

PART I

USE OF THE HAMMETT EQUATION IN THE PREDICTION
OF PRODUCT RATIOS IN THE SCHMIDT REACTION
OF UNSYMMETRICAL DIARYLETHYLENES

PART II

THE SYNTHESIS OF POSSIBLE EMETINE INTERMEDIATES

by

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PART I

USE OF THE HAMMETT EQUATION IN THE PREDICTION
OF PRODUCT RATIOS IN THE SCHMIDT REACTION
OF UNSYMMETRICAL DIARYLETHYLENES

INTRODUCTION

Hammett(1) has shown that a semi-quantitative relationship exists between the structures of certain organic molecules and their chemical reactivity. From his analysis of 52 reaction series involving the side-chain reactions of meta and para substituted benzene derivatives and also the nitration of benzene derivatives, he proposed an empirical equation

$$\log k - \log k_0 = \sigma \rho$$

where k_0 is the rate or equilibrium constant for the reaction involving the unsubstituted reactant, k is the rate or equilibrium constant for the substituted compound, ρ is a constant characteristic of the reaction and σ is a constant characteristic of the substituent. Experimental data can usually be fitted to this curve with a deviation of $\pm 15\%$.

Within the limits of certain inherent restrictions, such as the necessity that there be a constancy of entropy of activation within a given series of reactions and that relative rates or positions of equilibria be governed by potential energy quantities only, this relationship has been amply substantiated by many investigators since it was first proposed(2). Recently, Swain and Langsdorf(3)

have provided a reasonable physical interpretation of the reaction constant ρ with respect to nucleophilic displacement reactions of certain organic halides.

The fact that the Hammett relationship has been found adaptable to the correlation of reactivities of the meta and para positions in the nitration of benzene derivatives, plus the suggestion by Wheland(4) that the migration of an aryl group to a cationoid atom in a typical rearrangement resembles the process of electrophilic aromatic substitution, provided the stimulus for the work described in this thesis. Extending the analogy between aromatic substitution and the process of migration of aryl groups in competitive rearrangements, the Hammett equation in the latter situation might be modified to

$$\log \text{ Intrinsic Migratory Aptitude} = \sigma \rho$$

where the term "intrinsic migratory aptitude" refers to the relative rate of migration of a meta or para substituted phenyl group as compared to an unsubstituted phenyl group. An examination of the data in the literature(5) on the Schmidt reaction of five unsymmetrical diarylethylenes indicated that a linear relationship between the logarithms of the product ratios and the sigma values of the aryl groups undergoing migration does exist. To verify this relationship, five additional reactions of meta or para substituted diphenylethylenes with hydrazoic and sulfuric acids have been carried out and are described in this thesis.

A correlation of the rates of nitrogen evolution in the Schmidt reaction of meta and para substituted benzoic acids by the use of a suitable adaptation of the Hammett equation has also been made. Finally, an attempt has been made to correlate the results of the pinacol rearrangement of symmetrical pinacols by use of the Hammett relationship.

BACKGROUND AND HISTORICAL REVIEW

A. Survey of the Schmidt Reaction.

A complete review of the literature on the Schmidt reaction up to 1946 has been published(6). The following material is a brief summary of this review article.

There are four main applications of the Schmidt reaction. Carboxylic acids react with hydrazoic and sulfuric acids to give amines and carbon dioxide. Ketones give amides. Aldehydes yield mixtures of a nitrile and a formamide. Olefins afford amines and either aldehydes or ketones.

The most extensive application of the Schmidt reaction has been in the preparation of amines from carboxylic acids. As typical examples of this reaction, n-caproic acid yields 70% of n-amylamine and stearic acid yields 96% of heptadecylamine. Dibasic acids give diamines, the yields improving as the distance between the carboxyl groups is increased. Succinic acid, for example, gives only an 8% yield of ethylenediamine, whereas adipic acid affords tetramethylenediamine in 83% yield. Only one of the carboxyl groups of the various malonic acids is converted to an amino group, thus providing a synthesis of α -amino acids. Malonic acid itself, for example, gives a 29% yield of glycine. With respect to aromatic acids, the position and type of substituent on the ring has a marked effect on the rate of reaction and yield of amine. p-Toluic acid, for example, yields 70% of p-toluidine, whereas m-toluic acid gives only 24% of m-toluidine.

Symmetrical ketones give N-substituted amides in the Schmidt reaction, generally in high yields. Thus acetone and benzophenone afford N-methylacetamide and benzanilide, respectively, in quantitative yields. Unsymmetrical ketones can react in two different ways:



Aldehydes give nitriles plus formamides in the Schmidt reaction, the ratio of the products depending on the amount of sulfuric acid used to catalyze the reaction. Benzaldehyde gives a 70% yield of benzonitrile plus a 13% yield of form-anilide when the molar ratio of sulfuric acid to benzaldehyde is 0.72. On changing the ratio to 5.4, the yield of benzo-nitrile drops to 5% while the yield of formanilide rises to 50%.

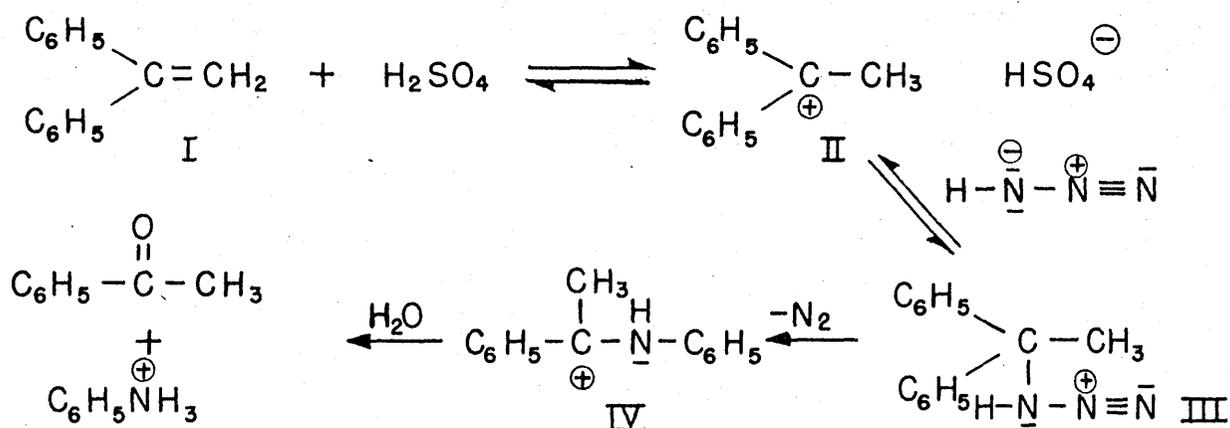
As examples of the Schmidt reaction of olefins, 2-methyl-2-butene has been reported to yield a mixture of acetone, methyl ethyl ketone, methylamine and ethylamine on reaction with hydrazoic and sulfuric acids, and cyclopentene has been reported to undergo ring enlargement, forming tetrahydro-pyridine.

B. Mechanisms of the Schmidt Reactions.

Most of the studies on the mechanisms of the various Schmidt reactions have been reported during the last five years. Consequently most of the statements concerning mechanisms in the above mentioned review article(6) are invalid

or out of date. The following paragraphs contain a summary of the current theories on the mechanisms.

McEwen, Gilliland and Sparr(5a) as well as Kuhn and DiDomenico(5b) have proposed a carbonium ion mechanism for the Schmidt reaction of 1,1-diphenylethylene(I). It was found that 1,1-diphenylethylene reacts with hydrazoic acid in chloroform solution, catalyzed by concentrated sulfuric acid, to give acetophenone (together with aniline) in 55% yield. It was suggested that I reacts with sulfuric acid to form the carbonium ion II, which then adds a molecule of hydrazoic acid to give the complex III. With essentially simultaneous loss of nitrogen from III and migration of a phenyl group and its binding pair of electrons, the conjugate acid of acetophenone anil(IV), is formed, which then affords acetophenone and the anilinium ion on hydrolysis.



In the rearrangement of the complex III, the group which migrates to nitrogen should be that one of the three groups in a position to migrate which possesses the greatest intrinsic migratory aptitude; i.e., the one which tends to migrate at

the fastest rate. In the corresponding reaction with hydrazoic acid of other unsymmetrical diarylethylenes, in which one or both of the phenyl groups bears a substituent in the meta or para position, the order of migratory aptitudes might reasonably be expected to show a correlation with that of the pinacol rearrangement of symmetrical pinacols, the mechanism of which has many features analogous to the one described here(7). Such a series of reactions was carried out by McEwen, Gilliland, and Sparr(5a), and the anticipated correlation was qualitatively realized (Table I).

Table I

Schmidt Reaction of Unsymmetrical Diarylethylenes

Starting Material

$\begin{array}{l} p\text{-XC}_6\text{H}_4 \\ p\text{-YC}_6\text{H}_4 \end{array} > \text{C} = \text{CH}_2$		% yield of ketones	
<u>X</u>	<u>Y</u>	<u>p-X-acetophenone</u>	<u>p-Y-acetophenone</u>
H	OCH ₃	49	8
H	CH ₃	40	8
H	C ₆ H ₅	39	17
H	H	55	--
H	Cl	18	29
OCH ₃	CH ₃	8	39
OCH ₃	C ₆ H ₅	11	36
CH ₃	C ₆ H ₅	6	21

Peter A. S. Smith and coworkers(8,9,10) have made an extensive study of the Schmidt reaction of ketones. Some of their results are summarized in Table II.

Table II

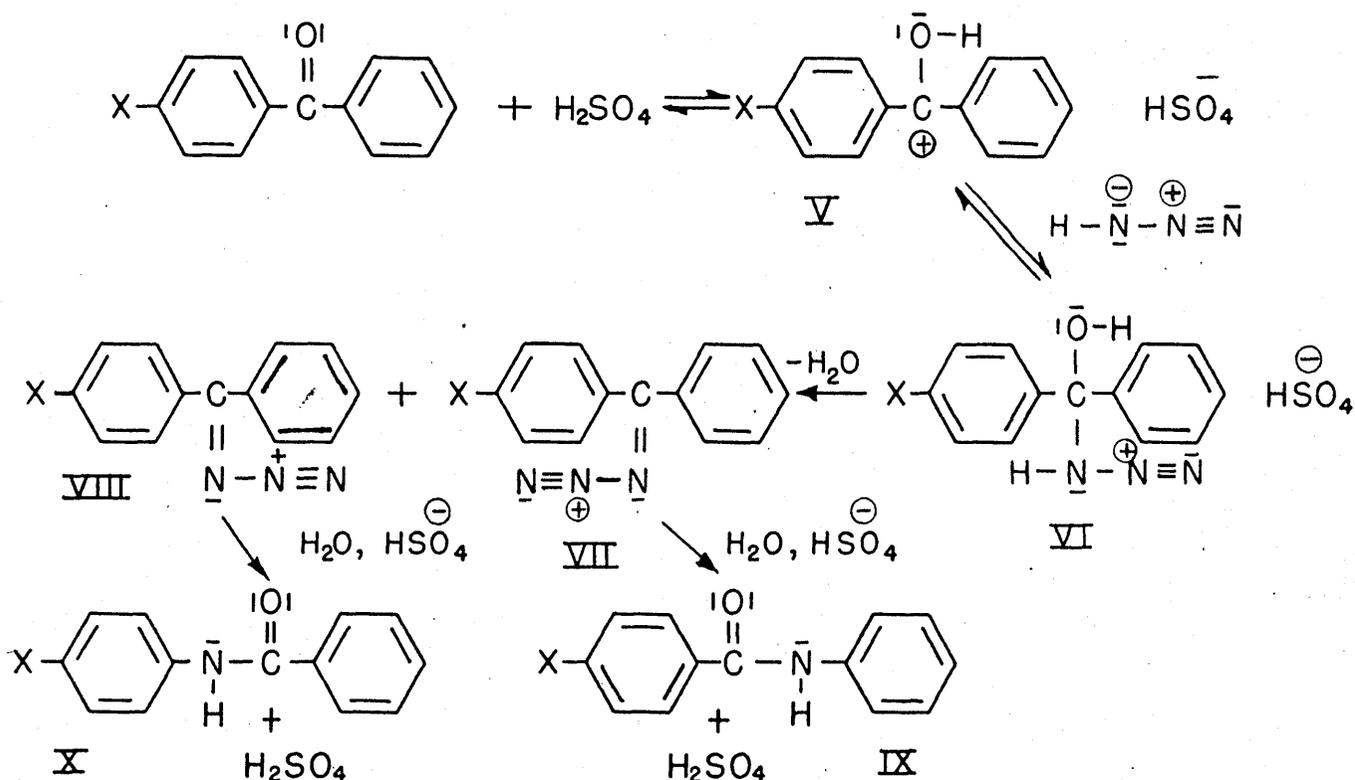
Schmidt Reactions of p-X-Benzophenones

Starting Materials		Product Ratios	
<u>p-X-C₆H₄COC₆H₅</u>	<u>p-X-C₆H₄CONHC₆H₅</u>	<u>C₆H₅CONHC₆H₄-X-p</u>	
X = Cl	41	59	
NO ₂	49	51	
CH ₃	46	54	
CH ₃ O	39	61	
C ₆ H ₅	48	52	

It can readily be seen that the ratios of the two amides formed are approximately 1:1 in most of the cases studied, despite a wide divergence in the electronic effects of the para substituents. Hence arguments based on the concept of the "intrinsic migratory aptitudes" of the various aryl groups cannot account for the ratios of products obtained in these rearrangements. The results show clearly that there is no step in these reactions in which a freely competitive migration of the aryl groups determines the product ratios. This case is therefore unlike that of the unsymmetrical diaryl-ethylenes discussed earlier.

To explain his results, Smith has proposed the following entirely reasonable mechanism: The p-substituted benzophenone reacts with sulfuric acid, the catalyst, to form the conjugate

acid V, which then combines with a molecule of hydrazoic acid to form the complex VI. This complex undergoes an acid-catalyzed dehydration to give nearly equal amounts of the geometrically isomeric cations, VII and VIII. Finally, VII and VIII undergo trans rearrangements (analogous to the Beckmann rearrangement), accompanied or followed by the addition of a molecule of water, to give the isomeric amides, IX and X, in nearly equal quantities.



The only factor which might reasonably influence the ratio of the syn and anti isomers, VII and VIII, formed in the dehydration step is a steric one. Since a steric effect would be manifested only in the immediate vicinity of the carbon-nitrogen double bond, a para substituent on one of the

phenyl groups of benzophenone would not be expected to exert any appreciable steric influence. Hence one would expect essentially equal quantities of the isomers VII and VIII to be formed.

In order to evaluate any possible steric influence on the course of the Schmidt reaction of ketones, Smith and Horwitz(10) studied the reactions of aryl alkyl ketones, in which the degree of chain branching on the alpha position of the alkyl group was systematically increased. The results are summarized in Table III.

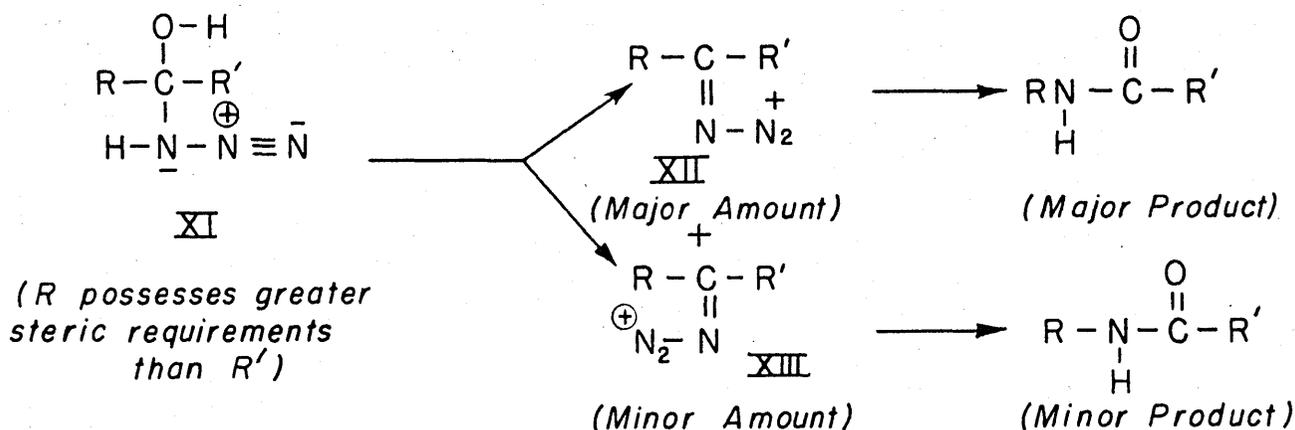
Table III

Relative Extents of Migration in Ketones, C_6H_5COR

<u>R</u>	Fraction Migrating	
	<u>C_6H_5</u>	<u>R</u>
Methyl	0.95	0.05
Ethyl	0.85	0.15
Isopropyl	0.51	0.49
t-Butyl	0.00	1.00

The migration ratios, as shown in Table III, show a progressive change from preferred phenyl migration to preferred alkyl migration as the alkyl group becomes increasingly branched at the alpha position. The Smith mechanism can readily accommodate this result as follows: When the complex XI, formed by combination of a molecule of the ketone,

a proton and a molecule of hydrazoic acid, undergoes dehydration, that one of the two geometrically isomeric cations, XII and XIII, which has the bulkier of the two groups trans to the N_2 group is formed in the larger amount. Hence the major product results from the trans migration of the bulkier group.



McEwen, Conrad and VanderWerf(11) have extended the study of the Schmidt reaction of aldehydes and have proposed a mechanism which accounts for the most interesting feature of the aldehyde reactions, viz., the fairly general overturn in product ratio that occurs on increasing the amount of sulfuric acid used to catalyze the reaction. Their results are summarized in Table IV. Since the hydrazoic acid used in these reactions was generated in situ by the use of sodium azide, the effective catalyst at the low sulfuric acid concentration was sodium bisulfate.

Table IV

The Schmidt Reaction of Aldehydes

<u>Aldehyde</u>	<u>Ratio of sulfuric acid to aldehyde</u>	<u>Yield, %</u>	
		<u>Nitrile</u>	<u>Formanilide</u>
Benzaldehyde	0.72	32	14
	5.4	10	59
p-Chlorobenzaldehyde	0.72	55	12
	5.4	15	48
p-Methylbenzaldehyde	0.72	50	6
	5.4	13	43
p-Nitrobenzaldehyde	0.72	72	2
	5.4	46	23
p-Methoxybenzaldehyde	0.72	86	0
	5.4	64	0

The fairly general increase in the ratio of formamide to nitrile formation that occurs on increasing the amount of sulfuric acid used to catalyze the reaction was explained in the following way: The aldehyde reactions are assumed to have many of the mechanistic features of the ketone reactions. The aldehyde reacts with sulfuric acid to form the conjugate acid XIV. This combines with hydrazoic acid to give the complex XV, which then undergoes dehydration to the syn and anti isomers XVI and XVII. The species XVI affords the nitrile by the trans elimination of a proton and a molecule of nitrogen,

exceeds the rate of conversion of XVI to the nitrile. Therefore the bulk of XVI is converted to XVII and the formanilide becomes the major product. In other words, as the acid concentration is increased, the overall rate leading from XIV to the formanilide by way of XVI and XVII, respectively, begins to compete favorably with the more direct route from XIV to the nitrile via XVI.

Briggs and Lyttleton(14) were the first to uncover useful data concerning the mechanism of the Schmidt reaction of carboxylic acids. They observed the rates of nitrogen evolution in the reactions of meta and para substituted benzoic acids, at 40°, in trichloroethylene solution, with sulfuric acid as the catalyst. Their results are summarized in Table V.

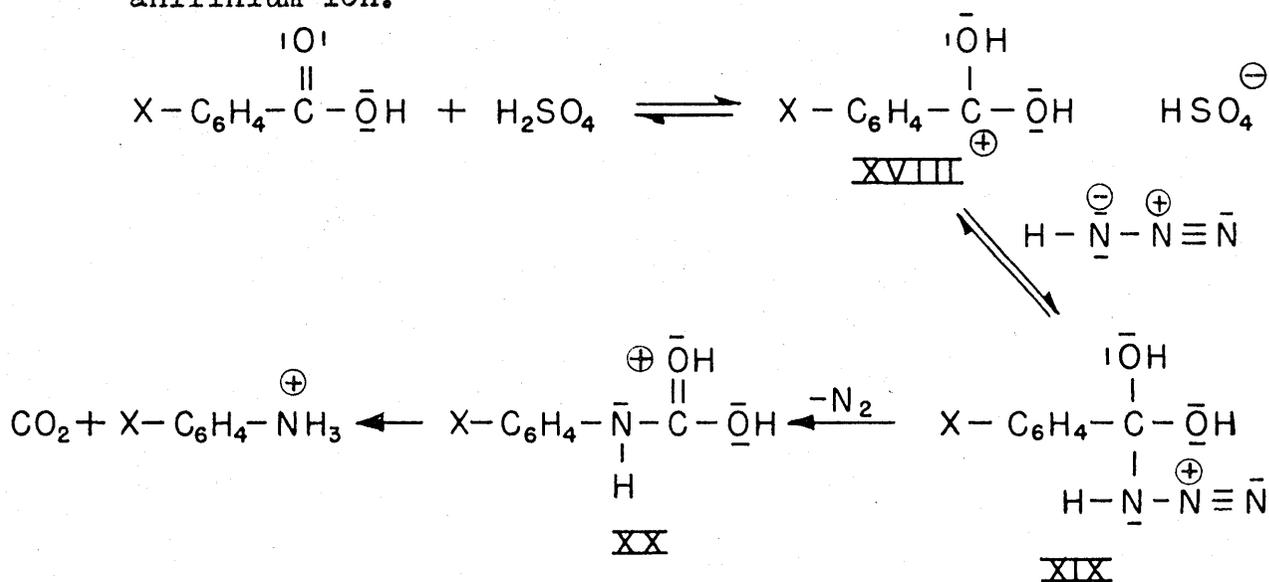
Table V

Schmidt Reaction of Benzoic Acids

<u>Benzoic Acid</u>	<u>% Amine Isolated</u>	<u>% Acid Recovered</u>	<u>Vol. N₂ S.T.P.</u>	<u>% N₂</u>	<u>T 1/2 (min).</u>
m-Cl	75	--	535	95.5	12
m-Br	72	--	515	92	10
m-I	62	32	452	80	15
m-OH	80	15	507	91	5
m-OCH ₃	77	16	500	89	4
m-OC ₂ H ₅	73	23	494	88	4
m-NO ₂	63	32	432	77	100
m-CN	59	38	404	72	18
m-COOH	57	40	447	80	17
m-CH ₃	42	51	448	80	2
H	69	25	552	98	3
p-OCH ₃	78	17	512	91	1.5
p-NO ₂	41	54	385	69	120
HN ₃	--	--	280	50	22
o-OCH ₃	80	17	558	99	5
o-NO ₂	68	26	541	96	2

A reasonable mechanism for the reaction of these acids consists of the following steps: The carboxylic acid accepts a proton from sulfuric acid forming the dihydroxycarbonium ion XVIII. This adds a molecule of hydrazoic acid to give the complex XIX, which then suffers loss of nitrogen and migration

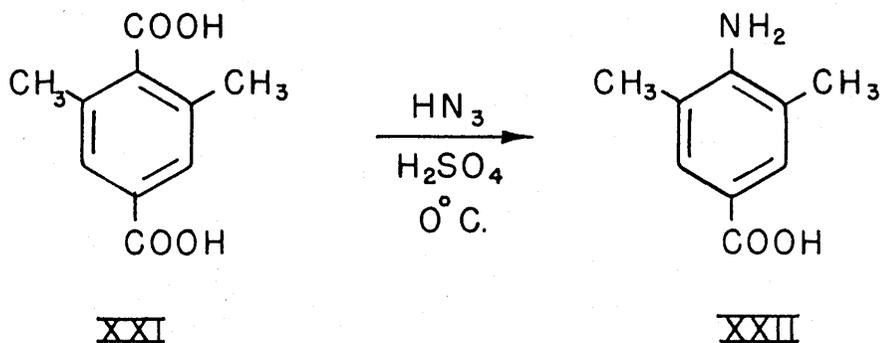
of the aryl group to give the conjugate acid of the carbamic acid, XX. This loses carbon dioxide with formation of an anilinium ion.



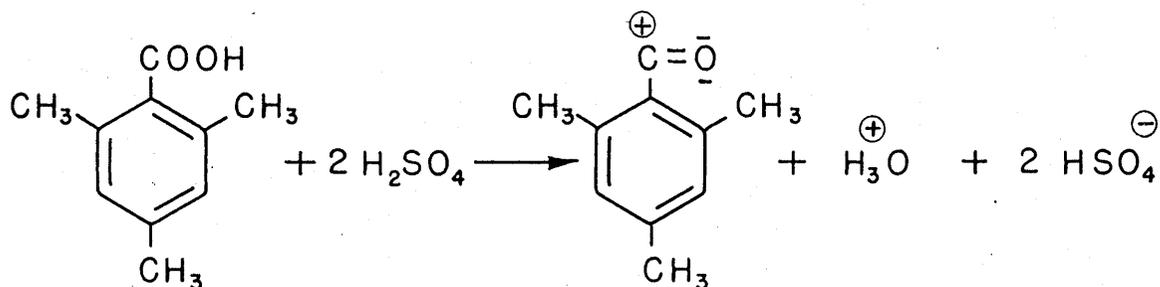
The rates of nitrogen evolution summarized in Table V suggest that the slow step in these reactions is the migration step involving loss of nitrogen. The rates of nitrogen evolution qualitatively parallel the migratory aptitudes of the aryl groups as observed in the Schmidt reaction of unsymmetrical diarylethylenes and the pinacol rearrangement of symmetrical pinacols.

At a later date, Newman and Gildenhorn(15) observed that 2,6-dimethylterephthalic acid(XXI) reacts with sulfuric and hydrazoic acids at 0° C. to give exclusively 4-amino-3,5-dimethylbenzoic acid(XXII). The sterically hindered carboxyl group reacts exclusively.

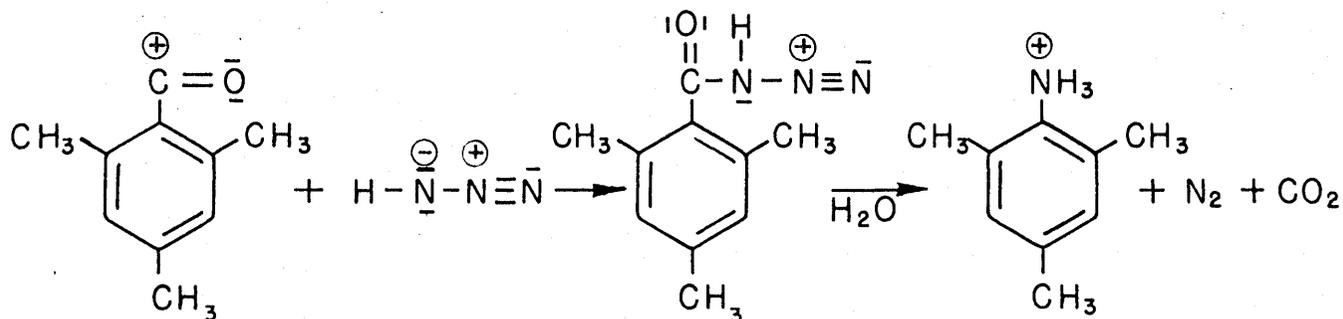
It was also observed that both methyl mesitoate and mesitoic acid react to give mesidine at 0° C., whereas benzoic acid and other unhindered aromatic acids require a temperature



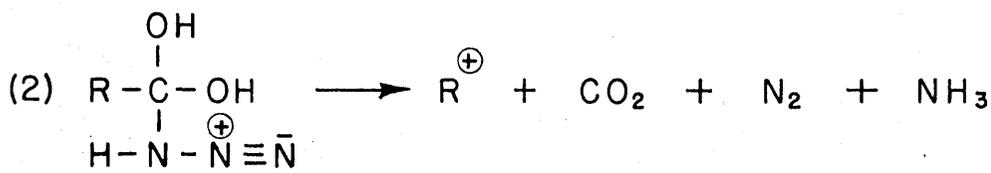
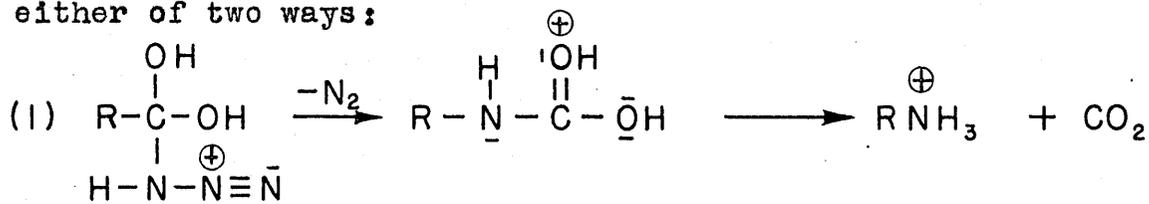
of 35-50° C. for the reaction to occur at a noticeable rate. Since it is known that mesitoic acid (and other hindered acids) undergoes a complex ionization in sulfuric acid in the neighborhood of 0° C. to form an oxocarboxonium ion(16),



it was suggested that the Schmidt reactions of hindered acids involve the oxocarboxonium ion as an intermediate. The oxocarboxonium ion combines with a molecule of hydrazoic acid to form the conjugate acid of the corresponding acid azide, which then rearranges to give the amine plus carbon dioxide as in the Curtius rearrangement.



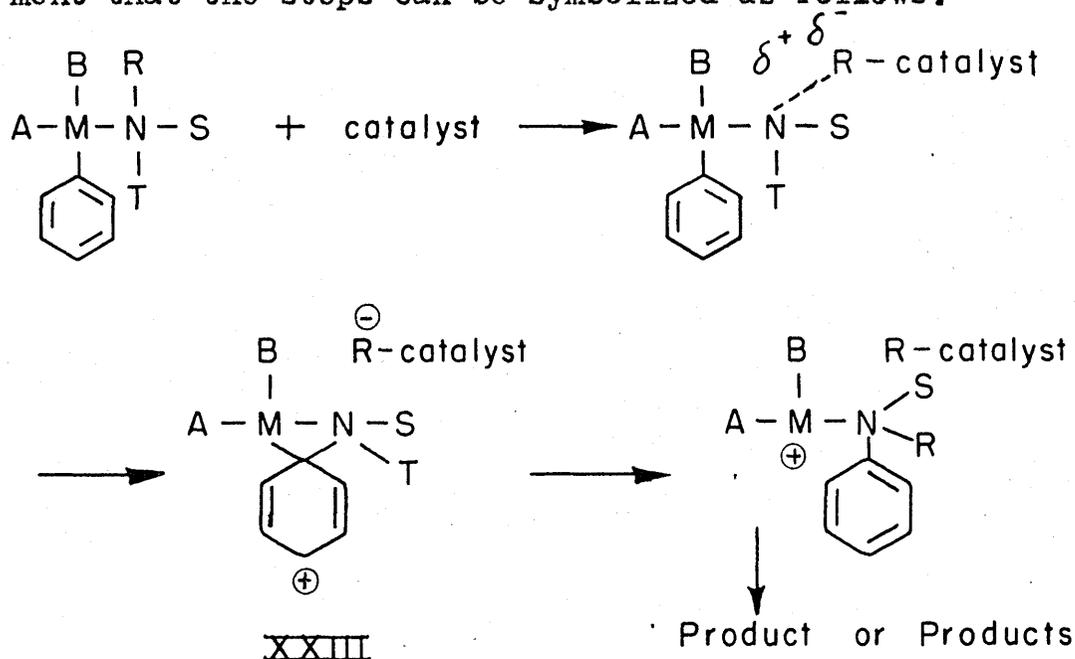
Yet another complexity of the Schmidt reaction of carboxylic acids was uncovered by Schuerch and Huntress (17). Trialkylacetic acids were found to react to a large degree in an abnormal manner. Reaction of trimethylacetic acid with hydrazoic and sulfuric acids gives only a 33% yield of t-butylamine, with acetone and methylamine being formed as by-products. Dimethylethylacetic acid gives a low yield of t-amylamine together with acetone, methyl ethyl ketone, methylamine and ethylamine. Triethylacetic acid gives rise to an even more complex mixture of products. Schuerch and Huntress interpreted these results by assuming that the adduct of the dihydroxycarbonium ion and hydrazoic acid can decompose in either of two ways:



The carbonium ion resulting from the second mode of decomposition would react with hydrazoic acid in much the same way as described earlier for the olefin reactions, where a carbonium ion is also considered to be an intermediate species. The formation of all of the by-products can be accommodated on the basis of this assumption.

C. Mechanism of the Migration of an Aryl Group to an Adjacent Cationoid Atom.

There have been many theories proposed as to how an aryl group migrates from one atom to an adjacent cationoid atom. At the present time there seems to be a fairly general agreement that the steps can be symbolized as follows:



The suggestion that the migration involves the intermediate formation of a transition ion of the type XXIII was made several years ago by Wheland(4). Since then, considerable evidence for this type of intermediate species (XXIII) has been published in the chemical literature.

Cram(18) has provided some convincing evidence for this type of intermediate in his study of the Wagner Meerwein rearrangement. Cram's work was based on the stereochemical course of the solvolysis in acetic acid of each of the stereoisomeric p-toluenesulfonates of 3-phenyl-2-butanol (XXIV).

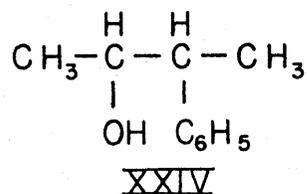
The four stereoisomers of XXIV were first prepared. One pair of enantiomorphs will be designated as

XXIV A and XXIV B, the other pair as

XXIV C and XXIV D. The isomer: XXIV A

was converted to its p-toluenesulfon-

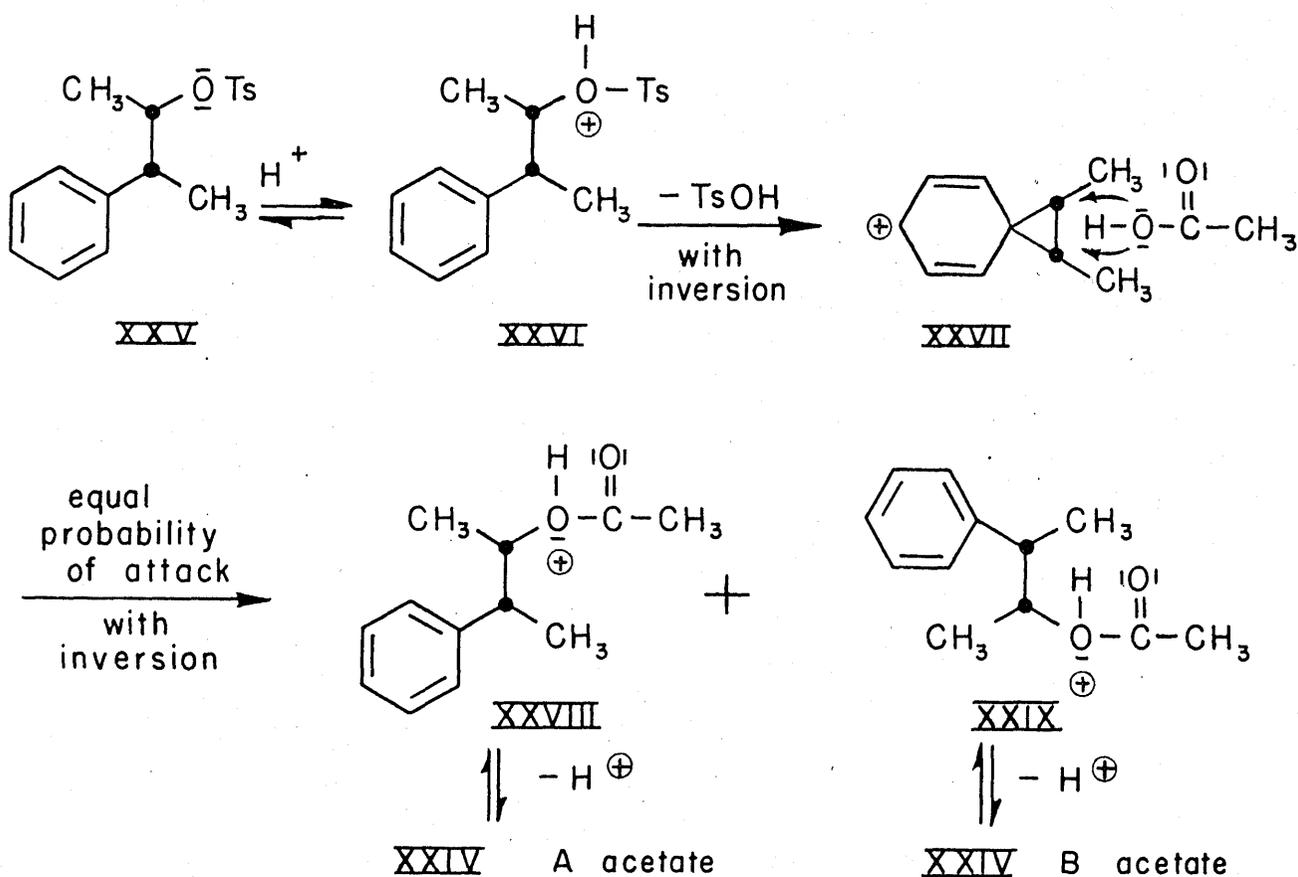
ate, then solvolyzed in acetic acid,



giving rise to a racemic acetate, which proved to be XXIV A acetate plus XXIV B acetate. When the p-toluenesulfonate of XXIV C was solvolyzed in acetic acid, however, an optically active acetate was obtained, which turned out to be XXIV C acetate. These results can be explained only in terms of the mechanism shown below. In this scheme, XXIV A p-toluenesulfonate is assigned the configuration denoted by XXV because the stereochemical results require this configuration. Of course no claim is made as to whether XXV represents the dextrorotatory or the levorotatory member of this particular pair of enantiomorphs. The heavy dot indicates a hydrogen atom coming out of the plane of the paper towards the reader.

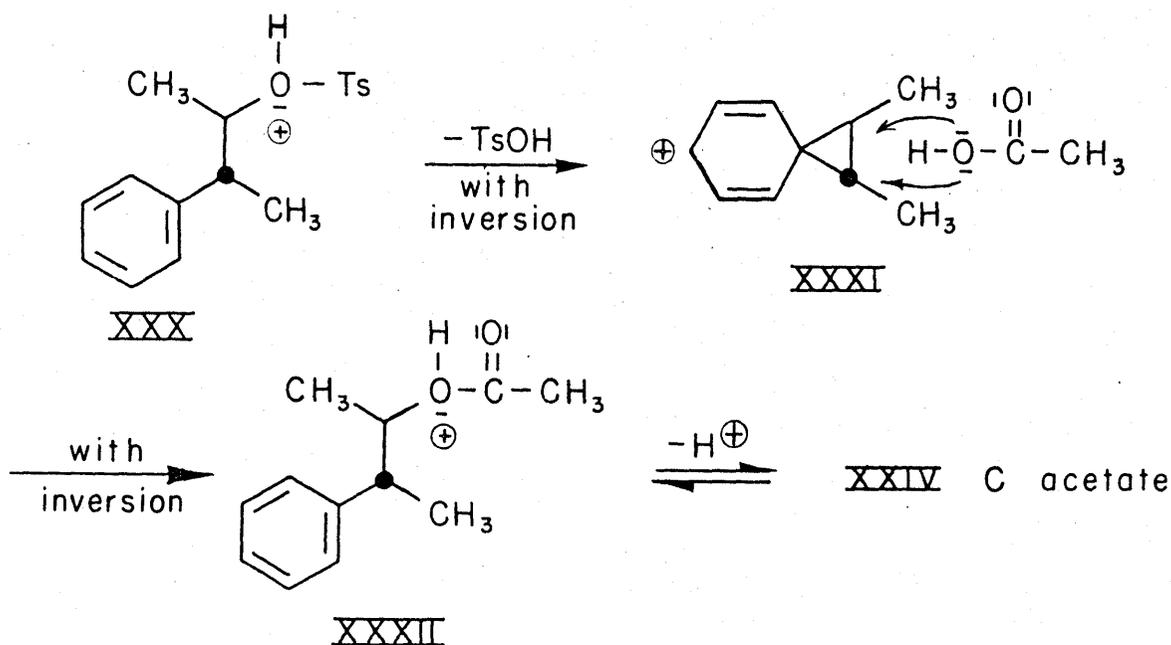
By addition of a proton, XXV is converted into its conjugate acid, XXVI. By an essentially simultaneous back-side attack of the phenyl group and loss of a molecule of p-toluenesulfonic acid, XXVI is converted into the meso intermediate, XXVII. A molecule of acetic acid then attacks either of the two central carbon atoms of XXVII, again with an inversion occurring, forming the conjugate acid (XXVIII) of XXIV A acetate together with the enantiomorphous conjugate acid (XXIX)

of XXIV B acetate. On losing protons to the solution, these give rise to XXIV A acetate and XXIV B acetate, respectively. Since there is an equal probability of attack by an acetic acid molecule at either of the two central carbon atoms of XXVII, both XXVIII and XXIX are formed in equal amounts; hence a racemic acetate (XXIV A acetate plus XXIV B acetate) is obtained.

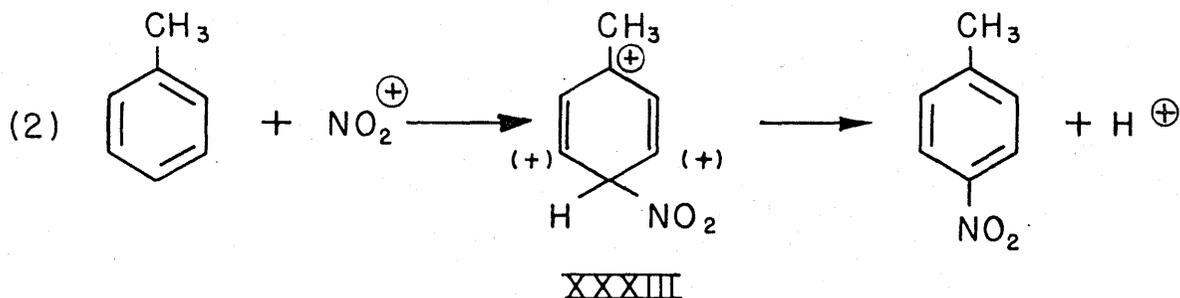


To be convincing, the same mechanism must explain how XXIV C p-toluenesulfonate affords the optically active XXIV C acetate on solvolysis in acetic acid. The mechanism satisfies this requirement, as shown below. The conjugate acid of XXIV C

p-toluenesulfonate (XXX) gives rise to the optically active intermediate XXXI, when the phenyl group displaces a molecule of p-toluenesulfonic acid with inversion. Attack by a molecule of acetic acid at either of the two central carbon atoms of XXXI, with inversion, provides the same molecule, the conjugate acid (XXXII) of XXIV C acetate.



Inasmuch as very nearly the same type of intermediate as XXIII is formed in electrophilic substitution reactions of benzene and its derivatives, it is reasonable and profitable to compare the process of aromatic electrophilic substitution with the process of migration of an aryl group from one atom to an adjacent cationoid atom. By way of illustration, the nitration of toluene in a mixture of concentrated nitric and sulfuric acids is thought to occur by the following mechanism:



It is clear that the transition ion XXXIII is similar to XXIII in type.

The analogy between these two processes seems to have first been proposed by Wheland(4), but numerous other chemists have applied the idea in somewhat more detailed form to a variety of chemical situations(19). The concept represents one of the central ideas of this thesis.

D. Origin and Uses of the Hammett Equation.

The organic chemist frequently applies the process of reasoning by analogy to many of his research problems. He frequently assumes that like substances react similarly and that similar structural variations produce similar changes in reactivity. All too frequently, however, these assumptions do not work. Even the organic chemist who is well versed in electronic theory can make "predictions" based only on his qualitative estimate of the contributions of potential energy quantities to reactions which are, of course, governed by free energy quantities. He seldom has any means at his disposal for estimating the contribution of entropy terms or kinetic energy terms to free energy quantities. Therefore valid predictions of reactivity can be made only when the reactions being compared are governed by differences in potential energy quantities only, i.e., when the reactions being compared have constant entropies of reaction or activation and a constant contribution of kinetic energy terms to the enthalpies of reaction or activation.

Hammett(1) observed that in the side chain reactions of meta and para substituted benzene derivatives and in the reaction of electrophilic substitution in the benzene ring, these criteria of constancy of entropy and kinetic energy terms hold true, and therefore the effect of structure on reactivity can be studied in a semi-quantitative manner.

In those series of reactions in which differences in

rate and equilibrium constants depend on potential energy quantities only, a simple semi-quantitative relationship appears when two series of rate or equilibrium constants are compared. For example, when the logarithms of the rate constants for the hydrolysis of meta and para substituted ethyl benzoates are plotted against the logarithms of the ionization constants for the corresponding benzoic acids, a linear relationship is observed, as given by the equation

$$\log k = \rho \log K_1 + A \quad (1)$$

The available data fit this curve with a deviation of about $\pm 15\%$. Similar linear relationships are found to apply to the rate and equilibrium constants of almost all side chain reactions of benzene derivatives. It is possible to relate these series to one standard of reference. Because the ionization constants of meta and para substituted benzoic acids are known very accurately, it is convenient to use these values as the standard of reference. By adding the term $\log K_1^0$, where K_1^0 refers to the ionization constant of benzoic acid itself, to both sides of equation(1) and rearranging the new expression

$$\log k = \rho (\log K_1 - \log K_1^0) + (A + \rho \log K_1^0) \quad (2)$$

is obtained. Here k represents any rate or equilibrium constant for the type reactions under discussion and $(A + \rho \log K_1^0)$ is necessarily equal to $\log k^0$, where k^0 is the rate or equilibrium constant for the unsubstituted

reactant. If the term σ is now defined as

$$\sigma = \log K_1 - \log K_1^0 \quad (3)$$

then equation(2) assumes the form of the well known Hammett equation,

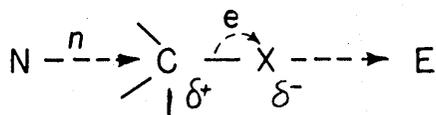
$$\log k - \log k_0 = \rho \sigma \quad (4)$$

The substituent constant σ is by definition determined by the nature of the substituent, and it is a measure of the change in electronic density produced by a meta or para substituent at or near the site of reaction. The reaction constant ρ is a constant for all substituents and depends only on a particular reaction series. It is a measure of the susceptibility of the reaction in question to changes in electron density at or near the site of reaction caused by the meta or para substituent.

Recently, Swain and Langsdorf(3) have provided a simple physical interpretation of ρ with respect to nucleophilic displacement reactions of organic halides. The following quotation summarizes their views:

"When an ordinary polar displacement occurs, there are two essential covalency changes involved: e, the breaking of the old bond, and n, the making of the new bond. Neither process has begun in the reactants, both processes are complete in the products, but either

process may have proceeded farther than the other at the tran-



sition state. The easiest route will not, in general, be

one which results in the same fraction of completion of e and n at the transition state. Depending on whether e or n is more complete at the transition state when following this easiest route, the partial positive charge on the central carbon will be greater or less than in the ground state; and the difference in fractions of completion of e and n will determine the magnitude of this change in charge. The reaction constant, ρ , is a measure of this change in charge, and hence a criterion of the deviation from perfect synchronism involved, since the greater the increase in positive charge on this carbon at the transition state, the more electron supplying substituents will aid (the more negative will be ρ), and the greater the decrease in positive charge, the more electron withdrawing substituents will aid (the more positive will be ρ)."

From the point of view of the usage in this thesis, one of the most interesting applications of the Hammett equation has been in the correlation of reactivities with respect to nitration. Using the data of Ingold and coworkers(20), Hammett(1) was able to show that a plot of $\log k/k^{\circ}$ vs. σ gave a straight line of slope (ρ) about -5. The values of k represent the reactivities of the meta and para positions in benzene derivatives, corrected by a statistical factor to account for the fact that there are two meta positions but only one para position, and the value of k° represents the reactivity of one of the carbons of benzene itself. The plot was drawn from data on the nitration of benzene, toluene, bromobenzene, chlorobenzene and ethyl benzoate.

DISCUSSION OF EXPERIMENTAL RESULTS

In the pinacol-pinacolone rearrangement of a symmetrical pinacol(21) or the Schmidt reaction of an unsymmetrical diarylethylene(5) a mixture of products is obtained, the ratio of the components depending on the relative rates of migration of the groups which, in the transition state, are in a position to migrate. This competitive migration, when applied to aryl groups, has been compared with the process of aromatic substitution(4). More detailed treatments of a similar nature, with reference to other rearrangements, have recently appeared(18,19).

Among numerous other applications, Hammett has shown that the relative reactivities of m- and p-positions in benzene derivatives with respect to nitration, are in accord with the Hammett equation(1). This being the case, and extending the analogy between aromatic substitution and the process of migration of aryl groups in competitive rearrangements, the Hammett equation in the latter situation might be modified to

$$\log \text{intrinsic migratory aptitude} = \sigma \rho \quad (5)$$

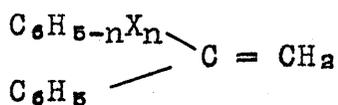
An examination of the previous data on the Schmidt reaction of unsymmetrical diarylethylenes(5) indicates that a linear relationship between the logarithms of the product ratios and the sigma values of the aryl groups undergoing migration does exist. To verify this relationship, five additional reactions of m- or p-substituted diphenylethylenes with hydrazoic and sulfuric acids have been studied. The

results are summarized in Table VI. With reference to the mechanism of these reactions(5), it should be kept in mind that the aryl group which undergoes migration ends up as aniline or an aniline derivative and the remaining aryl group appears finally as acetophenone or a m- or p-substituted acetophenone. Hence a high product ratio of acetophenone to the m- or p-substituted acetophenone indicates preferential migration of the m- or p-substituted phenyl group.

Table VI

Yields of Ketones in the Olefin Reactions

Starting material



Yield of ketones, %

<u>X</u>	<u>Acetophenone</u>	<u>m-or p-X-Acetophenone</u>
3,4-Di-CH ₃	36.6	6.76
p-C ₂ H ₅	44.6	9.75
m-CH ₃	34.2	14.5
p-F	45.8	26.1
p-Br	16.0	29.6

An analysis by the method of least squares of the new data, together with the data previously reported(5) indicates that the following relationship between product ratios (migratory aptitudes) and the sigma values of the groups undergoing migration holds

$$\log \text{ migratory aptitude} = -2.11\sigma + 0.293 \quad (6)$$

The experimental data fit this equation with an average accuracy of $\pm 18\%$. Figure 1B summarizes the data. In Table VII are listed the experimentally observed migratory aptitudes of the nine m- or p-substituted phenyl groups studied (phenyl = 1), and the modified values derived by use of equation(6). The intercept in equation(6) is probably due to some systematic error in the experimental data, possibly related to the by-products, which were not investigated in any of the reactions except that of 1,1-diphenylethylene itself(5).

Table VII

Migratory Aptitudes in the Schmidt Reaction of Olefins

<u>Group</u>	<u>Found</u>	<u>Modified</u>
p-Anisyl	6.12	7.20
3,4-Dimethylphenyl	5.41	5.95
p-Tolyl	5.00	4.47
p-Ethylphenyl	4.57	4.08
m-Tolyl	2.36	2.74
p-Biphenyllyl	2.30	1.88
p-Fluorophenyl	1.75	1.45
Phenyl	1.00	--
p-Chlorophenyl	0.62	0.85
p-Bromophenyl	0.54	0.84

If the rate-determining step in the Schmidt reaction of m- p-substituted benzoic acids were the migration of the aryl

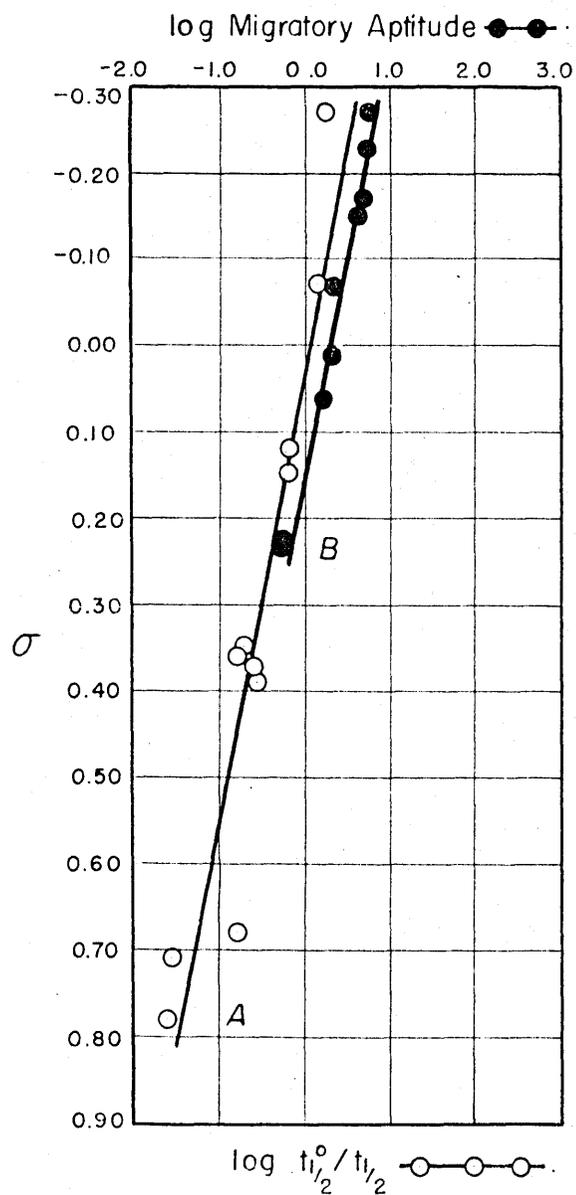
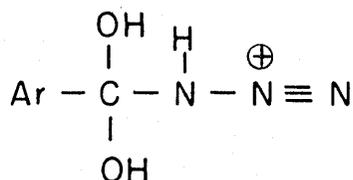


Fig. 1.--The Hammett equation applied to (A) the Schmidt reaction of *m*- and *p*-substituted benzoic acids and (B) the Schmidt reaction of *m*- and *p*-substituted unsymmetrical diarylethylenes.

group with simultaneous loss of nitrogen from the adduct, XXXIV, then a comparison of the rates of nitrogen evolution would afford a measure of the relative migratory aptitudes of the various aryl groups.



XXXIV

Briggs and Lyttleton have determined

the $t_{1/2}$ of nitrogen evolution for a number of m- and p-substituted benzoic acids in the Schmidt reaction, at 40°, in trichloroethylene solution, with sulfuric acid as the catalyst(14). A plot of $\log t_{1/2}^{\circ} / t_{1/2}$, where $t_{1/2}^{\circ}$ refers to benzoic acid itself and $t_{1/2}$ represents a substituted benzoic acid, versus sigma (Fig. 1A) indicates a good agreement with the Hammett equation.

Analysis of these data by the method of least squares shows rho to have a value of -1.97, almost identical with the slope in the 1,1-diarylethylene case (equation 6). This fact suggests that the slow step in the acid reactions is indeed the migration step and further that the relative rate of migration is not markedly affected by the other groups bonded to the carbon atom from which the aryl group migrates.

It is of obvious interest to attempt an extension of the above approach to the pinacol-pinacolone rearrangement of symmetrical pinacols. Examination of Fig. 2 reveals that the migratory aptitudes(21) in this reaction do not fit equation(5). Even in this case, however, the data crudely fit a plot of positive curvature(22). Perhaps the use of

this curve and available sigma values for m- and p-substituted phenyl groups not yet

investigated in the re-arrangement of symmetrical pinacols, would afford a fair prediction of the migratory aptitudes to be expected of these groups. In this connection, it is interesting that the migratory aptitude of the p-biphenyl group ($\sigma=0.009$),

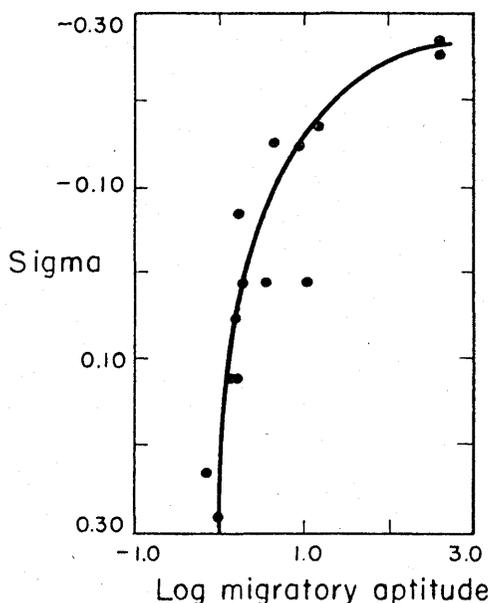


Fig. 2

11.5 according to Bachmann and Ferguson(21a), does not fit the curve at all well. The more recently determined values for the p-biphenyl group, 3.75 by the use of perchloric acid in effecting the rearrangement(21d) or 1.87 by the use of acetyl chloride, benzene, acetic acid mixture, (21d) fit the curve much better.

In view of the fact that the migratory aptitudes for the pinacol-pinacolone rearrangement of symmetrical pinacols have been determined by a variety of workers, using different experimental conditions for effecting the rearrangements, and using indirect methods of analysis of the products, it is not surprising that the results afford only a rough correlation with the sigma values of the migrating groups. Also, no differentiation has been made between rearrangements of

meso-pinacols as compared to racemic pinacols in most of the cases reported in the literature. Only Gaertner(21e) has reported the behavior of both stereoisomeric forms in the case of the two pinacols he subjected to the rearrangement. He found only a qualitative agreement on the migratory aptitudes of the aryl groups compared.

The main difference between the intrinsic migratory aptitudes found in the pinacol-pinacolone rearrangement of symmetrical pinacols and those found in the Schmidt reaction of olefins is the difference in the spread of the values. Perhaps the abnormally high heat of formation of molecular nitrogen, eliminated in the Schmidt reactions, as compared to water, eliminated in the pinacol rearrangements, influences this spread. Also, if the interpretation of Swain and Langsdorf(3) on the meaning of the various rho values found in the application of the Hammett equation to the correlation of the rates of displacement reactions of organic halides can be extended to the rearrangements under discussion, then the Schmidt reactions entail a more perfectly synchronous migration of the aryl group and elimination of nitrogen than the corresponding migration of the aryl group and loss of water in the pinacol rearrangements. The negative value of rho in both cases indicates that the atoms to which the aryl groups migrate, nitrogen in the Schmidt reactions and carbon in the pinacol rearrangements, are relatively more positive in the transition than in the ground states, with this effect

more pronounced in the pinacol rearrangements.

Although it would be interesting to compare the spread in the values of migratory aptitudes in carbon to oxygen migrations with the spread of values in carbon to carbon and carbon to nitrogen migrations, no quantitative data in this connection appear to be available at the present time.

Of course, nothing which has been said concerning the relative rates of migration of aryl groups in the Schmidt reaction of olefins (and possibly carboxylic acids also) can be applied to the Schmidt reaction of ketones and aldehydes. In one sense, however, the data on the olefin reactions make Smith's interpretation of the mechanism of the ketone reactions(8,9,10) seem all the more plausible. The olefin work provides a framework within which the apparent lack of influence of migratory aptitudes in determining product ratios in the ketone reactions can better be evaluated.

EXPERIMENTAL

Three methods are available for the synthesis of 1,1-diarylethylenes:

- (a) Reaction of ethyl acetate with two moles of a Grignard reagent (applicable only for the preparation of olefins having identical aryl groups).
- (b) Reaction of an acetophenone with arylmagnesium halide.
- (c) Reaction of a benzophenone with methylmagnesium iodide.

Method (c) gives the best yields (nearly quantitative), but method (b) is often more economical inasmuch as a number of different diarylethylenes can be prepared from the same acetophenone, whereas in method (c) a special synthetic route is required for each individual ethylene. The yields in method (a) are usually low, and this method is of little preparative value, except in the preparation of 1,1-diphenylethylene itself.

The following olefins were prepared by methods described in the literature:

- 1-phenyl-1-(p-bromophenyl)-ethylene (23)
- 1-phenyl-1-(p-ethylphenyl)-ethylene (24)
- 1-phenyl-1-(p-fluorophenyl)-ethylene (24)

For the preparation of the following olefins, which are

not reported in the literature, method (c) was employed. In each case the substituted benzophenone was obtained in high yield by the use of the Perrier modification(25) of the Friedel-Crafts reaction.

1-phenyl-1-(m-tolyl)-ethylene

1-phenyl-1-(3',4'dimethylphenyl)-ethylene

In all cases, the olefins were obtained in a high state of purity for the hydrazoic acid reactions.

The reactions of the olefins with hydrazoic acid were carried out according to the directions of McEwen, Gilliland and Sparr(5a). In all cases, the mole ratios of the reactants were the same. The temperature and sulfuric acid concentrations were maintained constant. The reaction mixtures were worked up in identical fashion. In every case but one (the reaction of 1-phenyl-1-(p-fluorophenyl)-ethylene) the ketone fractions were separated into their component parts by distillation in vacuo through an efficient column. Each of the m- or p-substituted acetophenones so obtained was characterized by at least one known solid derivative.

p-Ethylbenzoic Acid(26). In a fifteen liter, one-neck flask, fitted with a mechanical stirrer, was placed three liters of 10% sodium hydroxide solution saturated, at room temperature, with potassium permanganate. To this solution, freshly distilled p-ethylbenzaldehyde was gradually added with vigorous agitation. After a short time, a vigorous exothermic reaction took place. In all, 200 g. (1.49 mole) of p-ethylbenzaldehyde was added over a period of one hour, and agitation was continued for an additional hour.

The mixture was acidified with dilute sulfuric acid, and a saturated solution of sodium bisulfite was added to reduce all the manganese dioxide present. A clear white suspension of p-ethylbenzoic acid remained. The acid was filtered, washed with water several times and dried. Yield of crude product, m.p. 112-113^o C., was 160 g. (1.066 mole), 72% of theory.

p-Ethylbenzoyl Chloride. In a two-liter, three-neck flask, fitted with a mercury-sealed stirrer, condenser, and a dropping funnel, was placed 160 g. (1.066 mole) of p-ethylbenzoic acid dissolved in 100 cc. of benzene. Exactly 160 cc. of freshly distilled thionyl chloride was added at such a rate as to maintain a suitable reflux rate, the mixture being heated on the steam bath. The reaction mixture was agitated for a period of one and a half hours. Unreacted thionyl chloride and benzene were distilled under reduced pressure,

and the crude product was fractionated through a Vigreux Column. There was collected 165 g. (0.982 mole) of p-ethylbenzoyl chloride, 92% yield of theory.

1-Phenyl-(1-p-ethylphenyl)-ethylene(24). Exactly 120 g. (0.712 mole) of freshly distilled p-ethylbenzoyl chloride was placed in a three-liter Erlenmeyer flask and 120 g. (0.902 mole) of aluminum chloride was added in small portions with careful shaking and gentle heating over a "soft" free flame, such that fluidity of the mixture was maintained until the entire amount of aluminum chloride had been added. The solution was allowed to cool, whereupon the entire mass solidified. About 600 ml. of carbon disulfide was added to the reaction mixture with shaking until the entire amount of pink colored complex had dissolved. Then 166 ml. of benzene was gradually added, whereupon copious evolution of hydrogen chloride took place. The mixture was then warmed to about 80° C. on the steam bath for half an hour, then finally cooled. The solution was kept overnight at room temperature.

Carbon disulfide was removed under reduced pressure, and the dark-red viscous liquid residue was poured into ice-cold dilute hydrochloric acid solution. The acid solution was extracted several times with benzene. The benzene solution was washed with 5% sodium bicarbonate solution and with water, then distilled until the distillate was no longer turbid.

In a two-liter, three-neck flask fitted with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel, was placed the dry benzene solution of p-ethylbenzophenone. To this, 200 cc. of methylmagnesium bromide (4 molar solution in ether) was added dropwise fast enough to maintain a gentle reflux. The solution was agitated for one and a half hours after the addition of the Grignard reagent had been completed.

The mixture was hydrolyzed by a solution of 120 g. of ammonium chloride dissolved in 500 ml. of 10% sulfuric acid solution. The aqueous and ether layers were separated, and the aqueous layer was extracted with two 100 ml. portions of fresh benzene.

The benzene was removed by distillation. About 100 ml. of residue was left. It was mixed with 100 ml. of 20% sulfuric acid and refluxed for 6 hours. The organic layer was fractionated through an efficient column. There was obtained 90 g. (0.433 mole) (61%) of 1-phenyl-1-p-ethylphenylethylene, b.p. 118-120° C. / 0.2 mm., $n_D^{27.5} = 1.5864$.

Reaction of 1-(p-Ethylphenyl)-1-phenylethylene with

Hydrazoic Acid. This reaction was carried out with 55 g. (0.264 mole) of the olefin according to the direction of McEwen, Gilliland and Sparr(5a) with only a slight modification in working up the reaction mixture.

The reaction was carried out in a 500 ml., three-neck flask fitted with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel. To 29 g. (0.447 mole) of sodium azide in 89 ml. of chloroform, with external cooling, 66.5 ml. of

concentrated sulfuric acid was added dropwise. The ice-bath was replaced by a water-bath maintained at 25° C. To this, the olefin dissolved in 66.5 ml. of chloroform was added dropwise over a period of two and a half hours. A slight frothing accompanied the addition, and the initial yellow color changed to a clear green midway through the reaction. After another hour of vigorous agitation, the reaction mixture was allowed to stand overnight at room temperature.

Crushed ice was then added, and the mixture was made basic by the dropwise addition of a saturated solution of sodium carbonate, with external ice-cooling. The aqueous solution was first extracted with two 250 ml. portions of chloroform, and next with 400 ml. of benzene. The combined chloroform-benzene solution was extracted with three 300 ml. portions of 10% hydrochloric acid to remove the aniline and p-ethylaniline formed in the reaction. The aqueous acid layer was extracted with ether, and the ether added to the benzene-chloroform solution.

The combined chloroform-benzene and ether solution was dried over anhydrous sodium sulfate for 10 hours. After removing the solvents by distillation, the residue was fractionated at a low pressure.

<u>Fraction</u>	<u>B. P.</u>	<u>Ketone</u>	<u>Wt.</u>
1	60-62°/2.5 mm.	Acetophenone	14.2 g.
2	80-85°/2.5 mm.	4-Ethylaceto- phenone	2.0 g.
3	86-90°/2.5 mm.		2.4 g.
4	100-120°/1 mm.	Some liquid and approximately 6 g. of substance which solidified easily.	

Fractions 2, 3 and the liquid from 4 were refractionated in micro equipment. At a pressure of 1 mm., 3.8 g. of 4-ethylacetophenone was obtained (fraction 5).

<u>Fraction</u>	<u>Ketones</u>	<u>n_D^{25}</u>	<u>Derivative</u>	<u>% yield of ketone</u>
1	Acetophenone	1.5311	2,4-dinitrophenyl-hydrazone, m.p. 249° C.	44.6
5	4-Ethylacetophenone	--	semicarbazone, m.p. 195-196° C.	9.75

$$\text{Migratory aptitude of p-ethylphenyl group} = \frac{44.60}{9.75} = 4.57$$

m-Toluic Acid(26). This was prepared essentially the same way as for p-ethylbenzoic acid. Commerical m-tolu-aldehyde was added dropwise to a saturated solution of potassium permanganate in 10% sodium hydroxide solution. The mixture was agitated, at room temperature, for over an hour after the addition had been completed. The mixture was acidified with dilute hydrochloric acid, and saturated sodium bisulfite solution was added until all the manganese dioxide had been reduced. A clear white suspension of the solid acid remained. The acid was filtered, washed with water and dried under vacuum. From 200 g. (1.665 mole) of the aldehyde, 160 g. of the acid, m.p. 111° C., was obtained. Yield, 70.5%.

m-Toluyyl Chloride. In a two-liter, three-neck flask fitted with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel, was placed 32 ml. of freshly distilled thionyl chloride. To this, 32 g. (0.24 mole) of m-toluic acid dissolved in 100 ml. of benzene was gradually added in the course of half an hour. The flask was warmed on the steam-bath while the benzene solution was being added and also another half hour thereafter.

Benzene was distilled under reduced pressure, and the crude mixture was fractionated through a Vigreux Column. Exactly 37 g. (0.24 mole) of m-toluyyl chloride, b.p. 39-42° C. / 0.02 mm., was collected. Yield, 100%.

1-Phenyl-1(-m-toluyyl)-Ethylene. To 37 g. (0.34 mole) of freshly distilled m-toluyyl chloride in a three-liter Erlenmeyer flask was added 37 g. (a slight excess) of aluminum chloride. During the addition period, the flask was warmed over a free "soft" flame with shaking to keep the adduct fluid. After the complete addition, the mixture was allowed to cool to room temperature, whereupon the entire dark pink mass solidified.

About 210 ml. of carbon disulfide was added, and the mixture was warmed on the steam bath until all the solid had dissolved. Exactly 42 ml. of benzene was gradually added to the cold reaction mixture, which was continuously agitated. Copious evolution of hydrogen chloride was observed. The reaction mixture was next refluxed on the steam bath for half an hour.

The reaction mixture was cooled and kept overnight at room temperature. Carbon disulfide was removed under reduced pressure, and the viscous residual liquid was poured into 500 g. of crushed ice containing an excess of concentrated hydrochloric acid. The acid solution so obtained was extracted several times with fresh benzene. The benzene layer was washed with 5% sodium bicarbonate solution, next with water, and finally distilled until the distillate was clear. The residue containing m-tolyl phenyl ketone was employed as such for the Grignard reaction.

In a two-liter, three-neck flask, fitted with a mercury-sealed stirrer, a reflux condenser and a dropping funnel, was placed the dry benzene solution of phenyl m-tolyl ketone. Exactly 200 ml. of methylmagnesium bromide (4 molar solution in diethyl ether) was added dropwise fast enough to maintain a gentle reflux. The solution was agitated for half an hour after the addition of the Grignard reagent.

Hydrolysis was brought about with a solution of 120 g. of ammonium chloride dissolved in 500 ml. of 10% sulfuric acid solution. The aqueous and ether layers were separated, and the aqueous layer was extracted with two 100 ml. portions of fresh benzene.

Ether and benzene were removed by distillation until about 200 ml. of residue of the carbinol in benzene was left. It was mixed with an equal volume of 20% sulfuric acid and refluxed on the steam bath for one hour. Following the separation of the two layers, the crude olefin was

fractionated through an efficient column. Exactly 19 g. (0.094 mole) of 1-phenyl-m-tolyethylene, b.p. 134-38/5.6 mm., was collected. Yield, 61%. The olefin was again fractionated to prepare an analytical sample, and a fraction of b.p. 122-23° C / 0.85 mm. was sent for analysis(27).

<u>Anal.</u> Calcd. for C ₁₅ H ₁₄ :	C, 92.74	H, 7.26
Found:	C, 92.43	H, 7.43
	92.71	7.31

The preparation was repeated using 81 g. (0.52 mole) of m-toluyyl chloride, 70 g. of aluminum chloride, 42 ml. of benzene and 400 ml. of carbon disulfide. This time 61 g. (0.315 mole) of olefin was obtained, a yield of 60%.

Reaction of 1-(m-Tolyl)-1-phenylethylene with Hydrazoic Acid. The reaction was carried out in a 500 ml. three-neck flask, fitted with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel. To 42.5 g. (0.65 mole) of sodium azide in 130 ml. of chloroform, with external ice cooling, 97 ml. of concentrated sulfuric acid was added dropwise. The ice-bath was replaced by a water bath maintained at 25° C. To this solution, 76 g. (0.39 mole) of the olefin dissolved in 97 ml. of chloroform was added over a period of two and half hours. The mixture was straw-yellow in color. Agitation was continued for one additional hour after all the olefin had been added.

After having stood overnight, the mixture was poured into crushed ice and made basic by dropwise addition of a saturated sodium carbonate solution, with external ice-cooling. The chloroform layer was removed. The basic aqueous mixture was extracted with three 200 ml. portions of benzene. The combined benzene-chloroform extracts were washed with two 400 ml. portions of 10% hydrochloric acid to remove the aniline and m-toluidine formed in the reaction. The aqueous acid layer was extracted with ether. The combined, chloroform-benzene-ether solution was dried over anhydrous sodium sulfate for 10 hours. The solvents were distilled under reduced pressure. The residue was fractionated under low pressure.

<u>Fraction</u>	<u>B.P.</u>	<u>Ketone</u>	<u>Wt.</u>	<u>% yield</u>
1	79-84/8 mm.	Acetophenone	16 g.	34.2
2	94-97/7 mm.	m-Methylacetophenone	7.6 g.	14.5
3	125-27/7 mm.	fractionation was stopped.		

Acetophenone was identified by its 2,4-dinitrophenylhydrazone, m.p. 249° C., underpressed on admixture with an authentic sample. The semicarbazone gave a m.p. of 195-196°. m-Methylacetophenone was likewise identified by its ketoxime derivative, m.p. 57° C. and its semicarbazone, m.p. 200° C.

$$\text{Migratory aptitude of m-tolyl group} = \frac{34.2}{14.5} = 2.36$$

1-Phenyl-1-(3',4'-dimethylphenyl)-ethylene. Exactly 140 g. (1.0 mole) of freshly distilled benzoyl chloride was placed in a three-liter Erlenmeyer flask and 156 g. (1.165 mole) of anhydrous aluminum chloride was added in small portions with careful shaking and with gentle heating over a "soft" flame, such that the mixture was maintained fluid. It was then allowed to cool, whereupon the entire mass solidified. About 800 ml. of carbon disulfide was added to the reaction mixture and shaken until the entire amount of pink colored complex had dissolved. Then 106 g. (1.0 mole) of o-xylene was gradually added, whereupon copious evolution of hydrogen chloride took place. The reaction proceeded at room temperature and was completed by refluxing on the steam bath for thirty minutes. The reaction mixture was kept overnight at room temperature. The carbon disulfide was distilled, the last part in vacuo. The residue was added to ice and hydrochloric acid solution, then extracted with benzene. The benzene solution was washed with sodium bicarbonate solution, and the benzene was distilled until the distillate was no longer turbid.

In a two-liter, three-neck flask, fitted with a mercury-sealed stirrer, a reflux condenser and a dropping funnel was placed the dry benzene solution of 3,4-dimethylphenyl phenyl ketone. Exactly 400 ml. of a 4 molar solution of methylmagnesium bromide in diethylether was added dropwise at a rate rapid enough to maintain a gentle reflux. The solution

was agitated for an additional half hour after the Grignard reagent had been added. The hydrolysis was brought about by the addition of 120 g. of ammonium chloride dissolved in 500 ml. of 10% sulfuric acid solution. The aqueous and ether layers were separated, and the aqueous layer was extracted with two 100 ml. portions of fresh benzene. Ether and benzene were removed under reduced pressure. The residue was refluxed with an equal volume of 20% sulfuric acid for one hour. Following separation of two layers, the crude olefin was fractionated through an efficient column. Exactly 141.9 g. of 1-phenyl-1-(3',4'-dimethylphenyl)-ethylene, b.p. 203-206° / 15 mm., was collected. Yield, 70%.

Anal. Calcd. for C₁₆H₁₈: C, 92.25 H, 7.76

Found: C, 91.80 H, 7.92

Reaction of 1-Phenyl-1-(3',4'-dimethylphenyl)-ethylene with Hydrazoic Acid. The reaction was carried out in a 500 ml. three-neck flask, fitted with a mercury-sealed stirrer, a reflux condenser and a dropping funnel. To 43.5 g. (0.67 mole) of sodium azide in 134 ml. of chloroform, with external ice cooling, 100 ml. of concentrated sulfuric acid was added dropwise. The ice-bath was replaced by a water bath maintained at 25° C. Then 83.5 g. (0.402 mole) of olefin dissolved in 100 ml. of chloroform was added over a period of three hours. The mixture was agitated for one additional hour. After having stood overnight, the mixture was poured into crushed ice and made basic by addition of

saturated sodium carbonate solution, with external ice-cooling. The chloroform layer was removed, and the basic aqueous mixture extracted with three 200 ml. portions of benzene. The combined benzene-chloroform extracts were washed with two 400 ml. portions of 10% hydrochloric acid to remove the aniline and 3,4-dimethylaniline formed in the reaction. The aqueous acid layer was extracted with ether. The organic layers were combined and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure. The residue was fractionated under low pressure.

<u>Fraction</u>	<u>B.P.</u>	<u>Ketone</u>	<u>Wt.</u>	<u>% yield</u>
1	60-65°/2.5 mm.	Acetophenone	17.6 g.	36.6
2	138-140°/8 mm.	3,4-dimethyl-acetophenone	4.02 g.	6.76
3	150-160°/8 mm.	Higher boiling fractions		

The 3,4-dimethylacetophenone obtained in fraction (2) was identified by conversion to the semicarbazone, m.p. 233-234° (28).

$$\begin{array}{l} \text{Migratory aptitude of the } \\ \text{3,4-dimethylphenyl group} \end{array} = \frac{36.6}{6.76} = 5.41$$

1-Phenyl-1-(p-fluorophenyl)-ethylene(24). Exactly 140 g. (1.0 mole) of freshly distilled benzoyl chloride was placed in a three-liter Erlenmeyer flask and 156 g. (1.165 mole) of anhydrous aluminum chloride was added, with gentle warming. After cooling, 800 ml. of carbon disulfide was added, and

the mixture was warmed on the steam bath to dissolve the complex. To the cold reaction mixture, 96 g. (1.0 mole) of fluorobenzene was added. The reaction mixture was refluxed on the steam bath for thirty minutes. It was then cooled and kept overnight at room temperature. The carbon disulfide was removed under reduced pressure, and the residue was poured onto crushed ice containing an excess of hydrochloric acid. The mixture was extracted several times with benzene. The benzene extract was washed with 5% sodium bicarbonate solution, then water, and finally distilled until the distillate was clear. The benzene solution containing the p-fluorobenzophenone was employed for the Grignard reaction.

In a two-liter, three-neck flask, fitted with a mercury-sealed stirrer a reflux condenser and a dropping funnel was placed the benzene solution of p-fluorobenzophenone. Exactly 400 ml. of a 4 molar solution of methylmagnesium bromide in diethylether was added dropwise. The mixture was agitated for 30 minutes after the Grignard reagent had been added. Hydrolysis was effected by adding 120 g. of ammonium chloride in 500 ml. of 10% sulfuric acid solution. The aqueous layer was extracted with fresh benzene. The combined organic solution was distilled under reduced pressure to remove the solvent. The residue was refluxed with an equal volume of 20% sulfuric acid for one hour. Following the separation of the two layers, the crude olefin was dried and fractionated through an efficient column. Exactly 125 g. of 1-phenyl-1-

(p-fluorophenyl)-ethylene, b.p. 105-110 / 0.3 mm., was collected. Overall yield, 63%.

Reaction of 1-Phenyl-1-(p-fluorophenyl)-ethylene with Hydrazoic acid. The reaction was carried out in a 500 ml. three-neck flask, fitted with a mercury-sealed stirrer, a reflux condenser and a dropping funnel. To 33.5 g. (0.516 mole) of sodium azide in 106 ml. of chloroform, with external cooling, 80 ml. of concentrated sulfuric acid was added dropwise. The ice bath was replaced by a water-bath maintained at 25° C. Exactly 61.6 g. (0.31 mole) of 1-phenyl-1-p-fluorophenylethylene dissolved in 80 ml. of chloroform was added over a period of three hours.

The mixture was agitated for one additional hour. After having stood overnight, it was poured onto crushed ice and made basic by addition of saturated sodium carbonate solution, with external cooling. The chloroform layer was removed, and the basic aqueous mixture was extracted with three 300 ml. portions of benzene. The combined benzene-chloroform extracts were washed with two 400 ml. portions of 10% hydrochloric acid to remove the aniline and p-fluoroaniline formed in the reaction. The aqueous acid layer was extracted with ether. The combined organic solutions were dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure. As it was not possible to obtain a quantitative separation of acetophenone and p-fluoroacetophenone by fractional distillation, the entire ketone fraction, 27.9 g.,

b.p. 67-70° C. / 5 mm., was collected as one fraction.

Anal. Found: C, 76.23, 76.19 H, 6.59, 6.54 F, 6.19 (29)

On the basis of the carbon analysis it can be calculated that the mixture consisted of 36.3% of p-fluoroacetophenone and 63.7% of acetophenone. The fluorine analysis indicates 45% of p-fluoroacetophenone and 55% of acetophenone. The yields calculated on the basis of the carbon analysis are probably more accurate than those based on the fluorine analysis. Therefore the values calculated on the basis of the carbon analysis have been employed for the determination of product ratios.

Migratory aptitude of the p-fluorophenyl group = $\frac{63.7}{36.3} = 1.75$

1-Phenyl-1-(p-bromophenyl)-ethylene (23). Exactly 140 g. (1.0 mole) of freshly distilled benzoyl chloride was placed in a three-liter Erlenmeyer flask and 156 g. (1.165 mole) of anhydrous aluminum chloride was added, with gentle warming. On cooling, 800 ml. of carbon disulfide was added, and the mixture was warmed on the steam bath. To the cool reaction mixture, 157 g. (1.0 mole) of bromobenzene was added, and the mixture was refluxed on the steam bath for thirty minutes. It was then kept overnight at room temperature. Carbon disulfide was removed under reduced pressure, the residue poured onto ice-cooled hydrochloric acid solution and extracted several times with benzene. The benzene extract was washed with 5% sodium bicarbonate solution, next with water, and finally distilled until the distillate was clear. The residual benzene solution of p-bromobenzophenone was employed

for the Grignard reaction.

In a two-liter, three-neck flask, fitted with a mercury-sealed stirrer, a reflux condenser and a dropping funnel was placed the benzene solution of p-bromobenzophenone. Exactly 400 ml. of a 4 molar solution of methylmagnesium bromide in diethyl ether was added dropwise. The mixture was agitated for 30 minutes after the Grignard reagent had been added. Hydrolysis was effected by adding 120 g. of ammonium chloride in 500 ml. of 10% sulfuric acid. The layers were separated, and the aqueous layer was extracted with fresh benzene. The combined organic layers were distilled under reduced pressure to remove the solvent. The residue was next refluxed with an equal volume of 20% sulfuric acid for one hour. After separation of the aqueous and organic layers, the crude olefin was dried and fractionated through an efficient column. Exactly 155 g. of 1-phenyl-1-(p-bromophenyl)-ethylene, b.p. 199-201° C. / 19 mm., was collected. Overall yield, 60%.

Reaction of 1-Phenyl-1-(p-bromophenyl)-ethylene with Hydrazoic acid. The reaction was carried out in a 500 ml. three-neck flask, fitted with a mercury-sealed stirrer, a reflux condenser and a dropping funnel. To 33.5 g. (0.516 mole) of sodium azide in 106 ml. of chloroform, with external ice cooling, 80 ml. of concentrated sulfuric acid was added dropwise. The ice-bath was replaced by water bath maintained at 25° C. Exactly 80.3 g. (0.31 mole) of 1-phenyl-1-p-bromophenylethylene dissolved in 80 ml. of chloroform was added

over a period of three hours. The mixture was agitated for one additional hour. After having stood overnight at room temperature, it was poured onto crushed ice and made basic by addition of sodium carbonate solution, with external ice-cooling. The chloroform layer was removed, and the aqueous layer extracted with three 300 ml. portions of benzene. The combined benzene-chloroform extracts were washed with two 400 ml. portions of 10% hydrochloric acid solution to remove the aniline and p-bromoaniline formed in the reaction. The aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous sodium sulfate. The solvents were distilled under reduced pressure. On fractionating the residue, the following components were obtained.

<u>Fraction</u>	<u>B.P.</u>	<u>Ketone</u>	<u>Wt.</u>	<u>% yield</u>
1	60-62° C/2.5 mm.	Acetophenone	5.95 g.	16.0
2	102-103/2.5 mm.	p-bromo-acetophenone	18.3 g.	29.6
3	120-higher/1 mm.	Higher boiling fractions.		

The 2,4-Dinitrophenylhydrazone of fraction (2) showed a m.p. 235-37° C. The p-bromoacetophenone, itself a solid, melted at 49-50° C.

$$\text{Migratory aptitude of p-bromophenyl group} = \frac{16.0}{29.6} = 0.54$$

SUMMARY

1. Five unsymmetrical diarylethylenes have been prepared. Two of them are new to the literature.
2. The above olefins have been reacted with hydrazoic and sulfuric acids, and the resulting ketone fractions have been separated into their pure components by distillation.
3. A table of migratory aptitudes of the aryl groups in the Schmidt reaction of unsymmetrical diarylethylenes has been calculated on the basis of the acetophenone: substituted-acetophenone product ratios:
4. The results have been correlated by a suitable adaptation of the Hammett equation:

$$\log \text{ intrinsic migratory aptitude} = \rho \sigma$$

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PART II

THE SYNTHESIS OF POSSIBLE EMETINE INTERMEDIATES

INTRODUCTION

Five closely related alkaloids have been isolated from ipecac root (*Cephaelis Ipecacuanha*). Of these, emetine (I) has attracted the most attention because of its medicinal properties.

The main use of emetine in chemotherapy is in the treatment of amebiasis. Because of its toxicity, the alkaloid has been supplanted by other drugs to some degree. Emetine is still useful, however, in relieving the symptoms of acute dysentery and in the treatment of amebic hepatitis. Emetine is also effective in combatting other parasites, such as flatworms of the class of Trematodes(1), and it is frequently used as an expectorant and emetic.

Emetine was first isolated by Pelletier and Magendie(2) in 1817, but Paul and Cownley(3) obtained the first analytically pure sample of the alkaloid. Paul and Cownley also isolated the related alkaloids, cepheline and psychotrine, from ipecac root. Pyman(4) later isolated the remaining related alkaloids, emetamine and O-methylpsychotrine.

Because of the widespread occurrence of dysentery among the Allied and German armed forces during World War I, a considerable amount of research on the elucidation of the emetine

structure was begun at that time. A partial proof of structure was achieved by Pyman(4,5), Carr and Pyman(6), Windaus and Hermans(7) and Karrer(8). Another series of papers appeared in 1927, when Spath and Leithe(9), Brindley and Pyman(10) and Staub(11) proposed three different structures for emetine. None of these turned out to be correct.

During the past five years another fruitful series of researches have been carried out. The structure (I) has been established beyond question, the main credit belonging to Pailer(12,13,14,15). It is also of interest that Robinson(16) in 1948, using a scheme of biogenesis originally devised by Woodward(17), predicted the correct emetine structure.

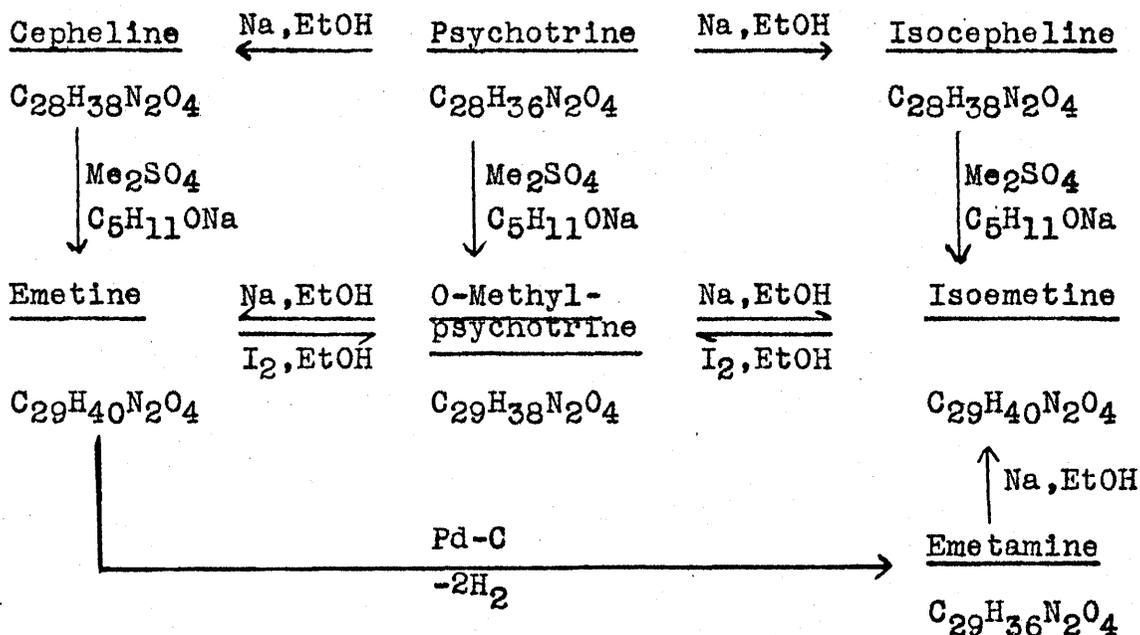
At the present time several groups of organic chemists are working on the synthesis of emetine. Battersby and Openshaw(18) and a group of Russian chemists(19) have claimed the synthesis of a dehydrogenation product of emetine, the rubremetinium cation, but experimental details are lacking.

This thesis contains a description of the synthesis of several β -substituted glutaric acid derivatives, which might prove to be satisfactory intermediates for the synthesis of emetine and related compounds.

BACKGROUND AND HISTORICAL REVIEW

A. Structure of the Ipecac Alkaloids.

The systematic characterization of emetine and its salts as well as the development of methods for the interconversion of the five related alkaloids of ipecac were due, for the most part, to the work of Pyman and coworkers (4,5,6). The following diagram summarizes the molecular formulas and the chemical interrelationships of the ipecac alkaloids and a few associated compounds:



A review article on emetine has recently appeared(20), and the following few paragraphs are a summary of that

portion of the article relating to the elucidation of the structure of emetine (I).

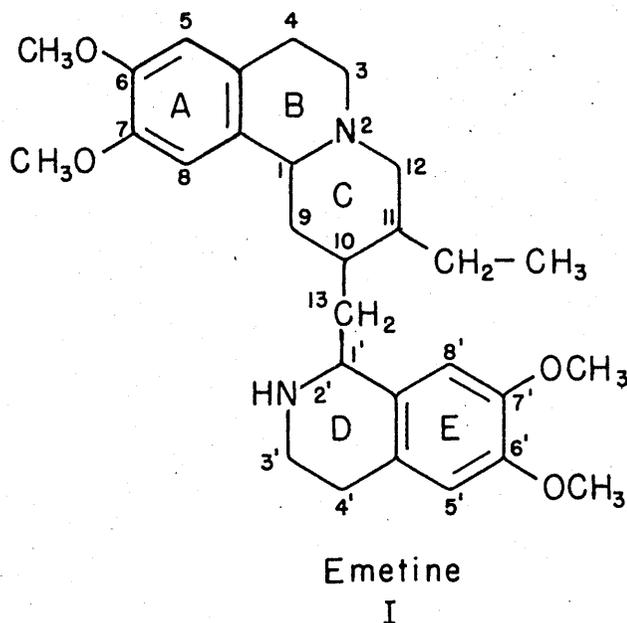
The assigned structure (I) of emetine is based on the following facts:

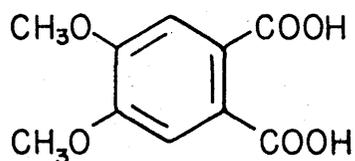
(a) All four oxygen atoms occur in methoxyl groups(21).

(b) By benzoylation of emetine, a monobenzoylemetine is obtained which still possesses a basic amino group(6). Thus, of the two nitrogen atoms, one is secondary and the other tertiary.

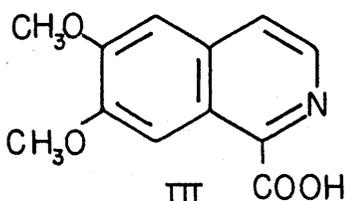
(c) Action of methyl iodide on emetine gives methyl-emetine diiodomethylate. By a Hofmann degradation this gives an amorphous methine base which still contains both nitrogen atoms. Only when this methine base is subjected to a second Hofmann degradation is one of the nitrogen atoms split off as trimethylamine(8). Therefore one nitrogen atom is a common member of two rings, while the other is a part of only one ring.

(d) Oxidation of emetine with potassium permanganate gives m-hemipinic acid (II)(7), 6,7-dimethoxyisoquinoline-1-carboxylic acid (III)(6,10), and corydaldine (IV)(9). Permanganate oxidation of the ethyl ether of cepheline affords m-hemipinic acid and 4-methoxy-5-ethoxyphthalic anhydride(V)(9).

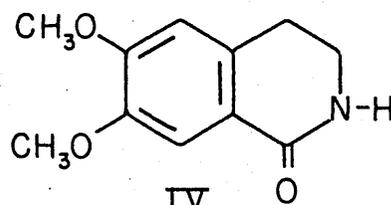




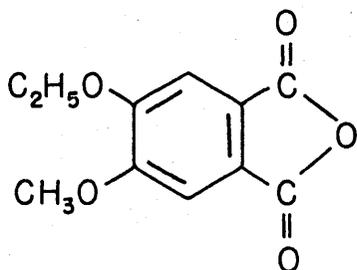
II



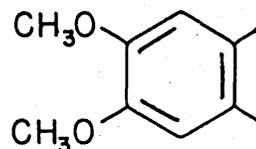
III



IV



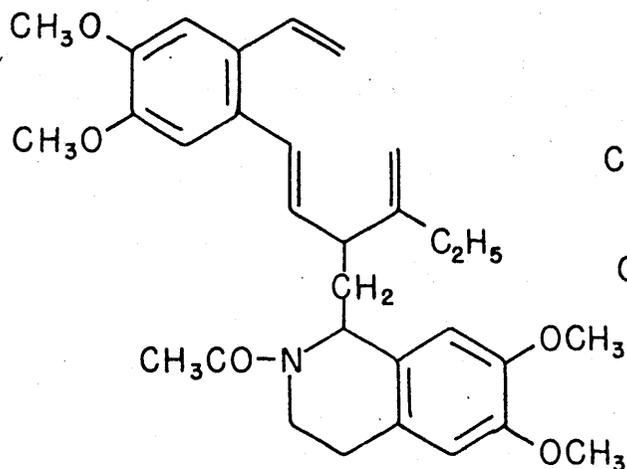
V



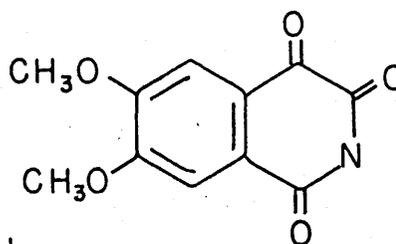
VI

Therefore emetine contains at least one tetrahydro-6,7-dimethoxyisoquinoline ring, and the group VI occurs twice in the molecule.

(e) A three-fold Hofmann degradation of N-acetylemetine gives the neutral product VII (structure not definitely known). Permanganate oxidation of VII gives 4,5-dimethoxyphthalonimide (VIII)(22), the same product obtained by chromic



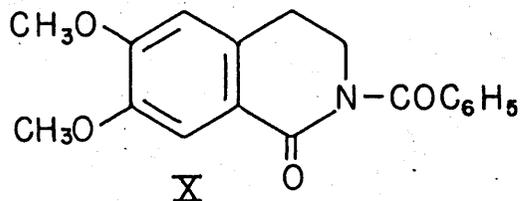
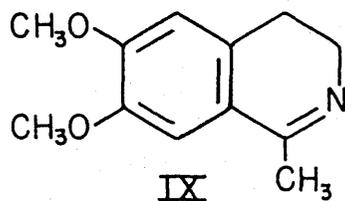
VII



VIII

acid oxidation of emetine(23). The same product (VIII) is also obtained by chromic acid oxidation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Therefore, the secondary nitrogen atom of emetine is known to be part of a 6,7-dimethoxy-tetrahydroisoquinoline ring.

(f) A zinc dust distillation of the neutral product VII affords 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IX)(22). Ozonization or perphthalic acid oxidation of N-benzoyl-O-methylpsychotrine affords N-benzoylcorydaldine (X)(24,25). Reduction of O-methylpsychotrine (differs from I in having a double bond at $C_1'-N_2'$ or $C_{13}-C_1'$) by means of sodium and ethanol affords emetine and isoemetine

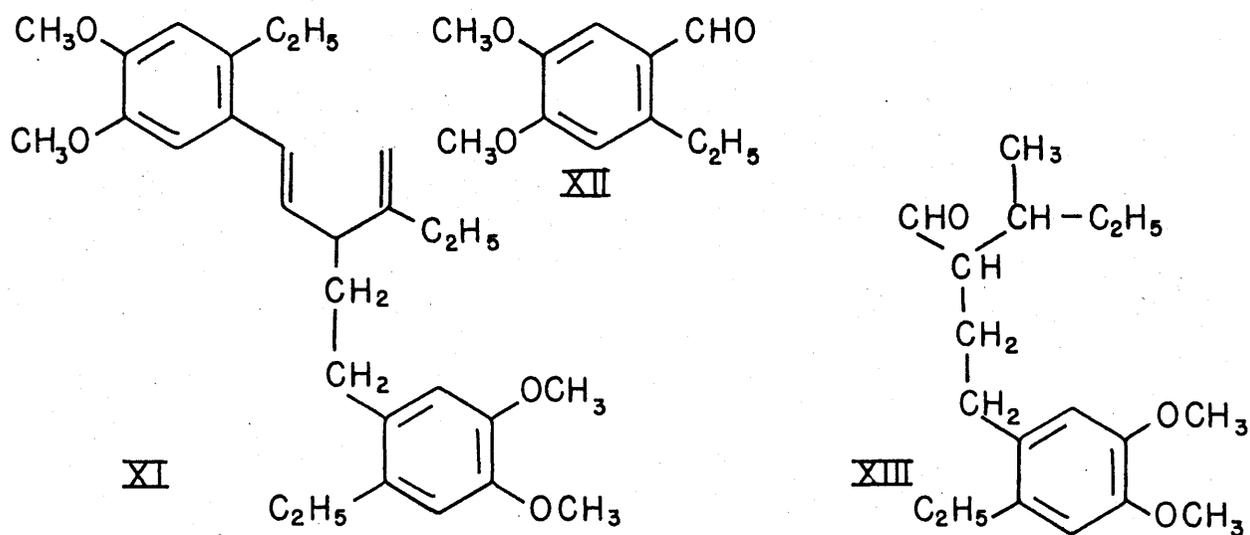


(differs from emetine in the configuration of C_1')(4).

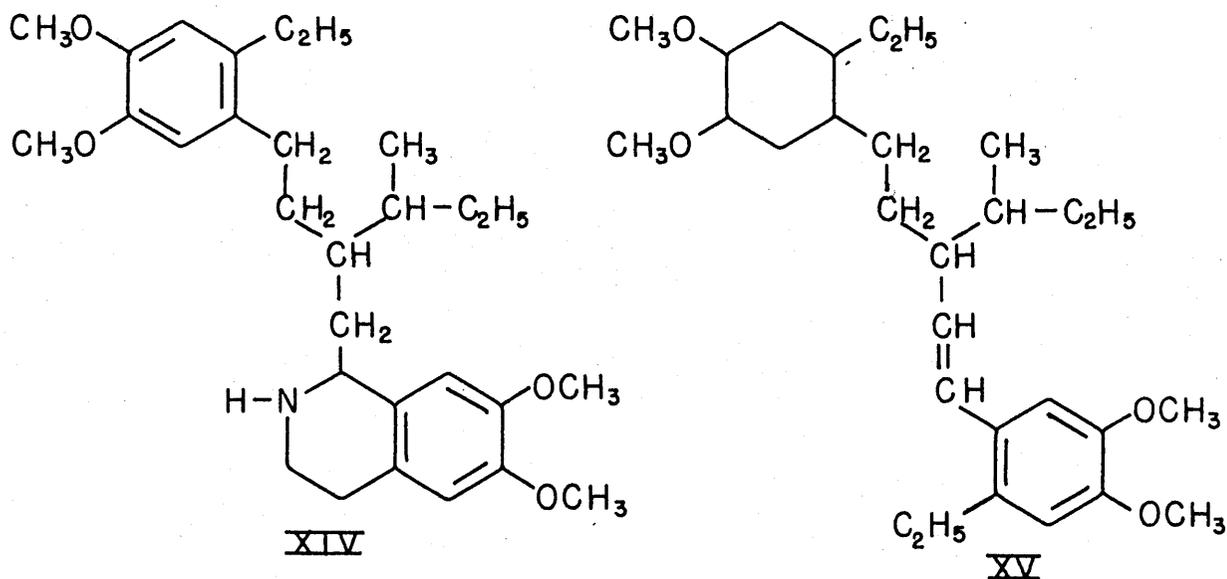
Oxidation of emetine with alcoholic iodine affords O-methylpsychotrine(4). All this furnishes argument for a methylene group at C_{13} in emetine and for a double bond at $C_1'-N_2'$ in O-methylpsychotrine.

(g) Catalytic dehydrogenation of emetine gives emet-amine. The loss of exactly two moles of hydrogen furnishes an argument for the tetrahydro ring (D) in emetine(22).

(h) A three-fold Hofmann degradation of emetine, with catalytic hydrogenation of the resulting olefin after each of the first two steps, gives the olefin XI. Ozonolysis of XI affords 2-ethyl-4,5-dimethoxybenzaldehyde (XII) together

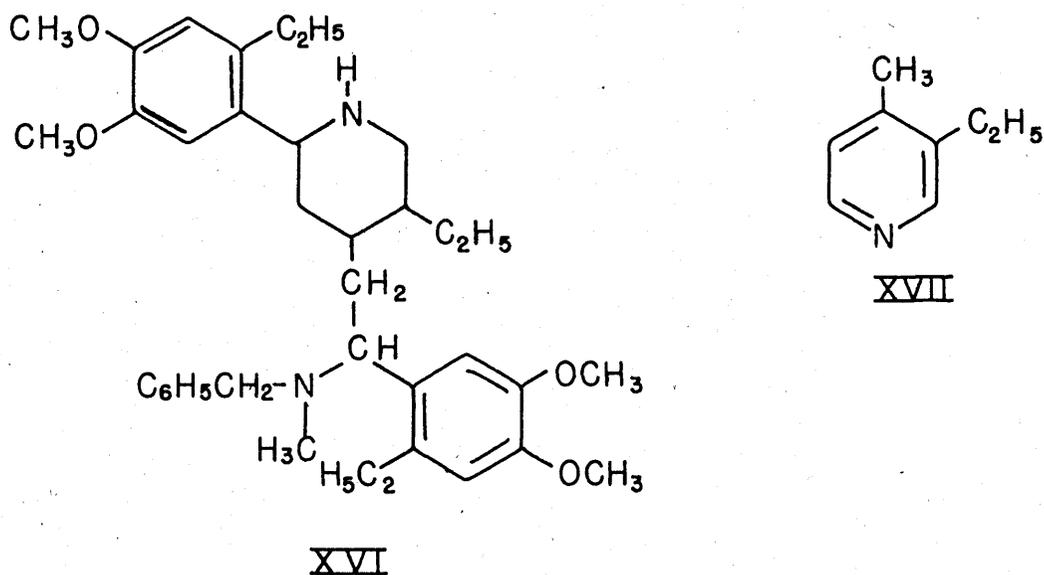


with an unsaturated aldehyde, catalytic hydrogenation of which affords the aldehyde XIII (12). The structure of the aldehyde XIII was proved by an independent synthesis from known compounds (13).



A three-fold Hofmann degradation of N-acetylemetine, followed by catalytic hydrogenation after each step, gives the compound XIV. A two-fold Hofmann degradation of XIV, with catalytic hydrogenation after the first step, affords the olefin XV. Ozonolysis of XV gives XII plus XIII, the same products obtained above(14).

Reaction of N-methylemetine with benzyl iodide affords a diiodobenzylate. This, on being heated with silver oxide



and then catalytically hydrogenated, gives XVI. A palladium dehydrogenation of XVI yields β -collidine (XVII)(15).

All of the material proves beyond doubt the structure of the central part of the emetine molecule (rings B, C, and D and the positions of the attached groups) and completes the proof of structure of emetine. Battersby and Opehshaw(26) have provided an independent proof of structure of the central portion of the emetine molecule, but since their work only

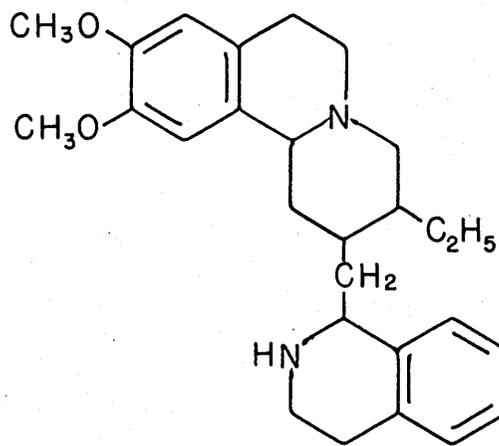
serves to confirm the structure I, details are not included here.

The elucidation of the structures of the other members of the Ipecac family follows from the structure of emetine and the known interconversions of these related alkaloids.

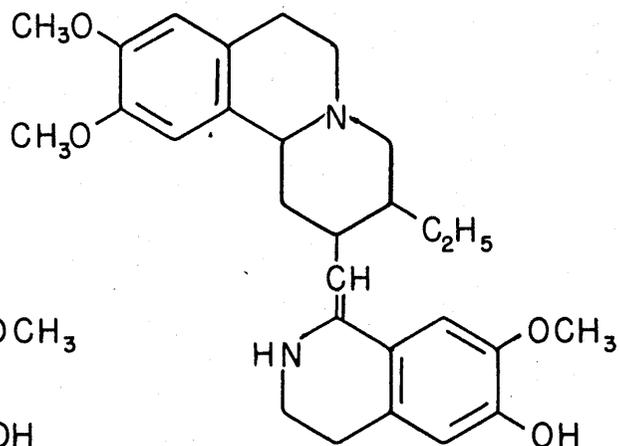
Cepheline (XVIII) differs from emetine in having a free phenolic hydroxyl group at C₆'. This was shown by Pailer and Porschinski(15), who subjected O-ethylcepheline to a two-fold Hofmann degradation, followed by cleavage of the olefin, to obtain an aldehyde whose semicarbazone was identified as that of 2-ethyl-4-ethoxy-5-methoxybenzaldehyde. This also confirms the position of the hydroxyl group in Psychotrine (XIX).

To demonstrate the presence of a carbon-carbon double bond at C₁₅-C₁' in N-benzoyl-O-methylpsychotrine, Karrer, Eugster and Ruttner(24) oxidized the compound with perphthalic acid and isolated N-benzoylcorydaldine (X). A synthesis of N-benzoylcorydaldine has been reported by Moyer and McEwen(25). This evidence coupled with the fact that hydrogenation of O-methylpsychotrine (XX) affords the diastereoisomers, emetine and isoemetine(4,5) confirms the structure of psychotrine (XIX) and establishes that of O-methylpsychotrine (XX).

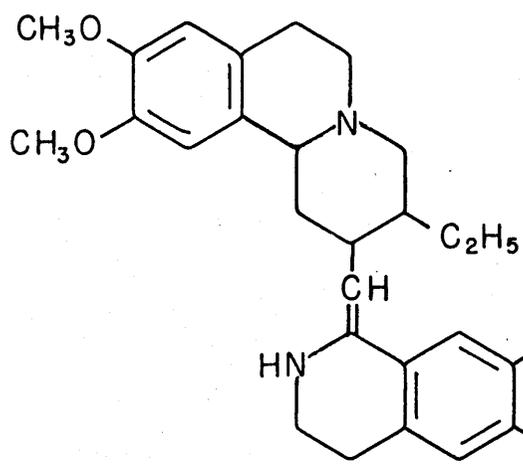
Regarding emetamine (XXI), the tertiary nature of both nitrogens(4) and the fact that emetine can be dehydrogenated to emetamine, which on reduction with sodium and alcohol gives isoemetine, establishes the fact that ring D is aromatic.

XVIII

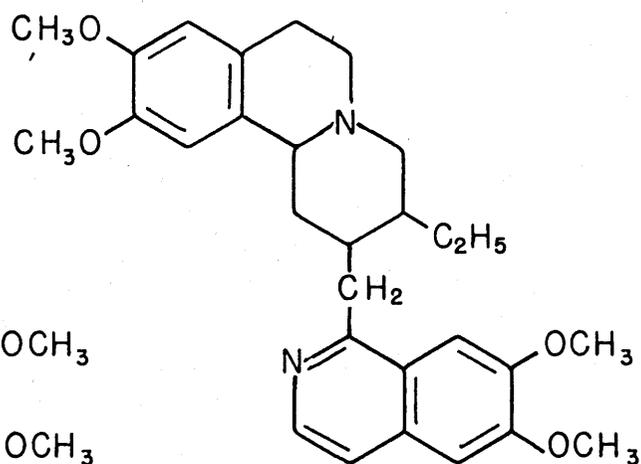
Cepheline

XIX

Psychotrine

XX

O - Methylpsychotrine

XXI

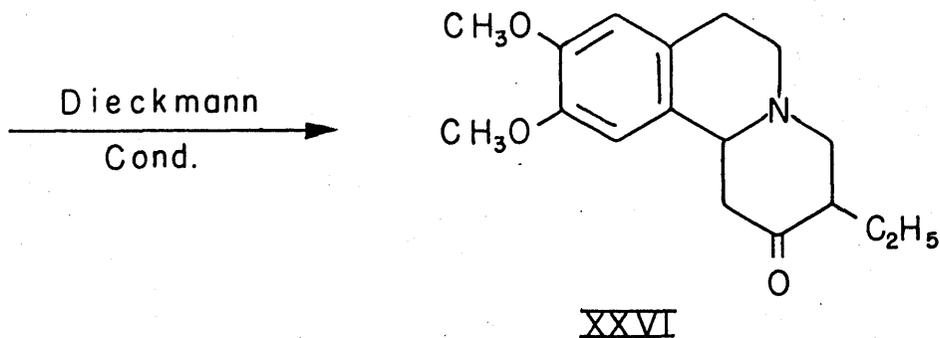
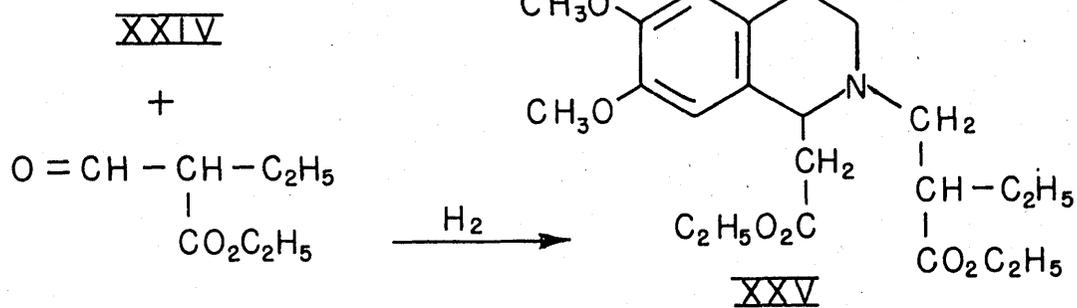
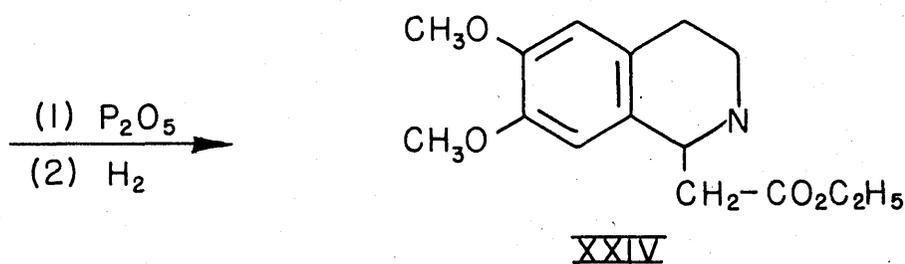
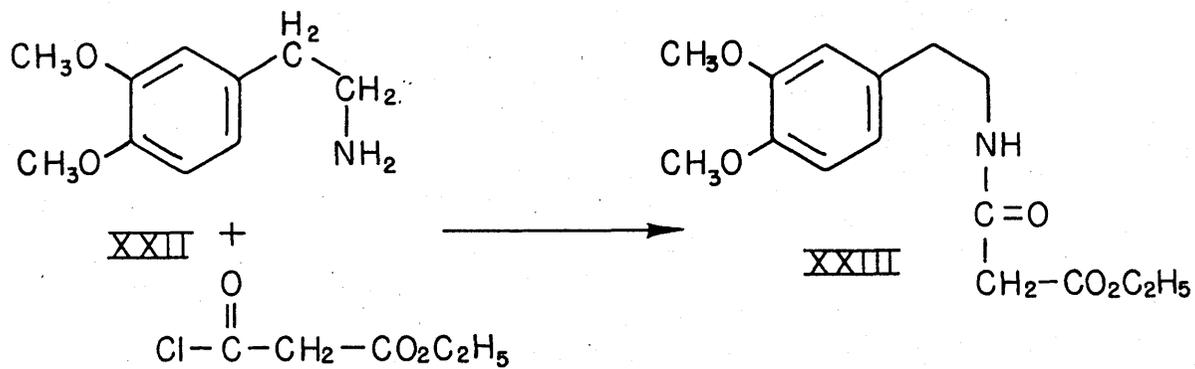
Emetamine

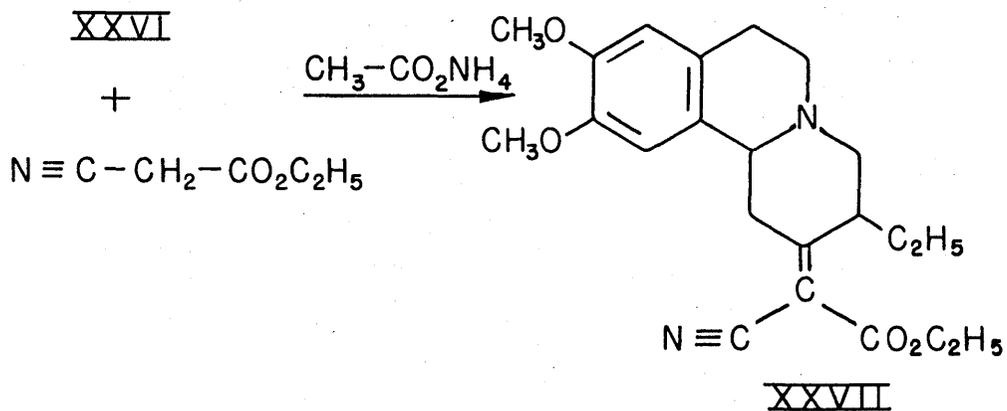
B. Contributions to the Total Synthesis of Emetine.

Two attempts at a total synthesis of emetine have recently appeared in the literature(18,19). Also the total synthesis of a racemic C-noremetine has been reported by Pailer and Strohmayr(27). All three of these reports are of a preliminary nature, and no experimental details are available as yet. The following paragraphs summarize the articles.

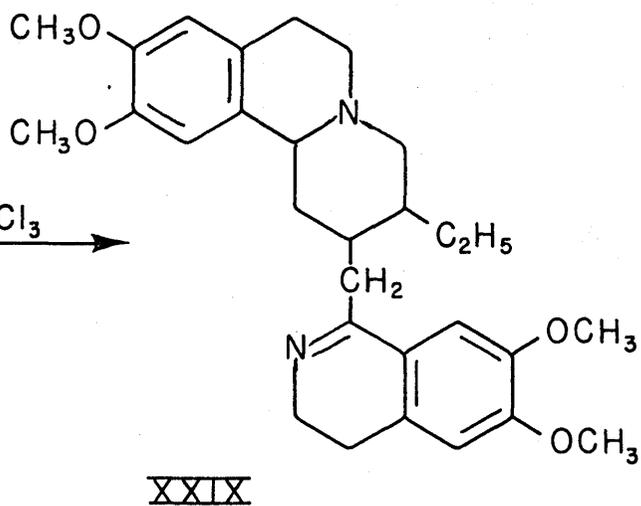
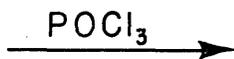
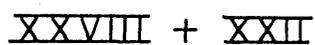
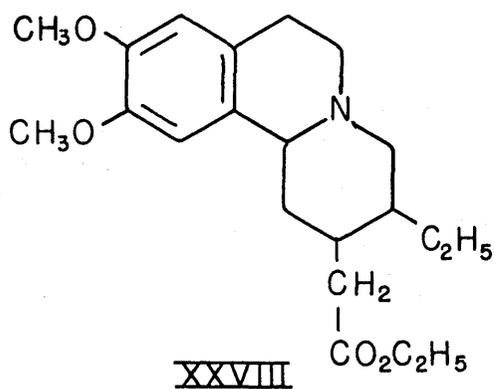
Battersby and Openshaw(18) in 1950 reported the synthesis of a racemic compound (XXIX) differing from the emetine structure (apart from stereochemical considerations) only in having a double bond at C₁'-N₂'. The compound (XXIX) was oxidized by mercuric acetate to d,l-rubremetinium bromide, the ultra-violet and visible absorption spectrum of which was identical with that of the active rubremetinium bromide obtained on oxidation of emetine itself.

The synthesis of XXIX was accomplished as follows: Carbethoxyacetyl chloride was reacted with homoveratrylamine (XXII) to give the amide, XXIII, m.p. 63-64° C. The Bischler-Napieralski ring closure of XXIII with phosphorus pentoxide gave ethyl 6,7-dimethoxy-3,4-dihydroisoquinoline-1-acetate, m.p. 85.5-86.5° C., catalytic hydrogenation of which afforded the tetrahydroisoquinoline, XXIV, m.p. 77-78° C. Treatment of XXIV with ethyl α -formylbutyrate and hydrogenation of the crude condensation product afforded the diethyl ester XXV, m.p. 76-77° C. Dieckmann cyclization, followed by hydrolysis yielded the ketone, XXVI, m.p. 109-109.5° C. Reaction of XXVI





- (1) Acid Hydrol.
 (2) Decarbox.
 (3) H_2
 (4) Esterification



with ethyl cyanoacetate in the presence of ammonium acetate gave XXVII. Hydrolysis of XXVII, followed by decarboxylation, hydrogenation and esterification afforded XXVIII. On heating XXVIII with homoveratrylamine (XXII), followed by ring closure of the crude amide by means of phosphoryl chloride, XXIX was formed and was isolated from the basic fraction by vacuum distillation.

From the products of oxidation of XXIX with mercuric acetate, Battersby and Openshaw isolated d,l-rubremetinium bromide, small bright red needles, m.p. 180-185° C. (dec.).

In 1950 Evstigneeva et al. (19) claimed the synthesis of a racemic emetine, which gave color reactions characteristic of the natural alkaloid, and which was oxidized to d,l-rubremetinium iodide, m.p. 178-180° C. The ultraviolet and visible spectrum was the same as that of the active rubremetinium iodide obtained by oxidation of emetine. Apart from d,l-rubremetinium iodide, there are only four compounds in the paper, the melting and/or boiling points of which are given. Only two of these compounds have any direct bearing on the synthesis. There is no step-wise characterization of the individual compounds obtained in the synthesis. In addition, no method of preparation for a key intermediate, ethyl β -(1-cyanopropyl)-glutarate, is given nor any reference to the literature pertaining to this compound.

Two alternate approaches to the synthesis of the racemic emetine are described in the paper. These are summarized below;

Method A. Ethyl β -(1-cyanopropyl)glutarate (XXX), b.p. 139-140^o/2.5 mm., was condensed with an excess of homoveratrylamine (XXII) under conditions of catalytic hydrogenation using nickel or platinum catalyst. This gives the diamide, XXXII, which was cyclized to a compound, catalytic hydrogenation of which gave I.

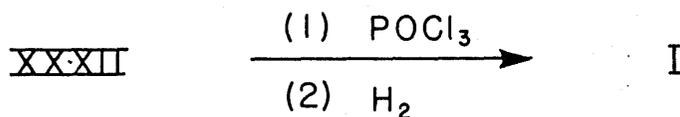
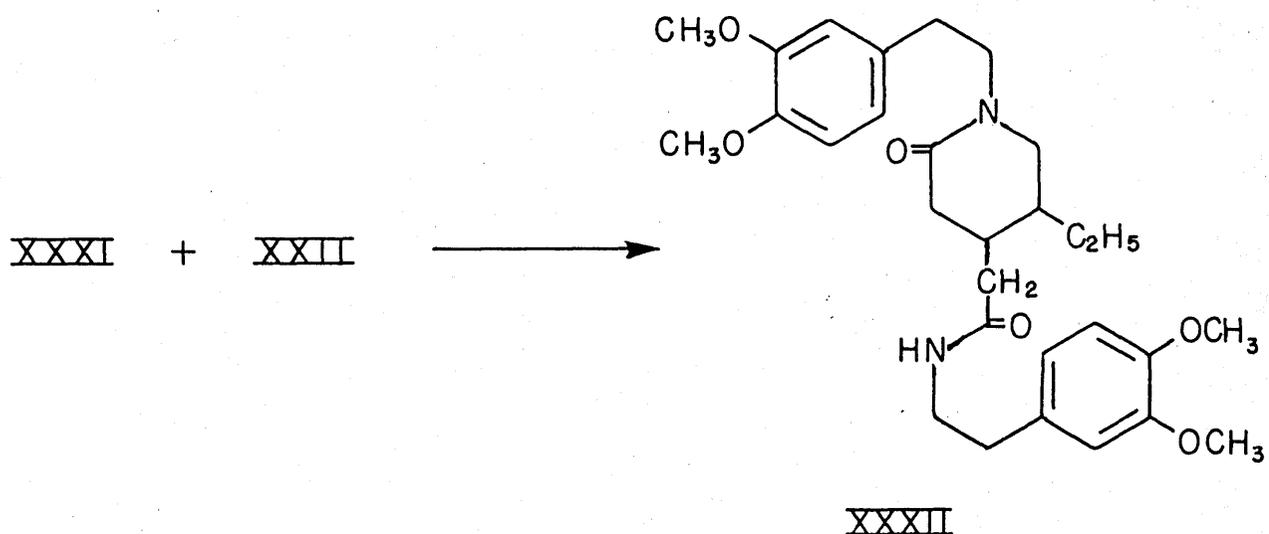
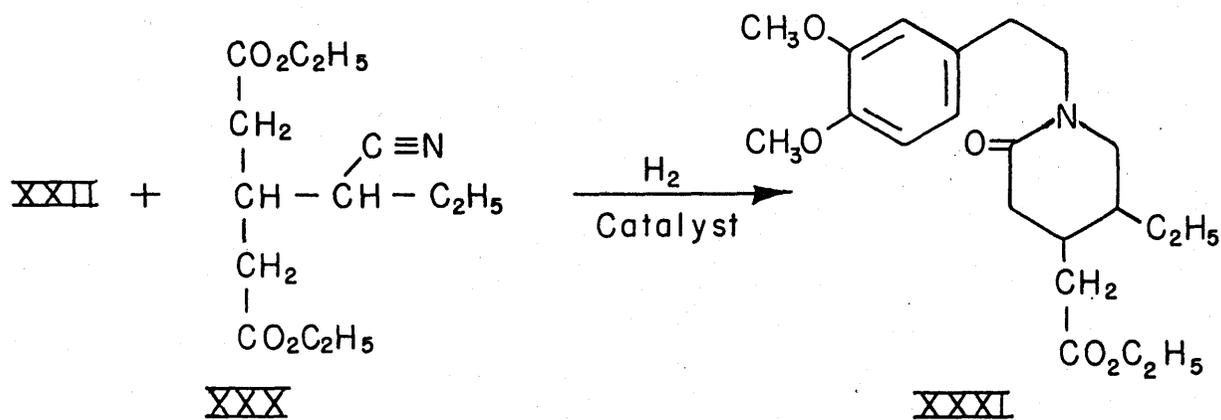
Method B. Reaction of XXX with a limited amount of homoveratrylamine and subsequent heating at 180-200^oC. gave XXXI. Reaction of XXXI with a second equivalent of homoveratrylamine (XXII) afforded XXXII, which was converted to I as in method A.

In another variation of the general scheme, XXXI was cyclized by the Bischler-Napieralski procedure and the cyclization product reacted further as in Method A.

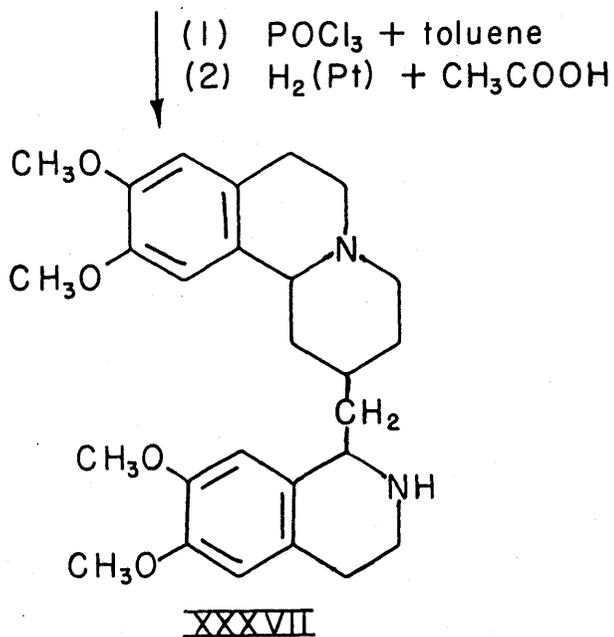
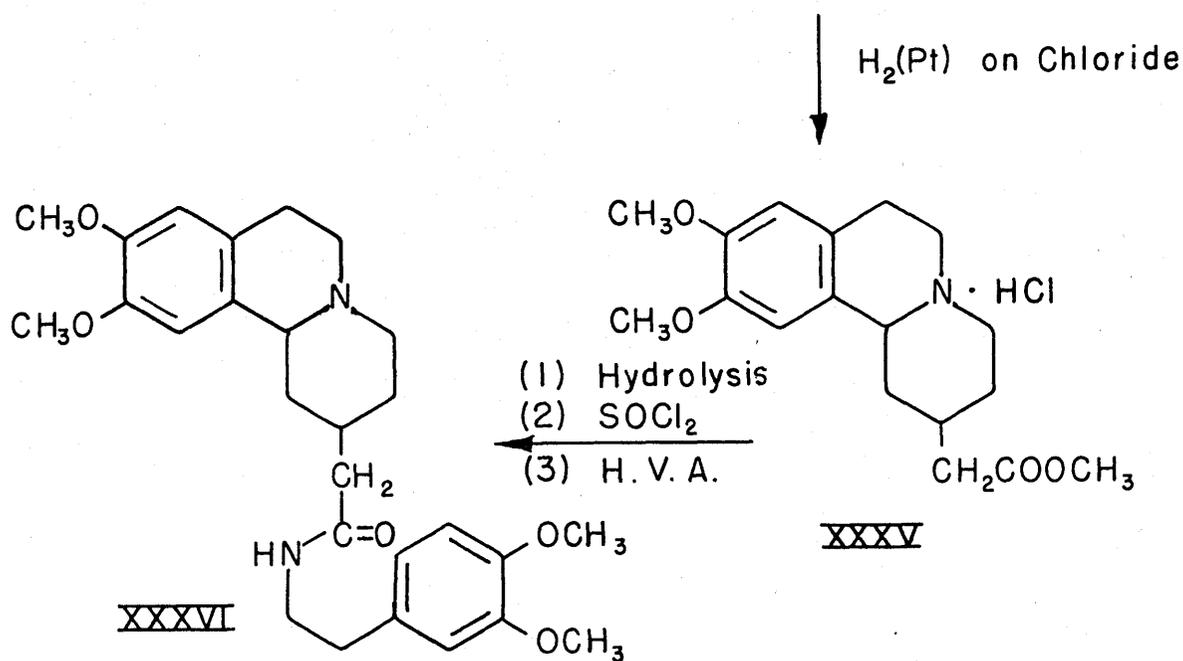
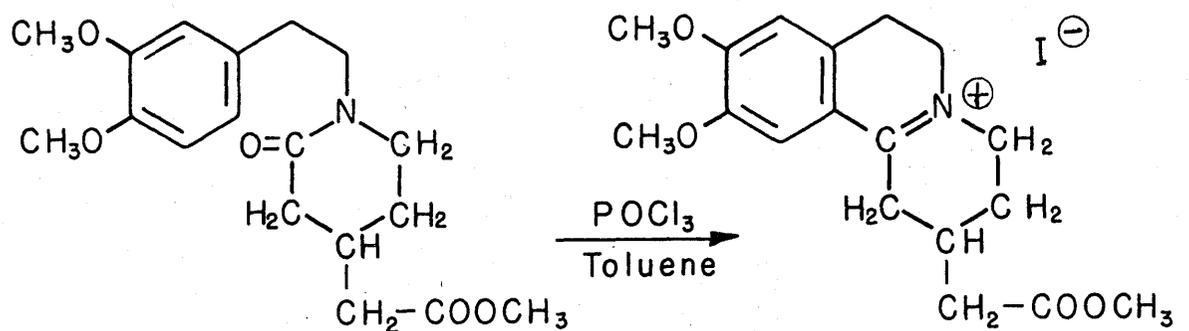
The following additional compounds were characterized by the Russian workers. Neither the methods of preparation nor the uses of the compounds were mentioned.

- (a) Ethyl β -[1-(bromomethyl)propyl] glutarate, m.p. 132.5-133.5^oC.
- (b) Anhydride of β -(1-diethylacetal)propylglutaric acid, b.p. 155-157^o/4 mm.
- (c) β -carboxymethyl- γ -ethyl- δ -valerolactone, m.p. 102.5-103.5^oC. and b.p. 170-173^oC./3 mm.

In 1951, Pailer and Strohmayer(27) published a description of the synthesis of d,l-G-noremetine (XXXVII). (γ -Phenoxypropyl)-malonic acid, the starting material, was brominated



under the influence of ultraviolet light to give (γ -phenoxypropyl)-bromomalonic acid. This was decarboxylated at 150-160° C. to form α -bromo- γ -phenoxyvaleric acid. The acid was esterified with ethanol and sulfuric acid, then treated.



with diethylaniline at 200° C. to remove the elements of hydrogen bromide and form ethyl 5-phenoxy-3-pentenoate. A Michael condensation of the α, β -unsaturated ester with ethyl malonate gave diethyl α -carbethoxy- β -(β' -phenoxyethyl)-glutarate. Hydrolysis and decarboxylation gave β -(β' -phenoxyethyl)-glutaric acid, which, on heating with 48% hydrobromic acid gave phenol and β -(β' -bromoethyl)-glutaric acid. The acid was esterified by diazomethane in methanol to provide dimethyl β -(β' -bromoethyl)-glutarate. This was condensed with homoveratrylamine, first by refluxing in ether, then by heating the resulting amino-ester at 190-200° C. This gave the lactam-ester XXXIII.

Ring closure of XXXIII was effected by heating with phosphoryl chloride in toluene. The ring-closed product was isolated as the quaternary ammonium iodide, XXXIV, m.p. 218-220° C. Digestion of XXXIV with silver chloride gave the quaternary ammonium chloride, which was hydrogenated over platinum to the hydrochloride, XXXV. Acid-catalyzed hydrolysis to the acid, conversion of the acid to the acid chloride by means of thionyl chloride in chloroform, and condensation of the acid chloride with homoveratrylamine, gave the amide, XXXVI.

Ring closure of XXXVI by means of phosphoryl chloride gave dehydro-C-noremetine, which was reduced with hydrogen and platinum in 50% acetic acid solution to give d,l-C-noremetine (XXXVII).

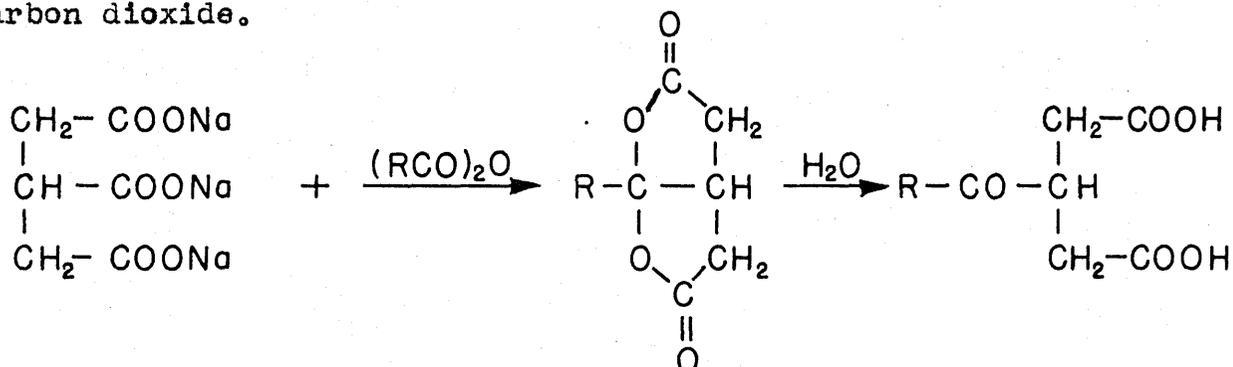
DISCUSSION OF THE EXPERIMENTAL RESULTS

Examination of the emetine structure (I) reveals that it consists, in a formal sense, of two homoveratrylamine units joined together by a skeleton containing nine carbon atoms. A reasonable approach to the synthesis of emetine would therefore consist in the preparation of a suitably branched nine carbon aliphatic molecule containing suitably located functional groups, which would permit combination with two molecules of homoveratrylamine and subsequent appropriate ring closures.

One aliphatic compound which could conceivably function as a starting material in the synthesis of emetine is β -propionylglutaric acid, $\text{CH}_3\text{CH}_2\text{COCH}(\text{CH}_2\text{COOH})_2$. Although this molecule contains only eight carbon atoms, the carbonyl group in the propionyl side chain could serve as the site for the introduction of the ninth carbon atom. An examination of the literature revealed that β -propionylglutaric acid was unknown. Therefore it was necessary to devise a synthesis of the keto-acid or one of its simple derivatives.

A further examination of the literature brought to light a novel synthesis of bislactones of β -acylglutaric acids in general, the method having been discovered by Fittig

and Roth(28). These workers reacted an acid anhydride with the trisodium salt of tricarballic acid at an elevated temperature and obtained the bislactone, with evolution of carbon dioxide.



Fittig and Roth also found that the bislactones could be hydrolyzed by hot water to give the corresponding β -acylglutaric acids. They successfully employed acetic, n-butyric, isobutyric and benzoic anhydride in this synthetic sequence (R = CH₃, CH₃CH₂CH₂, (CH₃)₂CH and C₆H₅, respectively). The melting points of the four bislactones and corresponding β -acylglutaric acids are given in Table I.

Table I

Melting Points of β -Acylglutarobislactones
and β -Acylglutaric Acids

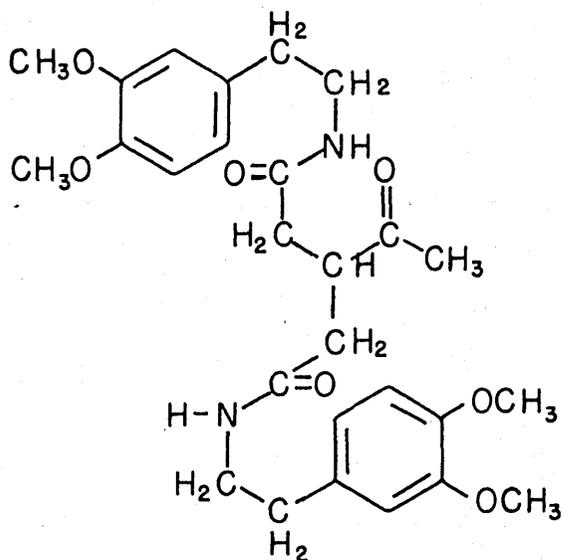
<u>Acyl Group</u>	<u>Bislactone</u>	<u>Acid</u>
CH ₃ CO-	99°C.	58°C.
CH ₃ CH ₂ CH ₂ CO-	55°	88°
CH ₃ CH(CH ₃)CO-	88-90°	99°
C ₆ H ₅ CO-	137°	--

It seemed entirely reasonable to attempt to prepare β -propionylglutaric acid by this synthetic sequence, propionic anhydride being used in the reaction with trisodium

tricarballylate. The reaction worked according to expectation, and β -propionylglutarobislactone was obtained in 80% of the theoretical yield. It melted at 62.5° C. Hydrolysis of the bislactone afforded β -propionylglutaric acid, m.p. 88° C.

Although the above described synthesis of β -propionylglutaric acid was entirely successful it nevertheless presents an arduous task to obtain the acid in sufficiently large quantities, inasmuch as the preparation of one of the starting materials, tricarballylic acid, is itself a many-step, time consuming process. Therefore, before consuming the β -propionylglutaric acid on hand in further experimentation towards the synthesis of emetine, it was decided to carry out model experiments with the readily accessible β -acetoglutamic acid. This was prepared easily and in large quantity by Emery's(29) method, This consisted in reacting ethyl sodioacetoacetate with ethyl bromoacetate to form ethyl acetosuccinate. This, in turn, was converted to the sodio derivative and reacted with ethyl bromoacetate to give ethyl β -acetotricarballylate. Hydrolysis and decarboxylation completed the synthesis of β -acetoglutamic acid.

In a model experiment, β -acetoglutamic acid was condensed with homoveratrylamine at a temperature of $200-240^{\circ}$ C. After treatment of the crude reaction product with dilute hydrochloric acid solution, there was obtained the dihomoveratrylamide (XXXVIII) of β -acetoglutamic acid in 25% of the theoretical yield.



XXXVIII

With the model experiment successfully concluded, an attempt was made to condense β -propionylglutaric acid with homoveratrylamine in the same way. This attempt was singularly unsuccessful. No crystalline amide could be obtained. The result was unfortunate, but it illustrates once again the profound difference in chemical reactivity between homologous compounds that sometimes exists.

Since an ester frequently reacts with an amine to form an amide more readily than does the corresponding acid, β -propionylglutaric acid was converted to its ethyl ester in 64% yield by an azeotropic esterification technique. However, the ethyl β -propionylglutarate so obtained also failed to give the desired amide on reaction with homoveratrylamine.

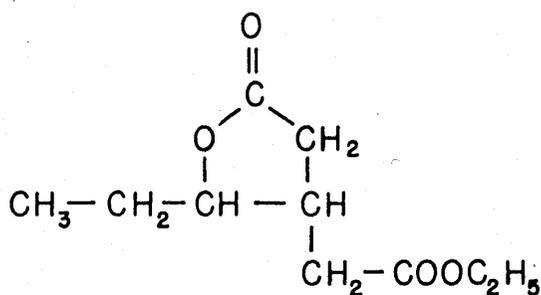
Inasmuch as to keto group can combine with a primary amine to form a Schiff base, and since the azomethine linkage present

in the Schiff base could conceivably react with a carboxyl or carbethoxyl group to form a cyclic compound, the possibility existed that this type of side reaction might have been responsible for the low yield of diamide in the reaction of β -acetoglutamic acid with homoveratrylamine and the failure to obtain any diamide at all in the reaction of β -propionylglutamic acid with homoveratrylamine. Therefore it was decided to reduce the keto group of ethyl β -propionylglutarate to an alcohol group, which would not react with homoveratrylamine, and then carry out the condensation reaction with homoveratrylamine.

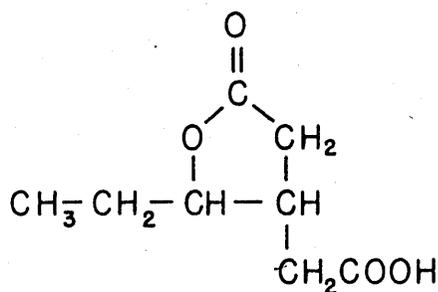
Keto groups in simple molecules can readily be reduced to secondary alcohol groups by catalytic hydrogenation. The use of platinum catalyst with hydrogen at low pressure, or the use of Raney nickel or copper oxide-chromium oxide catalyst with hydrogen at a high pressure and elevated temperature, are methods which have frequently been employed to convert a ketone to a secondary alcohol(30). Despite the existence of these analogous reactions, ethyl β -propionylglutarate was recovered unchanged after treatment with platinum catalyst and hydrogen at three atmospheres pressure, with Raney nickel and hydrogen at a pressure of 133 atmospheres and a temperature of 103°C ., and with copper oxide-chromium oxide catalyst at a hydrogen pressure of 104 atmospheres and a temperature of 125°C . Inasmuch as ester groups begin to be reduced at an appreciable rate at slightly higher temperatures and

hydrogen pressures, the decision was made to discontinue this approach and not to attempt more drastic hydrogenation conditions.

In recent years, the use of complex hydrides as reducing agents for organic compounds has assumed considerable importance. It has been reported(31), for example, that sodium borohydride will smoothly reduce a ketone to an alcohol but will not effect the reduction of an ester. This limited reactivity appeared to be exactly what was needed for the preferential reduction of the keto group in ethyl β -propionylglutarate. The reduction was attempted and proceeded according to expectation. Reaction of ethyl β -propionylglutarate with sodium borohydride in aqueous-ethanolic solution containing sodium hydroxide afforded a moderately good combined yield of ethyl γ -caprolactone- β -acetate (XXXIX) and δ -caprolactone- β -acetic acid (XL).



XXXIX

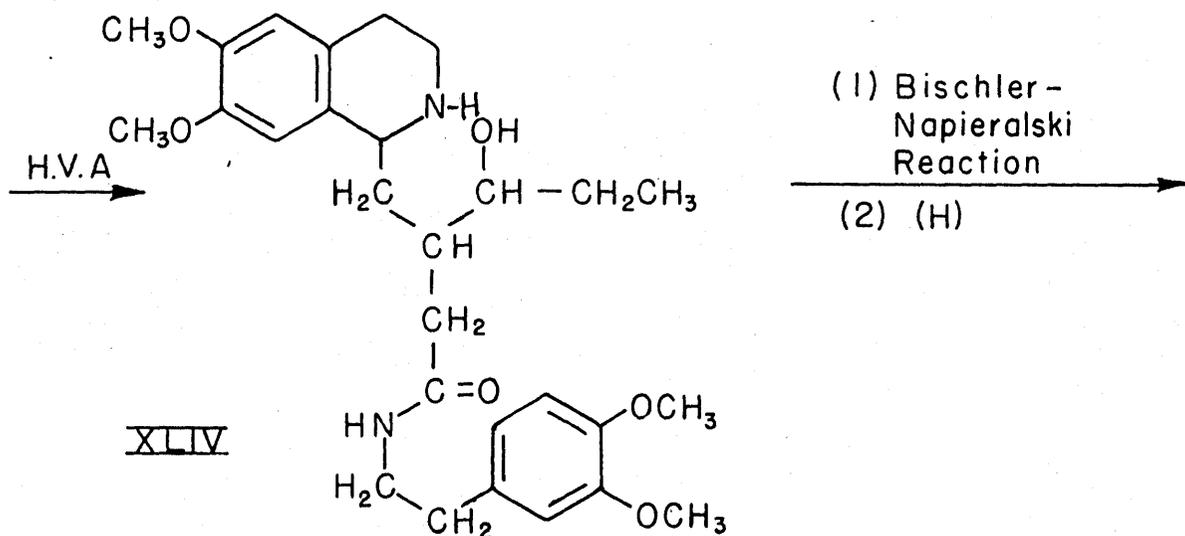
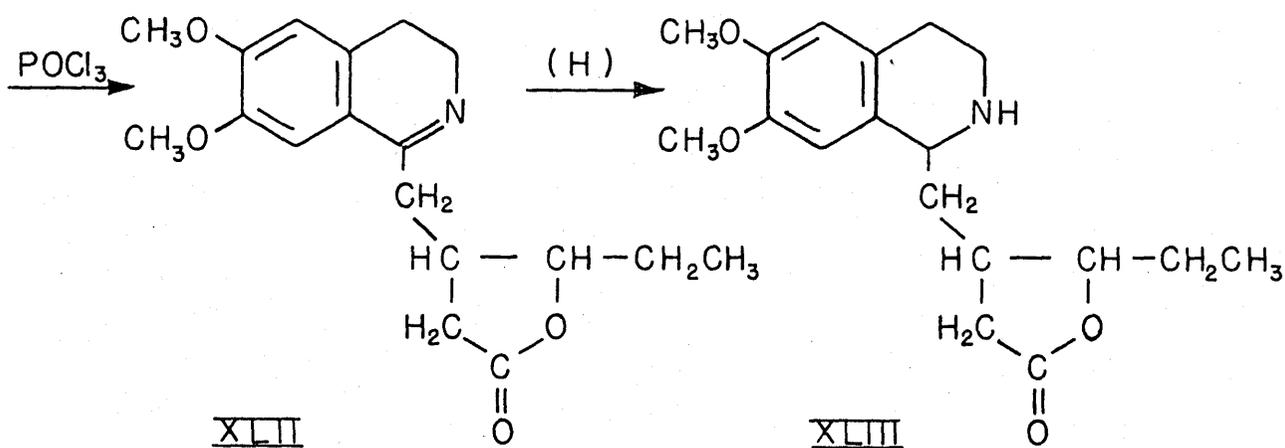
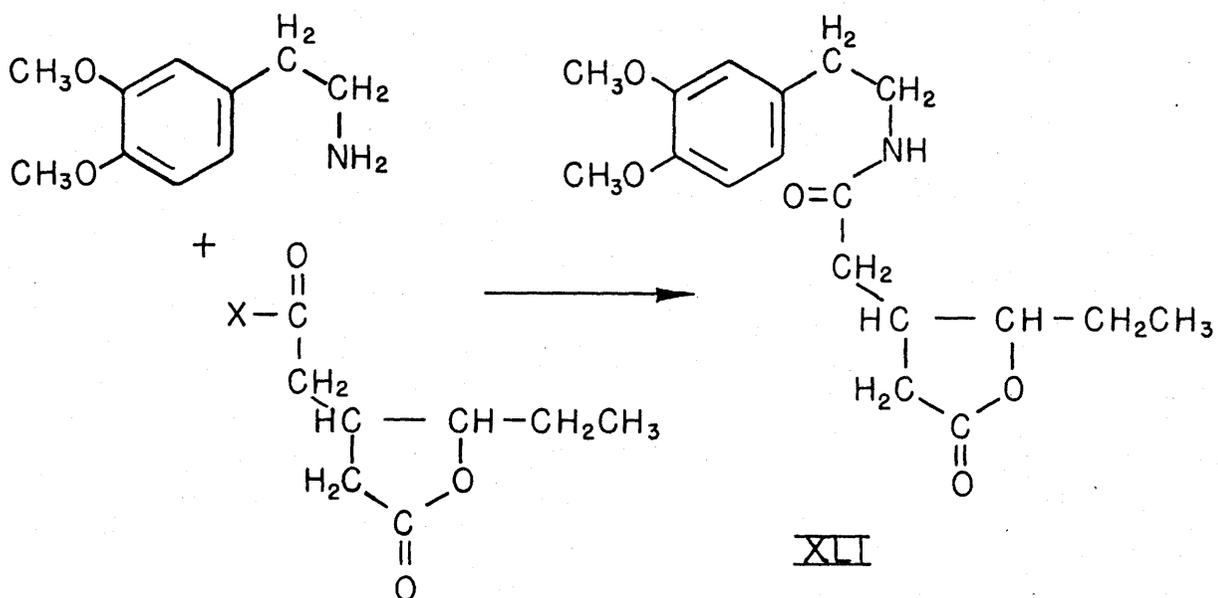


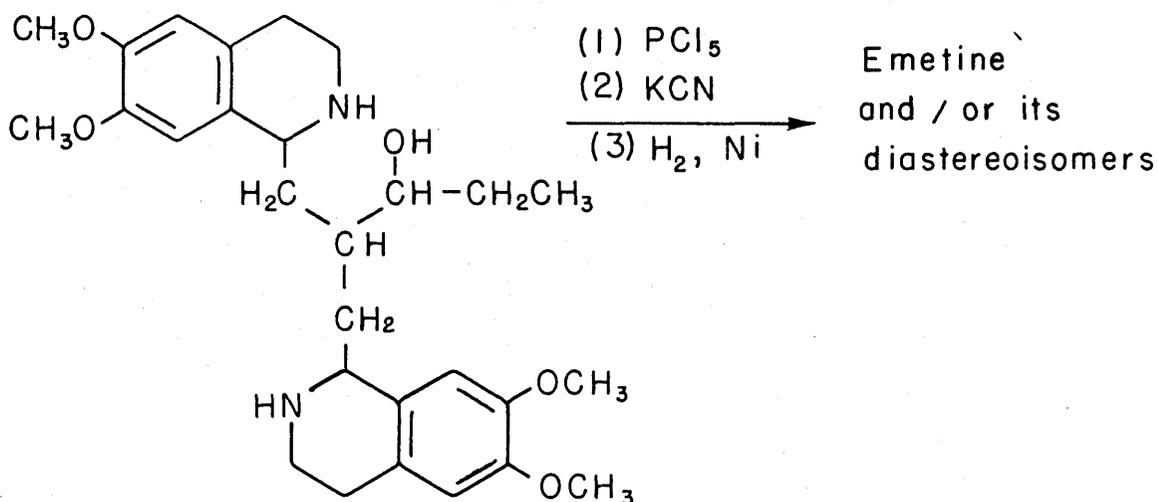
XL

In view of the reduced yield which inevitably resulted from the indirect process, β -propionylglutarobislactone \longrightarrow β -propionylglutaric acid \longrightarrow ethyl β -propionylglutarate \longrightarrow γ -caprolactone- β -acetic acid, a direct reduction of β -propionylglutarobislactone with sodium borohydride was attempted. In

a very smooth reaction, this direct reduction afforded γ -caprolactone- β -acetic acid in 93% of the theoretical yield. In subsequent experiments it was found that γ -caprolactone- β -acetic acid could be converted to ethyl γ -caprolactone- β -acetate via the acid chloride in 94% of the theoretical yield, and in 81% of the theoretical yield by an azeotropic esterification technique.

The next few paragraphs are speculative in nature, inasmuch as there has not been time to carry out the proposed reactions before the writing of this thesis. There is high expectation that γ -caprolactone- β -acetic acid or its ethyl ester or its acid chloride will react with homoveratrylamine to form the compound XLI. This might then be ring-closed by the Bischler-Napieralski procedure to give XLII. Reduction of XLII should afford XLIII. A reaction of XLIII, perhaps as an acyl derivative, with homoveratrylamine might produce XLIV. It should be possible to ring-close XLIV by the Bischler-Napieralski procedure and reduce the resulting dihydroisoquinoline group to give XLV. Finally, it might be possible to convert XLV, probably as a diacyl derivative, to a compound having a halogen atom in place of the secondary hydroxyl group, then to introduce a cyano group in place of the halogen, and lastly to ring-close the cyanide by a high pressure reductive amination to give one or more of the emetine racemates. Of course there is no way of predicting what experimental difficulties will arise in this projected synthesis. Only future work will clarify





XLV

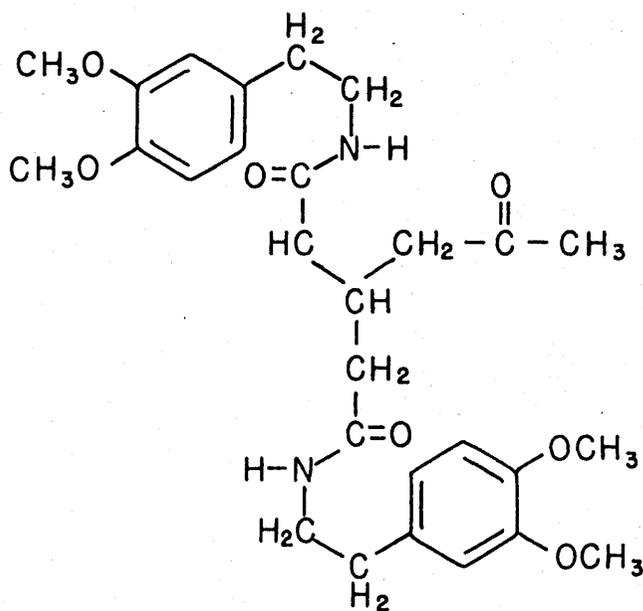
that issue. Also certain variations of the described procedure might prove profitable or necessary.

It is also worthwhile to mention that γ -caprolactone- β -acetic acid might serve as the precursor to ethyl β -(1-cyanopropyl)glutarate, the compound used by Evstingneeva et al. (19) in their synthesis of racemic rubremetinium iodide. The Russian chemists did not specify how they prepared ethyl β -(1-cyanopropyl)glutarate, and an examination of the literature other than the Russian article shows the compound to be unknown. Some preliminary trial runs in an attempt to convert γ -caprolactone- β -acetic acid or its ethyl ester to ethyl β -(1-cyanopropyl)glutarate are described in the experimental section.

To conclude this section of the thesis, a brief description of some early work carried out in cooperation with Melvin I. Moyer is offered. A large quantity of ethyl β -hydroxyglutarate was desired as an intermediate in the synthesis of β -acetylglutaric acid. While Mr. Moyer prepared the desired ester by the preparation and reduction of ethyl acetonedicarboxylate, the present author prepared it by converting glycerol α, γ -dibromohydrin to glycerol α, γ -dicyanohydrin, followed by acid-catalyzed ethanolysis of the dicyanohydrin.

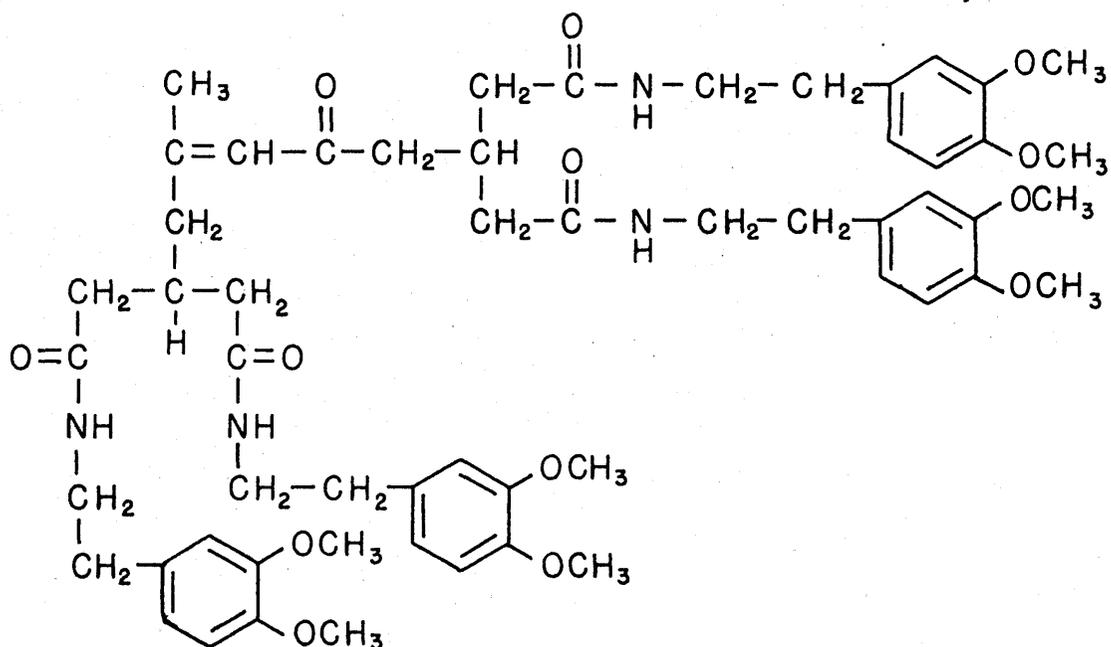
By use of the procedure of Dreifuss and Ingold(32) ethyl β -hydroxyglutarate was converted to ethyl β -chloroglutarate. This in turn, was condensed with ethyl sodioacetate to give ethyl ω -acetylmethanetriacetate. Hydrolysis and decarboxylation of ethyl ω -acetylmethanetriacetate afforded a moderate yield of β -acetylglutaric acid, which was also characterized as the ethyl ester.

A high temperature reaction of β -acetylglutaric acid with homoveratrylamine produced a very small amount of a



XLVI

crystalline substance, m.p. 178°C . It was hoped that the



XLVII

compound would turn out to be N, N'-dihomoveratryl- β -acetylglutaramide (XLVI), which might serve as an intermediate for the synthesis of emetine. Repeated analyses of the compound, m.p. 178°C., gave consistently high nitrogen values, however, which cast considerable doubt on the structure, XLVI. A molecular weight determination of the compound, m.p. 178°C., by the Rast method gave a value of 986. This suggests a condensation-dehydration derivative of XLVI, possibly of structure XLVII, which has a molecular weight of 1011. The nitrogen values fit the molecular formula C₅₆H₇₄N₄O₁₃, better than C₂₈H₃₈N₂O₇, but the carbon values are poorer.

EXPERIMENTAL

Ethyl β -Hydroxy-glutarate(32). Exactly 109 g. (0.5 mole) of glycerol α,γ -dibromohydrin in 100 ml. of methanol was heated under reflux for thirty minutes, with agitation. Following this, 65 g. (1.0 mole) of potassium cyanide in 60 ml. of water was added dropwise to the reaction mixture. After the initial exothermic reaction had subsided, the entire amount was added, and the mixture was refluxed on the steam bath for one hour. On cooling, potassium bromide precipitated, and 15 ml. of absolute ethanol was added to the cold reaction mixture. The inorganic salt was filtered and washed with 50 ml. of ethanol. The combined filtrates were distilled under reduced pressure until the residue was a dry mass. About 50 g. of crude glycerol α,γ -dicyanohydrin was obtained. It was dried in the vacuum oven at 40°C. for three hours. A small sample was crystallized from ethanol and gave a m.p. of 124°C.

The crude dicyanohydrin was mixed with 100 g. of absolute ethanol, and hydrogen chloride was passed into the solution at room temperature for one hour. The solution was then refluxed on the steam bath with hydrogen chloride being passed in for one additional hour. It was next refluxed for eight hours. On cooling, it was poured on crushed ice, the oily-product was extracted with ether and washed with aqueous

sodium carbonate solution. The ethereal solution of the ester was dried overnight over anhydrous sodium sulfate.

After removing the solvents, the residue was fractionated through an efficient column. The first fraction consisted of 5 g. of ethyl glutaconate, b.p. 135-40°C./11 mm. The second fraction consisted of 72 g. of pure ethyl β -hydroxyglutarate, b.p. 154-57°/11 mm.

Ethyl β -Chloroglutarate(32). The entire 72 g. (0.353 mole) of ethyl β -hydroxyglutarate in 500 ml. of dry ether was treated with 72 g. (0.353 mole) of phosphorus pentachloride, with stirring, at room temperature, for one hour. The ether layer was washed with ice-cold water and next with aqueous sodium carbonate. It was dried over anhydrous sodium sulfate, and, on evaporation of the ether, 63 g. of crude product was obtained. No attempt was made to purify the compound by distillation since it is reported to char at a very low temperature.

Ethyl ω -Acetylmethanetriacetate(32). This compound was prepared by the condensation of ethyl sodioacetoacetate with ethyl β -chloroglutarate as follows:

In a three-neck, 3-liter round bottom flask, fitted with a reflux condenser, mechanical stirrer and an addition funnel was placed 85 g. (1.85 mole) of absolute ethyl alcohol. Then 6.6 g. (0.28 mole) of sodium wire was reacted with the alcohol. To this sodium ethoxide solution, 37 g. (0.285 mole) of ethyl acetoacetate was gradually added, a steady reflux rate being

maintained. The 63 g. (0.285 mole) of the crude ethyl β -chloroglutarate was added dropwise. The reaction mixture was refluxed for forty-five minutes, after which it was found neutral to moist litmus paper. The mixture was poured on crushed ice, adjusted to a slightly acidic pH, and extracted with ether. The ether solution was washed with aqueous sodium carbonate and finally dried over anhydrous sodium sulfate.

After removing the ether on the steam bath, the residue was fractionated through an efficient column:

- Fraction 1. Ethyl acetoacetate, b.p. $45^{\circ}\text{C}/0.7$ mm.
- Fraction 2. Ethyl glutaconate, b.p. $135-40^{\circ}/11$ mm.
- Fraction 3. Ethyl β -hydroxyglutarate, b.p. $154-57^{\circ}/11$ mm.
- Fraction 4. Ethyl ω -acetylmethanetriacetate, b.p. $198-203^{\circ}/11$ mm.
- Fraction 5. Some high boiling residue.

Fraction 4 consisted of 22 g., which is a 34% yield on the basis of the crude ethyl β -chloroglutarate. (The reported yield(32) is 80% on the same basis; however, no mention is made of the fractions 2 and 3 as by-products of the reaction.)

Hydrolysis and Decarboxylation of Ethyl ω -Acetylmethanetriacetate. The procedure used was similar to that employed by Bently and Perkin to obtain γ -acetylbutyric acid from ethyl α -acetylglutarate(33).

A mixture of 22 g. (0.098 mole) of ethyl ω -acetylmethanetriacetate and 100 ml. of 5% potassium hydroxide was refluxed for two hours whereupon the solution became homogeneous.

About 200 ml. of 3 M hydrochloric acid solution was added, and the resulting solution was refluxed further for eight hours. By the end of this time the evolution of carbon dioxide had stopped. The solvents were removed at 40-50°C. under reduced pressure. The residue was mixed with dry acetone, and potassium chloride was filtered off. Acetone was removed from the filtrate under reduced pressure. The dark residue was treated with eight 100 ml. portions of anhydrous ether, whereupon 4.3 g. of ether insoluble organic solid was obtained. It was dissolved in 150 ml. of acetone containing 50 ml. of water and refluxed with 2 g. of activated carbon for one hour. The material failed to be decolorized and was recovered by distillation of the solvents. The crude brownish-white material showed a rough m.p. of 70-72°C. Thus a direct analysis of the sample was not possible.

Preparation of Ethyl β -Acetylglutarate. Four g. of the crude β -acetylglutaric acid was mixed with 25 ml. of absolute ethanol, 5 ml. of concentrated sulfuric acid and 20 ml. of benzene and subjected to an azeotropic esterification. After two hours, the temperature of this overhead vapor reached 68.4°C. Withdrawal of all the liquid in the azeotropic distillation head removed all the benzene and most of the alcohol present in the original mixture. The residue was made nearly neutral by addition of aqueous sodium carbonate, extracted with ether and dried over anhydrous sodium sulfate. The solvents were removed by distillation, the last part in vacuo,

and the residue was distilled. The only fraction collected was 2.7 g. of b.p. 116-17°C./1 mm. This was identical with the sample of ethyl β -acetylglutarate characterized by M. I. Moyer(34).

Reaction of Crude β -Acetylglutaric Acid with Homoveratrylamine. The reaction conditions were similar to those used by King and Robinson(35) in a similar reaction.

To 1.70 g. of crude β -acetylglutaric acid was added 5.10 g. of freshly distilled homoveratrylamine, and the mixture was heated in a distilling equipment at 200°C. (oil-bath temperature) for one hour.

On cooling, the mixture solidified and was digested with three 100 ml. portions of 3 M hydrochloric acid, whereupon a small amount of insoluble solid material was obtained. It was crystallized from methanol, and then from methanol-ethyl acetate mixture. Colorless crystals were obtained, m.p. 178°C.

Anal. Calcd. for $C_{28}H_{38}N_2O_4$: C, 65.35; H, 7.44; N, 5.45

Found: C, 64.90, 64.95; H, 7.24, 7.25; N, 6.34, 6.08

The sample was further purified by additional recrystallizations and again submitted for analysis.

Found: C, 64.91; H, 7.33; N, 6.34, 6.20

In view of the consistently high nitrogen values, it is doubtful that the compound is the desired N, N'-dihomoveratryl- β -acetylglutaramide. The molecular weight as determined by the Rast method suggests a condensation product of the amide.

Anal. Calcd. for $C_{56}H_{74}N_4O_{13}$: C, 66.51; H, 7.38; N, 5.54;

M.W. 1011

Found:

M.W. 986

Ethyl α -Acetosuccinate. The method employed was that of Adkins, Isbell and Wojcik(36).

In a three-liter, three-necked flask, fitted with a reflux condenser and a stirrer was placed 400 ml. of absolute ethyl alcohol. Then 23 g. (1 mole) of sodium metal was gradually added with warming on the steam-bath to complete the reaction. Exactly 143 g. (1.1 moles) of ethyl acetoacetate was introduced slowly. To the resulting mixture, 123 g. (1 mole) of ethyl chloroacetate was added slowly over a period of one hour, and the reaction mixture was refluxed for five to six hours. After this period the solution no longer gave an alkaline reaction with moist litmus paper.

The solution was filtered to remove the sodium chloride formed, and the salt was washed with several 50 ml. portions of absolute ethyl alcohol. After removing the alcohol on the steam bath, the residue was fractionated through an efficient column under reduced pressure. Ethyl α -acetosuccinate, 134 g., b.p. $121-24^{\circ}C/5$ mm., was collected. Yield, 62% of theory.

Ethyl β -Acetotricarballylate. The procedure was adapted from that of Miehle(37).

In a three-liter, three-neck flask, fitted with a reflux condenser and a stirrer were placed 128 g. of dry benzene and 128 g. (0.592 mole) of ethyl α -acetosuccinate. To this solution was added gradually 13.8 g. (0.6 mole) of metallic sodium

with heating on the steam bath. After the sodium had been consumed, 100 g. (0.6 mole) of ethyl bromoacetate was introduced dropwise from an addition funnel. An exothermic reaction occurred, and the mixture was refluxed for two hours. On cooling, 500 ml. of water was added to dissolve the precipitate of sodium bromide, and the organic layer was separated. The aqueous washings were re-extracted with two 50 ml. portions of benzene. After the removal of the benzene from the combined organic material by distillation through a Vigreux column, the residue was fractionated in vacuo. There was obtained 142 g. of ethyl β -acetotricarballylate, b.p. $190^{\circ}/16$ mm. Yield, 80% of the theoretical amount.

β -Acetoglutaric Acid(29). A mixture of 142 g. (0.472 mole) of ethyl β -acetotricarballylate and 65 ml. of concentrated hydrochloric acid was refluxed for nine hours. After this time evolution of carbon dioxide had completely stopped (as tested by $\text{Ba}(\text{OH})_2$). All the solvent was distilled, the last part in vacuo. The residue was an amber-colored highly viscous liquid. It was cooled in dry ice for over an hour, whereupon it crystallized.

A small sample of one gram was dissolved in boiling benzene, from which it crystallized as long needle-shaped crystals, m.p. 58°C . The yield of the crude product was 99%. The melting point checks with that of the keto-dilactone of β -acetylglutaric acid as reported by Fittig.(29c).

The entire bulk of the crude material was refluxed with 100 ml. of water for 24 hours. After this period, the aqueous solution was treated with one gram of activated carbon and filtered. The clear aqueous filtrate was distilled under reduced pressure. The clear viscous liquid residue was cooled in dry ice and thereupon crystallized in long needles, m.p. 99°C (29c).

Condensation of Succinic Acid with β -Phenylethylamine(38).

A solution of 5 g. (0.035 mole) of succinic acid in 9.36 g. of β -phenylethylamine was placed in a distilling flask and heated at 220°C . for three hours on an oil bath. On cooling the reaction mixture, a crop of long needle-shaped crystals formed. The crystals were powdered and triturated with two 50 ml. portions of 3 N hydrochloric acid, then washed with water. The di- β -phenethylamide of succinic acid was recrystallized from dry methanol, m.p. 200.6°C , the same as reported in the literature.

Reaction of β -Acetoglutaric Acid with Homoveratrylamine.

A solution of 20.0 g. (0.115 mole) of β -acetoglutaric acid in 61.0 g. (0.345 mole) of homoveratrylamine was placed in a distilling flask and heated at 220°C . for two and a half hours, 6 g. of water distilling during this period. On cooling, the residue became a hard amber-colored solid. It was ground to a powder, and 400 ml. of 5% sulfuric acid was added and the mixture stirred for half an hour. The gummy solid was then washed with two 200 ml. portions of 5% sulfuric

acid, 200 ml. of water and two 400 ml. portions of cold 5% potassium hydroxide solution. The yellow-white solid which had formed was washed with water and dried in a vacuum desiccator over potassium hydroxide. After two crystallizations from absolute ethyl alcohol, colorless crystals of N,N'-dihomo-veratryl- β -acetoglutaramide were obtained, m.p. 191.8°C.

Anal. Calcd. for $C_{27}H_{36}N_2O_7$: C, 64.78; H, 7.25; N, 5.60

Found: C, 64.79, 64.83; H, 7.10, 6.95; N, 6.04, 6.17

On the basis of several runs, the best yields were only 25% of theory.

Trisodium Tricarballylate(29c,39). Exactly 58 g. (0.33 mole) of tricarballylic acid was dissolved in 400 ml. of water containing 40 g. (1 mole) of sodium hydroxide. The solution was evaporated to dryness on the steam-bath, whereupon a hard, dry mass of the sodium salt of tricarballylic acid was obtained. It was ground to a fine powder and heated in a vacuum oven at 40-45°C. for six hours to constant weight. In all, 80 g. of the salt was obtained, which is 100% of the theoretical yield.

Reaction of Trisodium Tricarballylate with Propionic Anhydride. The method was modelled after that of Fittig(39). The entire 80 g. (0.33 mole) of trisodium tricarballylate was placed in a 250 ml. round bottom flask fitted with a thermometer well, and 80 g. of freshly distilled propionic anhydride, b.p. 168°C., was added. The reaction mixture was heated on an oil bath at a temperature of 130-132°C. The reaction mixture itself was maintained at a temperature

of 120°C. (Under no circumstance should the reaction mixture temperature be elevated.) An immediate evolution of carbon dioxide was observed. At intervals of 2 hours, 30 g. portions of propionic anhydride were added until a total of 192 g. (1.47 moles) was used. The reaction mixture turned brownish-white, and at the end of 50 hours, the evolution of carbon dioxide stopped. On cooling, the mixture solidified. Low boiling Skellysolve was added, and the solid mass was triturated. Seven 200 ml. portions of Skellysolve were required to extract all of the organic material soluble in the hydrocarbon solvent. On evaporation of the combined Skellysolve extracts, crystalline β -propionylglutarobislactone together with unreacted propionic anhydride was obtained. The Skellysolve insoluble solid was extracted with six 150 ml. portions of chloroform. The combined chloroform and Skellysolve extracts, after removal of as much crystalline bislactone as possible, was subjected to distillation. Distillates upto b.p. 62°C./10 mm. were rejected, wherein most of the propionic anhydride was removed. The residue in the flask solidified on cooling and contained the bislactone and some sodium propionate. The bislactone was extracted with chloroform, and on addition of ice-cold low boiling Skellysolve, the bislactone separated out.

The chloroform and Skellysolve insoluble solid of the reaction mixture was found to be sodium carbonate and sodium propionate.

A total of 45 g. (0.265 mole) of bislactone, m.p. 62.5°C. was obtained (80% yield). It was easily purified by dissolving it in the minimum quantity of dry acetone and adding a few drops of anhydrous ether. It crystallized from this solvent in the form of colorless needles.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92

Found: C, 56.89, 56.82; H 6.18, 6.24

56.78, 56.96; 6.48, 6.46

β -Propionylglutaric Acid. The method was modelled after that of Fittig(39).

Exactly 19.3 g. (0.1136 mole) of the crystalline β -propionylglutarobislactone was refluxed with 150 ml. of water at 110°C. on an oil bath for 18 hours. Water was removed under reduced pressure. Attempts to crystallize the oily product from chloroform, methanol and ethyl acetate failed. The oil was insoluble in ether and ligroin. It solidified on trituration with low boiling Skellysolve, m.p. 82-87°C. The yield was 19 g. (89%).

A pure sample of β -propionylglutaric acid was obtained by the hydrolysis of ethyl β -propionylglutarate (prepared as shown below) m.p. 88°C.

Anal. Calcd. for $C_8H_{12}O_5$: C, 51.06; H, 6.43

Found: C, 51.20, 51.51; H, 6.37, 6.23

Ethyl β -Propionylglutarate. A mixture of 20 g. (0.106 mole) of β -propionylglutaric acid, 200 ml. of absolute ethanol, 100 g. of benzene and 15 ml. of concentrated sulfuric acid was

distilled through a Vigreux column having an azeotropic distillation head. The pot temperature was maintained between 80-82°C. by the use of an oil bath. The distillate temperature was 64.8°C. and the lower layer of the distillate was drawn off at intervals and rejected. After 36 hours, the temperature of the overhead vapor increased to 68°C. Only one liquid phase appeared in the distillate, so all the distillate was removed. Most of the benzene-alcohol mixture was removed by distillation, and the residue was made neutral to litmus by the addition of aqueous sodium bicarbonate. The mixture was extracted with ether, and the ethereal layer dried over anhydrous sodium sulfate. On distillation of the organic solvents in vacuo, about 24 g. of the crude ester was obtained. The crude ester was fractionated as follows:

Bath temperature 165°C.

Pot temperature 140°C.

Lower End of Column temperature 129°C.

Under these steadily maintained conditions, 16.5 g. of the ester, b.p. 121-22°C./0.2 mm., was collected (69.5% of the theoretical yield).

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25

Found: C, 59.75; H, 8.27

59.71; H, 8.29

59.61; H, 8.45

The infra-red analysis of the ester showed characteristic carbonyl absorption bands at 1787 cm^{-1} and 1721 cm^{-1} .

In a second azeotropic esterification, the following proportions were employed, resulting in a higher yield:

β -propionylglutaric acid 40 g. (0.212 mole).

Absolute alcohol 200 ml.

Benzene 100 ml.

Sulfuric Acid 20 ml.

Time for the azeotropic esterification, 7 hours

On removal of the solvents, after neutralization and drying, 51 g. of crude product was obtained. Fractionation using the same condition as above gave the following fractions:

Fraction 1. b.p. 0.15 mm. = $52-53^{\circ}\text{C}$. 1 g.

Fraction 2. b.p. 0.2 mm. = $121-22^{\circ}\text{C}$. 41 g.

Fraction 3. b.p. 0.23 mm. = 137°C . 1.5 g.

When fraction 3 began coming over, the distillation was stopped and the residue was identified as β -propionylglutarobislactone, m.p. = 62.5°C . The fraction 3 was also identified as the same bislactone.

Attempted Hydrogenation of Ethyl β -Propionylglutarate.

The various attempts made to reduce the keto-group of this ester by catalytic hydrogenation were singularly unsuccessful. A brief summary of the procedures and experimental conditions is given below:

(a) Low Pressure Hydrogenation over Platinum Catalyst.

Exactly 16.5 g. (0.073 mole) of the ester was dissolved

in 50 g. of absolute ethanol and 0.125 g. of platinum oxide catalyst was added. The mixture was shaken with hydrogen in a Parr apparatus at 40 lbs./sq. in. absolute pressure for 24 hours. No fall in pressure, indicative of hydrogen uptake, was observed. About 12 g. of ketoester, b.p. $120-122^{\circ}\text{C}/0.2\text{ mm.}$, was recovered.

(b) High Pressure Reduction Using Raney Nickel. Exactly 50 g. of ethyl β -propionylglutarate dissolved in 200 ml. of absolute ethanol and 2 g. of Raney Nickel were placed in a hydrogenation bomb of 500 cc. capacity. The reaction mixture was shaken with hydrogen at a pressure of 123 atmospheres, and the temperature was raised to 103°C. for two hours. On working up the reaction product, no reduction products were isolated and 48 g. of the starting ketoester, b.p. $122-24^{\circ}$ /0.2 mm., $[\alpha]_{\text{D}}^{20} = 1.4417$, was recovered.

(c) High Pressure Reduction using CuCr_2O_4 . Exactly 111 g. of ethyl β -propionylglutarate and 4 g. of copper oxide-chromium oxide catalyst were employed without any solvent. The reaction mixture was shaken with hydrogen at a pressure of 104 atmospheres and a temperature of $120-125^{\circ}\text{C.}$ for six hours. No uptake of hydrogen was observed, and 101 g. of the ketoester, b.p. $110-113^{\circ}/0.16\text{ mm.}$, was recovered.

Reduction of Ethyl β -Propionylglutarate Using Sodium Borohydride (Cf. 31). Exactly 15 g. (0.067 mole) of the ketoester was dissolved in 50 ml. of ethanol in a one-liter Erlenmeyer flask. To this, a solution of 1.5 g. of sodium borohydride dissolved in 50 ml. of ethanol and 10 ml. of

0.2 N. sodium hydroxide was gradually added at room temperature. On addition of the first 5-10 ml. of the sodium borohydride solution a brisk exothermic reaction commenced, and the mixture was thoroughly mixed by a swirling motion of the flask. After addition of the entire amount of sodium borohydride a milk-white suspension of a complex was obtained. The solution was continuously agitated throughout the addition by means of a magnetic stirrer. A slight excess of sodium borohydride was employed in the reduction. Fifteen minutes after addition of the hydride solution had been completed, one drop of the reaction mixture was treated with mineral acid. Evolution of hydrogen indicated the presence of unreacted sodium borohydride.

Fifteen ml. of water was added to dissolve the complex. There was a noticeable evolution of hydrogen from the reaction mixture, and it was warmed to 45°C. on the steam bath. The solution was then kept at room temperature and stirred for an additional three hours. On standing for an additional half hour a trace of crystalline precipitate came down, which charred on heating. The solution was filtered and the alcohol removed under reduced pressure. The aqueous alkaline solution was acidified. Ammonium chloride was added and the solution was extracted repeatedly with ether. The ether solution was dried over anhydrous sodium sulfate. On evaporation of the ether about 12 g. of oily residue was obtained.

On cooling the oily residue, some crystalline material, m.p. 98.4°C., was obtained. The liquid filtrate was frac-

tionated as follows:

Fraction 1.

Pot temperature	180-84°C.
Bottom column temperature	160-62°C.
B.P. 0.06-0.08 mm.	133-36°C.

There was obtained ethyl γ -caprolactone- β -acetate, 4 g.

$$\bar{n}_{\text{white}}^{30.04^\circ} = 1.4525.$$

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.88; H, 8.06

Found: C, 59.77, 59.75; H, 8.33, 8.53

The infra-red analysis shown in Fig. 3 is consistent with the structure of the lactone-ester.

Fraction 2.

Pot temperature	200°C.
Bottom column temperature	200°C.
B.P. 0.03-0.05 mm.	175-80°C.

There was obtained 4.5 g. of γ -caprolactone- β -acetic acid, which solidified on cooling. This, on crystallization from toluene, showed a m.p. of 98.4°C.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03

Found: C, 56.03, 55.78; H, 7.15, 7.15

The sodium borohydride reduction was repeated on 55 g. (0.23 mole) of ethyl β -propionylglutarate. There was obtained 14.5 g. (25%) of ethyl γ -caprolactone- β -acetate and 15 g. (37.9%) of γ -caprolactone- β -acetic acid, m.p. 98.4°C.

Reduction of β -Propionylglutaro-bis-lactone with Sodium Borohydride. To a solution of 53 g. (0.312 mole) of the

bislactone dissolved in 250 ml. of water containing 11 g. of potassium hydroxide, 12 g. of sodium borohydride was added in small quantities. The reaction was carried out in an Erlenmeyer flask, and the reaction mixture was continuously stirred with a magnetic stirrer. The addition was complete after three hours, and the solution was agitated for an additional six hours. It was then kept overnight at room temperature, whereupon large crystals of a potassium salt formed. The mixture was acidified with 6 N hydrochloric acid and extracted with ether in a continuous liquid-liquid extractor.

As the extraction proceeded for a period of 48 hours, crystalline product appeared in the ether flask. The product was identified as γ -caprolactone- β -acetic acid, m.p. 98.4°C . In all, 50 g. (0.291 mole) of pure product was obtained, a 93% yield.

Esterification of γ -Caprolactone- β -Acetic Acid.

(a) Via the Acid Chloride. Exactly 20 g. (0.116 mole) of γ -caprolactone- β -acetic acid was placed in a 500 ml. Erlenmeyer flask, equipped with a magnetic stirrer and a reflux condenser. To this 14 g. of thionyl chloride was added dropwise from the top of the condenser. After the addition, the mixture was refluxed on the steam bath for one hour. Fifteen ml. of benzene was added and the reaction mixture distilled to remove the unreacted thionyl chloride and benzene. The residue was not purified by distillation, but 25 ml. of absolute ethyl alcohol was added and the reaction

mixture refluxed on the steam bath for one hour. Ethyl alcohol was removed under reduced pressure, and the residue was fractionated through an efficient column. Exactly 22 g. (0.110 mole) of the ester, b.p. 133-36°C./0.08-0.09 mm., was obtained, 94% of the theoretical yield.

(b) Azeotropic Esterification. Fifty grams (0.295 mole) of γ -caprolactone- β -acetic acid was placed in a 500 ml. flask, and 200 ml. of absolute ethyl alcohol, 70 ml. of benzene and 15 ml. of concentrated sulfuric acid were added. The mixture was subjected to an azeotropic distillation for a period of 18 hours, after which benzene and most of the alcohol were drawn off. The residue was made neutral and extracted with ether. The ether solution was washed with sodium carbonate solution and dried over anhydrous sodium sulfate for 5 hours. After removing the ether, alcohol was removed under reduced pressure and the residue fractionated. There was obtained 48 g. (0.24 mole) of ethyl γ -caprolactone- β -acetate, a yield of 81%. Two grams of the residue in the pot was recovered and found to have a m.p. of 98.4°C. and hence was the unesterified acid.

Reaction of γ -Caprolactone- β -acetic Acid with Potassium Cyanide. The procedure was modelled after that described in Organic Syntheses(40). A mixture of 2.5 g. of the lactone and 2.5 g. of potassium cyanide was heated with continuous agitation on an oil bath at 180°-190°C. for five hours. The mixture became dark but maintained fluidity during this period.

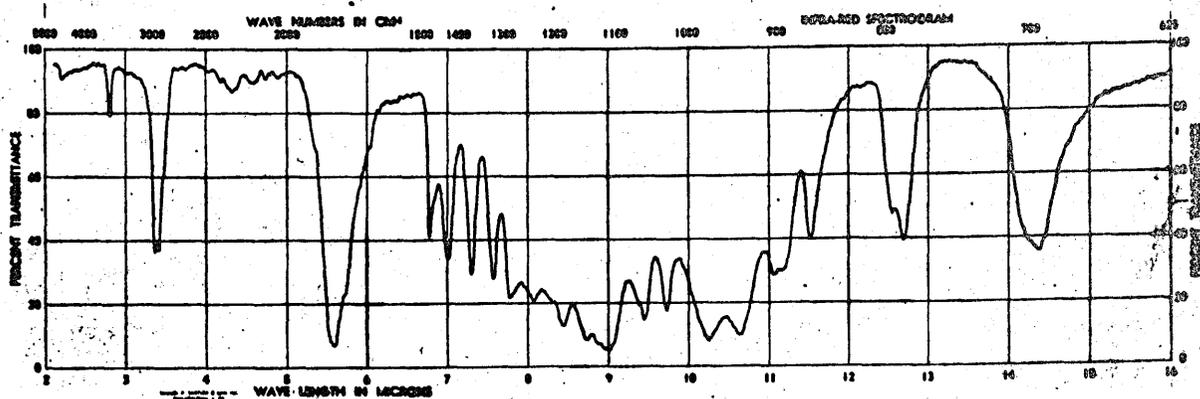


Fig. 1

β -Propionylglutarobis lactone

Carbonyl absorption Band $5.60 \mu = 1787 \text{ cm}^{-1}$

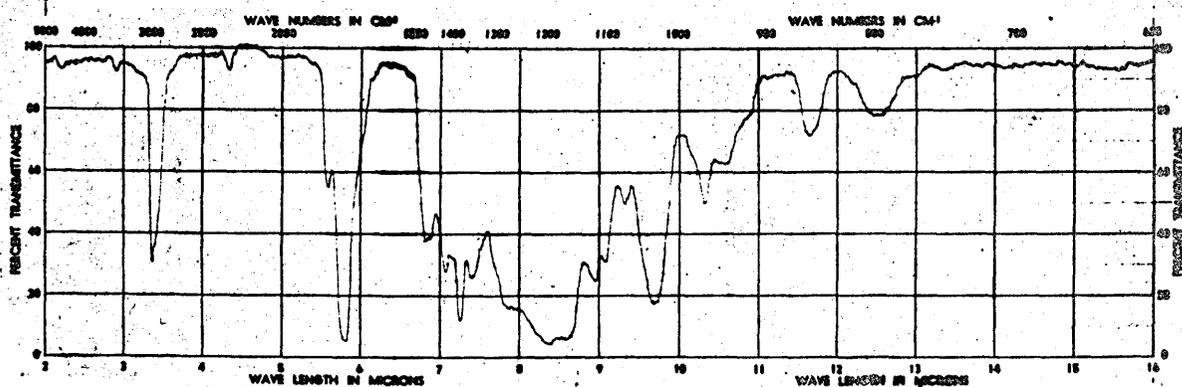


Fig. 2

Ethyl β -Propionylglutarate

Carbonyl absorption Bands $5.60 \mu = 1787 \text{ cm}^{-1}$

$5.81 \mu = 1721 \text{ cm}^{-1}$

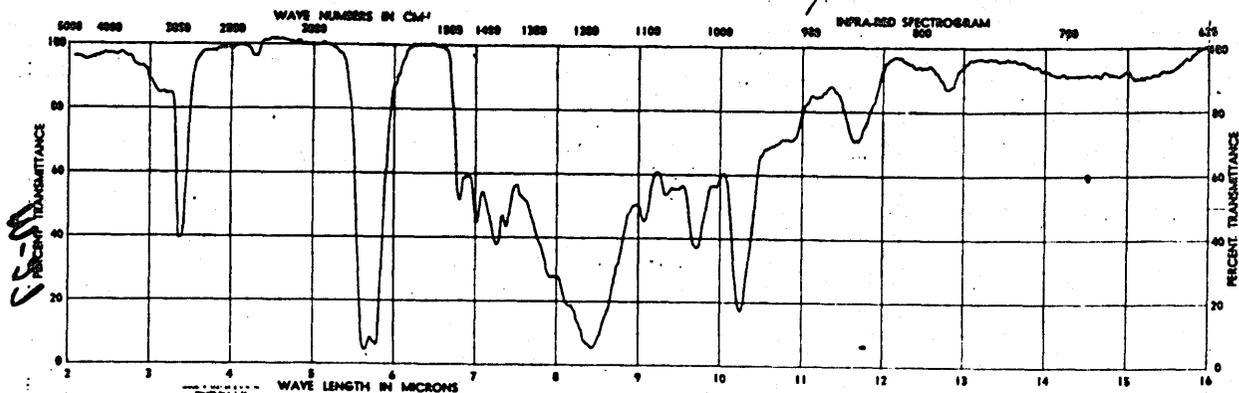


Fig. 3

Ethyl γ -Caprolactone- β -acetate

Carbonyl absorption Bands $5.63 \mu = 1778 \text{ cm}^{-1}$

It was dissolved in water, acidified with 6 N hydrochloric acid, extracted with ether and dried. On evaporation of the ether, a crystalline product was obtained. This was crystallized from boiling toluene, m.p. 98-98.4°C. The starting material had been recovered.

Reaction of Ethyl γ -Caprolactone- β -acetate with Potassium Cyanide (Cf. 40). Ten grams of the ester was mixed with 6 g. of potassium cyanide and heated on an oil bath at 280-300°C. for a period of 5 hours. The mixture was extracted first with water, and then with ether.

The aqueous extract was treated as follows: It was acidified with 6 N hydrochloric acid and extracted with ether and chloroform in succession. The combined organic layers were dried over anhydrous sodium sulfate (a large amount) overnight. On evaporation of the organic solvents some light yellow oily product, about 2 g., was obtained. The sodium fusion test for nitrogen was found to be positive. On standing for a few days, some crystalline product formed and was found to have a m.p. of 98°C. and contained no nitrogen. This was γ -caprolactone- β -acetic acid.

The crude non-crystalline residue may be the monoethyl ester of β -(1-cyanopropyl)-glutaric acid. In any event, the yield is very poor.

The ether extract of the reaction mixture gave a negligible amount of recovered ethyl γ -caprolactone- β -acetate.

Potassium β -(1-Hydroxypropyl)-glutarate. Nineteen grams

(0.11 mole) of γ -caprolactone- β -acetic acid was refluxed for four hours with 13 g. of potassium hydroxide in 100 ml. of water. The solution was then evaporated to dryness on the steam bath, and dried in a vacuum oven at 40°C. for two hours. Yield, 28 g. (0.105 mole), 95%.

Attempted Preparation of Ethyl β -(1-Chloropropyl)-glutarate. A mixture of 28 g. (0.105 mole) of the above potassium salt, 20 g. of phosphorus oxychloride and 5 g. of phosphorus pentachloride was refluxed on the steam bath for three hours. To this 100 ml. of absolute ethyl alcohol was added, whereupon a vigorous evolution of hydrogen chloride took place. The solution ^{WAS} refluxed for an additional half hour.

Next, most of the alcohol and phosphorus oxychloride was removed by distillation under reduced pressure. The residue was extracted with ether. The ether solution was extracted with sodium bicarbonate solution and then with water. The ether solution was dried over anhydrous sodium sulfate, filtered, and the ether evaporated.

On fractionation of the residue, the following fractions were obtained.

Fraction 1. b.p. = 92-96°/0.1 mm.

Bottom Temp. = 130-32°C. $[\bar{n}]^{21} = 1.3981$

Pot Temp. = 170-80°C.

14 g. of triethyl phosphate was collected

Fraction 2. b.p. = 133-34°/0.26 mm.

Bottom Temp. = 154-60° $[\bar{n}]^{21} = 1.4543$

Pot Temp. = 180°

5 g. of ethyl γ -caprolactone- β -acetate was obtained.

SUMMARY

1. Reaction of sodium tricarballylate with propionic anhydride gave an 80% yield of β -propionylglutarobislactone. The lactone was quantitatively hydrolyzed to β -propionylglutaric acid. An azeotropic esterification of the acid afforded a 63.5% yield of ethyl β -propionylglutarate. Reduction of the ester with sodium borohydride gave a 63% combined yield of ethyl γ -caprolactone- β -acetate and γ -caprolactone- β -acetic acid. Direct reduction of β -propionylglutarobislactone with sodium borohydride afforded a 93% yield of γ -caprolactone- β -acetic acid. Esterification of the acid via the acid chloride gave a 94% yield of ethyl γ -caprolactone- β -acetate, whereas an azeotropic esterification afforded an 81% yield of the ester. All of the above compounds are new to the literature.
2. β -Acetoglutaric acid was prepared by a known four step synthetic sequence, starting with ethyl acetoacetate and ethyl bromoacetate. A high temperature condensation reaction of β -acetoglutaric acid with homoveratrylamine gave a 25% yield of N,N'-dihomoveratryl- β -acetoglutaramide. A similar condensation could not be effected with β -propionylglutaric acid and homoveratrylamine.
3. β -Acetonylglutaric acid was prepared by a four step synthesis, starting with glycerol α,γ -dibromohydrin. A high temperature reaction between the acid and homoveratrylamine gave a small yield of a crystalline product of complex and incompletely determined structure.

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(c) Blaise, Compt. rend., 124, 89 (1897).
(d) Blanc, Compt. rend., 138, 579 (1904).