meislich, J. Amer. Chem. Soc., 74, 5905 (1952).

bulky nonmigrating groups as far apart as possible in the transition state--Curtin's "cis effect." However, the products are exactly reversed when the bromoethanol II is treated with the Grignard reagent. (This is shown for the erythro isomer in Chart IV.) The conformer through which the reaction apparently proceeds is A, the seemingly higher energy one, rather than B. Curtin suggested that this was due to the necessity of obtaining solvation of the Mg with the ether, while allowing a strong Mg-Br interaction. Examination of models suggested this solvation was more likely for conformer A than B. As a consequence, conformer A is the lower energy one, and reaction proceeds through it, rather than through B.

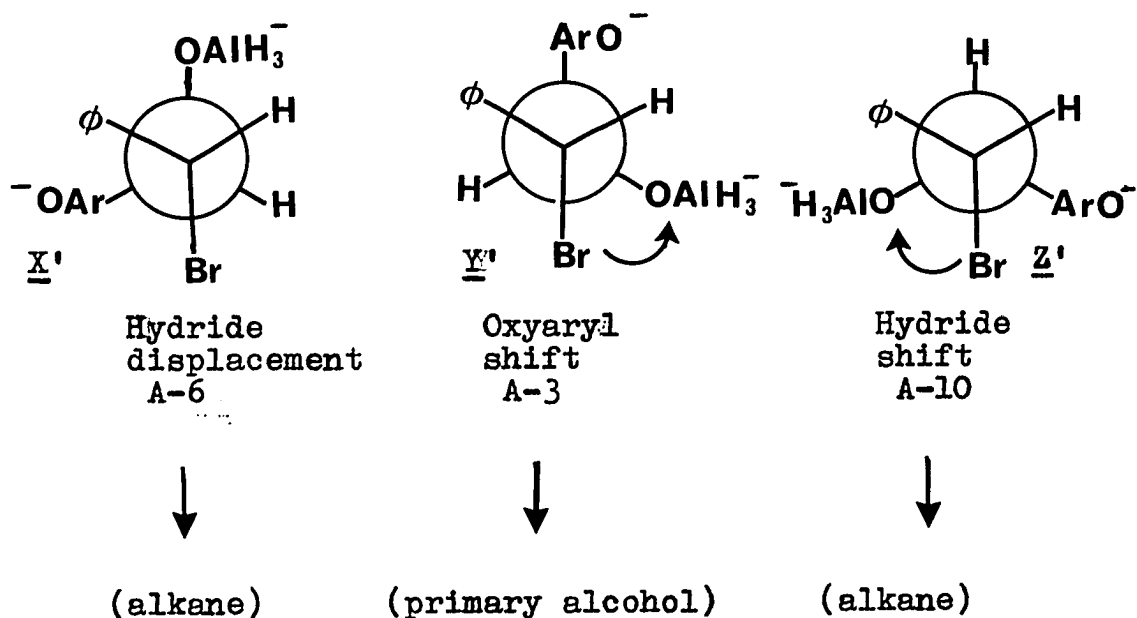
Inspection of Chart III, p 135, suggests that conformers Y, Z, Y' and Z' are suitable for the postulated Al-Br interaction. This implies that Z and Z' might be important, and allow a hydride shift via Step A-10, p 140, to occur. We do not know to what extent the ArO^- ring participates in the transition state: it might participate so extensively that Y and Y' are actually always the lowest energy conformers leading to the transition state where $R_1 \neq R_2 \neq \text{H}$, for the alkylphenol derivatives. Another objection is that compounds II_{4b} ($R_3 = \text{Me}$) and V_{4b} ($R_3 = \text{t-Bu}$) both have $R_1 = R_2 = \text{Me}$, and both yield the primary alcohol upon reduction. Replacement of the H, C_6H_5 in Chart III, p 135, with two CH_3 's reduces the system to

Chart III. The Possible Reactions of the Conformers of II_{5e}.

Erythro-II_{5e}



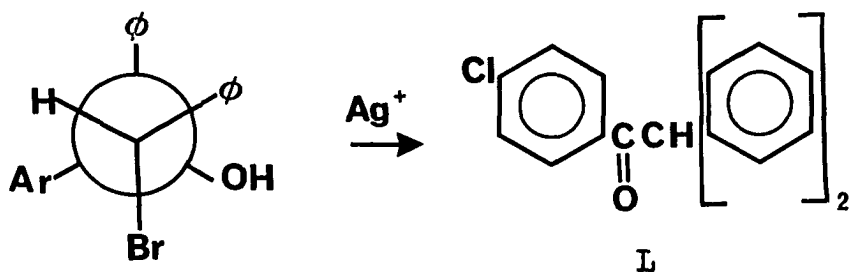
Threo-II_{5e}



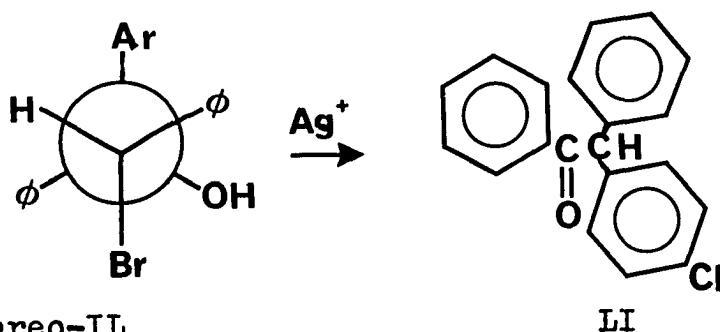
enantiomers with the pairs of conformers X and X', Y and Y', Z and Z' of the same energy for each pair and raises the question why conformer Y should dominate the product distribution. A possible explanation is that the transition state is a compromise between the Al-Br interaction and ether solvation, and ArO⁻ participation, which would be favorable for conformers Y and Y'. The question of the reality of the hydride shift, Step A-10, p 140, can be settled speedily by reduction with LiAlD₄ of the halohydrins II_{4e} (R₃ = Me) and the erythro- and threo- diastereomers of II_{5e} prepared by NaBH₄ reduction (which must be separated). For example, if the alkane from II_{4e} has the structure ArCHDCD(CH₃)₂, then the hydride shift, Step A-10, is a reality. In this eventuality it would be necessary to perform a similar reduction on one of the simpler halohydrins, e.g., II_{2e} (R₃ = Me), that yields a considerable amount of alkane product to check whether a hydride shift occurs there also. (It will be recalled that the alkane product was assumed to arise via the displacement step, A-6, p 64, and not via a hydride shift. This assumption is based on Eliel's work, see Eq 11, p 24 .)

There is another problem possible when we are no longer dealing with the simplest (i.e., non-substituted)

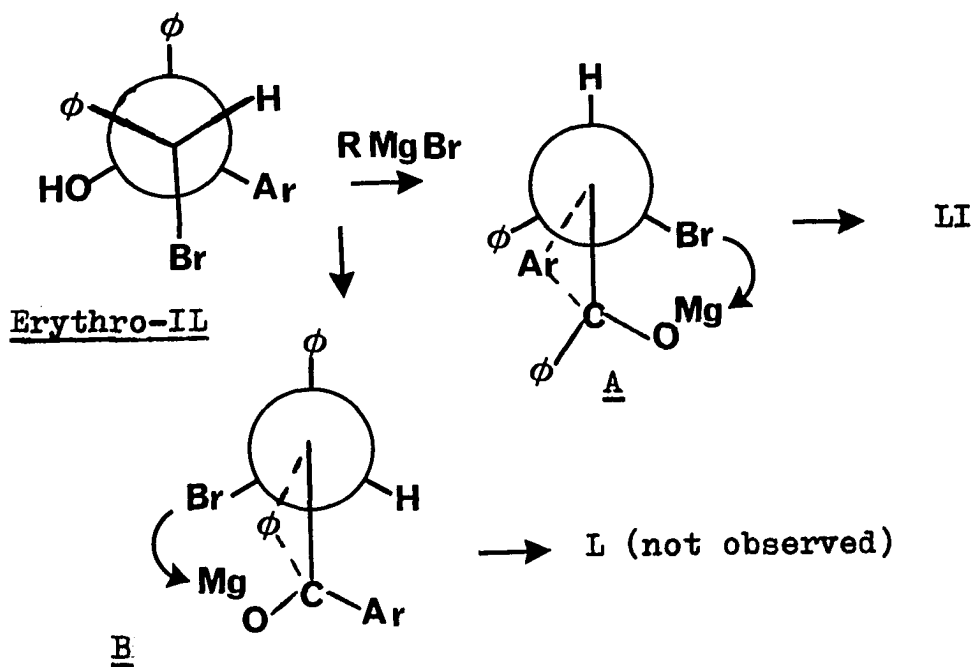
Chart IV. The Reactions of Erythro- and Threo-1-p-Chloro-phenyl-2-diphenyl-2-bromoethanol (IL) with Silver Salts and the Grignard Reagent.



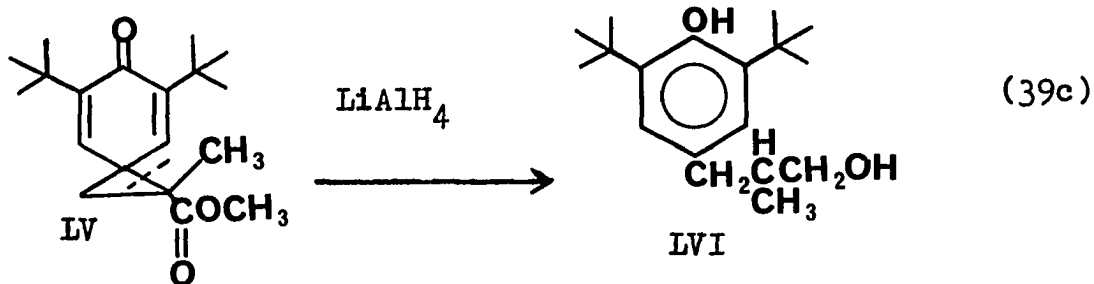
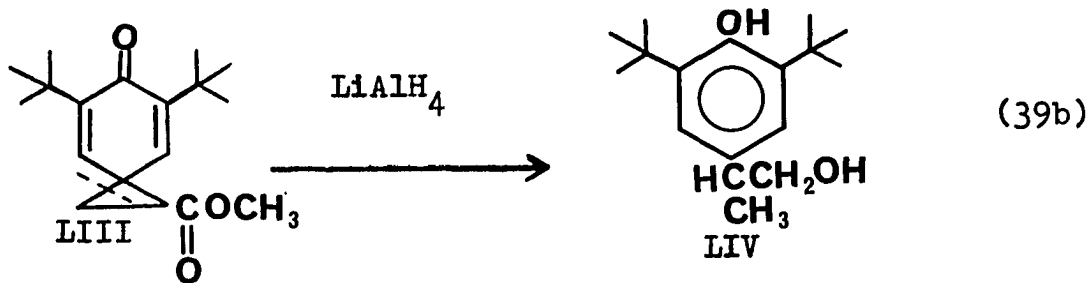
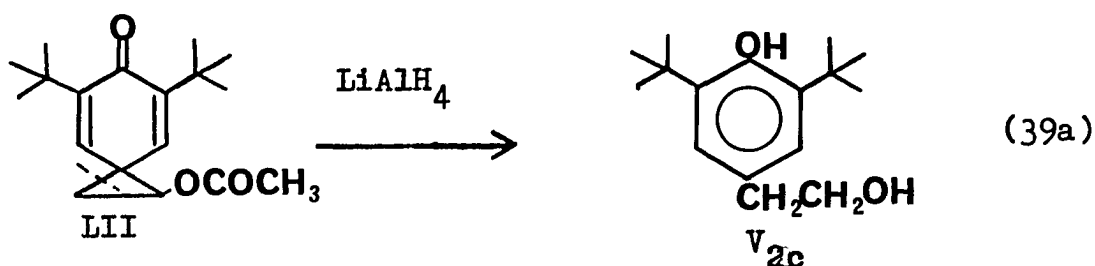
Erythro-IL



Threo-IL



spiro-cyclopropanols. Ershov and his coworkers⁴⁸ reported that a series of substituted spiranes shown below related to V_{2e} ($R_3 = t\text{-Bu}$) by adding groups to the cyclopropyl ring suffer LiAlH_4 reductive opening of the cyclopropyl ring but not in an unambiguous manner, as is shown in Eq 39 a - c:



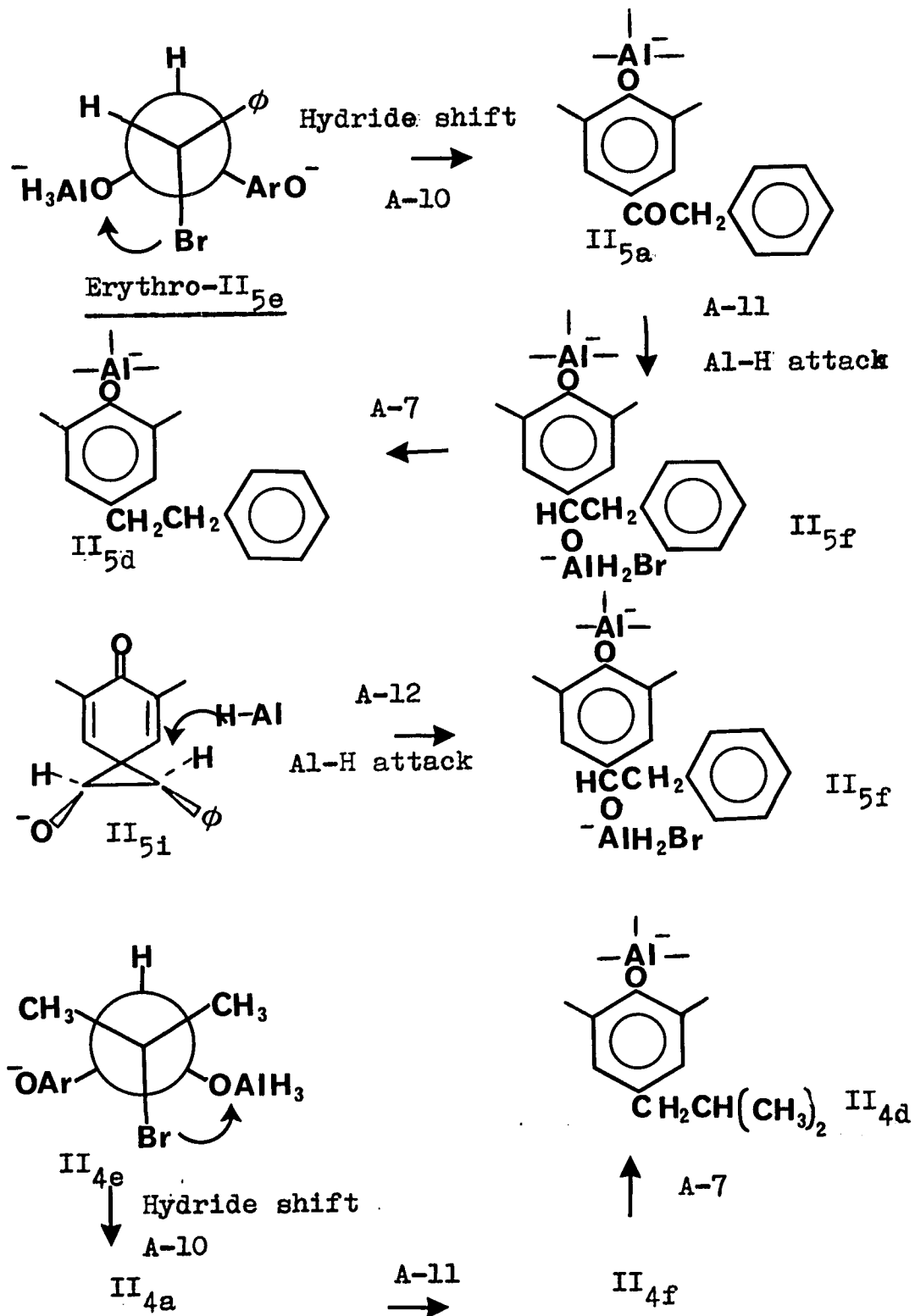
The reaction shown in Eq 39a can be construed as inferential support for our mechanism. It is entirely possible that the acetyl group is cleaved directly by the LiAlH_4 , thereby generating V_{2i} , which opens in the suggested manner to the aldehyde V_{2t} and is reduced to the observed product V_{2c} .

(48) G.A. Nikiforov, B.D. Sviridov, and V.V. Ershov, Bul. Acad. Sci. USSR, 542 (1968).

What is disturbing is the change in position of the cyclopropyl ring opening on substitution of a single methyl group. Although the nature of the substitution on the cyclopropyl ring is quite different between LIII and LV one hand and LII (which is more closely related to our structures), the change in position of the ring cleavage between Eq 39b and 39c remains troublesome. At this time we should consider if it is possible that the cyclopropyloxy ring can open in either direction if there is considerable substitution on carbon-2, e.g., two methyl groups or one phenyl ring. This raises the possibility that a very small amount of our spiro-cyclopropanol might be opening at the alkyl or phenyl substituted side--the "forbidden" side c of Eq 31.

It is solely the possibility that any or all of these effects might become important with the bulkiest cases: II_{4b,5b} ($R_3 = \text{Me}$), V_{4b,5b} ($R_3 = \text{t-Bu}$), and to a lesser extent, II_{3b} and VI_{3b} ($R_3 = \text{Cl}$) that causes us to hesitate to assume that only intramolecular displacement, via Step A-6, leads to the alkane product in these cases. To accommodate these two latter possibilities we have added Mechanism A - Extended, p 140, with the hydride shift steps, A-10, A-11, and attack upon the spirocyclopropanol, A-12 by unbound Al-H.

Mechanism A - Extended



(II) Summary of the Mechanism.

We believe that all of the haloketones mentioned in this thesis react via a common mechanism. All of the reductions are considered to pass through a key intermediate --the halohydrin formed by the reduction of the carbonyl group and the removal of the phenol H. From this junction, the product distribution is held to arise from the interplay of forces at two positions of the halohydrin dianion: the effectiveness of the bonding of a negative charge relieving species which is taken as Al, to the phenol oxygen, and the type of substitution upon the carbon bearing the halogen.

(1) The effectiveness of the bonding is meant to convey the ability of the Al to bound to the phenol oxygen. This ability is maximal, for steric reasons, when the Al species is AlH_3 and declines as more substituted Al species are encountered, e.g., H_2AlOR , HAL(OR)_2 , H_2AlOAr .

(2) The effectiveness of the bonding also conveys the ability of the phenol oxygen to donate charge to a proximate Al. This capability is dependent upon the immediate environment of the phenol oxygen, i.e., the ortho flanking groups. As they increase in size from $\text{R}_3 = \text{H}$ to $\text{R}_3 = \text{tert.}-\text{Butyl}$, the effectiveness of the bonding of the phenol oxygen to an Al species decreases. Halogens as flanking groups decrease the effectiveness of this phenol oxygen-Al bonding by their electron-withdrawing inductive effect. In a sense,

we may regard the negative charge on the aryloxygen as being dispersed or intensified by the variation of these factors. The oxygen of the reduced carbonyl group is believed to hold another AlH_3 .

The forces acting at the phenol oxygen largely determine the outcome of the reduction where $\text{R}_1 = \text{R}_2 = \text{H}$. The products are observed to arise from displacement of the halogen from carbon-2. The halohydrin intermediate partitions between two general reactions. Where the substitution on carbon-2 is $\text{R}_1 = \text{R}_2 = \text{H}$, clear-cut competition between the two routes is observed. There the basic reaction may be considered to be the rapid displacement of Br by the alkoxy bound Al-H. This process leads to benzylic alcohols, the hydrogenolysis of which to alkanes is rapid when the phenolic ring is not substituted with halogens. As the effectiveness of the aryloxy-Al bond decreases, negative charge intensity is imparted to carbon-1', and the alkoxy bound Al can then exhibit a different property--it can assist in the removal of the Br. This route generates a substituted spiro-cyclopropanol which rapidly opens to the aldehyde, giving net migration of the oxyaryl ring from carbon-1 to carbon-2. The aldehyde is readily reduced to the primary alcohol.

We observe the clear ascendancy of the oxyaryl ring migration route as the flanking groups increase in size from $\text{R}_3 = \text{H}$ to tert.-Butyl. In a sense, the aryloxy

negative charge may be regarded as progressively intensified. Substitution upon carbon-2 apparently alters the balance between formation of the two intermediates that arise from the halohydrin, leading to more primary alcohol than is the case where $R_1 = R_2 = H$. Marked decrease in the effectiveness of the aryloxy-Al bonding leads to exclusion of alkane product in the case where $R_3 = \text{tert.}-\text{Butyl}$ (V_{2b}). Apparently effective aryloxy-Al bonding leads to the exclusion of primary alcohol in the case where $R_3 = H$ (I_{2b}), which exclusion also extends to the halophenol derivatives VI_{2b} ($R_3 = Cl$), VII_{2b} ($R_3 = Br$) on somewhat different grounds--the inductive effect of the ortho halogens, as mentioned above. The balance of forces is altered dramatically in the alkylphenol derivatives where carbon-2 has an alkyl or phenyl substituent: then the alkane product is virtually excluded in favor of the primary alcohol. Equally interesting is the appearance of primary alcohol product by substitution upon carbon-2 in the reduction of VI_{3b} ($R_3 = Cl$), while VI_{2b} failed to yield primary alcohol.

The principal products are the respective alkanes and rearranged primary alcohols. Then we may regard the formation of alkyl halides as diversion from the major pathways. The dimeric products are then regarded as intervention into the halohydrin or benzylic alcohol stages of reduction by oxyanion species (ArO^- and/or RO^-). The appearance of benzylic alcohols may be regarded as special

cases of not yet completed reduction to the appropriate alkane.

There remain various uncertainties in the mechanism. Is Al bonding the controlling feature of this process? What, if any, is the role of the Li cation? Are the crucial Steps A-3 vs. A-6 intramolecular processes, however reasonable they might appear? We have no data to clarify the problem of intra- vs. intermolecular hydrogenolysis as the source of alkane from the benzylic alcohol, and alkyl halide from the halohydrin. The reduction of the chloro-ketones should be tied into the general mechanism.

The halohydrins of the halophenols, e.g., VI_{2b} (R₃ = Cl) must be prepared and shown to be the sole source of products. It is also highly desirable to repeat the critical halohydrin experiment done with IV_{2e} (R₃ = iso-Pr) on another case, specifically II_{2e} (R₃ = Me). Then both must be shown to be reduced in the same time that their respective precursors, IV_{2b} and II_{2b} are, in order to examine the assumption that the rate determining step is the consumption of the bromohydrin. Similar experiments with a chlorohydrin, e.g., IV_{2e-Cl}, would be equally desirable, and probably much easier to perform, given the known relative stability of the chlorohydrins vs. the bromohydrins. Thus far the formation of halohydrins for the entire series of higher substituted derivatives, e.g., II_{3b-5b} and V_{3b-6b} is an assumption which needs proof.

The two ambiguities must be resolved: (1) Can the V_{2b-6b} series undergo rearrangement and reduction with limited amounts of $LiAlH_4$ without the phenol H being removed? (2) What is the source of the ketone in those cases where it is a product? An exploration into the relative amounts of the diastereomers produced in the reduction of $II_{3b,5b}$ and possibly also $V_{3b,5b}$ is in order. This, in turn, is a prelude to finding out whether there are alternative sources of the alkane products, which would require expansion of the mechanism, as suggested in Mechanism A-Extended, p140.

(H) The Possible Origin and Role of Dimers.

We were concerned that the reduction pathways might involve extensive dimer formation, followed by cleavage of the dimers to yield the observed products. For the purpose of this discussion, the dimers are divided into two categories: (1) Those dimers which arise from attack by the phenolic oxygen upon carbon-1 or carbon-2; (2) Those dimers which arise from alkoxide attack upon carbon-1 or carbon-2. The dimers of category 1 were restricted to the products arising from reductions of derivatives of phenol (I) itself. Of these, the only one which has been identified is I_{2n} (Experimental Section, p 227). Apparently ortho substitution of methyl, or larger alkyl groups, for hydrogen R_3 terminates the tendency to form dimers of category 1. This point has already been noted in Section G, p 97. However, dimers of category 2 are found, as minor products, throughout the reduction of compounds II_{2b} - IV_{2b} (R_3 = Me, Et, iso-Pr) and II_{2b-Cl} - IV_{2b-Cl} reductions. (That they were not observed in the case of V_{2b} (R_3 = *t*-Bu) is due to the fact that no attempt was made to isolate them.)

The occurrence, structure and stability of the dimers of category 2, e.g., II_{2h} and II_{2g} has already been commented upon in Section B (8, 9, 11) p 50ff. The information already covered noted that the symmetrical dimer, $ArCH_2CH_2OCH_2CH_2Ar$ was found by mass spectral analysis as

only a trace for II_{2g} . The unsymmetrical dimer has the structure $\text{ArCH}_2\text{CH}_2\text{OCH}(\text{CH}_3)\text{Ar}$, and its deuterated analog has the structure $\text{ArCH}_2\text{CD}_2\text{OCD}(\text{CH}_2\text{D})\text{Ar}$ (by nmr analysis, with mass spectral confirmation of the molecular weight for some cases). Further, it has been indicated (Section B, p58) that the only dimers found in significant quantities, II_{2h} - IV_{2h} , cannot be significant precursors of the monomeric products because they were not found in greater percentages for the very short time (10 min) reductions as compared to the long time (360 min) reductions. The last observation was that the dimers II_{2h} - IV_{2h} are isolated as chromatographic fractions along with their (presumed) precursors II_{2q} - IV_{2q} ($\text{R}_3 = \text{Me}, \text{Et}, \text{iso-Pr}$) and $\text{II}_{2q-\text{Cl}}$ - $\text{IV}_{2q-\text{Cl}}$ (from the chloroketone reductions). We are cautious in calling II_{2q} the precursor of II_{2h} because it may be viewed as a precursor of II_{2h} if it suffers displacement of the Br--exactly as the alkyl bromide can be viewed as a precursor to the alkane. It is quite possible that the two are formed separately and the "precursor" is slowly converted to II_{2h} --which would be entirely analagous to the alkyl bromide-alkane relationship. This qualification holds for all of this group of compounds.

A schematic outline of the probable principal routes to dimeric products is shown in Chart V, p148 . Compound II_{2b} ($\text{R}_3 = \text{Me}$) is used as a model, and the reduction is with LiAlD_4 to emphasize what the attacking

Chart V: Possible Origin of Dimeric Products

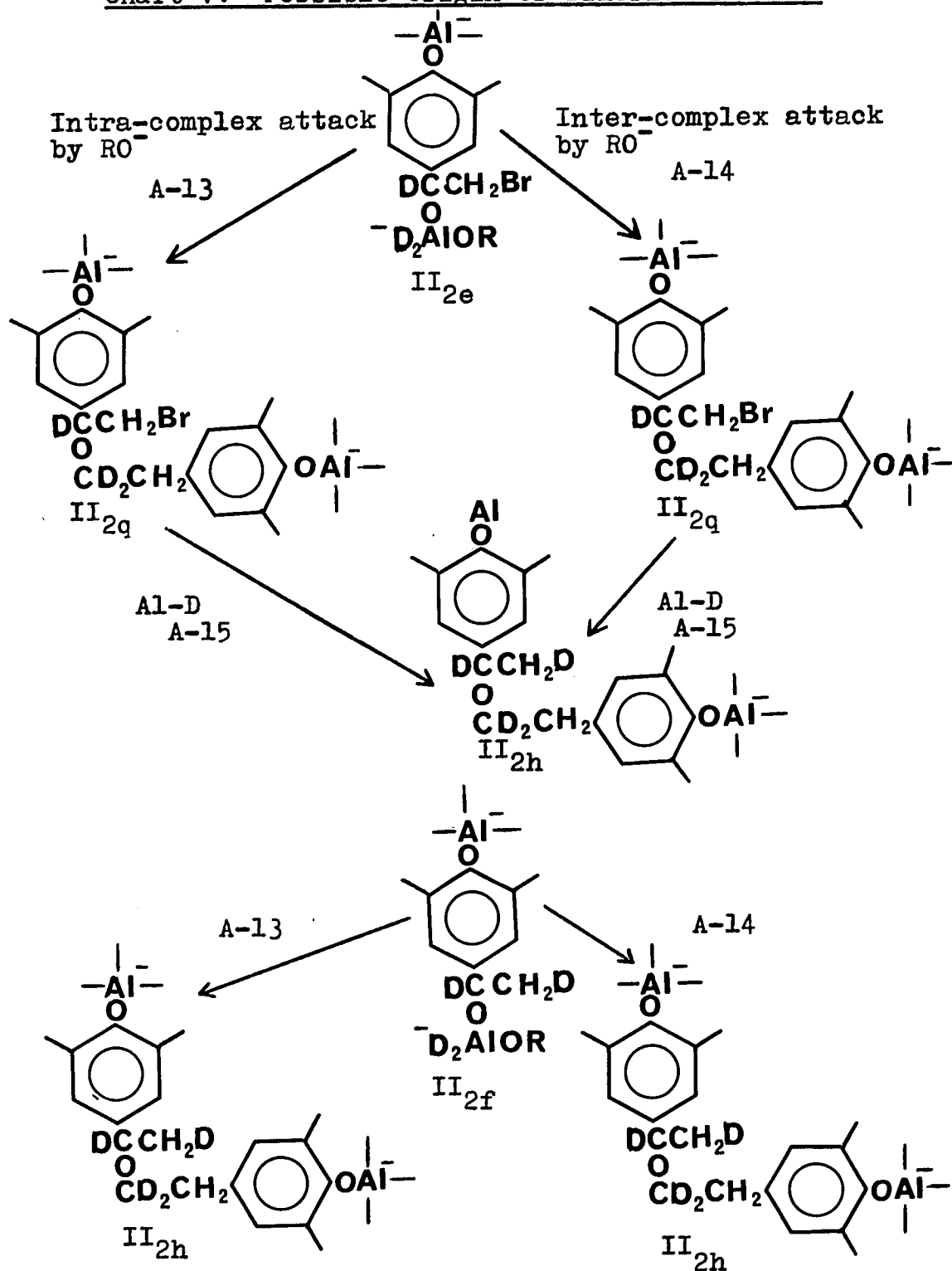


Chart V: Possible Origin of Dimeric Products, Continued

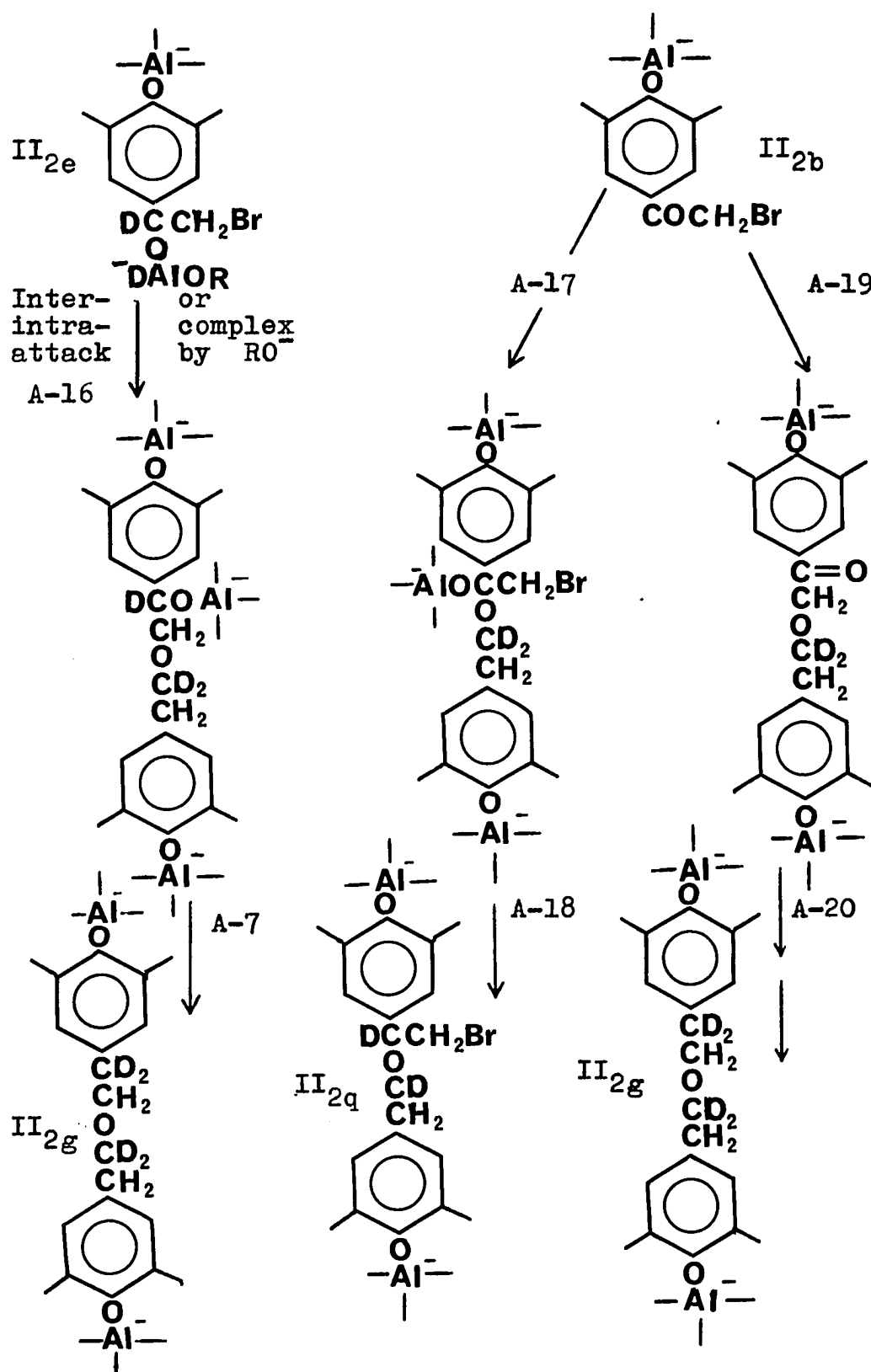
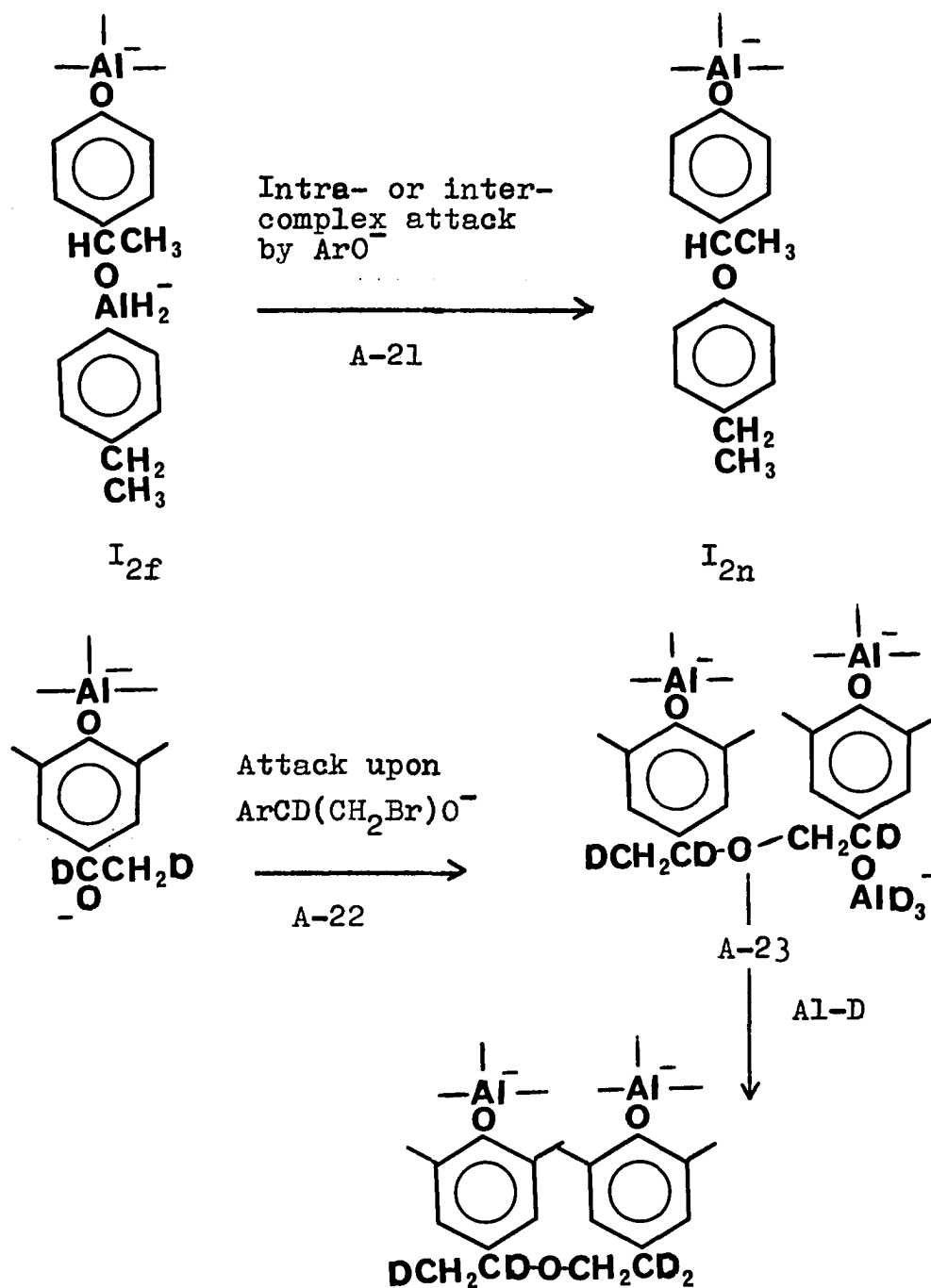


Chart V: Possible Origin of Dimeric Products, Continued



species are. (Also included is a likely route to I_{2n} , shown as Step A-21.) What the various steps shown in Chart V portray is a range of probable sources of the principal dimer, II_{2h} . (It will be understood that no fundamental change is expected if the chloroketone replaced the bromoketone.)

We must include pathways that lead through the halohydrin, i.e., A-13, A-14, p 147, because we obtain the dimer IV_{2h} ($R_3 = \text{iso-Pr}$) when the halohydrin IV_{2e} is reduced with $LiAlH_4$ (see Table X, Section F, p 79). However we cannot exclude the bromoketone as a source of the dimers, and have included Steps A-17, 18, 19, 20 as possible routes to those products. We know from the position of the deuterium label that the attacking species that leads to II_{2h} must be the already rearranged primary alcohol, and that it must attack carbon-1 of another molecule. (E.g., see p 256 for the $LiAlD_4$ reduction of IV_{2b} ($R_3 = \text{iso-Pr}$).) The deuterium labelling results exclude attack by the benzylic alcohol II_{2f} or bromohydrin II_{2e} upon carbon-2 (with displacement of Br) of another molecule. (Very simply because such attack would reverse the known position of the deuterium label.) We know nothing whatever about the mode of attack: whether it is intra-complex or inter-complex (Steps A-13, A-14) for either II_{2e} or II_{2f} .

Inasmuch as the deuterium labelled compounds produced in the reduction of the haloketones, Tables II -

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IV, p 3⁴ ff, all require attack by rearranged primary alcohol, we believe that such attack is a reasonable source of II_{2g}. If the attack upon CH₂Br follows the route for the unsymmetric dimer, then we would expect the position of the label to be ArCH₂CD₂OCH₂CD₂Ar, as was mentioned in Section B (9), p 51 . This is shown as Step A-16 in Chart V.

Only one study involving the deliberate production of large amounts of a dimer was performed. That was the reduction of IV_{2a} (R₃ = iso-Pr) in the presence of IV_{2b}, with the results tabulated in Table XIII, p 153. For ease of comparison, Entries 3 and 4 are shown from the reduction of the bromoketone IV_{2b} alone. It is quite obvious that the reduction of the bromoketone in the presence of an equimolar quantity of the ketone produces relatively large amounts of the dimer IV_{2h}--which is then the most abundant product found and almost half of the total. Most gratifying was the observation that there is no essential difference between the amount of dimer IV_{2h} produced in 10 min vs. that found after 20 min. (All the percentages as determined by nmr are within the usual limit of error. There is no real difference between the nmr spectra of the two runs.) These results suggest that the dimer, e.g., IV_{2h}, is not produced as a major product initially and is rapidly cleaved subsequently to give the monomeric products. At this point, we conclude that the role of dimers is

Table XIII. The Reduction of an Equimolar Mixture of IV_{2a} and IV_{2b}

Entry	Compounds	Reflux, min	Percent Product Distribution (Percent Yield)
1	IV _{2a} , IV _{2b}	10	23.7 IV _{2c} , 24.4 IV _{2d} , 51.8 IV _{2h} (97.2) ^{a,b}
2	IV _{2a} , IV _{2b}	20	24.1 IV _{2c} , 27.6 IV _{2d} , 48.3 IV _{2h} (98.0) ^{a,b} (23.5 IV _{2c} , 26.8 IV _{2d} , 43.1 IV _{2h} , 6.7 IV _{2p}) (70.4) ^{b,c}
3	IV _{2b}	360	67 IV _{2c} , 33 IV _{2d} (99.2) ^a
4	IV _{2b}	360	64 IV _{2c} , 36 IV _{2d} (99.0) ^a (63.4 IV _{2c} , 28.2 IV _{2d} , 2.5 IV _{2h} , 5.6 IV _{2p} , 0.5 IV _{2a}) (87.0) ^c

^a Analyses by nmr. ^b The dimer IV_{2h} was counted as two monomers. ^c Dry column chromatography results. Entries 3 and 4 are taken from Table V.

negligible in the reduction of the haloketones.

The reduction of the equimolar mixture of IV_{2a} and IV_{2b} of Table XIII, p 153, was not repeated with LiAlD₄. Consequently we do not know whether the benzylic alcohol IV_{2f} is a possible source of the increased amount of dimer IV_{2h} found in this reduction. (It will be noted that the LiAlD₄ reductions excluded that possibility in the reductions of the pure haloketones.) To illustrate this possibility and the position of the label which would result, Steps A-22 and A-23 have been included in Chart V, with IV_{2b} (R₃ = iso-Pr) as the model compound.

However, we cannot account for the distribution of the products in the reduction of IV_{2b} in the presence of IV_{2a}: if the ketone IV_{2a} (R₃ = iso-Pr) is assumed to reduce entirely to alkane IV_{2d}, and the bromoketone IV_{2b} is assumed to partition in exactly the percentages of Entries 3 and 4, then the mixture would produce (in the absence of significant dimer formation) 31.7% IV_{2c}, 64.1% IV_{2d}, 1.2% IV_{2h} and 2.8% IV_{2p}. On the other hand, if the actual results of the mixed substrates reduction are restated by dividing the dimer equally between primary alcohol and alkane products, we arrive at an expected distribution of 43.9% IV_{2c}, 47.2% IV_{2d}, 2.5% IV_{2h} and 6.7% IV_{2p}. This second calculation indicates that more primary alcohol IV_{2c} is produced in the mixed substrate reduction than from the reduction of bromoketone IV_{2b} alone, and

15.5

necessarily less alkane IV_{2d} is concurrently produced.

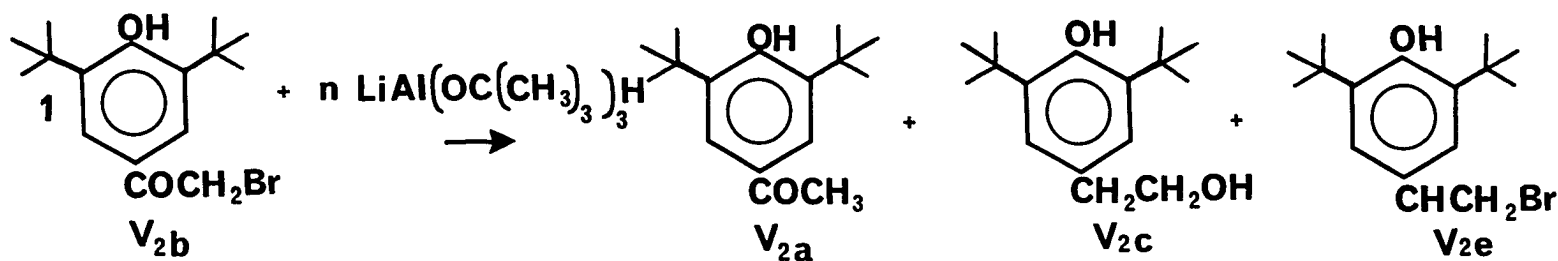
(I) The Effect of Other Reducing Agents

Let us turn to a few experimental results obtained by B. Kupfer⁴² in the area of other reducing agents. (1) Reduction of V_{4b} ($R_3 = t\text{-Bu}$) with 2.2 LiBH_4 for 3 hr in refluxing ether appears to yield ca. 90% V_{4c} and possibly 10% V_{4e} in ca. 97% yield. This is not unexpected because LiBH_4 is quite soluble in ether, and the halohydrin V_{4e} is apparently prone to rearrange to V_{4c} . This is unfinished work in the sense that chromatographic separation would be desirable to firmly establish that the other material is V_{4e} . We do not expect any of the alkylphenol bromohydrins to be stable in the presence of a hydride source, although LiBH_4 is a weaker reducing agent than LiAlH_4 (see Gaylord²⁷) so this possibility is not excluded here. (2) Reduction of V_{2b} ($R_3 = t\text{-Bu}$) with 2.8 NaBH_4 for 3 hr in refluxing ether gave no reaction, not even H_2 evolution was apparent, only starting material was recovered. NaBH_4 is poorly soluble in ether, so this finding is not unexpected. (3) Reduction of V_{2b} with 2.8 NaBH_4 for 5 hr in refluxing THF resulted in mostly rearrangement to V_{2c} , i.e., the normal reaction with $\text{LiAlH}_4\text{-Et}_2\text{O}$. The reaction also appeared to have undergone the usual sequence of events: generation of a yellow color, H_2 evolution, and finally a white paste-- in marked contrast to the lack of changes in Et_2O with NaBH_4 . This also serves to warn us about the complexity of these systems: THF is higher boiling (65.4°) than

ether (35°), and also a better solvent for NaBH₄ than ether is. Consequently it is reasonable that THF can induce reduction (apart from the longer reflux period) with NaBH₄, which is essentially insoluble in ether.

Some of the most interesting results of Kupfer's⁴² work are gathered in Table XIV, p158 . Examination of the entries reveals that the bromohydrin V_{2e} (R₃ = t-Bu) is a frequently encountered product. Its presence was confirmed by the mass spectrum, and subsequently by comparison of Kupfer's data to the nmr spectrum of Gullo's²⁶ pure sample. The experimental results are somewhat erratic, but certain significant patterns emerge: (a) The bromohydrin generally declines with the passage of time given sufficient reducing agent. This is most clearly seen in Entries 7 - 10. This was confirmed by taking such a reaction mixture and reducing it further with more LiAl(O-t-Bu)₃H: which resulted in still more primary alcohol V_{2c} at the expense of the bromohydrin. (b) Again we see some ketone, V_{2a}, produced and still cannot be certain of its source. (c) Possibly the most interesting result is the computation of hydride consumption. The results are somewhat erratic (Cf. Entry 3), reflecting the difficulty of estimating the product distribution by nmr analysis. However, the central result remains: the hydride consumption is too great for Entries 1 - 3 to allow for much if any ArOH reaction. This constitutes our best experimental

Table XIV.^a Reduction of V_{2b} with LiAl(O-tert.-Butyl)₃H



Entry	n, mol	Reflux, min	Percent Product Distribution ^b						Hydride Consumed, mol ^c
1	1.5	15	-- V _{2a} ,	-- V _{2b} ,	25	V _{2c} ,	75	V _{2e}	1.5
2	1.5	60	7.7 V _{2a} ,	30.8 V _{2b} ,	15.4	V _{2c} ,	46	V _{2e}	1.1
3	1.5	180	-- V _{2a} ,	-- V _{2b} ,	35	V _{2c} ,	65	V _{2e}	1.7
4	3.0	15	5.5 V _{2a} ,	27.8 V _{2b} ,	55.5	V _{2c} ,	11	V _{2e}	1.9
5	3.0	60	-- V _{2a} ,	-- V _{2b} ,	25	V _{2c} ,	75	V _{2e}	1.5
6	3.0	180	-- V _{2a} ,	-- V _{2b} ,	65	V _{2c} ,	35	V _{2e}	2.3
7	9.0	15	-- V _{2a} ,	-- V _{2b} ,	35	V _{2c} ,	65	V _{2e}	1.7
8	9.0	60	-- V _{2a} ,	-- V _{2b} ,	88	V _{2c} ,	12	V _{2e}	2.8
9	9.0	180	5 V _{2a} ,	5 V _{2b} ,	85	V _{2c} ,	5	V _{2e}	2.9
10	9.0	180	-- V _{2a} ,	-- V _{2b} ,	100	V _{2c}			3.0

^a Bess Bryna Kupfer, The City College, Unpublished observations. ^b Analysis by nmr.

^c Basis of calculation assumes no ArOH reaction, 1H for V_{2e}, 2H for V_{2a}, 3H for V_{2c}.

example of the migration of the V phenol without H loss. It would be extremely interesting to repeat those entries with 1.5 LiAl(O-t.-Bu)₃H with concomitant hydrogen evolution measurement. This would firmly establish within what limits the ArOH had been removed. Whether it is justified to apply the conclusion that the phenol V (R₃ = t-Bu) can migrate without H loss to the reduction of V_{2b} with limited amounts of LiAlH₄, Table IX³³, p 72, is open to question--pending a hydrogen evolution study there also.

A last finding from this work is the erratic appearance of the aldehyde V_{2t}. It is encountered particularly in the short time runs (ca. 1 hr) at low levels of LiAl(O-t.-Bu)₃H (ca. 2 mol). For example one such mixture was estimated to contain 8% V_{2a}, 5.8% V_{2b}, 23.8% V_{2c}, 46.0% V_{2e} and 16.4% V_{2t} after 1 hr reflux with 2.14 mol LiAl(O-t.-Bu)₃H. Unfortunately, these conditions generally always produce a host of other products (Cf. Entries 2 and 4 of Table XIV) which interfere with the complete nmr analysis. The compound V_{2t} is characterized by a triplet at δ 9.76, J = 3Hz, and the ArH at 7.14--the only otherwise unaccountable aromatic hydrogens. We cannot ascertain the position of the methylene doublet. It is probably somewhere in the region of δ 3.5. This region is confused by the welter of peaks from the accompanying V_{2c} and V_{2e}. We intend to repeat this work at some time in the future on a promising mixture in order to isolate the aldehyde V_{2t} via chromatography.

(J) Other Mechanisms. Epoxide Intermediates.

We noted in the Introduction, p 8, that Ershov's work^{1,2} prompted the LiAlD_4 reduction we performed on V_{2b} ($\text{R}_3 = \text{t-Bu}$).³ The product obtained, V_{2c} ($\text{ArCH}_2\text{CD}_2\text{OH}$), was stated as being incompatible with their previously proposed mechanism which involved an epoxide intermediate. Furthermore, we observed on p 10, that the products of the oxygen-shift, via the epoxide intermediate, V_{3r-6r} were not obtained when we repeated Ershov's work, rather the primary alcohols V_{2c-6c} from oxyaryl rearrangement were obtained.⁴ Apparently the Russian workers were misled for lack of the nmr spectra of our common products, V_{2c-6c} .

To illustrate the incompatibility of the observed position of the deuterium label with an epoxide intermediate, we have constructed Mechanism C, p 163, and employed II_{2b} ($\text{R}_3 = \text{Me}$) and II_{4b} as substrates rather than V_{2b} , which was the subject of our first paper.³ II_{2b} is somewhat more instructive as an example than V_{2b} because it adds to the products the alkane II_{2d} as well as the primary alcohol II_{2c} . We shall expand upon this point below.

For the purposes of this mechanism, we shall employ C-1 and C-2 as in the initial steps of Mechanism A, which lead to the halohydrin: II_{2e} . At this point, an epoxide intermediate could be formed in Step C-3. If the epoxide undergoes LiAlD_4 attack at the least hindered site,

as shown in Step C-4, the benzylic alcohol II_{2f} is formed. The benzylic alcohol II_{2f} , should then undergo inter- or intramolecular C-O bond cleavage as shown in Step C-5 to yield the alkane II_{2d} with the correct position of the deuterium label. Therefore the $LiAlD_4$ reduction of II_{2b} or IV_{2b} , etc., and examination of the alkane products does not distinguish between the halohydrin based mechanism (mechanism A) and the epoxide based mechanism (mechanism C).

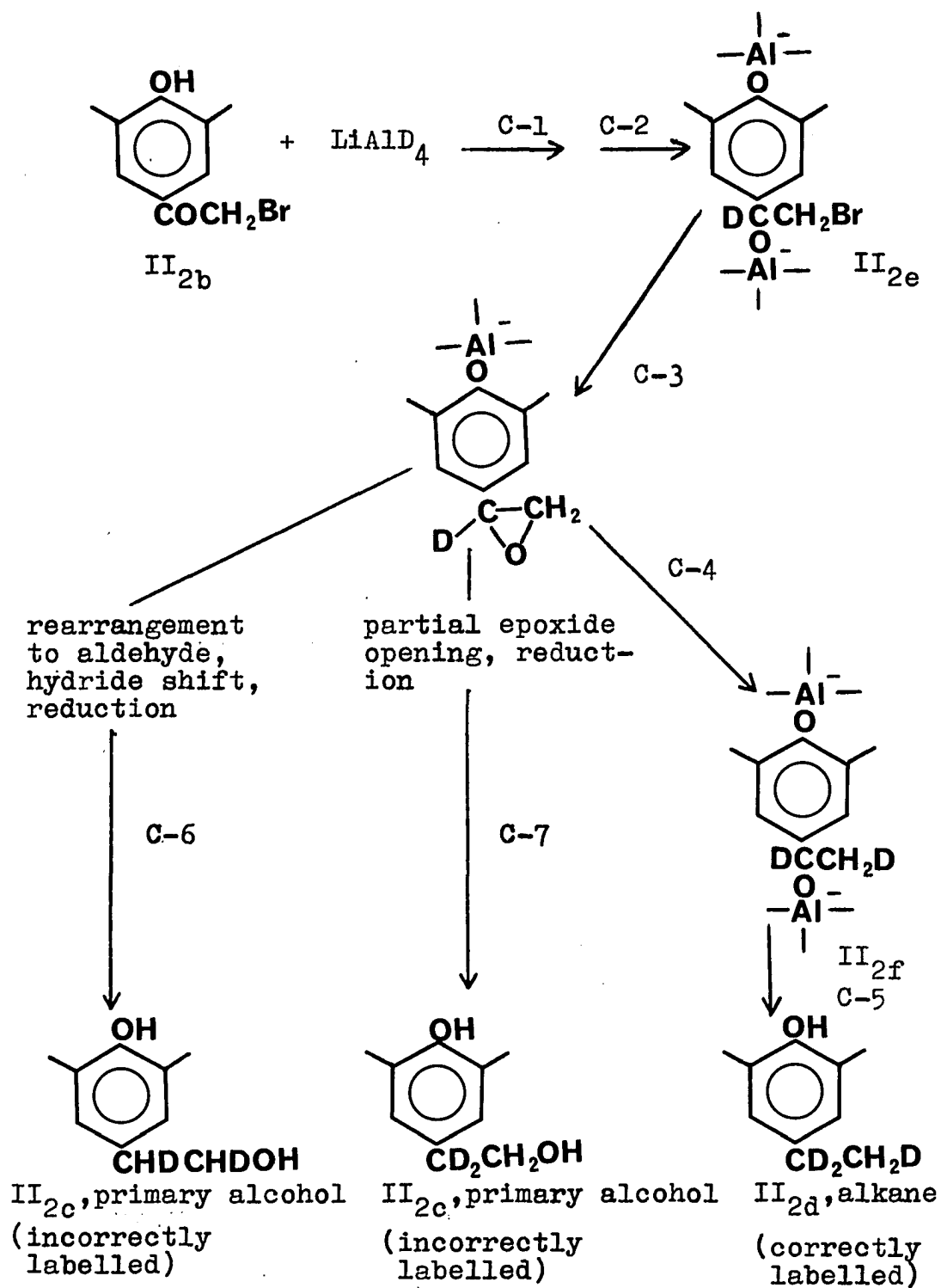
If the epoxide intermediate, II_{2k} , undergoes opening of the epoxide ring in the manner outlined by Ashby and Prather⁸ on p 17 for styrene oxide (XVI_c), one of two (or possibly both) things may happen. Either the epoxide ring undergoes Al catalyzed opening to an aldehyde with a hydride shift, followed by reduction to primary alcohol II_{2c} (incorrectly labelled) via Step C-6, or the epoxide ring may be partially opened and the incipient benzylic carbonium ion reduced, via Step C-7 to give II_{2c} (incorrectly labelled). The essential point is that neither of the two types of epoxide opening depicted by Ashby and Prather⁸ give the primary alcohol with the deuterium label in the correct position, i.e., $ArCH_2CD_2OH$.

For the epoxide mechanism to be operative it would have to be of: (a) A "hidden" opening type (which is the subject of the next Section), or, (b) Restricted only to generating the alkane product. This latter possibility does not appear to be reasonable in light of

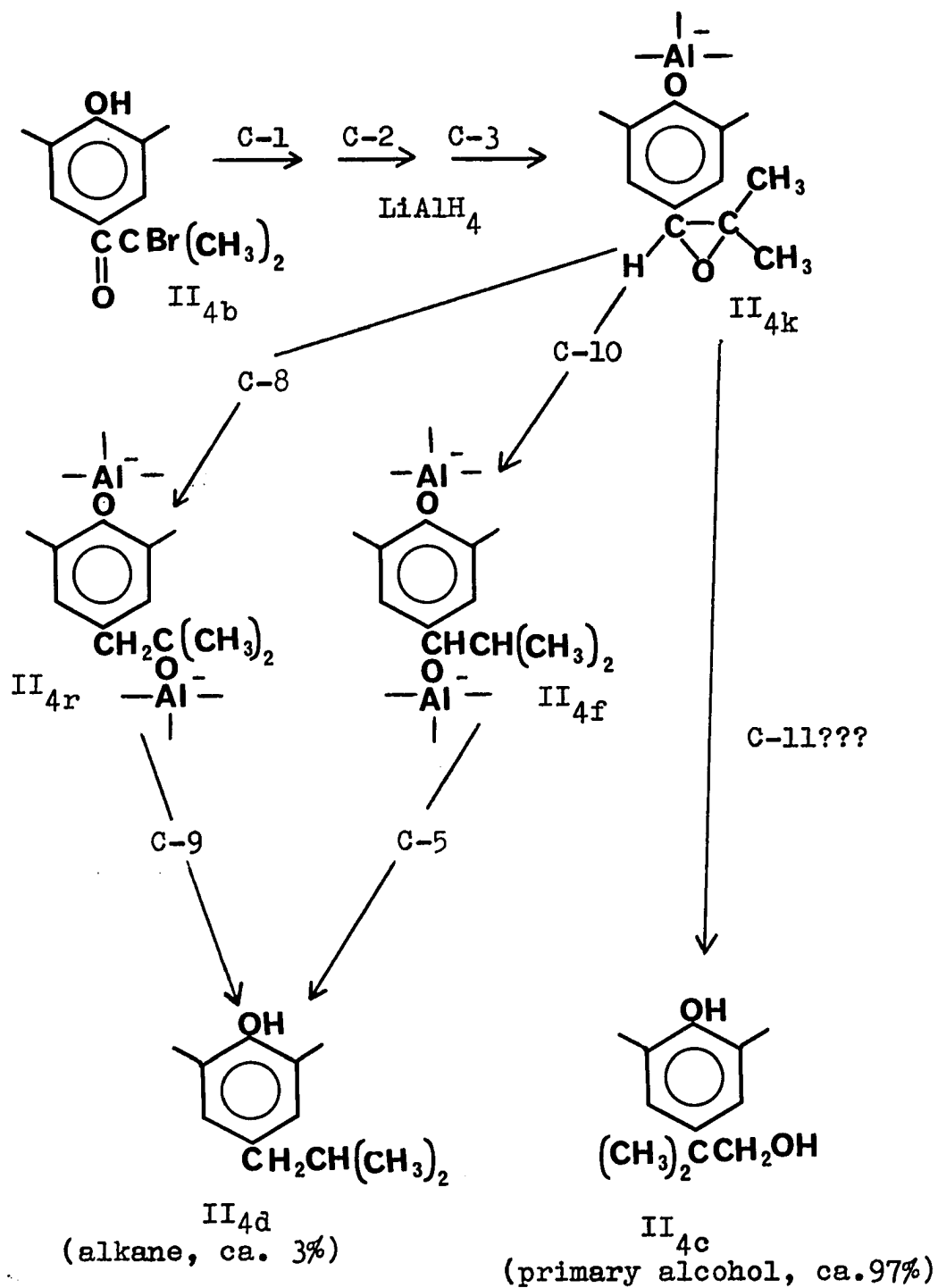
the work of Fuchs and Park^{6a,b} which has been discussed on p 15 and 16. These authors showed very clearly that the products of substituted styrene oxides (XVI) partition between the benzylic alcohols (XVIII) and primary alcohols (XVII) with the proportion of primary alcohol increasing as the electron-donating ability increases of substituents on the phenyl ring. Inasmuch as we are concerned with substituted phenoxides in this dissertation, it would appear unreasonable to maintain that a para-O⁻ is not a powerful electron-donating substituent which would lead to much primary alcohol. Further, it appears unreasonable that any epoxide formed would not follow the trend of opening suggested by the work of Fuchs and Park (on the ground that they used LiBH₄), but would only give rise to the benzylic alcohol and thence the alkane product. At this point an epoxide mechanism may be considered to be excluded for the lower members of the series of compounds I_{2b} - V_{2b}.

This simple epoxide mechanism fails rather badly when more highly substituted members of a series are reduced. The example shown is II_{4b} (R₃ = Me). This substrate could be reduced via Steps C-1, 2, 3, 10 (with or without a hydride shift), 5 to the alkane, II_{4d}--which is perhaps 3% of the product. Or this substrate could yield the same product via Steps C-1, 2, 3, 8 and 9. The apparent absence of II_{4r} could be explained by noting that

Mechanism C: An Epoxide Intermediate



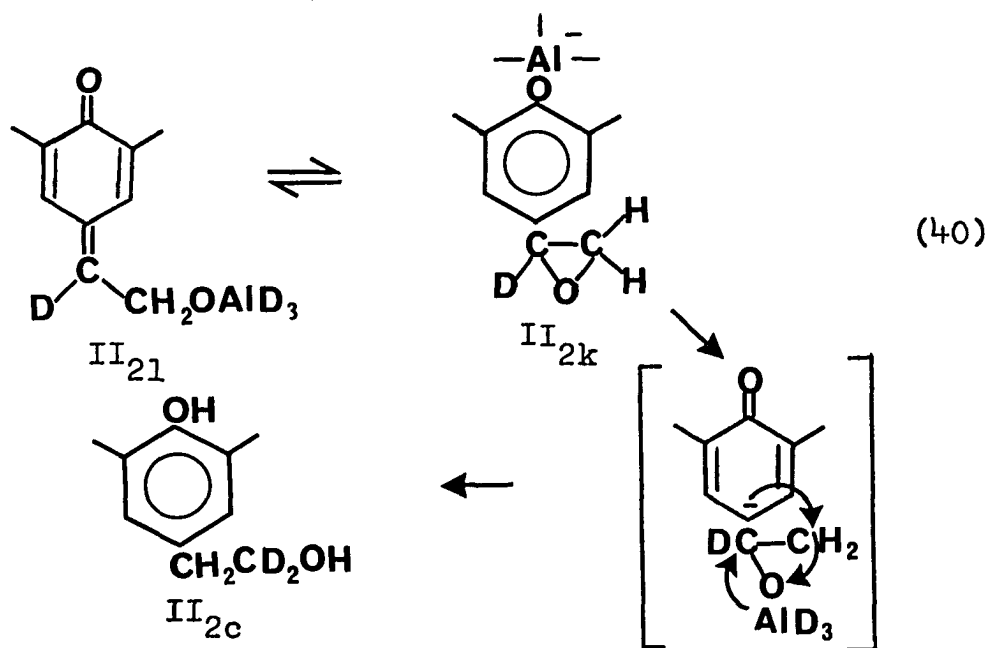
Mechanism C: An Epoxide Intermediate (continued)



it is a tertiary alcohol and is reduced to the alkane within 4 min under our reaction conditions. (We have no experimental evidence to support or refute this hypothesis.) The epoxide mechanism does not provide us with a pathway labelled C-11 to produce the 97% of the observed product. This conversion would have to occur via the "hidden" epoxide mechanism, which is the subject of the next Section. We regard a simple epoxide intermediate mechanism as an unsatisfactory means of rationalizing our data for either the lower or higher substituted haloketones.

(K) Other Mechanisms. A "Hidden" Epoxide Mechanism.

We have just mentioned in the preceding Section the possibility of a "hidden" epoxide mechanism. This involves a step which was suggested by W. Berkowitz:⁴⁹ an epoxide could be formed but not open in the manner outlined by Ashby and Prather⁸ (see p 18). Rather, the electron-donating ability of the para-O⁻ is sufficient to allow a different path to occur, as shown in Eq 40:



What Eq 40 depicts is an epoxide intermediate which undergoes an opening to the less stable incipient carbonium ion with the participation of the oxyaryl ring allowing this

(49) W.F. Berkowitz, Queens College. We wish to thank Professor Berkowitz for suggesting this possibility.

path to occur. This results in the migration of the aryl ring and the correct deuterium labelling. The expected epoxide ring openings, shown in Steps C-6 or C-7 may occur (see p 163). However, this would generate a structure which would resemble a neutral quinoid-methide structure, II_{21} , more than a carbonium ion. This structure might be sufficiently stable to deuteride reduction of the methide, that epoxide closure by the adjacent O^- may take precedence over such deuteride reduction. This would result in the equilibration shown on the left hand side of Eq 40. In that case, the product generating epoxide ring opening would be the seemingly less favored one, which could be assisted by oxyaryl ring participation, as shown. This would lead to aldehyde, and by further reduction to the primary alcohol. The total process shown in Eq 40 constitutes Step C-11, the "hidden" epoxide route to rearranged primary alcohol. We would expect alkyl substitution upon carbon-2 to facilitate the sort of opening depicted in Eq 40.

At this time, we cannot exclude the possibility of a hidden epoxide opening occurring because we have not synthesized any of these epoxides, and therefore cannot discuss how they open upon $LiAlH_4$ (or $LiAlD_4$) reduction. There is an interesting point of difference between the two suggestions. Mechanism A, p 64, requires that Step A-3 (which generates primary alcohol) occurs with a single

inversion at carbon-2, whereas Mechanism C, p 163, probably first gives an epoxide with inversion at carbon-2, then intervention of Eq 40 (i.e., Step C-11) should require another inversion of configuration at carbon-2. Given an optically active bromoketone, the two mechanisms require effectively total inversion (Mechanism A) or retention (Hidden Epoxide, Mechanism C) of configuration about carbon-2.

At this point it is sufficient to note that invoking a hidden epoxide opening allows the possibility that some or all of the halohydrin intermediate follows this route. The important point is that we are at most adding steps to Mechanism A.

(L) Other Mechanisms: A Favorskii Mechanism

A Favorskii-type mechanism differs from the proposed halohydrin mechanism in only one essential point: the Favorskii mechanism requires that the ArOH be removed by a source of hydride and that the oxyaryl ring closes to a spiro-cyclopropanone, e.g., II_{2j}, before the carbonyl group is reduced. The halohydrin mechanism (Mechanism A) requires that the carbonyl group is reduced before ring closure occurs, see p 64, Step A-3. We have constructed an example of a Favorskii-type mechanism as shown in Mechanism D. For clarity, the reduction is shown as performed with LiAlD₄, and the substrate is II_{2b}.

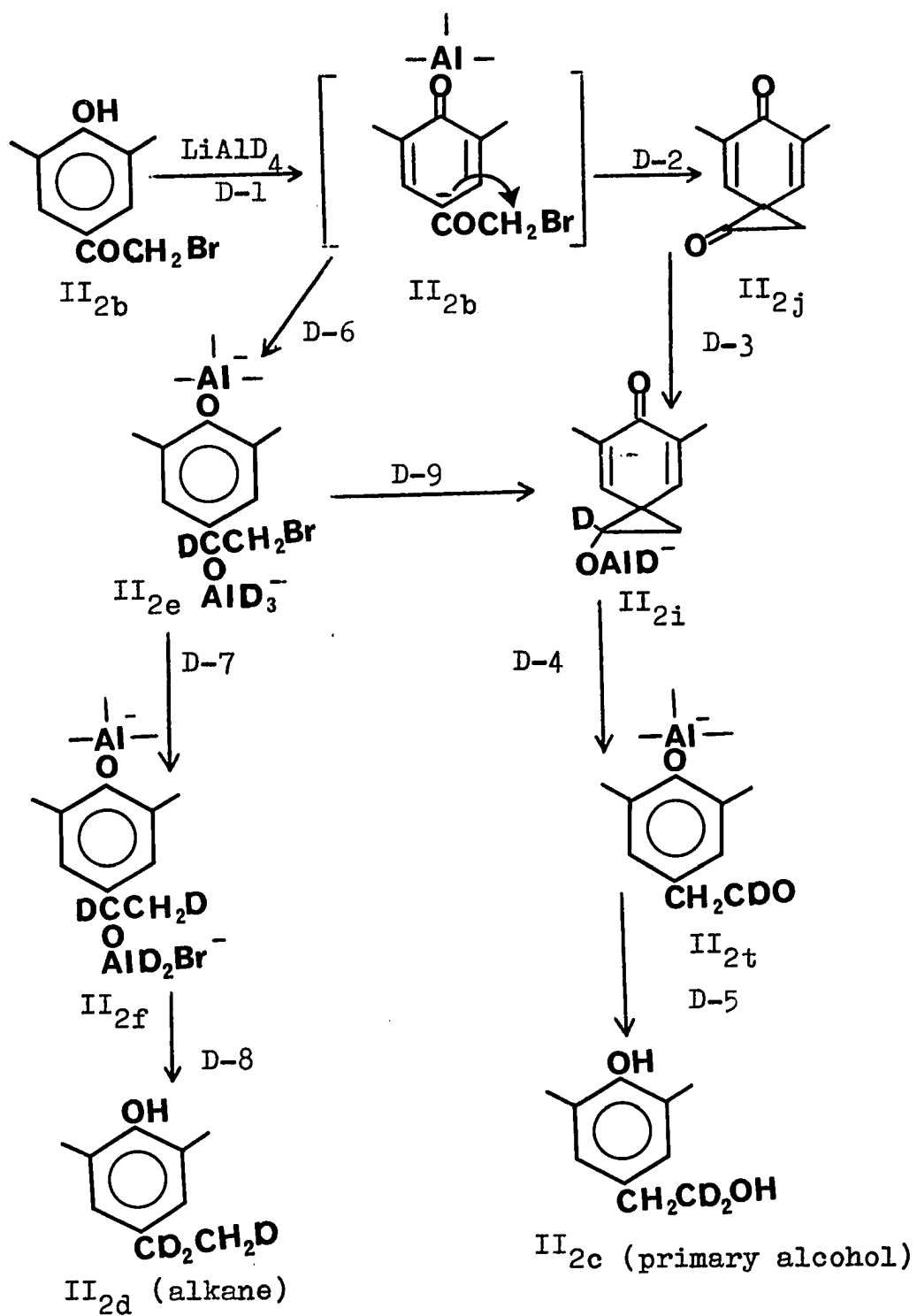
The Favorskii mechanism is less preferred over the halohydrin mechanism (Mechanism A) on a number of grounds. Perhaps the most obvious is that we did reduce the halohydrin IV_{2e} (see Section F, Table X, p 79) and this gave an acceptable reproduction of the results obtained from reduction of the bromoketone IV_{2b}. Given this set of results, and the scattered appearance of the various halohydrins, which was already noted in Section G (e.g., Table XII, p 110), there does not appear to be any need to invoke a Favorskii mechanism under our reaction conditions.

Our lack of preference for the Favorskii mechanism is based on positive evidence for the halohydrin mechanism, cited above, and the general observation that our

alkylphenol haloketones undergo very swift reduction of the carbonyl group. However, let us consider the steps we have suggested for the Favorskii mechanism. Step D-1 is the unexceptional reaction with ArOH and corresponds to Step A-1. Step D-6 is the reduction to the halohydrin, which is also Step A-2. Steps D-7 and D-8 are the same as Steps A-6 and A-7, respectively. This sequence generates alkane with the deuterium in the observed positions. We do not envision the alkane product as arising from the spiro-cyclopropanone II_{2j} , or the spiro-cyclopropanol II_{2i} because this would contradict the work of DePuy⁴⁰ and Turro.⁴¹ It will be recalled that discussion of the preferred direction of such ring openings on p 98 resulted in excluding those ring openings as probable sources of alkane products.

The core of the Favorskii mechanism is the extent to which Step D-2 occurs: the spiro-cyclopropanone ring closure. (It is obvious from the manner in which the mechanisms differ that substrates which suffer carbonyl group reduction before ArOH reaction, i.e., Steps A-1', A-2' p 64, are automatically excluded. That requirement may exclude the entire series of compounds derived from phenol V, see the discussion of this in Section E, p 78, and Section I, p 157.) The reduction in Step D-3 is reasonable, and leads to II_{2i} , which may then undergo Steps D-4 and D-5, which correspond to Steps A-4 and A-5

Mechanism D: A Favorskii Mechanism



respectively. This also results in a product, II_{2c} , with the correct deuterium labelling. Because we have shown in Section F, p 80, that a halohydrin leads to rearranged primary alcohol, we should include a shunt, Step D-9 which results in the spiro-cyclopropanol, thence primary alcohol. Although we have argued against the Favorskii mechanism as an important source of products (which should be only the primary alcohols), it should be realized that a very small contribution by Step D-2 (Favorskii mechanism) could add to Step D-9 (Halohydrin Mechanism). This would be difficult to detect: from the construction of the halohydrin mechanism, a slight increase in primary alcohol product from reduction of the bromoketone, over that obtained from reduction of the bromohydrin, could be ascribed to a Favorskii contribution to the generation of products.

That our reaction conditions do not appear to favor a Favorskii-type rearrangement does not preclude the possibility that they might react in that manner under other conditions. For example, our compounds, if reacted with aqueous ethanolic KOH could lose the ArOH , to form ArO^- , and then undergo a Favorskii closure, e.g., to II_{2j} . In the case of ethanolic base, we would expect that spiro-cyclopropanone to open to the ethyl ester of the acid; but this merely reflects the non-reducing nature of that system as compared to LiAlH_4 in ether.

(50) Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., 37921. Melting points were determined using a Thomas-Hoover apparatus, in open capillary tubes, and are corrected; boiling points are uncorrected. Mass spectra were determined using a Varian CH5 Mass Spectrometer at 70 ev under direct sample inlet conditions and linear mass scan. Infrared spectra were determined using a Perkin-Elmer 137 spectrophotometer. Absorption maxima are expressed in reciprocal centimeters. Proton magnetic resonance spectra were determined using a Varian A-60 spectrometer; spin-decoupled spectra were determined using a Bruker HFX-90 spectrometer. Chemical shifts are expressed in ppm (δ) downfield from internal tetramethylsilane ($\delta = 0$).

(A) Preparation of the Phenol Esters.

(1) Preparation of 2,6-Dimethylphenyl Acetate (II'_{2a}).⁵¹

2,6-Dimethylphenol (II) (169.4g, 1.39 mol), acetyl chloride (156.5g, 2.00 mol), and pyridine (5.93g, 0.0075 mol) were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer, and a condenser containing a drying tube. The flask was transferred to a preheated bath (135°) and the bath lowered, briefly, because the initial reaction accompanying the melting of the phenol proved excessively vigorous. Heating was continued at 135° for 360 min.

The solution was cooled, cautiously added to 1 l. of water, and NaCl was added to saturation. The crude ester was extracted with 200 ml ether. The ether layer was washed with two 1 l. portions of water saturated with NaCl, dried over MgSO₄, filtered, and the ether evaporated at reduced pressure with external heating (ca. 75°). The crude ester, 209.5g (92%), was distilled under reduced pressure to yield 199.1g (87.2%) of a colorless liquid: bp 68 - 70° (0.97 Torr). (lit⁵¹ bp 83 - 85° (0.6 Torr)); nmr (CDCl₃): δ 2.10 (s, 6H, ArCH₃), 2.15 (s, 3H, COCH₃), 7.00 (s, 3H, ArH); ir (liquid film): 1760 (s, ester), 1460, 1360 (m, CH₃), 1210 (s, aromatic acetate).

(51) F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, J. Org. Chem., 23, 1979 (1958).

(2) Preparation of 2,6-Dimethylphenyl Propionate (II'_{3a}).⁵²

2,6-Dimethylphenol (II) (183.2g, 1.50 mol) and propionyl chloride (152.5g, 1.65 mol) were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer, and a condenser containing a drying tube. The flask was transferred to a preheated bath (95°), and the solution was heated for 380 min.

The solution was cooled, cautiously added to 1 l. of water, and NaCl was added to saturation. The crude ester was extracted with 300 ml petroleum ether (bp 30 - 60°). The organic layer was washed with 1 l. of 10% aqueous Na₂CO₃, followed by three 1 l. portions of water, dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (60°). The crude ester, 257.6g (96.5%), was distilled under reduced pressure to yield 256.4g (96.0%) of a colorless liquid: bp 69 - 70° (0.20 Torr) (lit⁵² bp 112 - 113° (16 Torr)); nmr (CDCl₃): δ 1.18 (t, J = 7.0 Hz, 3H, CH₃), 2.07 (s, 6H, ArCH₃), 2.47 (q, J = 7.0 Hz, 2H, CH₂), 6.92 (s, 3H, ArH); ir (liquid film): 1760 (s, ester), 1460, 1380 (m, CH₃).

(52) P. Weiss and J. B. Niederl, J. Amer. Chem. Soc., 71, 2647 (1949).

4.

(3) Preparation of 2,6-Dimethylphenyl 2-Methylpropionate
(II'4a).⁵³

2,6-Dimethylphenol (II) (183.2g, 1.50 mol), and isobutyryl chloride (176.0g, 1.65 mol) were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The flask was transferred to a preheated bath (130°), and the solution was heated for 575 min.

The solution was cooled, cautiously added to 600 ml of water and the crude ester was extracted with 600 ml of petroleum ether (bp 30 - 60°). The organic layer was washed with two 600 ml portions of 5% aqueous Na₂CO₃, followed by three 600 ml portions of water saturated with NaCl, dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (75°). The crude ester, 276.7g (96.0%), was distilled under reduced pressure to yield 274.8g (92.0%) of a colorless liquid: bp 69 - 72° (0.6 Torr) (lit⁵³ bp 126 - 128° (22 Torr)); nmr (CDCl₃): δ 1.29 (d, J = 7.0 Hz, 6H, CH₃), 2.09 (s, 6H, ArCH₃), 2.78 (septet, J = 7.0 Hz, 1H, CH), 6.94 (s, 3H, ArH); ir (liquid film): 1760 (s, ester), 1380 (m, gem-dimethyl).

(53) D. S. Tarbell and P. E. Fanta, J. Amer. Chem. Soc., 65, 2169 (1943).

(4) Preparation of 2,6-Dimethylphenyl Phenylacetate.(II'^{5a}).

2,6-Dimethylphenol (II) (183.3g, 1.50 mol) and phenylacetyl chloride (254.0g, 1.65 mol) were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer, and a condenser containing a drying tube. The flask was transferred to a preheated bath (130°), and the solution was heated for 380 min.

The solution was cooled, cautiously added to 600 ml of water, which induced crystallization, and diluted with 600 ml of ether and 600 ml of ethyl acetate. The organic layer was washed with two 600 ml portions of 5% aqueous Na₂CO₃, followed by three 600 ml portions of water. The organic layer was dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (70°). The crude ester, 351.6g (97.5%), was judged to be pure from its nmr spectrum, mp 51.3 - 53.3°. A 63.0g portion was recrystallized from 100 ml hexane to yield the analytical sample: 30.1g, white crystals, mp 53.6 - 54.2°; nmr (CDCl₃): δ 2.00 (s, 6H, ArCH₃), 3.82 (s, 2H, CH₂), 6.95 (broad s, 3H, ArH); ir (KBr disc): 1740 (s, ester); mass spec: m/e = 240; 6% of base peak at m/e = 218.

Anal. Calcd for C₁₆H₁₆O₂: C, 79.97, H, 6.71.
Found C, 80.00; H, 6.72.

(5) Preparation of 2,6-Diethylphenyl Acetate (III'^{2a}).⁵⁴

(54) K. von Auwers and W. Mauss, Justus Liebigs Ann. Chem., 460, 240 (1928).

2,6-Diethylphenol⁵⁵ (III) (83.4g, 0.555 mol), acetyl chloride (56.6g, 0.721 mol), pyridine (2.2g, 0.028 mol), and 50 ml of chloroform were placed in a 250-ml 3-necked flask equipped with a magnetic stirrer, and a condenser containing a drying tube. The flask was transferred to a preheated bath (ca. 90°) and the solution heated at reflux for 24 hr.

The cooled solution was diluted with 300 ml of benzene and cautiously added to 700 ml of water. The organic layer was washed with two 700 ml portions of water, dried over MgSO₄, filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 55°). The crude ester, 103.8g (97%), was distilled under reduced pressure to yield 99.6g (93.1%) of a colorless liquid: bp 82 - 87° (0.10 Torr) (lit⁵⁴ bp 242 - 244° (760 Torr)); nmr (CDCl₃): δ 1.13 (t, J = 7.5 Hz, 6H, CH₃), 2.17 (s, 3H, COCH₃), 2.50 (q, J = 7.5 Hz, CH₂), 7.10 (s, 3H, ArH); ir (liquid film): 1760 (s, ester), 1460, 1360 (m, CH₃), 1210 (s, aromatic acetate).

(6) Preparation of 2,6-Diisopropylphenyl Acetate (IV'_{2a}).⁵⁶

2,6-Diisopropylphenol (IV) (100.0g, 0.561 mol), and

(55) Prepared by the diazotization of 2,6-diethyl-aniline. G.G. Ecke, J.P. Napolitano, A.H. Filbey, and A.J. Kolka, J. Org. Chem., 22, 639 (1957).

(56) W.F. Zimmer, Jr., (to Hooker Chemical Corp.), U.S. 3,028,410. April 3, 1962. Cf. Chem. Abstr. 57: P 8,503c.

acetic anhydride (111.5g, 1.09 mol) were placed in a 500-ml 1-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The flask was transferred to a preheated bath (ca. 165°) and the solution was heated at reflux for 570 min.

The cooled solution was diluted with 200 ml CHCl₃ and added to 1 l. of water. The organic layer was successively washed with two 1 l. portions of water, two 700 ml portions of 10% aqueous NaOH, and three 1 l. portions of water. The organic layer was dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (ca. 50°). The crude ester, 110.8g (89.5%) was distilled under reduced pressure to yield 106.3g (85.6%) of a light yellow fluid: bp 91 - 93° (1.0 Torr) (lit⁵⁶ bp 250° (736 Torr)); nmr (CDCl₃): δ 1.20 (d, J = 7.0 Hz, 12H, CH₃), 2.30 (s, 3H, COCH₃), 2.93 (m, J = 7.0 Hz, 2H, CH), 7.16 (s, 3H, ArH); ir (liquid film): 1760 (s, ester), 1380 (m, gem-dimethyl), 1210 (s, aromatic acetate).

(7) Preparation of 2,6-Dichlorophenyl Acetate (VI'_{2a}).⁵⁷

2,6-Dichlorophenol (VI) (204.5g, 1.256 mol), acetyl chloride (119.0g, 1.513 mol), and 150 ml of chloroform were placed in a 1-l. 1-necked flask equipped with a magnetic

(57) D. S. Tarbell and J. W. Wilson, J. Amer. Chem. Soc., 64, 1066 (1942).

stirrer and a condenser containing a drying tube. The flask was transferred to a preheated (121°) bath and the solution was heated at reflux for 330 min.

The cooled solution was diluted with 250 ml of chloroform and washed with three 1 l. portions of water. The organic layer was dried over MgSO_4 , filtered, and the solvent evaporated at reduced pressure with external heating (ca. 60°). The crude ester, 235.9g, was distilled at reduced pressure to yield a colorless fraction (200.9g, 79.5%): bp 90 - 96° (0.7 Torr) (lit⁵⁷ bp 125 - 126° (17 Torr)); nmr (CDCl_3): δ 2.30 (s, 3H, COCH_3), 6.81 - 7.36 (m, 3H, ArH); ir (liquid film): 1760 (s, ester), 1440, 1360 (m, CH_3), 1190 (s, aromatic acetate).

(8) Preparation of 2,6-Dichlorophenyl Propionate (VI'_{3a}).⁵³

2,6-Dichlorophenol (VI) (99.3g, 0.609 mol), and propionyl chloride (67.6g, 0.730 mol) were placed in a 500-ml 3-necked flask equipped with a magnetic stirrer, and a condenser containing a drying tube. The flask was transferred to a preheated bath (105°) and the solution was heated for 480 min.

The cooled solution was diluted with 500 ml of ether and the organic layer washed with four 500 ml portions of water. The organic layer was dried over MgSO_4 , filtered, and the solvent evaporated at reduced pressure with external heating (ca. 75°). The crude ester, 131.3g (98.4%), was

distilled under reduced pressure to yield 129.5g (97.0%)
of a colorless fluid: bp 77 - 79° (0.6 Torr) (lit⁵³ bp 113
- 115° (5 Torr)); nmr (CDCl₃): δ 1.28 (t, J = 7.2 Hz, 3H, CH₃),
2.66 (q, J = 7.2 Hz, 2H, CH₂), 6.86 - 7.40 (m, 3H, ArH); ir
(liquid film): 1760 (s, ester).

(B) Preparation of the Ketones

(1) Preparation of 3',5'-Dimethyl-4'-hydroxyacetophenone
(II_{2a}).⁵¹

2,6-Dimethylphenyl acetate (II'_{2a}) (208.4g, 1.270 mol) was placed in a 1-l. 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The ester was cooled using an ice-water bath. Aluminum chloride (178.0g, 1.333 mol) was added in portions over a period of 7 min, while external cooling was maintained. The flask was transferred to a preheated bath (115°) and heated for 240 min.

The molten reaction mixture was added, rapidly, to 1 l. of water. The crude mixture was dissolved in 900 ml of tetrahydrofuran, 800 ml of water were added, and NaCl added to saturation. The organic layer was washed, successively, with 900 ml of 1.2 M HCl saturated with NaCl, 1 l. of water saturated with NaCl and 473 ml of tetrahydrofuran, and 1 l. of water saturated with NaCl. The organic layer was dried over MgSO₄ and Na₂SO₄, filtered, and the solvent evaporated at reduced pressure with external heating (ca. 75°). The crude product, 191.2g of a red solid, was recrystallized from 650 ml of ethyl acetate to yield 128.0g (61.5% of an orange solid: mp 152.2 - 153.0° (lit⁵¹ mp 154 - 154.5°). A second crop of crystals was obtained by evaporation of the filtrate and recrystallization from a mixture of 50 ml of acetone and 50 ml of chloroform, to yield 35.7g (17.1%)

of an orange solid: mp 152.2 - 153.0°. The total product was 163.7g (78.6%). Nmr (acetone-d₆): δ 2.30 (s, 6H, ArCH₃), 2.50 (s, 3H, COCH₃), 4.42 (broad s, 1H, ArOH), 7.80 (s, 2H, ArH); ir (KBr disc): 1650 (m, ketone); mass spec: m/e = 164; 40% of base peak at m/e = 149.

(2) Preparation of 3',5'-Dimethyl-4'-hydroxypropiophenone
(II_{3a}).⁵²

2,6-Dimethylphenyl propionate (II'_{3a}) (214.6g, 1.20 mol) was placed in a 2-l. 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The ester was cooled using an ice-water bath. Aluminum chloride (168.0g, 1.26 mol) was added, in portions, over a period of 3 min, while maintaining external cooling. The flask was transferred to a preheated (115°) bath and heated for 410 min.

The molten reaction mixture was added, rapidly, to 1800 ml of water, the residue in the flask was transferred with 300 ml of water. The cream colored solid was crushed, 50 ml of 12 M HCl were added, and the product was extracted with 900 ml of chloroform. The organic layer was washed with two 1-l. portions of water, dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (ca. 65°). The crude product, a yellow-orange solid, 210.2g (98.4%), was recrystallized from 300 ml of benzene to yield 123.7g (57.6%) of a cream colored solid: mp 106.5 - 108°

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(lit⁵² mp 106 - 106.5°). The filtrate was evaporated and recrystallized from 150 ml of benzene to yield 45.7g of a cream colored solid: mp 107 - 109°. The total product was 169.4g (78.9%). Nmr (CDCl₃): δ 1.20 (t, J = 7.0 Hz, 3H, CH₃), 2.29 (s, 6H, ArCH₃), 2.93 (q, J = 7.0 Hz, 2H, CH₂), 6.50 (s, 1H, ArOH), 7.60 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone); mass spec: m/e = 178; 17.5% of base peak at m/e = 149.

(3) Preparation of 2,3',5'-Trimethyl-4'-hydroxypropionophenone (II_{4a}).⁵³

2,6-Dimethylphenyl 2-methylpropionate (II'_{4a}) (230.9g, 1.20 mol) was placed in a 1-l. 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The ester was cooled in an ice-water bath. Aluminum chloride (168.0g, 1.26 mol) was added, in portions, over a period of 2 min with stirring, while maintaining external cooling. The flask was transferred to a preheated (115°) bath and heated for 73 min. During this time, the material solidified, and 70 min of heating at 124° failed to melt the pink solid.

The solid was cooled and 250 ml of water were added, cautiously, to the flask. The flask was allowed to stand overnight. The solid was removed with 600 ml of hot ethyl acetate, diluted with 200 ml of ethyl acetate, 300 ml of water, 50 ml of 12 M HCl, and NaCl was added to saturation. The organic layer was washed with two 1 l. portions of water

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saturated with NaCl, dried over MgSO₄, filtered, and the solvent evaporated under reduced pressure with external heating (70°). The crude product, 211.0g (91.5%) of a light brown solid, was recrystallized from 250 ml of benzene to yield 155.3g (67.3%) of white crystals: mp 107 - 108° (lit⁵³ mp 106 - 106.5°). The filtrate was evaporated and recrystallized from 100 ml of benzene and 200 ml of hexane, to yield 36.6g (15.9%) of tan crystals: mp 106 - 107°. The total product was 191.9g (83.0%). Nmr (CDCl₃): δ 1.19 (d, J = 7.0 Hz, 6H, CH₃), 2.28 (s, 6H, ArCH₃), 3.53 (septet, J = 7.0 Hz, 1H, CH), 6.23 (s, 1H, ArOH), 7.55 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone), 1380 (m, gem-dimethyl); mass spec: m/e = 192; 9.2% of base peak at m/e = 149.

(4) Preparation of 3',5'-Dimethyl-4'-hydroxy-2-phenylacetophenone (II_{5a}).

2,6-Dimethylphenyl 2-phenylacetate (II'_{5a}) (288.4g, 1.20 mol) was placed in a 1-l. 3-necked flask equipped with a magnetic stirrer, and a condenser containing a drying tube. Aluminum chloride (168.0g, 1.26 mol) was added to the solid ester. The flask was transferred to a preheated (124°) bath. The initial reaction led to excessive foaming, and the bath was lowered, briefly, until the foaming subsided (ca. 2 min). Heating was continued for 430 min.

The molten reaction mixture was added, rapidly, to 1 l. of water. A portion of which did not pour from the

flask and solidified rapidly upon cooling. It was necessary to add 600 ml of water to the flask and allow the red solid to stand overnight. The white solid thereby generated was pulverized and dissolved in 1200 ml of ethyl acetate, diluted with 200 ml of 12 M HCl, and NaCl added to saturation. The organic layer was washed with two 1800 ml portions of water saturated with NaCl, dried over MgSO_4 , filtered, and the solvent evaporated under reduced pressure with external heating (65°). The crude material, 261.7g (91.6%) of tan solid, was recrystallized from 300 ml of chloroform and 100 ml of hexane, to yield 181.4g (62.8%) of white solid: mp $115.5 - 116.5^\circ$. This ketone becomes brown upon suction filtration in air and required vacuum evaporation of solvent. An analytical sample was prepared by recrystallization of 10.0g of the material from 40 ml of chloroform to yield 4.1g (41%) of a white solid: mp $118.0 - 118.8^\circ$. Nmr (CDCl_3): δ 2.24 (s, 6H, ArCH_3), 4.20 (s, 2H, CH_2), 5.75 (s, 1H, ArOH), 7.23 (s, 5H, phenyl), 7.65 (s, 2H, ArH): ir (KBr disc): 1650 (s, ketone); mass spec: $m/e = 240$; 2.4% of base peak at $m/e = 149$.

Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{O}_2$: C, 79.97; H, 6.71.
Found: C, 79.76; H, 6.73.

(5) Preparation of 3',5'-Diethyl-4'-hydroxyacetophenone
(III_{2a}).⁵⁴

2,6-Diethylphenyl acetate (III'_{2a}) (89.9g, 0.468 mol) was placed in a 500-ml 3-necked flask equipped with a

magnetic stirrer and a condenser containing a drying tube. The ester was cooled in an ice-water bath. Aluminum chloride (66.1g, 0.496 mol) was added, rapidly, to the stirred ester, while maintaining external cooling. The flask was transferred to a preheated (137°) bath and heated for 195 min.

The molten reaction mixture was added, rapidly, to 600 ml of 2.0 M HCl. The residue in the flask was transferred with 100 ml of methyl alcohol and 100 ml of water. The resulting purple solid was allowed to stand in the water overnight. The lumps were pulverized, and 400 ml of chloroform and 100 ml of 12 M HCl were added. The chloroform layer was washed with two 700 ml portions of water, dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (50°). The crude product, 86.7g (96.5%) of orange solid, was recrystallized from 100 ml of chloroform and 500 ml of hexane to yield 66.0g (76.0%) of white solid: mp 91.0 - 91.4° (lit⁵⁴ mp 92 - 92.5°); nmr (CDCl₃): δ 1.25 (t, J = 8.0 Hz, 6H, CH₃), 2.56 (s, 3H, COCH₃), 2.72 (q, J = 8.0 Hz, 4H, CH₂), 6.54 (s, 1H, ArOH), 7.70 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone); mass spec: m/e = 192; 74% of base peak at m/e = 177.

(6) Preparation of 3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}).

2,6-Diisopropylphenol (IV) (179.2g, 1.00 mol), ferric chloride (162.2g, 1.00 mol), and 250 ml of methylene chloride

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were placed in a 500-ml 3-necked flask equipped with a magnetic stirrer, a condenser containing a drying tube, and a 250-ml pressure-equalizing dropping funnel. The flask was placed in an ice-water bath. Acetyl chloride (82.5g, 1.04 mol) in 100 ml of methylene chloride was added over a period of 18 min to the cooled, stirred solution. The system was stirred an additional 60 min, with external cooling.

The reaction mixture was poured into 900 ml of water, the organic layer was separated, and the aqueous phase extracted with 100 ml of methylene chloride. The organic layers were combined and washed successively with 900 ml of water, two 900 ml portions of 1.2 M HCl, and two 900 ml portions of water. The organic layer was dried over MgSO_4 , filtered, and the solvent evaporated at reduced pressure with external heating (70°). The crude material was a liquid, 204.1g (93.0%). The nmr spectrum showed it to be 26% ketone (IV_{2a}) and 76% ester (IV'_{2a}). To the crude material was added 400 ml of petroleum ether (bp $30 - 60^\circ$), and the mixture was cooled to 4° . Scratching induced crystallization. The ketone was collected by filtration, to yield 36.8g of a light brown solid. This was recrystallized from 200 ml of hexane to yield 32.9g (14.9%) of white solid: mp $94.0 - 95.0^\circ$; nmr (CDCl_3): δ 1.28 (d, $J = 7.0$ Hz, 12H, CH_3), 2.60 (s, 3H, COCH_3), 3.32 (septet, $J = 7.0$ Hz, 2H, CH), 6.61 (s, 1H, ArOH), 7.76 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone); mass spec: $m/e = 220$; 36% of base peak at $m/e = 205$.

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Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.14.
Found: C, 76.09; H, 8.98.

(7) Preparation of 3',5'-Di-tert.-butyl-4'-hydroxyaceto-phenone (V_{2a}).⁵⁸

Ferric chloride (16.2g, 0.10 mol), acetyl chloride (7.85g, 0.10 mol), and 20 ml of chloroform were placed in a 250-ml 3-necked flask equipped with a magnetic stirrer, a condenser containing a drying tube, and a 150-ml pressure-equalizing dropping funnel. The flask was placed in an ice-water bath. 2,6-Di-tert.-butyl-phenol (V) (20.6g, 0.10 mol) dissolved in 15 ml of chloroform was added over a period of 7 min to the cooled, stirred solution. The reaction mixture was cooled and stirred for 10 min after the addition of the phenol.

The reaction mixture was washed, successively, with two 200 ml portions of 2.0 M HCl, and three 400 ml portions of water, dried over $MgSO_4$, filtered, and the solvent evaporated at reduced pressure with external heating (50°). The crude product, 18.0g (72.5%) of yellow-brown solid, was recrystallized from 10 ml chloroform and 150 ml of hexane to yield 8.7g (35.1%) of white solid: mp $146.5 - 148.5^\circ$ (lit⁵⁸ mp $146 - 147^\circ$); nmr ($CDCl_3$): δ 1.48 (s, 18H, CH_3), 2.55 (s, 3H,

(58) N.V. Portnykh, A. A. Volod'kin, and V. V. Ershov, Bul. Acad. Sci., USSR, 2181 (1966).

COCH₃), 5.80 (s, 1H, ArOH), 7.86 (s, 2H, ArH); ir (KBr disc): 1660 (s, ketone); mass spec: m/e = 248; 25% of base peak at m/e = 233.

(8) Preparation of 3',5'-Di-tert.-butyl-4'-hydroxypropio-phenone (V_{3a}).⁵⁸

Ferric chloride (162.2g, 1.00 mol), propionyl chloride (185.0g, 2.00 mol), and 300 ml of chloroform were placed in a 2-l. 3-necked flask equipped with a magnetic stirrer, a condenser containing a drying tube, and 1-l. pressure-equalizing dropping funnel. The flask was placed in an ice-water bath. 2,6-Di-tert.-butylphenol (V) (206.3g, 1.00 mol) dissolved in 250 ml of chloroform was added over a period of 160 min to the cooled stirred solution. The mixture was stirred with cooling for 200 min after the addition of the phenol.

The reaction mixture was poured into 1 l. of water and stirred overnight. The organic layer was separated, the aqueous layer extracted with 800 ml of chloroform, and the organic layers were combined. The organic layer was washed with 800 ml of water, dried over MgSO₄, filtered, and the solvent evaporated under reduced pressure with external heating (ca. 60°). The crude product, 279.7g (vs. 262.4g, theory) of brown solid, was recrystallized from 250 ml of benzene and 250 ml of hexane to yield 162.3g (61.8%) of white solid: mp 134.5 - 136.5° (lit⁵⁸ mp 134 - 135°); nmr

(CDCl₃): δ 1.21 (t, J = 7.0 Hz, 3H, CH₃), 1.47 (s, 18H, CH₃), 2.97 (q, J = 7.0 Hz, 2H, COCH₂), 5.76 (s, 1H, ArOH), 7.92 (s, 2H, ArH); ir (KBr disc): 1660 (s, ketone); mass spec: m/e = 262; 61% of base peak at m/e = 233.

(9) Preparation of 3',5'-Di-*tert.*-butyl-4'-hydroxy-2-methylpropiophenone (V_{4a}).⁵⁸

Aluminum chloride (97.5g, 0.730 mol) and isobutyryl chloride (145.0g, 1.36 mol) were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer, a condenser containing a drying tube, and a 1-l. pressure-equalizing dropping funnel. The flask was cooled in an ice-salt bath at -10°. 2,6-Di-*tert.*-butylphenol (V) (150.0g, 0.730 mol) dissolved in isobutyryl chloride (223.0g, 2.09 mol) was added to the cooled, stirred solution over a period of 20 min, causing the temperature to reach -5°. The solution was stirred an additional 13 min at -10°.

The reaction mixture was added to 200 ml of 12M HCl in 1500 ml of crushed ice, and the aqueous layer was extracted with 350 ml and 150 ml portions of chloroform. The organic layers were combined and washed with four 1 l. portions of water, two 600 ml portions of 2% NaOH, one 600 ml portion of 10% NaOH, three 1 l. portions of water, dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure (ca. 55°). The crude product, 187.0g of orange solid, was recrystallized from 200 ml of chloroform and 800 ml of hexane to yield 114.6g (56.7%) of white solid: mp 138 - 138.5°

(lit⁵⁸ mp 135 - 137°); nmr (CDCl₃): δ 1.48 (s, 18H, C(CH₃)₃), 1.23 (d, J = 7.0 Hz, 6H, CH₃), 3.58 (septet, J = 7.0 Hz, CH), 5.80 (s, 1H, ArOH), 7.94 (s, 2H, ArH); ir (KBr disc): 1660 (s, ketone); mass spec: m/e = 276; 5.3% of base peak at m/e = 233.

(10) Preparation of 3',5'-Di-tert.-butyl-4'-hydroxy-2-phenylacetophenone (V_{5a}).⁵⁸

2,6-Di-tert.-butylphenol (V) (30.0g, 0.146 mol), 80 ml of hexane, and phenylacetyl chloride (27.5g, 0.175 mol) were placed in a 300-ml 1-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The flask was immersed in an ice-salt bath, and the solution was cooled to -12°. Aluminum chloride (19.5g, 0.146 mol) was added, in portions, over a period of 6 min to the cooled, stirred solution, followed by 20 ml hexane. The solution was stirred and cooled an additional 90 min after the aluminum chloride addition.

The reaction mixture was poured over 400 ml of crushed ice and 50 ml of 12M HCl, the crude solid was dissolved in 250 ml of chloroform, the aqueous phase extracted with 150 ml of chloroform, and the organic layers combined. The organic layer was washed with two 400 ml portions of water, two 300 ml portions of 10% NaOH, three 500 ml portions of water, dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (57°). The crude

product, 45.9g, yellow-white crystals, was recrystallized twice from 400 ml of hexane to yield 18.9g (39.7%) of a white solid: mp 128 - 128.2° (lit⁵⁸ mp 120 - 122°); nmr (CDCl₃): δ 1.44 (s, 18H, CH₃), 4.24 (s, 2H, CH₂), 5.78 (s, 1H, ArOH), 7.22 - 7.43, 7.30 max (multiplet, 5H, phenyl), 7.98 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone); mass spec: m/e = 324; 0.40% of base peak at m/e = 233.

(11) Preparation of 3',5'-Di-tert.-butyl-4'-hydroxybutyrophenone (V_{6a}).⁵⁸

Butyryl chloride (155.3g, 1.46 mol) and aluminum chloride (97.5g, 0.730 mol) were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer, a 1-l. pressure-equalizing dropping funnel, and a condenser containing a drying tube. The flask was placed in an ice-salt bath at -8°. 2,6-Di-tert.-butylphenol (V) (150.0g, 0.730 mol) dissolved in butyryl chloride (310.7g, 2.91 mol) was added to the cooled, stirred solution over a period of 10 min. The solution was stirred an additional 70 min after the phenol was added.

The reaction mixture was poured onto 1500 ml of crushed ice and 200 ml of 12 M HCl, extracted with 300 ml of chloroform, and the aqueous layer was extracted with 200 ml of chloroform. The organic layers were combined, washed successively with four 1 l. portions of water, two 500 ml portions of 20% NaOH, five 1 l. portions of water, dried over MgSO₄.

filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 60°). The crude product, 200.0g of brown solid, was recrystallized first from 120 ml of hexane, then from 80 ml of hexane to yield 66.5g (33.0%) of pale yellow crystals: mp 91.4 - 92.4° (lit⁵⁸ mp 88 - 90°); nmr (CDCl₃): δ 1.03 (t, J = 7.5 Hz, 3H, CH₃), 1.50 (s, 18H, CH₃), 1.80 (multiplet, J = 7.5 Hz, 2H, CH₂), 2.95 (t, J = 7.5 Hz, 2H, COCH₂), 5.90 (s, 1H, ArOH), 7.93 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone); mass spec: m/e = 276; 20% of base peak at m/e = 233.

(12) Preparation of 3',5'-Dichloro-4'-hydroxyacetophenone (VI_{2a}).⁵⁷

2,6-Dichlorophenyl acetate (VI'_{2a}) (200.9g, 1.164 mol) was placed in a 1-l. 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The flask was immersed in an ice bath. Aluminum chloride (164.9g, 1.236 mol) was added rapidly to the ester. The flask was transferred to a preheated (ca. 125°) bath and stirred. The initial reaction caused excessive foaming, which required repeated lowering of the bath over the first 15 min. Heating was continued for an additional 195 min.

The reaction mixture solidified immediately the bath was removed. The material was removed from the flask by treatment with a total of 1 l. of 95% ethanol and 1.5 l. of 3M HCl added alternately in small portions. The salmon

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pink crystals were pulverized and allowed to stand in the solution for 3 days. The crystals were filtered, rinsed with 1 l. of water, and allowed to air dry for one week. The crude product, 186.4g (92.8%), mp 158.5 - 162°, was sublimed, in portions, at 178 - 186° and ca. 0.3 Torr to yield 152.5g (75.9%) of white crystals: mp 161 - 162.3° (lit⁵⁷ mp 164 - 165.5°); nmr (CDCl₃ plus acetone-d₆): δ 2.56 (s, 3H, COCH₃), 7.95 (s, 2H, ArH), the ArOH was not detected; ir (KBr disc): 1650 (s, ketone), 1470, 1380 (m, CH₃); mass spec: m/e = 204, 206, 208; 36, 23, 4% of base peak at m/e = 189.

(13) Preparation of 3',5'-Dichloro-4'-hydroxypropiophenone (VI_{3a}).⁵³

2,6-Dichlorophenyl propionate (VI'_{3a}) (109.5g, 0.500 mol) was placed in a 500-ml 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The flask was placed in an ice-water bath. Aluminum chloride (70.0g, 0.525 mol) was added, rapidly, to the cooled, stirred ester. The flask was transferred to a pre-heated (ca. 137°) bath and heating was continued for 300 min.

The reaction mixture was poured into 600 ml of water followed by 50 ml of 12M HCl. The residue in the flask was removed with 400 ml of water. The cream colored solid was pulverized and extracted with 1100 ml of ethyl acetate and 200 ml of ether. The organic layer was washed with

two 1 l. portions of water, dried over MgSO_4 , filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 70°). The crude product, 98.9g (90.4%) of a pink solid, was recrystallized from 150 ml of benzene and 200 ml of hexane to yield 60.5g (53.2%) of white solid: mp $108.5 - 110.0^\circ$ (lit⁵³ mp $110 - 111^\circ$). The filtrate was concentrated and recrystallized from 150 ml hexane and 10 ml acetone to yield 11.3g (12.4%) of white crystals: mp $110 - 110.6^\circ$. The total product was 71.8g (65.6%); nmr (CDCl_3 plus acetone- d_6): δ 1.20 (t, $J = 7.0$ Hz, 3H, CH_3), 2.92 (q, $J = 7.0$ Hz, 2H, COCH_2), 7.86 (s, 2H, ArH), the ArOH was not detected: ir (KBr disc): 1670 (s, ketone); mass spec: $m/e = 218, 220, 222$; 15, 9.8, 1.6% of base peak at $m/e = 189$.

(C) Preparation of the Alkanes.

(1) Preparation of 2,6-Dimethyl-4-ethylphenol (II_{2d}).⁵⁴

3',5'-Dimethyl-4'-hydroxyacetophenone (II_{2a}) (16.4g, 0.10 mol), and 100 ml of ether were placed in a 500-ml 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. Lithium aluminum hydride (7.6g, 0.20 mol) and 100 ml of ether were added to the flask. The flask was transferred to a preheated (60°) bath and the system was heated at reflux for 18 hrs.

The flask was cooled, 15 ml of ethyl acetate were added, dropwise, and the system was heated at reflux for 90 min. The flask was again cooled, 10 ml of water were added, dropwise, and then 10 ml of 12M HCl were added, followed by 800 ml of water. The aqueous layer was separated and extracted twice with a mixture of 150 ml of tetrahydrofuran and 100 ml of chloroform. The organic layers were combined and washed with two 500 ml portions of water, dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (ca. 50°). The crude product, 15.4g (vs. 15.0g, theory, solvent was present), was distilled under reduced pressure to yield 10.7g (71.2%) of a colorless liquid: bp 70° (0.60 Torr); mp 36.5 - 37.5° (lit⁵⁴ mp 36 - 37°); nmr (CDCl₃): δ 1.17 (t, J = 7.6 Hz, 3H, CH₃), 2.18 (s, 6H, ArCH₃), 2.50 (q, J = 7.6 Hz, 2H, CH₂), 4.55 (s, 1H, ArOH), 6.81 (s, 2H, ArH); ir (KBr disc): 1460, 1380 (m, CH₃); mass spec: m/e = 150, 9.8% of base peak at m/e = 135.

Anal. Calcd for $C_{10}H_{14}O$: C, 72.26; H, 8.49.

Found: C, 72.05; H, 8.55.

(2) Preparation of 2,4,6-Triethylphenol (III_{2d}).⁵⁴

3',5'-Diethyl-4'-hydroxyacetophenone (III_{2a}) (11.0g, 0.0571 mol), 100 ml of tetrahydrofuran and 50 ml of ether were placed in a 500-ml 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. The flask was placed in an ice-water bath. Lithium aluminum hydride (6.51g, 0.171 mol) was added to the solution. The flask was transferred to a preheated (70°) bath and heated at reflux for 24 hrs.

The solution was cooled, 25 ml of ethyl acetate and 25 ml of ether were added dropwise, and the cooled solution was stirred for 120 min. Then 20 ml of methyl alcohol and 30 ml of ether were added, dropwise. The solution was added to 900 ml of water, followed by 75 ml of 12M HCl and 500 ml of ether, and NaCl was added to saturation. The organic layer was washed with two 900 ml portions of water saturated with NaCl, dried over $MgSO_4$, filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 70°). The crude product, 9.7g (95%) of a dark brown oil, was distilled under reduced pressure using a Vigreux column to yield 5.8g (56.7%) of a pale yellow liquid: bp 83° (0.40 Torr) (lit⁵⁴ bp 244 - 246° at 760 Torr); nmr ($CDCl_3$): δ 1.18 (t, $J = 7.5$ Hz, 9H, CH_3), 2.54 (q, $J = 7.5$ Hz, 6H, CH_2), 4.53 (s, 1H, ArOH), 6.80 (s, 2H, ArH); ir (KBr disc): 1460, 1380 (m, CH_3); mass spec: $m/e = 178$; 34% of base peak at $m/e = 163$.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18.

Found: C, 80.72; H, 10.25.

(3) Preparation of 2,6-Diisopropyl-4-ethylphenol (IV_{2d}).

3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}) (12.4g, 0.050 mol) and 100 ml of ether were placed in a 500-ml 3-necked flask equipped with a mechanical stirrer, and a condenser containing a drying tube. Lithium aluminum hydride (5.7g, 0.15 mol) was added and the flask was transferred to a preheated (70°) bath. The solution was heated at reflux for 260 min, then stirred at room temperature for 18 hrs.

The flask was cooled in an ice-water bath, and 20 ml of water were added, dropwise, followed by 250 ml of 2.4M HCl. The organic layer was washed with three 250 ml portions of water, dried over $MgSO_4$, filtered and the solvent evaporated at reduced pressure with external heating (ca. 50°). The product, 11.1g (vs. 10.3g, theory) of pale yellow liquid, was distilled under reduced pressure to yield 9.0g (87.4%) of pale yellow liquid: bp 86° (0.19 Torr); nmr ($CDCl_3$): δ 1.20 (t, $J = 7.0$ Hz, 3H, CH_3), 1.22 (d, $J = 7.0$ Hz, 12H, CH_3), 2.58 (q, $J = 7.0$ Hz, 2H, CH_2), 3.14 (septet, $J = 7.0$ Hz, 2H, CH), 4.66 (s, 1H, ArOH), 6.90 (s, 2H, ArH), (the ethyl triplet is visible only at the 1.08 peak, the two downfield peaks appear as inflections on the isopropyl doublet, irradiation⁵⁰ of the methine H caused the isopropyl doublet to collapse to a singlet, revealing the other two peaks of the ethyl triplet); ir (liquid film): 1460 (m, CH_3), 1380 (w, gem-dimethyl);

mass spec: $m/e = 206$; 43% of base peak at $m/e = 191$.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75.

Found: C, 81.75; H, 10.71.

(4) Preparation of 2,6-Dichloro-4-ethylphenol(VI_{2d}).

3',5'-Dichloro-4'-hydroxyacetophenone (VI_{2a})

(10.25g, 0.050 mol) and 50 ml of tetrahydrofuran were placed in a 500-ml 3-necked flask equipped with a mechanical stirrer and a condenser containing a drying tube. Sodium dimethoxyethoxy aluminum hydride⁵⁹ (42.0 cc, 0.30 mol) was added dropwise to the solution, followed by 50 ml of tetrahydrofuran. The solution was transferred to a preheated (90°) bath and heated at reflux for 24 hrs.

The solution was cooled and cautiously added to 400 ml of water, followed by 100 ml of 2.4M HCl. The aqueous phase was separated and extracted with two 250 ml portions of ether. The organic layers were combined and washed with three 500 ml portions of water, dried over $MgSO_4$, filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 60°). The crude product, 5.60g of pale yellow liquid, was distilled under reduced pressure to yield 2.4g (25%) of a colorless liquid: bp 66° (0.12 Torr);

(59) Research Organic/Inorganic Chemical Co.,
11686 Sheldon St., Sun Valley, Calif. 91352. 70% solution
in benzene, 1 equivalent of hydride = 139.65 cc.

nmr (CDCl_3): δ 1.15 (t, $J = 7.0$ Hz, 3H, CH_3), 2.51 (q, $J = 7.0$ Hz, 2H, CH_2), 6.16 (s, 1H, ArOH), 7.06 (s, 2H, ArH); ir (liquid film): 1460, 1380 (m, CH_3); mass spec: $m/e = 190, 192, 194$; 48, 26, 6% of base peak at $m/e = 175$.

Anal. Calcd for $\text{C}_8\text{H}_8\text{OCl}_2$: C, 50.29; H, 4.22; Cl, 37.11.

Found: C, 50.08; H, 4.31; Cl, 37.22.

(D) Preparation of the 2-Haloketones.

(1) Preparation of 2-Bromo-4'-hydroxyacetophenone (I_{2b}).⁶⁰

4'-Hydroxyacetophenone (I_{2a}) (54.4g, 0.40 mol), cupric bromide (223.4g, 1.00 mol), and 300 ml of tetrahydrofuran were placed in a 1-l. 3-necked flask equipped with a mechanical stirrer and a condenser with an adapter directly connected to the hood vent. A preheated (111°) bath was raised immediately and the solution was heated at reflux for 150 min.

The dark green solution was cooled and filtered to remove cuprous bromide. The filtrate was diluted with 300 ml of chloroform and washed with three 1 l. portions of water, dried over MgSO₄, filtered and the solvent evaporated at reduced pressure with external heating (ca. 70°). The black crude mixture, 121.1g (vs. 93.9g, theory, tetrahydrofuran was present), was dissolved in 350 ml of acetone and treated three times with decolorizing carbon (Norit A). The solvent was evaporated at reduced pressure with external heating (ca. 40°). Above this temperature, the crude material darkens rapidly. The crude material, 100.9g of a brown solid: 1.8% ArCOCH₃, 87.0% ArCOCH₂Br, 11.2% ArCOCHBr₂ (by nmr), was recrystallized from 400 ml of chloroform and 30 ml of methanol to yield 15.0g (23.3%) of pink crystals:

(60) N. P. Buu-Hoi, N. D. Xuong, and D. Lavit, J. Chem. Soc., 1034 (1954).

mp 130.5 - 132° (lit⁶⁰ mp 130°); nmr (acetone-d₆): δ 4.61 (s, 2H, COCH₂Br), 6.90, 7.06, 7.90, 8.05 (AA'BB', 4H, ArH); ir (KBr disc): 1670, 1650 (s, ketone); mass spec: m/e = 214, 216; 3.3, 3.3% of base peak at m/e = 121.

(2) Preparation of 2-Bromo-4'-hydroxypropiophenone (I_{3b}).⁶¹

4'-Hydroxypropiophenone (I_{3a}) (75.1g, 0.50 mol), cupric bromide (223.4g, 1.00 mol), and 350 ml of dimethoxyethane were placed in a 1-l. 3-necked flask equipped with a mechanical stirrer and a condenser. A preheated (110°) bath was raised immediately and the system was heated at reflux for 90 min.

The dark green solution was cooled and filtered to remove cuprous bromide. The filtrate was diluted with 600 ml of ethyl acetate and washed with two 1 l. portions of water saturated with NaCl, dried over MgSO₄, filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 60°). The crude product, 117.0g (vs. 114.5g, theory) of dark green solid, was dissolved in 200 ml of boiling benzene, treated with decolorizing carbon (Norit A), and allowed to recrystallize. The product was a grey solid, 63.9g (55.8%), mp 97.5 - 98.5° (lit⁶¹ mp 95 - 96°); nmr (acetone-d₆): δ 1.77 (d, J = 7.0 Hz, 3H, CH₃), 5.51 (q, J =

(61) A. V. Dombrovskii, N. I. Shevchuk, and V. P. Kravets, Zh. Obsch. Chim., 32, 2278 (1961).

7.0 Hz, 1H, CH), 6.83, 6.96, 7.85, 8.00 (AA'BB', 4H, ArH), 1r (KBr disc): 1650 (s, ketone); mass spec: m/e = 228, 230; 1.9, 1.9% of base peak at m/e = 121.

(3) Preparation of 2-Bromo-3',5'-dimethyl-4'-hydroxyacetophenone (II_{2b}).

Aluminum chloride (53.3g, 0.40 mol) and 100 ml of ethylene dichloride were placed in a 500-ml 3-necked flask equipped with a magnetic stirrer, a 125-ml pressure-equalizing dropping funnel, and a condenser containing a drying tube. The flask was cooled in an ice-water bath, and bromoacetyl bromide (80.7g, 0.40 mol) diluted with 75 ml of ethylene dichloride was added, rapidly. 2,6-Dimethylphenol (II) (48.9g, 0.40 mol) dissolved in 75 ml of ethylene dichloride were added over a period of 19 min to the cooled, stirred solution. The yellow solution became deep red and remained thus for the 360 min of reaction time.

The reaction mixture was added to 500 ml of water and 200 ml of crushed ice. When cool, the organic material was extracted with 250 ml of methylene chloride. The organic layer was washed with three 1 l. portions of water, dried over MgSO₄, filtered, and the solvent was evaporated at reduced pressure with external heating (73°). The crude product, 87.4g (vs. 87.2g, theory, ca. 40% product by nmr) of a brown solid, was recrystallized from 100 ml of benzene to yield 15.4g (15.9%) of royal blue crystals: mp 130.2 - 131.2°. An analytical sample was prepared by recrystallization

from chloroform and hexane (3:1) and treating the hot solution with decolorizing carbon (Norit A) to yield pink crystals: mp 131.2 - 132.0°; nmr (acetone-d₆): δ 2.30 (s, 6H, ArCH₃), 4.60 (s, 2H, COCH₂Br), 7.71 (s, 2H, ArH); (CDCl₃): δ 5.55 (s, 1H, ArOH); ir (KBr disc): 1640 (m, ketone); mass spec: m/e = 244, 242; 8.2, 8.5% of base peak at m/e = 149.

Anal. Calcd for C₁₀H₁₁O₂Br: C, 49.41; H, 4.56; Br, 32.87. Found: C, 49.68; H, 4.60; Br, 33.03.

(4) Preparation of 2-Chloro-3',5'-dimethyl-4'-hydroxyacetophenone (II_{2b}-C₁).

Aluminum chloride (53.3g, 0.40 mol), chloroacetyl chloride (45.2g, 0.40 mol), 2,6-dimethylphenol (II) (48.9g, 0.40 mol), and a total of 250 ml of ethylene dichloride were combined in exactly the manner of II_{2b}, p 204 (vide supra). The phenol was added over a period of 35 min to the solution, and the reaction was continued for 300 min after phenol addition.

The dark red reaction mixture was added to 1 l. of water, and the organic material was extracted with 300 ml of chloroform. The organic layer was washed with three 1 l. portions of water, dried over MgSO₄, filtered and the solvent was evaporated with external heating (62°). The crude product, 66.6g (ca. 31.9% product by nmr), was diluted with 100 ml of chloroform and added to 300 ml of boiling hexane. The crystals were collected and recrystallized from 50 ml of chloroform and 30 ml of hexane to yield 13.4g (16.9%) of pale yellow

crystals: mp 96.5 - 98.2°. An analytical sample was prepared by recrystallization of 4.0g from 15 ml of chloroform and 5 ml of hexane to yield 1.4g of white crystals; mp: 102.3 - 102.9°; nmr (CDCl₃): δ 2.28 (s, 6H, ArCH₃), 4.61 (s, 2H, COCH₂Cl), 5.55 (s, 1H, ArOH), 7.62 (s, 2H, ArH); ir (KBr disc): 1660 (s, ketone); mass spec: m/e = 200, 198; 17, 52% of base peak at m/e = 149.

Anal. Calcd for C₁₀H₁₁O₂Cl: C, 60.46; H, 5.58; Cl, 17.83. Found: C, 60.68; H, 5.55; Cl, 18.02.

(5) Preparation of 2-Bromo-3',5'-dimethyl-4'-hydroxypropiophenone (II_{3b}).

3',5'-Dimethyl-4'-hydroxypropiophenone (II_{3a}) (79.6g, 0.446 mol), cupric bromide (200.0g, 0.892 mol), and 350 ml of dimethoxyethane were placed in a 1-l. 3-necked flask equipped with a mechanical stirrer, and a condenser containing a drying tube. A preheated (110°) bath was immediately raised and the solution was heated at reflux for 60 min.

The cooled solution was filtered to remove white cuprous bromide. The filtrate was diluted with 500 ml of ethyl acetate and washed with three 1 l. portions of water saturated with NaCl, dried over MgSO₄, filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 60°). The crude product, 113.3g (99%) of a dark brown solid, was recrystallized from 400 ml of benzene to yield 77.1g of grey crystals, which were then recrystallized from 150 ml of ethylene dichloride to yield 58.1g (50.6%) of white crystals:

mp 137 - 140.5°; nmr (CDCl₃): δ 1.87 (d, J = 6.7 Hz, 3H, CH₃), 2.30 (s, 6H, ArCH₃), 5.26 (q, J = 6.7 Hz, 1H, CHBr), 5.50 (s, 1H, ArOH), 7.69 (s, 2H, ArH); ir (KBr disc): 1660 (s, ketone); mass spec: m/e = 258, 256; 9.1, 9.9% of base peak at m/e = 149.

Anal. Calcd for C₁₁H₁₃O₂Br: C, 51.38; H, 5.10; Br, 31.08. Found: C, 51.21; H, 5.09; Br, 30.83.

(6) Preparation of 2-Bromo-2,3',5'-trimethyl-4'-hydroxypropio-
phenone (II_{4b}).

2,3',5'-Trimethyl-4'-hydroxypropio-phenone (II_{4a}) (96.1g, 0.50 mol), cupric bromide (223.4g, 1.00 mol), and 350 ml of dimethoxyethane were placed in a 1-l. 3-necked flask equipped with a mechanical stirrer and a condenser containing a drying tube. A preheated (110°) bath was immediately raised and the solution heated at reflux for 30 min.

The cooled solution was filtered to remove the white cuprous bromide. The filtrate was diluted with 500 ml of ethyl acetate and washed with three 1 l. portions of water saturated with NaCl, dried over MgSO₄, filtered, and the solvent was evaporated at reduced pressure with external heating (70°). The crude product, 137.5g (vs. 135.6g, theory, ca. 99%) of dark solid, was recrystallized from 100 ml of benzene and 400 ml of hexane to yield 19.8g (14.3% of pale grey crystals: mp 78.8 - 79.8°. The filtrate was concentrated and recrystallized from 250 ml of hexane to yield 65.5g (48.4%) of pale grey crystals: mp 78.5 - 79.8°. The total product was 85.3g (63.0%). Nmr (CDCl₃): δ 2.02 (s, 6H, CH₃), 2.29 (s, 6H, ArCH₃), 5.30 (s, 1H, ArOH), 7.86

(s,2H,ArH); ir (KBr disc): 1650 (s, ketone); mass spec: m/e = 272, 270; 1.3, 1.3% of base peak at m/e = 149.

Anal. Calcd for $C_{12}H_{15}O_2Br$: C, 53.16; H, 5.58; Br, 29.47. Found: C, 53.09, H, 5.30; Br, 29.56.

(7) Preparation of 2-Bromo-3',5'-dimethyl-4'-hydroxy-2-phenylacetophenone (II_{5b}).

3',5'-Dimethyl-4'-hydroxy-2-phenylacetophenone (120.2g, 0.50 mol), cupric bromide (223.4g, 1.00 mol), and 350 ml of dimethoxyethane were placed in a 1-l. 3-necked flask equipped with a mechanical stirrer and a condenser containing a drying tube. A preheated (110°) bath was immediately raised and the solution was heated at reflux for 60 min.

The cooled solution was filtered to remove white cuprous bromide. The filtrate was diluted with 750 ml of ether, washed with three 600 ml portions of water saturated with NaCl, dried over $MgSO_4$, filtered, and the solvent evaporated at reduced pressure with external heating (65°). The crude product, 157.1g (vs. 159.6g, theory, which contained approximately 8% solvent) of a brown solid, was recrystallized from 200 ml of benzene and 250 ml of hexane to yield 132.2g (83.0%) of pink crystals: mp 128 - 129°. An analytical sample was prepared by recrystallization of 10.0g from 20 ml of chloroform and 15 ml of hexane to yield 6.2g of cream colored crystals: mp 127.8 - 128.5°; nmr ($CDCl_3$): δ 2.25 (s,6H,ArCH₃), 5.57 (s,1H,ArOH), 6.38 (s,1H,COCHBr), 7.21 - 7.82 (multiplet, 5H, phenyl), 7.86 (s,2H,ArH); ir (KBr disc): 1650 (s, ketone); mass spec: m/e = 320, 318; 0.60, 0.55% of

base peak at $m/e = 149$.

Anal. Calcd for $C_{16}H_{15}O_2Br$: C, 60.21; H, 4.74; Br, 25.03. Found: C, 60.00; H, 4.52; Br, 24.94

(8) Preparation of 2-Bromo-3',5'-diethyl-4'-hydroxyacetophenone (III_{2b}).

2,6-Diethylphenol (III) (30.0g, 0.20 mol), aluminum chloride (26.7g, 0.20 mol), bromoacetyl bromide (40.4g, 0.20 mol), and a total of 125 ml of ethylene chloride were combined in exactly the manner of II_{2b}, p204, vide supra. The phenol was added over a period of 10 min to the solution. The solution was cooled and stirred for 300 min after addition of the phenol.

The dark red reaction mixture was added to 1 l. of water, and the organic material was extracted with 300 ml of methylene chloride. The organic layer was washed with two 1 l. portions of water, one 1 l. portion of water saturated with NaCl, dried over $MgSO_4$, filtered, and the solvent was evaporated at reduced pressure with external heating (65°). The crude product, 44.7g (by nmr: 28.3% starting phenol, 45.6% product, 15.2% ester, 10.9% ester-ketone) of purple solid, was recrystallized from 60 ml of benzene and 150 ml of hexane to yield 18.9g (34.8%) lavender crystals: mp 122.5 - 123.5°. An analytical sample was prepared by recrystallization from benzene and treatment with decolorizing carbon (Norit A) to yield pink crystals: mp 122.5 - 123.5°; nmr ($CDCl_3$): δ 1.26 (t, J = 7.0 Hz, 6H, CH_3), 2.70 (q, J = 7.0 Hz, 4H, CH_2), 4.41 (s, 2H, $COCH_2Br$), 5.65 (s, 1H, ArOH),

7.71 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone); mass spec: $m/e = 272, 270$; 13, 13% of base peak at $m/e = 177$.

Anal. Calcd for $C_{12}H_{15}O_2Br$: C, 53.16; H, 5.58; Br, 29.47. Found: C, 53.29; H, 5.67; Br, 29.69.

(9) Preparation of 2-Chloro-3',5'-diethyl-4'-hydroxyacetophenone (III_{2b}-C₁).

2,6-Diethylphenol (III) (30.0g, 0.20 mol), aluminum chloride (26.7g, 0.20 mol), chloroacetyl chloride (22.6g, 0.20 mol), and a total of 125 ml of ethylene chloride were combined in exactly the manner of II_{2b}, p 204, vide supra. The phenol was added over a period of 23 min to the solution. The solution was cooled and stirred for 300 min after the addition of the phenol.

The dark red solution was added to 1 l. of water, and the organic layer was extracted with 300 ml of methylene chloride. The organic layer was washed with two 1 l. portions of water, one 1 l. portion of water saturated with NaCl, dried over $MgSO_4$, filtered, and the solvent was evaporated at reduced pressure with external heating (62°). The crude product, 33.7g (by nmr: 55.6% starting phenol, 31.6% product, 4.2% ester, 8.4% ester ketone) of a brown solid, was recrystallized from 60 ml of benzene and 150 ml of hexane to yield 9.9g (21.8%) of tan crystals: mp 113.2 - 114.5°; nmr ($CDCl_3$): δ 1.25 (t, J = 7.0 Hz, 6H, CH_3), 2.66 (q, J = 7.0 Hz, 4H, CH_2), 4.63 (s, 2H, $COCH_2Cl$), 5.66 (s, 1H, ArOH), 7.64 (s, 2H, ArH); ir (KBr disc): 1660 (s, ketone); mass spec: $m/e = 228, 226$; 6.4, 18.3% of base peak at $m/e = 177$.

Anal. Calcd for $C_{12}H_{15}O_2Cl$: C, 63.58; H, 6.67; Cl, 15.64. Found: C, 63.80; H, 6.87; Cl, 15.80.

(10) Preparation of 2-Bromo-3',5'-diisopropyl-4'-hydroxy-acetophenone (IV_{2b}).

2,6-Diisopropylphenol (IV) (141.6g, 0.80 mol), aluminum chloride (107.4g, 0.80 mol), bromoacetyl bromide (161.6g, 0.80 mol), and a total of 500 ml of ethylene chloride were combined in exactly the manner of II_{2b}, p 204, vide supra. The phenol was added over a period of 18 min to the solution. The solution was cooled and stirred for 150 min after the addition of the phenol.

The dark red reaction mixture was added to 3 l. of ice-water, and the organic material was extracted with 500 ml of methylene chloride. The organic layer was washed with two 1 l. portions of water, one 1 l. portion of water saturated with NaCl, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure with external heating (56°). The molten crude product, 218.3g (by nmr: ca. 31.2% product), of purple liquid, was poured with continuous stirring into 1200 ml of petroleum ether (bp 30 - 60°) to yield 62.8g (26.9%) of lavender crystals: mp 104.8 - 105.5°. An analytical sample was prepared by recrystallization from chloroform and hexane (1:4) with treatment with decolorizing carbon (Norit A) to yield pink crystals: mp 105 - 106°; nmr ($CDCl_3$): δ 1.29 (d, $J = 7.0$ Hz, 12H, CH_3), 3.28 (septet, $J = 7.0$ Hz, 2H, CH), 4.46 (s, 2H, $COCH_2Br$), 6.31 (s, 1H, ArOH), 7.78 (s, 2H, ArH); ir

(KBr disc): 1650 (s, ketone); mass spec: m/e = 300, 298; 36.0, 37.0% of base peak at m/e = 205.

Anal. Calcd for $C_{14}H_{19}O_2Br$: C, 56.20; H, 6.40; Br, 26.71. Found: C, 56.47; H, 6.47; Br, 26.97.

(11) Preparation of 2-Chloro-3',5'-diisopropyl-4'-hydroxy-acetophenone (IV_{2b}-C₁).

2,6-Diisopropylphenol (IV) (71.3g, 0.40 mol), aluminum chloride (53.3g, 0.40 mol), chloroacetyl chloride (45.2g, 0.40 mol), and a total of 250 ml of dimethoxyethane were combined in exactly the manner of II_{2b,p} 20⁴, vide supra. The phenol was added over a period of 12 min to the solution. The reaction mixture was cooled and stirred for 360 min after phenol addition.

The dark red solution was added to 1 l. of ice-water, and the crude product was extracted with 250 ml of chloroform. The organic layer was washed with two 1 l. portions of water, one 1 l. portion of water saturated with NaCl, dried over $MgSO_4$, filtered, and the solvent was evaporated at reduced pressure with external heating (62°). The molten crude material, 89.1g of dark red liquid, was poured into 400 ml of petroleum ether (bp 30 - 60°) with continuous stirring to yield 40.0g (38.3%) of white crystals: mp 93.5 - 94.2°. An analytical sample was prepared by recrystallization from chloroform and hexane (1:5) to yield white crystals: mp 95 - 96°; nmr ($CDCl_3$): δ 1.28 (d, J = 7.0 Hz, 12H, CH_3), 3.22 (septet, J = 7.0 Hz, 2H, CH), 4.66 (s, 2H, $COCH_2Cl$), 5.83 (s, 1H, ArOH), 7.72 (s, 2H, ArH); ir (KBr disc): 1660 (s, ketone);

mass spec: $m/e = 256, 254; 4.0, 11.5\%$ of base peak at $m/e = 205$.

Anal. Calcd for $C_{14}H_{19}O_2Cl$: C, 66.01; H, 7.52; Cl, 13.92. Found: C, 66.28; H, 7.51; Cl, 14.20.

(12) Preparation of 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxy-acetophenone (V_{2b}).⁶²

3',5'-Di-tert.-butyl-4'-hydroxyacetophenone (V_{2a}) (15.3g, 0.0615 mol), phenyltrimethylammonium tribromide (29.2g, 0.0775 mol), and 500 ml of tetrahydrofuran were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer, and a condenser containing a drying tube. A pre-heated (38°) bath was raised immediately and heating was continued for 30 min.

The reaction mixture was filtered to remove the ammonium salt, the filtrate was concentrated under reduced pressure, and diluted with 400 ml of ether. The organic layer was washed with four 250 ml portions of water, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure at room temperature. The crude product, 30.0g of a purple solid, was recrystallized from 60 ml of hexane to yield 8.3g of pink crystals. This was recrystallized in turn from 40 ml of hexane to yield 5.7g (28.0%) of nearly white crystals: mp 104.5 - 105.1° (lit⁶² mp 95 - 97°); nmr ($CDCl_3$): δ 1.48 (s, 18H, CH_3), 4.36 (s, 2H, $COCH_2Br$), 5.88 (s,

(62) A. A. Volod'kin, N.V. Portnykh, and V.V. Ershov, Bul. Acad. Sci. USSR, 921 (1967).

1H,ArOH), 7.91 (s,2H,ArH); ir (KBr disc): 1680 (s, ketone); mass spec: $m/e = 328, 326$; 10, 10% of base peak at $m/e = 233$.

(13) Preparation of 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxy-propiophenone (V_{3b}).⁶²

3',5'-Di-tert.-butyl-4'-hydroxypropiophenone (V_{3a}) (56.5g, 0.216 mol), cupric bromide (96.1g, 0.431 mol), 216 ml of ethyl acetate and 144 ml of chloroform were placed in a 1-l. 1-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. A preheated (110°) bath was raised immediately and the solution heated at reflux for 75 min.

The crude solution was filtered to remove white cuprous bromide, and the solvent was evaporated at reduced pressure with external heating (ca. 55°). The crude product, 72.2g of brown solid, was treated with decolorizing carbon (Norit A) in 150 ml of chloroform and filtered. The solvent was concentrated by boiling, 50 ml of hexane were added dropwise, to yield grey crystals, which were recrystallized in turn from 60 ml of chloroform and 400 ml of hexane to yield white crystals, 42.2g (57.4%): mp 133.2 - 134.2° (lit⁶² mp 130 - 132°); nmr (CDCl₃): 1.50 (s,18H,CH₃), 1.89 (d, J = 7.0 Hz, 3H,CH₃), 5.33 (q, J = 7.0 Hz,1H,COCHBr), 5.86 (s,1H,ArOH), 8.00 (s,2H,ArH); ir (KBr disc): 1660 (s,ketone); mass spec: $m/e = 342, 340$; 12.0, 12.5% of base peak at $m/e = 233$.

Anal. Calcd for C₁₇H₂₅O₂Br: C, 59.83; H, 7.38; Br, 23.41. Found: C, 59.85; H, 7.37; Br, 23.54.

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(14) Preparation of 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxy-2-methylpropiophenone (V_{4b}).⁶²

3',5'-Di-tert.-butyl-4'-hydroxy-2-methylpropiophenone (V_{4b}) (80.0g, 0.290 mol), cupric bromide (149.0g, 0.666 mol), 333 ml of ethyl acetate and 222 ml of chloroform were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. A preheated (125°) bath was raised immediately and the solution was heated at reflux for 105 min.

The cooled solution was filtered to remove white cuprous bromide, and unreacted cupric bromide. The filtrate was concentrated under reduced pressure with external heating (ca. 60°). The crude product, 103.0g (100%) of brown solid, was dissolved in 500 ml of hexane and 100 ml of chloroform, treated with decolorizing carbon (Norit A), and the solvent concentrated to 400 ml. Cooling yielded 51.0g (49.5%) of white crystals: mp 141 - 142° (lit⁶² mp 138 - 139°); the filtrate was concentrated and recrystallized from 300 ml of hexane and 30 ml of chloroform to yield 33.8g (32.8%) of white crystals: mp 141 - 142°. The total product was 84.8g (82.4%) of white crystals. Nmr (CDCl₃): δ 1.48 (s, 18H, CH₃), 2.06 (s, 6H, CH₃), 5.76 (s, 1H, ArOH), 8.21 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone); mass spec: m/e = 356, 354; 1.8, 1.8% of base peak at m/e = 233.

Anal. Calcd for C₁₈H₂₇O₂Br: C, 60.85; H, 7.66; Br, 22.49. Found: C, 61.00; H, 7.73; Br, 22.47, 22.54.

(15) Preparation of 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxy-2-phenylacetophenone (V_{5b}).⁶²

3',5'-Di-tert.-butyl-4'-hydroxy-2-phenylacetophenone (V_{5a}) (18.9g, 0.0581 mol), cupric bromide (31.1g, 0.139 mol), 69.5 ml of ethyl acetate and 46.3 ml of chloroform were placed in a 300-ml 1-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. A pre-heated (125°) bath was raised immediately and the solution heated at reflux for 75 min.

The cooled solution was filtered to remove white cuprous bromide, and the filtrate was concentrated under reduced pressure with external heating (ca. 50°). The crude product, 24.5g of brown solid, was treated with decolorizing carbon (Norit A) in 150 ml of chloroform, filtered, and the filtrate concentrated to ca. 40 ml of solution. Addition of 30 ml of hexane and cooling produced 21.8g of pink crystals: mp 117.2 - 118°. This material was recrystallized from chloroform and hexane to yield 1.78g (9.4%) of white crystals, mp 118.5 - 119.5°, and the filtrate. The white crystals were recrystallized from chloroform and hexane to yield 0.93g of the analytical sample, mp 119.2 - 120.2° (lit⁶² mp 112 - 113°). The filtrate was evaporated and the residue was twice recrystallized from 400 ml of hexane to yield 13.84g (73.3%) of white crystals, mp 118.5 - 119.2°. The total product was 15.6g (82.6%) of white crystals. Nmr (CDCl₃): δ 1.43 (s, 18H, CH₃), 5.80 (s, 1H, ArOH), 6.40 (s, 1H, COCHBr), 7.24 - 7.74 (multiplet,

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5H,phenyl), 7.94 (s,2H,ArH); ir (KBr disc): 1675 (s, ketone);
mass spec: m/e = 404, 402; 0.05, 0.05% of base peak at m/e
= 233.

Anal. Calcd for $C_{22}H_{27}O_2Br$: C, 65.51; H, 6.75;
Br, 19.81. Found: C, 65.37; H, 6.79; Br, 19.98.

(16) Preparation of 2-Bromo-3',5'-di-tert.-butyl-4'-
hydroxybutyrophenone (V_{6b}).⁶²

3',5'-Di-tert.-butyl-4'-hydroxybutyrophenone (V_{6a})
(60.0g, 0.217 mol), cupric bromide (111.4g, 0.499 mol), 250
ml of ethyl acetate and 167 ml of chloroform were placed in
a 1-l. 1-necked flask equipped with a magnetic stirrer and
a condenser containing a drying tube. A preheated (180°)
bath was immediately raised and the solution heated at reflux
for 75 min.

The cooled solution was filtered to remove white
cuprous bromide, and the filtrate was concentrated under
reduced pressure with external heating (ca. 50°). The crude
product, 81.2g (vs. 79.6g, theory, for 15% dibromo and 85%
monobromo products) of a dark solid, was dissolved in 300 ml
of chloroform and 300 ml of hexane, treated with decolorizing
carbon (Norit A), and the solvent was evaporated to yield
77.8g of pink crystals, mp 113 - 123°. The crude material
was twice recrystallized from 500 ml of hexane to yield 52.2g
(79.8%) of white crystals; mp 125.8 - 126.8° (lit⁶² mp 120 -
122°); nmr ($CDCl_3$): δ 1.08 (t, J = 7.0 Hz, 3H, CH_3), 1.50

(s, 18H, CH₃), 2.22 (pentet, J = 7.0 Hz, 2H, CH₂), 5.10 (t, J = 7.0 Hz, 1H, COCHBr), 5.86 (s, 1H, ArOH), 7.99 (s, 2H, ArH); ir (KBr disc): 1650 (s, ketone); mass spec: m/e = 356, 354; 2.7, 2.7% of base peak at m/e = 233.

Anal. Calcd for C₁₈H₂₇O₂Br: C, 60.85; H, 7.66; Br, 22.49. Found: C, 60.84; H, 7.63; Br, 22.49.

(17) Preparation of 2-Bromo-3',5'-dichloro-4'-hydroxypropiophenone (VI_{3b}).

3',5'-Dichloro-4'-hydroxypropiophenone (VI_{3a}) (65.7g, 0.30 mol), cupric bromide (134.0g, 0.60 mol), and 210 ml of dimethoxyethane were placed in a 500-ml 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. A preheated (140°) bath was immediately raised and the solution heated at reflux for 50 min.

The cooled solution was filtered to remove white cuprous bromide. The filtrate was diluted with 460 ml of ether and 190 ml of ethyl acetate, washed with three 500 ml portions of water, dried over MgSO₄, filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 70°). The crude product, 82.7g (92.5%) of white solid, was dissolved in 450 ml of boiling benzene, filtered, and recrystallized to yield 62.3g (69.6%) of cream-colored crystals; mp 144.5 - 145.2°; nmr (acetone-d₆ plus CDCl₃): δ 1.85 (d, J = 6.0 Hz, 3H, CH₃), 5.25 (q, J = 6.0 Hz, 1H, COCHBr), 5.55 (s, 1H, ArOH), 7.90 (s, 2H, ArH); ir (KBr disc): 1680 (s, ketone); mass spec:

$m/e = 302, 300, 298, 296; 3, 13.2, 25,$ and 13.5% of base peak at $m/e = 189$.

Anal. Calcd for $C_9H_7O_2BrCl_2$: C, 36.28, H, 2.37; Br, 26.82; Cl, 23.80. Found: C, 36.05; H, 2.25; Br, 26.60; Cl, 23.81.

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(E) Preparation of Benzylic Alcohols.

(1) Preparation of 1-(3',5'-Dimethyl-4'-hydroxyphenyl)
ethanol (II_{2f}).

Sodium hydride (4.2g of a 57% dispersion in mineral oil, 0.10 mol) and 200 ml of tetrahydrofuran were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer, a 150-ml pressure-equalizing dropping funnel and a condenser containing a drying tube. 3',5'-Dimethyl-4'-hydroxyacetophenone (II_{2a}) (16.4g, 0.10 mol) dissolved in 125 ml of tetrahydrofuran were added over a period of 11 min to the sodium hydride, resulting in a bright lavender solution. Stirring was continued for 13 min. To the solution was added trimethylsilyl chloride (10.9g, 0.10 mol) diluted with 20 ml of tetrahydrofuran, over a period of 10 min. The solution was stirred for 120 min at room temperature. During this time the color changed to golden yellow and a considerable amount of white salt precipitated (NaCl). Sodium methoxyethoxy aluminum hydride⁵⁹ (28 ml of 70% solution in benzene, 0.050 mol) diluted to 55 ml with tetrahydrofuran was added over a period of 18 min. The almost colorless solution was stirred for 120 min.

The solution was cooled, 50 ml of water were added over a period of 5 min, followed by 100 ml of 2.4M HCl. The solution was stirred for 23 hrs, then added to 1 l. of ether and 1 l. of water. The organic layer was washed with

three 1 l. portions of water, dried over MgSO_4 , filtered, and the solvent evaporated at reduced pressure with external heating (70°). The crude product was recrystallized from 50 ml of chloroform and 125 ml of petroleum ether (bp $30 - 60^\circ$) to yield 2.7g (16.2%) of white crystals, mp $106.5 - 108^\circ$. An analytical sample was prepared by recrystallization from benzene: mp $107.5 - 108.5^\circ$; nmr (CDCl_3): δ 1.47 (d, $J = 7.0$ Hz, 3H, CH_3), 1.90 (s, 1H, ROH), 2.26 (s, 6H, ArCH_3), 4.80 (q, $J = 7.0$ Hz, 1H, CH), 4.82 (s, 1H, ArOH), 7.05 (s, 2H, ArH); ir (KBr disc): 3700, 3300 (s, OH), 1070 (m, benzylic OH); mass spec: $m/e = 166$; 53% of base peak at $m/e = 151$.

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2$: C, 72.26; H, 8.49.
Found: C, 72.34; H, 8.53.

(2) Preparation of 1-(3',5'-Dichloro-4'-hydroxyphenyl)ethanol (VI_{2f}).

3',5'-Dichloro-4'-hydroxyacetophenone (VI_{2a}) (20.5g, 0.10 mol), 200 ml of ether and 100 ml of tetrahydrofuran were placed in a 1-l. 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. Lithium aluminum hydride (11.38g, 0.30 mol) was added, in portions, to the solution, followed by 20 ml of tetrahydrofuran. A preheated (90°) bath was raised, and the solution heated at reflux for 24 hrs.

The solution was cooled, 60 ml of ethyl acetate were added over a period of 15 min, and the system was heated at

reflux for an additional 120 min. The solution was cooled, 150 ml of water were added over a period of 15 min, followed by 500 ml of 2.4M HCl. The organic layer was separated, the aqueous layer was extracted with 200 ml of ether, and the organic layers were combined. The organic layer was washed with three 300 ml portions of water, dried over MgSO_4 , filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 40°). The product, 16.1g of a white solid (by nmr: 75% product, 25% alkane (VI_{2d})), was recrystallized from 200 ml of chloroform to yield 9.6g (46.4%) of white crystals: mp $137.8 - 138.2^\circ$; nmr (acetone- d_6): δ 1.43 (d, $J = 6.2$ Hz, 3H, CH_3), 4.40 (s, 1H, ROH), 4.86 (q, $J = 6.2$ Hz, 1H, CH), 7.38 (s, 2H, ArH), 8.59 (s, 1H, ArOH); ir (KBr disc): 3600, 3400 (s, OH), 1065 (s, benzylic OH); mass spec: $m/e = 210, 208, 206; 3, 25, 38\%$ of base peak at $m/e = 191$.

Anal. Calcd for $\text{C}_8\text{H}_8\text{O}_2\text{Cl}_2$: C, 46.41; H, 3.89; Cl, 34.24. Found: C, 46.23; H, 3.74; Cl, 34.37.

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(F) Reduction of 2-Haloketones and Ketones. Identification of the Products.

(1) Reduction of 2-Bromo-4'-hydroxyacetophenone (I_{2b}).

(a) Reduction with LiAlH₄.

2-Bromo-4'-hydroxyacetophenone (2.1504g, 0.0100 mol) was placed in a 300-ml 3-necked flask equipped with a magnetic stirrer and a condenser containing a drying tube. Ninety ml of anhydrous ether (Baker Analyzed, typical analysis: 0.005% alcohols as ethanol, 0.006% water, 0.0002% acids as acetic acid) was placed into the flask. The ether was stirred until solution was effected. Lithium aluminum hydride (0.8550g, 0.225 mol) (Atomergic Chemetals Co., Div. of Gallard-Schlesinger Chem. Mfg. Corp., Carle Place, Long Island, N. Y. 11514. Supplied as a finely powdered white solid.) was added all-at-once into the vortex of the rapidly stirred solution, followed immediately by 10 ml of anhydrous ether. The solution was stirred for three min. The addition of LiAlH₄ caused bubbling (H₂) within seconds which was followed by the transformation of the clear solution to a paste of white particles rendering the stirrer ineffective. This became a yellow paste lasting about 60 seconds, at which point the ether began boiling vigorously and the yellow paste became mass of fine white particles. The stirrer was once again able to mix the contents. This sequence was always observed in the reduction of the haloketones, differing only in the violence of the initial hydrogen evolution, the length of time to reach the

highly colored paste, and the duration of said color.

The flask was transferred to a preheated (62°) bath, and heated at reflux for 360 min.

The flask was cooled for 5 min, immersed in an ice-water bath and further cooled for 5 min. Ten ml of water were added, cautiously, to the stirred solution. The ice-water bath was removed, and the solution was stirred at room temperature for 5 min. The aluminum salts were hydrolyzed by the addition of 150 ml of 2.4M HCl, and the two phases were stirred until the turbidity disappeared (ca. 10 min).

The contents of the flask were placed in a 1-l. separatory funnel and diluted with 100 ml of ether and 100 ml of water. NaCl was added to saturation. The layers were separated, and the aqueous phase was extracted with one 200 ml portion of ether. The ether layers were combined and washed with one 400 ml portion of water saturated with NaCl. The organic layer was dried over MgSO_4 , filtered and the solvent was evaporated at reduced pressure with external heating (ca. 60°).

The crude product, 1.1517g (93.6% molar recovery) of purple oil, appeared to be 91% alkane, I_{2d} , and 9% dimers (by nmr).

(b) Other Reductions with LiAlH_4 .

The reduction of this compound was repeated a number of times, in exactly the manner of (a), above, with the results listed in Table I, entries 1 - 5.

(c) Identification of the Products.

The crude product mixtures of entries 1, 2 and 5 of Table I were combined to yield ca. 4.5g of material for dry column chromatography.⁶³ The mixture was dissolved in acetone, and placed in a flask with 2.5 times its weight (11.0g) of silica gel (Woehlm, Activity Grade III, for dry column chromatography, available from Waters Associates, Inc., 61 Fountain Street, Framingham, Mass. 01701). The solvent was evaporated under reduced pressure with external heating (40°) until the material was a freely-flowing powder. This was the feedstock for the column.

The column was prepared by cutting a 150 cm length of 2½" flat diameter nylon tubing (M & Q Plastic Products, 1 Court House Square, Freehold, N. J. 07728). A 3 cm plug of glass wool was placed into one end of the tubing and moved sufficiently into the tubing to allow this end to be folded three times, 1 cm per fold. The fold was stapled shut and the glass wool pushed to the closed end. The nylon tubing was pierced about 15 times with a pin only in the region of the glass wool plug - to allow air to escape. The tubing was opened from the other end, 2 cm of sand were added and leveled, and 700g of silica gel (Woehlm, Activity Grade III) were added, in portions. The tube was gently bounced vertically during the addition of the silica gel. The length of tubing required to contain the 700g of silica gel was approximately

(63) B. Loev and M. M. Goodman, Chem. Ind. 2026 (1967).

100 cm. The silica gel was covered with a 1 cm layer of sand, the feedstock layer of silica gel, and a final 1 cm layer of sand. The whole assembly was mounted with the bottom in a clean glass dish and held vertical by three 3-pronged clamps. The clamps were used for alignment and were not shut tightly in order to avoid crushing the column. The surplus nylon tubing, beyond the 5 cm needed to hold the solvent safely, was cut off.

A 1-l. separatory funnel was mounted above the top of the column, with a 3 cm pressure head of ethylene chloride thereby maintained. The elution time was 89 min until the ethylene chloride was about 3 cm from the end of the silica gel, at that time further addition of solvent was stopped and the solvent above the top of the sand was allowed to drain to the center of the uppermost layer of sand.

The column was stapled shut at the top, placed on its side and cut with a sharp razor into 6 cm segments, starting at the sand layer below the feedstock. The segment immediately below the feedstock was labeled fraction 1 (Fr 1) and so on to the last segment which ended in glass wool and sand. The segments were placed in 400 ml beakers and covered to slow the evaporation of solvent, and to keep out dust. Each segment was placed into a Buchner funnel, and the organic material present was leached by treatment with three 100 ml portions of ether. The filtrate was dried over MgSO_4 , filtered, and the solvent was evaporated at reduced pressure with external heating (ca. 75°).

Fr 1: 0.5406g, solid, ca. 50% I_{2h}, 50% I_{2n};
Fr 2: 0.2578g, solid, ca. 100% I_{2n}; Fr 3: 0.0219g, solid,
ca. 100% I_{2n}; Fr 4: nil; Fr 5: 0.0333g, liquid, 100% I_{2d};
Fr 6: 0.2973g, liquid, 100% I_{2d}; Fr 7: 0.8739g, liquid,
100% I_{2d}; Fr 8: 0.9011g, liquid, 100% I_{2d}; Fr 9: 0.1674g,
liquid, 100% I_{2d}; Fr 10 - 16: nil. (Analyses by nmr).
Recovered wt: 3.0933g, 69% recovered.

Fr 5 - 9 (2.273g, 0.0186 mol) inclusive were dissolved in acetone, combined, and the solvent evaporated at reduced pressure with external heating (60°) to yield 2.00g for purification. The 4-ethylphenol (I_{2d}) was observed to have sublimed into the Kjeldahl bulb during this operation and whenever it was heated. The crude I_{2d} was purified by sublimation: 67° (0.4 Torr) to yield 1.3g (65% recovery) mp: 45 - 46° (lit⁶⁴ mp 45 - 46°); nmr (CDCl₃): δ 1.33 (t, J = 7.0 Hz, 3H, CH₃), 2.56 (q, J = 7.0 Hz, 2H, CH₂), 6.10 (s, 1H, ArOH), 6.68, 6.84, 6.99, 7.14 (AA'BB', 4H, ArH); ir (KBr): 1460, 1360 (m, CH₃); mass spec: m/e = 122; 100% of base peak at m/e = 122.

Fr 2 and 3 (0.2797g, 0.00107 mol) are identified as I_{2n} by the nmr spectra; but were not further characterized. Nmr (CDCl₃ plus acetone-d₆): δ 1.13 (t, J = 7.0 Hz, 3H, CH₂CH₃), 1.53 (d, J = 7.0 Hz, 3H, CHCH₃), 2.49 (q, J = 7.0 Hz, 2H, CH₂), 4.41 (q, J = 7.0 Hz, 1H, CH), 6.59-7.36 (multiplet, 8H, ArH), 7.56 (s, 1H, ArOH).

(64) G. Baddeley, J. Chem. Soc., 330 (1944).

Fr 1 appeared to contain some I_{2n} estimated at not more than one third. The remainder might be I_{2h} . The distinctive nmr peaks of I_{2h} are the two triplets of $ArO\text{CH}_2\text{CH}_2Ar$: nmr ($CDCl_3$ plus acetone- d_6): δ 3.85 (distorted triplet, $J = 7$ Hz, 2H, CH_2O), and 2.75 (distorted triplet, $J = 7$ Hz, ca. 2H, CH_2). The latter CH_2 partly overlaps the CH_2 of the $Ar\text{CH}_2\text{CH}_3$ signal of I_{2d} . The assignment of this fraction was complicated by the presence of a signal at 3.2 typical of ROH.

The product distribution in mole % was: 85.6% I_{2d} ; 8.1% I_{2n} ; and 6.3% I_{2h} . The molar recovery was 59.3%.

(2) Reduction of 2-Bromo-4'-hydroxypropiophenone (I_{3b}).

(a) Reduction with $LiAlH_4$.

2-Bromo-4'-hydroxypropiophenone (I_{3b}) (3.4359g, 0.0150 mol), lithium aluminum hydride (1.2833g; 0.0338 mol), and a total of 150 ml of anhydrous ether were combined for the reduction in exactly the manner of I_{2b} , p 223. The crude product was 1.9723g of dark brown oil. The nmr spectrum indicated ca. 80% I_{3c} ($C_9H_{12}O_2$) as product. Assuming a molecular formula of $C_9H_{12}O_2$, the molar recovery was 86.4%.

(b) Other reductions with $LiAlH_4$.

The reduction was repeated with the results listed in Table I, entries 6 - 8.

(c) Identification of the Products.

The crude product mixtures of entries 6 and 7 of Table I were combined to yield 4.0707g of material for dry

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column chromatography in exactly the manner of 1c, p 225 .
Conditions: 700g silica gel for column; eluting solvent:
chloroform; elution time: 83 min; pressure head; 4 cm.

Fr 1: 2.6658g, solid, ca. 100% I_{3c} ; Fr 2: 0.3843g
liquid, complex mixture; Fr 3: 0.0984g, liquid, ca. 100%
 I_{3d} ; Fr 4 - 15: nil. (Analyses by nmr.) Recovered wt:
3.1485g, 77.3%.

Fr 1 (2.6658g, 0.0175 mol), I_{3c} , was recrystallized
from 100 ml of chloroform and 100 ml of hexane to yield 1.1g
(41.3% recovery) of white solid; mp 96.8 - 100°; nmr ($CDCl_3$
plus acetone- d_6): δ 1.23 (d, J = 7.0 Hz, 3H, CH_3), 2.60 - 2.94
(multiplet, 1H, CH), 3.59 (d, J = 6 Hz, 2H, CH_2O), 3.64 (s, 1H, ROH),
6.65, 6.80, 7.00, 7.15 (AA'BB', 4H, ArH), 7.92 (s, 1H, ArOH);
ir (KBr disc): 1460, 1360 (m, CH_3), 1035 (s, primary ROH);
mass spec: m/e = 152; 13.7% of base peak at m/e = 121. The
material was not further characterized.

Fr 3 (0.0984g, 0.0072 mol) was assigned as I_{3d}
from the nmr spectrum: nmr ($CDCl_3$): δ 0.90 (t, J = 7.0 Hz, 3H,
 CH_3), 1.27 - 1.88 (multiplet, 2H, CH_2), 1.67 (t, J = 7.0 Hz, 2H,
Ar CH_2), 5.53 (s, 1H, ArOH), 6.63, 6.76, 6.84, 7.07 (AA'BB', 4H, ArH).
The material was not further characterized.

Fr 2, 0.3843g, appeared to contain I_{3d} and I_{3c} and
could not be quantitated due to the complexity of the mixture.
The difficulty was caused by extra signals possibly due to
dimeric materials e.g., I_{3h} , and also the benzylic alcohol,
 I_{3f} .

The total product distribution was approximately 84.5% I_{3c} , 12.2% unassigned, and 3.5% I_{3d} . The total recovery was 77.5%.

(3) Reduction of 2-Bromo-3',5'-dimethyl-4'-hydroxyacetophenone (II_{2b}).

(a) Reduction with $LiAlH_4$.

2-Bromo-3',5'-dimethyl-4'-hydroxyacetophenone (II_{2b}) (2.4312g, 0.0100 mol), lithium aluminum hydride (0.8558g, 0.0225 mol), and a total of 100 ml of anhydrous ether were combined for the reduction in exactly the manner of I_{2b} , p 223. The crude product was 1.5223g of purple liquid. The nmr spectrum indicated ca. 34.4% II_{2c} and 65.6% II_{2d} (98.6% recovery based on an average molecular weight of 154.1).

(b) Other Reductions with $LiAlH_4$.

The reduction was repeated several times with the results listed in Table II, entries 1 - 3.

(c) Identification of the Products.

The crude product mixtures of entries 1 and 2 of Table II were combined to yield 2.95g of material for dry column chromatography in exactly the manner of 1c, p 225. Conditions: 700g silica gel for column; eluting solvent: ethylene chloride; elution time: 95 min; pressure head: 2 cm.

Fr 1: 0.4877g, solid, 100% II_{2c} ; Fr 2: 0.3567g, solid, 100% II_{2c} ; Fr 3: 0.0938g, oil, trace II_{2a} , ca. 14% II_{2c} and 86% II_{2h} ; Fr 4 - 9: nil; Fr 10: 0.1538g, liquid,

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II_{2d}; Fr 11: 0.5027g, liquid, II_{2d}; Fr 12: 0.5779g, liquid, II_{2d}; Fr 13: 0.2156g, liquid, II_{2d}; Fr 14 - 16: nil. (Analyses by nmr.) Recovered wt: 2.3882g, 81.0%.

Fr 1 and 2 (0.8444g), II_{2c}, were combined and purified by sublimation: 110° (6 Torr) to yield 0.75g (89% recovery) of white crystals. This material was recrystallized from 10 ml of chloroform and 10 ml of hexane to yield 0.4g of white crystals: mp 64.0 - 64.5°; nmr (CDCl₃) δ 1.93 (s, 1H, ROH), 2.16 (s, 6H, ArCH₃), 2.67 (t, J = 7.0 Hz, ArCH₂), 3.75 (t, J = 7.0 Hz, CH₂O), 5.08 (s, 1H, ArOH), 6.79 (s, 2H, ArH); ir (KBr disc): 1480, 1370 (m, CH₃), 1065 (s, primary ROH); mass spec: m/e = 166; 20% of base peak at m/e = 135.

Anal. Calcd for C₁₀H₁₄O₂: C, 72.26; H, 8.49. Found: C, 72.05; H, 8.55.

Fr 3 was characterized by nmr as consisting of ca. 84% of the dimer, II_{2h}; nmr (CDCl₃): δ 1.40 (d, J = 6 Hz, CH₃), 2.22 (s, 12H, ArCH₃), 2.74 (distorted triplet, J = 7 Hz, 2H, ArCH₂), 3.46 (distorted triplet, J = 7 Hz, 2H, CH₂O), 4.31 (q, J = 6 Hz, 1H, CH), 4.83 (broad s, 2H, ArOH), 6.81 (s, 2H, ArH) of ArCH₂), 6.92 (s, 2H, ArH of ArCHO-). The material was not further characterized. This fraction consisted of 84% II_{2h} and 16% II_{2d}.

Fr 10 - 13 (1.4500g, 0.00966 mol), II_{2c}, were combined and purified by sublimation: 50° (0.20 Torr) to yield 1.1g (76% recovery) of white solid. The nmr spectrum confirms the material as the alkane, II_{2c}, but also shows ca. 2.2%

of this to be II_{2p} ; the alkyl bromide, and/or II_{2g} , the symmetrical dimeric ether. The characteristic nmr peaks for these compounds are the distorted triplet at 3.4 -- due to CH_2Br or CH_2O . The mass spectrum confirms the alkane, II_{2c} , the alkyl bromide, II_{2p} , ($m/e = 228, 230$), and the dimer, II_{2g} , ($m/e = 314$). The mass spectrum doesn't allow assessment of the relative amounts of II_{2g} and II_{2p} , but the lithium aluminum deuteride reduction (see below) does, from which it appeared that most of the minor component was II_{2p} .

The total product distribution was: 34.2% II_{2c} ; 1.4% II_{2h} ; 62.6% II_{2d} ; 1.7% II_{2p} and II_{2g} . The total molar recovery was 79.4%.

(d) Reduction with LiAlD_4 .

2-Bromo-3',5'-dimethyl-4'-hydroxyacetophenone (II_{2b}) (2.4315g, 0.0100 mol), lithium aluminum deuteride (1.2445g, 0.0296 mol) (Merck, Sharp and Dohme of Canada, Ltd., min assay 99.8% D) and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b} , p 223. The crude product was 1.5404g of red liquid. The nmr spectrum indicated ca. 32.6% II_{2c} and 67.4% II_{2d} (96.5% recovery based on an average molecular weight of 158.1).

(e) Other Reductions with LiAlD_4 .

The reduction was repeated with the results listed in Table II, entries 4 and 5.

(f) Identification of the Products.

The crude product mixtures of entries 5 and 6 of Table II were combined to yield 3.07g of material for dry column chromatography in exactly the manner of 1c, p 225. Conditions: 420g of silica gel for column; eluting solvent: ethylene chloride; elution time: 48 min; pressure head: 3.5 cm.

Fr 1: 0.7694g, liquid, II_{2c}; Fr 2: 0.0816g, liquid, II_{2c} and a trace of II_{2a}; Fr 3 - 5: nil; Fr 6: 0.0477g, liquid, II_{2d}; Fr 7: 0.5991g, liquid, II_{2d}; Fr 8: 0.7643g, liquid, II_{2d}; Fr 9: 0.2091g, liquid, II_{2d}; Fr 10: nil. (Analyses by nmr.) Recovered wt: 2.4712g, 80.4%.

Fr 1, 0.7694g, II_{2c}, was purified by sublimation: 135° (4 Torr) to yield white crystals, which were recrystallized from 10 ml of chloroform and 30 ml of hexane to yield 0.45g (58% recovery) of white crystals: mp 63.8 - 64.2°; nmr (CDCl₃): δ 1.82 (s, 1H, ROH), 2.16 (s, 6H, ArCH₃), 2.66 (broad s, 2H, ArCH₂), 5.00 (s, 1H, ArOH), 6.76 (s, 2H, ArH); ir (KBr disc): 2180, 2080 (w, CD), 1460, 1360 (m, CH₃), 1065 (m, primary ROH); mass spec: m/e = 168; 21% of base peak at m/e = 135. The nmr spectrum did not show a peak at 2.8 for ArCD₂CH₂OH. Unfortunately, the deuterated II_{2h} was not discernible in Fr 1, nor Fr 2 - 4.

Fr 7 - 9, 1.5725g, were combined and purified by sublimation: 75° (2.4 Torr) to yield 1.4g (89% recovery) of white crystals: mp 36.1 - 37.1°; nmr (CDCl₃): δ 1.13 (broad s, 2H, CH₂D), 2.15 (s, 6H, ArCH₃), 4.54 (s, 1H, ArOH), 6.74

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(s, 2H, ArH); ir (KBr disc): 2200, 2130 (w, CD), 1480, 1380 (m, CH₃); mass spec: $m/e = 153$; 7% of the base peak at $m/e = 137$. The alkane fractions contain 2.2% of a mixture of II_{2p} and II_{2g} as determined by the nmr integration of the 3.4 peak (ArCD₂CH₂Br). There appeared to be very little II_{2g}, which would have a 3.4 peak (ArCH₂CD₂OCH₂CD₂Ar) but also a 2.8 peak, and the latter was not discernible. However, the mass spectrum confirmed the dimer ($m/e = 318$), as well as the alkyl bromide, II_{2p} ($m/e = 230, 232$).

The total product distribution was: 32.4% II_{2c}; 66.1% II_{2d}; 1.5% II_{2p} and II_{2g}. The total moles recovered were 81.0%.

(g) Reduction with LiAlH₄ for Short Periods of Time. An Attempt to Produce the Bromohydrin, II_{2e}, with LiAlH₄.

2-Bromo-3',5'-dimethyl-4'-hydroxyacetophenone (II_{2b}) (2.4311g, 0.0100 mol), lithium aluminum hydride (0.8590g, 0.0225 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The reaction time was 2 min, and the ether was refluxing within the first minute. After 2 min the flask was immersed in an ice bath and 25 ml of 2.4M HCl were added cautiously. An additional 100 ml of 2.4M HCl were added and the usual treatment was followed.

The solvent was evaporated at reduced pressure (water aspirator) for 45 min, with external heating to 67°.

The crude product was concentrated to a dark yellow fluid, until the last few minutes of heating the fluid only darkened. When observed again, the crude product had become an opaque purple oil which evolved white fumes. The flask was removed, and the fumes gave an acid response to pH paper. The crude weight was 1.9421g. The nmr spectrum (CDCl_3) displayed no absorption for the starting material at δ 7.7, but had aromatic H at 6.8 (primary alcohol, II_{2c} , and alkane, II_{2d}). There was no absorption at ca. δ 5.0 ($\text{ArCH(OH)CH}_2\text{Br}$) nor at ca. 4.0 ($\text{ArCH(OH)CH}_2\text{Br}$). The crude material was not further characterized.

(4) Reduction of 2-Chloro-3',5'-dimethyl-4'-hydroxyacetophenone (II_{2b-C1}).

(a) Reduction with LiAlH_4 .

2-Chloro-3',5'-dimethyl-4'-hydroxyacetophenone (II_{2b-C1}) (1.9873g, 0.0100 mol), lithium aluminum hydride (0.8550g, 0.0225 mol) and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b} , p 223. The crude product, 1.4962g was a green viscous liquid. The nmr spectrum indicated ca. 53.1% II_{2c} , 34.3% II_{2d} , and 12.5% II_{2p-C1} (91.6% recovery based on an average molecular weight of 163.3).

(b) Other Reductions with LiAlH_4 .

The reduction was repeated with the results listed in Table II, entries 6 and 7.

(c) Identification of the Products.

The crude product mixtures of entries 6 and 7 of Table II were combined to yield 2.9868g of material for dry column chromatography in exactly the manner of 1c, p 225. Conditions: 700g silica gel for column; eluting solvent: methylene chloride; elution time: 66 min; pressure head: 3 cm.

Fr 1: 0.6244g, liquid, II_{2c} ; Fr 2: 0.8569g, liquid, II_{2c} ; Fr 3: 0.0890g, liquid, II_{2q-C1} ; Fr 4: 0.0633g, liquid, II_{2q-C1} and a trace of II_{2a} ; Fr 5 - 11: nil; Fr 12: 0.0481g, liquid, 40% II_{2d} and 60% II_{2p-C1} ; Fr 13: 0.3416g, liquid, 25% II_{2d} and 75% II_{2p-C1} ; Fr 14: 0.4113g, liquid, 64% II_{2d} and 36% II_{2p-C1} ; Fr 15 - 18: nil. (Analyses by nmr.) Recovered wt: 2.4346g, 81.5%.

Fr 1 and 2, II_{2c} , 1.4813g, 0.00890 mol were combined and purified by sublimation: 136° (0.6 Torr) to yield 0.90g of white crystals. This was recrystallized from 10 ml of chloroform and 20 ml of hexane to yield white crystals; mp $64.2 - 64.8^{\circ}$. The nmr spectrum confirmed this material as the primary alcohol, II_{2c} .

Fr 3 and 4 were assigned the structure II_{2q-C1} on the basis of the nmr spectrum. Nmr (CDCl_3): δ 2.18 (s, 12H, ArCH_3), 2.72 (distorted triplet, $J = 6.5$ Hz, 2H, ArCH_2), 3.38 - 3.62 (multiplet, 4H, CH_2O and CH_2Cl), 4.30 (distorted triplet, $J = 6.5$ Hz, 1H, CH), 4.55 (s, 1H, ArOH of ArCH_2), 4.75 (s, 1H, ArOH of ArCHO-), 6.75 (s, 2H, ArH of ArCH_2), 6.81 (s, 2H, ArH of ArCHO-). The material was not further characterized.

Fr 12 - 14 were characterized by the nmr spectrum which showed the alkane, II_{2d}, and the alkyl chloride, II_{2q-C1}. The latter had the following nmr spectrum, with the peaks taken from the mixture; nmr (CDCl₃): δ 2.17 (s, 6H, ArCH₃), 2.80 distorted triplet, J = 7.5 Hz, 2H, ArCH₂), 3.53 (distorted triplet, J = 7.5 Hz, 2H, CH₂Cl), 4.75 (s, 1H, ArOH), 6.74 (s, 2H, ArH). The presence of both compounds was confirmed by the mass spectrum of the mixture; mass spec: m/e = 184, 186 (II_{2p-C1}); 14.4, 4.6% of base peak at m/e = 135, and m/e = 150 (II_{2d}); 1.25% of base peak. The mixture was not resolved into the components.

The total product distribution was: 64.0% II_{2c}; 15.8% II_{2d}; 17.1% II_{2p-C1}; 3.2% II_{2q-C1}. The molar recovery was 78.3%.

(5) Reduction of 2-Bromo-3',5'-dimethyl-4'-hydroxypropio-phenone (II_{3b}).

(a) Reduction with LiAlH₄.

2-Bromo-3',5'-dimethyl-4'-hydroxypropio-phenone (II_{3b}) (2.5728g, 0.0100 mol), lithium aluminum hydride (0.8552g, 0.0225 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The crude product was 1.7413g of grey solid. The nmr spectrum indicated essentially 100% II_{3c}, the primary alcohol (96% recovery).

(b) Other Reductions with LiAlH₄.

The reduction was repeated several times with the results listed in Table III, entries 1 - 4. The only noteworthy change is for entry 4, the four minute reduction. For all reductions of less than 9 min, the reaction time was counted from the time of lithium aluminum hydride addition. The cooling period was altered to a 1 min immersion in an ice-water bath, followed by rapid addition of the water. The work-up remained the same.

(c) Identification of the Products.

The crude product of entries 1, 2 and 3 of Table III were combined (5.1g) and recrystallized from 25 ml of benzene to yield the analytical sample: 1.3g (25.5% recovery); mp 78.0 - 78.5°; nmr (CDCl₃): δ 1.20 (d, J = 7 Hz, 3H, CH₃), 1.85 (s, 1H, ROH), 2.20 (s, 6H, ArCH₃), 2.79 (sextet, J = 7H, 1H, CH), 3.61 (d, J = 7Hz, 2H, CH₂O), 5.00 (s, 1H, ArOH), 6.80 (s, 2H, ArH); ir (KBr disc): 1460, 1370 (m, CH₃), 1035 (s, primary ROH); mass spec: m/e = 180; 33% of base peak at m/e = 149.

Anal. Calcd for C₁₁H₁₆O₂: C, 73.30; H, 8.95.
Found: C, 73.16; H, 9.03.

The filtrate was evaporated and recrystallized from 23 ml of benzene and 40 ml of hexane to yield 2.4g of white crystals, mp 76.8 - 77.5°, also the primary alcohol, II_{3c}. The last filtrate, 1.1g (20% of original material), shows in the nmr spectrum a doublet at 1.6 which might be

the CHBrCH_3 of the alkyl bromide, II_{3p} , or the bromohydrin, II_{3e} . This was less than one-fifth of the total or less than 4% of the original product mixture. This additional product was not otherwise identified.

(6) Reduction of 2-Bromo-2,3',5'-trimethyl-4'-hydroxypropiophenone (II_{4b}).

(a) Reduction with LiAlH_4 .

2-Bromo-2,3',5'-trimethyl-4'-hydroxypropiophenone (II_{4b}) (2.7121g, 0.0100 mol), lithium aluminum hydride (0.8583g, 0.0226 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b} , p 223. The crude product was 1.8785g of white solid. The nmr spectrum indicated essentially 100% II_{4c} , the primary alcohol (96.7% recovery).

(b) Other Reductions with LiAlH_4 .

The reduction was repeated several times with the results listed in Table III, entries 5 - 8.

(c) Identification of the Products.

The crude products of entries 6, 7 and 8 of Table III were combined (7.5g) and recrystallized from 60 ml of benzene to yield the analytical sample: 5.3g (70.6% recovery); mp $119.5 - 120.6^\circ$; nmr (CDCl_3): δ 1.27 (s, 6H, CH_3), 1.45 (s, 1H, ROH), 2.22 (s, 6H, ArCH_3), 3.54 (s, 2H, CH_2), 4.82 (s, 1H, ArOH), 6.98 (s, 2H, ArH); ir (KBr disc): 1470, 1380

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(m, CH₃), 1030 (s, primary ROH); mass spec: $m/e = 194$;
14.2% of base peak at $m/e = 163$.

Anal. Calcd for C₁₂H₁₈O₂: C, 74.19; H, 9.34.
Found: C, 73.92; H, 9.36.

The filtrate was evaporated and recrystallized from 10 ml of benzene to yield 1.05g white crystals, mp 119.8 - 120.6°, which was also the primary alcohol, II_{4c}. The last filtrate (0.35g) was 40% II_{4c} and 60% of another material -- as determined by the new ArH at 6.7. This other material has a doublet at 0.88, and might be the alkane, II_{4d}. It was not otherwise characterized. This latter material was only 2.9% overall, the remainder was the primary alcohol.

(7) Reduction of 2-Bromo-3',5'-dimethyl-4'-hydroxy-2-phenylacetophenone (II_{5b}).

(a) Reduction with LiAlH₄.

2-Bromo-3',5'-dimethyl-4'-hydroxy-2-phenylacetophenone (II_{5b}) (3.1928g, 0.0100 mol), lithium aluminum hydride (0.8582g, 0.0226 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The crude product was 2.3536g of white solid, mp 123.5 - 125.3°. The nmr indicated essentially 100% II_{5c}, the primary alcohol (97% recovery).

(b) Other Reductions with LiAlH₄.

The reduction was repeated several times with

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the results listed in Table III, entries 9 - 12.

(c) Identification of the Products.

The crude products of entries 9, 10 and 11 of Table III were combined (9.5774g) and recrystallized from 100 ml of benzene to yield the analytical sample: 7.5g (78.3% recovery) of white crystals; mp 127.8 - 128.3°; nmr (CDCl₃): δ 1.60 (s, 1H, ROH), 2.21 (s, 6H, ArCH₃), 4.08 (s, 3H, CH and CH₂O), 6.83 (s, 2H, ArH), 7.24 (s, 5H, phenyl), the ArOH at approximately 4.7 was very broad; ir (KBr disc): 1460, 1360 (m, CH₃), 1015 (s, primary ROH); mass spec: m/e = 242; 10% of base peak at m/e = 211.

Anal. Calcd for C₁₆H₁₈O₂: C, 79.31; H, 7.49.
Found: C, 79.41; H, 7.46.

The filtrate was evaporated and recrystallized from 10 ml of benzene to yield 0.6g white crystals, mp 126.0 - 126.5°, also the primary alcohol, II_{5c}. The last filtrate, 0.8g, was 56.5% alkane, II_{5d}, and 43.5% primary alcohol, II_{5c}, by nmr integration. The distinctive peaks of the alkane were at 2.78 (s, 4H, both CH₂'s), 6.75 (s, 2H, ArH). The overall yield of alkane was 4.7%. It was not otherwise characterized.

(8) Reduction of 2-Bromo-3',5'-diethyl-4'-hydroxyacetophenone (III_{2b}).

(a) Reduction with LiAlH₄.

2-Bromo-3',5'-diethyl-4'-hydroxyacetophenone

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(III_{2b}) (2.7127g, 0.0100 mol), lithium aluminum hydride (0.8556g, 0.0225 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223 . The crude product consisted of purple crystals (1.7238g). The nmr spectrum indicated ca. 40% III_{2c} and 60% III_{2d} (92.5% recovery based on an average molecular weight of 184.6).

(b) Other Reductions with LiAlH₄.

The reduction was repeated with the results listed in Table IV, entries 1 - 4.

(c) Identification of the Products.

The crude product mixtures of entries 2 and 3 of Table IV were combined to yield 3.9624g of material for dry column chromatography in exactly the manner of 1c, p 225 . Conditions: 700g silica gel for column; eluting solvent: methylene chloride, elution time: 55 min; pressure head: 3 cm. The organic material was leached from each segment with 250 ml of acetone, in three portions, rather than the usual treatment with ether.

Fr 1: 0.3432g, solid, III_{2c} and acetone; Fr 2: 0.5200g, solid, III_{2c} and acetone; Fr 3: 0.7771g, solid, III_{2c} and acetone; Fr 4 - 6: nil; Fr 7: 0.1393g, liquid, III_{2h}; Fr 8: 0.1126g, liquid, III_{2h}; Fr 9 - 10: nil; Fr 11: 0.0210g, liquid, ca. 90% III_{2d} and 10% III_{2p}; Fr 12: 0.2398g, liquid, ca. 90% III_{2d} and 10% III_{2p}; Fr 13: 0.4798g, liquid, ca. 90% III_{2d} and 10% III_{2p}. Fr 14: 0.3590g,

liquid, ca. 90% III_{2d} and 10% III_{2p}; Fr 15: 0.2694g, liquid, ca. 90% III_{2d} and 10% III_{2p}; Fr 16: 0.1335g, liquid, ca. 90% III_{2d} and 10% III_{2p}. (Analyses by nmr.) Recovered wt: 3.2595g, 88.6%.

Fr 1, 2 and 3 (1.6403g) were combined and evaporated to remove the acetone to yield 1.5096g of III_{2c}. The solid was recrystallized from 20 ml of chloroform to yield 0.75g (50% recovery) of pink crystals, mp 99 - 100°. The analytical sample was prepared by sublimation of these crystals: 124° (5.1 Torr) to yield white crystals; mp 98.5 - 99.0°; nmr (CDCl₃): δ 1.24 (t, J = 7.0 Hz, 6H, CH₃), 1.57 (s, 1H, ROH), 2.61 (q, J = 7.0 Hz, 4H, ArCH₂CH₃), 2.75 (t, J = 7.0 Hz, 2H, ArCH₂CO), 3.80 (t, J = 7.0 Hz, 2H, CH₂O), 4.76 (s, 1H, ArOH), 6.84 (s, 2H, ArH); ir (KBr disc): 1040 (s, primary ROH); mass spec: m/e = 194, 18% of base peak at m/e = 163.

Anal. Calcd for C₁₂H₁₈O₂: C, 74.19; H, 9.34. Found: C, 74.31; H, 9.47.

Fr 7 and 8 (0.2519g, 0.00067 mol) were characterized as the dimer, III_{2h}, on the basis of the nmr spectrum; nmr (CDCl₃): δ 1.23 (q, J = 7 Hz, 12H, ArCH₂CH₃), 1.43 (d, J = 7H, 3H, CH₃), 2.58 (q, J = 7Hz, 8H, ArCH₂CH₃), 2.86 (distorted triplet, J = 7Hz, 2H, ArCH₂CO), 3.46 (distorted triplet, J = 7Hz, 2H, CH₂O), 4.33 (q, J = 7Hz, 1H, CH), 4.66 (broad s, 2H, ArOH), 6.75 (s, 2H, ArH of ArCH₂), 6.86 (s, 2H, ArH of ArCHO-); mass spec: m/e = 370; 4.7% of base peak at m/e = 177, also 404, 406; 5.2, 1.9% due to III_{2p}-C₁. The material was not further characterized.

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Fr 11 - 16, 1.4980g, 0.00818 mol, were combined and purified by short path distillation:⁶⁵ 83° (0.2 Torr) to yield 1.2g (80% recovery). The nmr spectrum showed the product as consisting of alkane, III_{2d}, and alkyl bromide, III_{2p}. The distinguishing peaks of the alkyl bromide, III_{2p}, were: nmr (CDCl₃): δ 3.05 (multiplet, 2H, ArCH₂), 3.48 (multiplet, 2H, CH₂Br). Integration gave 90% III_{2d} and 10% III_{2p}. The mass spectrum confirmed the presence of both materials: m/e = 256, 258 (III_{2p}) and m/e = 178 (III_{2d}). The dimeric ether, III_{2g}, was not found in the mass spectrum, m/e = 370.

The total product distribution was: 46.7% III_{2c}, 4.0% III_{2h}; 44.3% III_{2d}; 4.9% III_{2p}. The molar recovery was 86.4%.

(d) Reduction with LiAlD₄.

2-Bromo-3',5'-diethyl-4'-hydroxyacetophenone (III_{2b}) (2.7127g, 0.0100 mol), lithium aluminum deuteride (1.1335g, 0.0270 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The crude product was a red semisolid (1.8908g). The nmr spectrum indicated ca. 55.2% III_{2c} and 44.8% III_{2d} (99.7% recovery based on an average molecular weight of 189.6).

(65) Distilling apparatus, short path, catalog no. K-284500. Kontes Glass Co., Vineland, N. J.

(e) Other Reductions with LiAlD₄.

The reduction was repeated with the results listed in Table IV, entries 5 and 6.

(f) Identification of the Products.

The crude product mixture of entries 5 and 6 of Table IV were combined to yield 3.7878g of material for dry column chromatography in exactly the manner of 1c, p 225. Conditions: 420g silica gel for column; eluting solvent: benzene; elution time: 60 min; pressure head: 2 cm. The organic material was leached from each segment with two 100 ml portions of ether, rather than the usual three portions.

Fr 1: 1.4399g, solid, III_{2c}; Fr 2: ca. 33% III_{2a}, 67% III_{2h}; Fr 3 - 4: nil; Fr 5: 0.0755g, liquid, ca. 90% III_{2d}, 10% III_{2p}; Fr 6: 0.6019g, liquid, ca. 90% III_{2d}, 10% III_{2p}; Fr 7: 0.7881g, liquid, ca. 90% III_{2d}, 10% III_{2p}; Fr 8 - 10: nil. (Analyses by nmr.) Recovered wt: 3.0026g, 79.1%.

Fr 1, 1.4399g III_{2c} was purified by sublimation: 130° (0.8 Torr) to yield 1.15g (80% recovery) of white crystals which were recrystallized from 10 ml of chloroform and 150 ml of hexane to yield 0.85g (56% overall) of white crystals; mp 99.2 - 99.7°; nmr (CDCl₃): δ 1.24 (t, J = 7 Hz, 6H, CH₃), 1.57 (s, 1H, ROH), 2.61 (q, J = 7H, 4H, ArCH₂), 2.75 (broad s, 2H, ArCH₂CO), 4.76 (s, 1H, ArOH), 6.85 (s, 2H, ArH); ir (KBr disc): 2220, 2120 (w, CD), 1460, 1380 (s, CH₃), 1085 (s, primary ROH); mass spec: m/e = 196; 16.3% of base

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peak at $m/e = 163$.

Fr 2 was characterized as 32% ketone, III_{2a} , and 68% dimer, III_{2h} , based on the aromatic region of the nmr spectrum. It was not clear whether the ketone was $ArCOCH_3$ or $ArCOCH_2D$, due to the $ArCH_2CH_3$ peaks, which obscure the $COCH_3$ at 2.5. The dimer has the two aromatic peaks at 6.8 and 6.9, but lacks peaks at 3.4 δ . This requires the position of the label to be: $ArCH_2CD_2OCD(CH_2D)Ar$.

Fr 5, 6 and 7 were combined (1.4655g) and purified by short path distillation:⁶⁵ 80° (1.5 Torr) to yield 1.0g (68% recovery). The alkane, III_{2d} , and alkyl bromide were confirmed by the nmr spectrum. The distinctive peak of the alkyl bromide was: nmr ($CDCl_3$): δ 3.40 (broad s, 2H, $ArCH_2CH_2Br$). There was no peak at 2.8 for $ArCH_2CD_2Br$. Integration gave 9.4% III_{2p} and 90.6% III_{2d} . The mass spectrum confirmed the presence of both compounds: $m/e = 258$, 260 (III_{2p}) and $m/e = 181$ (III_{2d}); 25% of base peak at $m/e = 165$. The nmr spectrum of the alkane was: nmr ($CDCl_3$): δ 1.18 (t, $J = 7\text{Hz}$, 6H, $ArCH_2CH_3$), 1.15 (broad s, 2H, CH_2D), 2.53 (q, $J = 7\text{ Hz}$, 4H, $ArCH_2CH_3$), 3.72 (s, 1H, $ArOH$), 6.80 (s, 2H, ArH); ir (liquid film): 2120, 2200 (w, CD). These nmr and ir data are taken from the mixture. The dimeric ether III_{2g} , was not found in the mass spectrum, $m/e = 374$.

The total product distribution (mole %) was 47.9% III_{2c} ; 0.9% III_{2a} ; 2.2% III_{2h} ; 44.0% III_{2d} ; 4.5% III_{2p} . The molar recovery was 81.9%.

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(9) Reduction of 2-Chloro-3',5'-diethyl-4'-hydroxyaceto-
phenone (III_{2b-C1}).

(a) Reduction with LiAlH₄.

2-Chloro-3',5'-diethyl-4'-hydroxyacetophenone (III_{2b-C1}) (2.2674g, 0.0100 mol), lithium aluminum hydride (0.8575g, 0.0226 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The crude product (1.7994g) was a brown semi-solid. The nmr spectrum indicated 75.6% III_{2c} and 24.4% III_{2d} (94.5% molar recovery based on an average molecular weight of 190.6).

(b) Other Reductions with LiAlH₄.

The reduction was repeated with the results listed in Table IV, entries 7 and 8.

(c) Identification of the Products.

The crude product mixtures of entries 6 and 7 of Table IV were combined to yield 3.6356g of material for dry column chromatography which was performed in exactly the manner of 1c, p 225 . Conditions: 706.8g silica gel for column; eluting solvent: methylene chloride; elution time: 53 min; pressure head: 2 cm.

Fr 1: 0.3088g, solid, III_{2c}; Fr 2: 0.4617g, solid, III_{2c}; Fr 3: 0.8362g, solid, III_{2c}; Fr 4: 0.4776g, solid, III_{2c}; Fr 5: 0.1167g, liquid, 50% III_{2c}, 50% III_{2e-C1}; Fr 6: 0.0483g, liquid, III_{2h}; Fr 7: 0.0815g, liquid, III_{2h};

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Fr 8: 0.0774g, liquid, III_{2h}; Fr 9: 0.0348g, liquid, III_{2h};
Fr 10: 0.0177g, liquid, III_{2h}; Fr 11: 0.0580g, liquid, 50%
III_{2d}, 50% III_{2p-C1}; Fr 12: 0.1702g, liquid, 47% III_{2d},
53% III_{2p-C1}; Fr 13: 0.2594g, liquid, 53% III_{2d}, 47% III_{2p-C1};
Fr 14: 0.2171g, liquid, 52% III_{2d}, 48% III_{2p-C1}; Fr 15:
0.0980g, liquid, 57% III_{2d}, 43% III_{2p-C1}. (Analyses by nmr.)
Recovered wt: 3.2644g, 90.5%.

Fr 1 - 4, 2.0855g, III_{2c}, were combined and purified by sublimation: 116° (0.40 Torr) to yield 1.7g (85% recovery) of white crystals, mp 97.0 - 98.5°. The nmr spectrum confirmed the assignment as III_{2c}.

Fr 5 was identified as 50% III_{2c} and III_{2p-C1} by the nmr spectrum. The distinctive peaks of III_{2p-C1} were the ABX pattern of the ArCH(OH)CH₂Cl protons; nmr (CDCl₃):
δ 3.60, 3.62, 3.70 (2H, CH₂Cl), 4.68, 4.77, 4.80, 4.88 (1H, CH(OH)), 7.00 (s, 2H, ArH). The 3.70 peak integrated to 1H, the 3.60 and 3.62 peaks integrated to 1H. The chlorohydrin was not further characterized.

Fr 6 - 10, 0.2597g, III_{2h}, were combined and identified as the dimer by the nmr spectrum, which was the same as the previously obtained material, p 243. This material was not further characterized.

Fr 11 - 15, 0.7937g, were combined. The presence of the alkane, III_{2d}, and the alkyl chloride, III_{2p-C1}, was indicated by the nmr spectrum and confirmed by the mass spectrum. The distinctive peaks of the alkyl halide were:

nmr (CDCl_3): δ 2.93 (distorted triplet, $J = 7$ Hz, 2H, ArCH_2), 3.63 (distorted triplet, $J = 7$ Hz, 2H, CH_2Cl), 6.80 (s, 2H, ArH). The mass spectrum showed the alkyl chloride: $m/e = 212, 214$, and the alkane, $m/e = 178$. The mass spectrum did not show the dimer, III_{2g} , at $m/e = 370$.

The total product distribution (mole%) was: 68.4% III_{2c} ; 13.4% III_{2d} ; 12.4% III_{2p-C1} ; 4.4% III_{2h} ; 1.4% III_{2e-C1} . Molar recovery was 87.5%.

(10) Reduction of 3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}).

(a) Reduction with LiAlH_4 for Ten Minutes.

3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}) (2.2029g, 0.0100 mol), lithium aluminum hydride (0.8570g, 0.0226 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b} , p 223. The crude product was 2.1558g of viscous liquid.

The crude product was not clearly characterized by the nmr spectrum. There were five peaks in the aromatic region (peak height, mm); nmr (CDCl_3): δ 6.90 (7 mm), 6.96 (38 mm), 7.02 (60 mm), 7.07 (16 mm), 7.15 (13 mm). There were also a series of peaks from 4.1 - 4.6 that could be due to $(\text{ArCH}-(\text{CH}_3))_2\text{O}$, in addition to peaks attributed to the alkane, IV_{2d} , and benzylic alcohol, IV_{2f} (at 4.7 - 5.0). The starting material was absent. The mixture was not further characterized.

The reduction was repeated on 2.2027g, 0.0100 mol of ketone for ten min to yield 2.1399g of viscous yellow liquid. The nmr spectrum was virtually a duplicate of the previous run, except for the appearance of ca. 4% of starting material.

(b) Reduction with LiAlH₄ for Twenty-Four Hours.

3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}) (2.2032g, 0.0100 mol), lithium aluminum hydride (0.8555g, 0.0225 mol) and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223 . The crude product was 2.0191g of yellow liquid.

The nmr spectrum indicated 91% alkane, IV_{2d}, and 9% benzylic alcohol, IV_{2f}. The molar recovery was 96.5%. The distinguishing peaks of the benzylic alcohol were, nmr (CDCl₃): δ 1.42 (d, J = 7 Hz, 3H, CH₃), 4.78 (q, J = 7 Hz, 1H, CH), 7.06 (s, 2H, ArH). The benzylic alcohol was not otherwise characterized. The nmr spectrum was far simpler than for the 10 min reductions.

(c) Reduction with LiAlH₄ and LiBr for Ten Minutes.

3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}) (2.2047g, 0.0101 mol), lithium bromide (0.8723g, 0.0101 mol), lithium aluminum hydride (0.8557g, 0.0225 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The lithium bromide was added as a solid and not dissolved in refluxing ether prior

to the LiAlH_4 addition. The crude product was 2.1736g viscous yellow liquid.

The nmr spectrum was essentially the same as the 10 min reductions without LiBr , this time ca. 5% of starting ketone was present.

A 1.6115g portion of the crude product was again reduced with lithium aluminum hydride (0.8549g, 0.0225 mol) in 100 ml of anhydrous ether for 24hr to yield 1.4855g yellow liquid. The nmr spectrum indicated ca. 50% alkane (based on ArCH_2CH_3), and 50% unidentified products. The aromatic peaks were in new ratios (peak height, mm); nmr (CDCl_3): δ 6.90 (33 mm), 6.96 (12 mm), 7.02 (42 mm), 7.07 (12 mm), 7.15 (7 mm). The product mixture was not otherwise characterized.

(11) Reduction of 2-Bromo-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}).

(a) Reduction with LiAlH_4 .

2-Bromo-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}) (2.9943g, 0.0100 mol), lithium aluminum hydride (0.8615g, 0.0227 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b} , p 223 . The crude product was 2.1457g of brown semisolid. The nmr spectrum indicated 65% primary alcohol, IV_{2c} , and 36% alkane, IV_{2d} (99.0% molar recovery based on an average molecular weight of 216.7).

(b) Other Reductions with LiAlH₄.

The reduction was repeated several times with the results listed in Table V, entries 1 - 5, 8 and 9.

(c) Identification of the Products.

The crude product mixtures of entries 4 and 5 of Table V were combined to yield 4.2986g of material for dry column chromatography in exactly the manner of 1c, p 225 . Conditions: 700g silica gel for column; eluting solvent: benzene; elution time: 120 min; pressure head: 2 cm.

Fr 1: 1.0154g, solid, IV_{2c}; Fr 2: 1.3589g, solid, IV_{2c}; Fr 3: 0.0400g, liquid, 50% IV_{2a}, 50% IV_{2c}; Fr 4: 0.1271g, liquid, IV_{2h}; Fr 5: 0.0551g, liquid, IV_{2h}; Fr 6 - 10: nil; Fr 11: 0.0447g, liquid, 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 12: 0.2831g, liquid, 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 13: 0.5780g, liquid, 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 14: 0.3360g, liquid, 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 15 - 17: nil. Recovered wt: 3.8383g, 89.3 wt %.

Fr 1 and 2, 2.3743g, IV_{2c}, were combined and purified by sublimation: 118° (2.0 Torr) to yield 2.0g (85.6% recovery) white crystals, mp 98.5 - 100.0°. An analytical sample was prepared by recrystallization from 75 ml of hexane to yield 1.3g (65% recovery) white crystals; mp 98.5 - 99.8°; nmr (CDCl₃): δ 1.26 (d, J = 7 Hz, 12H, CH₃), 1.65 (s, 1H, ROH), 2.80 (t, J = 7H, ArCH₂), 3.06 (septet, J = 7 Hz, 2H, CH), 3.83 (t, J = 7H, CH₂O), 4.94 (s, 1H, ArOH), 6.92 (s, 2H, ArH); ir (KBr disc): 1460, 1380 (m, CH₃), 1040

(s, primary ROH); mass spec: $m/e = 222$; 55% of base peak at $m/e = 191$.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97.
Found: C, 75.35; H, 9.96.

Fr 4 and 5, 0.1822g, IV_{2h} , was identified as the dimer, IV_{2h} , by its nmr spectrum, and comparison with the spectrum of the dimer from Experiment 12, p260 .

Fr 11 - 14, 1.2418g, were combined and purified by short path distillation⁶⁵: 100° (0.3 Torr). The nmr integration established the presence of 16.7% alkyl bromide, IV_{2p} . The remainder was alkane, IV_{2d} . The distinctive peaks of the alkyl bromide were: nmr ($CDCl_3$): δ 3.45 (distorted triplet, $J = 7$ Hz, CH_2Br). The $ArCH_2$ peaks at ca. 2.8 were obscured by the $ArCH_2$ of the alkane. The mass spectrum confirmed the presence of both compounds: $m/e = 284$, 286 (IV_{2p}) and $m/e = 206$ (IV_{2d}). The dimeric ether, IV_{2g} , was not observed at $m/e = 246$ (IV_{2g}).

The total product distribution was: 63.4% mol IV_{2c} ; 0.5% IV_{2a} ; 2.5% IV_{2h} ; 5.6% IV_{2p} ; 28.2% IV_{2d} . The total molar recovered was 87.0%.

(d) Reduction with $LiAlH_4$ for Short Periods of Time. Attempts to Produce the Bromohydrin, IV_{2e} , with $LiAlH_4$.

(1)

2-Bromo-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}) (2.9992g, 0.0100 mol) was dissolved in 200 ml of

anhydrous ether. The solution was cooled to 0° with an ice-water bath, and lithium aluminum hydride (0.8581g, 0.0226 mol) was added all at once to the rapidly stirred solution, followed by 100 ml of ether at room temperature. The solution was stirred for 4 min while immersed in the ice bath, then 10 ml of water were added, dropwise. The usual treatment followed, except the solvent was evaporated at 40° (water aspirator) for 60 min, then at 25° (0.10 Torr) for 180 min. The crude product was 2.6750g purple oil.

The nmr spectrum indicated 6.7% ketone, IV_{2a}, and the remainder was unassigned. There were four major peaks in the aromatic region (peak ht, mm): nmr (CDCl₃): δ 6.79 (13 mm), 6.85 (32 mm), 6.98 (65 mm), 7.04 (36 mm). There did not appear to be much, if any, primary alcohol, IV_{2c}, at 3.8, nor alkane, IV_{2d}, at 2.6. There was no starting material. There was possibly some of the bromohydrin, IV_{2e}, at 4.8, perhaps as much as 30% of the total -- the integral was rendered uncertain by the HOD peak. The material was not further characterized.

(2)

2-Bromo-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}) (2.9930g, 0.0100 mol), lithium aluminum hydride (0.8620g, 0.0227 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The reaction time was 3 min, and the ether was refluxing nearly all that time. The crude product was

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2.2770g red-brown liquid.

The nmr spectrum indicated ca. two-thirds of the product was a mixture of IV_{2c} and IV_{2d}. About one-third the material was unassigned, having aromatic peaks clustered at 6.97 but not having assignable peaks in the 2 - 4 region. There was no sign of the ketone, IV_{2a}, nor the bromohydrin, IV_{2e}. There was no starting material.

(3)

2-Bromo-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}) (2.9938g, 0.0100 mol) was dissolved in 90 ml of anhydrous ether and cooled to 10° with the aid of a cold water bath. Lithium aluminum hydride (0.8550g, 0.0225 mol) was added all-at-once to the rapidly stirred solution, followed by 10 ml of ether at room temperature. The system was stirred for 2 min while immersed in the 10° bath, then 10 ml of water were added dropwise, rapidly. The crude product was 2.6439g lavender liquid.

The nmr spectrum indicated 14.6% ketone, IV_{2a}; 6.7% starting material, IV_{2b}; 21.6% primary alcohol, IV_{2c}, plus alkane, IV_{2d}. The remaining 58.7% was represented by four peaks in the aromatic region clustered around 6.97 which could not be assigned to known compounds. The material was not further characterized.

A 2.5184g portion of the above crude product mixture was again reduced with lithium aluminum hydride (0.8560g, 0.0225 mol) and a total of 100 ml of anhydrous

ether. The system was heated at reflux for 20 min. The crude product was 2.1697g dark brown liquid.

The nmr spectrum of the new crude product indicated 32% primary alcohol, IV_{2c}, plus alkane, IV_{2d}. The remaining 68% was represented by a cluster of aromatic peaks at 7.0 which could not be assigned. There was no ketone, IV_{2a}, or starting material, IV_{2b}, left. The product mixture was not further characterized.

(e) Reduction with LiAlD₄.

2-Bromo-3'-5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}) (2.9935g, 0.0100 mol), lithium aluminum deuteride (1.1533g, 0.02745 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The crude product was 2.1834g of tan semisolid. The nmr spectrum indicated 65.2% primary alcohol, IV_{2c}, and 34.8% alkane, IV_{2d} (99.5% molar recovery based on an average molecular weight of 218.9).

(f) Other Reductions with LiAlD₄.

The reduction was repeated with the results listed in Table V, entries 6 and 7.

(g) Identification of the Products.

The crude product mixtures of entries 6 and 7 of Table V were combined for dry column chromatography in exactly the manner of 1c, p 225. Conditions: 700g silica gel for column; eluting solvent: benzene; elution time:

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80 min; pressure head: 3.5 cm.

Fr 1: 0.5239g, solid, IV_{2c}; Fr 2: 1.2595g, solid, IV_{2c}; Fr 3: 0.6444g, solid, IV_{2c}; Fr 4: nil; Fr 5: 0.1063g, liquid, IV_{2h}; Fr 6: 0.1663g, liquid, IV_{2h}; Fr 7 - 11: nil; Fr 12: 0.0209g, liquid 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 13: 0.2250g, liquid, 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 14: 0.4129g, liquid, 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 15: 0.3622g, liquid, 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 16: 0.2282g, liquid, 83.3% IV_{2d}, 16.7% IV_{2p}; Fr 17: nil. Recovered wt: 3.9496g, 90.4%.

Fr 1 - 3, 2.4278g, IV_{2c}, were combined and purified by sublimation: 120° (1.0 Torr) to yield 2.3g (95% recovery) white crystals. This was recrystallized from 150 ml of hexane to yield 1.9g (82.5% recovery) white crystals; mp 98.6 - 100.0°; nmr (CDCl₃): δ 1.22 (d, J = 7 Hz, 12H, CH₃), 1.84 (s, 1H, ROH), 2.75 (broad s, 2H, ArCH₂), 3.15 (septet, J = 7 Hz, 2H, CH), 5.08 (s, 1H, ArOH), 6.90 (s, 2H, ArH), there was no peak at 3.8 for Ar CH₂CD₂OH; ir (KBr disc): 2200, 2100 (w, CD), 1080 (s, primary ROH); mass spec: m/e = 224; 20% of base peak at m/e = 191.

Fr 5 and 6, 0.2726g, was identified as the dimer IV_{2h} by the nmr spectrum; nmr (CDCl₃): δ 1.24 (d, J = 7 Hz, 24H, CH₃), 1.40 (broad s, 2H, CH₂D), 2.78 (broad s, 2H, ArCH₂), 3.14 (septet, J = 7 Hz, 4H, CH), 4.74 (s, 1H, ArOH of ArCH₂-), 4.82 (s, 1H, ArOH of ArCDO-), 6.86 (s, 2H, ArH of ArCH₂-), 7.00 (s, 2H, ArH of ArCDO-). There was no signal in the 3.5 -

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4.0 region, which eliminated $\text{ArCD}_2\text{CH}_2\text{O}-$, and required the structure to be: $\text{ArCH}_2\text{CD}_2\text{OCD}(\text{CH}_2\text{D})\text{Ar}$.

Fr 12 - 16, 1.2492g, were combined and purified by short path distillation:⁶⁵ 94° (0.6 Torr) to yield 0.70g (56% recovery) of pale orange fluid. The nmr spectrum established the presence of IV_{2d} and IV_{2p} , and the integration gave the distribution. The alkane spectrum was: nmr (CDCl_3): δ 1.13 (broad s, 2H, CDH_2), 1.24 (d, $J = 7$ Hz, 12H, CH_3), 4.74 (s, 1H, ROH), 6.90 (s, 2H, ArH). The distinctive peak of the alkyl bromide, IV_{2p} , was at 3.45 (broad s, 2H, CH_2Br). The mixture had ir (liquid film): 2200, 2120 (w, CD). The mass spectrum confirmed the presence of both compounds: $m/e = 286, 288$ (IV_{2p}) and $m/e = 209$ (IV_{2d}). The dimeric ether, IV_{2g} , was not observed at $m/e = 430$.

The total product distribution was: 63.4% IV_{2c} ; 3.7% IV_{2h} ; 27.5% IV_{2d} ; 5.4% IV_{2p} . The molar recovery was 89.2%.

(12) Reduction of a Mixture of 3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}) and 2-Bromo-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}).

(a) Reduction with LiAlH_4 .

3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}) (1.1016g, 0.0050 mol), 2-bromo-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}) (1.4971g, 0.0050 mol), lithium aluminum hydride (0.8548g, 0.0225 mol), and a total of 100 ml of

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anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223. The ether solution was heated at reflux for 10 min. The crude product was 2.0694g yellow-orange fluid. The nmr spectrum indicated 23.7% primary alcohol, IV_{2c}; 50.4% dimer, IV_{2h}, and 25.9% alkane, IV_{2d}. The dimer was counted as two monomers for this distribution. (The alcohol could be estimated separately, the dimer with rather more difficulty, and the alkane was calculated by difference from 100%.) Based on an average molecular weight of 213.4, the molar recovery was 97.2%.

(b) Other Reductions with LiAlH₄.

The reduction was repeated on twice the above scale, heating at reflux for 20 min. The crude product was 4.1579g, yellow-orange oil. The product distribution was indicated by the nmr spectrum as: 24.1% primary alcohol, IV_{2c}; 48.3% dimer, IV_{2h}; 27.6% alkane, IV_{2d}; again the dimer was counted as two monomers. The results are listed in Table XIII, entries 1, 2 .

(c) Identification of the Products.

The crude product mixtures of Table XIII, entries 1, 2 , were combined to yield 6.2278g for dry column chromatography in exactly the manner of 1c, p 225 .
Conditions: 700g silica gel; eluting solvent: benzene; elution time: 70 min; pressure head: 3.5 cm.

Fr 1: 0.6990g, solid, IV_{2c}; Fr 2: 0.4000g, solid, IV_{2c}; Fr 3: nil; Fr 4: 0.1118g, liquid, IV_{2h}; Fr 5: 0.2003g,

liquid, IV_{2h}; Fr 6: 0.3980g, liquid, IV_{2h}; Fr 7: 0.7370g, liquid, IV_{2h}; Fr 8: 0.4910g, liquid, IV_{2h}; Fr 9: nil; Fr 10: 0.0910g, liquid, ca. 80% IV_{2d}, 20% IV_{2p}; Fr 11: 0.2960g, liquid, ca. 80% IV_{2d}, 20% IV_{2p}; Fr 12: 0.5020g, liquid, ca. 80% IV_{2d}, 20% IV_{2p}; Fr 14: 0.1730g, liquid, ca. 80% IV_{2d}, 20% IV_{2p}; Fr 15: nil. Recovered wt: 4.6081g, 74.0%.

Fr 1 and 2, 1.0990g, were combined. The nmr spectrum indicated it to be IV_{2c} (p 252).

Fr 4 - 8, 1.9381g, IV_{2h}, were combined with chloroform and filtered repeatedly through glass wool to remove traces of silica gel. The solvent was evaporated. The dimer did not crystallize upon prolonged standing (months) at ca. 4°. The identity of this material was established by nmr. Nmr (CDCl₃): δ 1.23 (d, J = 7 Hz, 24H, CH₃), 1.43 (d, J = 6.5 Hz, 3H, CH₃), 2.82 (distorted triplet, J = 7 Hz, 2H, ArCH₂), 3.17 (multiplet, J = 7 Hz, 4H, CH), 3.48 (distorted triplet, J = 7 Hz, 2H, CH₂O), 4.40 (q, J = 6.5 Hz, 1H, CH₂O-), 4.74 (s, 1H, ArOH of ArCH₂-), 4.82 (s, 1H, ArOH of ArCHO-), 6.92 (s, 2H, ArH of ArCH₂-), 7.01 (s, 2H, ArH of ArCHO-); ir (liquid film): 1460 (s, CH₃), 1380 (w, gem.-dimethyl), 1190 (s, aliphatic ether); mass spec: m/e = 426; 2.8% of base peak at m/e = 191.

Fr 10 - 14, 1.5710g, were combined. The nmr spectrum indicated the presence of both IV_{2d} (80%) and IV_{2p} (20%), which was confirmed by comparison with the spectrum

of a similar mixture from Experiment 11, p 253, see above. The fraction was not further characterized.

The product distribution in mole % was: 29.9% IV_{2c}; 27.5% IV_{2h}; 34.2% IV_{2d}; 8.5% IV_{2p}. The molar recovery was 56.6%. Recalculated on the basis that IV_{2h} should be counted as two monomers, the product distribution was: 23.5% IV_{2c}; 43.1% IV_{2h}; 26.8% IV_{2d}; 6.7% IV_{2p}; and the molar recovery was 70.4% -- which aligns the calculation with the original nmr analysis, where the dimer, IV_{2h}, was counted as two monomers.

(13) Reduction of 2-Chloro-3',5'-diisopropyl-4'-hydroxy-acetophenone (IV_{2b-c1}).

(a) Reduction with LiAlH₄.

2-Chloro-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b-c1}) (2.5489g, 0.0100 mol), lithium aluminum hydride (0.85557g, 0.0225 mol), and a total of 100 ml of anhydrous ether were combined for reduction in exactly the manner of I_{2b}, p 223 . The crude product was 2.1446g beige solid. The nmr spectrum indicated ca. 79% primary alcohol, IV_{2c}, and 21% alkane, IV_{2d}. The molar recovery was 98.1% based on an average molecular weight of 218.9.

(b) Other Reductions with LiAlH₄.

The reduction was repeated, with the results listed in Table V, entries 10 and 11.

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(c) Identification of the Products.

The crude product mixture of entries 10 and 11 of Table V were combined to yield 3.7909g of material for dry column chromatography in exactly the manner of 1c, p 225. Conditions: 700g silica gel for column; eluting solvent: benzene; elution time: 82 min; pressure head: 2 cm.

Fr 1: 0.6030g, solid, IV_{2c}; Fr 2: 1.2752g, solid, IV_{2c}; Fr 3: 0.6295g, solid, IV_{2c}; Fr 4: 0.0646g, liquid, 8.6% IV_{2a}, 26.9% IV_{2c}; 64.5% IV_{2e}-C1; Fr 5: 0.0348g, liquid, IV_{2h}; Fr 6: 0.0543g, liquid, IV_{2h}; Fr 7: 0.0306g, liquid, IV_{2h}; Fr 8: 0.0217g, liquid, IV_{2h}; Fr 9 - 10: nil; Fr 11: 0.0195g, liquid, 23.5% IV_{2d}, 76.5% IV_{2p}-C1; Fr 12: 0.1386g, liquid, 23.5% IV_{2d}, 76.5% IV_{2p}-C1; Fr 13: 0.3047g, liquid, 42.3% IV_{2d}, 57.7% IV_{2p}-C1; Fr 14: 0.1582g, liquid, 57.2% IV_{2d}, 42.8% IV_{2p}-C1; Fr 15 - 17: nil. (Analyses by nmr.) Recovered wt: 3.3347g, 87.8%.

Fr 1 - 3, 2.5077g, were combined and identified as the primary alcohol, IV_{2c}, by the nmr spectrum. No further characterization was necessary.

2
3
Fr 4, 0.0646g, 0.00027 mol, was observed to be 6.8% ketone, IV_{2a}; 26.9% primary alcohol, IV_{2c}, and 64.5% chlorohydrin, IV_{2e}-C1 by the nmr spectrum. The last compound was readily assigned on the basis of the highly characteristic ABX pattern of the protons: ArCH₂OHCH₂Cl, and confirmed by comparison with authentic material, see Experiment 2, p 274. The components of this mixture were not further characterized.

Fr 5 - 8, 0.1414g, IV_{2h}, were combined and filtered repeatedly through glass wool to eliminate traces of silica gel. The nmr spectrum of the combined fractions was established as the dimer, IV_{2h}, by comparison with authentic material from Experiment 12, p 260.

Fr 11 - 14, 0.6210g, were combined and subjected to dry column chromatography. Conditions: 700g alumina for column; eluting solvent: chloroform; elution time: 26 min; pressure head: 1.5 cm. All the material was found in Fr 6 - 9 (out of 10 fractions), with no major improvement in resolution of the alkane, IV_{2d}, from the alkyl chloride, IV_{2p-C1}. The recovered wt was 0.5136g, and calculation showed the 0.1074g loss was entirely alkane -- perhaps due to volatilization during the solvent removal step. The material was subjected to wet column chromatography on acidic alumina (Woehlm, Activity Grade I), eluting with chloroform: no separation was achieved. The recovered wt was 0.4270g. Efforts to resolve the components were abandoned, and the assignment was based on the nmr and mass spectra. The nmr spectrum shows the alkane clearly, and gave the distinctive peaks of the alkyl chloride: nmr (CDCl₃): δ 2.97 (distorted triplet, J = 7 Hz, 2H, ArCH₂), 3.66 (distorted triplet, J = 7 Hz, 2H, CH₂Cl), 4.76 (s, 1H, ArOH). The mass spectrum confirmed the presence of both compounds: m/e = 240, 242 (IV_{2p-C1}) and m/e = 206 (IV_{2d}).

The total product distribution (mole %) was:

77.6% IV_{2c}; 7.8% IV_{2d}; 10.9% IV_{2p-C1}; 2.3% IV_{2h}; 1.2% IV_{2e-C1}; 0.1% IV_{2a}. The total molar recovery was 86.3%.

(14) Reduction of 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxy-acetophenone (V_{2b}).¹

(a) Reduction with LiAlH₄.

2-Bromo-3',5'-di-tert.-butyl-4'-hydroxyacetophenone (V_{2b}) (3.2730g, 0.0100 mol), lithium aluminum hydride (0.8553g, 0.0225 mol), and a total of 100 ml of anhydrous ether were combined for reduction in the manner of I_{2b}, p 223. (The solution was cooled in an ice-water bath during the LiAlH₄ addition.) The crude product was 2.5g. The nmr indicated 90% primary alcohol, V_{2c}, 10% alkyl bromide, V_{2p} (97.5% molar recovery based on an average molecular weight of 256.3).

The crude product was recrystallized from 20 ml of hexane to yield 1.2g (50% recovery) white crystals: mp 99.0 - 100.3° (lit¹ mp 99 - 101°); nmr (CDCl₃): δ 1.48 (s, 18H, CH₃), 1.75 (s, 1H, ROH), 2.78 (t, J = 7Hz, 2H, ArCH₂), 3.82 (t = 7 Hz, 2H, CH₂O), 5.11 (s, 1H, ArOH), 7.05 (s, 2H, ArH); ir (KBr disc): 1110 (m, primary ROH); mass spec: m/e = 250; 43% of base peak at m/e = 219.

The nmr spectrum of the crude product displayed the distinctive peaks of the alkyl halide: nmr (CDCl₃): δ 3.12, 3.25 (multiplet, 2H, ArCH₂), 3.47, 3.58 (multiplet, 2H, CH₂Br), 5.06 (s, 1H, ArOH). The mass spectrum confirmed

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the presence of the alkyl halide: $m/e = 312, 314$ (V_{2p}).

(b) Reduction with $LiAlD_4$.³

2-Bromo-3',5'-di-tert.-butyl-4'-hydroxyacetophenone (V_{2b}) (0.5028g, 0.0015⁴ mol), lithium aluminum deuteride (0.3131g, 0.007⁴⁵ mol), and a total of 40 ml of anhydrous ether were combined for reduction in the manner of I_{2b} , p 223. (The solution was cooled in an ice-water bath during the $LiAlD_4$ addition.) The crude product was 0.3720g of white solid. The nmr spectrum indicated 90% primary alcohol, V_{2c} , and 10% alkyl bromide, V_{2p} (93.5% molar recovery).

The crude product was recrystallized from hexane to yield 0.25g (67% recovery) of white crystals: mp 97 - 98°; nmr ($CDCl_3$): δ 1.48 (s, 18H, CH_3), 1.87 (s, 1H, ROH), 2.76 (broad s, 2H, $ArCH_2$), 5.10 (s, 1H, $ArOH$), 7.00 (s, 2H, ArH), there was no peak at 3.8 for $ArCH_2CD_2OH$; ir (KBr disc): 2210, 2120 (w, CD), 1120 (s, primary ROH); mass spec: $m/e = 252$; 39% of base peak at $m/e = 237$.

The nmr spectrum of the crude product displayed the distinctive peak of the alkyl halide: nmr ($CDCl_3$): δ 3.5⁴ (broad s, 2H, CH_2Br). The signals at 3.12 and 3.25 were absent. The mass spectrum confirmed the presence of the alkyl halide: $m/e = 314, 316$ (V_{2p}).

(15) Reduction of 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxy-propiophenone (V_{3b}).²

(a) Reduction with LiAlH₄.

2-Bromo-3',5'-di-tert.-butyl-4'-hydroxypropiophenone (V_{3b}) (6.4263g, 0.0188 mol), lithium aluminum hydride (1.7110g, 0.0450 mol), and a total of 200 ml of anhydrous ether were combined for reduction in the manner of I_{2b}, p 223. (The solution was cooled in an ice-water bath during the LiAlH₄ addition.) The crude product was 4.90g of white solid. The nmr spectrum indicated this was 100% primary alcohol, V_{3c}, 98.9% molar recovery.

The crude product was recrystallized from 75 ml of hexane to yield the analytical sample: 2.7g (55% recovery) white crystals: mp 93.2 - 94.5° (lit² 85 - 88°); nmr (CDCl₃): δ 1.28 (d, J = 7Hz, 3H, CH₃), 1.45 (s, 18H, CH₃), 1.62 (s, 1H, ROH), 2.87 (sextet, J = 7 Hz, 1H, CH), 3.66 (d, J = 7 Hz, 2H, CH₂O), 5.13 (s, 1H, ArOH), 7.06 (s, 2H, ArH); nmr (DMSO-d₆): δ 4.54 (t, J = 5.5 Hz, 1H, CH₂OH); ir (KBr disc): 1030 (s, primary ROH); mass spec: m/e = 264; 13% of base peak at m/e = 233.

Anal. Calcd for C₁₇H₂₈O₂: C, 77.22; H, 10.67, Found: C, 77.11; H, 10.80.

(b) Other Reductions with LiAlH₄.

The reduction was repeated with the results listed in Table VI, entries 3 - 5. (The 4 min reduction was

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performed without external cooling.)

(c) Hydrogen Evolution Studies.

Lithium aluminum hydride (0.8550g, 0.0225 mol) was added to 100 ml of anhydrous ether in a 500-ml 1-necked flask equipped with a magnetic stirrer and fitted with a Friedrichs condenser-adaptor. The adaptor was connected with Tygon tubing through two dry-ice acetone traps in series to an inverted 500-ml graduated cylinder, filled with water and immersed in a 4-l. beaker. The ether was stirred until bubbling ceased. 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxypropiophenone (V_{3b}) (3.4133g, 0.0100 mol) was added to the $LiAlH_4$ all-at-once.

The gas evolution was monitored: time, ml: 15 sec, 245 ml; 30 sec, 252 ml; 45 sec, 255 ml; 60 sec, 255 ml; 75 sec, 256 ml; 90 sec, 257 ml; 105 sec, 260 ml; 240 sec, 260 ml. Corrected to standard conditions, with air temp = 26° , $P = 1$ atm, water temp = 20° , this was 242 ml. The gas law requires 224 ml (0.01 mol H_2). Therefore, the experimental value was 8% too high. The gas evolved was not studied further, it was assumed to be hydrogen.

At the end of the 4 min, 10 ml of water were rapidly added, followed by the usual work-up. The crude product was 2.6015g, ca. 100% primary alcohol, V_{3c} , or 0.00984 mol, 98.4% molar recovery.

The experiment was repeated: using one dry-ice

acetone trap, 3.4126g, 0.0100 mol V_{3b} ; 0.8612g, 0.0226 mol $LiAlH_4$, and 100 ml of anhydrous ether. The gas evolution was monitored: time, ml: 30 sec, 240 ml; 60 sec, 265 ml; 90 sec, 270 ml; 120 sec, 270 ml; 150 sec, 270 ml; 240 sec, 270 ml. Corrected to standard conditions, this was 248 ml. The experimental value was 10.8% high. The crude product, 2.6425g, was a pale yellow solid (99.9% molar recovery). The nmr spectrum indicated this was pure V_{3c} .

(16) Reduction of 2-Bromo-3',5'-di'tert.-butyl-4'-hydroxy-2-methylpropiophenone (V_{4b}).²

(a) Reduction with $LiAlH_4$.

2-Bromo-3',5'-di'tert.-butyl-4'-hydroxy-2-methylpropiophenone (V_{4b}) (7.1063g, 0.0200 mol), lithium aluminum hydride (1.7106g, 0.0450 mol), and a total of 200 ml of anhydrous ether were combined for reduction in the manner of I_{2b} , p 223. (The solution was cooled in an ice-water bath during the $LiAlH_4$ addition.) The crude product was 4.5g of ivory solid, mp 148.5--149.0°. The nmr spectrum indicated this to be pure, 81.0% molar recovery.

The crude product was recrystallized, first from 75 ml of hexane to yield white crystals, mp 149.2 - 150.2°, then from 50 ml of hexane to yield the analytical sample: 2.97g (65% recovery) white crystals; mp 149.8 - 150.3° (lit² mp 148 - 150°); nmr ($CDCl_3$): δ 1.32 (s, 6H, CH_3), 1.47 (s, 19H, t-butyl and ROH), 3.57 (s, 2H, CH_2O), 5.14 (s, 1H, ArOH), 7.24

(s, 2H, ArH); nmr (DMSO- d_6): δ 4.54 (t, $J = 5.5$ Hz, 1H, CH_2OH);
ir (KBr disc): 1045 (s, primary ROH); mass spec: $m/e =$
278; 7% of base peak at $m/e = 247$.

Anal. Calcd for $\text{C}_{18}\text{H}_{30}\text{O}_2$: C, 77.65, H, 10.86.
Found: C, 77.85; H, 10.82.

(b) Other Reductions with LiAlH_4 .

The reduction was repeated with the results listed
in Table VI, entries 6 - 9. (The 4 min reduction was per-
formed without external cooling.)

(17) Reduction of 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxy-
2-phenylacetophenone (V_{5b}).²

(a) Reduction with LiAlH_4 .

2-Bromo-3',5'-di-tert.-butyl-4'-hydroxy-2-phenyl
acetophenone (V_{5b}) (8.0683g, 0.0200 mol), lithium aluminum
hydride (1.7106g, 0.0450 mol), and a total of 200 ml of
anhydrous ether were combined for reduction in the manner of
 I_{2b} , p 223. (The solution was cooled in an ice-water bath
during the LiAlH_4 addition.) The crude product was 6.40g pale
orange solid, mp 106.0 - 108.0°. The nmr spectrum indicated
this was pure primary alcohol, V_{5c} , 98.3% molar recovery.

The crude product was recrystallized twice: from
100 ml then 50 ml of hexane to yield the analytical sample:
4.1722g (65.3% recovery); mp 107 - 108° (lit² mp 102 - 103°);
nmr (CDCl_3): δ 1.42 (s, 18H, CH_3), 1.58 (s, 1H, ROH), 4.11
(s, 3H, CH and CH_2O), 5.11 (s, 1H, ArOH), 7.10 (s, 2H, ArH),

7.31 (s, 5H, phenyl); nmr (DMSO- d_6): δ 4.70 (t, J = 5.0 Hz, 1H, CH_2OH); ir (KBr disc): 1020 (s, primary ROH); mass spec: m/e = 326; 10% of base peak at m/e = 295.

Anal. Calcd for $\text{C}_{22}\text{H}_{30}\text{O}_2$: C, 80.94; H, 9.26.
Found: C, 80.70; H, 9.13.

(b) Other Reductions with LiAlH_4 .

The reduction was repeated with the results listed in Table VI, entries 10 - 12. (The 4 min reduction was performed without external cooling.)

(18) Reduction of 2-Bromo-3',5'-di-tert.-butyl-4'-hydroxybutyrophenone (V_{6b}).²

(a) Reduction with LiAlH_4 .

2-Bromo-3',5'-di-tert.-butyl-4'-hydroxybutyrophenone (V_{6b}) (7.1060g, 0.0200 mol), lithium aluminum hydride (1.7112g, 0.0450 mol), and a total of 200 ml of anhydrous ether were combined in the manner of I_{2b} , p 223. The solution was cooled in an ice-water bath during the addition of the LiAlH_4 . The crude product was 5.40g white solid, mp 80.7 - 82.5°. The nmr spectrum indicated this was pure primary alcohol, V_{6c} , 98.1% molar recovery.

The crude product was recrystallized twice: first from 80 ml hexane, then from 50 ml of hexane to yield the analytical sample: 0.4791g (8.9% recovery) white crystals; mp 86.0 - 86.5° (lit² mp 76 - 77°); nmr (CDCl_3): δ 0.85 (t, J = 7 Hz, 3H, CH_3), 1.45 (s, 18H, CH_3), 1.52 (s, 1H, ROH),

1.76 (multiplet, 2H, ArCHCH₂), 2.59 (quintet, J = 7 Hz, 1H, CH), 3.71 (d, J = 7 Hz, 2H, CH₂O), 5.11 (s, 1H, ArOH), 7.01 (s, 2H, ArH); nmr (DMSO-d₆): δ 4.46 (t, J = 5.5 Hz, 1H, CH₂OH); ir (KBr disc): 1025 (s, primary ROH); mass spec: m/e = 278; 16% of base peak at m/e = 247.

Anal. Calcd for C₁₈H₃₀O₂: C, 77.65; H, 10.86, Found: C, 77.73; H, 10.92.

(b) Other Reductions with LiAlH₄.

The reduction was repeated with the results listed in Table VI, entries 13 and 14.

(G) Preparation of Halohydrins.

(1) Preparation of 2-Bromo-1-(3,5-diisopropyl-4-hydroxy-phenyl) ethanol (IV_{2e}).

(a) Reduction with NaBH₄.

2-Bromo-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}) (5.9852g, 0.0200 mol) and 200 ml of absolute ethanol were placed in a 500-ml 3-necked flask equipped with a magnetic stirrer, a 150-ml pressure-equalizing dropping funnel, a thermometer, and a condenser containing a drying tube (CaSO₄). The flask was placed into a large crystallizing dish which contained acetone and sufficient added amounts of dry ice to maintain a bath temperature from -61 to -56°. Sodium borohydride (2.2735g, 0.0600 mol) dissolved in 100 ml of absolute ethanol were added over a period of 23 min to the rapidly stirred solution.

The rate of borohydride addition, and the rate of addition of dry ice to the cooling bath was continuously adjusted to maintain the solution temperature between -49 and -51°. The initially yellow solution became a pale green and remained thus for the entire reduction period. The solution was stirred for an additional 7 min after the borohydride addition. While maintaining external cooling, 120 ml of 2.4M HCl were added dropwise over a period of 13 min (caution: foaming). The solution became brown.

The contents were placed in a 2-l. separatory funnel

and diluted with 900 ml of water and 100 ml of 2.4M HCl. After cautious shaking (gas evolution), 400 ml of methylene chloride were added. The organic layer was washed with two 900-ml portions of water, dried over MgSO_4 , filtered, and the solvent was evaporated at reduced pressure with external heating (39°) for 30 min, then for 30 min at 0.3 Torr. This compound must not be heated above $40 - 45^\circ$.

The pale orange crude product weighed 6.0724g. The nmr spectrum indicated 20.0% CH_2Cl_2 and 80.0% bromohydrin, IV_{2e} (93.8% recovery based on an average molecular weight of 259.0). There were no traces of starting material, nor the primary alcohol, IV_{2c} , nor the alkane, IV_{2d} . The crude product was estimated to be at least 95% pure, excluding the solvent.

This bromohydrin could be only partially characterized. Efforts at recrystallization (boiling hexane) led to total decomposition of the material. Low temperature immersion of the crude product mixture in a dry-ice acetone bath for 4 hr at -78° failed to induce crystallization. Similarly, immersion in liquid nitrogen only led to a glassy solid. Nmr (CDCl_3): δ 1.22 (d, $J = 7$ Hz, 12H, CH_3), 2.83 (s, 1H, ROH), 3.00 (septet, $J = 7$ Hz, 2H, CH), 3.48, 3.52, 3.60 (AB of ABX, 2H, CH_2Br), 4.75, 4.85, 4.86, 4.96 (X of ABX, 1H, CHOH), 5.13 (s, 1H, ArOH), 7.05 (s, 2H, ArH), the 3.60 peak integrated to 1H, the 3.48 and 3.52 peaks together integrated to 1H; mass spec: $m/e = 300, 302; 5, 5\%$ of base peak at $m/e = 207$.

(b) Other Reductions with NaBH₄.

The reduction was repeated several times to produce the bromohydrin, IV_{2e}. In every case the product was recovered in over 95% yield (corrected for solvent). Because of the thermal instability of the compound it was not found desirable to remove the last amounts of solvent. A typical example follows: 5.9848g, 0.0200 mol IV_{2b} and 2.2723g, 0.0600 mol of sodium borohydride were combined exactly as in (G) (1a) above: the reduction temperature was maintained between -48 and -51^o, to yield 6.4384g crude product. This was 30% ether and 70% bromohydrin, IV_{2e}, or 96.8% recovery based on an average molecular weight of 233.0.

The bromohydrin may be stored in a refrigerator for a day or two at 4^o, but not at room temperature for that time. It should never be heated above 40^o, and when heated, only for periods of less than 40 min.

(2) Preparation of 2-Chloro-1-(3,5-diisopropyl-4-hydroxy-phenyl) ethanol (IV_{2e}-C₁).

(a) Reduction with LiAlH₄.

2-Chloro-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2b}-C₁) (2.5498g, 0.0100 mol) was dissolved in 190 ml of anhydrous ether, and cooled to 0^o with an ice-water bath. Lithium aluminum hydride (0.8554g, 0.0225 mol) was added all-at-once followed by 10 ml of ether at room temperature. The reaction time was 3 min. After the usual work-up, the

crude product was obtained by evaporation of the ether for 60 min at 50°. The product was 2.5380g or 98.9 mol % recovery.

A 2.2373g portion of the crude product was recrystallized from 5 ml of chloroform and 45 ml of hexane with brief, gentle warming - not vigorous boiling, to yield, after scratching, white crystals: 0.90g (39.6% recovery); mp 75.0 - 75.8°.

(b) Other Reductions with LiAlH₄.

This experiment was repeated several times with striking variation in results, which are listed in Table XII, entries 1 - 10.

(c) Reduction with NaBH₄.

2-Chloro-3',5'-diisopropyl-4'-hydroxyacetophenone (IV_{2e-C1}) (5.0957g, 0.0200 mol) dissolved in 100 ml of absolute ethanol, and sodium borohydride (2.2717g, 0.0600 mol) dissolved in 150 ml of absolute ethanol were combined for reduction in the manner of (G) (1a), above. The borohydride was added over a period of 12 min to the stirred solution at 0°. The reaction was allowed to continue for 120 min, when it was quenched by the addition of 150 ml of 2.4M HCl over a period of 15 min. The work-up of (G) (1a), above, was followed. The ether solvent was evaporated for 60 min at 60° at reduced pressure to yield 3.8875g.

The nmr spectrum indicated the product was essentially pure (75.6% yield). The analytical sample was prepared by

recrystallization from 40 ml of hexane. Continuous scratching was required to produce white crystals: 2.10g (54% recovery); mp 76.6 - 77.5°; nmr (CDCl₃): δ 1.24 (d, J = 7Hz, 12H, CH₃), 2.76 (s, 1H, ROH), 2.80 (septet, J = 7Hz, 2H, CH), 3.58, 3.62, 3.70 (AB of ABX, 2H, CH₂Cl), 4.70, 4.80, 4.82, 4.92 (X of ABX, 1H, CHOH), 5.03 (s, 1H, ROH), 7.05 (s, 2H, ArH), the 3.70 peak integrated to 1H, the 3.58 and 3.62 peaks together integrated to 1H; ir (KBr disc): 1460, 1380 (m, CH₃), 1050 (s, benzylic ROH); mass spec: m/e = 256, 258; 11, 4% of base peak at m/e = 207.

Anal. Calcd for C₁₄H₂₁O₂ Cl: C, 65.49; H, 8.24; Cl, 13.81. Found: C, 65.26; H, 8.11; Cl, 14.07.

(d) Other Reductions with NaBH₄.

The reduction was repeated several times with excellent results as long as the low temperature procedure outline in (G) (2c) above, was followed. Note also that this chlorohydrin, although decidedly more stable than the bromohydrin, does display slow discoloration at room temperature and should not be heated excessively.

(H) Reduction of a Halohydrin.

(1) Reduction of 2-Bromo-1-(3,5-diisopropyl-4-hydroxyphenyl) ethanol (IV_{2e}).

(a) Reduction with LiAlH₄.

2-Bromo-1-(3,5-diisopropyl-4-hydroxyphenyl) ethanol (IV_{2e}) (5.8291g, 0.1080 mol bromohydrin, IV_{2e}, 0.0036 mol methylene chloride), lithium aluminum hydride (3.8006g, 0.1002 mol), and a total of 400 ml of ether were combined for reduction in the manner of I_{2b}, p 223. The bromohydrin was prepared 150 min prior to reduction and stored at 25°. It was transferred to the hot oil bath within 2 min of the lithium aluminum hydride addition. The reflux period was 30 min. The crude product was 3.8092g red-brown solid. The nmr indicated this to be 60% primary alcohol, IV_{2c} and 31% alkane, IV_{2d} (97.5% recovery based on an average molecular weight of 217.1).

(b) Identification of the Products.

A 3.65g portion of the above crude product was subjected to dry column chromatography in exactly the manner of 1c, p 225. Conditions: 700g silica gel for column; eluting solvent: benzene; elution time: 80 min; pressure head: 2.5 cm.

Fr 1: 0.8437g, solid, IV_{2c}; Fr 2: 1.1386g, solid, IV_{2c}; Fr 3: nil; Fr 4: 0.1868g, liquid, IV_{2h}; Fr 5: 0.2278g, liquid, IV_{2h}; Fr 6-8: nil; Fr 9: 0.0747g, liquid, IV_{2d} and

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IV_{2p}; Fr 10: 0.1093g, liquid, IV_{2d} and IV_{2p}; Fr 11: 0.1448g, liquid, IV_{2d} and IV_{2p}; Fr 12: 0.2259g, liquid, IV_{2d} and IV_{2p}; Fr 13: 0.1841g, liquid, IV_{2d} and IV_{2p}; Fr 14-15: nil. (Analyses by nmr.) Recovered wt: 3.1357g, 85.8%.

Fr 1 and 2, 1.9823g, were identified as primary alcohol, IV_{2c}, by the nmr spectrum and required no further characterization.

Fr 4 and 5, 0.4146g, were identified as the dimer, IV_{2h}, by the nmr spectrum and required no further characterization.

Fr 9-13, 0.7388g, were combined, filtered through glass wool to remove traces of silica gel and the product distribution was established by nmr integration (80% alkane, IV_{2d}, and 20% alkyl bromide, IV_{2p}). The fraction required no further characterization.

The total product distribution by mole percent was: 67.4% IV_{2c}; 7.35% IV_{2h}; 20.2% IV_{2d}; 5.06% IV_{2p}. The molar recovery was 84.0%.

(c) Additional Reductions with LiAlH₄.

2-Bromo-1-(3,5-diisopropyl-4-hydroxyphenyl) ethanol (IV_{2e}) (5.8826g, 0.0185 mol bromohydrin, IV_{2e}, 0.0040 mol ether), lithium aluminum hydride (3.9116g, 0.1030 mol), and a total of 400 ml of anhydrous ether were combined for reduction in the manner of I_{2b}, p 223. The bromohydrin was prepared 120 min prior to reduction and was transferred to the hot oil bath within 1 min of the lithium aluminum hydride addition. The reflux period was 30 min. The crude product

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was 3.8605g red-brown solid. The nmr spectrum indicated this to be 67% primary alcohol, IV_{2c}, and 33% alkane, IV_{2d} (94.0% recovery based on an average molecular weight of 217.0).

(d) Identification of the Products.

A 3.70g portion of the above crude product mixture was subjected to dry column chromatography in exactly the manner of 1c, p 225. Conditions: 700g silica gel for column; eluting solvent: benzene; elution time: 77 min; pressure head: 2.5 cm.

Fr 1: 0.6835g, solid, IV_{2c}; Fr 2: 1.2921g, solid, IV_{2c}; Fr 3: 0.3681g, solid, IV_{2c}; Fr 4: 0.0705g, liquid, IV_{2h}; Fr 5: 0.1962g, liquid, IV_{2h}; Fr 6: 0.0783g, liquid, IV_{2h}; Fr 7: nil; Fr 8: 0.0316g, liquid, IV_{2d} and IV_{2p}; Fr 9: 0.0440g, liquid, IV_{2d} and IV_{2p}; Fr 10: 0.1244g, liquid, IV_{2d} and IV_{2p}; Fr 11: 0.1980g, liquid, IV_{2d} and IV_{2p}; Fr 12: 0.2669g, liquid, IV_{2d} and IV_{2p}; Fr 13: 0.0587g, liquid, IV_{2d} and IV_{2p}; Fr 14: nil. Recovered wt: 3.4123g, 92.0%.

Fr 1, 2 and 3, 2.3437g, were identified as primary alcohol, IV_{2c}, by the nmr spectrum, and required no further characterization.

Fr 4, 5 and 6, 0.3450g, were identified as the dimer, IV_{2h}, by the nmr spectrum and required no further characterization.

Fr 9-13, 0.7388g, were combined, filtered through

glass wool to remove traces of silica gel and the product distribution was established by nmr integration (83.3% alkane, IV_{2d}, and 16.7% alkyl bromide, IV_{2p}.) This fraction required no further characterization.

The total product distribution by mole percent was 71.9% primary alcohol, IV_{2c}; 5.53% dimer, IV_{2h}; 18.8% alkane, IV_{2d}; 3.77% alkyl bromide, IV_{2p}. The molar recovery was 92.5%.

The results are gathered in Table X, entries 5, 6.

(I) Preparation of Model Compounds

(1) Preparation of 1-(3,5-Diisopropyl-4-hydroxyphenyl)
ethyl ethyl ether. (XXXII).

(a) Reduction with NaBH₄.

Sodium borohydride (4.5440g, 0.120 mol) was dissolved in 150 ml of absolute ethanol and placed into a 500-ml 3-necked flask equipped with a magnetic stirrer, a 125-ml pressure-equalizing addition funnel, and a condenser containing a drying tube. The flask was placed in an ice-water bath and the solution was cooled to 0°. 3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}) (4.4093g, 0.0200 mol) was dissolved in 100 ml of absolute ethanol and added to the cooled, stirred borohydride solution over a period of 9 min. The solution was stirred with external cooling for an additional 135 min.

The excess borohydride was cautiously decomposed by the addition of 130 ml of 2.4M HCl over a period of 12 min. The solution was then added to a 2-l. separatory funnel, and 100 ml of 2.4M HCl, 900 ml of water and 400 ml of ether were added. The organic layer was washed with two 900 ml portions of water, adding 200 ml of ether each time. The ether layer was dried over MgSO₄, filtered, and the solvent evaporated at reduced pressure with external heating (60°).

The crude product was 4.6400g of pale yellow liquid. The nmr spectrum indicated the mixture to be 89% product, 2.8% starting material, IV_{2a}, and 8.1% unassigned material.

The latter was distinguished by an aromatic peak at 7.05, but did not appear to be the benzylic alcohol, IV_{2f}.

The crude product was recrystallized from 15 ml of petroleum ether (bp 30 - 60°) to yield white crystals: 0.60g (12% of theory); mp 71.3 - 72.8°; nmr (CDCl₃): δ 1.15 (t, J = 7H, 3H, CH₂CH₃), 1.26 (d, J = 7Hz, 12H, CH₃), 1.42 (d, J = 7H, 3H, CHCH₃OEt), 3.17 (septet, J = 7H, 2H, CH), 4.34 (q, J = 7H, 1H, CHCH₃OEt), 4.86 (s, 1H, ArOH), 7.00 (s, 2H, ArH); ir (KBr disc): 1460, 1380 (s, CH₃), 1190 (s, aliphatic ether); mass spec: m/e = 250; 20% of base peak at m/e = 235.

Anal. Calcd for C₁₆H₂₆O₂: C, 76.75; H, 10.47.
Found: C, 76.93; H, 10.62.

(b) Other Reductions with NaBH₄.

The reduction was repeated several times with essentially the same results.

(2) Preparation of 1-(3,5-Dimethyl-4-hydroxyphenyl) ethyl-ethyl Ether (XXXIII).

(a) Reduction with NaBH₄.

3',5'-Dimethyl-4'-hydroxyacetophenone (II_{2a}) (3.2854g, 0.0200 mol) dissolved in 100 ml of absolute ethanol was cooled to 0°. Sodium borohydride (2.2714g, 0.0600 mol) dissolved in 100 ml of absolute ethanol was added to the cooled, stirred ketone solution over a period of 8 min. The

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solution was stirred with external cooling for an additional 109 min.

Treatment of the reaction solution in exactly the manner of the preceding experiment yielded 2.5422g of semi-solid. The nmr spectrum indicated it to be starting material II_{2a} , and the product ether. Apparently no benzylic alcohol, II_{2f} , was formed. The nmr spectrum of the product ether was: nmr ($CDCl_3$): δ 1.16 (t, $J = 7\text{Hz}$, 3H, CH_2CH_3), 1.41 (d, $J = 7\text{Hz}$, 3H, $CHCH_3OEt$), 1.34 (s, 6H, $ArCH_3$), 3.36 (q, $J = 7\text{Hz}$, 2H, OCH_2), 4.28 (q, $J = 7\text{Hz}$, 1H, CH), 5.06 (s, 1H, $ArOH$), 6.94 (s, 2H, ArH). This material was not further characterized.

(3) Preparation of 1-(3,5-Diisopropyl-4-hydroxyphenyl) ethanol (IV_{2f}).

(a) Reduction with $NaBH_4$.

3',5'-Diisopropyl-4'-hydroxyacetophenone (IV_{2a}) (4.4089g, 0.0200 mol) dissolved in 150 ml of dimethylformamide and sodium borohydride (2.2730g, 0.0600 mol) dissolved in 100 ml of dimethylformamide were combined in exactly the manner of experiment (1), p 281. The borohydride solution was added over a period of 14 min and the solution was allowed to react an additional 65 min at 0° .

The crude material was treated in exactly the manner of experiment (1), p 281. The crude product was 3.8053g of pale yellow solid. The nmr spectrum indicated 86.7% starting material, IV_{2a} , and 13.3% benzylic alcohol, IV_{2f}

(86.1% molar recovery based on an average molecular weight of 220.7). The nmr spectrum of the benzylic alcohol was: nmr (CDCl₃): δ 1.24 (d, J = 7Hz, 12H, CH₃), 1.52 (d, J = 7Hz, 3H, CH₃), 3.30 (septet, J = 7Hz, 2H, CH), 4.89 (q, J = 7Hz, 1H, CH), 7.11 (s, 2H, ArH), the ROH was not discernible, and the ArOH was very broad at ca. 6.6. This material was not further characterized.

See also Experiment 10b, Section F, p 250 for another source of this compound.

(4) Preparation of 3',5'-Dimethyl-4'-methoxy-2-phenylpropiophenone (MeO-II_{5a}).

Sodium hydride (11.6g of a 57% dispersion in mineral oil, 0.275 mol) (Alfa Inorganics) and 200 ml of tetrahydrofuran (Baker Analyzed: 0.020% water) were placed in a 2-l. 3-necked flask equipped with a powerful magnetic stirrer, a 1-l. pressure-equalizing addition funnel and a condenser containing a drying tube. 3',5'-Dimethyl-4'-hydroxy-2-phenylacetophenone (II_{5a}) (60.1g, 0.250 mol) dissolved in 300 ml of tetrahydrofuran were added to the rapidly stirred sodium hydride slurry over a period of 47 min. The resulting solution was bright green. The solution was stirred an additional 15 min at room temperature, then methyl iodide (71.0g, 0.500 mol) dissolved in 100 ml of tetrahydrofuran were added over a period of 13 min.

The green solution was stirred an additional 60

min, then 200 ml of water were cautiously added, but no hydrogen evolution was noticed. The solution was placed in a 4-l. separatory funnel, diluted with 2 l. of water and 500 ml of chloroform. The chloroform layer was separated and the aqueous phase was extracted with a 200 ml portion of chloroform. The chloroform layers were combined, washed with three 2 l. portions of water, dried over MgSO_4 , filtered, and the solvent was evaporated at reduced pressure with external heating (70°).

The crude product was 34.5g of semisolid. The nmr spectrum indicated this to be 27.7% carbon methylated product (2,3',5'-trimethyl-4'-hydroxy-2-phenylpropylphenone) MeO-II_{5a} and 72.3% material not methylated on the 2-carbon. Both materials were partially methylated at oxygen for a total of four compounds, which could not be further subdivided into percentages.

The nmr spectrum of MeO-II_{5a} was: nmr (CDCl_3):
 δ 1.46 (d, $J = 7\text{Hz}$, 3H, $\text{HC}(\text{CH}_3)$), 2.24 (s, 6H, ArCH_3), 3.60 (s, 3H, OCH_3), 4.63 (q, $J = 7\text{Hz}$, 1H, CH), 7.21 (s, 5H, phenyl), 7.66 (s, 2H, ArH). The products were not further characterized.