PART I

THE SCHMIDT REACTION OF UNSYMMETRICAL BENZHYDROLS

PART II

REDUCTION PRODUCTS OF THE RUBREMETINIUM CATION

by

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B.S.
DePaul University, 1950

Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1954

ACKNOWLEDGEMENT

I wish to thank Dr. William E. McEwen whose unfailing enthusiasm and ability to make truly constructive suggestions made my research much more productive than it otherwise might have been. I also wish to thank the Office of Naval Research and The National Science Foundation who supported parts of the work reported in this thesis, and especially E. I. du Pont de Nemours and Company whose fellowship made possible my last year of research.

TABLE OF CONTENTS

PART I

PART II

PART I

THE SCHMIDT REACTION OF UNSYMMETRICAL BENZHYDROLS

INTRODUCTION

In recent years the Schmidt reaction has been investigated extensively with respect to its mechanism. Results from its application to unsymmetrical diarylethylenes seemed to indicate, however, that this particular reaction possesses a very individual character. It was found that a competitive migration between substituted and unsubstituted phenyl groups occurred and the extent of migration of each group seemed to depend on its electronic character (10). In this respect the reaction resembles the pinacol rearrangement of symmetrical benzopinacols. A qualitative correlation was observed between the "migratory aptitudes" of the various m- and p- substituted phenyl groups in the two reactions.

Later, a significant difference between the two reactions was observed (14). Only the data from the Schmidt reaction fitted a modified Hammett equation,

$\log$ "migratory aptitude" = $\rho\sigma$ where

"migratory aptitude" = ratio of products obtained from substituted phenyl migration to products obtained from unsubstituted phenyl migration.

rho = a constant for the reaction.

sigma = a "substituent constant" whose value depends on the identity of the m- or p- substituent (see Section C in Background and Historical Review).

The types of reactions previously found to follow the Hammett relationship were nucleophilic displacement and addition reactions of m- and p- substituted benzene derivatives. The extension of the Hammett relationship to migration reactions was found, however, to be very limited in applicability. Besides the unsymmetrical diarylethylenes, only the rates of nitrogen evolution in the Schmidt reaction of m- and p- substituted benzoic acids were found to follow the Hammett relationship.

In order to determine whether this application of the modified Hammett equation could be broadened, and secondarily to extend the Schmidt reaction to a larger group of compounds, the ratio of products in the reactions of seven m- and p- substituted benzhydrols were investigated and are described in this thesis.

The rates of reaction of m- and p- substituted N-bromobenzamides in the Hofmann rearrangement and m- and p- substituted o-benzoylbenzhydroxamic acids in the Lossen rearrangement have also been correlated by use of the Hammett relationship.

BACKGROUND AND HISTORICAL REVIEW

A. Nature and Scope of the Schmidt Reaction

A review of the Schmidt reaction covering the literature through 1945 is available (1). Since the number of new applications of the reaction is limited, this section of the thesis will be mainly a very short resume of Wolff's review article. Reaction between equimolar amounts of hydrazoic acid and compounds yielding carbonium ions in the presence of strong acids is the essence of the Schmidt reaction.

Most applications of the reaction have been made in the preparation of amines from carboxylic acids. The products obtained are the same as those from the Curtius and Hoffman reactions; i.e., amines containing one less carbon atom than the acid are produced. The three reactions are competitive as far as yields and convenience of operation are concerned.

Aromatic aldehydes give mixtures of the corresponding nitriles and formanilides, the ratio depending on the concentration of sulfuric acid used as catalyst.

Symmetrical ketones react to give the corresponding substituted acid amide; for example, acetone gives N-methylacetamide and benzophenone gives benzanilide, both in quantitive yield. Unsymmetrical ketones give the two possible N-substituted acid amides, usually in about the same ratio as obtained in the Beckmann rearrangement of the

corresponding ketoximes. The greater reactivity of a keto group as compared to a carboxyl group makes it possible to obtain N-acetyl amino acids from α-substituted acetoacetic acids or esters.

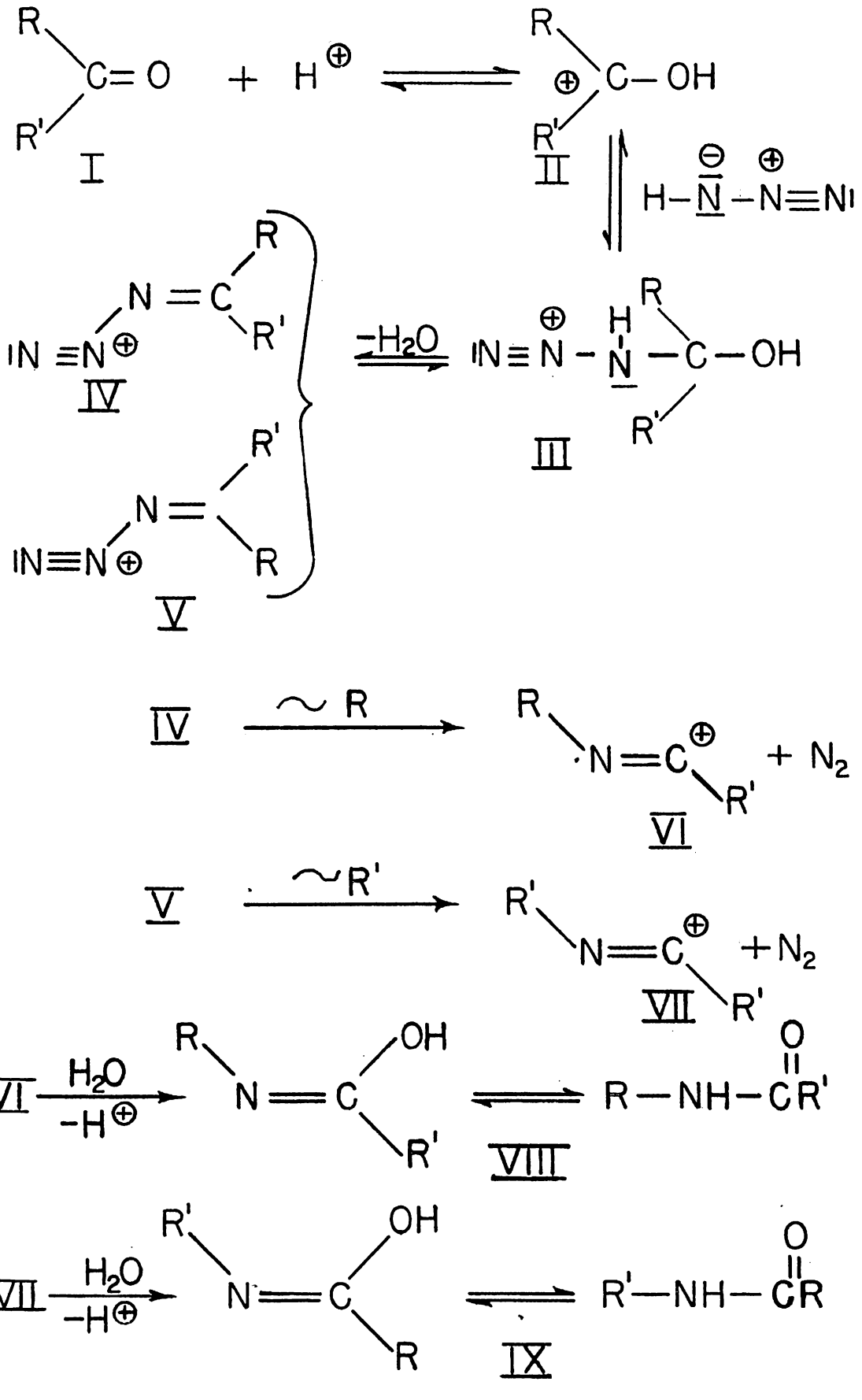
Tetrazoles are the usual by-products in the Schmidt reactions of aldehydes and ketones, and they can be obtained as main products by the use of two equivalents of hydrazoic acid.

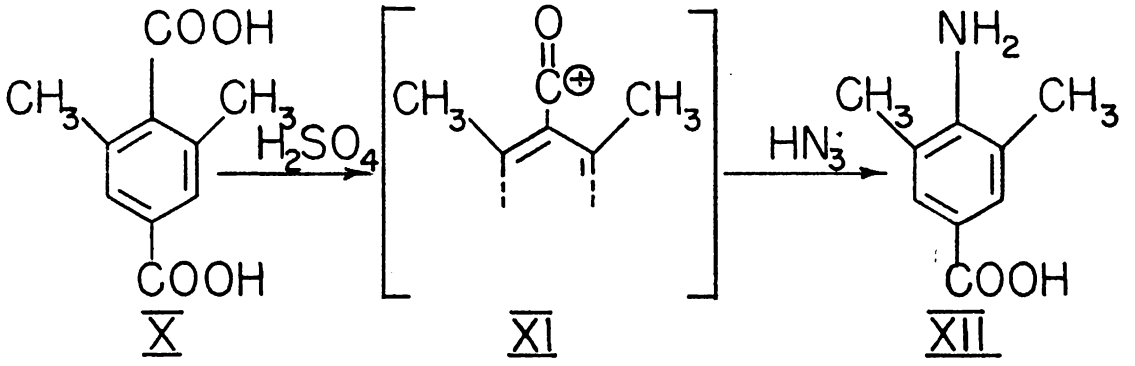
Ring enlargement results with cyclic olefins. Thus cyclopentene yields 3,4,5,6-tetrahydropyridine. Other olefins give hydrolysis products arising from Schiff bases. Unsymmetrical diphenylethylene, for example, gives acetophenone and aniline.

Tertiary alcohols and halides, as well as benzhydryl alcohols, also react to give Schiff bases or their hydrolysis products. Tertiary butyl chloride gives a 70% yield of acetone and an 80% yield of methylamine, these products undoubtedly arising from the corresponding Schiff base, while benzhydrol gives a 90% yield of benzalaniline. Some of these reactions are discussed in more detail in the following section.

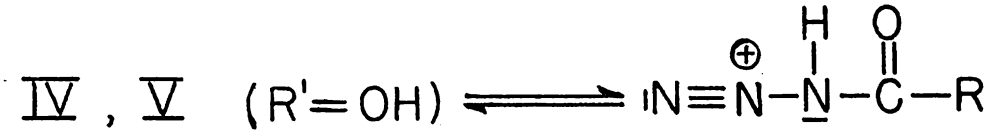
B. Mechanisms of the Schmidt Reactions

The mechanisms which have been proposed for the Schmidt reactions of carboxylic acids, ketones and aldehydes can all be accommodated, with a few reservations, by the general sequence I-IX (for acids R' = OH, for ketones R' = an alkyl

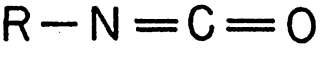




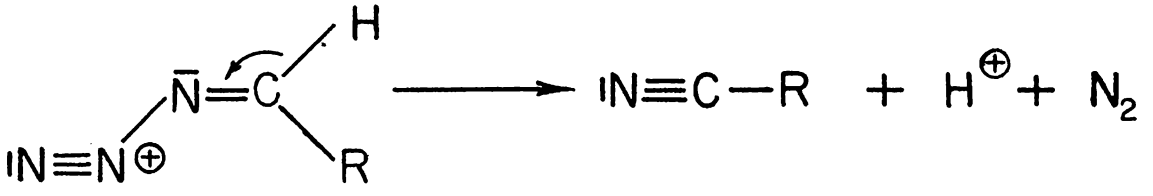
X XI XII



XIII



XIV



V (R'=H) XV

or aryl group, for aldehydes R' = H). This general mechanism involves formation of an hydroxycarbonium ion (II) by the addition of a proton to the carbonyl compound, addition of hydrazoic acid to this ion, dehydration of this adduct (III) to iminodiazonium ions (IV,V) and trans rearrangement of these ions. Addition of water and loss of a proton gives the products.

With carboxylic acids, the first carbonium ion (II, R' = OH) is only one of two possible alternatives. Newman and Gildenhorn (2) have shown that 2,6-dimethylterephthalic acid (X) reacts with hydrazoic acid at 0° C. in sulfuric acid solution to give 4-amino-3,5-dimethylbenzoic acid (XII). Under these conditions, sterically hindered benzoic acids, such as X, yield appreciable concentrations of oxocarbonium ions, XI, while benzoic acid yields a dihydroxycarbonium ion of type II (R' = OH). Since it was found that benzoic acid does not react with hydrazoic acid at 0° C., but requires higher temperatures, ions of type XI must either be in equilibrium with ions of type II (R' = OH), or else, as has been considered more likely (3), reaction proceeds by addition of hydrazoic acid to the dihydroxycarbonium ion, followed by dehydration of the complex, III (R' = OH). Such dehydration products would be expected to exist as syn and anti isomers, IV and V (R' = OH). It would further be expected that the isomer having the bulkier group trans to the diazo group would be more stable and that rearrangement

would proceed predominantly through it.* Such considerations would indicate that reaction by the path III → IV → VI would be favored. The intermediate, VI (R' = OH), would yield the amine either by the process shown, followed by loss of carbon dioxide from the carbamic acid, VIII (R' = OH), or by loss of a proton from VI (R' = OH) giving the isocyanate, XIV, which would decompose in the presence of acid to give the amine.

Products resulting from migration of R' (OH) by reaction path III → V → VII have apparently never been observed. In this connection it may be noted, however, that in many cases acid has been recovered, even though almost theoretical amounts of nitrogen were evolved (4). Since the hydroxamic acid IX (R' = OH) would not be expected to survive the hydrolysis procedure used for isolating the products, it may be that the consequences of the latter reaction path have been observed but not recognized.

Briggs and Lyttleton (4) have shown that in the Schmidt reaction of various substituted benzoic acids the rate of nitrogen evolution depends on the electron releasing tendency of the substituent. This implies that the slow or rate-determining step is decomposition of the azide.

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* This is especially true here because an easy interconversion between the two forms through the tautomer XIII is possible. Note also that the tautomeric form is that intermediate expected from the reaction of hydrazoic acid with an oxocarbonium ion of type XI.

Concerning the mechanism of the Schmidt reaction of ketones, it has been shown (5) that the strength of the acid catalyst necessary to bring about reaction depends on the basicity of the ketone. With aliphatic ketones it was possible to get good yields of products using aqueous, concentrated hydrochloric acid, while with diaryl ketones this catalyst was insufficient to bring about reasonably rapid reaction, and at least anhydrous trichloroacetic acid was required. This was taken as indicative of the importance of the formation of the hydroxycarbonium ion II (R' = aryl or alkyl).

Smith postulated (5) loss of a molecule of water from the complex III to give an intermediate which can exist in <u>syn</u> or <u>anti</u> forms (IV or V) in order to account for the observation that, as in the Beckmann rearrangement with unsymmetrical ketoximes, the bulkier group is the one that migrates preferentially in the Schmidt reaction (See Table I).

TABLE I (6)

<u>Schmidt Reaction of Phenyl Alkyl Ketones, C_6H_5COR</u>

	Percent Migrating	
<u>R</u>	<u>C_6H_5</u>	<u>R</u>
methyl	95	5
ethyl	85	15
isopropyl	51	49
t-butyl	0	100

On the basis that the intermediate (IV or V) having the larger group trans to the diazo group will be of lower energy and therefore present in larger concentration in the equilibrium mixture, it will be the larger group which will migrate preferentially in a trans elimination of nitrogen.

In confirmation of the corollary that steric considerations should overshadow electronic influences in the rearrangement, it was found that when various p-substituted benzophenones were subjected to the Schmidt reaction, migration of the substituted and unsubstituted phenyl groups occurred in practically equal amounts (see Table II).

TABLE II (6,7)

Schmidt Reactions of Benzophenones, p-X-$C_6H_4COC_6H_4$-p-Y

Substituents		Percent of Groups Migrating	
		p-X-C_6H_4	p-Y-C_6H_4
X	Y		
Cl	H	59	41
NO_2	H	51	49
CH_3	H	54	46
CH_3O	H	61	39
C_6H_5	H	52	48
NO_2	OCH_3	51	49
Cl	OCH_3	47	53

This is the expected result, since when R and R' in III are sterically equivalent (as phenyl and p-substituted

phenyl are), there is no reason why formation of either IV or V should be preferred; therefore equivalent amounts of the isomeric amides should be obtained.

Interesting exceptions to the generalization that the bulkier group will migrate in the Schmidt reaction of an unsymmetrical ketone (as well as in the Beckmann rearrangement of the corresponding oxime) occur among some of the o-substituted benzophenones (see Table III).

TABLE III (8)

Schmidt Reactions of Unsymmetrical Benzophenones, $o\text{-}X\text{-}C_6H_4\text{-}COC_6H_5$

	Percent of Migration	
X	$o\text{-}X\text{-}C_6H_4$	C_6H_5
CH_3	12	88
COOH	98	2
Cl	30	70
Br	19	81
CH_3O	50	50
NO_2	70	30
C_6H_5	95	5

Smith points out that actually with the oximes, molecular models can be constructed showing that there is no internal strain when the OH and o-substituted phenyl groups are cis, as long as the substituent is of moderate size. Complete rotation, however, is hindered. While this does

not account for the apparent greater stability of these configurations, it at least shows there is no barrier to them.

When the ortho substituent becomes large enough, rotation of the substituted phenyl is sharply restricted by a cis OH group, possibly increasing the internal potential energy difference between the syn and anti forms. Such an effect may possibly be coming into play with the o-phenyl, o-carboxy and o-nitro groups.

In the Schmidt reaction of an aldehyde the products obtained are a nitrile and a formamide. The general reaction mechanism I-IX indicates that the products would be an amide and a formamide (VIII, IX, R = H). To explain this discrepancy the special nature of ion V when R' is H must be considered. Apparently the intramolecular elimination of the relatively stable proton is exclusively favored over an intermolecular hydration of the rearranged ion, VII (R' = H), thus leading to a nitrile, XV, rather than an amide.

Another even more singular feature of the Schmidt reaction with aromatic aldehydes is the variation in the ratio of the products obtained when the concentration of sulfuric acid catalyst is changed. (see Table IV).

TABLE IV (9)

Schmidt Reactions of Aromatic Aldehydes, p-XC_6H_4CHO

X	Ratio of sulfuric acid to aldehyde	Percent Yield nitrile	formanilide
H	0.72	32	14
	5.4	10	59
CH_3O	0.72	86	0
	5.4	64	0
Cl	0.72	55	12
	5.4	15	48
NO_2	0.72	72	2
	5.4	46	23
CH_3	0.72	50	6
	5.4	13	43

This has been explained (9) within the framework of the mechanism for the Schmidt reaction of ketones with some necessary extensions. On the basis of steric influence, the free energy of the ion, IV (R' = H), will no doubt be less than that of the ion, V (R' = H), with its two bulkier groups *cis*. It must be assumed, however, that the rate of formation of ion V (R' = H), is greater than that of ion IV (R' = H), but that interconversion between IV and V is possible, subject to acid catalysis. Now when the reaction is catalyzed by a small amount of acid, if the rate of nitrile formation from V (R' = H) exceeds the rate of interconversion of IV and V, the major product will be nitrile. In a high concentration of acid, the acid-catalyzed interconversion of IV and V will be so rapid compared to the rate of nitrile

formation that most of the higher energy ion, V (R' = H), will be converted to the lower energy ion, IV (R' = H), which leads to formanilide on rearrangement.

All the above mechanisms are similar with regard to the fact that in the complex, III, formed between hydrazoic acid and the carbonium ion, II, there exists the possibility of dehydration with all the real and potential complications described above. In a second group of Schmidt reactions, including those proposed for 1,1-diphenylethylene, XVI (X = H) (10) (11), benzhydrol XXV (X = Y = H) (12) and diphenylmethyl carbinol XVII (X = H) (13), such a possibility does not exist. This can be seen by considering the complexes XIX and XXVII.

The necessity for the formation of a carbonium ion, XVIII or XXVI, was originally based on analogy with the mechanisms for the reactions of acids, aldehydes and ketones. Confirmation of the addition of a molecule of hydrazoic acid to the carbonium ion was obtained when Ege and Sherk (13) isolated azides from the reaction of hydrazoic acid and diarylethylenes in the presence of trichloroacetic acid.* These azides rearrange in the presence of sulfuric acid, presumably by depressing loss of a proton from XIX, which decomposes because of the inhibition of resonance in the azide group. Isolation of the azide also indicates that the slow step in this system is the decomposition of

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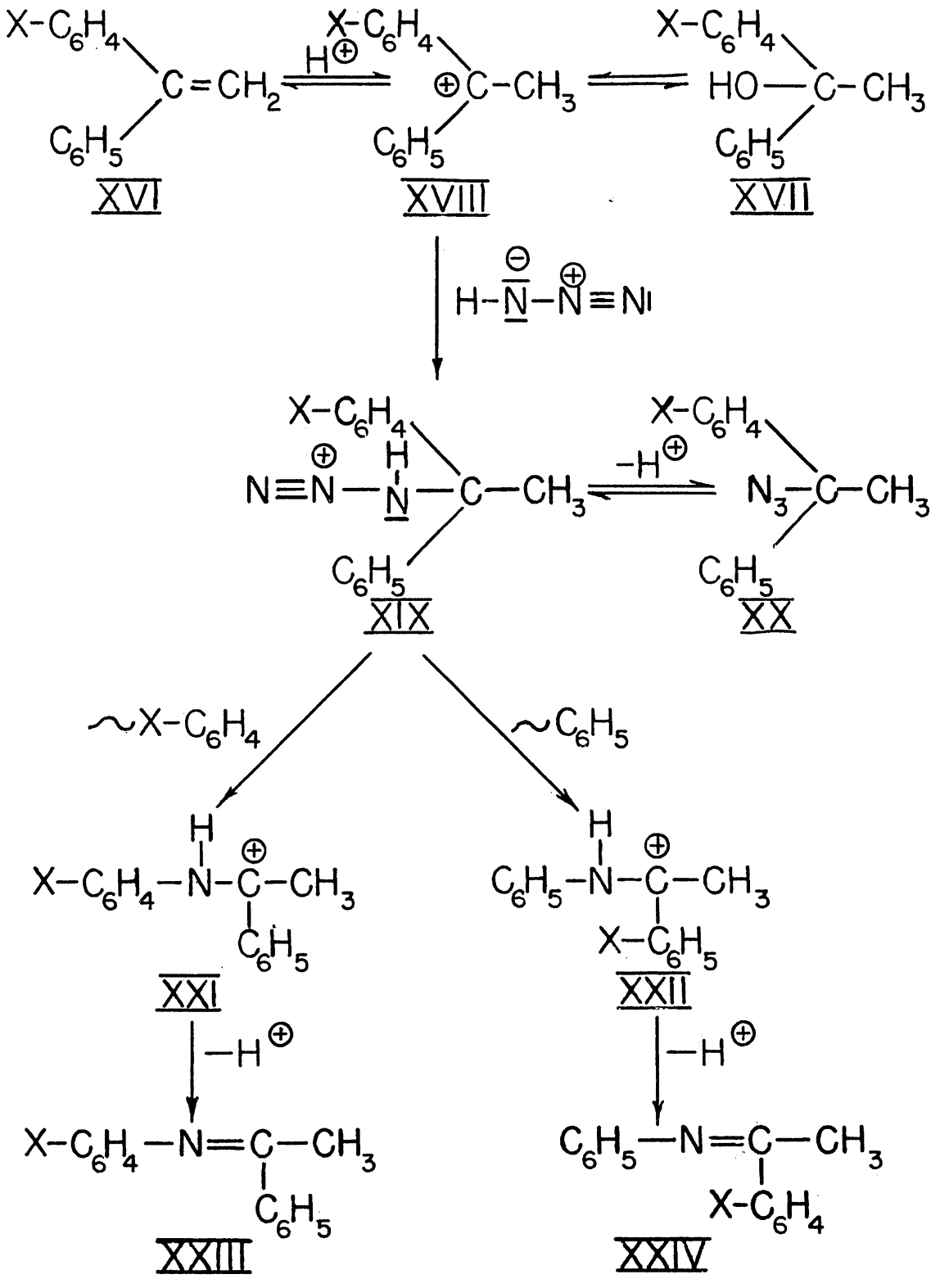
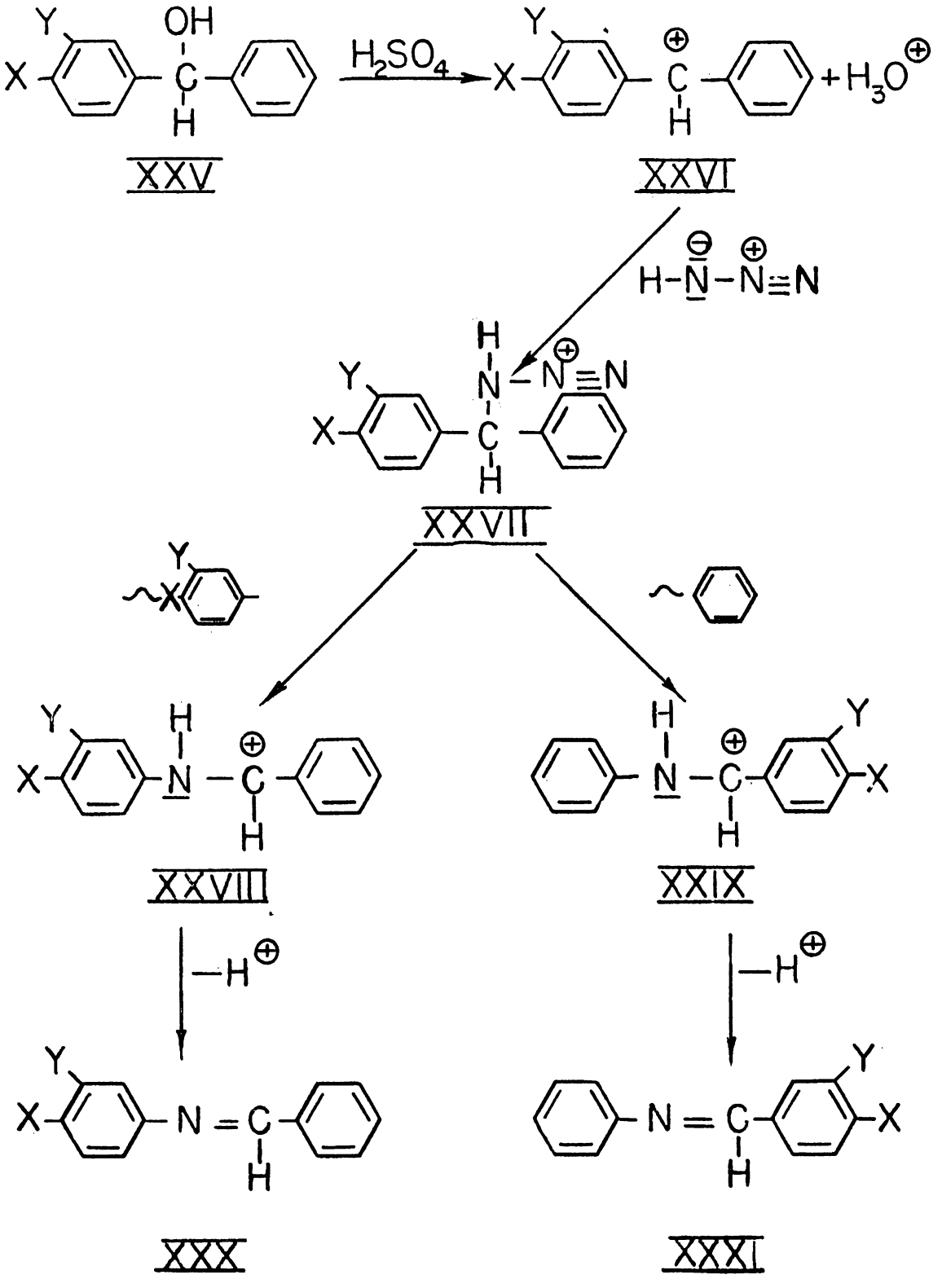
* Arcus and Mesley (12) isolated 9-azidofluorene from fluoren-9-ol and diphenylmethyl azide from benzhydrol.


X-C6H4
C=CH2
H⊕
⊕C-CH3
HO—C-CH3
C6H5
XVI
XVIII
XVII
H-N-N≡N
-H⊕
N≡N—N—C—CH3
N3—C—CH3
XIX
XX
~X-C6H4
~C6H5
X-C6H4-N-C-CH3
C6H5-N-C-CH3
XXI
XXII
-H⊕
X-C6H4-N=C-CH3
C6H5-N=C-CH3
XXIII
XXIV


Y
OH
X
C
H
H_2SO_4
$+H_3O^{\oplus}$
XXV
XXVI
$H-\overset{\ominus}{N}-\overset{\oplus}{N}\equiv N$
XXVII
XXVIII
XXIX
$-H^{\oplus}$
N=C
XXX
XXXI

the protonated azide, XIX. In this decomposition migration of any one of the groups attached to the central carbon can take place. There should be some correlation, therefore, between the results obtained in this rearrangement and those obtained in the rearrangement of symmetrical pinacols, since in both there is a freely competitive migration to an electron deficient atom. This expectation is borne out, as shown in Table V.

TABLE V (10)(14)

Schmidt Reactions of Diarylethylenes, $\begin{matrix} X\text{-}C_6H_4 \\ Y\text{-}C_6H_4 \end{matrix}\!\!>\!C{=}CH_2$

Substituent		Percent Yield of Products	
X	Y	$X\text{-}C_6H_4$ migration	$Y\text{-}C_6H_4$ migration
H	p-OCH_3	8	49
H	p-CH_3	8	40
H	p-C_6H_5	17	39
H	p-Cl	29	18
H	3,4 diCH_3	6.76	36.6
H	p-C_2H_5	9.75	44.6
H	m-CH_3	14.5	34.2
H	p-F	26.1	45.8
H	p-Br	29.6	16.0
p-OCH_3	p-CH_3	39	8
p-OCH_3	p-C_6H_5	36	11
p-CH_3	p-C_6H_5	21	6

It can be seen from the discussion above that the mechanisms of the various Schmidt reactions are fairly well elucidated and can be correlated with each other pretty well. What does remain to be done, not only for this reaction but for many others also, is to discover and evaluate the factors which influence rearrangement.

C. The Hammett Equation and Its Applications

Hammett observed (15) that there is a simple linear relationship,

$$\log k_1 = \rho \log k_2 - A, \qquad (1)$$

where k_1 = rate or equilibrium constant in a reaction of some m- or p-substituted benzene derivative.

k_2 = rate or equilibrium constant in a second such reaction of a derivative with the same substituent.

ρ, A = constants

between the side chain reactions of m- and p-substituted benzene derivatives. By relating all such reactions to a standard reference reaction, the equation

$$\log (k/k_o) = \rho \sigma \qquad (2)$$

was derived in which

k = rate or equilibrium constant of a m- or p-substituted benzene derivative in a given reaction.

k_o = rate or equilibrium constant of the unsubstituted benzene derivative in the same reaction.

ρ = a "reaction constant" which is constant for all substituents in a given reaction series.

σ = a "substituent constant" which is constant for a given substituent in all reaction series.

Sigma values are defined as $\log (K/K_0)$ (K is the rate or equilibrium constant for a substituted benzene derivative, while K_0 is the same constant for the unsubstituted derivative), so by using some suitable reference reaction they may be determined independently of any other reaction. The standard of reference was taken by Hammett as the equilibrium constants for the benzoic acids, since these have been determined quite accurately.

It can be seen, therefore, that in essence the Hammett equation (equation 2) compares the effect which a given substituent has on the acidity of benzoic acid with the effect it has on the reaction in question. Theoretically, the basis for such a relationship lies in a dependence of the rates or equilibria in a reaction series upon only the potential energy differences between the products and reactants; i.e., the kinetic energy and entropy differences are either zero or proportional to the potential energy differences. It happens that this requirement is met fairly well by side chain reactions of m- and p-substituted benzene derivatives.

In its application to nucleophilic displacement and addition reactions, the Hammett equation is very successful. It has been stated (16) that by 1940 it correlated the rates

of 1763 reactions. Of these, 332 had been measured experimentally, and the median deviation between observed and calculated rates was only ± 15%, in spite of an average change of rate of thirtyfold in going from p-methoxy to p-nitro and as much as a thousandfold change in some cases.

Swain and Langsdorf (16) have related the sign and magnitude of rho with the magnitude of the partial positive charge on the central carbon in the transition state of a nucleophilic displacement reaction, symbolized by XXXII. If, in this transition state, the old bond e has been broken to a greater extent than the new bond n has been formed, a partial positive charge will reside on the central carbon atom. Electron-donating substituents will aid such a reaction; i.e., the greater this positive charge, the more negative will be rho.

It was also pointed out that in nucleophilic displacements, it would be expected that strongly electron-supplying substituents, such as p-methoxyl, would not only stabilize the transition state having a partial positive charge on the central carbon atom, but would also increase the <u>capacity</u> for positive charge. The net result would be more bond breaking in the transition state and an even more negative rho than the mean. An electron attracting group would favor bond making and a more positive rho. This combined effect would show itself as an upwards concavity in the plot of sigma <u>vs</u>. log (k/k_o). Also, if such an effect were due to

resonance in the transition state, there would be a difference between m- and p-substituents, since reasonable resonance structures cannot be written for interaction involving a m- substituent. Both these hypotheses were verified by data selected from the literature.

Hammett also applied his equation, using the sigma values derived from the acidities of benzoic acids (hereafter referred to as sigma (n) values), to electrophilic substitution reactions (17).

Using data obtained for relative rates of nitration, the log of the reactivity of a given position in a substituted benzene compared to a position in benzene was plotted against sigma (n) values. The linear relationship required by the Hammett equation (2) was not observed exactly, but there was a very definite parallelism between the values plotted. A value of about -5 for rho was obtained.

Other applications of the Hammett equation to electrophilic substitution reactions have been made (18) using data from bromination and chlorination of monoalkylbenzenes. This data is very limited in the type of substituents studied, since it was the effect of hyperconjugation that was being studied.

If in the plot of sigma (n) vs. the log of the relative rates of halogenation, the rates for benzene and toluene are taken as establishing a "normal" linear Hammett

relationship (rho = -15*), the rates for ethyl, isoprophy and t-butyl are progressively slower than this "normal". These results have been taken (20) to indicate the importance or hyperconjugation in the transition state of electrophilic substitution.

Since the Hammett equation compares the electrical effects in a given reaction with those in the ionization of benzoic acids, it might be stated that hyperconjugation is of more importance in determining the rate of electrophilic substitution than it is in determining the degree of ionization of benzoic acids.

As it has been pointed out (18), however, variable ortho-para ratios of substitution products in electrophilic substitution make it difficult to assign definite substituent influence to any one position. The accuracy of such applications is limited to the extent of variation of ortho-para ratios.

There is another type of reaction which has been compared (21) to electrophilic substitution -- migration of an aryl group to a neighboring cationic atom (see following section). On the basis of such a concept, the Hammett equation has been applied to the rates of reaction of the substituted acetophenone oximes in the Beckmann rearrangement

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* In this paper the authors use a value of -0.138 for sigma (n) of the p-methyl group and get a different rho. In a later paper (19) they return to Hammett's value, -0.170.

(18) (19), the rates of nitrogen evolution in the Schmidt reaction of benzoic acids (14), the migratory ratios in the Schmidt reaction of diarylethylenes (14) and the migratory ratios in the pinacol rearrangement of symmetrical benzopinacols (14).

In the Beckmann rearrangement series it was assumed that certain groups would have a constant effect as far as electrophilic and nucleophilic displacement is concerned. For these groups (m- and p-nitro, m-methyl and 3,5-dimethyl) sigma (n) would not significantly differ from sigma (e)* values. When the log of the relative rates of rearrangement of the acetophenone oximes having these substituents were plotted against sigma (n) values, a good linear relationship was observed. It was found that p-methylacetophenone also fell on this line, so it was concluded that any aid which hyperconjugation gave to the reaction was insignificant. The interesting observation was also made that the p-methoxy and p-chloro compounds reacted 3.8 and 1.8 times as fast, respectively, as would be predicted from the linear relationship. This was attributed to the extra pairs of electrons in these substituents which can exert a favorable electromeric effect at the demand of the electrophilic reagent. It was suggested (19) that sigma (e) values of -0.56 for p-methoxyl and -0.086 for p-chloro be assigned in order to

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* Used (18) to signify sigma values for electrophilic substitution reactions.

restore a linear relationship in electrophilic substitutions.

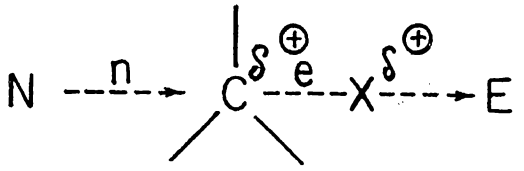
When these sigma (e) values were applied to the pinacol rearrangement in which there was obtained (14) a curved Hammett plot using sigma (n) values, it was found (18) that, while the line was straightened considerably, there was still a large discrepancy.

On the other hand, in Schmidt reactions of diarylethylenes and benzoic acids, it was found (14) that, when plots of the log of the migratory ratios and log of the relative rates, respectively, were made -- both vs. sigma (n) values -- a good linear relationship was found.

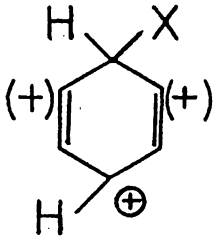
To the present time these Schmidt reactions are the only rearrangements found to obey the Hammett equation using sigma (n) values. Results presented in this thesis show that the Schmidt reactions of benzhydrols follow this relationship, as well as the Hofmann and Lossen rearrangements of benzoic acid derivatives.

D. Mechanism of the Migration of a Phenyl Group

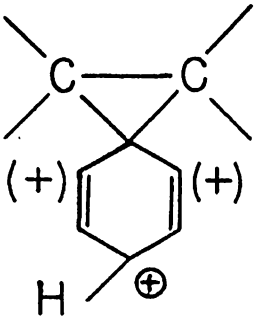
The analogy between the migration of a phenyl group to a neighboring cationic atom, on the one hand, and the electrophilic substitution of a benzene derivative, on the other, has been a fascinating one to many chemists. Such an analogy is based on the similar transition ions probably formed in each case. Compare, for example, XXXIII, which represents a resonance structure of the transition ion for attack of an X cation on benzene, and XXXIV, which



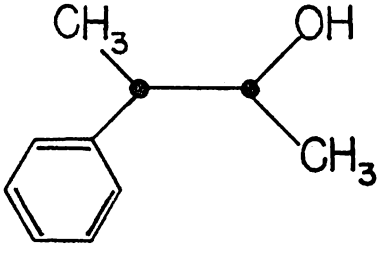
XXXII



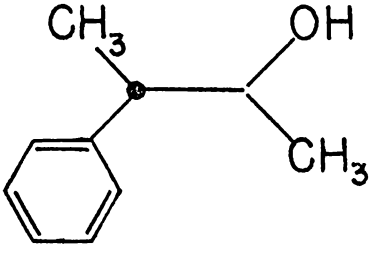
XXXIII



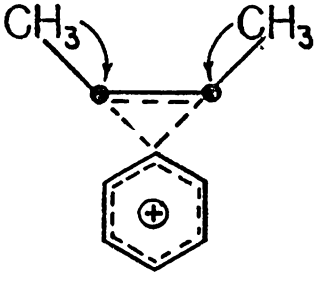
XXXIV



d-XXXV



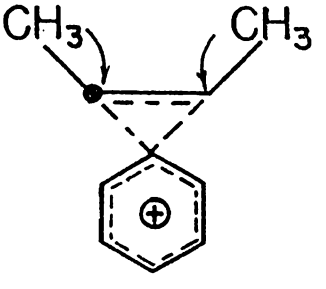
d-XXXVI



XXXVII

HOAc

d,l-XXXV ACETATE



XXXVIII

HOAc

d-XXXVI ACETATE

corresponds to the transition ion in migration of a phenyl group to a cationic carbon.

Some evidence concerning the exact nature of the transition ions in migrations of phenyl groups to cationic carbon has been published in the last few years. Cram found it necessary to postulate the "existence of a discrete molecular species, a carbocyclic three-membered carbonium ion as an intermediate in a Wagner-Meerwein rearrangement..." (22), on the basis of an investigation of the solvolysis in acetic acid of the p-toluenesulfonates of optically pure enantiomorphs of both racemates of 3-phenyl-2-butanol (XXXV and XXXVI).*

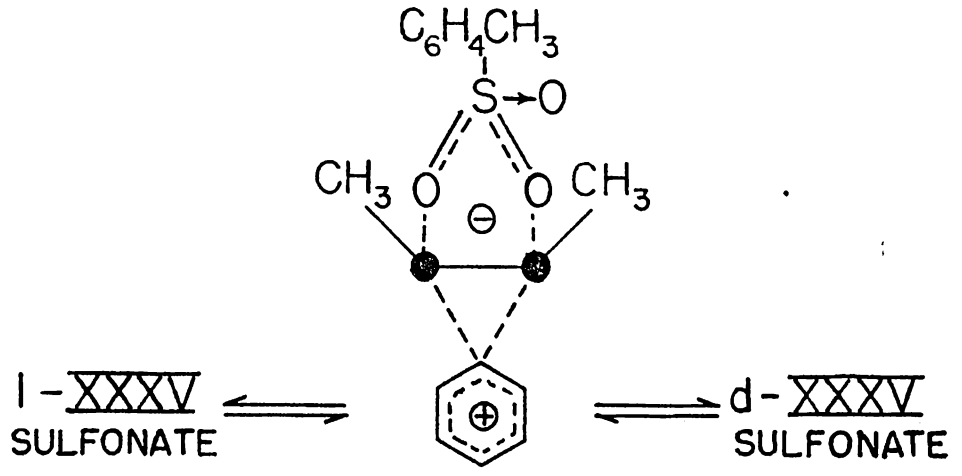
The results and conclusions of this earlier work may be summarized briefly. With pure enantiomorph d-XXXV, the essentially racemic d,l XXXV acetate was obtained; while with pure d-XXXVI, the almost optically pure d-XXXVI acetate was isolated. The explanation of these results involves discrete "phenonium" ions XXXVII and XXXVIII, which arise by <u>trans</u> attack of the phenyl group (displacing a p-toluenesulfonic acid molecule) in d-XXXV and d-XXXVI p-toluenesulfonate, respectively. Inspection of these ions show that one (XXXVII) has a plane of symmetry, so the products of further reaction must be racemic (i.e., attack, with inversion, by an acetic acid molecule must occur to the same extent at each of the

---

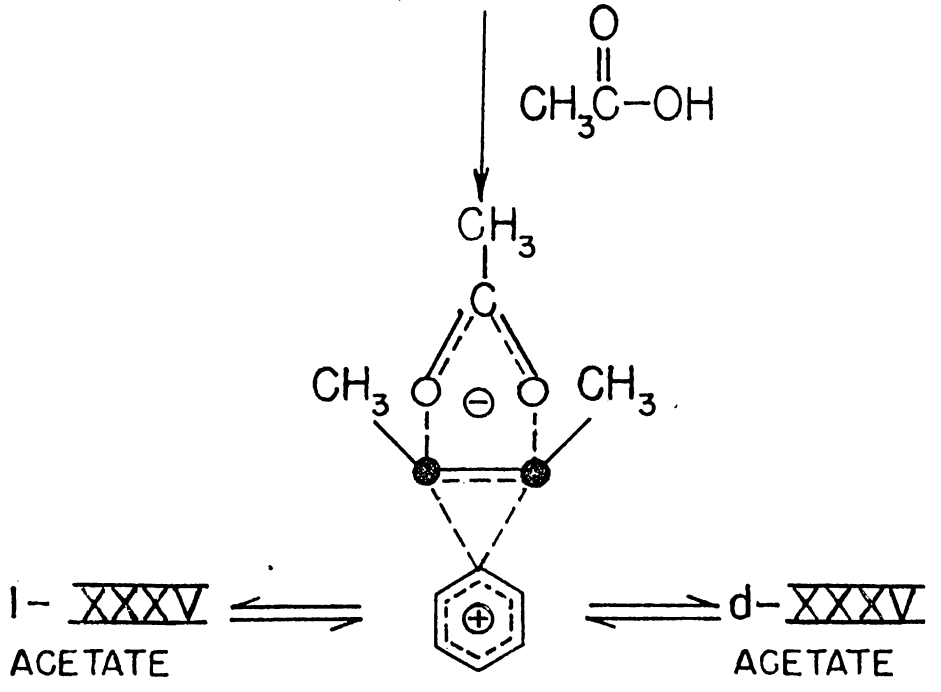
* In the formulae heavy dots signify carbon atoms with hydrogens projecting upward from the plane of the paper.

indicated carbons since both are identical; therefore equal amounts of d- and l-XXXV acetate are formed). Ion XXXVIII, on the other hand, is asymmetric. Attack, with inversion, by an acetic acid molecule at either of the indicated positions gives d-XXXVI acetate.

Winstein and Trifan (23) initiated further work on this type of system when they observed in the solvolysis of optically active exo norbornyl p-bromobenzenesulfonate that racemization was markedly faster than could be accounted for by evolved p-bromobenzenesulfonic acid. This indication that racemization and solvolysis are not necessarily dependent processes caused a reinvestigation (24) of the solvolyses of the sulfonate esters of 3-phenyl-2-butanol. It was found that indeed, racemization was faster than solvolysis (in acetic acid at 75° C., about four times as fast). Since the solvolysis is irreversible, however, at least 20% of the racemization must still be due to some type of bridged phenonium intermediate. Both racemization and solvolysis can be accounted for by a single species -- the phenonium tosylate ion pair XXXIX (written as it would arise from d- or l-XXXV). This ion pair may with equal probability revert to d-XXXV p-toluenesulfonate or form l-XXXV p-toluenesulfonate (racemization). It has been shown that this "internal return" (25) is an intramolecular process unaffected by added sulfonate ion. This indicates that there are definite, appreciable forces holding the ion pair together. Depending


C6H4CH3
S→O
CH3
O
O
CH3
⊖
⊕
l-XXXV
SULFONATE
d-XXXV
SULFONATE

XXXIX


O
CH3C-OH
CH3
C
CH3
O
O
CH3
⊖
⊕
l-XXXV
ACETATE
d-XXXV
ACETATE

XL

on the ionizing power of the solvent, the ions will dissociate to some degree, and anions derived from the solvent will replace the sulfonate anions (solvolysis). The resulting phenonium acetate XL, arising from the solvolysis in acetic acid, will collapse to the same extent in each direction giving d,l-XXXV acetate.

The novel suggestion that ion pairs, such as XXXIX and XL, represent distinct intermediates of some stability in this reaction leads to the implication that such ion pairs may play a part in determining the course of other reactions and rearrangements, including electrophilic substitution and solvolysis.

DISCUSSION OF EXPERIMENTAL RESULTS

Schmidt reactions of m- and p-substituted benzhydrols were carried out with two objectives in mind: first, to extend the reaction to an enlarged group of reactive alcohols; and second, to determine how substituents of differing electronic character affected the ratio of products obtained.

Benzhydrol itself has been subjected to the Schmidt reaction (12) (26), yielding, after hydrolysis, benzaldehyde and aniline (see section on mechanism). In the only reported Schmidt reaction involving an unsymmetrically substituted benzhydrol, it has been claimed (27) that only p-toluidine and benzaldehyde are obtained from the Schmidt reaction of p-methylbenzhydrol.

In the first attempts to carry out Schmidt reactions with m-chloro, p-chloro and p-methoxybenzhydrol by adding the compound to an excess of sulfuric and hydrazoic acids, large amounts of nitriles were detected in the neutral products of hydrolysis. These undoubtedly arose by a secondary reaction of the initially formed Schiff bases with the excess hydrazoic acid. Since one of the objectives of this investigation involved finding the relative amounts of migration of the substituted and unsubstituted phenyl groups, this additional reaction was an undesirable one -- especially in view of the fact that indeterminate amounts of formamides were also undoubtedly obtained in conjunction with the nitriles (see mechanism section). This difficulty was

surmounted by using a modified procedure introduced (13) by Ege and Sherk, which involves preliminary formation of an azide by a trichloroacetic acid-catalyzed condensation of the benzhydrol with hydrazoic acid. Rearrangement of the azide with sulfuric acid is carried out only after the excess hydrazoic acid has been washed out of the reaction mixture, so no secondary Schmidt reactions are possible. This procedure was successfully applied to seven substituted benzhydrols (see Table VI).

TABLE VI

Product Ratios in Schmidt Reactions with Benzhydrols $ArCH(OH)C_6H_5$

Ar	Migratory Ratios[a] from distillation of amines	Migratory Ratios[a] from oxidation of aldehydes
$p\text{-}CH_3OC_6H_4$	3.7	6.5[b,d], 6.5[b,c,d]
$p\text{-}C_2H_5OC_6H_4$	2.9	8.8[c,d]
$p\text{-}CH_3C_6H_4$	-- g	3.53, 3.35[e,f]
$p\text{-}C_6H_4C_6H_4$	-- g	-- g
$p\text{-}ClC_6H_4$	0.5	0.60[e,h], 0.75[c,f]
$p\text{-}BrC_6H_4$	-- g	0.58[e,h], 0.58[c,f]
$m\text{-}ClC_6H_4$	0.20	0.27[c,h]

[a]Ratio of substituted aniline to aniline or benzoic acid to substituted benzoic acid. [b]Corrected value, see Discussion. [c]Acids obtained by silver oxide oxidation of neutral products. [d]Analysis of mixed acids by alkoxyl analysis. [e]Acids obtained by bisulfite extraction of mixed aldehydes followed by oxidation with permanganate. [f]Analysis of mixed acids by solubility difference, see Experimental. [g]Products identified only qualitatively. [h]Analysis of acids by halide determination.

In all cases the Schmidt reaction products were worked up by first hydrolyzing the reaction mixture and then separating the aqueous acid layer containing the basic products from the chloroform layer containing the neutral products. The amines obtained from the aqueous layer were distilled, in some cases with sufficient care so that quantitative values of the product ratios could be obtained. Usually, however, it was considered sufficient to obtain two relatively pure fractions which were identified qualitatively by making solid derivatives. With every benzhydrol studied, aniline and the expected substituted aniline were identified as products.

It was felt at the beginning of the investigation that the determination of the ratio of aldehydes obtained as products would be more reliable than the determination of the amine ratio, since the anilines might be susceptible to sulfonation under the reaction conditions. The good agreement between values of product ratios obtained by investigation of both the amine fraction and aldehyde fraction in some of the runs, however, indicates that the assumption was probably incorrect.

Various methods of determining the ratio of benzaldehyde to substituted benzaldehyde were tried. Simple distillation was discarded mainly because of interference by appreciable amounts of ethyl trichloroacetate, formed from ethanol (used as a stabilizer in chloroform(and trichloroacetic acid

(used as a catalyst in the Ege and Sherk procedure). Two other procedures were successfully employed: extraction of the aldehydes from the neutral fraction of the products with saturated sodium bisulfite solution, followed by oxidation of the recovered aldehydes to the mixed benzoic acids with potassium permanganate, and selective oxidation of the aldehydes in the neutral fraction with silver oxide to yield the mixed acids. In either case the composition of the acid mixtures was determined by solubility differences or suitable elementary or functional group analyses (i.e., methoxyl, chlorine, bromine). The methods used for analyzing the acids were shown to be quite accurate. An oxidation of a synthetic mixture of p-tolualdehyde and benzaldehyde gave a value within 2% of the simulated ratio. A silver oxide oxidation of a mixture of benzaldehyde and p-chlorobenzaldehyde gave a value within 2.5% of the simulated ratio. The precision of the elementary and functional group analyses (see Experimental) indicates that great reliance can be attached to them.

Since the greatest error in determining the product ratios probably lies in the separation procedures, greater confidence is placed in the results obtained by direct silver oxide oxidation of the neutral products, the procedure in which the least number of manipulations were required.

The determination of the ratio of products from repeated Schmidt reactions of p-methoxybenzhydrol gave many varied results. This difficulty was eventually traced to a selective

loss of anisaldehyde under the conditions of the reaction and not to the analytical method. By running control experiments, it was found that only 41% of the anisaldehyde initially present could be recovered after a synthetic mixture of benzaldehyde and anisaldehyde was treated with warm concentrated sulfuric acid. The molar ratio of recovered products was 13.9 in a control experiment in which the initial ratio was 5.8. The value of 6.5 given in Table VI for the migratory ratio was obtained by averaging the apparent migratory ratios obtained in reactions II, III and VI (see Experimental) and multiplying by the correction factor, 5.8/13.9.

When rearrangement of p-methoxybenzhydryl azide was carried out with 91% sulfuric acid in an attempt to minimize loss of anisaldehyde, a migratory ratio of 7.0 ± 0.2 was obtained. A control carried out as above, but using 91% sulfuric acid, indicated a correction factor of 5.8/6.2; therefore the other value given in Table VI is 6.5.

Because of the necessity for applying the somewhat crude corrections, the migratory ratio, p-anisyl/phenyl, was not used for calculating rho in the application of a modified Hammett equation to the data. By plotting log migratory ratio against sigma (n) values for the four reactions in which the values of product ratios were determined most accurately (p-methyl, p-chloro, p-bromo, m-chloro), it was found that a linear relationship prevailed, (Fig. I). Analysis of the data by the "least squares" method gave as

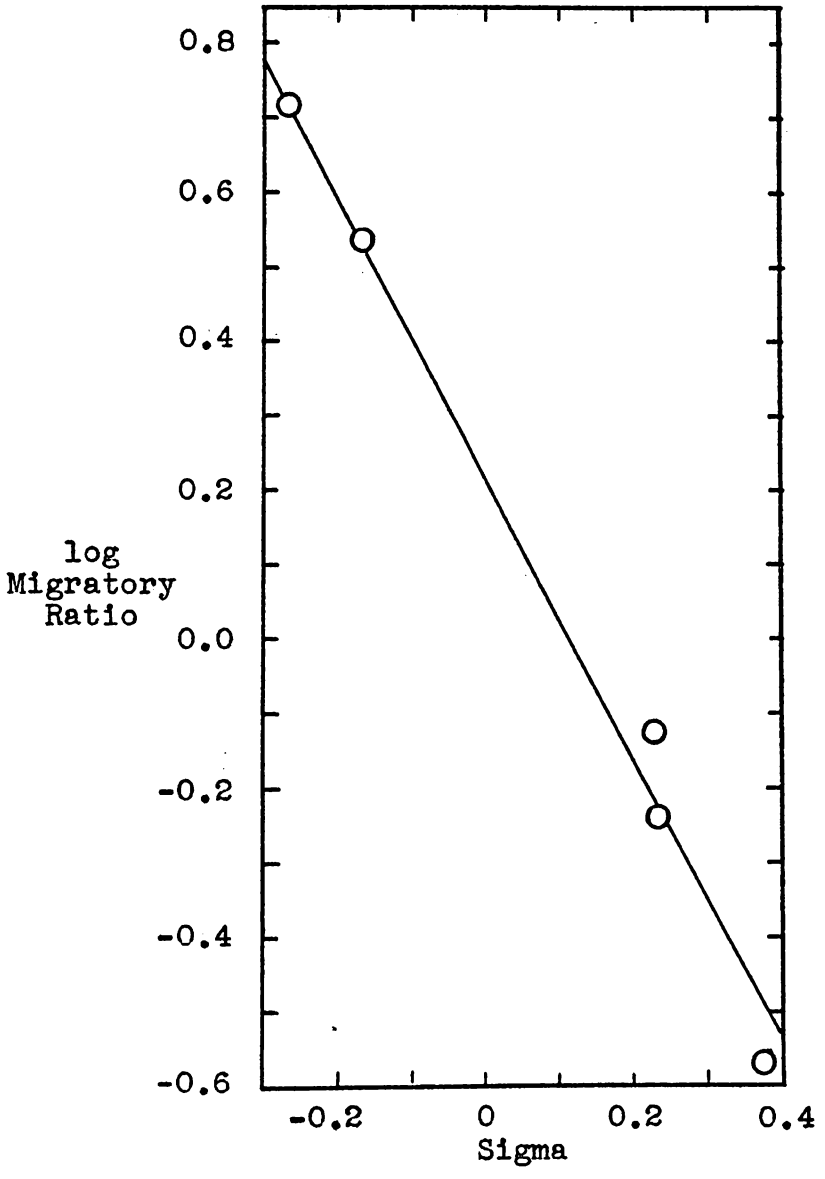


Fig. 1. -- The Hammett equation applied to the Schmidt reaction of m- and p-substituted benzhydrols.

the equation of the line,

$$\log \text{migratory ratio} = -1.88\,\sigma + 0.212 \qquad (3)$$

(Substituting the sigma (n) value for p-methoxyl gives a value of 5.2 for the p-anisyl/phenyl migratory ratio.)

It is apparent that the value for the slope, rho, is significantly less than that found in a similar plot based on data from the Schmidt reaction of unsymmetrical diarylethylenes (14) (rho = -2.11).

The fact that rho for the diarylethylenes is more negative than rho for the benzhydrols means that for substituents with negative sigma values (electron donors) the tendency to migrate is greater in the diarylethylene series than in the benzhydrol series, while with substituents having positive sigma values the tendency to migrate is less. By considering the probable intermediates, XIX and XXVII, it can be seen that the only difference in the two systems is the degree of substitution on the central carbon atom. In XIX there is a methyl group present, while XXVII there is a hydrogen.

That a methyl group on the carbon from which migration of an aryl group takes place should increase the ratio of migration of phenyl groups having electron donating substituents to the phenyl group itself is not obvious. However, some work of Winstein and associates (28-33) on the effect of neighboring carbon and hydrogen on solvolysis of sulfonate esters indicates that such a finding is not without precedent.

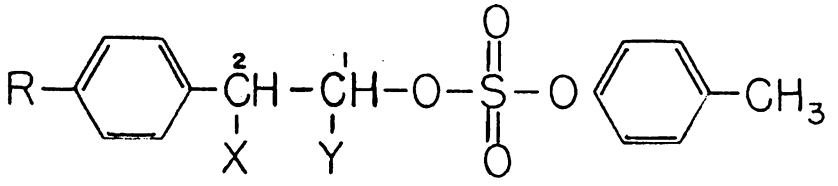
In systems of type XLI, in which compounds having varying degrees of phenyl substitution on C_2 are solvolyzed in acetic acid, a substantial and even overpowering increase in rate due to phenyl participation in the ionization process is observed (see Table VII).

TABLE VII (28)

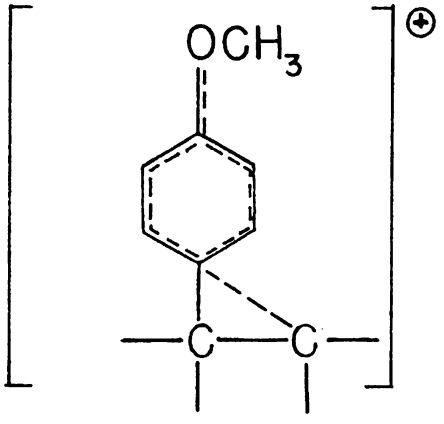
Relative Rates of Solvolysis of Substituted Ethyl p-Toluenesulfonates (XLI)

Substitution on C_2	Relative k(HOAc)	Estimated* k/k_c
trimethyl	1	1
diphenyl	53	5.3×10^3
dimethylphenyl	460	4.6×10^3
triphenyl	7.7×10^3	7.7×10^6

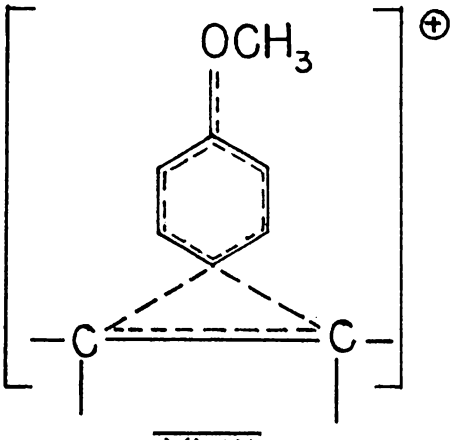
In the solvolysis of 2-phenylethyl p-toluenesulfonate (XLI, R,X,Y = H), it was found (33) that in ethanol and acetic acid, phenyl participation is not very important in determining the rate of solvolysis, but that in formic acid it may play a prominent role. In the solvolysis of 2-p-anisylethyl p-toluenesulfonate (XLI, R = OCH_3; X,Y = H), however, the rates are "most easily understood on the basis that there is anchimeric assistance to ionization....in acetic and formic acid" (see Table VIII).



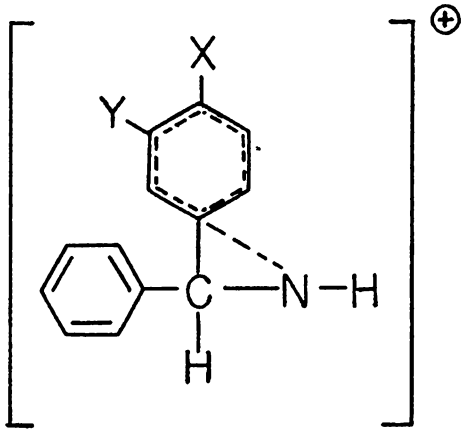
XLI



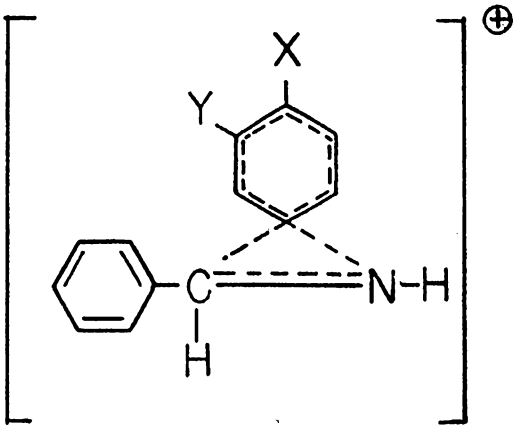
XLII



XLIII



XLIV



XLV

TABLE VIII (33)

Solvolysis of p-Toluenesulfonates

	Relative Rates		
p-toluenesulfonate	EtOH	HOAc	HCOOH
ethyl	1	1	1
2-phenylethyl	0.24	0.37	2.0
2-anisylethyl	0.45	10.0	94

When a methyl group is introduced on C_2 in the latter two compounds, a definite and different enhancement of rate is observed (see Table IX).

TABLE IX (33)

Solvolysis of p-Toluenesulfonates

p-toluenesulfonate	relative rate (HOAc, 49.7°)	relative rate (HCOOH, 25.12°)
2-anisylethyl (XLI; R = OCH_3; X,Y = H)	1	--
2-anisyl-2-methylethyl (XLI; R = OCH_3; X = CH_3; Y = H)	15.2	--
2-phenylethyl (XLI; R,X,Y = H)	--	1
2-phenyl-2-methylethyl (XLI; R,Y = H; X = CH_3)	--	8.4

Though the above comparisons are made under apparently very different conditions, they are both made under conditions where phenyl and p-anisyl participation are important. (The fact that there is probably less participation of the phenyl group in the solvolysis of 2-phenylethyl p-

toluenesulfonate than in the other three cases* would not account for the difference observed. An enhanced rate due to more participation in 2-phenylethyl p-toluenesulfonate would mean that the relative rate of solvolysis of 2-phenyl-2-methylethyl p-toluenesulfonate would be even less than 8.4).

It was found (33) possible to correlate the relative rates of solvolysis of compounds of the type XLI by an equation,

$$2.303\ RT \log k/k_o = d_1N_1 - d_2N_2 \qquad (4)$$

where k/k_o = relative solvolysis rate compared to the unmethylated p-toluenesulfonate

d_1, d_2 = parameters for the stabilization of the transition state per methyl group added to C_1 or C_2

N_1, N_2 = number of C_1 or C_2 methyl groups

The parameters for p-anisyl and phenyl neighboring groups are given in Table X.

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* Winstein and Schreiber (32) have shown that the phenyl group has taken over substantial control of the rate determining step in solvolysis of 2-phenyl-2-methylethyl p-toluenesulfonate (more exactly, 2-phenyl-1-propyl p-toluenesulfonate).

TABLE X (33)

Parameters for Equation (4)

neighboring group	solvent	Temp.(°C.)	d_1	d_2
p-anisyl	HOAc	49.7	2.13	1.74
phenyl	HCOOH	25.12	2.68	1.36
phenyl	HOAc	49.7	2.80*	1.23*

It can be seen that as far as enhancing rate is concerned a 2-methyl group is more effective when p-anisyl is the migrating group. Winstein correlates the smaller d_1 in the case of p-anisyl with a smaller cationic character of C_1 in the transition state involving p-anisyl as the neighboring group.

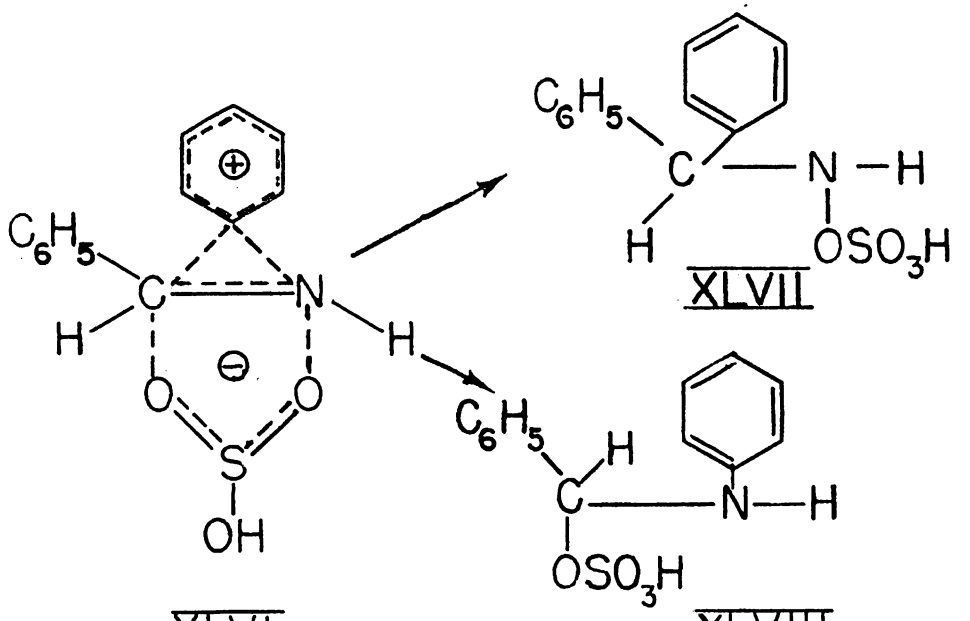
In a sense this correlation may be taken as evidence that in the Schmidt reactions of benzhydrols and diarylethylenes the degree of participation of a phenyl group in ionization of the adjacent nitrogen (and therefore departure of molecular nitrogen) determines the relative rates of migration of these groups. For example, with phenyl groups having electron donor substituents, delocalization of the binding electrons between the central carbon atom and the phenyl group will be easier, leading to greater participation and therefore a greater fraction of migration. Winstein, et. al. (28-33) write structures, such as XLII and XLIII, for the

* Actually based on 2-phenyl-1-propyl p-toluenesulfonate as reference.

transition states to indicate participation of a phenyl group in ionization at C_1. (Transition ion XLIII may or may not be of lower energy than XLII). Such structures, indicating participation, may also be written for the migrations taking place in the Schmidt reaction of benzhydrols (XLIV and XLV).

In the systems studied by Cram and Winstein, participation in ionization is not synonymous with rearrangement, due to the phenomenon of "internal return" (see Section D in Background and Historical Review). In the case of the Schmidt reaction, however, it would seem that "internal return" could not take place. Participation would be identical with migration since a nitrogen molecule would not be expected to take part in the formation of ion pairs, such as XXXIX. There is a chance, however, that the transition ions might be relatively stable, thus allowing solvation to occur. Since sulfuric acid is usually the medium used for Schmidt reactions, association would be with a bisulfate ion. The resulting ion pair, XLVI, would be quite similar to that formulated by Cram (XXXIX).

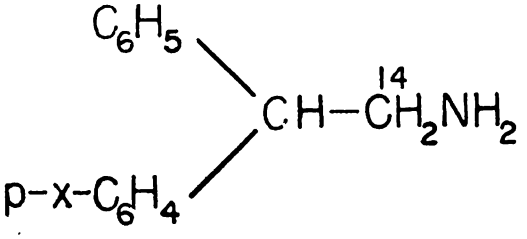
The products resulting from the collapse of such an ion pair would be the N-alkyl hydroxylamine o-sulfonic acid, XLVII, and the sulfate, XLVIII, which is merely the species to be expected on dissolving a Schiff base in sulfuric acid. Experimental proof of the intervention of such an ion pair as XLVI in the rearrangement would be very difficult to come by, since XLVIII would be obtained from the Schiff bases



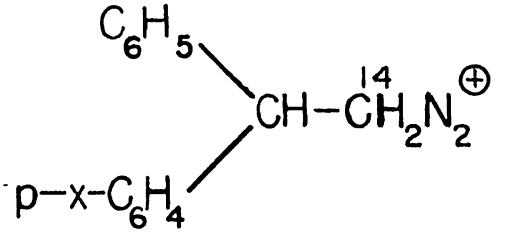
XLVI

XLVII

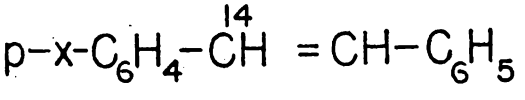
XLVIII



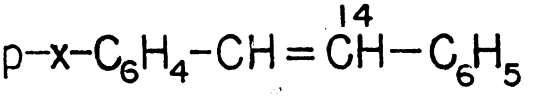
XLIX



L



LI



LII

which are the ordinary products obtained from the reaction, and XLVII would probably rearrange in a manner analagous to that of the original azide,* yielding bisulfate ion (instead of nitrogen) and the usual Schiff bases. Only if the rate of rearrangement of XLVII were significantly slower than that of the protonated azide (XIX or XXVII) would it be possible to isolate the hydroxylamine. It could also be true that formation of the ion pair would have no effect on the products obtained (collapse to give only products of type XLVIII). In that case it still might have an effect on the energy of the transition state and therefore the rate of rearrangement. It might be of interest in this connection to study the effect of added bisulfate or sulfate ion on the rate of rearrangement in the Schmidt reaction of symmetrically substituted benzhydrols.

Some recent work by Burr and Ciereszko (35) must be considered in view of the fact that a distinct order of participation (migratory) aptitudes has been found for various m- and p-substituted phenyl groups in the Schmidt reactions with both unsymmetrical diarylethylenes and benzhydrols.

By reaction of a series of α-C (14) β,β-diarylethylamines (XLIX) with nitrous acid, a rearrangement occurred, presumably by way of the diazonium cation L, to

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* Sherk, et. al. (34) found that hydroxylamine o-sulfonic acid reacts with ketones to give products similar to those obtained from a Schmidt reaction with the same ketones.

give the isomeric stilbenes LI and LII. It was found that phenyl, p-tolyl and p-biphenylyl groups all migrated at almost equal rates, while p-anisyl migrated only slightly faster.

For an explanation of these differences it is necessary to consider the one difference in the two systems. In one case molecular nitrogen departs from a nitrogen atom while in the other case it departs from a carbon atom. Since carbon has a lower ionization potential than nitrogen, it would be easier for molecular nitrogen to leave from carbon than from nitrogen. When the very stable nitrogen molecule departs from the carbon atom, it leaves a high energy carbonium ion which attacks neighboring aryl groups on an almost statistical basis.

The process of a nitrogen molecule leaving nitrogen, however, is a sufficiently more difficult process so that the aid to ionization offered by aryl participation can show its effect. (It is interesting that in systems where aryl participation has been proved to be very important much larger negative rho values (-7.1 (30) and -7.65 (32)) were obtained in comparisons of p-anisyl with phenyl.)

An examination of the literature revealed that rate studies have been carried out on the Hoffmann reaction of some m- and p-substituted N-bromobenzamides (36) and the Lossen rearrangement of the potassium salts of m- and p-substituted o-benzoylbenzhydroxamic acids (37). Both these

reactions involve migration of aryl groups to an electronically deficient nitrogen atom, as does the Schmidt reaction of benzoic acids. By plotting log relative rate vs. sigma (n) values, a linear relationship was found to hold for the Hofmann and Lossen reaction data (Fig. II). A similar relationship had already been noted (14) with rate data from the Schmidt reaction of p- and m- substituted benzoic acids.

Analysis by the method of "least squares" gave a rho value of -2.53 for the Hofmann and -2.51 for the Lossen rearrangement series. Comparison with the rho value (-1.76) observed in the Schmidt reaction series indicates that aryl participation is more important in the Hofmann and Lossen reactions that it is in the Schmidt reaction. This again may be due to an increased opportunity for participation by neighboring aryl groups in the former two reactions, since molecular nitrogen might be expected to depart with greater ease than bromide or benzoate ion.

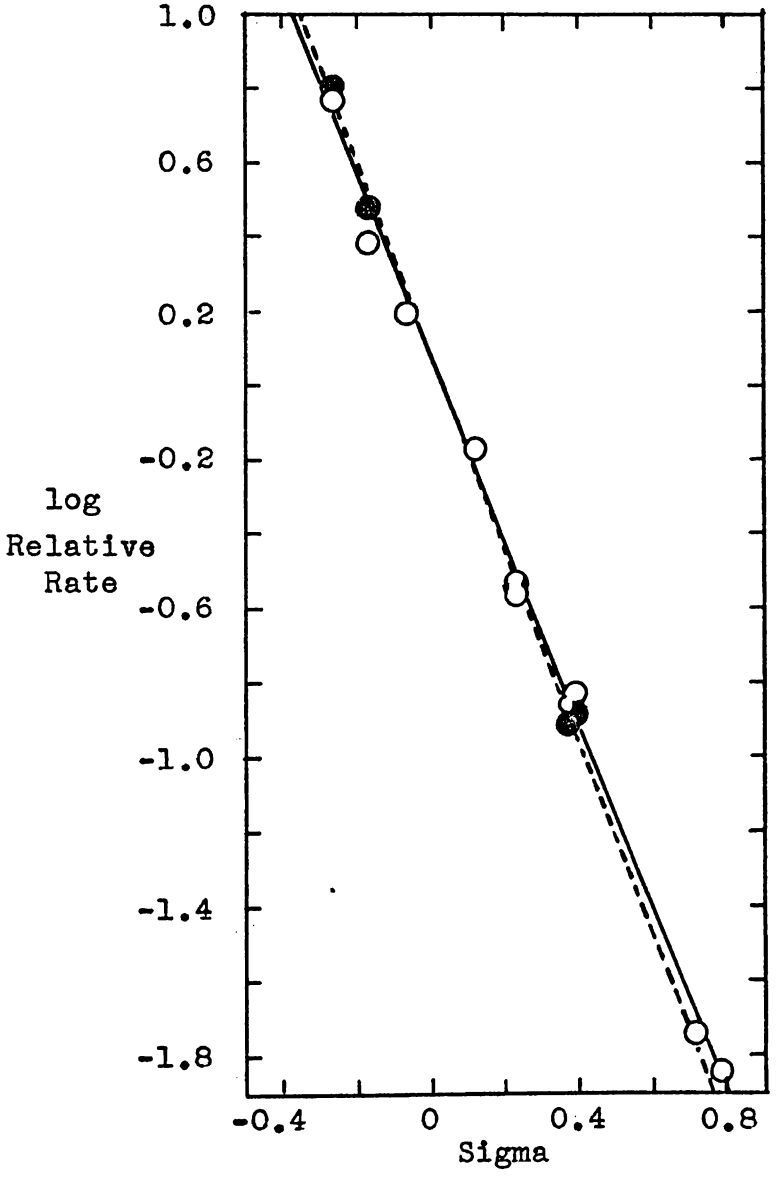

Fig. 2. -- The Hammett equation applied to (----) the Hofmann rearrangement of m- and p-substituted N-bromobenzamides and (——) the Lossen rearrangement of m- and p-substituted O-benzoylbenzhydroxamic acids.

m-Chlorobenzophenone -- This compound was prepared by the Perrier modification of the Friedel-Crafts reaction (39). The necessary m-chlorobenzoyl chloride was prepared as follows:

In a 1 l., 2-necked flask fitted with a reflux condenser, which had a hydrochloric acid gas trap attached to the top, were placed 105.9 g. (0.676 mole) of m-chlorobenzoic acid and 81 ml. (134 g., 1.13 mole) of redistilled thionyl chloride. An oil bath was used to heat the mixture at 50-60° until no more hydrogen chloride was evolved. Excess thionyl chloride was distilled off under aspirator pressure with some warming to insure removal of all traces of the volatile reagent. The resulting crude m-chlorobenzoyl chloride was used without further purification in the Friedel-Crafts reaction described below.

One hundred grams of anhydrous aluminum chloride was added to the crude acid chloride in small portions. Warming was necessary to keep the mixture fluid; after addition of the aluminum chloride had been completed, however, the liquid was cooled, giving a dark solid. A liter of dry carbon disulfide was used to dissolve the solid complex, then 100 ml. (88 g., 1.13 mole) of dry, thiophene-free benzene was added quickly through a dropping funnel. After refluxing for four hours, hydrogen chloride evolution had

ceased. Roughly one-half of the carbon disulfide was removed by distillation, and four hundred milliliters of water containing 150 ml. of concentrated hydrochloric acid was added to the residue. The aqueous layer was separated and extracted with a few hundred milliliters of benzene. The benzene extract and carbon disulfide layer were combined and extracted twice with 100 ml. of 10% sodium bicarbonate solution. (Acidification of these extracts yielded 6.0 g. of m-chlorlbenzoic acid.) Removal of solvent by distillation gave a solid residue of m-chlorobenzophenone, 102.6 g. (0.474 mole, 74%), n.p. 78-80°, without recrystallization (reported (40, 82-83°).

m-Chlorobenzhydrol -- Reduction of m-chlorobenzophenone to m-chlorobenzhydrol has been accomplished using alcoholic potassium hydroxide (41), sodium amalgam and alcohol (42), and aluminum amalgam with 80% alcohol (43). The procedure used here is adapted from that described in Organic Reactions (44) for the reduction of benzophenone by means of aluminum isopropoxide and isopropyl alcohol.

In a 2.l., 2-necked flask fitted with a modified Hahn partial condenser (45) were placed 94.7 g. (0.438 mole) of m-chlorobenzophenone, 90 g. (0.441 mole) of aluminum isopropoxide and 800 ml. of dry isopropyl alcohol. Heating of the reaction mixture in an oil bath was adjusted so that distillation through the partial condenser was very slow. A total of 320 ml. of distillate was collected during eleven hours.

At the end of this time a test for acetone using 2,4-dinitrophenylhydrazine (46) was negative.

Most of the isopropyl alcohol was distilled off under aspirator pressure and the residual oil poured on a mixture of 800 g. of ice and 140 ml. of concentrated hydrochloric acid. One liter of ether, in portions, was used to extract the resulting oil. This ethereal solution was dried over Drierite, distilled, and the yellow liquid remaining recrystallized from ligroin. The yield of m-chlorobenzhydrol was 57.5 g. (0.263 mole, 60%), m.p. 38.4-39.6° C. (corr.) (reported, 38° (43), 40° (41) (42)).

p-Bromobenzophenone -- Preparation of this compound was carried out by using the Perrier modification of the Friedel-Crafts reaction (39).

The required p-bromobenzoyl chloride was made by heating together at 50-60°, 100 g. (0.497 mole) of p-bromobenzoic acid, 96.5 g. (0.81 mole) of redistilled thionyl chloride, and a few drops of pyridine. Evolved hydrogen chloride was led from the top of the condenser into a trap containing sodium hydroxide solution. After five hours the reaction was apparently complete, so excess thionyl chloride was removed under aspirator pressure with some warming. The crude p-bromobenzoyl chloride solidified in the flask.

In a 2 l., 3-necked flask fitted with a reflux condenser (with an HCl trap) and a mercury seal stirrer was placed the crude p-bromobenzoyl chloride. While this was warmed on an

oil bath, 110 g. (0.82 mole) of anhydrous aluminum chloride was added in small portions. Once addition of the aluminum chloride had been completed and the complex cooled, one liter of dry carbon disulfide was added and the mixture refluxed in an attempt to dissolve the solid. All did not dissolve, however, and it was therefore suspended by stirring vigorously. Through a dropping funnel 100 ml. (87.9 g., 1.14 mole) of dry, thiophene-free benzene was added rather quickly. After refluxing for four hours, hydrogen chloride stopped coming off, and the mixture was poured into 800 ml. of ice water containing 100 ml. of concentrated hydrochloric acid. Separation of the carbon disulfide layer, washing twice with 50 ml. of 10% sodium bicarbonate solution and once with 100 ml. of water, followed by distillation of the solvent, gave a residue which yielded 24.8 g. of slightly yellow solid on recrystallization from benzene. Further concentration of the mother liquor gave only oil, so the benzene was removed completely and the residue distilled under reduced pressure. A fraction, b.p. 148-152° (1.3 mm.), was collected, which solidified to a grayish crystalline solid. This was combined with the solid obtained by crystallization, yielding 81.3 g. (0.312 mole, 63%) of p-bromobenzophenone, m.p. 77-79° (reported (47), 82.5°).

p-Bromobenzhydrol -- Reduction of p-bromobenzophenone to p-bromobenzhydrol has been reported using alcoholic potassium hydroxide (48), sodium amalgam in alcohol (48), zinc

dust and acetic acid (49), aluminum amalgam in 80% alcohol (50), hydrogen and Raney nickel (51), and aluminum sec-butoxide with 2-butanol (52). The reduction described here, using aluminum isopropoxide and iso-propyl alcohol, was adapted from that given in Organic Reactions (44) for benzophenone.

In a 1 l., 2-necked flask fitted with a modified Hahn partial condenser (45), 50 g. (0.245 mole) of aluminum isopropoxide was dissolved in 600 ml. of dry isopropyl alcohol by refluxing on an oil bath. To the slightly yellow solution was added 60.6 g. (0.232 mole) of p-bromobenzophenone. Heating was adjusted so that about 5 drops of distillate per minute came through the partial condenser. After seven hours the distillate gave a negative test for acetone (46), so the bulk of the alcohol was removed under aspirator pressure and the remaining oil poured on 500 ml. of ice water containing 75 ml. of concentrated hydrochloric acid. Extraction with ether, drying over sodium sulfate and removal of the solvent by distillation gave 59.5 g. of an oily residue which solidified on cooling. Recrystallization from petroleum ether gave 44.7 g. (0.170 mole, 73%) of p-bromobenzhydrol, m.p. 62-63° (reported, 61-62° (51), 63.5° (48), 65° (50)).

An attempted reduction of p-bromobenzophenone with zinc dust and sodium hydroxide, the Organic Synthesis (53) method for the reduction of benzophenone, yielded none of the desired alcohol. Montagne (54) has shown that under

similar conditions bromine is lost and benzhydrol obtained.

p-Chlorobenzhydrol -- Reduction of p-chlorobenzophenone to p-chlorobenzhydrol has been carried out using 3% sodium amalgam with alcohol (55), alcoholic potassium hydroxide (56), aluminum amalgam with 80% alcohol (57), irradiation in the presence of isopropyl alcohol and sodium isopropylate (58), aluminum isopropoxide with isopropyl alcohol (59), aluminum t-butoxide in (-) 2-methylbutanol (60), and zinc dust and sodium hydroxide in alcohol (61). Two methods of preparation are described below. The first is patterned after the Organic Reactions (44) procedure, which calls for the use of aluminum isopropoxide and isopropyl alcohol, and the other after the Organic Synthesis (53) procedure, employing zinc dust and sodium hydroxide in alcohol.

I. In a 2 l., 2-necked flask fitted with a modified Hahn partial condenser (45) were placed 104 g. (0.51 mole) of aluminum isopropoxide and one liter of dry isopropyl alcohol. By warming the reaction mixture on an oil bath most of the aluminum isopropoxide could be dissolved. Into the hot solution was dropped 110.7 g. (0.51 mole) of p-chlorobenzophenone. Heating was adjusted so that a very slow rate of distillation (5 drops per minute) was maintained. After twelve hours the distillate gave a negative test for acetone (46), so the remainder of the isopropyl alcohol was distilled off under aspirator pressure. The viscous residue was dropped on a mixture of one kilogram

of ice and 150 ml. of concentrated hydrochloric acid. Some of the acid was used to wash out the flask. Extraction with ether followed by drying over sodium sulfate, removal of the solvent by distillation and recrystallization of the residue from petroleum ether gave 55 g. (0.25 mole, 49%) of p-chlorobenzhydrol, m.p. 60-61° (reported, 60-61° (60), 62° (55), 67.5° (57)).

II. In a 2 l., 3-necked flask fitted with a reflux condenser and a mercury seal stirrer were placed 143 g. (3.6 mole) of sodium hydroxide pellets and 1350 ml. of 95% alcohol. This mixture was heated on an oil bath until most of the sodium hydroxide had dissolved. Then 145 g. (0.668 mole) of p-chlorobenzophenone was added and the solution refluxed until it turned dark brown (about two hours). Over a period of half an hour 136 g. of zinc dust (technical, 85% zinc, 1.8 mole) was sprinkled in. Refluxing was continued for sixteen hours, after which the hot mixture was filtered through a Buchner funnel. (Care should be taken in disposing of the precipitate of zinc and zinc salts, since upon drying in contact with air, enough heat is generated to start a fire.) The clear yellow filtrate was poured into four liters of ice water containing 300 ml. of concentrated hydrochloric acid, causing a yellow solid to precipitate. Recrystallization, once from ethanol and twice from ligroin, gave 82 g. (0.374 mole, 56%) of p-chlorobenzhydrol, m.p. 60-61°.

p-Methylbenzhydrol -- Reduction of phenyl p-tolyl ketone to p-methylbenzhydrol has been accomplished with sodium amalgam in alcohol (62), alcoholic potassium hydroxide (63), aluminum amalgam in 80% alcohol (64) and irradiation in the presence of isopropyl alcohol and sodium isopropoxide (58). The method described below is patterned after that given in Organic Syntheses (53) for the reduction of benzophenone.

In a 2 l., 3-necked flask fitted with a mercury seal stirrer and reflux condenser were placed 142 g. (3.6 mole) of sodium hydroxide pellets and 1350 ml. of 95% alcohol. This was heated until most of the sodium hydroxide had dissolved, and then 131.4 g. (0.670 mole) of phenyl p-tolyl ketone was added. After heating the reaction mixture under reflux for half an hour, the solution was deep brown. While stirring was continued vigorously, 135 g. of zinc dust (technical, 85% zinc, 1.8 mole) was dropped in carefully in small portions over half an hour. Refluxing was continued for another hour until the solution became light yellow. Filtration of the hot mixture gave a clear yellow filtrate which was poured into a 4 l. beaker containing ice and 300 ml. of concentrated hydrochloric acid. A light green precipitate was filtered off, dried in vacuo and taken up in petroleum ether. Cooling gave 113.2 g. (0.571 mole, 85%) of p-methylbenzhydrol, m.p. 52-53° (reported, 48° (64), 52-53° (62), 53-54° (65), 58° (66)).

Unsuccessful attempts were made to reduce phenyl p-tolyl ketone with aluminum isopropoxide - isopropyl alcohol

and by the irradiation method of Bachmann (58).

p-Methoxybenzophenone -- The procedure used in this preparation was that of Peterson (67).

Into a 2 l., 2-necked flask fitted with a dropping funnel and a reflux condenser (the top of which was connected to an HCl trap) were placed one liter of dry carbon disulfide, 125 g. (0.89 mole) of benzoyl chloride and 140 g. (1.05 mole) of anhydrous aluminum chloride. To this suspension was added slowly from the dropping funnel 100 g. (0.92 mole) of anisole. A dark layer formed after addition of the aluminum chloride had been completed. The mixture was swirled until no more hydrogen chloride evolved. (In other preparations of this compound the use of a mercury seal stirrer was found to be convenient.) All the carbon disulfide was then distilled off on the steam bath and the orange solid residue decomposed by cautious addition of 250 ml. of water to which 50 ml. of concentrated hydrochloric acid had been added. Extraction with ether, drying with sodium sulfate and distillation of the solvent gave an orange crystalline solid. Recrystallization from 95% alcohol gave 151.5 g. (0.715 mole, 80%) of p-methoxybenzophenone, m.p. 58-60° (reported, 62° (67), 63° (68)).

p-Methoxybenzhydrol -- The reduction of p-methoxybenzophenone to p-methoxybenzhydrol has been carried out with aluminum amalgam in 80% alcohol (69), sodium amalgam in alcohol (70), zinc dust and sodium hydroxide in alcohol (71)

(61) and irradiation in isopropyl alcohol in the presence of sodium isopropoxide (58). Below, two procedures are described. The first is adapted from Organic Syntheses (53) and the second developed along lines suggested for sodium borohydride reductions by Chaikin and Brown (72).

I. In a 2 l., 3-necked flask fitted with a reflux condenser and mercury seal stirrer, 105 g. (2.6 mole) of sodium hydroxide pellets were refluxed with one liter of 95% ethanol until almost dissolved. Addition of 107 g. (0.505 mole) of p-methoxybenzophenone and further refluxing for forty-five minutes gave a dark brown solution. Vigorous stirring was employed while 100 g. of zinc dust (technical, 85% zinc, 1.3 mole) was sprinkled in slowly during twenty minutes. Stirring and refluxing were continued for an hour before the hot solution was filtered through a Buchner funnel. Pouring the filtrate into 3 liters of ice water containing 225 ml. of concentrated hydrochloric acid gave a white precipitate which was removed and dried in vacuo. This crude material weighed 104 g. (96%), m.p. 61-63°. Recrystallization from 100 ml. of isopropyl alcohol gave 82.1 g. of material, m.p. 64-65°, and a further recrystallization from ligroin gave 78.1 g. of white needles. By dilution of the isopropyl alcohol mother liquor with water and recrystallization of the resulting precipitate from fresh isopropyl alcohol, a further 10.4 g. of material was obtained. The yield of purified material was 88.5 g. (0.413 mole, 82%),

m.p. 65-66° (reported, 60° (69), 59-60° (71), 66-68° (61), 68° (70)).

II. In a 400 ml. beaker, 28.8 g. (0.136 mole) of p-methoxybenzophenone was dissolved in 150 ml. of methyl alcohol. In a separate 50 ml. beaker 1.5 g. (0.040 mole) of sodium borohydride was dissolved in 30 ml. of methyl alcohol containing a few milliliters of 20% sodium hydroxide solution. This solution was gradually added to the stirred solution of p-methoxybenzophenone, the reaction mixture becoming quite warm in the process. The resulting clear solution was evaporated on the steam bath to about seventy-five milliliters and 150 ml. of water, in which 5 g. of sodium hydroxide had been dissolved, was added. Extraction with ether, drying and removal of the solvent left a solid residue which, after recrystallization from ligroin, amounted to 25.4 g. (0.119 mole, 88%) of p-methoxybenzhydrol, m.p. 65-66°.

p-Ethoxybenzophenone -- This compound was prepared by the same procedure used by Peterson (67) for p-methoxybenzophenone.

Into a 2 l., 3-necked flask fitted with a dropping funnel, a mercury seal stirrer and a reflux condenser (to the top of which was attached an HCl trap) were placed 140.6 g. (1.0 mole) of benzoyl chloride and 800 ml. of dry carbon disulfide. Anhydrous aluminum chloride (140 g., 1.05 mole) was added in portions with stirring. Then, through the

dropping funnel, 122.2 g. (1.0 mole) of phenetole was slowly added with continued vigorous stirring. After addition of the phenetole had been completed and no more hydrogen chloride was being evolved, the carbon disulfide was completely removed by distillation on the steam bath. The remaining solid was decomposed cautiously with 200 ml. of water to which 50 ml. of concentrated hydrochloric acid had been added. Extraction with ether, washing the ethereal solution with portions of 5% sodium hydroxide solution until no more color change was apparent, followed by removal of the solvent by distillation, gave an oily residue. Recryatallization from petroleum ether-benzene yielded 107.6 g. (0.475 mole, 47.5%) of p-ethoxybenzophenone, m.p. 47-48°, (reported, 47-48° (73)).

p-Ethoxybenzhydrol -- Reduction of p-ethoxybenzophenone to p-ethoxybenzhydrol has been accomplished with alcoholic potassium hydroxide (74) and 8% sodium amalgam in alcohol (74). The method described below is patterned after a general method for sodium borohydride reduction of ketones (72).

In a 500 ml. flask 37.5 g. (0.166 mole) of p-ethoxybenzophenone was dissolved in 150 ml. of methyl alcohol. Separately 3.5 g. (0.092 mole) of sodium borohydride was dissolved in 30 ml. of methyl alcohol containing a few milliliters of 20% sodium hydroxide solution. The hydride solution was slowly added to the stirred ketone solution. Distillation of the bulk of the methanol and addition of

50 ml. of 10% sodium hydroxide solution gave an oil which was extracted with ether. Removal of the ether left the oil again, which was then taken up in benzene-petroleum ether. Cooling gave 35.3 g. (0.155 mole, 93%) of p-ethoxybenzhydrol, m.p. 40-41° (reported, 40.7° (74)).

In an attempted reduction of p-ethoxybenzophenone with lithium aluminum hydride, a large excess of the hydride (6.5 equivalents) was used and the reaction mixture left for 17 hours. On working up the reaction mixture the only product obtained, besides high boiling residue, was roughly 50% by weight of a liquid, b.p. 128-130° (0.4 mm.) (n_D^{26} = 1.5468), whose infrared spectra showed the absence of an hydroxyl or keto group. A reduction of p-ethoxybenzophenone to ethyl (4-benzylphenyl) ether with sodium and alcohol has been reported (75), but if this product was obtained here, it apparently would be the first such hydrogenolysis reported using lithium aluminum hydride. An attempted synthesis of authentic ethyl (4-benzylphenyl) ether gave mixtures which were difficult to separate.

p-Phenylbenzophenone -- This compound was prepared in a manner similar to that used by Montagne (76).

In a 1 l., 3-necked flask fitted with a condenser (having an HCl trap attached to the top) and mercury seal stirrer were placed 45 g. (0.32 mole) of benzoyl chloride and 150 ml. of dry carbon disulfide. To this stirred solution was added in small portions, 43 g. (0.32 mole) of anhydrous

aluminum chloride. Using a dropping funnel, 48 g.(0.31 mole) of biphenyl, dissolved in 100 ml. of dry carbon disulfide, was dropped in. As the last of the biphenyl was introduced, a yellow solid precipitated. Stirring was continued for another hour, however, before the carbon disulfide was distilled off and the solid residue decomposed with 100 ml. of water containing 35 ml. of concentrated hydrochloric acid. Chloroform was used to extract the crude product, and the chloroform solution was washed twice with 25 ml. of 10% sodium bicarbonate solution before the solvent was distilled off. Traces of chloroform were removed by drying in vacuo. Without recrystallization, 75.8 g. (0.294 mole, 95%) of p-phenylbenzophenone, m.p. 99-100° (reported, 101° (69), 102° (76), 106° (77)) was obtained.

p-Phenylbenzhydrol -- Reduction of p-phenylbenzophenone to p-phenylbenzhydrol has been carried out with alcoholic potassium hydroxide (78), aluminum amalgam in dilute alcohol (79) (80), and isopropyl magnesium bromide (81). The procedure described below is adapted from a general procedure for reduction of ketones with sodium borohydride (72).

In a 1 l. beaker, 75.8 g. (0.294 mole) of p-phenylbenzophenone was dissolved in 800 ml. of hot methyl alcohol. Into this solution, 3.5 g. (0.093 mole) of sodium borohydride dissolved in 30 ml. of methyl alcohol (containing a few milliliters of 20% sodium hydroxide solution) was slowly stirred. Most of the methanol was distilled off and 300 ml.

of 5% sodium hydroxide solution added. The resulting oil quickly solidified and was filtered off. Recrystallization from acetone yielded 70.5 g. (0.271 mole, 92%) of p-phenylbenzhydrol, m.p. 93.5-94°. One recrystallization from methyl alcohol gave crystals of m.p. 95-95.5° (reported, 95-96° (80), 96° (78), 97° (79)).

SCHMIDT REACTIONS

In the first three experiments described below, Schmidt reactions were carried out under the conventional Schmidt conditions, i.e. with excess hydrazoic acid, which were suitable in reactions with diarylethylenes (82) (83). For reasons which will be apparent in the description of the reactions of m-chlorobenzhydrol and p-methoxybenzhydrol, it was found necessary also to use modified conditions involving prior formation of the benzhydryl azide, followed by acid-catalyzed rearrangement (84). These modified conditions were employed in all the reactions described beyond the first three.

Schmidt Reaction of p-Chlorobenzhydrol -- A 500 ml., 3-necked flask was fitted with a dropping funnel, mercury seal stirrer, and reflux condenser (to the top of which was attached in order, a safety bottle, a bubbler filled with sodium hydroxide solution, and a reservoir bottle filled with water to measure evolved gas). Into the flask were placed 100 ml. of chloroform and 32.5 g. (0.50 mole) of

sodium azide. The flask was cooled with an ice bath and 75 ml. (1.4 mole) of concentrated sulfuric acid dropped in slowly. When addition of the sulfuric acid had been completed, the flask was transferred to an unheated oil bath at room temperature, and a solution of p-chlorobenzhydrol (55 g., 0.25 mole in 100 ml. of chloroform) was added slowly through the dropping funnel with vigorous stirring. The addition of p-chlorobenzhydrol was almost complete before gas evolution began. In the course of half an hour, the bulk of the nitrogen was evolved; the oil bath was slowly warmed to 50°, however, and a little more gas was evolved. In all, approximately 50% of the theoretical amount of nitrogen was obtained. Heating was discontinued after two hours and the reaction mixture left overnight.

Three hundred grams of ice were added to hydrolyze the products. An emulsion formed which was finally broken by filtering the whole reaction misture. This filtration yielded a yellow-green solid, which, after recrystallization from hot water, was white and had a neutralization equivalent of 166 (p-chloroaniline sulfate 176.6, aniline sulfate 142.2). When a water solution of this solid was made basic with sodium hydroxide, a white precipitate was obtained, m.p. 67.5-69.5° (reported for p-chloroaniline, 69-70° (85)).

The filtrate from the reaction mixture, which consisted of a chloroform and an aqueous layer, was separated and the water layer washed once with chloroform. Distillation of

the combined chloroform extracts, first under atmospheric pressure to remove the solvent and then under reduced pressure through a short Vigreux column, yielded four fractions,

(1) $b.p._{28}$ = 82-85°, 5.2g.
(2) $b.p._{28}$ = 85-98°, 0.6g.
(3) $b.p._{28}$ = 98-109°, 2.1g.
(4) $b.p._{28}$ = 109-114°, 10.9g.

(Using Cox chart tables (86) the $b.p._{30}$ of benzaldehyde = 82° and $b.p._{30}$ of p-chlorobenzaldehyde = 116°). All the above fractions gave a positive 2,4-dinitrophenylhydrazine test (87). Oxidation of fraction (1) with hydrogen peroxide (88) gave benzoic acid, m.p. 120-121° (reported, 121.7° (89)). Oxidation of fraction (3) gave an acid, m.p. 225-229° (reported for p-chlorobenzoic acid, 241.5° (90)). No attempt was made to completely identify these products since they were certainly not pure fractions (see following reactions with m-chlorobenzhydrol and p-methoxybenzhydrol).

When the acidic aqueous layer from the original reaction mixture was cooled, a white fluffy precipitate was obtained, which, after drying, had a neutralization equivalent of 141.5 (aniline sulfate, 142.2). A further 7.9 g. of aniline, $b.p._{25}$ = 83-90° (using the Cox chart tables (86), $b.p._{25}$ of aniline = 83.5°), was recovered by making the mother liquor basic, extracting with chloroform and distilling. In all about 11 g. of aniline and 8 g. of p-chloroaniline were recovered as the mixed sulfates, sulfates and free amines.

This represents about a 50% yield of mixed amines and corresponds to a migratory ratio, p-chlorophenyl/phenyl = 0.5.

Schmidt Reaction of m-chlorobenzhydrol -- A 500 ml., 3-necked flask was fitted with a dropping funnel, a mercury seal stirrer and a reflux condenser. To the top of the reflux condenser were attached a safety bottle and a bubbler filled with sodium hydroxide solution. In the flask were placed 100 ml. of chloroform and 32.5 g. (0.50 mole) of sodium azide. While this was cooled with an ice bath, 75 ml. (1.4 mole) of concentrated sulfuric acid was dropped in with stirring. After all the acid had been added, the flask was removed from the ice bath and placed in an unheated oil bath at room temperature (26°). A solution containing 55 g. (0.25 mole) of m-chlorobenzhydrol in 100 ml. of chloroform was added in ten minutes. There was foaming during addition of the m-chlorobenzhydrol, and gradually an orange solid precipitated. After an hour at room temperature, the bath was heated slowly, the temperature reaching 55° at the end of two hours. To hydrolyze the products, 300 g. of ice was added and the mixture stirred. The chloroform layer was separated and the aqueous layer extracted several times with chloroform. Distillation of the combined chloroform extracts, first to remove solvent, then through a short Vigreux column under reduced pressure, gave three fractions,

(1) $b.p._{28}$ = 86-90°, 1.0g.
(2) $b.p._{28}$ = 91-104°, 0.9g.
(3) $b.p._{26}$ = 104-111°, 10.5g.

Oxidation of fraction (2) with hydrogen peroxide gave an acid, which, after 3 recrystallizations from benzene, had m.p. 152-153° (reported for m-chlorobenzoic acid, 154.5° (90)).

Infra-red spectra of fractions (1) and (3) showed, besides absorption peaks characteristic of an aromatic aldehyde and acid, a pronounced absorption at 2245 cm^{-1}, indicative of aromatic nitrile. A sodium fusion also showed the presence of nitrogen in each fraction. An analysis (91) of fraction (3) gave 2.82% and 2.92% nitrogen, indicating the presence of about 28% of m-chlorobenzonitrile. The presence of substantial amounts of nitrile indicates that the primary products of the reaction react further when excess hydrazoic acid is present. It has been shown (92) that aldehydes react under the Schmidt conditions to give nitriles and formamides.

The acidic aqueous layer from the reaction mixture was made basic with sodium hydroxide and extracted thoroughly with chloroform. Distillation of the chloroform followed by fractionation of the residue through a short Vigreux column gave 2 fractions,

(1) $b.p._{28}$ = 81-95°, 12.1g.
(2) $b.p._{28}$ = 118-120°, 3.4g.

(Using the Cox chart tables (86), $b.p._{25}$ of aniline = 83.5°, $b.p._{25}$ of m-chloroaniline = 121.8°).

The benzamide of fraction (1) was prepared, m.p. 159-160° (reported for benzanilide, 160-161° (93)).

Fraction (2) was dissolved in ether and the hydrochloride precipitated with dry hydrogen chloride gas. Its neutral equivalent was 165 (neutral equivalent of m-chloroaniline hydrochloride is 164).

Thus 0.130 mole of aniline and 0.0266 mole of m-chloraniline were obtained, corresponding to a migratory ratio, m-chlorophenyl/phenyl = 0.20, and a yield of 63% of mixed amines.

Schmidt Reaction of p-Methoxybenzhydrol -- This experiment was designed only to see whether any nitrile would be obtained in the Schmidt reaction with p-methoxybenzhydrol.

To a suspension of 6.1 g. (0.094 mole) of sodium azide in 20 ml. of chloroform, contained in a 500 ml., 3-necked flask fitted with a mercury seal stirrer, reflux condenser, and dropping funnel, was added slowly, while stirring and cooling with ice, 14 ml. (0.26 mole) of concentrated sulfuric acid. The ice bath was removed and 10.0 g. (0.047 mole) of p-methoxybenzhydrol dissolved in 10 ml. of chloroform was dropped in quickly. In the space of ten minutes about 60% of the theoretical amount of nitrogen had evolved and the mixture became deep brown. Crushed ice was added causing formation of a chartreuse precipitate. Filtering through a Buchner funnel gave a yellow chloroform layer which was separated from the water, dried with magnesium sulfate and

distilled through a short Vigreux column. A fraction of 0.7 g., b.p.$_{10}$ = 50-60°, was collected which gave a positive 2,4 dinitrophenylhydrazine test (87). A sodium fusion showed the presence of nitrogen, so apparently some nitrile is formed in this reaction also.

Modified Schmidt Reaction of p-Methoxybenzhydrol (I)--This experiment was designed merely to see whether nitrile would be formed under the modified conditions of Ege and Sherk (84).

In a 500 ml., 3-necked flask fitted with a mercury seal stirrer, dropping funnel and condenser (to the top of which was attached a bubbler containing sodium hydroxide solution) were placed 5.2 g. (0.024 mole) of p-methoxybenzhydrol and 10 g. of trichloroacetic acid dissolved in 75 ml. of chloroform. While this solution was vigorously stirred, 33 ml. of a 1.6 molar chloroform solution of hydrazoic acid (0.053 mole) was dropped in. The resulting light yellow solution was allowed to stand for four hours, then extracted with water until no longer acidic to litmus, and finally dried over sodium sulfate.

Rearrangement of the azide was accomplished by dropping 5.5 ml. of concentrated sulfuric acid into the solution in the same apparatus described above. No cooling bath was employed, and the reaction mixture became quite warm. After five minutes evolution of gas had stopped, so 150 ml. of water was added and the mixture stirred. A small amount

of solid remained suspended; therefore the whole reaction mixture was filtered before separating the chloroform layer. This layer after drying yielded 1.2 g. of aldehyde (positive 2,4 dinitrophenylhydrazine test (87)), $b.p._{10}$ = 50-55°. A sodium fusion showed no nitrogen to be present in this fraction. Apparently no nitrile is formed under these conditions. Confirmation of this conclusion was obtained by infrared examination of the aldehyde fraction obtained in the next experiment.

Modified Schmidt Reaction of p-Methoxybenzhydrol (II) -- In a 500 ml., 3-necked flask fitted with a mercury seal stirrer, condenser and dropping funnel were placed 49.7 g. (0.232 mole) of p-methoxybenzhydrol, 98 g. of trichloroacetic acid and 300 ml. of chloroform. While this solution was stirred, 330 ml. of a 1.6 molar chloroform solution of hydrazoic acid (0.528 mole) was dropped in slowly. There was no gas evolution. After standing overnight, the clear yellow solution was extracted exhaustively with water until it was no longer acidic to litmus and then dried over sodium sulfate.

Rearrangement of the azide was accomplished by dropping the solution slowly with vigorous stirring into 55 ml. of concentrated sulfuric acid. Addition of the azide was regulated according to the rate of nitrogen evolution, which was followed by a bubbler attached to the top of the condenser. No cooling bath was used, and the operation required

a total of four hours.

Four hundred grams of ice were stirred into the reaction mixture and the resulting two layers separated. The aqueous layer was extracted a few times with chloroform and these extracts combined with the chloroform layer. Removal of the solvent by distillation, followed by fractionation through a column under reduced pressure, gave a total of 24.39 g. of liquid, b.p.$_{26}$ = 73-80° (from Cox chart tables (86), b.p.$_{25}$ of benzaldehyde = 78°). An infrared spectrogram of this material showed no aromatic nitrile absorption at 2245 cm^{-1}. To this fraction was added the material washed out of the fractionating column with chloroform. The whole was oxidized by stirring with a mixture of 24.8 g. of potassium permanganate, 10 g. of sodium hydroxide, and 300 ml. of water for one hour. After acidification with dilute sulfuric acid and decolorization with a sodium bisulfite solution, chloroform was used to exhaustively extract the acids present. These combined chloroform extracts were in turn extracted with 250 ml. of 5% sodium bicarbonate solution, in portions, in order to separate the acids from any neutral material. Acidification of the basic extracts and reextraction with chloroform followed by evaporation of the solvent gave 13.1 g. of solid acids (dried <u>in vacuo</u>). Analysis for methoxyl gave 1.57%, 1.42% (91) and 0.02%, 0.45% (94). The first pair of analyses correspond to a migratory ratio, p-anisyl/phenyl = 14.9 and 16.6, respectively, and a

yield of mixed acids of 46%. The second pair of analyses correspond to a negligible amount of anisic acid. A neutral material was recovered by distilling the chloroform layer left after the acids were extracted, $b.p._{26}$ = 71-73°, which was identified as ethyl trichloroacetate by infrared spectra and analysis. This ester undoubtedly arises during the formation of the azide, when trichloroacetic acid and ethyl alcohol, used as a stabilizer in chloroform, are both present.

The aqueous acidic layer from hydrolysis of the original reaction mixture was made basic with sodium hydroxide and extracted exhaustively with chloroform. After drying with sodium sulfate the chloroform was distilled off and the residue fractionated through a short Vigreux column yielding three fractions,

(1) $b.p._{26}$ = 86-88°, 2.08g.
(2) $b.p._{26}$ = 89-133°, .52g.
(3) $b.p._{28}$ = 134-136°, 12.27g.

A benzamide of fraction (1) was prepared, m.p. 160-161° (reported for benzanilide, 160-161° (93)).

The intermediate fraction was taken up in ether and dry hydrogen chloride passed in. Titration of the precipitated hydrochlorides gave a neutralization equivalent of 132.8. (This corresponds to a mixture of 0.43 g. of aniline and 0.09 g. of p-anisidine.)

Preparation of the benzamide of fraction (3) gave white leaves, m.p. 154.5-155.5° (reported for benzanisidide, 156°

(95)).

Thus a total of 2.51 g. (0.0270 mole) of aniline and 12.36 g. (0.1003 mole) of p-anisidine were obtained, corresponding to a migratory ratio, p-anisyl/phenyl = 3.72, and a yield of 55% of the mixed amines.

Modified Schmidt Reaction of p-Methoxybenzhydrol (III) -- A repetition of the above experiment using 26.8 g. (0.125 mole) of p-methoxybenzhydrol, 53 g. of trichloroacetic acid and 210 ml. of 1.36 molar hydrazoic acid solution (0.286 mole) to form the azide and 30 ml. of concentrated sulfuric acid to rearrange it, yielded 8.40 g. of mixed acids which analyzed (89) 1.68% and 2.19% methoxyl. This corresponds to a migratory ratio, p-anisyl/phenyl = 13.9 and 9.6 and a yield of 54% of the mixed acids.

Modified Schmidt Reactions of p-Methoxybenzhydrol (IV,V) -- Schmidt reactions were repeated twice more using exactly the same amounts of reactants and the same conditions as used in reaction III above. In the course of these two experiments it was ascertained that the residue from the distillation of the aldehydes contained a negligible amount of acid or potential aldehyde. The residue was refluxed with 20% hydrochloric acid for one hour, neutralized and extracted with sodium bisulfite. Oxidation of this extract with potassium permanganate gave a negligible amount of solid acid. Yields of acids in the Schmidt reactions were 61.8% and 62.2%. Analysis of these products, as well as the

products from reactions II and III, was attempted by infrared spectrophotometry. Synthetic mixtures of anisic and benzoic acid were prepared and spectra measured. Calibration curves prepared from these synthetic mixtures indicated that a quantitative analysis might be possible; when spectra of the unknown mixtures were compared, however, large and inconsistent variations were encountered, making such analysis impossible.

Modified Schmidt Reaction of p-Methoxybenzhydrol (VI) -- Repetition of the Schmidt reaction was carried out using 13.0 g. (0.0608 mole) of p-methoxybenzhydrol, 25 g. of trichloroacetic acid and 130 ml. of a 1.14 molar chloroform solution of hydrazoic acid (0.148 mole). For the rearrangement, 15 ml. of concentrated sulfuric acid was employed.

A different method of separating the aldehydes from the remainder of the neutral products was tried in this case. The chloroform layer and extracts from the hydrolyzed reaction mixture were treated twice with 35 ml. of saturated sodium bisulfite solution. A precipitate resulted from the first treatment and was filtered off before the second extraction. The combined solid bisulfite additon compounds and bisulfite extracts were acidified with hydrochloric acid to release the aldehydes. These were carefully extracted with chloroform which was finally distilled off through a fractionating column. Oxidation of the remaining aldehydes was accomplished with potassium permanganate as described

in reaction II, yielding 4.49 g. of acid which analyzed 1.19% (96) and 1.30% (94) methoxyl, corresponding to a migratory ratio, p-anisyl/phenyl = 20.1 and 18.3, respectively. The yield of mixed acids was 60.5%.

Control Experiment with Anisaldehyde, Benzaldehyde and Sulfuric Acid -- This experiment was carried out in an attempt to see what effect concentrated sulfuric acid had on the products of the Schmidt reaction under the conditions used.

In a 200 ml., round-bottomed flask were placed 3.909 g. (0.0372 mole) of benzaldehyde and 0.874 g. (0.00642 mole) of anisaldehyde, dissolved in 50 ml. of chloroform. To this solution was added 15 ml. of concentrated sulfuric acid. The mixture became quite warm, but no attempt was made to cool it while stirring for 15 minutes. Separation of the chloroform layer was followed by exhaustive extraction of the aqueous layer with chloroform. Distillation of the combined chloroform extracts through a fractionating column gave a dark residue of aldehydes which was oxidized with silver oxide in a procedure similar to that used for analysis of aldehydes in the presence of ketones (97).

To the above residue was added 17 g. (0.10 mole) of silver nitrate dissolved in 30 ml. of water. This mixture was stirred vigorously with a mechanical stirrer while 8 g. (0.20 mole) of sodium hydroxide dissolved in 20 ml. of water was slowly added. After stirring for two hours the silver-silver oxide precipitate was filtered off and washed

thoroughly with hot water and hot dilute sodium hydroxide solution. These basic washes and the filtrate were filtered once more, quickly, to remove traces of silver oxide and then acidified with 6 molar sulfuric acid. The precipitated acids were filtered off through a tared sintered glass funnel and dried in vacuo. Once the acids had dried thoroughly, they were washed with 40 ml. of benzene. The residue of anisic acid (which is fairly insoluble in benzene) weighed 0.179 g. It was shown that when a powdered sample of pure anisic acid was treated with benzene in exactly the same way, a total of 0.219 g. of anisic acid was washed through; thus the corrected weight of anisic acid is 0.398 g. (0.00261 mole, 40.7%).

The acidic filtrate from which the solid acids had been precipitated was extracted thoroughly (20 portions of 20 ml. each) with chloroform. These extracts were combined with the benzene used to wash the solid acids and the whole evaporated and then dried in vacuo. A yield of 4.642 g. of acid was obtained. Since it had been shown that 0.219 g. of anisic acid was washed through, the corrected weight of benzoic acid is 4.423 g. (0.0362 mole, 97.4%).

In order to establish that loss of anisic acid did not occur under the oxidation conditions, an oxidation of anisaldehyde was undertaken. In a 200 ml. flask were placed 1.2109 g. (0.00889 mole) of anisaldehyde and about 0.7 g. of p-methoxybenzhydrol. A small amount of benzene was used

to wash in these reactants. A solution of 5.0 g. (0.029 mole) of silver nitrate dissolved in 20 ml. of water was added, and the mixture stirred vigorously while 2.4 g. (0.06 mole) of sodium hydroxide dissolved in 20 ml. of water was added. Stirring was continued for 40 minutes before the mixture was filtered and worked up as described above. The water insoluble acid, as anisic acid, weighed 1.289 g. (0.00847 mole, 95.3%).

In order to get some idea as to what concentration of sulfuric acid might not cause loss of anisaldehyde, qualitative experiments were carried out involving addition of hot samples of various concentrations of sulfuric acid to anisaldehyde in chloroform solution. It was found that acid above 95% by weight colored anisaldehyde irreversibly.

Modified Schmidt Reaction of p-Methoxybenzhydrol (VII) -- A solution of p-methoxybenzhydryl azide was made in the usual manner from 9.6 g. (0.045 mole) of p-methoxybenzhydrol, 24.3 g. of trichloroacetic acid and 65 ml. of 1.4 molar hydrazoic acid solution (0.091 mole) in a twelve hour reaction period. After thorough extraction with water and drying over sodium sulfate, the solution was dropped into five milliliters of concentrated sulfuric acid which had been diluted with 0.88 ml. of water (approximately 88% acid by weight). There seemed to be an appreciable evolution of nitrogen as the addition was made over a period of half an hour with vigorous stirring.

On hydrolysis of the products and extraction with chloroform, followed by oxidation of the neutral residue with silver oxide as described in the control experiment, only a trace of acids was obtained, and no further attempt was made to analyze the mixture.

Modified Schmidt Reaction of p-Methoxybenzhydrol (VIII) -- When the above experiment was conducted again using the same amounts of reactants, except that ten milliliters of concentrated sulfuric acid diluted with 1.12 ml. of water (approximately 91% acid by weight) was used in the rearrangement step, 2.134 g. of mixed acids was isolated. Only a trace of this solid was insoluble in benzene, so it was all recombined, dissolved in dry acetone and an aliquot removed for methoxyl analysis. Results of 3.04% (96) and 3.15% (94) methoxyl, corresponding to a migratory ratio of p-anisyl/phenyl of 7.1 and 6.8, respectively, were obtained.

Modified Schmidt Reaction of p-Ethoxybenzhydrol -- The modified reaction was attempted three times with p-ethoxybenzhydrol under identical conditions. Twice difficulties occurred in working up the mixture obtained on oxidation of the neutral products of the reaction with silver oxide. These products were therefore discarded; however, the amine fraction from one of the reactions was combined with that of the reaction described below.

In a 500 ml. flask, 10.3 g. (0.045 mole) of p-ethoxybenzhydrol, 24.3 g. of trichloroacetic acid and 65 ml. of

a 1.4 molar chloroform solution of hydrazoic acid (0.091 mole) were combined and allowed to stand overnight. The trichloroacetic acid and excess hydrazoic acid were extracted thoroughly with water and the dried (sodium sulfate) chloroform solution of p-ethoxybenzhydryl azide dropped into fifteen milliliters of concentrated sulfuric acid in twenty minutes, with vigorous stirring and no cooling. Enough ice and water were added to the reaction mixture to dissolve all the solid material. The chloroform layer was separated and the acidic aqueous layer extracted carefully with more chloroform. Combining the extracts and distilling the chloroform off through a fractionating column gave the aldehyde residue which was oxidized with silver oxide.

To the residue contained in a 200 ml. flask was added 17 g. (0.10 mole) of silver nitrate dissolved in 30 ml. of water. This mixture was stirred vigorously with a mechanical stirrer while 8.0 g. (0.20 mole) of sodium hydroxide dissolved in 30 ml. of water was slowly introduced. At this stage the reaction mixture was cooled with an ice bath. The ice was not replenished as the mixture was stirred for two hours. Silver and silver oxide were filtered off and washed thoroughly with hot water and hot dilute sodium hydroxide solution. In order to remove traces of silver oxide, these filtrates were combined and filtered once more through a sintered glass funnel. Acidification with 6 molar sulfuric acid precipitated the acids, which were filtered

off through a tared sintered glass funnel. Drying in vacuo was followed by a wash with 40 ml. of benzene. This left a residue weighing 0.297 g. After another wash with 40 ml. of benzene, the residue weighed 0.281 g. (By washing a pure sample of p-ethoxybenzoic acid in a similar manner, it was found that this loss in weight was that expected of a pure sample.) On this basis 0.016 g. of p-ethoxybenzoic acid is lost during each 40 ml. benzene wash, and the corrected weight is therefore 0.313 g. (0.00188 mole). Dissolving this material in acetone and then cooling gave white crystals, m.p. 195-195.5° (reported for p-ethoxybenzoic acid, 196° (98)).

The filtrate from which the solid acids had been precipitated was extracted exhaustively (20 times with 20 ml. portions) with chloroform. These chloroform extracts were combined with the benzene used to wash the solid acids and the whole evaporated at room temperature. Drying the residue in vacuo yielded 2.052 g. of acid. Since 0.032 g. of this should be p-ethoxybenzoic acid, the weight of benzoic acid is 2.030 g. (0.0165 mole), m.p. 118-119° (reported, 121.7° (89)). This corresponds to a migratory ratio, p-ethoxyphenyl/phenyl of 8.8, and a yield of 41% of mixed acids.

The aqueous acidic layer from the rearrangement step was combined with a similar layer from another identical reaction mixture and made basic with solid sodium carbonate. Thorough extraction with chloroform, followed by removal of

the solvent by distillation through a fractionating column, gave a dark residue which was distilled under reduced pressure through a short Vigreux column. Two fractions were obtained,

(1) $b.p._{14}$ = 70-80°, 0.50g.
(2) $b.p._{14}$ = 120-125°, 2.16g.

(Using Cox chart tables (86), $b.p._{14}$ aniline is 71.3° and $b.p._{14}$ p-phenetidine is 124.8°.)

A benzamide of fraction (1) was prepared, m.p. 159-160° (reported for benzanilide, 160-161° (93)).

The benzamide of fraction (2) had m.p. 171-172° (reported for benz-p-phenetidide, 173° (99)).

Assuming these fractions are the pure amines, this corresponds to a migratory ratio of 2.9. The yield was only 23%.

Trial Oxidations of p-Tolualdehyde and Benzaldehyde -- Various procedures were tried for oxidizing mixtures of p-tolualdehyde and benzaldehyde to benzoic and terephthalic acids, which can easily be separated due to their differing solubility in ether. Methods using acidic potassium dichromate gave little or no terephthalic acid. By the use of basic potassium permanganate, however, with a sufficiently long reaction period, satisfactory oxidations could be obtained.

In a 500 ml. flask were placed 4.591 g. (0.0432 mole) of benzaldehyde and 0.999 g. (0.00833 mole) of p-tolualdehyde,

washed in with ten milliliters of t-butyl alcohol. To this was added 12 g. of sodium hydroxide dissolved in 50 ml. of water, followed by 150 ml. of a solution of potassium permanganate (13.3 g. in 200 ml. of water). The suspension was heated in an oil bath at 80° for one hour. Excess permanganate and manganese dioxide were destroyed by acidifying with dilute sulfuric acid and treating with saturated sodium bisulfite solution. The resulting precipitate was filtered off, dried, suspended in 100 ml. of dry ether and filtered through a tared sintered glass crucible, yielding 0.618 g. of acid (m.p.> 200°) (0.00372 mole, 44.7% of terephthalic acid).

Extraction of the original oxidation mixture from which the solid acids had been removed with twenty, 10 ml. portions of chloroform and combination of these extracts with the ether used to wash the solid acids gave 5.77 g. of residue after evaporation of the solvents. If this is considered to be a mixture of p-toluic and benzoic acid, it represents a total yield of acids of 98%.

The above oxidation was repeated starting with 4.677 g. (0.0441 mole) of benzaldehyde and 1.026 g. (0.00854 mole) of p-tolualdehyde. As the oxidizing mixture 20 g. of sodium bicarbonate and 150 ml. of the permanganate solution were employed and the temperature was maintained at 70° for four hours instead of for only one hour. The products were isolated as described above. A total of 1.346 g. (0.00810 mole,

95%) of terephthalic acid and 5.192 g. (0.0425 mole, 96%) of benzoic acid were obtained. The original synthetic mixture simulated a migratory ratio, p-tolyl/phenyl of 5.16 for the Schmidt reaction of p-methylbenzhydrol, while the experimental results gave 5.25.

Modified Schmidt Reaction of p-Methylbenzhydrol (I) -- In a 1 l., 3-necked flask fitted with a mercury seal stirrer and reflux condenser (to the top of which was attached a bubbler filled with sodium hydroxide solution) were placed 20.0 g. (0.101 mole) of p-methylbenzhydrol, a dried (sodium sulfate) solution of 50 g. of trichloroacetic acid in 100 ml. of chloroform, and 175 ml. of a 1.36 molar chloroform solution of hydrazoic acid (0.238 mole). Stirring was started and continued at room temperature for two hours after which excess hydrazoic acid and trichloroacetic acid were extracted by bubbling tap water continuously through the solution. When the chloroform layer no longer was acidic to litmus, it was separated and dried over sodium sulfate.

In a 500 ml., 3-necked flask fitted with a mercury seal stirrer, dropping funnel and condenser (with bubbler attached to the top) was placed 30 ml. of concentrated sulfuric acid. The dried azide solution was dropped into the sulfuric acid while the mixture was stirred vigorously. In twenty minutes the addition of the azide had been completed. No cooling bath was employed during this period, and the mixture became almost hot enough to reflux the chloroform. About one

hundred grams of ice was added with vigorous stirring. A light yellow precipitate was obtained which was filtered off and washed well with chloroform. The chloroform layer from the reaction mixture was combined with these washes, as well as two additional extracts of the aqueous layer, and placed in a separatory funnel. Treatment with 50 ml. of saturated sodium bisulfite solution gave a voluminous precipitate after ten minutes of violent shaking. This was filtered off and the filtrate treated with an additional 10 ml. of bisulfite solution. No additional precipitate was obtained; this extract was combined with the solid, however, and placed in a separatory funnel. (Further extraction of the chloroform layer with 5% sodium bicarbonate solution showed that the amount of acid formed by air oxidation was very small, since no solid acid could be obtained on acidification of these extracts.) Careful acidification of the bisulfite extracts with concentrated hydrochloric acid was followed by exhaustive extraction of the liberated aldehydes with chloroform. Distillation of the chloroform through a fractionating column left the residue which was oxidized with permanganate as described above in the second trial oxidation. Double the quantities of oxidizing agent were used since there is a possibility of twice the amount of aldehydes being present. A yield of 2.429 g. (0.0146 mole) of terephthalic acid (identified as the dimethyl ester, m.p. 138.5-139°; reported for dimethyl terephthalate, 138.5-139°

(100)) and 6.300 g. (0.0516 mole) of benzoic acid (identified as the amide, m.p. 127-128°; reported for benzamide, 130° (10)) were obtained. This corresponds to a migratory ratio p-tolyl/phenyl of 3.53 and a yield of 66%.

In order to determine qualitatively the identity of the amine fraction, the yellow precipitate from the hydrolyzed reaction mixture was combined with the acidic aqueous layer and the whole made basic with sodium hydroxide solution. Extraction with chloroform followed by removal of the solvent by distillation gave a residue which was distilled through a short Vigreux column. A fraction, $b.p._{15}$ = 70-73° (from Cox chart tables (86), $b.p._{15}$ of aniline is 72.7°) was taken off before the distillate began to solidify in the apparatus. Distillation was halted and the solid removed and recrystallized from alcohol-water. Slightly brown leaves, m.p. 42-43.5° (reported for p-toluidine, 45° (102)) were collected. A benzamide of this solid had m.p. 155.5-156° (reported for benz-p-toluidide 158° (103)).

The liquid fraction obtained by distillation was redistilled and a small amount of product having a $b.p._{15}$ of 72° was taken off. A phenylthiourea was prepared (104) from this material. After five recrystallizations the m.p. was 147.5-149° (reported for thiocarbanilide, 149-150° (105), 154-155° (106)).

By dissolving the residue from the distillation of the amines in ether and extracting the basic material with

aqueous dilute hydrochloric acid, a small neutral residue could be obtained which smelled of aldehyde and gave a positive 2,4 dinitrophenylhydrazine test. This probably indicates that filtering off the solid amine sulfates from the hydrolyzed reaction mixture is not the ideal procedure for separating them from the aldehydes, even though subsequent washing with chloroform is as thorough as possible.

Modified Schmidt Reaction of p-Methylbenzhydrol (II) -- On repetition of the above experiment, using the same amounts of reactants, the azide was formed by allowing the trichloroacetic acid, hydrazoic acid, and p-methylbenzhydrol to stand overnight. Rearrangement of the azide was carried out as described above. In working up the hydrolyzed products, however, enough water was added to dissolve all the amine sulfates and the subsequent extraction of the neutral products was from a clear solution.

Oxidation with permanganate was carried out as before. The yield was 3.069 g. (0.0185 mole) of terephthalic acid and 7.571 g. (0.0620 mole) of benzoic acid, corresponding to a migratory ratio, p-tolyl/phenyl of 3.35 and a yield of 80%.

Modified Schmidt Reaction with p-Chlorobenzhydrol (I) -- In a 500 ml., 3-necked flask fitted with a mercury seal stirrer and a reflux condenser, having a bubbler filled with sodium hydroxide solution attached to the top, were placed 15.0 g. (0.0685 mole) of p-chlorobenzhydrol, a solution of

25 g. of trichloroacetic acid in 100 ml. of chloroform and 120 ml. of a 1.14 molar chloroform solution of hydrazoic acid (0.139 mole). The resulting yellow solution was stirred at room temperature for an hour and a half, after which the excess hydrazoic acid and trichloroacetic acid were extracted thoroughly with water. Drying briefly over sodium sulfate gave a clear light yellow solution which was dropped into 25 ml. of vigorously stirred concentrated sulfuric acid contained in the usual apparatus. Nitrogen evolution was complete after half an hour, so enough ice and water were then added to dissolve all the suspended solid amine sulfates.

The chloroform layer was separated and the aqueous layer extracted with chloroform several times. These chloroform extracts were combined, placed in a separatory funnel and then treated with 50 ml. of saturated sodium bisulfite solution. After several minutes of violent shaking, a solid precipitated and was filtered off. The chloroform filtrate was again treated with 10 ml. of saturated sodium bisulfite solution and shaken vigorously. No more precipitate formed, but both this extract and the wet solid were combined, acidified with concentrated sulfuric acid and extracted thoroughly with chloroform. Removal of the chloroform from these extracts by distillation through a fractionating column gave a residue which was oxidized with permanganate.

To the above residue contained in a 250 ml. flask was added 10 g. of solid sodium bicarbonate and then gradually,

with mechanical stirring 125 ml. of a solution of potassium permanganate (13.3 g. in 200 ml. of water). After one hour the reaction mixture was carefully acidified with dilute sulfuric acid and decolorized with saturated sodium bisulfite solution. Thorough extraction with chloroform removed the precipitated acids. Reextraction with 5% sodium bicarbonate solution separated the acids from any neutral material. Acidification, reextraction with chloroform, and evaporation yielded 2.865 g. of mixed acids (dried in vacuo).

Analysis: Cl, 15.48% (96) and 15.42% (94).

This corresponds to 68.1% and 68.4% of p-chlorobenzoic acid, respectively, a migratory ratio, p-chlorophenyl/phenyl of .60 and a yield of 29.2%.

Control Oxidation of p-Chlorobenzaldehyde and Benzaldehyde in the Presence of p-Chlorobenzhydrol -- This experiment was designed to see whether aldehydes could be oxidized quantitatively to acids in the presence of other easily oxidizable substances which may be present in the neutral products of the Schmidt reaction. There has recently been reported (97) an analytical method involving oxidation of aldehydes in the presence of ketones and the method used here is similar.

In a 100 ml., round bottomed flask fitted with a mechanical stirrer were placed 1.0866 g. (0.01023 mole) of benzaldehyde, 1.8199 g. (0.01296 mole) of p-chlorobenzaldehyde, and 2.0 g. of p-chlorobenzhydrol. A little thiophene-free

benzene was used to wash in these samples. To this solution was added 13.6 g. (0.080 mole) of silver nitrate dissolved in 25 ml. of water. While this mixture was cooled with an ice bath and stirred vigorously, 6.4 g. (0.16 mole) of sodium hydrozide pellets dissolved in 25 ml. of water was added dropwise during ten minutes. After stirring ten minutes more, the black precipitate was filtered off and washed thoroughly with hot water. The resulting cloudy filtrate and washings were combined and extracted with four portions of chloroform, then filtered through a sintered glass funnel to remove traces of silver oxide. Acidification with 25 ml. of 4 molar sulfuric acid gave a voluminous precipitate which was filtered through a tared sintered glass crucible and dried in vacuo. The dried acids weighed 2.53 g. After one washing with 40 ml. of benzene, the weight of acid was 2.054 g. One more 40 ml. wash left 1.977 g. (0.01262 moles of p-chlorobenzoic acid, 97.4%).

By extracting the filtrate from which the acids were precipitated with twenty, 10 ml. portions of chloroform, combining these with the benzene washes and evaporating, 1.243 g. (0.01018 mole, 99.5%) of benzoic acid was collected.

The original mixture simulated a migratory ratio, p-chlorophenyl/phenyl of 0.79, while the experimentally obtained ratio is 0.81.

Modified Schmidt Reaction with p-Chlorobenzhydrol (II) -- In a 500 ml., 3-necked flask fitted with a mercury seal

stirrer and condenser (to the top of which was attached a bubbler filled with sodium hydroxide solution) were placed a dried (sodium sulfate) solution of 24.3 g. of trichloroacetic acid in 50 ml. of chloroform and 9.9 g. (0.045 mole) of p-chlorobenzhydrol. After stirring to dissolve the alcohol, 65 ml. of a 1.4 molar chloroform solution of hydrazoic acid (0.091 mole) was added quickly. After standing for an hour, excess hydrazoic acid and trichloroacetic acid were extracted by washing several times with equal volumes of water. The resulting light yellow chloroform solution was dried briefly over sodium sulfate. In the same apparatus described for the formation of the azide solution was placed 15 ml. of concentrated sulfuric acid. The solution of p-chlorobenzhydrylazide was dropped slowly from a dropping funnel into the vigorously stirred acid. After fifteen minutes, addition of the azide and its reaction with the sulfuric acid were both complete, as shown by the cessation of nitrogen evolution. No cooling bath was employed in the course of the reaction, and the chloroform refluxed weakly towards the end of the reaction period. About two hundred grams of ice-water was added with stirring. Separation of the layers was complicated by some emulsion formation, but repeated extractions with chloroform finally cleared the solution. Distillation of the combined chloroform extracts through a fractionating column left a residue which was oxidized with silver oxide in the manner described in detail above.

There was obtained 0.954 g. (0.00781 mole) of benzoic acid and 1.620 g. (0.01034 mole) of p-chlorobenzoic acid (identified as the methyl ester, m.p. 42-43°; reported for methyl p-chlorobenzoate, 43-43.5° (107)). This corresponds to a migratory ratio, p-chlorophenyl/phenyl of 0.75 and a yield of 41%.

Modified Schmidt Reaction with m-Chlorobenzhydrol -- In a 500 ml. flask were placed 9.9 g. (0.045 mole) of m-chlorobenzhydrol, 24.3 g. of trichloroacetic acid in 25 ml. of chloroform and 65 ml. of a 1.4 molar chloroform solution of hydrazoic acid (0.091 mole). This flask was connected in series to a safety bottle and a bubbler containing sodium hydroxide solution. The reaction mixture was allowed to set thus for twenty-four hours. Then excess trichloroacetic acid and hydrazoic acid were extracted thoroughly with several portions of water. Drying the chloroform solution briefly over sodium sulfate gave a clear, light yellow solution.

In a 500 ml., 3-necked flask fitted with a mercury seal stirrer, condenser, and dropping funnel were placed 15 ml. of concentrated sulfuric acid. While this acid was vigorously stirred, the dried azide solution was dropped in during ten minutes. As soon as nitrogen stopped evolving (a few minutes), 150 ml. of ice-water was added while stirring was continued.

The chloroform layer was separated and the aqueous layer extracted several times with chloroform. Distillation

of these combined extracts through a fractionating column removed the solvent. Oxidation of the residue was carried out with silver oxide.

To the distillation residue, contained in a 200 ml. flask, was added 17 g. (0.10 mole) of silver nitrate dissolved in 25 ml. of water. While this mixture was stirred vigorously with a mechanical stirrer and cooled in an ice bath, 8 g. (0.20 mole) of sodium hydroxide dissolved in 25 ml. of water was gradually added. After a further ten minute stirring period, the reaction mixture was filtered and the filter cake washed thoroughly with hot water and dilute sodium hydroxide solution. The combined filtrate and washings was filtered again to remove traces of silver oxide, then extracted with several portions of chloroform to remove neutral substances. The acids were precipitated by addition of 6 molar sulfuric acid and extracted carefully with twenty, 20 ml. portions of chloroform. These chloroform extracts were evaporated at room temperature yielding a white solid residue which was dried in vacuo. By redissolving this solid in dry acetone traces of inorganic solid could be filtered off. An aliquot of the acetone solution was evaporated and dried. It analyzed 18.67% (96) and 18.69% (94) chlorine, respectively, corresponding to 82 .5% m-chlorobenzoic acid and a migratory ratio, m-chlorophenyl/phenyl of 0.27. A total of 3.66 g. (53%) of acid was obtained.

Modified Schmidt Reaction of p-Bromobenzhydrol (I) -- In a 500 ml., 3-necked flask fitted with a mercury seal

stirrer and a condenser (to the top of which was attached a bubbler filled with sodium hydroxide solution) was placed 100 ml. of a 1.15 molar chloroform solution of hydrazoic acid (0.115 mole). In a separate flask, 28 g. of trichloroacetic acid was dissolved in 50 ml. of chloroform and dried briefly over sodium sulfate. This dried solution was filtered into the hydrazoic acid and 15.0 g. (0.052 mole) of p-bromobenzhydrol added. After stirring at room temperature for one hour, the reaction mixture was extracted several times with equal volumes of water and then dried over sodium sulfate.

In the same apparatus described above was placed 15 ml. of concentrated sulfuric acid. The dried azide solution was introduced slowly from a dropping funnel while the reaction flask was cooled in ice. Evolution of nitrogen was very slow, however, so the ice bath was removed and the addition of the azide completed without external cooling. The reaction mixture was immediately hydrolyzed with 100 g. of ice. A yellow precipitate of amine sulfates resulted, but they were dissolved by adding more water.

The chloroform layer was separated and the aqueous layer extracted several times with chloroform. To separate the aldehydes from the other neutral components of the reaction mixture, the combined chloroform extracts were treated with 25 ml. of saturated sodium bisulfite solution and shaken vigorously for ten minutes. A white precipitate was filtered off and washed with chloroform. Another treatment of the chloroform filtrate with 5 ml. of sodium bisulfite gave

no more precipitate, but this extract was combined with the solid in a separatory funnel. Careful acidification with 35 ml. of concentrated hydrochloric acid followed by thorough extraction with chloroform removed all the aldehydes (as shown by a negative 2,4 dinitrophenylhydrazine test on the aqueous layer). Distillation of the chloroform through a fractionating column gave the aldehyde residue which was oxidized with permanganate.

Using the same flask employed as a distillation pot, 10 g. of sodium bicarbonate was added to the residue, followed by 50 ml. of a saturated potassium permanganate solution. This mixture was stirred for half an hour before the excess permanganate and manganese dioxide were destroyed by acidifying with dilute sulfuric acid and treating with sodium bisulfite solution. The acids were extracted thoroughly with chloroform and then reextracted with 35 ml. of 10% sodium bicarbonate solution. Acidification of this extract gave a voluminous precipitate which was extracted with chloroform. Even though some of the solid did not dissolve, it was suspended in the organic layer and separated. Twenty extractions were made to insure complete removal of all acids. Evaporation of the solvent yielded 1.762 g. of acid (dried in vacuo). This was taken up in acetone and an aliquot taken for analysis. The result was 29.35% (94) bromine, which corresponds to a migratory ratio, p-bromophenyl/phenyl of 0.584 and a 20% yield of mixed acids.

Modified Schmidt Reaction of p-Bromobenzhydrol (II) -- In a 500 ml. flask were placed 11.8 g. (0.045 mole) of p-bromobenzhydrol, a dried (sodium sulfate) solution of 24.3 g. of trichloroacetic acid in 50 ml. of chloroform, and 65 ml. of a 1.4 molar chloroform solution of hydrazoic acid (0.091 mole). The flask was connected to a bubbler filled with sodium hydroxide solution and allowed to remain at room temperature for twelve hours. Remaining hydrazoic acid and trichloroacetic acid were extracted by washing several times with equal volumes of water. The chloroform layer was dried briefly over sodium sulfate.

In a 500 ml., 3-necked flask fitted with a mercury seal stirrer, condenser (to the top of which was attached a bubbler), and a dropping funnel were placed 15 ml. of concentrated sulfuric acid. No attempt was made to cool the reaction mixture as the azide solution was added. The solution became warm enough to reflux the solvent towards the end of the reaction. Evolution of nitrogen stopped soon after the azide had been added (total reaction time, about twenty minutes). About 250 ml. of ice-water was added with stirring. Some yellow solid remained, but enough water was added to dissolve it completely. The water layer was extracted with several portions of chloroform and these extracts were combined with the original chloroform layer before distillation through a fractionating column to remove the solvent. A residue of aldehydes which was to be oxidized

with silver oxide remained.

A solution of 15.3 g. (0.090 mole) of silver nitrate in 25 ml. of water was added to the stirred, cooled distillation residue. Then 7.2 g. (0.18 mole) of sodium hydroxide pellets dissolved in 25 ml. of water was poured in. The resulting slurry was stirred for fifteen minutes before being filtered. Several hot water washes of the filter cake were combined with the filtrate and the whole filtered once more through a sintered glass funnel to remove traces of silver oxide. This basic solution was extracted several times with chloroform then acidified with 25 ml. of 4 molar sulfuric acid. A voluminous precipitate was obtained which was filtered off through a tared sintered glass crucible and dried in vacuo. These dried acids were washed two times with 40 ml. portions of benzene and dried again in vacuo. This residue weighed 4.176 g. after subtracting a 0.014 g. residue which was insoluble in sodium bicarbonate solution. That this residue was p-bromobenzoic acid was confirmed by preparation of the methyl ester, m.p. 77.5-78.5° (reported for methyl p-bromobenzoate, 78° (108)). An authentic sample of methyl p-bromobenzoate, m.p. 77.5-78.5°, showed no melting point depression with the derivative.

By extracting the solution from which the solid acids were precipitated with twenty, 20 ml. portions of chloroform, combining these with the benzene used to wash the solid acids, and evaporating, 1.466 g. of benzoic acid was

obtained. The acid was identified as the anilide, m.p. 159-160° (reported for benzanilide, 160-161° (93)). An authentic sample of benzanilide, m.p. 160-161°, showed no noticeable melting point depression with the derivative.

Thus 0.0208 mole of p-bromobenzoic acid and 0.0120 mole of benzoic acid were obtained, corresponding to a migratory ratio, p-bromophenyl/phenyl of 0.58 and a yield of 73%.

By making the aqueous layer from the original rearrangement reaction mixture basic with sodium hydroxide solution, extracting with chloroform and distilling, a residue of amines was obtained. No attempt was made to determine the composition of this mixture quantitatively, but distillation yielded a fraction, $b.p._{15}$, 70-72° (from Cox chart tables (86), $b.p._{15}$ of aniline, 72.7°), which on treatment with bromine water gave a solid, m.p. 118°, after recrystallization from alcohol (reported for 2,4,6 tribromoaniline, 118° (109), 122° (110)). When the residue from the distillation was taken up in alcohol and cooled, it gave slightly brown crystals, m.p. 63-64° (reported for p-bromoaniline, 66° (111)).

Modified Schmidt Reaction with p-Phenylbenzhydrol -- In a 500 ml. flask were placed 11.7 g. (0.045 mole) of p-phenylbenzhydrol, 24.3 g. of trichloroacetic acid and 65 ml. of a 1.14 molar chloroform solution of hydrazoic acid (0.091 mole). A deep red solution was obtained. After connecting the flask to a bubbler containing sodium hydroxide solution,

the mixture was allowed to remain overnight before excess hydrazoic acid and trichloroacetic acid were washed out with water. (The red color disappeared at this time.) The light yellow chloroform solution was dried over sodium sulfate.

This dried solution was dropped into 15 ml. of concentrated sulfuric acid in the usual apparatus. Reaction was complete in fifteen minutes. Hydrolysis gave a great deal of solid which could not be dissolved by adding a reasonable amount of water, so it was filtered off and washed with chloroform. The combined chloroform washes and the chloroform layer were distilled leaving the neutral residue containing aldehydes. Oxidation was attempted using silver oxide. Quantitative separation of sodium p-phenylbenzoate from the silver-silver oxide precipitate was impossible, however, due to the relative insolubility of this salt in water. By acidification of the filtrate and washing the precipitated acids with benzene, a residue of acid, m.p. 215-217° (reported for p-phenyl benzoic acid, 216-217° (112), 228° (113)) was obtained. Evaporation of the benzene washes gave crude benzoic acid, m.p. 117.5- 119°. From the solid, which was filtered from the original acidic hydrolyzate, p-phenylaniline, m.p. 53-53.5° (reported, 53° (114)) could be isolated by heating with dilute sodium hydroxide solution, followed by recrystallization of the resulting solid from alcohol.

SUMMARY

1. Seven unsymmetrically substituted benzhydrols were prepared by reduction of the corresponding benzophenones and subjected to the Schmidt reaction.
2. The expected reaction products were qualitatively identified in each case.
3. The ratio of products obtained from the reactions of six of the benzhydrols were determined quantitatively and correlated by means of a modified Hammett equation.
4. The Hammett equation has been applied to rate data from the Hofmann reactions of m- and p-substituted N-bromobenzamides and the Lossen reactions of m- and p-substituted O-benzoylbenzhydroxamic acids.

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PART II

REDUCTION PRODUCTS OF THE RUBREMETINIUM CATION

INTRODUCTION

Rubremetinium salts are obtained upon mild oxidation of the alkaloid emetine. These products are interesting because of their salt-like character and intense red color. In an effort to establish their structure, various reduction procedures (8)(10)(12)(14) have been employed, leading to apparently different products. Stable dihydro and tetrahydro derivatives have both been reported.

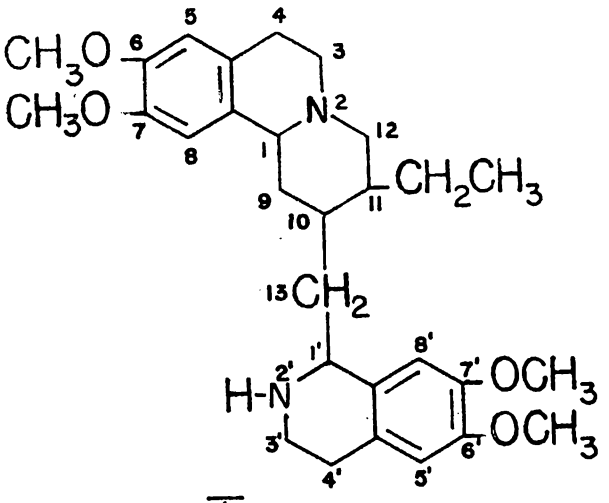
For this investigation it was originally decided to study more intensively the hydrogenation products of dehydrohalorubremetine, a derivative of rubremetine obtained by treatement of the salt with refluxing alcoholic sodium hydroxide (10). In order to establish definitely the identity or non-identity of the products isolated with those previously reported, the other procedures described for the reduction of rubremetinium chloride were repeated. By comparison of the products, it was possible to resolve most of the previous discrepancies and substantiate XII as the structure of rubremetinium chloride.

On the basis of the analytical data obtained for the hydrogenation products of dehydrohalorubremetine, it was possible to tentatively identify dehydrohalorubremetine as a Hofmann degradation product.

BACKGROUND AND HISTORICAL REVIEW

Long before the structure of the alkaloid emetine (I) was established definitely (1)(2), Carr and Pyman obtained scarlet, crystalline rubremetinium chloride on oxidizing emetine with ferric chloride (3). Since then rubremetinium salts have been obtained by oxidation of emetine with bromine (4), iodine (5) and mercuric acetate (6). Of the other members of the emetine family of alkaloids, o-methylpsychotrine (II) (7)(8) and isoemetine (which differs from emetine only in the configuration at C_1) (9) have been oxidized to rubremetinium salts. Compounds derived from emetine which have been oxidized to the rubremetinium cation include tetradehydroemetine hydrogen oxalate (6) (III) (8) and isotetradehydroemetine (10) (IV) (11). Oxidation of emetamine (V) gives a colored product which is similar to, but differs from a rubremetinium salt (12).

The molecular formula of rubremetinium chloride has been reported as $C_{29}H_{33}N_2O_4Cl$ (3) (4) (5); however, it may be noted that analytical methods are not sufficiently accurate to establish without question the exact number of hydrogens. One of the first observations concerning the nature of the compound was that it behaved as a monoacidic quaternary base on potentiometric titration (3) despite the presence of two nitrogen atoms in the molecule.



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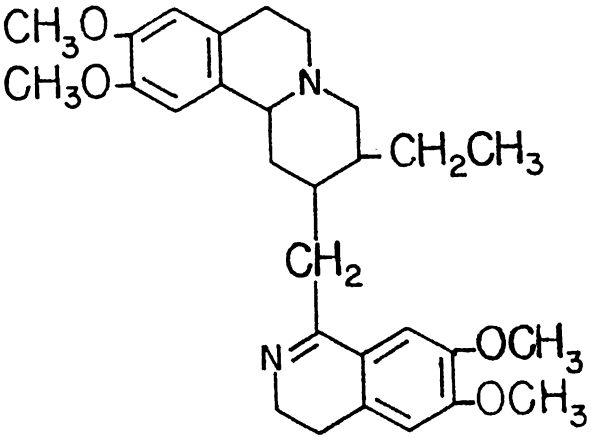

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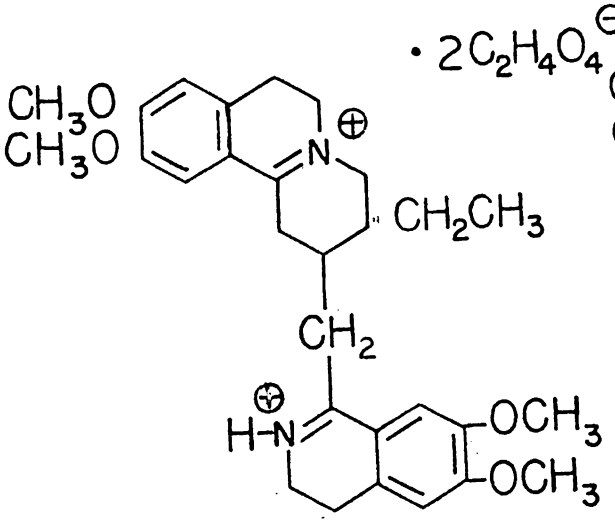

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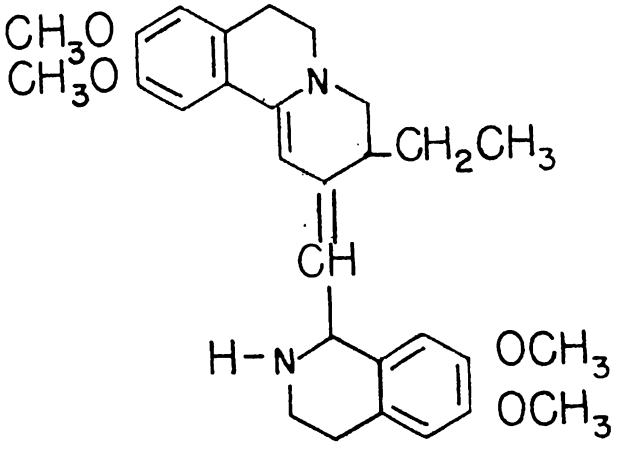

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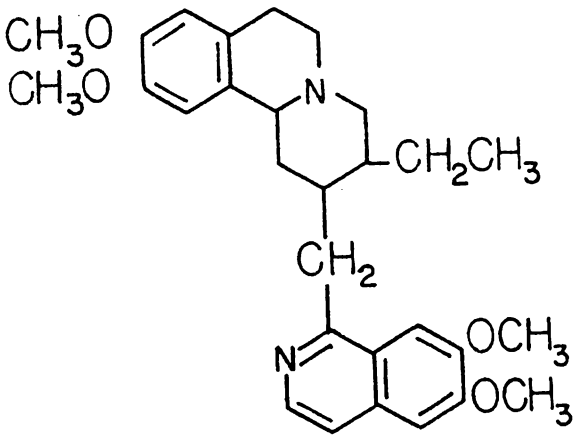

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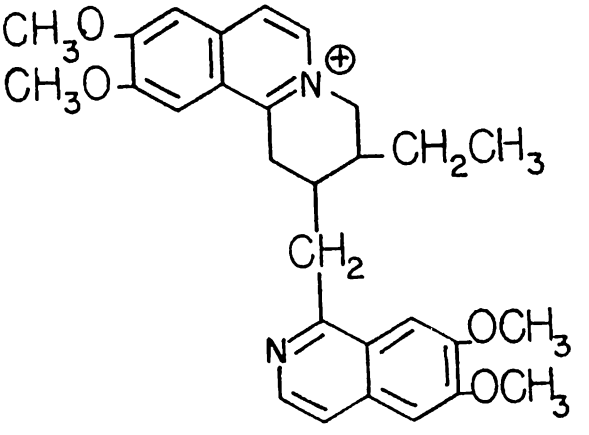

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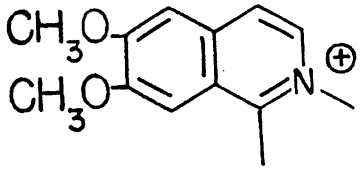

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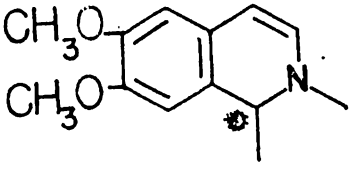

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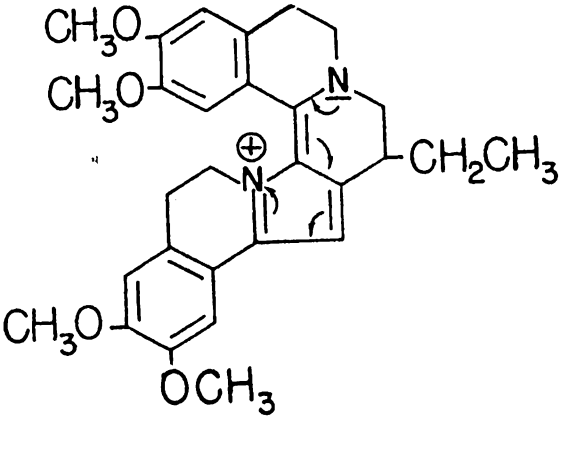


IX

Since the structure of emetine was not yet known, the first structure proposed (13) for the rubremetinium cation was incorrect.

The next proposal as to the nature of the rubremetinium ion was in the form of a partial structure, VI (12), which, when applied to the subsequently established emetine structure, gives VII. Support for this formula was based first on the reduction of rubremetinium bromide with zinc and acetic acid to tetrahydrodehydroemetine.* This compound is optically active and resists further catalytic hydrogenation. It is known that quaternary isoquinolinium systems, such as VI, are easily reduced, while non-quaternary systems resist reduction. Tetrahydrodehydroemetine would therefore have a structure identical with emetamine (V). Since the two products had different properties, it was assumed they were stereoisomers (12). An important objection to structure VII is the fact that emetamine does not give the rubremetinium cation on oxidation. Another objection is that VII does not explain the lack of basicity of the non-quaternary nitrogen.

Further work by Karrer and Ruttner (14), intended to support the quaternary <u>iso</u>quinolinium structure, seems on the contrary to make it an even less likely possibility. It was found that when rubremetinium bromide was treated

*Karrer uses dehydroemetine instead of rubremetine to signify the hypothetical base which would yield the cation in question.

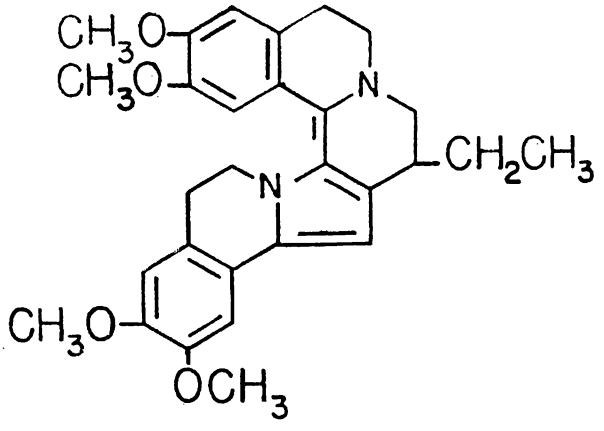
with lithium aluminum hydride, an unstable compound, "o-dihydrodehydroemetine", was obtained which should have the partial structure VIII on the basis of structure VII for the rubremetinium ion. (Simple isoquinolinium salts give 1, 2-dihydro products on lithium aluminum hydride reduction.) Catalytic reduction of this "dihydro" compound apparently resulted in the uptake of one mole of hydrogen. Two tetrahydro derivatives were isolated, one identical with the product from the direct zinc-acetic acid reduction, and the other, isotetrahydrodehydroemetine, differing in rotation and melting point. Openshaw and Wood (8) have pointed out how unlikely it is that reduction to VIII, which involves formation of an asymmetric carbon, would give only one isomer, while further hydrogenation would yield two stereoisomers although no new asymmetric center is formed.

The first structure, IX, which came close to explaining all the properties of the rubremetinium cation was proposed by Battersby, Openshaw and Wood (15). The highly conjugated, mesomeric nature of this ion, similar to that of a cyanine dye, would account for both the intense color and the monobasic behavior of rubremetinium salts. Oxidation of emetamine (V) would not be expected to give IX. A crude product obtained by zinc dust reduction of rubremetinium chloride gave pyrrole color reactions. This is consistent since IX contains a pyrrole ring.

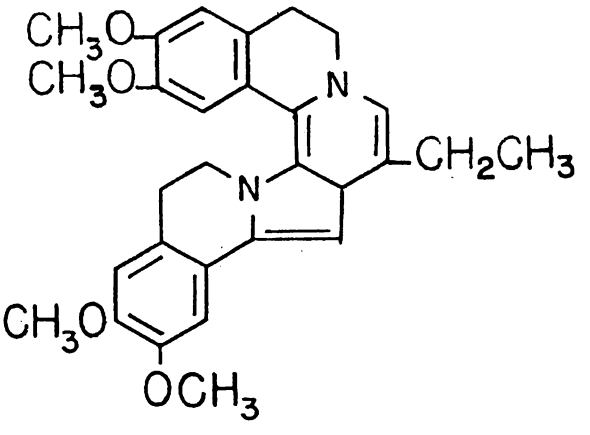
To further substantiate structure IX, the products of catalytic reduction of rubrementinium chloride in the presence of platinum and sodium acetate were investigated. It was found that 1 mole of hydrogen was absorbed and 2 "dihydrorubrementines", alpha and beta, could be isolated. The alpha isomer had a m.p. of 198° and a specific rotation of -395°, and the more insoluble beta isomer had a m.p. of 202° and a specific rotation of -406°. Both these products gave color tests for a pyrrole ring. Potentionmetric titration showed them to be monoacidic bases and their ultraviolet spectra were nearly identical. Mercuric acetate oxidation converted both back to rebremetine. These findings are all consistent with structure X, in which an asymmetric center has been formed at C_1 by the reduction.

An objection (14) was raised that structure IX would not be expected as the final product of an oxidation since it contains two dihydropyridine rings. It was shown (8), however, that mercuric acetate will not oxidize 1-n-butyl-3:4-dihydroisoquinoline or 3:4-dihydro-6:7-dimethoxy-1-methylisoquinoline under the conditions used for formation of rubremetinium salts. Additional stability was postulated for the other dihydropyridine ring due to the resonance hybrid character of the molecule.

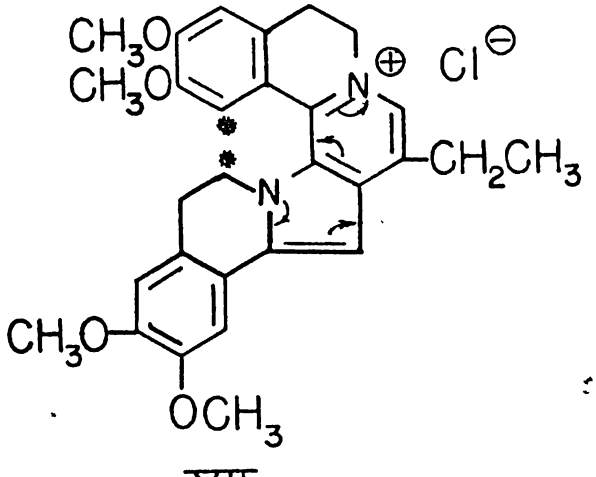
A more difficult objection to answer arises from the fact that tetrahydrorubremetine compounds have been obtained on mild reduction (14). Structure IX would be expected to



X



XI



XII

give only dihydro derivatives under these conditions. Openshaw and Wood (8) have questioned the designation of these compounds as tetrahydro derivatives.

A derivative of rubremetinium chloride which may have a bearing on determination of the structure of the cation was obtained (10) by heating the salt with alcoholic sodium hydroxide. The product had the formula $C_{29}H_{32}O_4N_2$, apparently the result of dehydrochlorination; therefore it was called dehydrohalorubremetine. Treatment of this compound with hydrocloric acid solution failed to give back rubremetinium chloride. Low pressure catalytic reduction resulted in the uptake of two moles of hydrogen and the isolation of an optically inactive substance by fractional crystallization of the products.

Treatment with benzoyl chloride or p-toluenesulfonyl chloride gave no acyl derivative. It was considered possible that dehydrohelorubremetine was racemic tetrahydrodehydroemetine or isotetrahydrodehydroemetine since their ultraviolet spectra were almost identical. Openshaw and Wood (8), of course, considered dehydrohalorubremetine to be racemic dihydrorubremetine. Structure IX, in which there are no asymmetric centers, was considered as probable for dehydrohalorubremetine.

DISCUSSION OF EXPERIMENTAL RESULTS

Since the original approach to an investigation of the structure of the rubremetinium cation involved obtaining information concerning the structure of dehydrohalorubremetine, a large quantity of this material was prepared and then catalytically reduced. About two moles of hydrogen were taken up and two products were isolated from the reaction mixture. One of these products corresponded to tetrahydrodehydrohalorubremetine (10). It showed no rotation in alcohol, benzene or acetone solution. Analysis for terminal methyl groups by the Kuhn-Roth procedure gave a value slightly over one, and a Zerewitinoff determination showed the presence of one active hydrogen. The other reduction product had a m. p. of 165.8-166.0° and a specific rotation of -15.1 in acetone. A Kuhn-Roth determination again gave a value slightly in excess of the theoretical value for one terminal methyl group, but the result of a Zerewitinoff determination corresponded to only half that expected for active hydrogen. The ultraviolet spectra of the two compounds were similar but not identical (Fig. 1). Even though there are minor discrepancies, these two substances are probably the racemic and active forms of the same compound.

It appeared that in view of the previously reported reduction products of the rubremetinium cation these

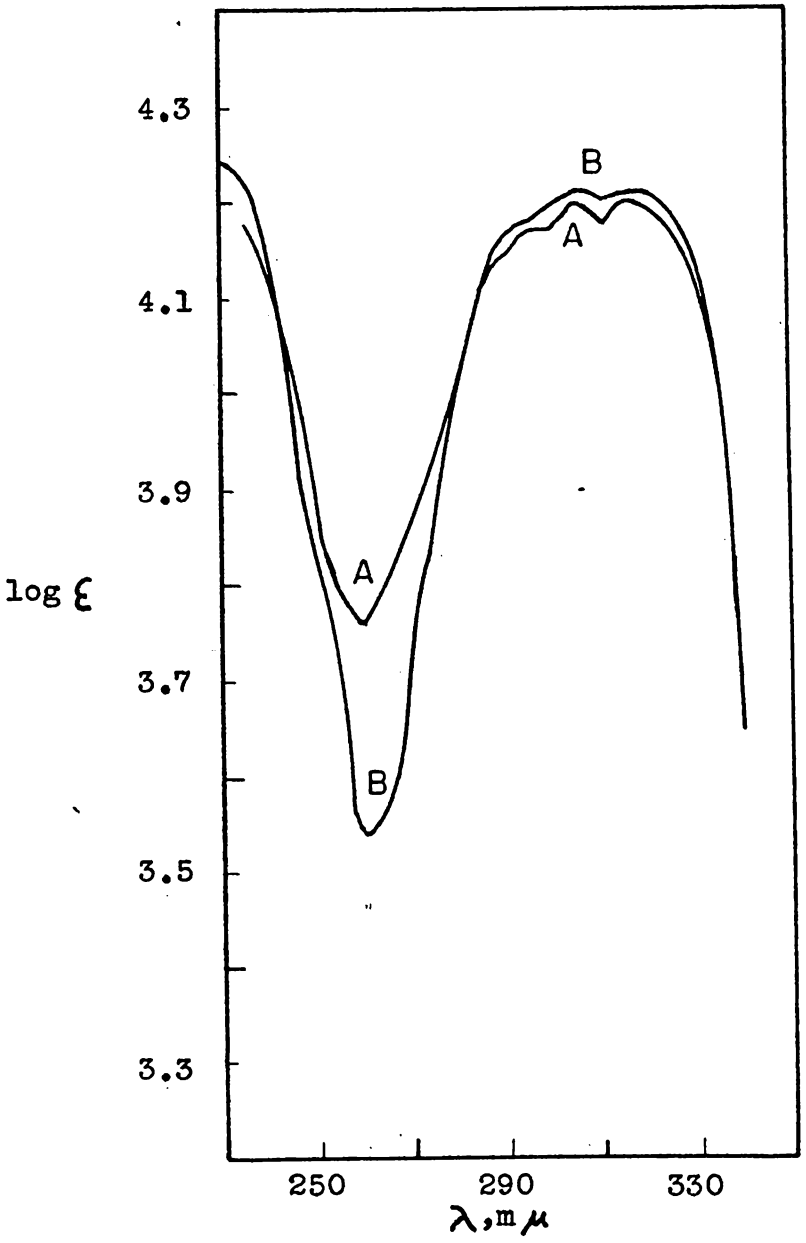


Fig. 1. -- Ultraviolet absorption spectra in ethanol solution of (A) racemic tetrahydrodehydrohalorubremetine and (B) dextrorotatory tetrahydrodehydrohalorubremetine.

results did nothing toward making the picture clearer. It was decided to repeat the previously reported reductions of rubremetinium chloride.

On treatment of rubremetinium chloride with lithium aluminum hydride, "o-dihydrodehydroemetine" was isolated as described by Karrer and Ruttner (14). Catalytic reduction of this product, however, consumed two moles of hydrogen and not one as previously reported. Two products were isolated. One had a m. p. of 195.0-195.6° and corresponded to isotetrahydrodehydroemetine. The other had a m.p. of 131.4-132.4° and corresponded to tetrahydrodehydroemetine. Ultraviolet spectra of these compounds (Fig. 2) corresponded to those given by Karrer and Ruttner (14).

Direct catalytic reduction of rubremetinium chloride by the method of Openshaw and Wood (8) was also carried out. It was found that 2.0 moles of hydrogen were absorbed in 139 hours. Actually, the first mole of hydrogen was absorbed in one hour. The remaining time was required for the uptake of the second mole. This may explain why Openshaw and Wood report that reduction required only one mole of hydrogen.

Two products were isolated from the reduction mixture. The first had a m.p. of 196.2-197.2° and a specific rotation of -392°. It corresponds to the " -dihydrorubremetine" of Openshaw and Wood (8) and was shown to be identical with isotetrahydrodehydroemetine by a mixed melting point and a

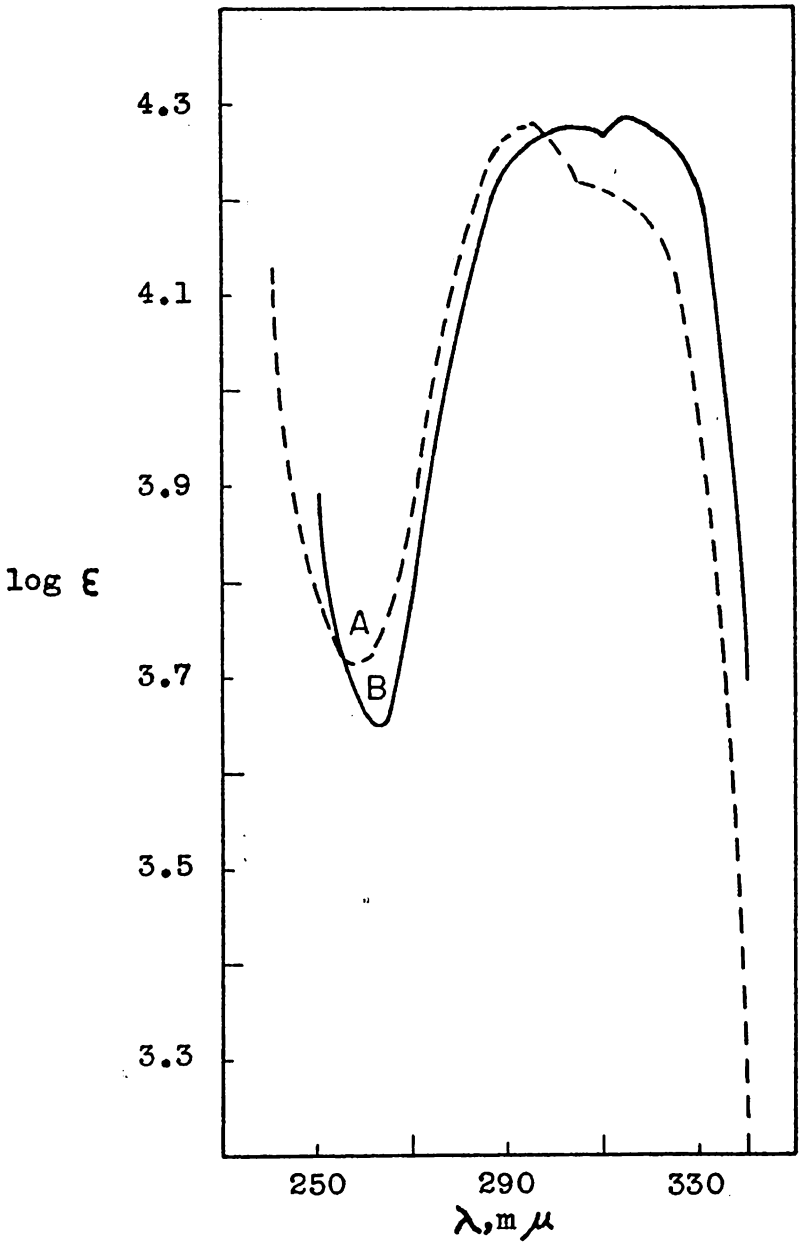


Fig. 2. -- Ultraviolet absorption spectra in ethanol solution of (A) tetrahydrodehydroemetine and (B) isotetrahydrodehydroemetine.

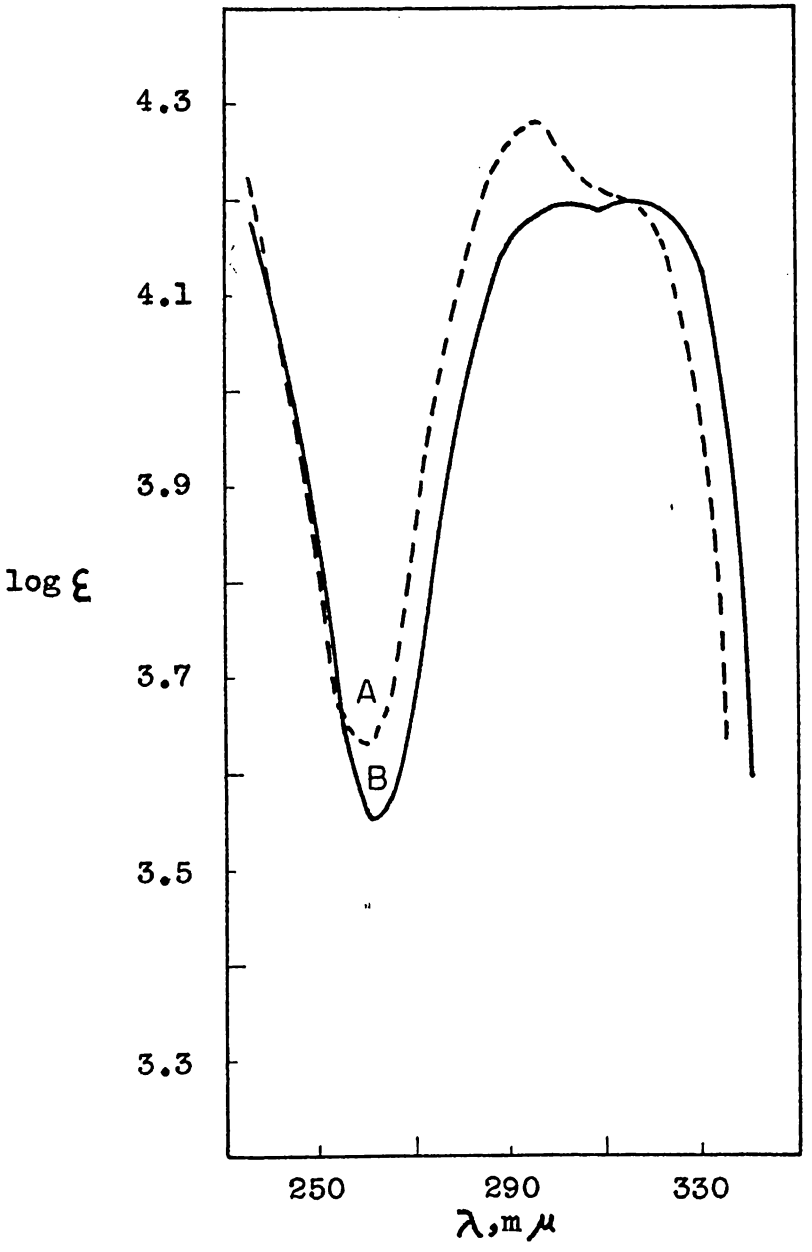


Fig. 3. -- Ultraviolet absorption spectra in ethanol solution of (A) the product having m.p. 132.0-132.8° from direct reduction of rubremetinium chloride and (B) α-dihydrorubremetine.

comparison of ultraviolet spectra (Fig. 3B and Fig. 2B). The second product had a m.p. of 132.0-132.8° and a specific rotation of -18° in acetone and -41.9° in ethanol. It gave no melting point depression with tetrahydrodehydroemetine and its ultraviolet spectrum (Fig. 3A) was identical with that of tetrahydrodehydroemetine (Fig. 2A).

No product was obtained which corresponded to β-dihydrorubremetine. This indicates that this compound is truly a dihydro derivative. [Observations by McEwen (16) substantiate this. During hydrogenation of rubremetinium chloride in ethanol, a heavy precipitate formed shortly after one mole of hydrogen was absorbed, which disappeared as the second mole was taken up. (Openshaw and Wood (8) indicated that β-dihydrorubremetine was not very soluble in ethanol.) By stopping the reduction when one mole of hydrogen had been absorbed, the precipitate was identified as β-dihydrorubremetine by m.p. and rotation. This compound took up one mole of hydrogen on catalytic hydrogenation.]

The fact that two moles of hydrogen are taken up and the same products are obtained, both in direct catalytic reduction of rubremetinium chloride and reduction of "o-dihydrodehydroemetine", indicates that the latter substance cannot be a reduction product. It may be the product of an elimination reaction.

Tetrahydrodehydroemetine and isotetrahydrodehydroemetine probably correspond to the general structure X,

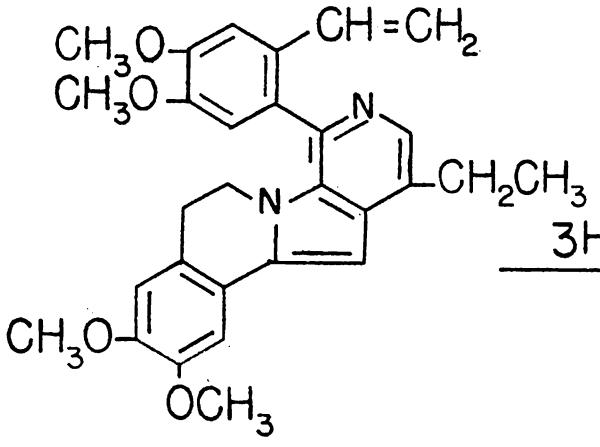
for Openshaw and Wood (8) have demonstrated the presence of a pyrrole ring in both their "dihydrorubremetines". Since both of these products are produced from rubremetinium chloride by the uptake of two moles of hydrogen, two double bonds must be added to X to give the skeleton of the rubremetinium cation.

Woodward (17) had proposed a structure (XII) for the rubremetinium cation which accommodates these experimental findings. The placement of the second double bond between the 11 and 12 positions destroys the last asymmetric carbon in the molecule. The optical activity of the cation is attributed to molecular dissymmetry resulting from interference of the starred positions.

The relationship between XII and its tetrahydro derivatives, having the general structure X, is obvious. The relationship between XII and tetrahydrodehydrohalorubremetine is not as apparent. There are three facts which distinguish this product from the tetrahydrodehydroemetines: 1. It is extensively racemized (indicating that dehydrohalorubremetine is also racemized). 2. It has an active hydrogen as shown by a Zerewitinoff determination. 3. It probably has two terminal methyl groups even though the Kuhn-Roth analysis indicates slightly more than one. It is known that in these determinations considerably less than the theoretical value is obtained. (See, for example, the data for Kuhn-Roth determination of terminal methyl

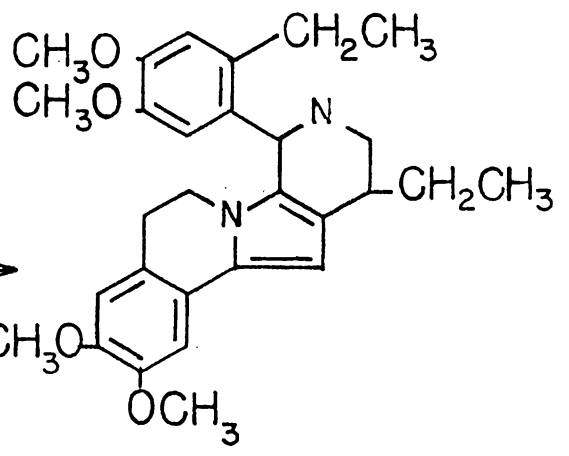
groups in the case of tetrahydrodesdimethylapoerysotrine (18) (19).) These three facts indicate that a Hofmann degradation probably occurred in forming the dehydrohalorubremetine. Such a reaction should give XIII or XV on the basis of structure XII for rubremetinium chloride. The analytical data are consistent with formulae XIV or XVI for tetrahydrodehydrohalorubremetine. The only inconsistency is the fact that dehydrohlorubremetine apparently took up only two moles of hydrogen on catalytic reduction. Since dehydrohalorubremetine cannot be completely purified and the reductions were run on crude material, this does not seem like too serious an objection.

Some subsequent work by Williams and McEwen (11) clears up this discrepancy however. It was found that dehydrohalorubremetine actually absorbed 2.7 moles of hydrogen on reduction in a slightly acidified medium. It was also discovered that dehydrohalorubremetine yielded formic acid on potassium permanganate oxidation, indicating a terminal methylene group. The fact that tetrahydrodehydrohalorubremetine yields no acyl derivative even on treatment with acetyl chloride was as tentative evidence that XV is the correct structure for dehydrohalorubremetine. Uptake of three moles of hydrogen would give XVI (which should be renamed hexahydrodehydrohalorubremetine) which has pryyole and tertiary nitrogens, neither of which would be acylated.

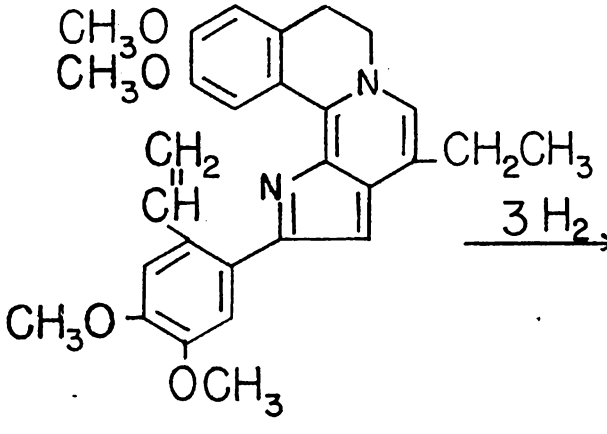


XIII

$3H_2$

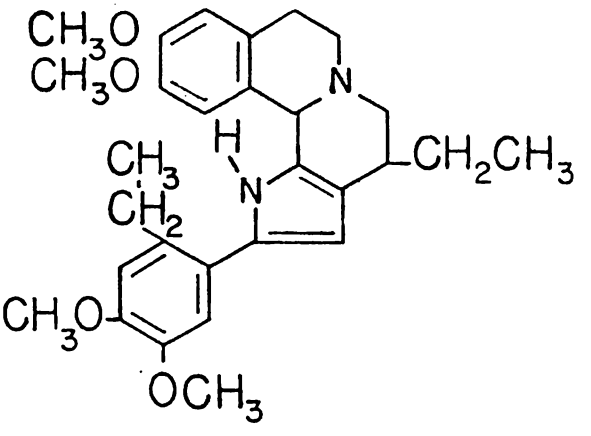


XIV



XV

$3H_2$



XVI

EXPERIMENTAL (20) (21)*

Dehydrohalorubremetine -- This material was prepared as previously described (10). The m.p. behavior of the crude material depends on the rate of heating and on the temperature at which the sample is introduced into the m.p. bath. With a very slow rate of increase of temperature and introduction of the sample at 130°, the material melts at 150-157°, with sintering several degrees lower.

Hydrogenation of Dehydrohalorubremetine -- The crude dehydrohalorubremetine obtained from 19.2 g. of rubremetinium chloride hexahydrate was dried in a vacuum desiccator for one week over anydrous calcium chloride. A 2.03 g. sample of the material was taken from the 13.00 g. batch of dried material and added to 75 cc. of absolute ethanol together with 0.20 g. of Adams catalyst. The suspension was hydrogenated at atmospheric pressure for 40 hours, 93 cc. (S.T.P.) of hydrogen being consumed. An additional 0.20 g. of catalyst was added, the hydrogenation was started again, and, after 150 hours, an additional 144 cc. (S.T.P.) of hydrogen had been consumed. About 100 cc. of ethanol was added to the greenish-white suspension, the mixture warmed to effect solution of the organic material and filtered. The filtrate was concentrated to 75cc. in vacuo. A colorless solid crystallized, m.p. 165-168°.

The remaining 11.00 g. of dehydrohalorubremetine

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*The results of this investigation have already been published; R. F. Tietz and W. E. McEwen, J. Am. Chem. Soc., 75, 4945 (1953).

was suspended in 200 cc. of ethanol together with 0.50 g. of Adams catalyst. The mixture was hydrogenated in a Parr apparatus for 75 hours at room temperature and a pressure of 50 lb. per sq. in. initially. The greenish-white suspension which resulted was treated as described above for the 2.03 g. sample. The colorless precipitate which was obtained had a m.p. of 164-169°.

The two crops of solid material were combined as were the ethanol mother liquors, and the material was subjected to six stages of a fractional crystallization by the "triangle scheme." The least soluble fraction consisted of pale yellow needles, m.p. 179.2-180.2°. The material showed no rotation in alcohol, benzene or acetone solution.

Anal. Calcd. for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 7.22: N, 5.90; CH_3O, 26.16; one terminal methyl, 3.17; one active H, 0.21. Found: C, 73.59; H, 7.36, 7.55; N, 5.60, 5.94; CH_3O, 25.3, 25.8; terminal methyl, 3.44, 4.13; active H, 0.18, 0.16.

From one of the more soluble fractions there was obtained colorless crystalline material, m.p. 167.8-169.0°, $[\alpha]_D^{19}$ +15.1° (c. 1.06 in acetone).

Anal. Found: C, 72.77, 72.73; H, 7.06, 7.11; N, 7.6, 7.6; CH_3O, 25.9, 25.1; terminal methyl, 3.7, 3.4; active H, 0.05, 0.08.

The more insoluble intermediate fractions, those melting close to 180°, were combined, and a 3.50 g. sample was placed in a Soxhlet extractor. After 48 hours of continuous ether extraction, at such a rate of refluxing that the ether solution siphoned into the reservoir three times per hour, there remained in the thimble 2.20 g. of colorless solid, m.p. 180.2-181.8°. This showed no rotation in acetone solution.

The more soluble fractions, those melting in the vicinity of 170°, were combined, a 1.80 g. sample placed in a Soxhlet extractor and extracted with ether. As soon as any solid material began to crystallize in the reservoir, the solutionwas removed and fresh ether substituted. The first three extracts gave material of the same m.p., but the following extracts gave material of gradually ascending m.p. The first three extracts yielded 0.50 g. of material, m.p. 165.8-166.0 , $[\alpha]_D^{23}$ +11.4° (c 2.10 in acetone).

Anal. Calcd. for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 7.22: N, 5.90. Found: C, 73.36, 73.42; H, 7.01, 7.20; N, 5.92, 6.10.

"o-Dihydrodehydroemetine" -- In a 1 l., 3-necked flask fitted with a mercury seal stirrer, an inlet tube and a reflux condenser fitted with a calcium chloride tube were place 2.30 g. of pulverized, thoroughly dried, rubremetinium chloride and 400 cc. of anhydrous ether. A stream

of dry nitrogen was passed over the suspension and 0.60 g. of lithium aluminum hydride was added. The suspension was refluxed for 2.5 hours, the solution becoming decolorized except for a few specks of unreacted rubremetinium chloride. The excess lithium aluminum hydride was destroyed by addition of wet ether. The ether solution was filtered and dried over anhydrous sodium sulfate. The solution was concentrated to a small volume, whereupon 1.10 g. of yellow crystals precipitated, m.p. 156.5-157.5° (reported (14), m.p. 157-158°).

Isotetrahydrodehydroemetine -- To a solution of 0.96 g. of the yellow material, m.p. 156.5-157.5°, in 50 cc. of glacial acetic acid was added 0.10 g. of Adams catalyst. During 12 hours of hydrogenation at atmospheric pressure, 110 cc. (S.T.P.) of hydrogen was taken up. A separate experiment showed that 20 cc. (S.T.P.) of hydrogen was required for reduction of the catalyst.

The solution was filtered and the acetic acid distilled *in vacuo*. The residue was treated with dilute sodium carbonate solution and extracted with ether. The ether solution, dried over anhydrous sodium sulfate, was concentrated to a small volume. About 0.10 g. of colorless isotetrahydrodehydroemetine crystallized, m.p. 183.4-186.6°. Recrystallization, first from ether, then from absolute methanol, gave colorless needles, m.p. 195.0-195.6° (reported (14) m.p. 194°).

Tetrahydrodehydroemetine -- The ether mother liquor was concentrated further. The solid material which crystallized was recrystallized from fresh ether, giving colorless tetrahydrodehydroemetine, m.p. 131.4-132.4° (reported (14), m.p. 134°), $[\alpha]^{26}D$ + 47.5° (c 0.464 in absolute ethanol), $[\alpha]^{25}D$ + 24° (c 0.368 in acetone). Karrer and Rüttner (14) reported $[\alpha]^{18}D$ + 42° (in absolute ethanol).

Hydrogenation of Rubremetinium Chloride -- To 4.00 g. of rubremetinium chloride, dried in a vacuum desiccator over anhydrous calcium chloride for several days, was added 3.5 g. of sodium acetate trihydrate, 55 cc. of absolute ethanol and 0.15 g. of Adams catalyst. The mixture was hydrogenated at atmospheric pressure for 29 hours, 286 cc. (S.T.P.) of hydrogen being consumed. (Of this quantity of hydrogen, the first 220 cc. was absorbed in the course of an hour, a thick suspension being formed in the process.) An additional 0.10 g. of Adams catalyst was added and the hydrogenation continued for 120 hours, an additional 106 cc. (S.T.P.) of hydrogen being consumed. There was no uptake of hydrogen during the last 12 hours of this period.

The yellow solution was filtered and the filtrate concentrated to dryness in vacuo. Dilute sodium hydroxide solution was added to the residue, and the mixture was extracted with ether. The ether solution, dried over anhydrous sodium sulfate, was evaporated to dryness. Crystallization of the

residue from absolute ethanol afforded 2.63 g. of pale yellow crystals. Recrystallization from absolute methanol gave colorless material, m.p. 127.5-130.6°, 2.14 g. This was placed in a Soxhlet extractor and extracted with 125 cc. of ether for a period of 8 hours. A second and a third extraction, each involving 125 cc. of ether and carried out for an 8-hour period, brought all of the material in the thimble into solution. Concentration of the second ether extract afforded 0.77 g. of colorless crystals, m.p. 132.0-132.8°, $[\alpha]^{22}D$ + 18.2° (c 0.275 in acetone), $[\alpha]^{26}D$ + 41.9° (c 0.691 in absolute ethanol). A mixed m.p. with tetrahydrodehydroemetine, described above, showed no depression.

The mother liquor from the methanol recrystallization was concentrated to a small volume, whereupon 0.19 g. of colorless needles, m.p. 196.2-197.2°, $[\alpha]^{26}D$ - 392° (c 0.255 in absolute ethanol), was obtained. Openshaw and Wood (8) report a m.p. of 197-198°, $[\alpha]^{15}D$ - 395° (c 0.165 in acetone) for α-dihydrorubremetine. A mixed m.p. with isotetrahydrodehydroemetine, described above, showed no depression.

SUMMARY

1. Previous reduction procedures used on rubremetinium salts were repeated and it was found:
   a. "o-dihydroemetine" absorbs two moles of hydrogen on catalytic reduction, yielding tetrahydrodehydroemetine and isotetrahydrodehydroemetine.
   b. Direct catalytic reduction of rubremetinium chloride results in the uptake of two moles of hydrogen, and yields tetrahydrodehydroemetine and isotetrahydrodehydroemetine.
2. The above results were shown to be accommodated by structure XII for rubremetinium chloride.
3. Both racemic and optically active "tetrahydrodehydrohalorubremetine" were isolated from the catalytic reduction of dehydrohalorubremetine.
4. Analytical data for "tetrahydrodehydrohalorubremetine" led to a tentative identification of dehydrohalorubremetine as a Hofmann degradation product of rubremetinium chloride.

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