REATIONS OF 1-METHYL-4-HALO-4-PIPERIDYL PHENYL KETONE AND DERIVATIVES

HENRY JOSEPH TROSCIANIEC
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[Signature]
# TABLE OF CONTENTS

## I. INTRODUCTION .................................................. 1

## II. DISCUSSION ...................................................... 3

1. Preparation of Starting Materials ............................... 3
2. Reactions of 1-Methyl-4-halo-4-piperidyl Aryl Ketone Hydrohalides with Nucleophilic Agents ................................................................. 10
3. Reactions of 6-Methyl-2-alkoxy-2-aryl-1-ox-6-azaspiro(2,5)octanes with Organic and Mineral Acids ................................................................. 19
4. Reactions of 1-Methyl-4-hydroxy-4-piperidyl Phenyl Ketone ......... 25
5. Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide with Phenyl-Lithium ................................................................. 25
6. Reaction of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride with Phenyl-magnesium bromide ............................................................. 30
7. Catalytic Reduction of 1-Methyl-4-halo, hydroxy, acyloxy and aryl-4-piperidyl Phenyl Ketone Hydrohalides ............................................................. 34
8. Reduction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide with Sodium Borohydride ............................................................. 38
9. Reduction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide with Lithium Aluminum Hydride ............................................................. 46

## III. EXPERIMENTAL ..................................................... 59

1. Preparation of 1-Methyl-4-piperidyl Aryl Ketones ............... 60
2. Preparation of 1-Methyl-4-halo-4-piperidyl Aryl Ketone Hydrohalides ................................................................. 65
3. Reactions of 1-Methyl-4-halo-4-piperidyl Aryl Ketone Hydrohalides with Nucleophilic Agents ................................................................. 68
4. Preparation of 6-Methyl-2-alkoxy-2-aryl-1-ox-6-azaspiro(2,5)octanes ................................................................. 76
5. Reactions of 6-Methyl-2-methoxy-2-aryl-1-ox-6-azaspiro(2,5)octanes with Organic Acids ................................................................. 78
6. Preparation of 1-Methyl-4-hydroxy-4-piperidyl Aryl Ketones by Reaction of 6-Methyl-2-methoxy-2-aryl-1-ox-6-azaspiro(2,5) octanes with Hydrochloric Acid ................................................................. 89

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7. Reduction of 6-Methyl-2-methoxy-2-phenyl-1-oxo-6-azaaspiro(2.5)octane with Lithium Aluminum Hydride ........................................ 93
8. Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide with Phenyl-Lithium ......................................................... 94
9. Preparation of 1-Methyl-4-piperidylidene-α-benzoyloxy-α-phenylmethanol .............................................................. 97
10. Reaction of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride with Phenyl-magnesium bromide .................................................. 99
11. Reaction of Demerol (Ethyl 1-Methyl-4-phenylisonipecotate) Hydrochloride with Phenylmagnesium bromide .............................................. 107
12. Preparation of 1-Methyl-4-phenyl-4-piperidylidiphenylmethanol .......................................................... 108
13. Preparation of 1-Methyl-4-hydroxy-4-piperidylphenylmethane .......................................................... 109
14. Catalytic Reduction of 1-Methyl-4-halo, hydroxy and aryl-4-piperidyl Phenyl Ketone Hydrohalides .................................................. 111
15. Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide with Sodium Borohydride ...................................................... 116
16. Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide with Lithium Aluminum Hydride ................................................ 122
17. Preparation of 1-Methyl-4-benzyl-1,2,3,6,-tetrahydropyridine .......................................................... 135
18. Reaction of 1-Methyl-4-benzyl-1,2,3,6,-tetrahydropyridine with Alcoholic Potassium Hydroxide at High Temperatures ...................... 136
19. Reactions of 1-Methyl-1,2,3,6,-tetrahydro-4-pyridylphenylmethanol .......................................................... 139

IV. APPENDIX

1. Table I ........................................................................... 142
2. Table II ........................................................................... 143
3. Ultraviolet Absorption Spectrum of 1-Methyl-4-piperidylidene-α-benzoyloxy-α-phenylmethane Hydrobromide .......................................................... 144
4. Ultraviolet Absorption Spectra of Products Obtained from the Reduction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide with Sodium Borohydride ...................................................... 145
5. Ultraviolet Absorption Spectra of Products Obtained from the Reduction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide with Lithium Aluminum Hydride ...................................................... 146

V. SUMMARY ............................................................................. 147
VI. BIBLIOGRAPHY ................................................................. 153

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INTRODUCTION
INTRODUCTION

The investigation of the physical properties and reactions of α-haloketones has led to the discovery of many interesting features of these compounds which have two strong dipoles in close proximity.* A variety of different reaction pathways apparently are available for the α-haloketones to lose halogen, for acids (1) or their derivatives (2), epoxides (3) or acetals (4), saturated ketones (5), α-substituted ketones (6), and α-ethylenic ketones (7) have been isolated from such reactions. The relative importance of the factors which govern the particular pathway that the dehalogenation will follow have not been evaluated so that it is often difficult, if not impossible, to predict which type or types of compounds will arise as products from a given reaction of a α-haloketone. These factors include such variables as; the structure (8) and conformation (9) of the α-haloketone, the nature of the reagent (10), the solvent medium (11), the nature of the halogen (12), and the reaction conditions (13).

Although numerous acyclic, carbocyclic, aromatic, and aliphatic α-haloketones have been studied, heterocyclic α-haloketones have not been investigated to any great extent. In view of this, a study of the effect of a heterocyclic

*One important series of investigations concerning the conformation of cyclic α-haloketones is not pertinent to this Thesis but is reviewed (15) elsewhere.
ring system, containing a basic nitrogen atom, on the reaction of \( \alpha \)-haloketones could offer an important contribution to this area, and thus an investigation was undertaken. 1-Methyl-4-halo-4-piperidyl phenyl ketone (XIII) was selected for this purpose for the conformation of the groups could be predicted as being halo (axial) and benzoyl (equatorial) and the reaction products had the potential of being pharmacologically active. The latter advantage is particularly true of any 4,4-disubstituted piperidines which could result from this study. Considerable interest, in recent years, has developed in this class of compounds since the discovery of their value as synthetic pharmaceuticals (14).

The synthesis and reactions of 1-methyl-4-halo-4-piperidyl phenyl ketone (XIII) and its derivatives are herein described. Reactions characteristic of organic halogen and carbonyl compounds using nucleophilic, organometallic, and homolytic agents were investigated, and the way in which the influence of the heterocyclic ring system and the unreactive dipole altered the properties of the dipole undergoing reaction, was demonstrated.
DISCUSSION
DISCUSSION

The most direct method of synthesis of 1-methyl-4-halo-4-piperidyl phenyl ketone (XIII) appeared to be the halogenation of 1-methyl-4-piperidyl phenyl ketone (IXa). For this procedure to be practical it was necessary, therefore, to find a suitable synthesis of 1-methyl-4-piperidyl phenyl ketone (IXa).

The synthesis of 1-methyl-4-piperidyl phenyl ketone (IXa) has been accomplished by several different series of reactions. Grob and Renk (16) obtained a small yield of 1-methyl-4-piperidyl phenyl ketone (IXa) by the reaction of 1-methyl isonipecotonitrile with phenyl sodium. Villani (17a) converted 4-benzylpyridine to 1-methyl-4-piperidyl phenyl ketone (IXa) by sodium and alcohol reduction of the pyridine ring, methylation of the secondary nitrogen with formaldehyde and formic acid, and oxidation of the benzyl carbon to the carbonyl by chromic acid. The oxidation of 1-methyl-4-benzylpiperidine (LIV) to 1-methyl-4-piperidyl phenyl ketone (IXa) could be accomplished only in low yield thus making this approach undesirable also. Villani (17), however, was able to obtain satisfactory yields of 1-methyl-4-piperidyl phenyl ketone (IXa) by the Friedel-Crafts acylation of benzene with 1-methylisonipecotic acid chloride, which was prepared in three steps from isonicotinic acid. Finally, Sugimoto (18) reported the reduction of the methyl iodide salt of 4-benzoylpyridine (XIV) to 1-methyl-4-piperidyl-
phenylmethanol (XVII), which on subsequent oxidation by chromic acid gave 1-methyl-4-piperidyl phenyl ketone (IXa) in 70% yield.

Consideration of the steps involved and of the starting materials which were commercially available, the preparations of 1-methyl-4-piperidyl aryl ketones (IX) used in this study were the Friedel-Crafts procedure reported by Villani (17) and the oxidative method reported by Sugimoto (18). When this work was initiated, isonicotinic acid and methyl isonicotinate (I) were the only logical starting compounds commercially available* and necessitated the use of the procedure of Villani (17). During the course of this investigation 4-benzylpyridine and 4-benzoylpyridine (XIV) also were made available commercially and allowed a more comprehensive evaluation of the available methods.

The Friedel-Crafts approach to the synthesis of 1-methyl-4-piperidyl aryl ketones (IX) required methyl 1- methylisonipecotate (IV) which was prepared by either of two methods. By the first method (Procedure IA) methyl isonicotinate methobromide (II) was reduced over platinum oxide to the desired methyl 1-methylisonipecotate hydrobromide (III) which was easily converted to the desired compound (IV) on neutralization. The corresponding reduction with methyl isonicotinate methiodide was unsatisfactory for the reaction was slow and frequently gave partially reduced pyridines (19).

*Reiley Tar and Chemical Company.
A second satisfactory synthesis (Procedure IB) of methyl 1-methylisonipecotate (IV) followed the procedure of Feldkamp (20) for the preparation of ethyl 1-methylisonipecotate. Methyl isonicotinate (I) was reduced over platinum oxide in aqueous acetic acid to methyl isonipecotate (V), which was reductively methylated in acetic acid with formaldehyde over palladium-on-charcoal catalyst. Although both methods gave satisfactory yields of methyl 1-methylisonipecotate (IV), the limitation in the quantity of material that could be prepared in each run by Procedure IA due to the low solubility of the methyl bromide salt (II), made Procedure IB the more desirable process.

The methyl 1-methylisonipecotate (IV) obtained by either of these two methods was converted to the hydrochloride of 1-methylisonipecotic acid chloride (VIII) by hydrolysis with hydrochloric acid and subsequent reaction of the amino acid with thionyl chloride. The Friedel-Crafts acylation of benzene and toluene with this acid chloride gave 1-methyl-4-piperidyl phenyl ketone (IXa) and 1-methyl-4-piperidyl p-tolyl ketone (IXb)* in 80% yields. The corresponding Friedel-Crafts acylation of anisole, however, gave only a small amount of product which was not further characterized.

*That this ketone was indeed the para isomer and not the ortho or meta, was established from the infrared absorption spectra of derivatives of this ketone (see pages 19 and 90).
The synthesis of 1-methyl-4-piperidyl phenyl ketone (IXa) from 4-benzoylpyridine (XIV) (Procedure II), was accomplished by the procedure described by Sugimoto (18) as modified by Leone (21). The reduction of the pyridine ring and methylation of the nitrogen was achieved by hydrogenation of the 4-benzoylpyridine methobromide (XV) over platinum oxide. The reduction of the pyridine ring was accompanied by the reduction of the carbonyl group to produce 1-methyl-4-piperidylphenylmethanol hydrobromide (XVIa). Thus an oxidation with chromic acid was necessary to give the 1-methyl-4-piperidyl phenyl ketone (IXa) which was isolated in 80% overall yields. The catalytic hydrogenation of 4-benzoylpyridine methobromide (XV) required the use of platinum oxide as the catalyst since palladium-on-charcoal or Raney nickel catalyst resulted in incomplete reduction of the pyridine ring. A very sensitive indication of the presence of incompletely reduced materials was the production of an intense purple color on treatment of the hydrogenation mixture with base. This purple color was observed when the reduction was attempted with palladium-on-charcoal or Raney nickel catalysts and, in some instances, with platinum oxide. In the latter case however, the reduction could be completed by adding fresh catalyst and continuing the treatment with hydrogen. A neutral or acidic medium was required for the reduction of 4-benzoyl pyridine methobromide (XV) with platinum oxide, for in alkaline solution XV gave only a carbonaceous like solid.
The 1-methyl-4-piperidyl aryl ketones (IXa and IXb) as their hydrogen halide salts (X) were found to be halogenated readily by treatment with bromine or chlorine in chloroform. From each reaction the 1-methyl-4-halo-4-piperidyl aryl ketone hydrohalide (XII) was isolated as the per halide (XI). Since preliminary investigations revealed that reactions using the 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide per bromide (XIa) were complicated with respect to the isolation of the products, the 1-methyl-4-halo-4-piperidyl aryl ketone hydrohalide per halides (XI) were freed of the extra halogen by treatment with phenol in methanol. The per bromide free 1-methyl-4-halo-4-piperidyl aryl ketone hydrohalides (XII) were precipitated from the methanol solution by the addition of ether thus separating them from the halogenated phenols.

\[
\begin{align*}
\text{IX} & \quad \text{X} \\
\text{a, } R=H & \quad \text{a, } X=\text{Br}; \quad R=H \\
\text{b, } R=\text{CH}_3 & \quad \text{b, } X=\text{Cl}; \quad R=H \\
\text{c, } X=\text{Br}; \quad R=\text{CH}_3
\end{align*}
\]
l-Methyl-4-bromo-4-piperidyl phenyl ketone (XIIIa) was found to be unstable as the base, for a sample of the base prepared by neutralization of the hydrobromide (XIIa) with sodium bicarbonate darkened on standing overnight to give a red, ether insoluble oil. This probably results from dehydrohalogenation catalyzed by the basic nitrogen atom; however, the decomposition product was not investigated further. That the dehydrohalogenation was not rapid was ascertained by precipitation of the l-methyl-4-bromo-4-piperidyl phenyl ketone (XIIIa) hydrobromide or hydrochloride on treatment of the base, which had been obtained in the manner described above and had been dried for 20 minutes, with the appropriate hydrogen halide. l-Methyl-4-chloro-4-piperidyl phenyl ketone (XIIIb) on the other hand was quite stable as the base, for when l-methyl-4-chloro-4-piperidyl
phenyl ketone hydrochloride (XIIb) was neutralized and the base isolated in the manner employed for the bromo analog, the 1-methyl-4-chloro-4-piperidyl phenyl ketone (XIIIb) was recovered as its hydrochloride after standing for one week. These differences are not surprising in view of the fact that bromo compounds are known to be more reactive than their chloro analogs (22).

\[
\begin{align*}
\text{On Standing} & \rightarrow \text{Decomposed} \\
\text{XIIIa} & \xrightarrow{\text{HBr}} \text{Et}_2\text{O} \rightarrow \text{XIIa} \\
& \xrightarrow{\text{HCl}} \text{Et}_2\text{O} \rightarrow \text{XIIId}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{N} & \xrightarrow{\text{X}} \text{C} \xrightarrow{\text{O}} \text{X} \\
\text{XII} & \xrightarrow{1) \text{NaHCO}_3} \text{Et}_{2}\text{O} \xrightarrow{2) \text{Ether Extract}} \text{Dried 20 min.} \rightarrow \text{CH}_3\text{N} & \xrightarrow{\text{X}} \text{C} \xrightarrow{\text{O}} \text{X} \\
\text{a, X}=\text{Br} & \text{b, X}=\text{Cl} \\
\text{XII} & \xrightarrow{\text{On Standing}} \text{Stable} \\
\text{XIIIb} & \xrightarrow{\text{HCl}} \text{Et}_2\text{O} \rightarrow \text{XIIb}
\end{align*}
\]
The nature of the products from the reaction of 1-methyl-4-halo-4-piperidyl phenyl ketone (XIII) with sodium hydroxide or alkoxides was found to be largely dependent on the solvent. 1-Methyl-4-chloro-4-piperidyl phenyl ketone (XIIb) was recovered unchanged after being heated with powdered sodium hydroxide for 14 hours in ether. On the other hand, the greater reactivity of the bromo analog (XIIIa) was clearly demonstrated, by the reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIla), either as the hydrobromide XIIa or as the base XIIIa, formed by neutralization of XIIIa hydrobromide with butyl amine (thus avoiding formation of water of neutralization), with oven-dried sodium hydroxide in anhydrous ether. Yields as high as 46\% of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) were obtained from this reaction. The 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) thus formed, was characterized by analysis, and was converted to derivatives which in turn were analyzed. In addition, the infrared absorption spectrum of XVIIIa showed absorption of the OH stretching from 3400 cm.\(^{-1}\) to 3000 cm.\(^{-1}\), where CH absorption begins. The aromatic ketone of XVIIIa was indicated by the absorption of carbonyl stretching at 1660 cm.\(^{-1}\) and the mono-substituted benzene ring by absorption at 782 cm.\(^{-1}\) and 708 cm.\(^{-1}\). Absolute confirmation of this structure was obtained by the conversion of XVIIIa to 1-methyl-4-hydroxy-4-piperidyl diphenylmethanol (XIX), a compound prepared in these Laboratories (23) by an alternate method.
The reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIIa), formed from the hydrobromide by neutralization with sodium bicarbonate extraction into ether and drying of the ether extract for 20 minutes, with a suspension of sodium methoxide or ethoxide in ether again gave 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) in 60% yield. If however, the 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) were treated directly with sodium methoxide in ether, only a small amount of solid product could be isolated. This latter substance depressed the melting point of an
authentic sample of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) but was not further characterized. Apparently under the former conditions sufficient water was introduced through the neutralization process so that sodium hydroxide probably was the base present rather than the sodium alkoxides. Under the latter conditions however, probably the stronger base, sodium methoxide, was present in greater concentration and led to an increase in dehydrohalogenation decomposition products along with a small amount of an unidentified product, possibly, the dimethyl ketal of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XX). The susceptibility of the 1-methyl-4-halo-4-piperidyl phenyl ketone (XIII) to give dehydrohalogenation decomposition products was further demonstrated by the reaction of XIIIa hydroiodide with silver nitrate and diethylamine in methanol, and the reaction of XIIIb hydrochloride with sodium amide in ether; all of these reactions gave an uncharacterizable red oil similar to the spontaneous decomposition products of XIIIa.

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The reactivities of the 1-methyl-4-halo-4-piperidyl phenyl ketones (XIIa and XIIb) with sodium hydroxide and alkoxides in ether are contrary to that found in the cyclohexane series, for 1-chloro-1-benzoylcyclohexane on reaction with sodium hydroxide in ether has been reported to give a mixture of 1-phenylcyclohexane carboxylic acid and 1-benzoylcy clohexene by Tchoubar (10). On the other hand, from the reaction of sodium hydroxide in ether with 1-chloro (and bromo)-1-benzoylcyclohexane, Stevens (35) isolated 1-phenylcyclohexane carboxylic acid and 1-hydroxy-1-benzoylcyclohexane but no 1-benzoylcyclohexene. However, he did obtain 1-benzoylcyclohexene merely by refluxing the 1-halo-1-benzoylcyclohexanes in a water-dioxane mixture.

The failure to isolate the 1-methyl-1,2,3,6-tetrahydro-4-pyridyl phenyl ketone (LXVI), corresponding to 1-benzoylcyclohexene is attributed to the instability of the former. The instability of the tetrahydropyridyl system was encountered in other reactions studied in this series. For example, 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII) and 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine (LVI) were observed to decompose on standing.

The product of rearrangement, 1-phenylcyclohexane carboxylic acid, from 1-chloro-1-benzoylcyclohexane on reaction with sodium hydroxide in ether was first reported by Tchoubar (10). Subsequently, this reaction became of interest since 1-chloro-1-benzoylcyclohexane cannot form the cyclopropanone intermediate required by Loftfield's (36) mechanism for the Favorski (1b) rearrangement of α-haloketones to acids or
esters in the presence of base. As a result, Stevens (35) made a thorough examination of the reactions of the 1-halo-1-benzoylcyclohexane with sodium hydroxide. He established that the 1-halo-1-benzoylcyclohexane did produce the product of rearrangement, 1-phenylcyclohexane carboxylic acid on reaction with sodium hydroxide and was always accompanied with 1-hydroxy-1-benzoylcyclohexane. A generalization evolved from his study indicates that the formation of the 1-phenylcyclohexanecarboxylic acid from treatment of the 1-halo-1-benzoylcyclohexane with sodium hydroxide was favored by reaction in heterogeneous media and high boiling solvents while the 1-hydroxy-1-benzoylcyclohexane formation was favored in homogeneous reaction media.

Thus the failure to obtain any product of rearrangement in this series, which would have been Demerol (ethyl 1-methyl-4-phenylisonipecotate (XXXII) or a derivative, from the reaction of the 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIII) with sodium hydroxide in ether is attributed to the instability of the latter. The heterogeneous conditions used in these reactions (sodium hydroxide in ether) by analogy with Steven's results are favorable for rearrangement from the standpoint of the heterogeneous reaction conditions, but unfavorable from the standpoint of the low boiling solvent used. Recourse to a higher boiling solvent in which the reaction conditions remained heterogeneous, however, would be expected to hasten the basic nitrogen-catalyzed dehydrohalogenation leading to decomposition products.

The reaction of 1-methyl-4-bromo-4-piperidyl phenyl
ketone (XIIIa) with sodium alkoxides in ether also was contrary to that found in the cyclohexane series since the corresponding 1-bromo-1-benzoylcyclohexane is reported (37) to give 2-methoxy-2-phenyl-1-oxaspiro(2.5)octane with sodium methoxide in ether. Failure to obtain the corresponding 6-methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (or the ethyl analog) (XXIa and XXIb) in this series by the treatment of 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIIa) with sodium alkoxides in ether is again attributed to the instability of the 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIIa). As mentioned previously, the sodium alkoxide reactions with the 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIIa) obtained via the sodium bicarbonate neutralization process were probably reactions with sodium hydroxide, formed from the hydrolysis of the sodium alkoxides. However, it may be possible that some of the 6-methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) was formed in the reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIIa) with sodium methoxide in ether, but reacted further with the sodium methoxide to give the small amount of solid which was suggested to be the dimethyl ketal XX of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone. Dimethyl ketals of α-hydroxyketones have been isolated from the reactions of α-haloketones with sodium alkoxides in ether (4).

The importance of the solvent in determining the reaction products of the 1-methyl-4-halo-4-piperidyl phenyl ketones (XIIIa and XIIIb) was amply demonstrated by their reaction with base in an alcoholic medium. 1-Methyl-4-bromo-4-piperidyl...
phenyl ketone hydrobromide (XIIa) when heated under reflux with sodium hydroxide or sodium methoxide in anhydrous methanol or with sodium methoxide in commercial grade methanol gave 80% yields of 6-methyl-2-phenyl-1-ox-6-azaspiro (2.5)octane (XXIa). XXIa was obtained also by the reaction of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) with sodium methoxide in boiling methanol. With sodium ethoxide in boiling ethanol 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) gave an 82% yield of 6-ethyl-2-ethoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIb); however, when a bulkier base was used, sodium t-butoxide in t-butyl alcohol, apparently dehydrohalogenation resulted since a red oil was obtained from which only a small amount of solid, probably crude 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa), was isolated.

This reaction was also successful for the preparation of 6-methyl-2-(p-tolyl)-1-ox-6-azaspiro(2.5)octane (XXIc) from XXIc with sodium methoxide in refluxing methanol. The epoxyether (XXIc) was prepared as an intermediate for further synthesis (See Table I ).

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The infrared absorption spectra of the epoxyethers XXIa and XXIc did not show absorption in the OH or carbonyl stretching regions. The spectra of both XXIa and XXIc showed a strong band at $1075 \text{ cm}^{-1}$ characteristic of aliphatic ethers and two strong bands, one at $1280 \text{ cm}^{-1}$ and another at $1220 \text{ cm}^{-1}$ which are indicative of the epoxide ring. In addition, the spectrum of XXIa showed strong bands at $745 \text{ cm}^{-1}$ and $700 \text{ cm}^{-1}$ to be expected for a mono-substituted benzene ring; while the spectrum of XXIc did not show absorption at $700 \text{ cm}^{-1}$ but showed a strong band at $823 \text{ cm}^{-1}$ as would be expected for a para-substituted benzene ring. The latter observation was used to establish that the $1$-methyl-$4$-piperidyl $p$-tolyl ketone (IXc), from which the epoxyether XXIc was derived, prepared by the Friedel-Crafts reaction (see page 5) was indeed the para isomer.

Epoxyethers (compounds of the type XXI) are a relatively new class of compounds in the field of organic chemistry. Since 1929 when Ward (4a) investigated the displacement of chlorine from desyl chloride, epoxyethers have appeared in the literature (2b, 4b, 39) as intermediates in several synthesis, but an epoxyether was not knowingly isolated until 1949. Temnikova (3a) and Stevens (3b) at that time independently reported the first actual isolation of an epoxyether. Since then, the latter author has published a number of excellent papers (38) on the chemistry of this class of compounds.

One of the most characteristic reactions of the epoxyethers observed by Stevens, is their rapid, exothermic, acid-
catalyzed ring opening reactions. However, exception to this behavior was found by Stevens for an amino epoxyether (XXII), 1-phenyl-1-(2-dimethylamino)-ethoxy-2-methyl-1,2-epoxypropane (40) which was noted to be quite resistant to acid hydrolysis. To rationalize this difference Stevens suggested that the positive charge developed on the nitrogen atom in acidic media, effectively hindered the further approach of a proton to catalyze the ring-opening reaction. This observation and hypothesis are of interest, since the only other epoxyether known to this date which contains a basic nitrogen atom within the same molecule is the epoxyether XXI prepared in this study. In marked contrast to the behavior of Stevens' amino epoxyether (XXII), the epoxyether XXI was found to be attacked readily by acid conditions to lead to products of ring opening. Mineral acids such as hydrogen chloride either in aqueous or ether medium hydrolyzed the epoxyether to give 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) in quantitative yields. Similarly on treatment of the epoxyether XXI with hydroxyl amine hydrochloride in pyridine or with picric acid in methanol, the oxime and picrate of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) were isolated in near quantitative yields.

\[
\text{XXII}
\]

A possible explanation of the differences between the epoxyether XXI and Stevens' epoxyether XXII arises on closer
examination of the structure of the two epoxyethers. A feature common to the amino epoxyether XXII and the epoxyether XXI is that both contain the basic nitrogen atom three atoms removed from the cyclic acetal carbon. However, an essential difference is that in the former the nitrogen atom is incorporated in a side chain which, due to freedom of movement, would be more disposed to exert proximity effects on protonation than the nitrogen atom held in the relatively rigid ring system of XXI. Steric considerations are apparently not involved since no difficulty was encountered in the reaction of the amino epoxyether XXII with an organic acid (see below).

Similar to the observations made by Stevens, the epoxyether XXI was found to undergo reaction with organic acids to give 1-methyl-4-acyloxy-4-piperidyl aryl ketones (XXIV). The relative ease of formation of the epoxyether XXI and its facile ring opening by organic acids allowed the use of this reaction for the preparation of a series of 1-methyl-4-acyloxy-4-piperidyl aryl ketones (XXIV) for testing for potential pharmacological activity. The synthesis of these compounds via acylation of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) did not seem feasible since in a preliminary investigation treatment of XVIIIa with benzoyl chloride in ether gave XVIIIa hydrochloride.

The method of preparation and the compounds XXIV prepared in this series are listed in Table I. In general, the 1-methyl-4-acyloxy-4-piperidyl aryl ketones (XXIV) were prepared by the addition of 6-methyl-2-methoxy-2-phenyl(and
n-tolyl)-1-ox-6-azaspiro(2.5)octane (XXIa and XXIc) in ether to an excess of an organic acid in ether or an ether-methanol mixture depending on the solubility of the organic acid. The 1-methyl-4-acyloxy-4-piperidyl aryl ketones (XXIV) precipitated as their organic acid salts (XXIII). The XXIII were then neutralized to the base with sodium carbonate, and the base was converted to the hydrochloride or quaternary salt.

From the reaction of mandelic and p-aminobenzoic acids with the epoxyether XXIa, 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) was isolated as the sole product. Failure to obtain 1-methyl-4-(p-aminobenzoxyloxy)-4-piperidyl phenyl ketone (XXIVf) could result from the zwitterion nature of p-aminobenzoic acid. Thus attempts were made to circumvent this difficulty by modification of the amino group.
In one approach the desired \( p \)-aminobenzoyloxy compound XXIVf was anticipated from the hydrolysis of the corresponding \( p \)-acetamido compound. However, the reaction of \( p \)-acetamido-benzoic acid with the epoxyether XXIa gave a product for which no reasonable structure could be deduced from the analytical data of the hydrochloride of the product. In a second approach the desired \( p \)-aminobenzoyloxy compound XXIVf was anticipated from the reduction of the corresponding \( p \)-nitro compound. Thus, the reaction of \( p \)-nitrobenzoic acid with the epoxyether XXIa apparently gave 1-methyl-4-(\( p \)-nitrobenzoyloxy)-4-piperidyl phenyl ketone (XXIVe). Reduction of the latter compound with Raney nickel catalyst gave a nickel complex, and with Adams catalyst the carbonyl and not the nitro group underwent reduction. In view of the ultimate success of obtaining XXIVf by a third approach (see below) that was being conducted simultaneously, these reduction products were not investigated further.

The difficulty in the preparation of 1-methyl-4-(\( p \)-aminobenzoyloxy)-4-piperidyl phenyl ketone (XXIVf) was finally resolved by altering the solvent medium for the reaction of \( p \)-aminobenzoic acid with the epoxyether XXIa. Since \( p \)-aminobenzoic acid probably exists as a zwitterion which interfered with the desired reaction, a basic solvent was used to convert the zwitterion to the anion form. As a result the reaction of \( p \)-aminobenzoic acid with the epoxyether XXIa was carried out in pyridine, and 1-methyl-4-(\( p \)-aminobenzoyloxy)-4-piperidyl phenyl ketone (XXIVf) was isolated in nearly quantitative yield. A similar reaction of isonicotinic acid with the epoxyether
XXIa in pyridine gave 1-methyl-4-isonicotinoyloxy-4-piperidyl phenyl ketone (XXIVg).

On treatment of the epoxyether XXII with methyl iodide in ether, Stevens obtained the XXII methiodide without hydrolysis of the epoxide ring (40). On treatment of the epoxyether XXIa with methyl iodide in ether, an unidentified solid which was difficult to purify was obtained. When methanol was used as the solvent, treatment of the epoxyether XXIa with methyl iodide gave a quantitative yield of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) methiodide. The infrared absorption spectrum of XVIIIa methiodide showed the absorption of OH stretching at 3300 cm\(^{-1}\) and the absorption of carbonyl stretching of the aromatic ketone at 1670 cm\(^{-1}\). Comparable results were obtained, however, when the epoxyether XXIa was treated with lithium aluminum hydride in ether. An 84.5% yield of 1-methyl-4-hydroxy-4-piperidyl-\(\alpha\)-methoxy-\(\alpha\)-phenyl-methane (LX) was obtained, similar to a methoxy alcohol obtained by Stevens on treatment of an epoxyether with lithium aluminum hydride (53). The infrared absorption spectrum of LX showed strong absorption due to OH stretching from 3600 cm\(^{-1}\) to 3000 cm\(^{-1}\), the region where OH absorption begins and the aliphatic ether was indicated by absorption at 1093 cm\(^{-1}\).

Since the epoxyether XXI was hydrolyzed quantitatively to 1-methyl-4-hydroxy-4-piperidyl aryl ketones (XVIIIa and XVIIIb) by mineral acids, this method was used for the preparation of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) and 1-methyl-4-hydroxy-4-piperidyl \(p\)-tolyl ketone (XVIIIb). Both XVIIIa and XVIIIb were tested for potential
pharmacological activity and the results are listed in Table II.

In contrast to the α-haloketone (XIII), the α-hydroxyketone (XVIII) was ascertained to be quite stable. The hydroxyl group of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) did not undergo either replacement or elimination in aqueous hydrochloric or hydrobromic acid solutions. For treatment of XIIIa with sodium hydroxide in water-methanol mixture, acidification with hydrochloric acid of this mixture and evaporation to dryness of the acid solution, produced XVIIIa. The XVIIIa was isolated as the hydrobromide rather than the hydrochloride on extraction of the salt residue, due to the greater insolubility of hydrobromide salts. The hydrobromide or hydrochloride of XVIIIa was similarly isolated on evaporation to dryness of the respective aqueous acid solutions in which XVIIIa had been dissolved. The hydroxyl group of XVIIIa, as mentioned previously on page 21 was not acylated on treatment of XVIIIa with benzoyl chloride in ether, but the carbonyl group readily was converted to an oxime by either of the standard procedures (25). The oxime of XVIIIa was reduced catalytically over Adams catalyst to an oil which was not further investigated but which probably was 1-methyl-4-hydroxy-4-piperidyl-α-amino-α-phenylmethane (LXIV).

The influence of the halogen on the reactions of the carbonyl group of 1-methyl-4-halo-4-piperidyl phenyl ketone (XIII) was demonstrated by the reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) with phenyllithium
and 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) with phenylmagnesium bromide. The reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) with phenyllithium in ether gave a 30% yield of 1-methyl-4-piperidyl phenyl ketone (IXa) and a 32% yield of 1-methyl-4-piperidyl-diphenylmethanol (XXV). Since the products of the reaction contained hydrogen at the carbon originally having the bromine substituent and no rearrangement had occurred, apparently the halogen had undergone a metal-halogen interchange as the first step. Such a reaction would produce the anion XXVIa or XXVIb, corresponding to one of the resonanace forms of XXVI. On hydrolysis this intermediate XXVI would of course produce 1-methyl-4-piperidyl phenyl ketone (IXa). It would be difficult, however, to explain the attack of a second phenyllithium on this anion to form the second product, 1-methyl-4-piperidyl-diphenylmethanol (XXV). Thus a more plausible explanation for the formation of XXV might be the reaction of phenyllithium with IXa during a slow hydrolysis of the reaction mixture. This hypothesis is supported by the previously observed facile reaction of 1-methyl-4-piperidyl phenyl ketone (IXa) with phenyllithium.
This view was substantiated by the isolation of only 3.6% yield of 1-methyl-4-piperidylphenylmethanol (XXV) and an 88% yield (crude) of 1-methyl-4-piperidyl phenyl ketone (IXa) when the reaction mixture of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) with phenyllithium was hydrolyzed by dropwise addition to an aqueous hydrochloric acid solution.

Indirect proof of the nature of the intermediate XXVI, was obtained by the conversion of the anion to a more stable product. Thus, after 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) had been treated with phenyllithium as in previous reactions, the reaction mixture was treated with benzoyl chloride. 1-Methyl-4-piperidylidene-α-benzoyloxy-α-phenylmethane (XXVII) was isolated as the hydrobromide in 54% yield. Characterization of XXVII was based on the analysis of the hydrobromide and the picrate and the physical and chemical properties. The presence of the PhC—C— system was indicated by the ultraviolet absorption spectrum of XXVII hydrobromide. An absorption maximum at 253 μm with a Log value of 4.424 was observed and is characteristic of this system. The infrared absorption spectrum of XXVII hydrobromide showed bands at 1660 cm.⁻¹, 1240 cm.⁻¹, and 1160 cm.⁻¹ characteristic of the PhCOO group. (For the ultraviolet absorption spectrum of XXVII hydrobromide see page 144). Further evidence for the structure of XXVII was obtained by the quantitative isolations of 1-methyl-4-piperidyl phenyl ketone (IXa) and benzoic acid from the hydrolysis of XXVII with aqueous hydrochloric acid.
From the foregoing experimental results, the conclusion follows that 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIa) undergoes reaction with phenyllithium largely if not completely to give metal-halogen interchange rather than addition to the carbonyl double bond. From the reactions of organolithium compounds with other halogen containing organic compounds, the ease of metal-halogen interconversion appears to be directly proportional to the degree of positive polarization of the halogen atoms (41). The halogen of the haloketone (XIII) studied here thus was shown to be extremely positive in nature, for XIII underwent the metal-halogen interconversion with ease and in high yield. This positive character of the bromine atom is undoubtedly caused by the adjacent carbonyl group, which through resonance and inductive effects has decreased the electron density on the neighboring atoms. That the carbonyl oxygen does have a high electron density was supported by the reaction of the intermediate XXVI with benzoyl chloride to form the product of O-acylation, XXVII, rather than one of C-acylation, XXVIII.

\[
\begin{align*}
\text{XXVIII}
\end{align*}
\]
l-Methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) on reaction with phenylmagnesium bromide, in addition to undergoing the metal-halogen interchange encountered in the phenyllithium reaction, gave some addition to the carbonyl double bond. The reaction of l-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) with phenylmagnesium bromide in ether, on slow hydrolysis of the reaction mixture by the dropwise addition of water, gave yields of 36% of l-methyl-4-piperidyl phenyl ketone (IXa), 34% of l-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX), 18% of l-methyl-4-phenyl-4-piperidyl diphenylmethanol (XXX), and 33% of l-methyl-4-piperidyl diphenylmethanol (XXV). These yields are based on the isolated products of two reactions, one for the ketones and the second for the alcohols. The yields of the ketones IXa and XXIX are considered the maximum possible yields since they are based on the crude distillates obtained from a mixture of the four components from which most of the alcohols XXV and XXX were removed. Since the alcohol XXX formed a very insoluble hydrobromide, the yield of XXX is considered to be representative since the same value was obtained from several reactions. The yield of XXV is a maximum yield based on non crystalline hydrobromide from which XXX had been removed. The reaction mixture was decomposed by the slow, dropwise addition of water so that the ketone IXa, considered to be present in the reaction mixture as the magnesium halide enolate, might be converted completely to the alcohol XXV during the hydrolysis thus giving only three products to separate. This modification, however, did not allow the
complete conversion of IXa to XXV, apparently due to the slow reaction of IXa with phenylmagnesium bromide, for yields as high as 36% of IXa were isolated. The alcohol XXV could be isolated from the other three components only as a crude oil which as a maximum represented a 33% yield. However, as was found with the phenyllithium reaction, the formation of 1-methyl-4-piperidyldiphenylmethanol (XXV) was eliminated by dropwise addition of the reaction mixture to a hydrochloric acid solution. The formation of 1-methyl-4-phenyl-4-piperidyl-diphenylmethanol (XXX) was not affected by this modification since it was isolated in 10% yield along with 20% of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) regardless of the method of hydrolysis. Thus it would appear that the obvious precursor, 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX), for the formation of 1-methyl-4-phenyl-4-piperidyldiphenylmethanol (XXX), existed in the reaction mixture as such, i.e. it was not bound as a metal complex or salt (compare this with the formation of XXV in the phenyllithium reaction).

Thus phenylmagnesium bromide underwent reaction with the 1-methyl-4-chloro-4-piperidyl phenyl ketone (XIIIb) partially by addition to the carbonyl double bond, since the most plausible (42) method of formation of the 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) would be via the halo-magnesium salt of the halohydrin, XXXI, which on rearrangement during the reaction gave the 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX). The 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) thus formed on further reaction with the phenylmagnesium bromide produced the 1-methyl-4-phenyl
4-piperidyldiphenylmethanol (XXX). The explanation for the failure of the complete conversion of the 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) to 1-methyl-4-phenyl-4-piperidyldiphenylmethanol (XXX) in the reaction mixture lies in the steric retardation of addition to the carbonyl double bond by the bulky phenyl group on the C-4 carbon of the piperidine ring in XXIX. Evidence in support of this view was encountered in other reactions of compounds in this series with organometallic agents. Demerol (XXXII), a compound which also contains a bulky phenyl group on the C-4 carbon, was recovered in 88% on treatment with phenylmagnesium bromide in ether. However, that the phenyl group retarded and not completely inhibited reaction with organometallic agents was demonstrated by the conversion of a Demerol derivative, 1-methyl-4-phenylisonipecotonitrile XXXIII to 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) by reaction with phenylmagnesium bromide in ether and the subsequent conversion of the 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) to XXX by reaction with phenyllithium in ether under prolonged reflux.

\[
\begin{align*}
\text{CH}_3\text{N} & \quad \text{Cl} \quad \text{Cl} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{OH} \\
\text{HCl} & \quad \text{PhMgBr,} \quad \text{Et}_2\text{O} \quad \text{H}_2\text{O} \\
\text{XIIb} & \quad \text{IXa} \quad \text{XXV} \\
\quad & \quad \text{XXIX} \quad \text{XXX}
\end{align*}
\]
In general, organolithium compounds undergo all the reactions that are characteristic of the well-known Grignard reagents. However, it will be recalled that in the reaction of phenyllithium with the haloketone XIII, the reaction proceeded completely via metal-halogen interconversion. The reaction of the haloketone XIII with phenylmagnesium bromide might be said to have undergone only 50% of this type of metal-halogen interconversion. To explain this difference it is necessary to consider both the nature of the reagent and the nature of the halogen. Organolithium compounds
because of steric considerations have been found to be more reactive than their Grignard analogs (43). Similarly, the bromine of organic halides has been observed to be more positive in nature than the chloro analog (44). Thus the conditions for metal-halogen interconversion were more favorable with phenyllithium than with the Grignard reagent so that these differences would be expected.

The possibility of obtaining a α-halohydrin, 1-methyl-4-halo-4-piperidylphenylmethanol (XXXIV), which might serve as a useful synthetic intermediate, from the reduction of the 1-methyl-4-halo-4-piperidyl phenyl ketone (XIII) led to some interesting observations of the behavior of the halogen and carbonyl groups in this heterocyclic system. Catalytic hydrogenation in methanol of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) and 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb), or the latter in a methanolic sodium carbonate solution, over platinum oxide catalyst gave 1-methyl-4-piperidylphenylmethanol (XVII). Apparently reduction of the carbonyl group in XIIa and XIIb was facilitated in some manner by the presence of the halogen in the 4-position, since according to the observation of Leone (21) 1-methyl-4-piperidyl phenyl ketone hydrobromide (Xa) under similar conditions could not be reduced to XVII. Because of the polar nature of the halogen it could aid in the adsorption of the molecule on the surface of the catalyst (as depicted in Figure I).
This view found support in part from the observations of catalytic hydrogenation of other compounds in this series. For 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) as the hydrochloride, a compound which also bears a polar atom on the C-4 carbon, readily underwent carbonyl reduction over platinum oxide in methanol to give 1-methyl-4-hydroxy-4-piperidylphenylmethanol (XXXV). Under similar conditions the acetate derivative of XVIIIa, with hydrochloric acid added, was observed by Leone (21) to undergo carbonyl reduction. Also the p-nitrobenzoate (XXIVe) of XVIIIa as was mentioned previously (see page 23) appeared to undergo reduction of the carbonyl. Thus, the juxtaposition of a polar group on the C-4 carbon of IXa gave products of carbonyl reduction. However, a non-polar bulky group on the C-4 carbon of IXa in addition to increasing not the attraction of the molecule to the surface of the catalyst might in fact retard the adsorptive process thru steric considerations. Thus, when 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) hydrochloride was
treated with hydrogen over platinum oxide in methanol apparently only partial reduction of the carbonyl occurred. There was no appreciable change in the hydrogen pressure, and the product that was isolated appeared to be a mixture, melting only slightly below that of the original compound. The infrared absorption spectrum of the mixture showed the absorption of the stretching carbonyl of the aromatic ketone at 1680 cm.\(^{-1}\) and the absorption due to OH stretching from 3600 cm.\(^{-1}\) to 3200 cm.\(^{-1}\) indicating that only partial reduction occurred.

The juxtaposition of a polar group on the C-4 carbon of IXa was not the only factor found to govern the possibility of carbonyl reduction. For when 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) was treated with hydrogen over palladium-on-charcoal in methanol or platinum oxide in chloroform the product was one of reductive dehalogenation and not carbonyl reduction, namely, 1-methyl-4-piperidyl phenyl ketone (IXa). Similarly, carbonyl reduction of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) hydrochloride was retarded when it was treated with hydrogen over platinum oxide with chloroform as the solvent. The product isolated was a mixture.

The influence of a polar group and solvent on the course of hydrogenation has found parallel in a hydrogenation of a codeinone derivative XXXVI by Conroy (45). On hydrogenating 14-bromocodeinone (XXXVI), Conroy found that the reductive removal of the bromine atom was accompanied with a shift of a double-bond out of conjugation with a carbonyl group to give neopinone (XXXVII). To rationalize this odd behavior he
suggested that in the transition state XXXVI would acquire the position shown in Figure II because of the attraction of the molecule to the surface of the catalyst by the bromine atom. The cleavage of the C-Br bond might then occur by the removal of the bromine by a hydrogen atom with concomitant attack of hydrogen on the C-7 carbon, a position perfectly accessible to the catalyst, resulting in a shift of the double-bond to the C-8 - C-14 position. In addition, Conroy found the hydrogenation of 14-bromocodeinone (XXXVI) to neopine (XXXVII) to be solvent dependent. With chloroform as the solvent the hydrogenation did not proceed to any great extent, but the addition of a slight amount of methanol resulted in a rapid increase in the rate. This solvent dependenc, he suggested, might be merely associated with the adsorptive or desorptive process and not be mechanistically significant.

![Figure II](image_url)
In view of the facile reductive dehalogenation of 1-methyl-4-halo-4-piperidyl phenyl ketone (XIII) by metal catalyst, the possibility of obtaining the α-halohydrin XXXIV by reduction of XIII with metal hydrides was investigated. Reduction of α-haloketones with sodium borohydride has been reported to give α-halohydrins and in no case has reduction of the halogen or change in the skeletal system been reported (46). From the reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) with sodium borohydride, however, no α-halohydrin was isolated. Instead a novel type of rearrangement was encountered.

Treatment of XIIa in methanol by the inverse addition of sodium borohydride at room temperature in methanol produced a 73.7% yield of compound XXXVIII and a small amount of an intractable oil, assumed to be the dehydrohalogenation decomposition product of XXXVIII. XXXVIII was found to be very unstable as the base, since on standing it gave an orange intractable oil. XXXVIII could not be distilled under reduced pressure for at a pressure of 5 mm. the colorless XXXVIII turned orange within 15 seconds after the distillation flask was immersed in a woods metal bath at 90°. On raising the temperature of the metal bath to 260° no distillate was obtained and the colorless XXXVIII changed to a dark red oil. A Volhard analysis (acid medium) of the crude XXXVIII, after it had stood for several hours at room temperature, showed only 2-4% bromine to be present. The addition of ether to this same crude XXXVIII produced an oily precipitate indicating that XXXVIII on standing dehydrohalogenated, forming the hydro-
bromides of the resulting mixture.

XXXVIII could be converted to its stable hydrobromide if it were treated with dry hydrogen bromide in ether shortly after its isolation. The C, H, and Br analysis of the hydrobromide of XXXVIII indicated the compound to have an empirical formula C13H17Br2N. A Volhard analysis (acid medium) was used to determine the halogen, and with this method of analysis both of the bromine atoms were titrated as ionic indicating that XXXVIII hydrobromide possessed a very reactive bromine substituent in addition to the hydrobromide bromine. The infrared absorption spectrum of XXXVIII hydrobromide showed no absorption in the OH and C=O stretching regions, but showed the presence of a mono-substituted benzene ring by absorption at 747 cm.\(^{-1}\) and 700 cm.\(^{-1}\). The presence of the Ph-C=C- system in XXXVIII hydrobromide was indicated by the ultraviolet absorption spectrum of XXXVIII hydrobromide. An absorption maximum at 247.5 m\(\mu\) (Log \(\varepsilon\) 4.228) was observed and is characteristic of the disubstituted styrene system. Similarly, an absorption maximum at 249.5 m\(\mu\) (Log \(\varepsilon\) 3.794) was observed on a crude sample of XXXVIII prior to conversion to its hydrobromide.

The reduction of XXXVIII hydrobromide with lithium aluminum hydride in ether gave a 78.7% yield of XXXIX as an oil. XXXIX gave a negative Beilstein test indicating that reductive dehalogenation of XXXVIII had occurred. That the Ph-C=C- system, present in XXXVIII, was not destroyed by treatment of XXXVIII hydrobromide with lithium aluminum hydride was indicated by the ultraviolet absorption spectrum of XXXIX.
for an absorption maximum of 245 μν (Log ε 4.144) was observed on determination of the ultraviolet absorption spectrum of XXXIX. XXXIX was converted to its hydrobromide which had a melting point considerably lower than XXXVIII hydrobromide and 1-methyl-4-benzilidene piperidine (LIIIA) hydrobromide (see page 145). Similarly, the ultraviolet absorption spectrum of XXXIX hydrobromide showed the presence of the Ph—C=C— system found in the base XXXIX; λ max 245.5 μν (Log ε 4.191). XXXIX was also converted to the methiodide, XL, which depressed the melting point of 1-methyl-4-benzilidene piperidine (LIIIA) methiodide (see page 145). The methiodide XL on catalytic hydrogenation over platinum oxide gave a saturated compound believed to be 1-methyl-4-phenyl-1-aza-cycloheptane methiodide (XLI). 1-Methyl-4-phenyl-1-aza-cycloheptane methiodide (XLI), depressed the melting point of XL and the melting point of 1-methyl-4-benzylpiperidine (LIV) methiodide. This indicates that the double bond present in XL was reduced on catalytic hydrogenation and that XXXVIII, XXXVIII hydrobromide, XXXIX and XL did not have a 4-substituted piperidine skeletal system. The ultraviolet absorption spectrum of XLI (see page 145) was observed to have a Log ε value of only 2.538 at 246 μν, the region of absorption of the Ph—C=C— system, indicating the absence of this system. Absorption maxima were observed at 258 μν (Log ε 1.614), 265 μν (Log ε 1.356), and 268 μν (Log ε 1.238). This absorption is characteristic of a non-conjugated benzene ring.
On the basis of the experimental evidence presented, the structure of the product XXXVIII from the reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) with sodium borohydride must meet the following requirements.

A Ph-C=C- system must be present since the ultraviolet absorption spectra of XXXVIII, XXXVIII hydrobromide, the reductively dehalogenated product, XXXIX, and the hydrobromide of the latter all were observed to have absorption maximum at a wavelength characteristic of this system. Since 1-methyl-4-benzylpiperidine (LIV) methiodide was not the product of catalytic hydrogenation of XL, the carbon skeletal system of XXXVIII must be a substituted pyrrolidine XLII, a 3-substituted piperidine XLIV or a phenyl-substituted azacycloheptene XXXIX.

\[
\text{CH}_2\text{N-CH=CH-Ph} \xrightarrow{[\text{H}]} \text{CH}_2\text{N-CH=CH-CH}_2\text{CH}_2\text{-Ph}
\]

\[
\text{CH}_3\text{N-CH=CH-Ph} \xrightarrow{[\text{H}]} \text{CH}_3\text{N-CH=CH-CH}_2\text{CH}_2\text{-Ph}
\]
Of the three possible ring systems the five-membered ring 
XLII is not favored on the basis of the ultraviolet absorption 
spectra of XXXIX and XXXIX hydrobromide. The juxtaposition 
of a substituent on the \( \xi \)-carbon of styrene has been observed 
to have little effect on the absorption spectrum of styrene 
which has maxima of absorption at about 290 \( \mu \mu \), 280 \( \mu \mu \), 273 \( \mu \mu \), 
and 245 \( \mu \mu \) (47). If there are two \( \xi \)-substituents (48) or a 
\( \alpha \)-substituent (47) on styrene, the 290, 280, and 270 maxima 
disappear which results in an absorption maximum only at 245 \( \mu \mu \) 
due to steric inhibition of resonance (47). Thus, the five-
membered ring compound XLII would have been expected to have 
maxima of absorption in the region of 290 \( \mu \mu \), 280 \( \mu \mu \), and 
273 \( \mu \mu \), since XLII possess only a single \( \xi \)-substituted styrene 
structure. However, the ultraviolet absorption spectrum of 
XXXIX was observed to have a maximum of absorption at only 
245 \( \mu \mu \), which would be expected for the \( \alpha \)-substituted styrene 
structure shown for XXXIX or the \( \xi,\xi \)-disubstituted structure 
XLIV. Since no logical mechanistic scheme (see below) is 
readily suggested for the formation of the five-membered XLII 
or the six-membered XLIV, the carbon skeletal system of XXXVIII 
is considered to be more nearly represented by the seven-
membered ring compound shown for XXXIX.

Since the bromine atom was so readily removed on 
titration with silver nitrate in acid medium an allyl, rather 
than a vinyl, position is assigned to the bromine substituent 
since a vinyl bromide would not have been expected to react 
so readily with silver nitrate. In addition comparison of 
the maximum of absorption of XXXVIII and the dehalogenated
XXXVIII, XXXIX, shows that the bromine atom produced a bathochromic shift of 3 μm, on the absorption maximum of XXXIX. This is consistent with the assignment of an allyl position for the halogen atom, for a vinyl bromide would have been expected to produce a bathochromic shift of about 14 μm in the absorption maximum of XXXIX (49).

In order to rationalize the formation of a compound that would meet these requirements the following mechanism is suggested. Since α-halohydrins have been the products reported (46) to result from treatment of α-haloketones with sodium borohydride, it would seem plausible that in this instance a α-halohydrin as a metal derivative XLVI is the initial product of the reaction. By assigning an acidic nature to the sodium borohydride, whereby it acts as the rearranging agent in a Wagner-Meerwein shift of the intermediate α-halohydrin XLVI, a carbonium ion would be produced on the benzyl carbon as shown in XLVII. Ring expansion of XLVII would produce the new carbonium ion XLVIII. Two reaction pathways seem possible for the carbonium ion XLVIII to reach a stable product. In one case, the 1-2 shift of a hydride ion would lead to XLIX which would then be stabilized by loss of a proton to produce XXXVIIIa. XXXVIIIa might conceivably undergo an allylic rearrangement to produce XXXVIIIb. The other possible pathway would involve the migration of the phenyl to produce L which similarly would be stabilized by loss of a proton to produce LI. LI would then achieve further stabilization by an allylic rearrangement to form XXXVIIIc.
This postulation of the formation of the initial carbonium ion XLVII by the action of sodium borohydride finds support from two sources. The reaction of 1-methyl-4-hydroxy-4-piperidylphenylmethanol (XXXV) with concentrated sulfuric acid, followed by treatment of the reaction product with lithium aluminum hydride and hydrogen bromide, has been observed by Leone (21) to give a small amount of XXXVIII hydrobromide. The isolation of XXXVIII hydrobromide can be rationalized similarly to the mechanistic scheme presented here. In addition the reactions of 2-methyl-2,3'-(2'-methyldindyl)-pseudoindoxyl and 2,2-bis-(3'-indyl)-pseudoindoxyl with lithium aluminum hydride have been reported (50) to result in migration in the course of reduction forming the alkyl substituted indoles, which suggests an acidic nature of the lithium aluminum hydride.
The unusual reactivity of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa), as evidenced by the products isolated from the reaction of XIIa with sodium borohydride, was also observed on treatment of XIIa with lithium aluminum hydride in ether. The products isolated were other than the usual α-halohydrins (46) or saturated carbinols (46) reported to form from α-haloketones on treatment with lithium aluminum hydride. Treatment of 1-methyl-4-bromo-4-piperidyl phenyl
ketone hydrobromide (XIIa) with lithium aluminum hydride in ether gave 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII) (55\%), 1-methyl-4-benzylideneepiperidine (LIIIA) (maximum yield 34\%), and small amounts of XXVIII and 1-methyl-4-piperidylphenylmethanol (XVII).

1-Methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII) was characterized by comparison with known LII, by mixture-melting point determination, by the observation of its facile decomposition, and by analysis. The characterization of 1-methyl-4-benzylideneepiperidine (LIIIA) was complicated by the fact that it had not been reported previously, and attempts to prepare this compound had always led to 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine. The proof of structure of LIIIA is given below.

Since 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII) and 1-methyl-4-piperidylphenyl methanol (XVII) were also products of the reaction of XIIa with lithium aluminum hydride, the isolation of pure 1-methyl-4-benzylideneepiperidine (LIIIA) was greatly impaired. In the isolation of LIIIA, most of the alcohol LII was removed by precipitation of LII from petroleum ether. Nevertheless, on distillation of the crude LIIIA, the alcohol LII as well as the alcohol XVII were found to be present in the distillate. It was thus not surprising that the infrared absorption spectrum of the distilled LIIIA showed the absorption of OH stretching from 3600 cm.\(^{-1}\) to the 3000 cm.\(^{-1}\) region of CH stretching absorption. The ultraviolet absorption spectrum of LIIIA showed a maximum absorption at 243 \(\mu\)m (Log \(\varepsilon\) 3.962) indicative of the disubsti-
tuted styrene system. The log molar extinction coefficient would have been expected to be greater than 4.0; however, the low value observed here is attributed to the contamination of LIIIA with the alcohols LII and XVII. Further evidence that LIIIA was contaminated by an oxygen containing compound was shown by the carbon and hydrogen analysis of LIIIA. The experimental values are 1.39% C and 0.46% H lower than those expected for LIIIA (C_{13}H_{17}N) and 5.22% C and 0.33% H greater than those for an oxygen containing compound of the empirical formula C_{13}H_{17}NO.

Since 1-methyl-4-benzylidene piperidine (LIIIA) apparently could not be obtained pure by distillation, chromatography was employed in an attempt to separate the reaction products. It was found that the separation of a mixture of known composition of the picrates of 1-methyl-4-piperidylidenediphenyl-methane (LV) and 1-methyl-4-piperidyldiphenylmethanol (XXV) could be achieved by a chromatographic separation on a column of silicic acid. Development of the column containing the mixture of picrates with chloroform produced two distinct yellow zones which were eluted with chloroform. The first zone was identified as the picrate of the olefin LV and the second zone as the picrate of the alcohol XXV. Application of this procedure to the resolution of the oily picrate mixture of the products from the reduction of XIIa led to the isolation of one pure picrate, probably the picrate of 1-methyl-4-benzylidene piperidine (LIIIA). This was the first component eluted, but elution of the second zone gave no crystalline picrate.

The impure 1-methyl-4-benzylidene piperidine (LIIIA)
on treatment with dry hydrogen bromide in ether gave LIIIA hydrobromide. The infrared absorption spectrum of LIIIA hydrobromide showed no absorption in the OH stretching region when determined in Nujol; however, absorption in the OH stretching region at 3400 cm$^{-1}$ was observed when the infrared absorption spectrum of LIIIA hydrobromide was determined in a chloroform solution. This indication of an OH group is attributed to the contamination of LIIIA hydrobromide with the hydrobromide of 1-methyl-4-piperidylphenylmethanol (XVII) and/or the hydrobromide of the hydroxyl analog of XXXVIII (see below). The hydrobromide of 1-methyl-1,2,3,6-tetrahydro-4-pyridylmethanol (LII) is not considered to be a contaminant of LIIIA hydrobromide since, according to the observations of Leone (21), a hydrobromide of LII could not be prepared by treatment of the base LII with dry hydrogen bromide in ether. Similarly, a hydrobromide of LII could not be prepared from an aqueous hydrogen bromide solution, since, as with Leone, a red intractable oil was produced. The analysis of LIIIA hydrobromide was 58.60% C, 5.70% H, and 4.99% N. These values are 0.40% higher in C, 0.05% higher in H, and 0.13% lower in N than the theoretical values for a compound of the empirical formula $C_{13}H_{18}BrN$. However, the analysis is 3.77% higher in C, 0.32% higher in H, and 0.03% lower in N, than the calculated analysis for a compound of the empirical formula $C_{13}H_{18}BrNO$. The ultraviolet absorption spectrum of LIIIA hydrobromide showed the presence of the disubstituted styrene system with an absorption maximum at 241 mp ($\log \varepsilon =$ 4.163). Since LIIIA hydrobromide would be expected to have
a log molar extinction coefficient value the same as the base LIIIA, an indication of the extent of impurity present in LIIIA is obtained by a comparison of the ultraviolet absorption spectrum curves of LIIIA and LIIIA hydrobromide (see page 146).

The impure 1-methyl-4-benzilidenepiperidine (LIIIA) on treatment with methyl iodide in methanol gave LIIIA methiodide. The detection of the PhC=CH-system in LIIIA methiodide by ultraviolet absorption spectroscopy was hindered because the absorption maximum characteristic of the styrene system was obscured by the absorption of the iodine ion. The log molar extinction coefficient, 4.267, for the absorption of LIIIA methiodide at 242 μm, the region of maximum absorption of LIIIA and LIIIA hydrobromide, suggests the presence of the styrene system, since a methiodide derivative of a compound possessing only a non-conjugated benzene ring would be expected to have a log molar extinction coefficient no greater than 2.934 in this region (see page 145). In addition, a point of inflection at 234 μm was observed in the ultraviolet absorption curve of LIIIA methiodide, indicating the absorption of the styrene system (see page 146). The analysis of LIIIA methiodide similarly indicated the absence of an oxygen atom. The presence of the double bond in LIIIA was further indicated and the skeletal system of LIIIA was established by the catalytic reduction of LIIIA methiodide. Treatment of LIIIA methiodide with hydrogen over Raney nickel catalyst gave 1-methyl-4-benzylpiperidine (LIV) methiodide which did not depress the melting point of an authentic sample, but which did depress the melting point of the unreduced LIIIA methiodide.
An alternate synthesis of 1-methyl-4-benzylidene-piperidine (LIIIA) by the treatment of 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine (LVI) with alcoholic potassium hydroxide at high temperatures in a sealed tube, produced LIIIB (a mixture of LIIIA and LVI). The migration of the double bond of LVI under the conditions used here has been observed elsewhere (52). Evidence that some of LVI had been converted to LIIIA under these conditions was obtained by the
ultraviolet absorption spectrum of LIIIb (see page 146). An absorption maximum characteristic of the styrene system was observed at 242 μ (Log ε 3.655), but the low degree of purity of LIIIb was indicated by the low extinction coefficient. A log molar extinction coefficient greater than 4.0 would have been expected if the non-conjugated benzene ring containing LVI were not a component of LIIIb. The LIIIb gave, on treatment with methyl iodide, LIIIb methiodide whose ultraviolet absorption spectrum indicated the presence of some LIIIa methiodide (see page 146). No absorption maximum was observed in the ultraviolet absorption spectrum because of the absorption of the iodide ion in the region of styrene absorption, however, a point of inflection at 240 μ was observed in this region. In addition, the spectrum of LIIIb methiodide gave a log molar extinction coefficient of 3.926 in this region (242 μ). A log molar extinction coefficient not greater than 2.934 would have been expected if the methiodide contained only a non-conjugated benzene ring (see page 146). From the treatment of LIIIb with hydrogen bromide in either ethereal or aqueous medium only the hydrobromide of LVI was isolated. The absence of the styrene system in LVI was observed from the ultraviolet absorption spectrum which showed absorption characteristic of a non-conjugated benzene ring (see page 145).
From the reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIa) with lithium aluminum hydride a small amount of XXXVIII was isolated in two instances. In one case the impure distillate of LIIIA was heated under reflux with acetic acid containing one drop of sulphuric acid. The oil obtained on neutralization of the acid solution was distilled under reduced pressure and dissolved in aqueous hydrobromic acid. On evaporation of the aqueous hydrobromic acid solution under reduced pressure and addition of acetone to the residue, a small amount of XXXVIII hydrobromide was isolated. In the second instance a small amount of crude XXXVIII hydrobromide was isolated after the impure LIIIA was treated with lithium aluminum hydride, and the oil isolated from this reaction was treated with dry hydrogen bromide in ether. Crystallization of the hydrobromide was accomplished by treatment of the ethereal solution with a small amount of acetone. The identity of XXXVIII hydrobromide produced in this series of reactions
with the XXXVIII hydrobromide isolated from the sodium boro-
hydride reduction of XIIa (refer back to page 38) was established
by mixture melting point determinations and superimposable
infrared absorption spectra.

The presence of small amounts of 1-methyl-4-piperidyl-
phenylmethanol (XVII) produced by the reaction of XIIa with
lithium aluminum hydride was ascertained by the crystallization
of crude solid from the impure distilled LIIIA. The solid was
present in such small quantities that its purification by
recrystallization was not completely achieved, but the impure
solid was observed to melt in the vicinity of the melting
point of authentic XVII.

On the basis of the observed reactions of XXXVIII, the
small amounts of XXXVIII, isolated from the reaction of 1-methyl-4-
bromo-4-piperidyl phenyl ketone (XIIa) with lithium aluminum
hydride, would not have been expected to be present in the
distillate of LIIIA. Evidence in support of this view, was
the failure to obtain a positive Beilstein test on the impure
LIIIA. Also, XXXVIII would have been expected to undergo
decomposition on distillation, and during the reduction
XXXVIII would have been expected to be reductively dehalo-
genated to XXXIX by the lithium aluminum hydride. A possible
explanation for the isolation of XXXVIII might be the assumption
that an hydroxyl derivative of XXXVIII was formed in the reaction,
and on treatment with hydrogen bromide this derivative produced
XXXVIII. This view is consistent with the isolation of a small
amount of XXXVIII hydrobromide by Leone (21) from the reaction
of 1-methyl-4-hydroxyl-4-piperidylphenylmethanol (XXXV) with
concentrated sulphuric acid on subsequent treatment of the reaction products with hydrogen bromide.

The previous discussion has shown that the reactions of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) with sodium borohydride, or with lithium aluminum hydride resulted in the formation of products for which there is no direct analogy in the literature. \( \alpha \)-Haloketones on treatment with lithium aluminum hydride, as mentioned previously, have been reported to give in some instances saturated alcohols, but more often \( \alpha \)-halohydrins. A \( \alpha \)-halohydrin was not isolated as a product from the reaction of XIIa with lithium aluminum hydride, but it would seem plausible that it was an initial product of this reaction and may be used to explain the formation of 1-methyl-1,2,3,6-tetrahydro-4-pyrindylphenylmethanol (LII) and 1-methyl-4-piperidylphenylmethanol (XVII). However, 1-methyl-4-benzylidene piperidine (LIiIA) does not arise in an obvious manner from this \( \alpha \)-halohydrin. A possible explanation was considered. The intermediate \( \alpha \)-halohydrin as a metal derivative, (LVII), on dehydrohalogenation could lead to the anion LVIII of 1-methyl-1,2,3,6-tetrahydro-4-pyrindyl phenylmethanol (LII) or the enolate anion LIX of 1-methyl-4-piperidyl phenyl ketone (IXa). This intermediate, LIX, is similar to the intermediate XXVIc formed in the reaction of XIIa with phenyllithium and for which structural evidence was presented (see page 25). A nucleophilic attack of a hydride ion on the benzyl carbon of LIX would then lead to the replacement of the OMe group by hydrogen, producing LIIIA. A similar displacement of an OMe group has been suggested previously in
a study of the reduction of substituted acetophenone oximes with lithium aluminum hydride (51). In this mechanistic scheme, however, this explanation is adequate only if the allyl OM group (in LVIII) and the vinyl OM group (in LIX) react differently with nucleophilic agents from that usually found for allyl and vinyl compounds, since treatment of LVIII with lithium aluminum hydride gave no reaction (see below).
The formation of 1-methyl-4-benzylidene-piperidine (LIIIA) or XXXVIII from 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII) is considered unlikely on the basis of a study of the reactions of LII. On treatment of LII with lithium aluminum hydride under the same conditions that produce LIIIA and XXXVIII, 90% of LII was recovered unchanged. Similarly, a quantitative recovery of LII was obtained after it was heated under reflux with alcoholic potassium hydroxide. As mentioned previously, treatment of LII with aqueous hydrogen bromide produced a red intractable oil similar to that observed by Leone (21) on treatment of LII with dry hydrogen bromide in an ether solution. The heating of LII under reduced pressure effected no change. Heating LII under reflux with acetic acid containing two drops of sulphuric acid, gave an oil which was observed to decompose on standing and from which no crystalline hydrobromide could be isolated.

The explanation of the formation of two different types of products on reduction of XIIa, the rearranged product XXXVIII produced by the sodium borohydride, and the dehydrohalogenated products LII and LIIIA produced by lithium aluminum hydride, apparently lies in the difference in the ability of the metal hydrides to remove the bromine atom. Of the organic halides that have been subjected to treatment with sodium borohydride, none has been reported (46) to undergo reductive dehalogenation. Reactions with halogens however, have been observed with lithium aluminum hydride. The order of reactivity of organic halides with lithium aluminum hydride is primary \( \rightarrow \) secondary \( \rightarrow \) tertiary. The reaction of the latter type usually
gives olefins (46). Thus, since lithium aluminum hydride acts as a better dehydrohalogenating agent than sodium borohydride, treatment of XIIa with lithium aluminum hydride produces the dehydrohalogenated products LII and LIIIA. Since sodium borohydride is apparently such a poor dehydrohalogenating agent, the reaction of XIIa with sodium borohydride proceeds with rearrangement to form XXXVIII as the product.
EXPERIMENTAL

The infrared absorption spectra of the compounds prepared in this study were recorded by Meade Johnson and Company (32), Sadtler (33) and the Department of Chemistry, University of New Hampshire (34). Those obtained from Meade Johnson and Company and Sadtler were recorded on a Baird infrared spectrophotometer; the former were measured as mulls in Nujol while the latter were measured as 0.5% discs in 0.5 mm potassium bromide wafers.

The infrared absorption spectra determined at the Department of Chemistry, University of New Hampshire were recorded on a Perkin-Elmer Model 21, double beam infrared spectrophotometer operated with a resolution of 927, response 1, speed 4-6, gain 5.5, suppression 0, and standard scale using sodium chloride optics. Solids were measured as mulls in Nujol, and liquids were measured as smears unless otherwise noted. These spectra are on file at the Department of Chemistry, University of New Hampshire.

Ultraviolet absorption spectra were measured on a Beckman Model DU quartz spectrophotometer. Microdeterminations of carbon and hydrogen were performed by Drs. G. Weiler and F.B. Strauss, Oxford, England, unless otherwise noted.
Preparation of Methyl 1-Methyl Isonipecotate (IV) (Procedure IA). (a) Preparation of Methyl Isonicotinate Methobromide (II).—-A mixture of 20.0 g. of methyl isonicotinate (I) and 20 ml. of methyl bromide in 100 ml. of methanol in a suction flask was stoppered and allowed to stand at room temperature for 21 hours. Evaporation of the solution under reduced pressure gave 37.0 g. (95%) of methyl isonicotinate methobromide (II), m.p. 70-124°. Recrystallization of a small sample of the salt from chloroform gave pure methyl isonicotinate methobromide (II), m.p. 163-165° dec. The infrared absorption spectrum (Sadtler No. 9439) of II showed the absorption of the stretching carbonyl of the carboxylic acid ester at 1710 cm.⁻¹.


(b) Reduction of Methyl Isonicotinate Methobromide (II).—-A solution of 10.0 g. of methyl isonicotinate methobromide (II) in 100 ml. of methanol was shaken with 0.2 g. of platinum oxide under 2-3 atm. of hydrogen. After the pressure of hydrogen remained constant during a period of 1 hour, the solution was filtered, and the solvent was removed from the filtrate by evaporation under reduced pressure. The residual solid, after recrystallization from methanol-ether, gave 8.9 g. (90%) of methyl 1-methylisonipecotate hydrobromide (III), m.p. 137-138°. The infrared absorption spectrum (Sadtler No. 9441) of III showed the absorption of the carbonyl stretching of the
carboxylic acid ester at 1710 cm\(^{-1}\).

Anal. Calcd. for C\(_{16}\)H\(_{15}\)BrNO\(_2\): Br, 33.56. Found: Br, 33.46.

(c) Neutralization of Methyl 1-Methyisonipecotate Hydrobromide (III).—A solution of 10.0 g. of methyl 1-methyisonipecotate hydrobromide (III) in 20 ml. of water was basified with a saturated sodium carbonate solution and extracted with ether. The ether extract was dried over sodium carbonate, filtered, and evaporated. Distillation of the oily residue under reduced pressure gave 4.9 g. (83%) of methyl 1-methyisonipecotate (IV), b.p. 98-100\(^\circ\) at 20 mm., \(n_\text{D}^{29}\) 1.4515; lit. (16) b.p. 80-82\(^\circ\) at 12 mm., \(n_\text{D}^{25}\) 1.4510.

Preparation of Methyl 1-Methyl Isonipecotate (IV)
(Procedure 1B).——Freshly distilled methyl isonicotinate (I) (70.0 g. (0.5 mole) ) was dissolved in a solution of 56 ml. (0.6 mole) of glacial acetic acid and 83 ml. of water. Water was added to bring the volume to 250 ml. and 1.25 g. of platinum oxide was introduced. The mixture was hydrogenated at 1200 p.s.i. at room temperature until no further hydrogen was absorbed. The catalyst was removed by filtration and 50 ml. (0.6 mole) of 36% formalin and 5 g. of 10% palladium-on-charcoal were added. Hydrogenation was continued at 1200 p.s.i. until no further absorption of hydrogen occurred. The catalyst was removed by filtration, and the clear filtrate, chilled at 10\(^\circ\), was basified with a 35% sodium hydroxide solution. The strongly basic solution was
saturated with anhydrous potassium carbonate and extracted with ether. The ether extract was dried over anhydrous sodium sulphate, and after evaporation of the ether, a clear colorless oil remained. Distillation of this oil at reduced pressure gave 70.2 g. (88%) of methyl 1-methyl isonipecotate (IV), b.p. 70-74° at 5 mm. The picrate of IV melted at 146-147°, lit. (19) m.p. 147-148°.

Preparation of 1-Methyl Isonipecotic Acid Hydrochloride (VII). Methyl 1-methylisonipecotate (IV) (69.6 g. (0.48 mole) ) was mixed with 350 ml. of 1:1 hydrochloric acid solution. The mixture was evaporated to dryness on a water bath under reduced pressure, and 79.0 g. (99.5%) of 1-methyl isonipecotic acid hydrochloride (VII) as a white powdery solid, m.p. 225-227°, lit. (24) m.p. 223-225°, remained. The infrared absorption spectrum (Sadler No. 9435) of VII showed the absorption due to the OH stretching of the carboxylic acid at 2940 cm.-1 and the absorption of the stretching carbonyl of the carboxylic acid at 1698 cm.-1.

Preparation of 1-Methyl-4-piperidyl Phenyl (and p-Tolyl) Ketone (IXa and IXb) by the Friedel-Crafts Method (Procedure I). A. 1-Methyl-4-piperidyl Phenyl Ketone (IXa).

To 79.0 g. (0.44 mole) of 1-methyl isonipecotic acid hydrochloride (VII) in a three-necked apparatus was added dropwise 280 ml. of thionyl chloride, and the mixture was heated under reflux for 2 hours. The clear yellow solution was concentrated under reduced pressure until most of the
excess thionyl chloride was removed. Anhydrous benzene (350 ml.) was added, the mixture was cooled in an ice-water bath, and 175 g. of aluminum chloride were added with stirring over a period of 1-1.5 hours. The reaction mixture was heated under reflux for 10 hours and then was poured into a mixture of 200 g. of ice and 175 ml. of concentrated hydrochloric acid. The benzene was removed by steam-distillation, the residue was extracted with ether, and the ether extract was discarded. The aqueous layer was made strongly basic with sodium hydroxide and was extracted with ether. The ether extracts were dried over sodium sulphate and filtered, and the ether was removed by evaporation. The oily residue which remained was distilled under reduced pressure to give 79.9 g. (89.3%) of 1-methyl-4-piperidyl phenyl ketone (IXa), b.p. 148-152° at 5 mm., n_D^{20} 1.5592, lit. (17a) b.p. 120-125° at 1 mm., n_D^{25} 1.5420.

The picrate, hydrobromide (Xa), and hydrochloride (Xb) of IXa were prepared by standard procedures to give solids, m.p. 201-203° (lit. (16) m.p. 200.5-202°), m.p. 204-206° (lit. (16) m.p. 211-212°), and m.p. 201-205°, respectively.

The infrared absorption spectrum (Sadtler No. 9443) of Xb showed the absorption of the stretching carbonyl of the aromatic ketone at 1670 cm.⁻¹ and the absorption of a mono-substituted benzene at 788 cm.⁻¹ and 700 cm.⁻¹.
B. l-Methyl-4-piperidyl \( p \)-Tolyl Ketone (IXb).----
Using the Friedel-Crafts procedure described above, 20.0 g. of methyl \( l \)-methylisonipecotate (IV) was converted to 22.2 g. (82%) of impure \( l \)-methyl-4-piperidyl \( p \)-tolyl ketone (IXb). A small sample of the crude IXb was recrystallized from methanol-water to give pure \( l \)-methyl-4-piperidyl \( p \)-tolyl ketone (IXb), m.p. 85-86.5°.

Preparation of \( l \)-Methyl-4-piperidyl Phenyl Ketone (IXa) by the Oxidation Procedure (Procedure II). (a) Preparation of 4-Benzoyl Pyridine Methobromide (XV).----A mixture of 250 g. (1.37 mole) of 4-benzoyl pyridine (XIV) and 177 g. (1.87 mole) of methyl bromide in 500 ml. of methanol in a suction flask was stoppered and allowed to stand at room temperature for several days. After concentration of the methanol solution under reduced pressure, the addition of ethyl acetate gave 310.6 g. (87%) of 4-benzoyl pyridine methobromide (XV), m.p. 162-167°, lit. (21) m.p. 168-172°.

(b) Reduction of 4-Benzoyl Pyridine Methobromide (XV).----A solution of 95.4 g. (0.32 mole) of 4-benzoyl pyridine methobromide (XV) in 200 ml. of methanol was treated with hydrogen at 600 p.s.i. in the presence of 1.0 g. of platinum oxide. After the pressure of hydrogen remained constant during a period of 1 hour, the solution was filtered and the filtrate concentrated on a steam bath. The oily residue was dissolved in water and basified with sodium hydroxide to give 66.0 g. (98%) of \( l \)-methyl-4-piperidyl
phenyl carbinol (XVII),* m.p. 153-156°, lit. (18) m.p. 157-159°. The infrared absorption spectrum (Sadtler No. 9440) of XVII showed absorption due to OH stretching at 3120 cm.⁻¹ and the absorption of a mono-substituted benzene at 758 cm.⁻¹ and 700 cm.⁻¹.

On some occasions, treatment of an aliquot of the hydrogenation mixture with base produced an intense purple color. This indicated incomplete reduction, for after continued treatment with hydrogen and fresh platinum oxide, a colorless solution was obtained on adding base. Attempted reductions of 4-benzoyl pyridine methobromide (XV) with Raney nickel or palladium-on-charcoal catalysts in every instance produced the intense purple color on the addition of base to the hydrogenation mixture. An attempted reduction of XV in alkaline medium with platinum oxide gave only a carbonaceous like solid.

Preparation of 1-Methyl-4-bromo-4-piperidyl Phenyl (and p-Tolyl) Ketone Hydrobromide (XIIa and XII c). A. 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa).

--- Hydrogen bromide was bubbled through 34.7 g. of 1-methyl-4-piperidyl phenyl ketone (IXa) in 300 ml. of ether until precipitation ceased. The precipitate was collected by filtration to give 47.5 g. (97.5%) of IXa hydrobromide. Recrystallization of the solid from methanol-ether solvent

*The conversion of 1-methyl-4-piperidyl phenyl carbinol (XVII) by chromic acid oxidation to 1-methyl-4-piperidyl phenyl ketone (IXa) was executed by Leone (21).
mixture gave an analytically pure sample of IXa hydrobromide, m.p. 204-206°, lit. (16) m.p. 211-212°.

The IXa hydrobromide (25 g.) was dissolved in 90 ml. of chloroform in a 250 ml. suction flask, and 12 ml. of bromine was added. The mixture was loosely stoppered and allowed to stand for 12 hours. The mixture was then evaporated to dryness under reduced pressure giving 50.5 g. of orange XIIa per bromide. The per bromide was treated with 100 ml. of methanol, and solution was completed on addition of a small amount (6.5 g.) of phenol. Dry ether then was added to precipitate the 28.0 g. (93%) of the per bromide-free XIIa. Recrystallization of the solid from methanol-ether gave an analytical sample of XIIa, m.p. 155-156° dec. The infrared absorption spectrum (Sadtler No. 9436) of XIIa showed the absorption of the stretching carbonyl of the aromatic ketone at 1670 cm.⁻¹ and the absorption of a mono-substituted benzene at 759 cm.⁻¹ and 706 cm.⁻¹.

Anal. Calcd. for C₁₃H₁₇Br₂NO: 1 Br, 22.1; 2 Br, 44.2. Found: Br (Volhard), 22.2, 22.45; Br (Stepanow), 44.3, 44.2.

B. 1-Methyl-4-bromo-4-piperidyl p-Tolyl Ketone (XIIc).—Using the procedure described above for the preparation of XIIa, 22.2 g. of 1-methyl-4-piperidyl p-tolyl ketone (IXb) gave a quantitative yield of IXb hydrobromide, m.p. 217.5-219.5° (after recrystallization from isopropyl alcohol).

An 18.7 g. sample of IXb hydrobromide was then similarly converted in 96% yield to 1-methyl-4-bromo-4-piperidyl p-tolyl ketone hydrobromide (XIIc), m.p. 157-158° dec. (after recrystallization from acetone).


Preparation of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride (XIIb). 1-Methyl-4-piperidyl phenyl ketone hydrochloride (Xb) was prepared in quantitative yield from the base by precipitation from a solution of hydrogen chloride in ether. The hydrochloride, after recrystallization from methanol-chloroform melted at 201-205°.

A chloroform solution of 6.4 g. of 1-methyl-4-piperidyl phenyl ketone hydrochloride (Xb) was saturated with chlorine and allowed to stand for 12 hours. The solvent was removed under reduced pressure, and the residue was dissolved in methanol and treated with phenol. After filtration, the solution was diluted with anhydrous ether to give 5.3 g. (73%) of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb), m.p. 179-180° dec., as a precipitate. The infrared absorption spectrum (Sadtler No. 9442) of XIIb showed the absorption of the stretching carbonyl of the aromatic ketone at 1682 cm.\(^{-1}\) and the absorption of a mono-substituted benzene at 764 cm.\(^{-1}\) and 710 cm.\(^{-1}\).
Anal. Calcd. for C_{13}H_{17}Cl_{2}NO: 1 Cl, 12.90. Found: Cl, 12.88, 12.67.

Neutralization of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa) with Sodium Bicarbonate.——To 0.5 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 6 ml. of water was added a slight excess of sodium bicarbonate, and the colorless oil which separated was extracted into ether. Removal of the ether by distillation on a steam bath gave 0.35 g. (92%) of a colorless oily residue. On standing overnight the oil changed to an ether insoluble reddish tar.

Neutralization of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa) with Sodium Bicarbonate and Precipitation of XIIa as the Hydrobromide or Hydrochloride.——A solution of 1.0 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 10 ml. of water was saturated with sodium bicarbonate, and extracted with two 30 ml. portions of ether. The ethereal extract was dried for 20 minutes with Dryerite, filtered, and divided in half. One portion was treated with dry hydrogen bromide gas to precipitate the 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa), m.p. 155-156° dec., and the second portion on treatment with dry hydrogen chloride gave an oil which on standing crystallized to give the XIIa hydrochloride, m.p. 154-156° dec. Recrystallization of the hydrochloride from methanol-ether gave a pure sample m.p. 150-151° dec.
Reactions of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa).  (a) With Sodium Hydroxide in Ether. To 150 ml. of anhydrous ether (pipetted) in the conventional three-necked reaction apparatus was added 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) and 1 g. of powdered, oven-dried sodium hydroxide. The mixture was heated under reflux for 16 hours and was allowed to stand overnight at room temperature. The solution then was filtered, concentrated on a steam bath, and cooled to give 0.25 g. (37%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa), m.p. 130-132°. The infrared absorption spectrum (Sadtler No. 9437) of XVIIIa showed the absorption due to OH stretching from 3400 cm.⁻¹ to the 3000 cm.⁻¹ region of OH stretching absorption and showed the absorption of a mono-substituted benzene at 782 cm.⁻¹ and 708 cm.⁻¹.

Anal. Calcd. for C₁₃H₁₇NO₂: C, 71.18; H, 7.82.  
Found: C, 71.46, 71.55; H, 7.99, 7.90.

By the reaction of phenyllithium in ether, 0.8 g. of XVIIIa was converted in 91% yield to 1-methyl-4-hydroxy-4-piperidyl diphenyl carbinol (XIX) (m.p. 159-161°) which gave no depression of melting point on mixing with an authentic sample (23). The infrared absorption spectrum (Sadtler No. 6925) of XIX showed the absorption due to OH stretching at 3515 cm.⁻¹ and the absorption of a mono-substituted benzene at 754 cm.⁻¹ and 700 cm.⁻¹.

The picrate, m.p. 200-203°, and hydrochloride, m.p. 170-172°, of XVIIIa were prepared by conventional methods.
Anal. Calcd. for C_{13}H_{18}ClNO_2: Cl, 13.74. Found: Cl, 13.62, 13.65.

The hydrochloride and hydrobromide of XVIIIa were prepared by the evaporation of solutions of XVIIIa dissolved in concentrated hydrochloric acid and 48% hydrobromic acid, respectively to dryness under reduced pressure. After recrystallization from ethanol-ether, the hydrobromide of XVIIIa melted at 205.5-207°.

The oxime, m.p. 204-205° of XVIIIa was prepared by either method described by Shriner and Fuson (25).

Anal. Calcd. for C_{13}H_{18}N_2O_2: C, 66.64; H, 7.74. Found: C, 66.78; H, 7.68.

The methiodide of XVIIIa, m.p. 207-208.5° was obtained on treatment of the epoxyether XXIa with methyl iodide in methanol. The infrared absorption spectrum (Spectrum No. 173) of XVIIIa methiodide showed the absorption due to OH stretching at 3300 cm.^{-1}, the absorption of the stretching carbonyl of the aromatic ketone at 1670 cm.^{-1}, and the absorption of a mono-substituted benzene at 790 cm.^{-1} and 708 cm.^{-1}.

(b) With Sodium Hydroxide in Ether as the Free Base Obtained by Neutralization of XIIa with Butyl Amine.-----In the conventional three-necked apparatus 0.8 g. (.01 mole) of n-butyl amine was added to 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) suspended in 150 ml. of ether. The mixture was stirred for 5 hours after which time it was filtered by suction; the filtrate was collected in a second three-necked flask. To the filtrate
was added 0.4 g. (.01 mole) of powdered oven-dried sodium hydroxide, and the mixture was heated under reflux for 11.25 hours. The mixture then was filtered, and evaporation of the filtrate gave 1.0 g. (45.5%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIa) m.p. 130-131°.

(c) With Sodium Alkoxides in Ether as the Free Base

Obtained by Neutralization of XIIa with Sodium Bicarbonate.

--- A solution of 1.35 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 10 ml. of water was saturated with sodium bicarbonate and extracted with two 30 ml. portions of ether. After drying with Dryerite for 20 minutes, the ether extract was filtered into a suspension of 1.0 g. of sodium methoxide in 50 ml. of ether contained in a conventional three-necked flask. The mixture was heated under reflux for 3 hours and was allowed to stand at room temperature overnight. The mixture then was filtered by gravity, and after evaporation of the ether, 0.5 g. (62%) of crude 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIa), m.p. 115-122°, was obtained. Recrystallization of XVIIa from ether-petroleum ether gave pure XVIIa, m.p. 130-131.5°.

Using the same procedure as that outlined above with sodium ethoxide instead of sodium methoxide, a 1.15 g. (95%) yield of crude 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIa) was obtained from 2.0 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa). After recrystallization, the melting point of this product showed
no depression on mixing with the product from the sodium methoxide reaction.

(d) **With Sodium Methoxide in Ether.** — To a mixture of 2.0 g. of sodium methoxide and 150 ml. of anhydrous ether (pipetted) in the conventional three-necked apparatus, was added 3.6 g. (.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa), and the mixture was heated under reflux for 8 hours. Filtration and evaporation of the ether gave a brownish tar from which a small amount of solid, m.p. 134.5-136.5°, was isolated by trituration with petroleum ether. A mixture melting point (m.p. 100-111°) with authentic 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) was depressed. A few milligrams of this solid readily dissolved in approximately 4 ml. of water, and on addition of sodium carbonate to the solution a solid, m.p. 136-137°, precipitated.

(e) **With Silver Nitrate in Methanol.** — To a boiling solution of 4.0 g. of silver nitrate in 50 ml. of methanol was added dropwise, over a period of 0.5 hours, 2.0 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 50 ml. of methanol. After the addition was complete, the mixture was heated under reflux for an additional hour. The mixture was then cooled, and filtered (to remove a sizeable amount of silver bromide and nitrate), and the filtrate was concentrated by evaporation of the methanol to give inorganic salts (silver bromide and nitrate) and the characteristic red oil.
(f) With Sodium Hydroxide in Methanol-Water.------A solution of 2.0 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIa) in 20 ml. of a 15% methanol-water mixture was stirred for 2 hours, and 30 ml. of concentrated hydrochloric acid was added. The mixture was evaporated to dryness under reduced pressure. Extraction of the residue with methanol and fractional crystallization from the methanol gave 0.4 g. (24%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) hydrobromide m.p. 203-205°. The identity of this material was established by the fact that the authentic hydrobromide of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) melted at 205.5-207°.

(g) With Diethyl Amine in Methanol.------A solution of 3.6 g. (.01 mole) 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) and 7.3 g. (0.1 mole) of diethyl amine in 75 ml. of methanol was heated under reflux for 4 hours. Removal of the methanol by distillation under reduced pressure left a mixture of a solid (diethyl amine hydrobromide) and the characteristic red oil.

Neutralization of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride (XIIb) with Sodium Carbonate.------Sodium carbonate was added to a solution of 1.0 g. of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) in 20 ml. of water until the solution was basic. The mixture then was extracted with ether, and the ether layer was dried over Dryerite for several hours. Filtration, and evaporation of the ether solution gave an oily residue.
which did not appear to change on standing for several days.

**Reaction of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride (XIIb) with Sodium Hydroxide in Ether.**

To 1.0 g. of powdered, oven-dried sodium hydroxide in 150 ml. of ether in the conventional three-necked apparatus was added 2.4 g. (0.01 mole) of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb). The mixture was heated under reflux for 14 hours. After this time the reaction mixture was filtered by gravity, and the ether was removed by distillation to give an oily residue. The oil gave a positive Beilstein test. The oil was converted to the hydrochloride and seemed to be 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb), m.p. 180-183° dec.

**Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa) with Sodium Methoxide (and Sodium Hydroxide) in Absolute Methanol.**

A. With Sodium Methoxide—

A mixture of 500 ml. of commercial grade methanol and 6.3 g. of calcium hydride was heated under reflux for 7.5 hours. After this time approximately 75 ml. of methanol was removed by distillation and discarded, and 150 ml. of the anhydrous methanol was transferred by distillation into a conventional three-necked flask. The 3-necked flask and its related parts had been preheated in an oven to remove adsorbed water. A sample (50 ml.) of the distilled methanol was removed from the flask by a pipette and was added to 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in the dropping
funnel. Sodium (3.2 g. weighed under benzene) was added to the dry methanol in the flask. The XIIa in methanol was then added dropwise over a period of 1 hour to the boiling alcoholic sodium methoxide solution. The mixture was heated under reflux for an additional 5 hours and allowed to stand overnight. The solution was then transferred to a suction flask and evaporated to dryness. The residue then was triturated with several portions of ether (totaling 150 ml.), and the ether solution was evaporated on the steam bath to give 1.9 g. (83%) of crude 6-methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa). Distillation of this material gave 1.05 g. (52%) of pure epoxyether XXIa, b.p. 150-151° at 10 mm., nD 26.5 1.5170. The infrared absorption spectrum (Spectrum No. 129) of XXIa showed no absorption in the OH and carbonyl stretching regions but showed the absorption of an epoxide ring at 1280 cm.⁻¹ and 1220 cm.⁻¹, the absorption of an aliphatic ether at 1075 cm.⁻¹, and the absorption of a mono-substituted benzene at 745 cm.⁻¹ and 700 cm.⁻¹.

B. With Sodium Hydroxide.---Following the procedure outlined above, but using 5.0 g. of sodium hydroxide (oven-dried) instead of the sodium methoxide gave an 86.5% yield of the epoxyether XXIa, b.p. 145-146° at 8 mm. nD 27.5 1.5165.

Anal. Calcd. for C₁₄H₁₉N₂O₂: C, 72.07; H, 8.21. Found: C, 71.59, 71.91; H, 8.10, 8.27.
Reaction of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride (XIIb) with Sodium Methoxide in Methanol. — To 100 ml. of methanol in a conventional three-necked apparatus was added 4.0 g. (0.17 gram-atom) of sodium. The solution was heated to boiling and 2.8 g. (0.01 mole) of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) in 30 ml. of methanol was added dropwise over a period of one hour. The mixture then was heated under reflux for an additional hour and allowed to stand overnight. The reaction mixture then was poured into 30 ml. of water, and the methanol was removed by distillation under reduced pressure. The residual oil was taken up in ether, dried over sodium carbonate, and filtered, and the ether was removed by evaporation on a steam bath. Distillation of the residual oil gave 2.0 g. (84%) of 6-methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa), b.p. 170-175° at 25 mm., n_D^20 1.5158.

Preparation of 6-Methyl-2-alkoxy-2-aryl-1-ox-6-azaspiro(2.5)octanes (XXI). (a) 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa). — To 100 ml. of commercial grade methanol in the conventional three-necked reaction set-up was added 6.0 g. (0.26 gram-atom) of sodium. After all the sodium had dissolved, the solution was heated to boiling, and 9.3 g. (0.025 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIa) in 60 ml. of methanol was added dropwise over a period of 4.75 hours. After heating for an additional 0.75 hour the mixture was
poured into 100 ml. of water in a suction flask, and the methanol was removed by distillation under reduced pressure by heating on a steam bath. The aqueous solution was then extracted with portions of ether (totaling 300 ml.), and the ether extract was dried over sodium carbonate. Filtration of the extracts, removal of the ether by distillation, and distillation of the residual oil under reduced pressure gave 5.2 g. (87%) of 6-methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa), b.p. 158° at 13 mm., n_D^28 1.5173.

(b) 6-Methyl-2-ethoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIb).—Using the procedure outlined above, but using sodium ethoxide in ethanol instead of the sodium methoxide in methanol gave an 82% yield of 6-ethyl-2-ethoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIb), b.p. 160-165° at 15 mm., n_D^19 1.5100.

(c) 6-Methyl-2-methoxy-2-(para-tolyl)-1-ox-6-azaspiro(2.5)octane (XXIc).—Using the procedure outlined above, 19.65 g. of 1-methyl-4-bromo-4-piperidyl para-tolyl ketone hydrobromide (XIIc) was converted by reaction with sodium methoxide in methanol to 9.0 g. (87%) of 6-methyl-2-methoxy-2-(para-tolyl)-1-ox-6-azaspiro(2.5)octane (XXIc), b.p. 135-140° at 3 mm. The infrared spectrum (Spectrum No. 127) of XXIc showed no absorption in the region of OH and carbonyl stretching but showed the absorption of an epoxide ring at 1280 cm.^-1 and 1220 cm.^-1, the absorption of an aliphatic ether at 1075 cm.^-1, and the absorption of a para-disubstituted benzene at 823 cm.^-1.
Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-
azaspiro(2.5)octane (XXIa) with Propionic Acid in Ether.

To 2.8 g. of the epoxyether XXIa in 50 ml. of ether was added 2.5 g. of freshly distilled propionic acid in 20 ml. of ether; the solution was stoppered and allowed to stand for 6 hours. The ether was removed by distillation on a steam bath, and the oily residue was dissolved in 30 ml. of water. The aqueous solution was made basic with sodium carbonate, and the liquid which separated was extracted with ether and dried over sodium carbonate. Filtration of the extract followed by the addition of dry hydrogen chloride to the ether solution gave 3.5 g. (99% yield from the epoxyether XXIa) of 1-methyl-4-propionoxy-4-piperidyl phenyl ketone (XXIVa) hydrochloride. Recrystallization from chloroform-methanol-ether gave 3.0 g. (85%) of the hydrochloride of XXIVa, m.p. 254-255° dec.

*Anal.* Calcd. for C_{16}H_{22}ClN_{3}: C, 61.64; H, 7.11; Cl, 11.37. Found: C, 61.44; H, 7.34; Cl, 11.44, 11.46.

Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-
azaspiro(2.5)octane (XXIa) with Benzoic Acid in Ether.

To 0.3 g. of the epoxyether XXIa in 10 ml. of ether was added 0.25 g. of benzoic acid in 10 ml. of ether. The mixture was stoppered and allowed to stand for 3 hours. The ether then was removed by evaporation on a steam bath leaving an oil which crystallized after standing 2 hours. After

*The microdeterminations of carbon and hydrogen were performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee.*
trituration with ether, the residue gave 0.5 g. (88%) of l-methyl-4-benzoyloxy-4-piperidyl phenyl ketone (XXIVb) as the benzoic acid salt. After two recrystallizations from ether-petroleum ether the benzoic acid salt of XXIVb melted at 122-125°, and after drying under reduced pressure at 100° it melted at 128.5-130.5°.

*Anal.* Calcd. for C_{27}H_{27}NO_{5}: C, 72.79; H, 6.11.

Found: C, 72.16, 72.07; H, 6.17, 6.16.

A solution of 0.1 g. of the benzoic acid salt of XXIVb in 20 ml. of a water-methanol mixture was neutralized with sodium carbonate precipitating an oil which crystallized on continuous scratching to give 0.05 g. (68%) of l-methyl-4-benzoyloxy-4-piperidyl phenyl ketone (XXIVb), m.p. 111.5-113°. Recrystallization from petroleum ether gave XXIVb, m.p. 112.5-114.5°.

*Anal.* Calcd. for C_{20}H_{21}NO_{3}: C, 74.28; H, 6.55.

Found: C, 74.02, 74.23; H, 6.45, 6.49.

To 2.15 g. of the epoxyether XXIa in 40 ml. of ether was added 2.5 g. of benzoic acid in 40 ml. of ether. The solution was stoppered and allowed to stand for 12 hours. The ether was removed by distillation, and the residual solid was dissolved in methanol. Water was added, and the 1-methyl-4-benzoyloxy-4-piperidyl phenyl ketone (XXIVb) was precipitated by the addition of sodium carbonate and more water to give 2.8 g. (92%) of XXIVb. The addition of hydrogen chloride gas to 2.65 g. of XXIVb in an ether solution yielded 2.7 g. (90%) of the hydrochloride of 1-methyl-4-benzoyloxy-4-piperidyl phenyl ketone (XXIVb). After two recrystallizations from
methanol-ether and drying under reduced pressure, 2.3 g. of
the hydrochloride of 1-methyl-4-benzoyloxy-4-piperidyl phenyl
ketone (XXIVb) was obtained which melted at 256-258° dec.

**Anal.** Calcd. for $C_{20}H_{24}ClNO_3$: Cl, 9.86. Found:
Cl, 9.96, 10.03.

Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-
azaspiro(2.5)octane (XXIa) with Diphenylacetic Acid in
Ether. — — To 4.0 g. of diphenylacetic acid in 100 ml. of
erther was added 2.2 g. of the epoxyether XXIa in 50 ml. of
ether. The mixture was allowed to stand for 3 hours, and
during this time a precipitate formed. The solution then
was decanted and the ether supernatant was concentrated on
a steam bath leaving a solid residue. This solid residue
was combined with the main precipitate, and the solid was
dissolved in hot methanol. Addition of a saturated solution
of sodium carbonate caused 1.65 g. of a solid, m.p. 120-123°;
to precipitate. The solid was recrystallized from chloroform
(soluble)-ether (slightly soluble) to give 1.3 g. (34.9%) of
1-methyl-4-diphenylacetoyloxy-4-piperidyl phenyl ketone
(XXIVc), m.p. 122-124°. Concentration of the basic solution
gave 0.5 g. of crude 1-methyl-4-hydroxy-4-piperidyl phenyl
ketone (XVIIIa), m.p. 129-134°.

**Anal.** Calcd. for $C_{27}H_{27}NO_3$: C, 78.43; H, 6.58.
Found: C, 78.54; H, 6.51.

The 1.3 g. of XXIVc was dissolved in ether diluted
with a small amount of acetone and was precipitated as the
hydrochloride by the usual method. The yield was 1.35 g.
of XXIVc hydrochloride, m.p. 235-248°. This was recrystallized from chloroform-ether to give 1.3 g. of XXIVc hydrochloride, m.p. 243-245°. A third recrystallization from ethyl acetate-methanol gave 1.1 g. of XXIVc hydrochloride, m.p. 246-248°.

**Anal.** Calcd. for C_{27}H_{28}C1NO_3: C1, 7.88. Found: C1, 8.02.

Following the procedure outlined above, 3.4 g. of the epoxyether XXIa was converted, by reaction with 4.0 g. of diphenylacetic acid, to 2.0 g. (33.5%) of pure 1-methyl-4-diphenylacetoxyloxy-4-piperidyl phenyl ketone (XXIVc), m.p. 122-124°. The 2.0 g. of XXIVc was dissolved in 75 ml. of methanol to which was added 20 g. of methyl bromide. This mixture was allowed to stand for 6 hours, after which time, the methanol solution was concentrated on a steam bath. Addition of ether to the hot concentrated solution gave 2.4 g. of precipitate, m.p. 238-240°. Recrystallization from methanol-ether gave 2.4 g. of the methobromide of XXIVc, m.p. 238-240°. Recrystallization from hot ethyl acetate with a small amount of methanol gave 1.85 g. of the pure methobromide of XXIVc, m.p. 245-247°.

**Anal.** Calcd. for C_{28}H_{30}BrNO_3: Br, 15.72. Found: Br, 15.74.

**Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with Hippuric Acid in Ether-Methanol.** To 2.5 g. of hippuric acid dissolved in 150 ml. of an ether-methanol mixture was added 2.0 g. of the epoxy-ether XXIa. The mixture was stoppered and allowed to stand
overnight. The solvents then were removed by distillation on a steam bath, and the residue was dissolved in water. An oil formed on the addition of sodium carbonate, consequently dilute hydrochloric acid was added in order to bring the oil back into solution so that a solid might be obtained by the slow neutralization with sodium carbonate. However, the readdition of sodium carbonate again caused the oil to separate. The oil was then taken up in ether and the aqueous layer was extracted with ether. The combined ether solutions were dried over sodium carbonate. Filtration and evaporation of the ether gave 2.2 g. (58%), of 1-methyl-4-hippuroyloxy-4-piperidyl phenyl ketone (XXIVd), m.p. 104-111°. The 2.2 g. of XXIVd was then dissolved in acetone, and hydrogen chloride gas was added giving 2.2 g. of the hydrochloride of XXIVd. Recrystallization of the hydrochloride from acetone-methanol mixture gave 1.7 g. of XXIVd hydrochloride, m.p. 170° dec.

Anal. Calcd. for C_{22}H_{25}ClN_{2}O_{4}: Cl, 8.51. Found: Cl, 8.43, 8.39.

Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with Mandelic Acid in Ether-Methanol.----To a solution of 3.4 g. of mandelic acid in 100 ml. of ether and 10 ml. of methanol was added 2.1 g. of the epoxyether XXIa in 10 ml. of ether. A precipitate formed after 2 minutes; therefore, an additional 10 ml. of methanol was added. On standing, as further precipitation occurred more methanol was added to maintain a homogeneous solution. Approximately 40 ml. of methanol was required.
The mixture was then allowed to stand for 10 hours. The solution then was evaporated to dryness on a steam bath, and the residue was dissolved in methanol-water mixture. Sodium carbonate was added, and the solid that precipitated was collected by filtration and dried. The solid was dissolved in acetone, and dry hydrogen chloride was added to the solution. The hydrochloride which precipitated was collected by filtration. This hydrochloride and 0.65 of hydrochloride prepared from another run were combined and recrystallized from acetone to give 1.75 g. of the hydrochloride of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIa), m.p. 170-173.5°, rather than the expected ester.

**Anal.** Calcd. for C_{13}H_{18}ClNO_{2}: Cl, 13.74. Found: Cl, 13.69, 13.72.

Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with p-Aminobenzoic Acid in Ether. To 2.5 g. of the epoxyether XXIa in 50 ml. of ether was added a solution of 3.0 g. of p-aminobenzoic acid in about 300 ml. of ether (acid difficultly soluble); the solution was stoppered and allowed to stand overnight. After evaporation of the ether on a steam bath approximately three fourths of the solution was lost due to bumping. The remaining solution was concentrated to dryness, and the solid residue was dissolved in water. Addition of a small amount of sodium carbonate gave an oily precipitate which was collected by filtration. Addition of more sodium carbonate to the filtrate gave a solid, m.p. 118-128°. Recrystallization of this solid from ether-petroleum ether
gave crude 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa), m.p. 118-130°. A small portion of this solid was converted to a crude hydrochloride, m.p. 158-170°, of XVIIIa.

Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with p-Acetamidobenzoic Acid in Ether-Methanol.——To 2.3 g. of p-acetamidobenzoic acid dissolved in 200 ml. of an ether-methanol mixture was added 2.2 g. of the epoxyether XXIa in 30 ml. of ether. The mixture was stoppered and allowed to stand overnight. The mixture then was evaporated to dryness on a steam bath. The residual solid was dissolved in a water-methanol mixture, filtered, and neutralized with sodium carbonate to give three fractions of the base; 1st fraction, 1.2 g., m.p. 175-176°; 2nd fraction, 0.7 g., m.p. 174-176°; 3rd fraction, 0.6 g., m.p. 175-181°. These fractions were combined and recrystallized from chloroform (soluble)-ether (insoluble). The base then was dissolved in acetone and dry hydrogen chloride was added to give 2.4 g. of an unknown hydrochloride, m.p. 183° dec. Recrystallization from acetone gave the solid, m.p. 180° dec.

Anal. Calcd. for C$_{22}$H$_{25}$ClN$_2$O$_4$: Cl, 8.51. Found: Cl, 7.47, 7.43, 7.46, 7.52.

Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with p-Nitrobenzoic Acid in Ether.——To a filtered solution of 4.5 g. of p-nitrobenzoic acid in 350 ml. of ether was added dropwise over a period of 4 hours 3.0 g. of the epoxyether XXIa in 50 ml. of ether with stirring by a magnetic stirrer. The mixture was permitted
to stand overnight. A solution of 5.0 g. of sodium carbonate in 65 ml. of water then was added, and the mixture was stirred until two clear liquid phases formed. The ether layer then was separated and concentrated to give 4.6 g. (95.5%) of 1-methyl-4-(p-nitro benzoyloxy)-4-piperidyl phenyl ketone (XXIVe), m.p. 164-168°.

A solution of 0.6 g. of XXIVe in 50 ml. of chloroform was hydrogenated at low pressure using 0.1 g. of platinum oxide as catalyst. After 1.5 hours only 0.2 lb. of hydrogen had been consumed. The reduction mixture was filtered, the chloroform was concentrated to about 25 ml., and ether was added to give 0.3 g. of a solid, m.p. 233-235° dec. The 0.3 g. of reduced product was treated with hydrochloride in chloroform-ether mixture to give 0.25 g. of solid, m.p. 235-240° dec. Two recrystallizations of the hydrochloride from acetone, and one recrystallization from acetone-ethyl acetate mixture gave 0.1 g. of pure hydrochloride of 1-methyl-4-(p-nitrobenzoyloxy)-4-piperidyl phenyl carbinol (LXIII) m.p. 232-234° dec.

Anal. Calcd. for C_{20}H_{21}ClN_{2}O_{5}: Cl, 8.71. Found: Cl, 8.48, 8.36.

Raney nickel catalyst was added to 3.5 g. of the p-nitro benzoyloxy compound XXIVe in a mixture of 40 ml. of chloroform and 20 ml. of methanol, and the mixture was subjected to low pressure hydrogenation. Since no hydrogen was consumed after 0.5 hours, more catalyst was added, and high pressure hydrogenation was attempted. After 3.25 hours, 90 lbs. of hydrogen had been consumed. The mixture then was
filtered, concentrated and a green solid, probably a nickel complex, was obtained.

Reaction of 6-Methyl-2-methoxy-2-phenyl-l-ox-6-azaspiro(2.5)octane (XXIa) with p-Aminobenzoic Acid in Pyridine. To 3.5 g. of p-aminobenzoic acid in 25 ml. of pyridine was added 3.0 g. of the epoxyether XXIa in 50 ml. of ether. The mixture was allowed to stand overnight. The solution was concentrated under reduced pressure, and water was added to dissolve the residue. The addition of sodium carbonate produced an oil which crystallized when seeded with base obtained from a smaller preliminary run to give 4.3 g. (97.0%) of 1-methyl-4-(p-aminobenzoyloxy)-4-piperidyl phenyl ketone (XXIVf). The XXIVf then was permitted to dry for one week on a watch glass and recrystallized from acetone-petroleum ether to give 3.6 g. of XXIVf as a first fraction and 0.2 g. as a second.

The 3.6 g. of XXIVf was converted to 3.5 g. of hydrochloride in a chloroform-ether solution. The hydrochloride became tacky when exposed to air but after recrystallization from chloroform-ether and drying under reduced pressure it was crystalline.

Anal. Calcd. for C$_{20}$H$_{23}$ClN$_2$O$_3$: Cl, 9.46; C$_{20}$H$_{24}$Cl$_2$N$_2$O$_3$: Cl, 17.24. Found: Cl, 14.10.

Since the hydrochloride analysis was not definitive the salt was converted to the base by neutralizing a water solution with sodium carbonate. The oil, which formed first, crystallized on seeding with a sample of 1-methyl-4-(p-aminobenzoyloxy)-4-piperidyl phenyl ketone (XXIVf). Recrystallization
of the solid from acetone-petroleum ether gave 2.3 g. of pure XXIVf, m.p. 179-180°. The solubility of the base XXIVf in 0.1N hydrochloric acid was found to be 0.050 g./1.3 ml.

**Anal.** Calcd. for C_{20}H_{22}N_{2}O_{3}: C, 70.98; H, 6.71.
Found: C, 70.67; H, 6.61.

**Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with Isonicotinic Acid in Pyridine.**——A solution of 3.15 g. of the epoxyether XXIa in 20 ml. of ether was added to 3.5 g. of isonicotinic acid dissolved in 50 ml. of hot pyridine. After standing overnight, the mixture was concentrated under reduced pressure and water was added to the oily residue. The addition of sodium carbonate produced an oil which crystallized when seeded with base obtained from a smaller preliminary run to give 4.1 g. (94.5%) of 1-methyl-4-isonicotinoyloxy-4-piperidyl phenyl ketone (XXIVg). The base XXIVg then was permitted to dry for one week on a watch glass. It was recrystallized from acetone-petroleum ether to give 3.25 g. as a first fraction and 0.35 g. as a second.

The 3.25 g. of XXIVg was converted to 3.7 g. of the hydrochloride in an acetone-ether solution. On exposure to air the salt became tacky; however, after drying under reduced pressure the hydrochloride (3.4 g.) was stable to air.

**Anal.** Calcd. for C_{19}H_{21}ClN_{2}O_{3}: Cl, 10.1:
C_{19}H_{22}Cl_{2}N_{2}O_{3}: Cl, 17.85. Found: Cl, 16.5.

Since the hydrochloride did not analyze for a pure salt it was converted to the base by neutralization of a water
solution with sodium carbonate. The oil which formed crystallized when seeded to give 2.5 g. of XXIVg. Recrystallization of XXIVg from acetone-petroleum ether gave 1.9 g. of pure XXIVg, m.p. 126-128°. The solubility of XXIVg in 0.1N hydrochloric acid was found to be 0.050 g./1.4 ml.

**Anal.** Calcd. for C_{19}H_{20}N_{2}O_3: C, 70.35; H, 6.22. Found: C, 70.28, 70.21; H, 5.78, 6.07.

Reaction of 6-Methyl-2-methoxy-2-(p-tolyl)-1-ox-6-azaspiro(2.5)octane (XXIc) with Propionic Acid in Ether.

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A solution of 3.0 g. of the epoxyether XXIc in 50 ml. of ether was added dropwise to 4.0 g. of propionic acid in 50 ml. of ether. After completion of the addition, the mixture was allowed to stand overnight. The ether solution then was concentrated, the residue was dissolved in water, and the solution was basified with sodium carbonate to give solid 1-methyl-4-proprionyloxy-4-piperidyl p-tolyl ketone (XXIVh). Recrystallization of the solid from ether-petroleum ether gave 3.2 g. (89.8°) of XXIVh.

The 3.2 g. of XXIVh was converted to the hydrochloride by the conventional method in ether to give, after recrystallization from acetone, 2.7 g. of the hydrochloride of XXIVh, m.p. 231-233°.

**Anal.** Calcd. for C_{17}H_{24}ClNO_3: Cl, 10.88. Found: Cl, 10.73.

Reaction of 6-Methyl-2-methoxy-2-(p-tolyl)-1-ox-6-azaspiro(2.5)octane (XXIc) with Benzoic Acid in Ether.---

A solution of 2.7 g. of the epoxyether XXIc in 50 ml. of ether
was added dropwise to 4.0 g. of benzoic acid in 75 ml. of ether. After completion of the addition, the mixture was allowed to stand overnight. The ether solution then was concentrated, the residue was dissolved in water and the solution was basified with sodium carbonate to give the solid 1-methyl-4-benzoyloxy-4-piperidyl p-tolyl ketone (XXIVi). Recrystallization of the base from ether-petroleum ether gave 3.0 g. (71.6%) of XXIVi.

The 3.0 g. of XXIVi was converted to the hydrochloride. Recrystallization from acetone gave 2.8 g. of the hydrochloride of XXIVi, m.p. 255-256°. The infrared spectrum (Meade Johnson) of 1-methyl-4-benzoyloxy-4-piperidyl p-tolyl ketone (XXIVi) hydrochloride showed the absorption of the stretching carbonyl of the carboxylic acid ester at 1710 cm.⁻¹, the absorption of the stretching carbonyl of the aromatic ketone at 1640 cm.⁻¹, and the absorption of a para-disubstituted benzene at 747 cm.⁻¹, and the absorption of a mono-substituted benzene at 725 cm.⁻¹ and 708 cm.⁻¹.


Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with Dilute Hydrochloric Acid.

To 2.9 g. of the epoxyether XXIa in 30 ml. of water was added 5 ml. of concentrated hydrochloric acid. The mixture was stirred, and the 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) was isolated by the addition of sodium carbonate. The yield, 2.7 g., was quantitative. After drying, the 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa)
was dissolved in ether, filtered, and precipitated as the hydrochloride to give 2.9 g. of l-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) hydrochloride. Two recrystallizations from methanol, chloroform-ether gave 2.45 g. of pure l-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) hydrochloride, m.p. 171.5-172.5°.

The analysis of l-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) was previously reported on page 69, of the hydrochloride on page 70; and the infrared absorption spectrum on page 69.

**Reaction of 6-Methyl-2-methoxy-2-(p-tolyl)-1-ox-6-azaspiro(2.5)octane (XXIc) with Dilute Hydrochloric Acid.**

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The addition of 3.2 g. of the epoxide ether XXIc to a dilute hydrochloric acid solution gave 3.9 g. of crude l-methyl-4-hydroxy-4-piperidyl p-tolyl ketone (XVIIIb) after neutralization with sodium carbonate. The crude solid was recrystallized from ethyl acetate to give 2.4 g. of pure l-methyl-4-hydroxy-4-piperidyl p-tolyl ketone (XVIIIb), m.p. 156-158°.

The 2.4 g. of XVIIIb was converted to 2.6 g. of the hydrochloride by addition of dry hydrogen chloride to an ether-methanol solution of XVIIIb. Recrystallization of the hydrochloride from acetone gave 2.5 g. of pure l-methyl-4-hydroxy-4-piperidyl p-tolyl ketone (XVIIIb) hydrochloride, m.p. 223-225°. The infrared absorption spectrum (Meade Johnson) of l-methyl-4-hydroxy-4-piperidyl p-tolyl ketone (XVIIIb) hydrochloride showed the absorption of the stretching OH at 3125 cm.⁻¹, the absorption of the stretching
carbonyl of the aromatic ketone at 1640 cm.\(^{-1}\), and the absorption of a \textit{para}-disubstituted benzene at 755 cm.\(^{-1}\).


**Reaction of 6-Methyl-2-ethoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIb) with Hydroxylamine Hydrochloride in Ethanol-Pyridine.**—To 0.4 g. of the epoxyether XXIb in a round bottomed flask equipped with a reflux condenser was added 1.0 g. of hydroxylamine hydrochloride, 5 ml. of absolute ethanol, and 5 ml. of pyridine. The mixture was heated under reflux for 2 hours, after which time the solvents were removed by evaporation under reduced pressure. The residue then was treated with 5 ml. of water, and after neutralization with base, the mixture was extracted with ether. The ether extract gave only a negligible amount of solid. The aqueous layer was made strongly basic with sodium hydroxide to give 0.15 g. of crude 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) oxime, m.p. 198-203°, authentic XVIIIa oxime, m.p. 204-205°.

**Reaction of 6-Methyl-2-ethoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIb) with Picric Acid in Methanol.**—To 0.3 g. of the epoxyether XXIb was added 9 ml. of a saturated solution of picric acid in methanol. After heating the mixture to boiling and allowing it to cool to room temperature, 0.1 g. of a picrate, m.p. 200-203°, was collected.

*The nitrogen analysis were performed by Meade Johnson(32).
In another picrate preparation, 0.15 g. of the epoxyether XXIb and 10 ml. of a saturated solution of picric acid in methanol was allowed to evaporate to dryness. The solid residue was then triturated several times with water and the remaining solid was dissolved in hot methanol. On cooling, the methanol solution deposited 0.2 g. of a picrate, m.p. 199.5-200.5°. A mixture melting point with 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) picrate gave no depression melting at 199-200.5°.

Reaction of 6-Methyl-2-ethoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIb) with Hydrogen Chloride in Ether.——Dry hydrogen chloride was bubbled into 0.15 g. of the epoxyether XXIb dissolved in anhydrous ether, and the hydrochloride which precipitated was collected by filtration to give 0.19 g. of a hydrochloride, m.p. 168-171.5°. Two recrystallizations from chloroform-ether gave 0.09 g. of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) hydrochloride, m.p. 170-172°, authentic XVIIIa hydrochloride, m.p. 170-172°.

Reaction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with Methyl Iodide.——To 0.1 g. of crude epoxyether XXIa in ether was added a slight molar excess of methyl iodide. After long standing less than 0.05 g. of impure precipitate, m.p. 70-150°, had formed. Attempts to recrystallize this solid from chloroform-ether gave an oil.

To 0.3 g. of pure epoxyether XXIa in 10 ml. of methanol
was added a slight molar excess of methyl iodide. After standing for 3 hours, the solution was evaporated to dryness under reduced pressure to give 0.4 g. of a crystalline methiodide, m.p. 205-210°. Recrystallization from acetone gave 0.3 g. of pure 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) methiodide, m.p. 207-208.5°. The infrared absorption spectrum (Spectrum No. 173) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) methiodide showed the absorption of the stretching OH at 3300 cm.⁻¹, the absorption of the stretching carbonyl of the aromatic ketone at 1710 cm.⁻¹, and the absorption of a mono-substituted benzene at 790 cm.⁻¹ and 708 cm.⁻¹.

Reduction of 6-Methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXIa) with Lithium Aluminum Hydride.

To 100 ml. of anhydrous ether was added 3.0 g. (0.08 mole) of lithium aluminum hydride. The mixture was stirred for 1 hour, and 2.0 g. (0.009 mole) of epoxyether XXIa in 20 ml. of ether was added dropwise over a period of 0.5 hour. The mixture then was stirred and heated under reflux for 6 hours, and after cooling, the excess lithium aluminum hydride was decomposed by the cautious addition of water. The voluminous white precipitate which formed was separated by filtration and triturated with ether. The ethereal triturate was dried over sodium carbonate, filtered, and evaporated on a steam bath leaving an oily residue. The oil was distilled under reduced pressure to give 1.7 g. (84.5%) of 1-methyl-4-hydroxy-4-piperidyl-2-methoxy phenyl methane (LX), b.p. 141-143° at
2 mm. The infrared absorption spectrum (Spectrum No. 161) showed the absorption of the OH stretching from 3700 cm$^{-1}$ into the 3000 cm$^{-1}$ region of CH absorption, the absorption of an aliphatic ether at 1093 cm$^{-1}$, and the absorption of a mono-substituted benzene at 780 cm$^{-1}$ and 700 cm$^{-1}$.

A 0.4 g. sample of LX was treated with a slight molar excess of methyl iodide in methanol for a few hours. Concentration of the mixture under reduced pressure left an oil which when dissolved in acetone and treated with ether gave 0.6 g. of LX methiodide. Two recrystallizations from acetone-ethyl acetate gave 0.25 g. of LX methiodide, m.p. 164-205°.

**Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa) with Phenyllithium in Ether and Decomposition of the Reaction Mixture by the Addition of Water.** A suspension of 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 50 ml. of anhydrous ether was added over a period of 0.75 hour to a solution of phenyllithium prepared from 1.4 g. (0.2 g. atom) of lithium and 10.05 g. (0.07 mole) of bromobenzene. After the addition was completed, the reaction mixture was heated under reflux and stirred for 3.75 hours. The reaction mixture then was poured onto 75 g. of ice, the ether layer was separated, and the aqueous layer was washed with ether. The combined ether solutions were dried over sodium carbonate, filtered, and evaporated to give an oily residue. Addition of 10-20 ml. of water and 3 ml. of a 1:1 hydrochloric acid solution to the oil caused precipitation of 1.0 g. (32%) of the hydrochloride of 1-methyl-4-piperidyl diphenylmethanol.
(XXV), m.p. 283-287°. A small sample was recrystallized from methanol to give pure XXV hydrochloride, m.p. 310-312° dec., lit. (26) m.p. 310-311° dec. The infrared absorption spectrum (Sadtler No. 9438) of XXV hydrochloride showed the absorption of the stretching OH at 3350 cm.⁻¹ and the absorption of a mono-substituted benzene at 755 cm.⁻¹ and 710 cm.⁻¹.

**Anal.** Calcd. for C₂₉H₂₃NClO: Cl, 11.16. Found: Cl, 10.38, 11.52.

A small sample of the hydrochloride was converted to the base which on recrystallization from ether-petroleum ether gave pure 1-methyl-4-piperidyl diphenylmethanol (XXV), m.p. 134-135°. The melting point of XXV was not depressed when mixed with a sample of 1-methyl-4-piperidyl diphenylmethanol (XXV) donated by Lyle. (27)

The aqueous solution from which the hydrochloride of XXV had precipitated, was made basic with sodium carbonate and extracted with ether, and the ether extract was dried over sodium carbonate. Filtration, evaporation of the ether solution, and distillation of the residual oil under reduced pressure gave 0.6 g. (30%) of 1-methyl-4-piperidyl phenyl ketone (IXa), b.p. 152° at 4 mm. IXa was characterized by conversion of a small sample to IXa hydrochloride, m.p. 204-206°, which showed no depression of mixed melting point with an authentic sample (m.p. 204-206°); by conversion of a small sample by reaction with phenyllithium in ether to 1-methyl-4-piperidyldiphenylmethanol (XXV), m.p. 131.5-134°, again showing no depression of mixed melting point with an authentic sample, and by analysis.
Anal. Calcd. for C_{13}H_{18}Cl NO: Cl, 14.79. Found: Cl, 14.68.

Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa) with Phenyllithium in Ether and Decomposition of the Reaction Mixture by Addition to a Hydrochloric Acid Solution.---A suspension of 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 50 ml. of anhydrous ether was added over a period of 0.75 hour to an ethereal solution of phenyllithium prepared from 1.4 g. (0.2 g. atom) of lithium and 10.05 g. (0.07 mole) of bromobenzene. The conventional three-necked apparatus was used but modified by having an outlet from the bottom of the three-necked flask controlled by a stopcock. After the addition was complete, the reaction mixture was heated under reflux and stirred for 3.75 hours. The reaction mixture then was added dropwise, over a period of 3 hours, thru a capillary tube to 150 ml. of 10% hydrochloric acid, stirred by a magnetic stirrer. The acid solution was washed with ether and made basic with sodium carbonate. The basic solution was extracted with ether; the ether extract was dried over sodium carbonate, filtered, and evaporated to give 2.25 g. of an oily residue. Addition of 20 ml. of water and 3 ml. of concentrated hydrochloric acid to the oil caused the precipitation of a solid which was collected by filtration to give 0.1 g. (0.03%) of 1-methyl-4-piperidyl diphenylmethanol (XXV) hydrochloride, m.p. 295-298°. Recrystallization from acetone gave 0.02 g. of pure XXV hydrochloride, m.p. 310-312° dec. The melting point was not
depressed on mixing with an authentic sample.

The acid solution from which the hydrochloride had precipitated, was made basic with sodium carbonate and extracted with ether, and the ether extract was dried over sodium carbonate. Filtration and evaporation of the ether solution, and distillation of the residual oil under reduced pressure gave 1.3 g. (65%) of 1-methyl-4-piperidyl phenyl ketone (IXa), b.p. 140° at 3 mm.

Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa) with Phenyllithium in Ether and Decomposition of the Reaction Mixture by Addition of Benzoyl Chloride.

A suspension of 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 75 ml. of anhydrous ether was added over a period of 0.75 hour to a solution of phenyllithium prepared from 1.4 g. (0.2 atom) of lithium and 10.05 g. (0.07 mole) of bromobenzene. After the addition was complete, the reaction mixture was heated under reflux and stirred for 3.75 hours. An excess of benzoyl chloride, 1.6 ml., was added dropwise causing a very exothermic reaction. The reaction mixture then was stirred for 2 hours, filtered, and concentrated under reduced pressure to give a pasty solid. Addition of a small amount of methanol gave 1.95 g. (54%) of impure 1-methyl-4-piperidylidene-α-benzoyloxy-α-phenylmethane (XXVII) hydrobromide, m.p. 247-253°. Recrystallization of a small sample of the hydrobromide from chloroform-acetone gave pure XXVII hydrobromide, m.p. 255-257°. The infrared absorption spectrum (Sadtler No. 9434) of XXVII hydrobromide showed the absorption of the
stretches carbonyl of the carboxylic acid ester at 1660 cm\(^{-1}\),
the absorption of the stretching C=O of the carboxylic acid ester at 1240 cm\(^{-1}\) and 1160 cm\(^{-1}\), and the absorption of a mono-substituted benzene at 695 cm\(^{-1}\) and 720 cm\(^{-1}\). The ultraviolet absorption spectrum (see page 144) of XXVII hydrobromide was determined in 95% ethanol and showed a minimum at 223 \(\mu\)m, absorbance 0.108 (Log \(\varepsilon\) 3.938); a maximum at 253 \(\mu\)m, absorbance 0.321 (Log \(\varepsilon\) 4.424), at a concentration of 0.00468 g/l.

*Anal. Calcd. for C\(_{20}\)H\(_{22}\)BrNO\(_2\): C, 61.68; H, 5.71; Br, 20.58. Found: C, 60.49, 60.42; H, 5.69, 5.77; Br, 21.25.

The picrate of XXVII was prepared in ethanol to give a derivative, m.p. 211-213°.


**Hydrolysis of 1-Methyl-4-piperidylidene-\(\alpha\)-benzoyloxy-\(\alpha\)-phenylmethanol (XXVII) Hydrobromide.**—An attempted hydrolysis of XXVII with sodium hydroxide was inconclusive. However, 0.55 g. of XXVII hydrobromide on heating under reflux in 20 ml. of a 20% hydrochloric acid solution, gave 0.35 g. of 1-methyl-4-piperidyl phenyl ketone (IXa), which was characterized as its picrate, m.p. 200-201°, and 0.1 g. of recrystallized (from hot petroleum ether) benzoic acid, m.p. 121-122.5°, which showed no melting point depression when mixed with an authentic sample.

*The microdeterminations of carbon and hydrogen were performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee.
Reaction of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride (XIIb) with Phenylmagnesium Bromide.

This general procedure was followed for five runs of the reaction of 1-methyl-4-chloro-4-piperidyl phenyl ketone (XIIb) hydrochloride with phenylmagnesium bromide. Run No. 3 is given as an example with the following pertinent departures from this procedure: Run No. 1 used 3.5 g. (0.013 mole) of XIIb and the Grignard reagent was prepared from 2.4 g. (0.1 g. atom) of magnesium turnings and 15.7 g. (0.1 mole) of bromobenzene. Run No. 2 used 5.5 g. (0.02 mole) of XIIb. The reaction mixture in run No. 5 was heated under reflux for an additional hour.

A suspension of 3.5 g. (0.013 mole) of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) in anhydrous ether was added over a period of 0.5 hour, to an ethereal solution of phenylmagnesium bromide prepared from 3.6 g. (0.15 g. atom) of magnesium turnings and 22 g. (0.14 mole) of bromobenzene. After the addition was complete, the reaction mixture was heated under reflux and stirred for 1.0 hour. The reaction mixture was then processed accordingly:

Run No. 1.——After standing overnight, the reaction mixture was poured into 50 ml. of water and extracted with ether, and the ether extracts were dried over potassium carbonate. After filtration of the dried ether extracts, the addition of dry hydrogen chloride to the ethereal solution caused 3.0 g. of an oily precipitate, which could not be crystallized, to separate. Removal of the ether by evaporation and neutralization of an aqueous solution of the residue with
sodium carbonate gave a new oil which was extracted with ether, and dried over sodium carbonate. Filtration and evaporation of the ether solution gave the dried oil from which no crystalline product could be isolated. On redissolving the oil in ether and adding dry hydrogen chloride, 2.6 g. of a semi-solid was again obtained.

To 0.5 g. of the semi-solid dissolved in a small amount of water was added an ethanolic picric acid solution which caused the precipitation of 0.4 g. of a solid. Recrystallization of the solid from methanol gave 0.1 g. of impure 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) picrate, m.p. 215-217° (XXIX picrate prepared from an authentic sample melted at 223-225°) as a first fraction and 0.1 g. of impure 1-methyl-4-piperidyl phenyl ketone (IXa) picrate, m.p. 178-187°, (lit. (16) m.p. 204-206°) as a second. No further attempt was made to purify these picrates.

Another 0.5 g. portion of the semi-solid on recrystallization from acetone-ether gave 0.1 g. of impure 1-methyl-4-phenyl-4-piperidyl diphenylmethanol (XXX) hydrochloride, m.p. 215-217°, lit. m.p. 310-312° (26), m.p. 290-291° (17b). Recrystallization from acetone-ether gave 0.05 g. of pure XXX, m.p. 218-221°.

**Anal.** Calcd. for C_{25}H_{28}ClNO: Cl, 9.00 Found: Cl, 9.30.

The remainder of the semi-solid was dissolved in water, neutralized with sodium carbonate, and extracted into ether, and the ether extracts were dried over sodium carbonate. After filtration, evaporation of the dried ether solution gave an oily residue which on the addition of an ethanolic picric acid
solution yielded 0.4 g. of a mixture of picrates, m.p. 185-208\(^{\circ}\). One recrystallization from methanol raised the melting point of the mixture (m.p. 205-217\(^{\circ}\)) and gave 0.35 g. of the solid. A second recrystallization from methanol gave 0.12 g. of impure l-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) picrate, m.p. 218-219\(^{\circ}\), which when mixed with the picrate of XXIX (m.p. 223-225\(^{\circ}\)) prepared from a known sample (27), melted at 222-225\(^{\circ}\). A micromolecular weight determination of the impure picrate by the spectrophotometric method (28), showed an average molecular weight of 271.5. (The molecular weight of XXIX is 279.8).

Molecular weight determination: A 0.001 g/l 95% ethanol solution of the impure XXIX picrate showed the following pertinent readings:

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Run No. 2.------The reaction mixture was poured onto 75 g. of ice, and the aqueous solution was extracted with ether. The ether extract was washed with three portions (totaling 125 ml.) of dilute hydrochloric acid, and the acid extracts were made basic and extracted with ether. This ether extract was dried over potassium carbonate. After filtration and evaporation of the ether, the oily residue

*These values were freely given by Lyle(27).
(4.9 g.) was distilled under reduced pressure to give 3.8 g. of an oil, b.p. 160-250° at 3 mm., and approximately 0.5 g. of residue which was not characterized. The 3.8 g. of oil was redistilled under reduced pressure to give two fractions.

The first fraction was collected at 110-112° at 1 mm. and was 1.45 g. (35.7%) of impure 1-methyl-4-piperidyl phenyl ketone (IXa), lit. (18) b.p. 157-159° at 5 mm. A 0.3 g. sample of this fraction was precipitated as the hydrobromide from an ether solution, and after recrystallization from isopropyl alcohol gave 0.1 g. of pure 1-methyl-4-piperidyl phenyl ketone hydrobromide (Xa), m.p. 202-204° which showed no depression when mixed with the hydrobromide prepared from a known sample of IXa. The second fraction distilled at 140-182° at 1 mm. The majority of the fraction boiled at the higher temperature. This fraction was 1.9 g. (34.0%) of impure 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXXIX) as an oil, lit. (23) b.p. 160-170° at 2 mm.

A 0.15 g. sample of the higher boiling fraction was treated with 15 ml. of a dilute hydrochloric acid solution to give 0.03 g. of 1-methyl-4-piperidyldiphenylmethanol (XXV) hydrochloride, m.p. 313-315°. The melting point of this hydrochloride was not depressed when mixed with an authentic sample.

A solution of 0.5 g. of the higher boiling fraction in 20 ml. of concentrated sulphuric acid was stirred for 1 hour at 0° in a salt-ice bath. The acid solution was made basic with potassium carbonate, the alkaline solution was extracted with ether, and the ether extract was dried over
potassium carbonate. Filtration and evaporation of the ether solution left an oil which on the addition of a methanolic picric acid solution yielded 0.3 g. of impure 1-methyl-4-phenyl-4-piperidyl phenyl ketone picrate (XXIX), m.p. 195-211°. One recrystallization from methanol gave 0.15 g. of pure XXIX picrate, m.p. 223-225°, which showed no melting point depression when mixed with the picrate of XXIX prepared from a known sample (27).

A 0.4 g. sample of the higher boiling fraction was heated under reflux for 3 hours with 2.0 g. of lithium aluminum hydride in 30 ml. of ether. The reaction mixture was decomposed with water, the residue was extracted with ether, and the ether extracts were dried over potassium carbonate. After filtration and evaporation of the ether the addition of a methanolic picric acid solution to the residual oil caused precipitation of a solid which after recrystallization from methanol gave 0.2 g. of what is presumed to be, 1-methyl-4-phenyl-4-piperidylphenylmethanol (LXV) picrate, m.p. 199-201°. The picrate showed a melting point depression when mixed with the picrate (m.p. 203-205°) of 1-methyl-4-piperidylidiphenylmethanol (XXV) prepared from a known sample of XXV.

Run No. 3.----To the reaction mixture was added drop-wise, over a period of 2 hours, 30 ml. of water with stirring. The voluminous inorganic precipitate was dissolved by the addition of 50 ml. of a 1:1 hydrochloric acid solution. Extraction of the acid solution with ether caused the precipitation of 3.0 g. of a solid which was collected by
filtration. On addition of a small amount of acetone to the 3.0 g. of solid, part of it dissolved, leaving 1.2 g. (18.2%) of impure 1-methyl-4-phenyl-4-piperidylidendiphenylmethanol (XXX) hydrobromide, m.p. 230-235°C. Recrystallization of 1.0 g. of this hydrobromide from acetone gave 0.6 g. of pure XXX hydrobromide, m.p. 225-227°C. The melting point of XXX hydrobromide showed a depression (m.p. 195-210°C) when mixed with a sample of the hydrochloride (m.p. 249-251°C) of XXIX prepared from a known sample (27) of XXIX. A solution of the remaining 0.2 g. of crude XXX hydrobromide in water on treatment with sodium carbonate gave 0.15 g. of crude XXX, m.p. 82-90°C. Recrystallization from ether-petroleum ether gave 0.1 g. of pure XXX, m.p. 122-124°C.

The acetone filtrate which contained 1.8 g. of the original solid was evaporated to dryness under reduced pressure to leave an oil. The addition of sodium carbonate to an aqueous solution of the oil produced a new oil which was not characterized further, but the oil was presumed to be 1-methyl-4-piperidylidendiphenylmethanol (XXV) (in a maximum yield of 33.2%).

The acid solution from which the 3.0 g. of solid had precipitated, was made basic with sodium carbonate. The alkaline solution was extracted with ether, and the extracts were dried over sodium carbonate and filtered. The ether was removed by evaporation leaving 1.3 g. of an oil. The oil was dissolved in 15 ml. of a 1:1 mixture of methanol and pyridine, 1.5 g. of hydroxylamine hydrochloride was added, and the mixture was heated under reflux for 2 hours. The reaction
mixture was evaporated to dryness under reduced pressure, and the oily residue was dissolved in water. The addition of sodium carbonate to the aqueous solution produced a new oil which was separated by extraction with ether. The ether extract was dried over sodium carbonate, filtered and concentrated on a steam bath precipitating 0.45 g. of a solid m.p. 145-151°. Recrystallization of the solid from ether-petroleum ether gave 0.25 g. of a mixture (m.p. 145-160°) presumed to be the oximes of 1-methyl-4-piperidyl phenyl ketone (IXa) and 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX). No further attempt was made to separate these oximes. The literature reports the oximes of IXa and XXIX to melt at 186-187° (29) and 184-186°(17a), respectively.

Run No. 4.---To the reaction mixture was added drop-wise, over a period of 2 hours, 30 ml. of water with stirring. The voluminous inorganic precipitate was triturated with several portions of ether, and the ether triturate was extracted with four 40 ml. portions of 10% hydrochloric acid. The acid solution was made basic with sodium carbonate and extracted with ether, and the ether extract was dried over sodium carbonate. Addition of dry hydrogen chloride to the filtered dry ether extract caused the precipitation of 4.8 g. of a semi-solid, which was collected by filtration. Addition of acetone to the semi-solid failed to give a crystalline product; consequently, the acetone was removed by evaporation. The oily residue was dissolved in water, and the solution was neutralized with sodium carbonate. The alkaline solution was extracted with ether. After drying the ether extract over
sodium carbonate and filtering the solution, dry hydrogen bromide was added causing the separation of an oil. On evaporation of the ether and addition of a small amount of acetone, the oil partially crystallized to give 1.2 g. (18.2%) of impure 1-methyl-4-phenyl-4-piperidyl diphenylmethanol (XXX) hydrobromide, m.p. 230-233° dec.

The acetone filtrate, from which the hydrobromide had been removed, was concentrated under reduced pressure, and the residual oil was dissolved in water. The addition of sodium carbonate to the aqueous solution produced a new oil which was separated by extraction with ether. The ether extract was dried over sodium carbonate, filtered, and evaporated, and the residual oil was distilled under reduced pressure to give two fractions. The first fraction boiled at 150-160° at 12 mm. and gave 0.55 g. (13.5%) of impure 1-methyl-4-piperidyl phenyl ketone (IXa); lit b.p. 157-159° at 5 mm. (18), 160-163° at 13 mm. (16). The second fraction boiled at 215-220° at 12 mm. and gave 0.95 g. (17.1%) of impure 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX), lit. (23) b.p. 160-170° at 2 mm. Treatment of a 0.4 g. sample of the impure XXIX with dry hydrogen chloride in ether produced an oil which, on removal of the ether by evaporation and addition of a small amount of acetone to the residue, crystallized to give 0.2 g. of impure 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) hydrochloride, m.p. 235-240°. One recrystallization from acetone-ether gave 0.18 g. of XXIX hydrochloride, m.p. 245-249°. The hydrochloride of XXIX prepared from an authentic sample melts at 249-251°.
Run No. 5.—The reaction mixture was added dropwise over a period of 2 hours, to 150 ml. of 10% hydrochloric acid stirred by a magnetic stirrer. The reaction mixture was added through a capillary tube immersed in the acid solution and the conventional three-necked apparatus used was modified by having an outlet from the bottom of the three-necked flask controlled by a stopcock. Extraction of the acid solution with ether caused the precipitation of 0.7 g. (10.6%) of impure 1-methyl-4-phenyl-4-piperidyl diphenylmethanol (XXX) hydrobromide, m.p. 215-225°.

The acid solution was made basic with sodium carbonate, and the alkaline solution was extracted with ether. The ether extract was dried over sodium carbonate and filtered, and the ether was removed by evaporation leaving 3.6 g. of an oil residue. The oil was distilled under reduced pressure to give two fractions. The first fraction boiled at 140-146° at 6 mm. and gave 0.45 g. (11.1%) of impure 1-methyl-4-piperidyl phenyl ketone (IXa). The second fraction boiled at 210-212° at 6 mm. and gave 0.95 g. (17%) of impure 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX).

Reaction of Demerol (Ethyl 1-Methyl-4-phenylisonipeo-
tag) (XXXII) Hydrochloride with Phenylmagnesium Bromide.

-----To an ethereal solution of phenylmagnesium bromide prepared from 23.6 g. (0.15 mole) of bromobenzene and 3.6 g. (0.15 g. atom) of magnesium turnings, was added over a period of 0.5 hour, 4.2 g. (0.015 mole) of ethyl 1-methyl-4-phenylisonipeo-
tag (XXXII) hydrochloride as a powdered solid. After the mixture was heated under reflux for 8 hours with stirring,
the reaction mixture was poured onto a mixture of 30 ml. of concentrated hydrochloric acid and 20 g. of ice. The acid solution was extracted with ether, and the ether extracts were discarded. The acid solution was made basic with sodium carbonate. This alkaline solution was extracted with ether and the ether extract was dried over Dryerite. The ether then was filtered, and since an oily material would not dissolve on rinsing the drying agent with ether, the drying agent was rinsed with acetone which was added to the ether filtrate. Addition of dry hydrogen bromide to the ether-acetone solution effected no change, thus the solvents were removed by evaporation under reduced pressure leaving an oil as the residue. The oil was dissolved in water, the solution was made basic with sodium carbonate, and the alkaline solution was extracted with ether. After the ether extract was dried over sodium carbonate, filtered, and evaporated, a residue of 3.2 g. (88% recovery) of crude ethyl 1-methyl-4-phenylisonipecotate (XXXII) was left as a residual oil. A solution of 0.2 g. of this oil in ether was treated with dry hydrogen chloride causing the precipitation of 0.15 g. of impure XXXII hydrochloride, m.p. 149-154°. Two recrystallizations from acetone gave 0.05 g. of XXXII hydrochloride, m.p. 185-186°, lit. (14) m.p. 187-188°.

Preparation of 1-Methyl-4-phenyl-4-piperidylidiphenylmethanol (XXX).—An ethereal solution of phenyllithium was prepared from 10.5 g. (0.06 mole) of bromobenzene and 1.4 g. (0.2 g. atom) of lithium wire in the conventional three-necked apparatus. To this solution was added over a period of 0.5
hour, 1.1 g. (0.004 mole) of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX), prepared by the method of Eisleb (30), m.p. 76-78°, lit. (23) m.p. 77-78°, in 30 ml. of ether. The mixture was heated under reflux for 11.5 hours. After this time, the reaction mixture was poured onto a mixture of 20 ml. of concentrated hydrochloric acid and 50 g. of ice causing the precipitation of 1.3 g. (76.5%) of crude 1-methyl-4-phenyl-4-piperidylidiphenylmethanol (XXX) hydrobromide. Recrystallization of 0.9 g. of this crude hydrobromide from acetone gave 0.3 g. of XXX hydrobromide, m.p. 225-227° dec., as a first fraction, and 0.25 g. of XXX hydrobromide, m.p. 219-221°, as a second fraction. A sample of the first fraction did not depress the melting point of a sample of XXX hydrobromide obtained in the reaction of XIIc and phenylmagnesium bromide.

Preparation of 1-Methyl-4-hydroxy-4-piperidylphenylmethane (LXI).---To an ethereal solution of benzylmagnesium chloride prepared from 9.9 g. (0.08 mole) of benzyl chloride and 1.9 g. (0.08 g. atom) of magnesium turnings was added dropwise, 3.0 g. (0.026 mole) of 1-methyl-4-piperidone (LXII)* in 30 ml. of ether, over a period of 0.5 hour. The reaction mixture was heated under reflux for 2.5 hours and then added to a dilute hydrochloric acid solution. The acid solution was extracted with ether, the ether extract was discarded, and the acid solution was made basic with sodium carbonate. The gelatinous alkaline solution was extracted with ether; the ether

*Kindly donated by Lyle (27).
extract was dried over sodium carbonate, filtered, and evaporated on a steam bath leaving 2.3 g. of 1-methyl-4-hydroxy-4-piperidylphenylmethane (LXI) as an oil. A re-extraction of the gelatinous alkaline solution with chloroform, drying of the chloroform extract over sodium carbonate, and concentration of the chloroform solution on a steam bath gave an additional 1.1 g. (total of 63.0%) of LXI as an oil.

The 2.3 g. of LXI obtained from the ether extraction was distilled under reduced pressure to give 1.6 g. of pure LXI, b.p. 125-130° at 17 mm. Addition of petroleum ether to this liquid LXI induced crystallization giving 0.8 g. of LXI, m.p. 79-82°, as a first fraction and on evaporation of the solvent, 0.8 g. of LXI as a residue.

The addition of petroleum ether to the 1.1 g. of LXI obtained from the chloroform extraction also induced crystallization giving 0.6 g., m.p. 80°, the heating was too rapid. Two recrystallizations from petroleum ether gave 0.05 g. of LXI, m.p. 80-82°. The infrared absorption spectrum (Spectrum No. 94) of LXI showed no distinct OH band but did show absorption due to OH stretching from 3300 cm⁻¹ into 3000 cm⁻¹ region of CH absorption, and showed the absorption of a mono-substituted benzene at 770 cm⁻¹ and 700 cm⁻¹.


Treatment of a 0.2 g. sample of LXI with a slight molar excess of methyl iodide in methanol gave 0.3 g. of LXI methiodide, m.p. 199-201°. Recrystallization from acetone gave 0.2 g. of LXI methiodide, m.p. 199-201°. The infrared
absorption spectrum (Spectrum No. 92) of LXI methiodide showed absorption due to OH stretching at 3338 cm.$^{-1}$, and the absorption of a mono-substituted benzene at 763 cm.$^{-1}$ and 710 cm.$^{-1}$.

**Catalytic Reduction of 1-Methyl-4-bromo-4-piperidyl phenyl Ketone Hydrobromide (XIIa) Over Platinum Oxide in Methanol.**——A solution of 3.6 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 75 ml. of methanol was subjected to 3 atm. of pressure of hydrogen at room temperature with 0.1 g. of platinum oxide as catalyst. After the pressure of hydrogen had ceased to change, the reaction mixture was filtered, and the solvent was removed by evaporation on a steam bath leaving an oil as the residue. A portion, 0.2 g. of the oil was dissolved in water, and the solution was filtered. Addition of sodium carbonate caused the precipitation of a solid, m.p. 152-155°. The solid was recrystallized from ether-petroleum ether to give pure 1-methyl-4-piperidylphenylmethanol (XVII), m.p. 154-157°. The melting point was not depressed when a sample was mixed with authentic XVII, obtained from the catalytic reduction of XV. The remainder of the oil was dissolved in methanol, and ether was added causing an oil to form. The solvents were allowed to evaporate slowly, and on treating the oil again with methanol and ether 1.35 g. (54.5% overall yield) of 1-methyl-4-piperidylphenylmethanol hydrobromide (XVIa), m.p. 133-136°, precipitated.
Catalytic Reduction of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride (XIIb) Over Platinum Oxide in Methanol.---Results similar to those above were obtained when 2.4 g. of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) in 50 ml. of methanol was subjected to hydrogenation. The reduction mixture, after filtration, was concentrated on a steam bath. The residual oil was dissolved in water and neutralized with sodium hydroxide to give 1.7 g. of crude 1-methyl-4-piperidylphenylmethanol (XVII). Recrystallization from hot benzene afforded 1.1 g. (46.0%) of pure XVII, m.p. 154-156°.

Catalytic Reduction of 1-Methyl-4-chloro-4-piperidyl Phenyl Ketone Hydrochloride (XIIb) over Platinum Oxide in Methanol-Sodium Carbonate Mixture.---To a solution of 1.0 g. of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) in 50 ml. of methanol was added 0.5 g. of sodium carbonate, and the mixture was subjected to 3 atm. of pressure of hydrogen at room temperature with 0.1 g. of platinum oxide as catalyst. After the pressure of hydrogen had ceased to change, the reaction mixture was filtered, and the solvent was removed under reduced pressure leaving a solid residue. Addition of water and sodium carbonate gave 0.4 g. (53.4%) of 1-methyl-4-piperidylphenylmethanol (XVII), m.p. 142-150°. Recrystallization from benzene gave 0.25 g. of XVII, m.p. 153-155°. An additional 0.1 g. of XVII was isolated from the aqueous solution.
Catalytic Reduction of l-Methyl-4-hydroxy-4-piperidyl Phenyl Ketone (XVIIIa) Hydrochloride over Platinum Oxide in Methanol.—-A solution of 1.0 g. of the hydrochloride of l-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) in 50 ml. of methanol was subjected to 3 atm. of pressure of hydrogen at room temperature with 0.1 g. of platinum oxide as catalyst. After the pressure of hydrogen had ceased to change, the reaction mixture was filtered, and the methanol solution was concentrated on a steam bath. Addition of ether caused an oil to separate. All attempts to crystallize the oil failed. Conversion of the oil to the base with sodium carbonate gave a new oil, an ether solution of which deposited l-methyl-4-hydroxy-4-piperidylphenylmethanol (XXXV), m.p. 142-144°. The infrared absorption spectrum (Sadtler No. 9445) of XXXV showed the absorption of the stretching OH at 3510 cm.\(^{-1}\) and the absorption of a mono-substituted benzene at 748 cm.\(^{-1}\) and 705 cm.\(^{-1}\).

Catalytic Reduction of l-Methyl-4-phenyl-4-piperidyl Phenyl Ketone (XXIX) Hydrochloride over Platinum Oxide in Methanol.—-A solution of 1.0 g. of the hydrochloride of l-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) in 50 ml. of methanol was subjected to 3 atm. of pressure of hydrogen at room temperature with 0.1 g. of platinum oxide as catalyst. Only a negligible change in the pressure of hydrogen occurred after 1.75 hours. The reaction mixture was filtered, and concentrated, and ether was added to give 0.7 g. of precipitate, m.p. 190-217°. This solid was recrystallized from acetone to give two fractions totaling about 0.5 g.; 1st fraction, m.p.
195-235°; 2nd fraction, m.p. 225-229°. 1-Methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) as the hydrochloride melts at 249-251°. The infrared absorption spectrum (Spectrum No. 174) of a sample taken from a mixture of the two fractions showed the absorption of the stretching OH from 3600 cm.$^{-1}$ to 3200 cm.$^{-1}$, the absorption of the stretching carbonyl of the aromatic ketone at 1680 cm.$^{-1}$, and the absorption of a mono-substituted benzene at 757 cm.$^{-1}$ and 700 cm.$^{-1}$.

**Catalytic Reduction of 1-Methyl-4-hydroxy-4-piperidyl Phenyl Ketone (XVIIIa) Hydrochloride over Platinum Oxide in Chloroform.**——A solution of 0.75 g. of the hydrochloride of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XVIIIa) in 130 ml. of chloroform was subjected to 3 atm. of pressure of hydrogen at room temperature with 0.1 g. of platinum oxide as catalyst. After the pressure of hydrogen had ceased to change, the reaction mixture was filtered, and the chloroform solution was concentrated under reduced pressure leaving an oil as the residue. Methanol was added to dissolve the oil, and the solvents then were evaporated on a steam bath again yielding an oil. The oil was dissolved in water, and sodium carbonate was added causing a second liquid phase to separate. This organic layer was taken up in ether and the aqueous layer was extracted with ether. The ether solutions were dried over sodium carbonate, filtered, and concentrated on a steam bath. Addition of petroleum ether to the ether solution during concentration then afforded 0.35 g. of precipitate, m.p. 115.5-119.5°. One recrystallization from ether-petroleum ether
solvent pair gave 0.2 g. of solid, m.p. 117-129°. A second recrystallization from ether gave 0.1 g. of solid, m.p. 117-135°. No further attempts were made to purify this compound.

**Catalytic Reduction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa) over Platinum Oxide in Chloroform.**—A solution of 2.0 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 150 ml. of chloroform was subjected to 3 atm. of pressure of hydrogen at room temperature with 0.1 g. of platinum oxide as catalyst. After the pressure of hydrogen had ceased to change, the reaction mixture was filtered, and the solvent was removed by evaporation under reduced pressure to leave a residual oil. The oil was dissolved in about 10 ml. of methanol, and ether was added to give 0.7 g. (44.7%) of crude 1-methyl-4-piperidyl phenyl ketone hydrobromide (Xa), m.p. 196-201°.

**Catalytic Reduction of 1-Methyl-4-bromo-4-piperidyl Phenyl Ketone Hydrobromide (XIIa) over Palladium-on-Charcoal in Methanol.**—A solution of 1.0 g. of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) in 50 ml. of methanol was subjected to 3 atm. of pressure of hydrogen at room temperature with 0.2 g. of palladium-on-charcoal as catalyst. Since there was only a negligible change in the pressure of hydrogen after 1.5 hours, the mixture was subjected to 110-180 atm. of pressure of hydrogen. After the pressure of hydrogen had ceased to change, the reaction mixture was filtered, and the methanol solution was concentrated on a steam bath. Addition of ether then afforded crude 1-methyl-4-piperidyl phenyl ketone hydrobromide (Xa), m.p. 201-204°.

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Reaction of 1-Methyl-4-bromo-4-piperidyl Phenyl
Ketone Hydrobromide (XIIa) with Sodium Borohydride by Inverse
Addition.* A. Isolation of XXXVIII as the Hydrobromide.

To 10.0 g. (0.03 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) dissolved in 50 ml. of methanol in the conventional three-necked apparatus was added dropwise, 6.0 g. (0.16 mole) of sodium borohydride dissolved in 50 ml. of methanol. The initial addition of 1-2 ml. of the sodium borohydride solution produced a very exothermic reaction so that the reaction mixture was cooled with an ice-bath. The remainder of the sodium borohydride solution then was added at room temperature over a period of 0.75 hour. The reaction mixture was stirred for an additional hour at room temperature. Evaporation of the methanol under reduced pressure left a solid residue to which was added 50 ml. of water. The alkaline solution thus produced was extracted with ether, and the ether extract was dried over sodium carbonate. Filtration of the ether and removal of the ether by distillation on a steam bath left an oily residue. The oil was treated with petroleum ether, and two layers formed; one layer appeared to be water, but it probably was a mixture of hydrobromides formed by the decomposition of the oil. The petroleum ether

*A reaction of 3.6 g. (0.01 mole) of XIIa in methanol with 6.6 g. (0.01 mole) of sodium borohydride at the boiling temperature of methanol produced 1.9 g. of an oil, b.p. 154-157° at 12 mm., nD20 1.5271. Attempts to repeat this experiment produced largely a high boiling oil, b.p. 215-225° at 2 mm. and only a small amount of a low boiling oil, b.p. 90-105° at 2 mm. The infrared absorption spectrum (Spectrum No. 154) of this lower boiling oil was inconclusive since the Perkin-Elmer infrared spectrophotometer was not functioning properly at the time.
solution was dried over sodium carbonate. Filtration, and concentration of the petroleum ether solution on a steam bath gave 5.4 g. (73.5%) of XXXVIII as an oil which gave a positive Beilstein test. The 5.4 g. of XXXVIII was dissolved in ether and treated with dry hydrogen bromide to produce a new oil. This new oil was dissolved in acetone, and on concentration of the acetone solution on a steam bath 4.7 g. of XXXVIII hydrobromide, m.p. 161-163°, precipitated. The melting point of this XXXVIII hydrobromide was not depressed on mix-melting with the XXXVIII hydrobromide (m.p. 163.5-165.5°) obtained in the reaction of XIIa with lithium aluminum hydride, melting at 161-163°. Similarly the infrared absorption spectrum (Spectrum No. 159) of this XXXVIII hydrobromide was superimposable on the infrared absorption spectrum (Spectrum No. 97) of XXXVIII hydrobromide obtained from the reaction of XIIa with lithium aluminum hydride.

**Anal.** Calcd. for C13H17Br2N: 1 Br, 23.03; 2 Br, 46.06. Found: Br, 45.70 (Volhard), 44.86 (Stepanow).

**B. Isolation of XXXVIII as the Base.**——In a similar treatment of 10.0 g. of XIIa by the inverse addition of 6.0 g. of sodium borohydride, 7.75 g. of crude XXXVIII, as an oil was obtained after the reaction mixture was treated as before. Addition of petroleum ether to the 7.75 g. of crude XXXVIII produced two layers which were separated in a separatory funnel. The orange colored heavier layer, presumed to be a mixture of the hydrobromide of XXXVIII and its dehalogenated decomposition products, weighed 2.3 g. Concentration of the petroleum ether layer gave 4.7 g. of colorless XXXVIII as an
oil. Both oils gave intense positive Beilstein tests. The ultraviolet absorption spectrum (see page 145) of the impure XXXVIII was determined in 95% ethanol and showed a minimum at 227 μm, absorbance 0.817 (Log ε 3.557); a maximum at 249 μm, absorbance 1.24 (Log ε 3.791), at a concentration of 0.0530 g/l.

An attempted distillation of 2.0 g. of the colorless XXXVIII under a pressure of 5 mm. using a woods metal bath resulted in the decomposition of XXXVIII. The colorless XXXVIII changed to an orange oil within 15 seconds after it was immersed in the woods metal bath at 90°. Raising the bath temperature to 260° caused no distillation to occur, and the colorless XXXVIII changed to a dark red oil.

A Volhard analysis (acid medium) of the crude XXXVIII, after it had stood for several hours at room temperature, showed only 2.59-3.79% bromine to be present. Addition of ether to this crude XXXVIII caused the separation of an oily solid, presumably a hydrobromide mixture of XXXVIII and its dehydrohalogenated decomposition products. Addition of dry hydrogen bromide to the ether solution produced an oil from which no XXXVIII hydrobromide could be isolated.

**Attempted Preparation of XXXVIII Methiodide.** An 0.65 g. sample of XXXVIII hydrobromide was treated with 25 ml. of water. XXXVIII hydrobromide did not appear to dissolve but the slow addition of sodium carbonate to the heterogeneous mixture produced a clear solution and then a milky suspension. This alkaline solution was treated with ether, the ether extract
was dried over sodium carbonate, and after filtering, the ether solution was concentrated leaving an oily residue. The addition of a slight molar excess of methyl iodide to a methanol solution of the oily residue and evaporation of the methanol under reduced pressure produced a new oil. No solid product could be isolated from this new oil.

Reaction of XXXVIII with Lithium Aluminum Hydride in Ether.-----To 100 ml. of ether was added 3.0 g. (0.078 mole) of lithium aluminum hydride, and the mixture was stirred for 2 hours. A 2.0 g. (0.006 mole) sample of XXXVIII hydrobromide then was added as a powder over a period of 0.5 hour, and the mixture was heated under reflux for 8 hours. After cooling, the excess lithium aluminum hydride was decomposed by the cautious addition of water, and the voluminous precipitate which formed was triturated with ether. The ether tritrate was dried over sodium carbonate and filtered, and the ether was removed by distillation leaving 1.45 g. (78.7%) of XXXIX as a crude oil. The crude oil was distilled under reduced pressure, and the distillate was collected in three fractions. The first fraction weighed 0.2 g., b.p. 104-105° at 5 mm., the second fraction weighed 0.15 g., b.p. 104-105° at 5 mm., and the third fraction weighed 0.50 g., b.p. 104-105° at 5 mm. The ultraviolet absorption spectrum (see page 145) of the second fraction of XXXIX was determined in 95% ethanol and showed a minimum at 222 μ, absorbance 0.218 (Log ε 3.817); a maximum at 245 μ, absorbance 0.462 (Log ε 4.144), at a concentration of 0.00622 g/l.
Treatment of 0.35 g. of the third fraction with dry hydrogen bromide in ether gave 0.4 g. of XXXIX hydrobromide as a semi-solid. Recrystallization of the hydrobromide from acetone, in which the hydrobromide was very soluble, gave 0.05 g. of pure XXXIX hydrobromide, m.p. 137.5-140°. Addition of ether and ethyl acetate to the acetone filtrate gave an additional 0.1 g. of impure XXXIX hydrobromide, m.p. 130-137°. The ultraviolet absorption spectrum (see page 145) of the pure XXXIX hydrobromide was determined in 95% ethanol and showed a minimum at 224 mµ, absorbance 0.125 (Log ε 3.854); a maximum at 245.5 mµ, absorbance 0.272 (Log ε 4.191), at a concentration of 0.0047 g/l.

Treatment of the remaining 0.15 g. of the third fraction with a slight molar excess of methyl iodide in 20 ml. of acetone caused the precipitation of 0.25 g. of XXXIX methiodide, m.p. 199-201°. Recrystallization from acetone, in which the solid was difficultly soluble, gave 0.15 g. of pure XXXIX methiodide, m.p. 203-204°. Concentration of the acetone filtrates from which XXXIX methiodide had precipitated resulted in the recovery of 0.1 g. of impure XXXIX methiodide. The melting point of pure XXXIX methiodide was depressed, m.p. 175-192°, when mixed with a sample of known 1-methyl-4-benzilidene-piperidine (LIIIA) methiodide (m.p. 212-214°) obtained from the lithium aluminum hydride reduction of XIIa. The melting point of pure XXXIX methiodide was also depressed when mixed with a known (21) sample of 1-methyl-4-benzylpiperidine (LIV) methiodide (m.p. 208-209°), melting at 166-182°.
Catalytic Reduction of XXXIX Methiodide over Platinum Oxide.---To 0.1 g. of XXXIX methiodide dissolved in 30 ml. of methanol was added 0.1 g. of platinum oxide, and the mixture was shaken with hydrogen at 2-3 atm. After the pressure of hydrogen remained constant for a period of 1 hour, the reduction mixture was filtered, and the methanol solution was concentrated under reduced pressure. The oily solid which remained was dissolved in acetone, and the addition of ether to the acetone solution caused the precipitation of 0.75 g. of XLI, m.p. 200-209°, believed to be 1-methyl-4-phenyl-1-aza-cycloheptane methiodide (XLI). The melting point of the impure methiodide XLI was depressed, m.p. 165-190°, when mixed with a sample of the unsaturated XXXIX methiodide (m.p. 203-204°). The melting point of the impure methiodide XLI was depressed, m.p. 151-193°, when mixed with a known (21) sample of 1-methyl-4-benzylpiperidine (LIV) methiodide (m.p. 208-209°). Recrystallization of the impure methiodide XLI from acetone, in which the methiodide was very soluble, by precipitation with ether gave 0.05 g. of the pure methiodide XLI, m.p. 207.5-209.5°. The melting point of the pure methiodide XLI was similarly depressed when re-mixed with samples of XXXIX methiodide and LIV methiodide. The mixtures melted at 165-182° and 155-191°, respectively.

The ultraviolet absorption spectrum (see page 145) of the pure methiodide XLI was determined in 95% ethanol and showed a minimum at 257 μν, absorbance 0.036 (Log ε 1.591); a maximum at 258 μν, absorbance 0.038 (Log ε 1.614); a minimum at 264 μν, absorbance 0.020 (Log ε 1.335); a maximum at 265 μν, absorbance 0.021 (Log ε 1.356); a minimum at 267 μν, absorbance
0.010 (Log $\varepsilon$ 1.003); and a maximum at 268 µm, absorbance 0.016
(Log $\varepsilon$ 1.238), at a concentration of 0.306 g/l. In the region
of styrene absorption, 242 µm and 246 µm, the methiodide
XLI showed an absorbance of 0.795 (Log $\varepsilon$ 2.935) and 0.319
(Log $\varepsilon$ 2.538), respectively, thus indicating the methiodide
XLI not to have this system. The molecular weight of the
methiodide XLI was calculated from the formula, $C_{14}H_{22}IN$.

Reduction of 1-Methyl-4-bromo-4-piperidyl Phenyl
Ketone Hydrobromide (XIIa) with Lithium Aluminum Hydride.

---This general procedure was used for the reduction of 1-
methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa)
with lithium aluminum hydride. The various approaches to the
isolation and identification of the reduction products are
then prefixed by a run number, and any pertinent departures
from this reduction procedure are noted.

To 100 ml. of anhydrous ether in the conventional three-
necked apparatus was added 3.0 g. (0.078 mole) of lithium
aluminum hydride. The mixture was stirred for 1 to 1.5 hours,
and 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl
ketone hydrobromide (XIIa) suspended in ether was added drop-
wise over a period of 0.5 to 1 hour. The mixture was stirred
and heated under reflux for 1 to 2 hours, and after cooling,
the excess lithium aluminum hydride was decomposed by the
cautious addition of water. The voluminous white precipitate
which formed was separated by filtration and triturated with
ether. The ethereal triturate was dried over sodium carbonate
and filtered, and the ether was removed by evaporation on a
steam bath leaving an oil as a residue.
Run No. 1.------Addition of petroleum ether to the oil caused the precipitation of 0.15 g. (7.5%) of crude 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII), m.p. 110-114°, which was collected by filtration. Evaporation of the petroleum ether filtrate left an oil. A 0.2 g. sample of this oil was dissolved in 3 ml. of a dilute hydrochloric acid solution. Addition of sodium carbonate again gave an oil which was not further investigated.

The remainder of the oil was distilled under reduced pressure to give 0.55 g. of a clear oil, b.p. 125-168° at 13 mm. A portion of this distilled oil showed a negative Beilstein test. Attempts to prepare solid hydrochloride or picrate derivatives of the distilled oil by the conventional methods gave only oily products.

Run No. 2.------The oil was distilled under reduced pressure to give 1.05 g. of a clear oil, b.p. 165-170° at 13 mm., n D 26.5 1.5270. A 0.45 g. sample of the distilled oil was treated with a methanolic picric acid solution which caused the separation of a new oil. After decanting the methanol a small amount of acetone dissolved the new oil, and on adding ether to the acetone solution, 0.2 g. of a picrate, m.p. 197-200° precipitated. No further attempt was made to characterize this derivative.

Run No. 3.------A 5.0 g. (0.014 mole) sample of XIIa was reduced with 3.4 g. of lithium aluminum hydride. The addition of petroleum ether to the oil caused the precipitation of 1.0 g. (37%) of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenyl-
methanol (LII), m.p. 107-110° which was collected by filtration. Evaporation of the petroleum ether filtrate left 1.7 g. of an oily residue. The residue was distilled under reduced pressure to give 0.95 g. of an oil, b.p. 100-160° at 3 mm. A 0.35 g. sample of the distilled oil on treatment with a methanolic picric acid solution gave only 0.05 g. of a crude picrate, m.p. 180-190°.

The remaining 0.6 g. of distilled oil was heated under reflux for 3 hours with 1.0 g. of lithium aluminum hydride. The excess hydride was decomposed with water, the residue was extracted with ether, and the ether extracts were dried over sodium carbonate. Filtration, and evaporation of the ether gave 0.55 g. of an oily residue. The oil was redissolved in ether, and the addition of dry hydrogen bromide to the ether solution produced a new oil. The ether layer was decanted, and the addition of a small amount of acetone to the oil caused the separation of 0.1 g. of impure XXXVIII hydrobromide, m.p. 156-160°. The addition of ether to the acetone filtrate caused the separation of an oil which was not further characterized.

**Chromatographic Separation of a Mixture of Known Picrates.** A chromatographic column was prepared by pouring a chloroform slurry of silicic acid (chromatographic grade) into a 25 mm. glass tube 76 cm. in length with a 8 cm. delivery tube of 6 mm. diameter. The silicic acid was prevented from escaping from the tube by a wad of glass wool placed in the constricted bottom of the tube. After the translucent silicic acid had settled after continued washing with chloroform a column 35 cm. in height was obtained. A chloroform solution

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of 0.4 g. of the picrate (m.p. 173-175°) of L-methyl-4-
benzhydrylideneepiperidine (LV) and 0.2 g. of the picrate
(m.p. 203-205°) of L-methyl-4-piperidyldiphenylmethanol
(XXV), prepared from known samples of LV (27) and XVII (27),
was poured on to the column. Elution of the column with
chloroform produced two distinct yellow zones. After the
first zone had reached within 1 cm. of the bottom of the
column by continued elution with chloroform, fractions of the
eluate were collected, and the amount of residue on evaporation
of the chloroform was determined.

<table>
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<tr>
<th>Fraction No.</th>
<th>Volume of Eluent (ml.)</th>
<th>Total Volume (ml.)</th>
<th>Wt. of Residue (g)</th>
<th>Wt. of Recrys.* Picrate (g)</th>
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*The picrates were recrystallized from methanol.
**Fraction 15 contained 10% acetone-chloroform.
***Fractions 17-20 were eluted with undiluted acetone.
Run No. 4.——The 2.2 g. of oil was redissolved in ether, and an ethereal picric acid solution was added until no more oil separated. The yellow oil was then triturated with several portions of ether. One-half of the undissolved yellow oil was dissolved in a small amount of chloroform and poured onto a chromatographic column made by pouring a chloroform slurry of silicic acid* (chromatographic grade) into a 50 ml. burette to give a column of silicic acid 300-350 cm. in height. Continued elution of the column with chloroform produced two yellow zones. The first zone was eluted with chloroform and was collected in a volume of 40 ml. after it first appeared at the bottom of the column. On concentration of the chloroform eluate on a steam bath, 0.2 g. of a picrate, m.p. 150-160° was obtained. One recrystallization from methanol raised the melting point and gave 0.1 g. of a picrate, m.p. 171-173°. This picrate was not further characterized.

After the first zone had been collected, 50 ml. of chloroform was collected before the second zone reached the bottom of the column. The second zone then was collected in five 75 ml. portions of chloroform. On evaporation of the chloroform from these fractions oily residues remained, from which no crystalline product could be isolated.

* A similar preliminary attempted chromatographic separation of the picrate mixture using activated alumina instead of the silicic acid was inconclusive. A very high melting solid, probably an aluminum salt of picric acid, was obtained indicating that the alumina had neutralized the picrates.
Run No. 5.——The 1.9 g. of oily residue was dissolved in 75 ml. of methanol, 0.1 g. of platinum oxide was added, and the mixture was treated with hydrogen at 1700 p.s.i. Filtration of the reduction mixture and removal of the methanol by distillation gave 1.9 g. of an oil. The oil was dissolved in petroleum ether, and on concentration of the petroleum ether solution on a steam bath; the precipitation of a solid caused the solution to lump, thus incurring a large loss. As a result only a small amount of solid was obtained on further concentration of the solution. The solid appeared to be in two different crystalline forms. A 0.2-0.3 g. sample of one form was mechanically separated from the mixture and on recrystallization from ether-petroleum ether gave 0.1 g. of solid, m.p. 145-157°. Recrystallization from ether-petroleum ether of the remaining solid gave 0.1 g. of solid, m.p. 137-153°. No further attempt was made to purify these solids, but they were presumed to be mostly 1-methyl-4-piperidylphenylmethanol (XVII) which when pure melts at 157-159° (18).

Run No. 6.——A 5.4 g. (0.015 mole) sample of XIIa was used for the reduction. The 2.7 g. of oily residue was treated with petroleum ether which caused the precipitation of 0.35 g. (11.6%) of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII), m.p. 107-108.5°. A mixed melting point with an authentic sample of LII (m.p. 107-108°) (27) showed no depression.

Anal. Calcd. for C_{13}H_{17}NO: C, 76.78; H, 8.43. Found: C, 76.83; H, 8.51.
The petroleum ether filtrate was concentrated on a steam bath, and the oily residue was distilled under reduced pressure to give 1.95 g. of impure LIIIA, b.p. 95-125° at 4 mm. The infrared absorption spectrum (Spectrum No. 25) of the impure LIIIA showed diffuse absorption due to OH stretching vibrations from 3400 cm.⁻¹ to the 3000 cm.⁻¹ region of OH absorption and showed the absorption of a mono-substituted benzene at 735 cm.⁻¹ and 697 cm.⁻¹.

On standing a small portion of the oil solidified. Decantation of the oil and treatment of the solid residue with petroleum ether gave 0.1 g. of a solid, m.p. 98-110°. One recrystallization from ether-petroleum ether raised the melting point and gave 0.1 g. of solid, m.p. 116-140°. No further attempts were made to characterize this solid but it was presumed to be 1-methyl-4-piperidylphenylmethanol (XVII) which when pure melts at 157-159° (18).

Run No. 7.----A 5.4 g. portion of XIIa was used for the reduction. The 3.1 g. of oily residue was treated with petroleum ether which caused the precipitation of 1.2 g. (40.0%) of 1-methyl-1,2,3,6-tetrahydro-4-pyrrolidylphenylmethanol (LII). The petroleum ether filtrate was concentrated on a steam bath leaving 1.65 g. of an oily residue which was distilled under reduced pressure. The distillate was collected in two fractions; the first fraction weighed 0.85 g., b.p. 106-112° at 4 mm., the second fraction weighed 0.5 g., b.p. 120-136° at 4 mm.

A 0.55 g. sample of the lower boiling fraction was heated under reflux in 20 ml. of acetic acid to which one
A drop of sulphuric acid had been added. The acetic acid solution was made basic with sodium carbonate, the alkaline solution was extracted with ether, and the ether extracts were dried over sodium carbonate. Filtration and evaporation of the ether from the ether solution left 0.5 g. of an oil which was distilled to give 0.4 g. of a clear oil, b.p. 115-120° at 5 mm. The 0.4 g. of distillate was treated with 10 ml. of a 1:1 48% hydrobromic acid solution, and the acid solution was evaporated to dryness under reduced pressure on a steam bath. The addition of a small amount of acetone to the residue gave 0.15 g. of XXXVIII hydrobromide, m.p. 162-164°. Recrystallization from acetone gave 0.1 g. of XXXVIII hydrobromide, m.p. 163.5-165.5°. A melting point depression was obtained on mixing this hydrobromide with the hydrobromide (m.p. 151-153°) prepared from a known (31) sample of 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine (LVI). The infrared absorption spectrum (Spectrum No. 97) of this XXXVIII hydrobromide showed no absorption in the OH and carbonyl stretching regions, but showed a band at 1223 cm$^{-1}$ for which no structural feature was suggested and showed the absorption of a mono-substituted benzene at 747 cm$^{-1}$ and 700 cm$^{-1}$.

The infrared absorption spectrum of this XXXVIII hydrobromide was superimposable on the infrared absorption spectrum (Spectrum No. 159) of XXXVIII hydrobromide obtained from the reaction of XIIa with sodium borohydride. The ultraviolet absorption spectrum (see page 145) of XXXVIII hydrobromide was determined in 95% ethanol and showed a minimum at 223 μm, absorbance 0.075 (Log ε 3.741); a maximum at 247 μm, absorbance 0.230.
(Log £ 4.228), at a concentration of 0.0047 g/l.

**Anal.** Calcd. for C13H17Br2N: C, 44.97; H, 4.94.

Found: C, 45.00; H, 5.17.

The remaining 0.3 g. of the lower boiling oil was treated with a slight molar excess of methyl iodide in methanol. After standing for several hours, the methanol solution was concentrated under reduced pressure leaving an oil as the residue. Addition of acetone to the residue and scratching induced the precipitation of 0.2 g. of impure 1-methyl-4-benzylidene piperidine (LIIIA) methiodide, m.p. 194-200°. One recrystallization of the impure methiodide of LIIIA from acetone in which the methiodide was difficultly soluble, gave 0.1 g. of pure LIIIA methiodide, m.p. 212-214°. A mixed melting point of LIIIA methiodide with a methiodide (m.p. 212-214°) of 1-methyl-4-piperidyl phenylmethanol (XVII) prepared from a known (21) sample of XVII showed a depression (m.p. 180-195°). The infrared absorption spectrum (Spectrum No. 90) of LIIIA methiodide showed no absorption in the OH and carbonyl stretching regions, but showed the absorption of a mono-substituted benzene at 745 cm.⁻¹ and 710 cm.⁻¹.

The acetone filtrate from which the LIIIA methiodide had precipitated, was evaporated to dryness under reduced pressure leaving an oil as the residue. Since no crystalline product could be isolated from the oily residue, it was dissolved in methanol and treated with hydrogen at 2-3 atm. with 0.1 g. of platinum oxide catalyst. When the pressure of hydrogen remained constant over a period of 1 hour, the reduction mixture was filtered, and addition of ether to the
filtrate caused the precipitation of 0.1 g. of a solid. One recrystallization from acetone gave 0.05 g. of an impure methiodide, m.p. 191-195°. No further attempt was made to purify this material but was presumed to be either 1-methyl-4-benzylpiperidine (LIV) methiodide or 1-methyl-4-piperidylphenylmethanol (XVII) methiodide which when prepared from known samples of LIV (21) and XVII (21) melt at 208-209° and 212-214°, respectively.

The addition of petroleum ether to the 0.5 g. of the higher boiling fraction caused the precipitation of 0.1 g. of a solid, m.p. 109-112°. Recrystallization from hot petroleum ether gave 0.75 g. of the solid, m.p. 112-130°. The petroleum ether filtrate was concentrated on a steam bath, and the residue was treated for a few hours with a slight molar excess of methyl iodide in methanol. Evaporation of the methanol solution gave 0.05 g. of an impure methiodide, m.p. 133-145°, which on recrystallization from acetone gave 0.01 g. of an impure methiodide, m.p. 144-185°. The 112-130° melting solid was observed to decompose after standing for several days to a dark brown oily solid similar to the decomposition product of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII), which when pure melts at 107-108.5°. Since the 112-130° solid melted at a higher temperature than LII, the unknown was presumed to be contaminated with 1-methyl-4-piperidylphenylmethanol (XVII) which when pure melts at 157-159° (18). Similarly, the methiodide prepared from this solid of m.p. 112-130°, was presumed to be a mixture of the methiodides of LII and XVII which when prepared from known samples of LII (31) and XVII (21) melt at 144-146° and 212-214°, respectively.
Run No. 8.—A 20.0 g. (0.055 mole) sample of XIIa was reduced with 4.0 g. (0.11 mole) of lithium aluminum hydride. The 11.2 g. of oily residue was treated with petroleum ether which caused the precipitation of 6.1 g. (55.5%) of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII). The petroleum ether filtrate was concentrated on a steam bath leaving 4.55 g. of an oily residue. After standing at room temperature for 3 weeks, thereby allowing the readily decomposable LII that might not have precipitated an opportunity to decompose, the dark oil was distilled under reduced pressure and collected in four fractions. The first fraction weighed 1.0 g. and boiled at 115-130° at 7 mm., the second fraction weighed 0.5 g. and boiled at 130-126° at 7 mm., the third fraction weighed 1.05 g. and boiled at 126-115° at 7 mm., and the fourth fraction weighed 0.95 g. and boiled at 115-128° at 7 mm.

A 0.5 g. sample of the first fraction was treated with a slight molar excess of methyl iodide in methanol. After standing for a few hours at room temperature, the methanol solution was concentrated under reduced pressure, and the solid residue was rinsed with acetone to give 0.7 g. of 1-methyl-4-benzylidene-piperidine (LIIIA) methiodide, m.p. 208-212°. One recrystallization of this methiodide from about 300 ml. of hot acetone gave 0.4 g. of pure LIIIA methiodide, m.p. 212-214°. The ultraviolet absorption spectrum (see page 146) of this methiodide was determined in 95% ethanol, and it showed no minimum or maximum from 210 μ to 320 μ at a concentration of 0.00436 g/l.

The remaining 0.4 g. of the first fraction was converted to 0.4 g. of the methiodide of LIIIA by the method described above. One recrystallization from acetone gave 0.3 g. of pure LIIIA methiodide, m.p. 212-214°. The 0.3 g. of LIIIA methiodide was dissolved in 75 ml. of methanol and treated with hydrogen at 1400 p.s.i. with Raney nickel catalyst. After 25 lbs. of hydrogen had been absorbed and the pressure of hydrogen remained constant over a period of 1 hour, the reduction mixture was filtered, and the methanol solution was concentrated to dryness under reduced pressure. The solid residue was rinsed with acetone to give 0.2 g. of 1-methyl-4-benzylpiperidine (LIV) methiodide, m.p. 208-210°. One recrystallization from acetone, in which the methiodide was moderately soluble, gave 0.15 g. of pure LIV methiodide, m.p. 208-209°. The melting point of this methiodide showed no depression when mixed with the methiodide (m.p. 208-209°) of LIV prepared from a known sample of LIV (21). This methiodide, isolated from the reduction mixture, did depress the melting point of the starting methiodide, m.p. 212-214°. The mixture melted at 204-205.5°.

The ultraviolet absorption spectrum (see page 146) of the second fraction was determined in 95% ethanol and showed a minimum at 224 mζ, absorbance 0.107 (Log $\varepsilon$ 3.693); a maximum at 243 mζ, absorbance 0.199 (Log $\varepsilon$ 3.962), at a concentration of 0.0046 g/l. The infrared absorption spectrum (Spectrum No. 122) of a sample from the second fraction showed diffused absorption in the OH stretching region from 3600 cm.$^{-1}$ to 3000 cm.$^{-1}$ at which frequency the CH stretching absorption
begins. The infrared absorption spectrum also indicated the presence of a mono-substituted benzene due to absorption at 697 cm.\(^{-1}\) and 740 cm.\(^{-1}\). A portion of the second fraction was analyzed for carbon and hydrogen.

Anal. Calcd. for \(\text{C}_{13}\text{H}_{17}\text{N}\): C, 83.39; H, 9.16; \(\text{C}_{13}\text{H}_{17}\text{NO}\): C, 76.78; H, 8.43. Found: C, 82.00; H, 8.70.

The remaining 0.15 g. of the second fraction was converted to 0.2 g. of a methiodide by the method used for the preparation of the methiodide of the first fraction. Two recrystallizations from acetone gave 0.05 g. of the methiodide of LIIIA, m.p. 213-215°.


The third fraction was treated with dry hydrogen bromide in ether, and 1.2 g. of a tacky hydrobromide precipitated. The ether was removed by decantation and the residue was washed with a small amount of acetone to give 0.6 g. of a crystalline hydrobromide, m.p. 177-192°. One recrystallization from acetone gave 0.35 g. of impure hydrobromide of LIIIA m.p. 192-198°. An infrared absorption spectrum (Spectrum No. 140) of this impure hydrobromide showed no absorption in the OH and carbonyl stretching regions but indicated a mono-substituted benzene by absorption at 752 cm.\(^{-1}\) and 698 cm.\(^{-1}\). The 0.35 g. of hydrobromide was recrystallized from acetone to give 0.3 g. of LIIIA hydrobromide, m.p. 199-201°. The ultraviolet absorption spectrum (see page 146) of this twice recrystallized hydrobromide was determined in 95% ethanol and showed a minimum at 221 \(\text{nm}\), absorbance 0.094 (Log \(\varepsilon\) 3.786); a maximum at 241 \(\text{nm}\), absorbance
0.224 \( \log \epsilon \ 4.163 \), at a concentration of 0.0042 g/l. The infrared absorption spectrum (Spectrum No. 151) of this twice recrystallized hydrobromide of LIIIA determined in a 10% chloroform solution showed absorption at 3400 cm\(^{-1}\) characteristic of \( \text{OH} \) stretching and absorption at 697 cm\(^{-1}\) characteristic of a mono-substituted benzene. The 750 cm\(^{-1}\) band for a mono-substituted benzene was obscured by the chloroform absorption.

Anal. Calcd. for \( \text{C}_{13}\text{H}_{18}\text{BrN} \): C, 58.20; H, 6.75; N, 5.22; \( \text{C}_{13}\text{H}_{18}\text{BrNO} \): C, 54.93; H, 6.38; N, 4.93. Found: C, 58.68, 58.52; H, 6.82, 6.58; N, 4.99.

Preparation of 1-Methyl-4-benzyl-1,2,3,6,-tetrahydro-pyridine (LVI).---To 30.0 g. (0.11 mole) of 4-benzylpyridine (XIV) methobromide in 100 ml. of methanol was added 7.0 g. (0.19 mole) of sodium borohydride over a period of 1 hour with stirring. The reduction mixture was allowed to stand overnight and the methanol was removed by evaporation under reduced pressure. The excess sodium borohydride was decomposed by adding 50 ml. of water, and the alkaline solution was extracted with ether. The ether extract was dried over sodium carbonate and filtered, and the ether was removed by evaporation on a steam bath. The residual oil was distilled under reduced pressure to give 15.0 g. (73.4%) of 1-methyl-4-benzyl-1,2,3,6,-tetrahydropyridine (LVI), b.p. 120-125° at 6 mm.

A 0.5 g. sample of the distilled liquid was dissolved in 10 ml. of a 1:1 48% hydrobromic acid solution and the solution concentrated under reduced pressure on a steam bath. The oily residue was dissolved in acetone, and ether was added with scratching causing the precipitation of 0.4 g. of impure 1-methyl-
4-benzyl-1,2,3,6-tetrahydropyridine (LVI) hydrobromide, m.p. 150-155°. Recrystallization of the solid from acetone gave 0.25 g. of pure LVI hydrobromide, m.p. 150-152.5°. The ultraviolet absorption spectrum (see page 146) of this hydrobromide was determined in 95% ethanol and showed the characteristic absorption of a non-conjugated benzene ring at a concentration of 0.448 g/l.

A 4.0 g. sample of LVI was converted to the hydrobromide by the addition of dry hydrogen bromide to an ethereal solution. After recrystallization from acetone 5.1 g. of LVI hydrobromide m.p. 151-153°, was obtained.

Reaction of 1-Methyl-4-benzyl-1,2,3,6-tetrahydropyridine (LVI) with Alcoholic Potassium Hydroxide at High Temperatures.——A mixture of 10.0 g. (0.05 mole) of 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine (LVI), 15 g. of powdered potassium hydroxide, and 40 ml. of ethanol were sealed in a pyrex glass tube 25 mm. in diameter and 212 cm. in length. The glass tube was placed in a high pressure hydrogenation bomb, and 100 ml. of ethanol was added to surround the tube. The mixture in the tube then was shaken and heated over a period of 14 hours while the temperature was raised from room temperature to 140°. The heating and shaking were continued over a period of 12 hours at temperatures of 140° to 168°. After cooling the tube was removed from the bomb and it was found that approximately one-half of the solution had leaked from the tube. The methanol solution removed from the tube was concentrated under reduced pressure. The oily potassium hydroxide residue was triturated with ether, the ether triturate was filtered, and the ether was
removed by distillation to give 3.9 g. of an oil. The oil was distilled under reduced pressure to give 2.8 g. of LIIIB b.p. 125-126° at 6 mm.

A 1.0 g. sample of this liquid was treated with a slight molar excess of methyl iodide in methanol for a few hours. The methanol solution then was concentrated under reduced pressure leaving a solid residue which on washing with acetone gave 0.9 g. of LIIIB methiodide, m.p. 175-178°. The acetone filtrate yielded an additional 0.5 g. of solid which was combined with the 0.9 g. of solid, and the mixture was recrystallized from acetone to give 0.9 g. of LIIIB methiodide, m.p. 177.5-179.5°. The ultraviolet absorption spectrum (see page 146) of LIIIB methiodide was determined in 95% ethanol and showed no minimum or maximum from 210 μ to 320 μ, at a concentration of 0.0042 g/l.


A 0.4 g. sample of this methiodide was dissolved in 50 ml. of methanol and treated with hydrogen and Raney nickel catalyst at 1300 p.s.i. When the pressure of the hydrogen remained constant over a period of 1 hour, the reduction mixture was filtered and concentrated under reduced pressure. The solid residue that remained was washed with acetone to give 0.4 g. of a solid. Recrystallization from acetone gave 0.25 g. of 1-methyl-4-benzylpiperidine (LIV) methiodide, m.p. 207.5-208°. The melting point of this methiodide was not depressed when mixed with the methiodide (m.p. 207.5-208°) of LIV prepared from a known sample (21).
The remaining 1.8 g. of distilled liquid was redistilled to give 1.6 g. of \textit{LIIIb}, b.p. 105-110° at 3 mm. The ultraviolet absorption spectrum (see page 146) of this liquid was determined in 95\% ethanol and showed a minimum at 227 m\u, absorbance 0.065 \((\log \varepsilon = 3.539)\); a maximum at 242 m\u, absorbance 0.085 \((\log \varepsilon = 3.655)\), at a concentration of 0.00352 g/l.

The 1.6 g. of liquid darkened after standing several days and was redistilled under reduced pressure to give 1.1 g. of \textit{LIIIb}. A 0.5 g. sample of this freshly distilled \textit{LIIIb} was treated with 5 ml. of 1:1 48\% hydrobromic acid solution and the acid solution concentrated under reduced pressure. Addition of acetone to the oily residue gave 0.6 g. of a solid hydrobromide, m.p. 148-152°. Recrystallization from acetone gave 0.2 g. of pure 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine hydrobromide (\textit{LVI}), m.p. 151-153°. A melting point of this hydrobromide showed no depression when mixed with the hydrobromide (m.p. 151-153°) prepared from a known sample of \textit{LVI} (31).

To the remaining 0.6 g. of freshly distilled liquid was added dry hydrogen bromide in ether which caused the separation of an oil. The ether was removed from the oil by evaporation under reduced pressure, and the oil was dissolved in acetone. Concentration of the acetone solution on a steam bath, and cooling, gave 0.4 g. of 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine (\textit{LVI}) hydrobromide, m.p. 152-153°. A melting point of this hydrobromide showed no depression when mixed with the hydrobromide (m.p. 151-153°) of \textit{LVI} prepared by the conventional method from a known sample of \textit{LVI} (31).
Reactions of 1-Methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII). (a) With Lithium Aluminum Hydride.

To 100 ml. of anhydrous ether in the conventional three-necked apparatus was added 2.0 g. (0.05 mole) of lithium aluminum hydride. The mixture was stirred for 1 hour, and 3.0 g. (0.015 mole) of LII dissolved in ether was added over a period of 0.5 hour. The mixture was stirred and heated under reflux for 10 hours, and after cooling, the excess lithium aluminum hydride was decomposed by the cautious addition of water. The voluminous white precipitate which formed was separated by filtration and triturated with ether. The ether tritrate was dried over sodium carbonate and then filtered. Concentration of the ether solution on a steam bath with simultaneous addition of petroleum ether caused the precipitation of 2.7 g. (90% recovery) of LII, m.p. 107-108.5°.

(b) With Acetic-Sulphuric Acid Mixture.-----A 0.55 g. sample of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylmethanol (LII) was dissolved in 20 ml. of acetic acid, two drops of sulphuric acid were added, and the mixture was heated under reflux for 4 hours. On cooling, the acid solution was made basic with sodium carbonate, and the alkaline solution was extracted with ether. The ether extract was dried over sodium carbonate and filtered, and the ether was removed by distillation leaving 0.75 g. of an oily residue. Distillation of the oil under reduced pressure gave 0.15 g. of an oil, b.p. 118-120° at 2 mm. as a first fraction, and 0.3 g. of an oil, b.p. 120-125° at 2 mm. as a second fraction. Treatment of the 0.3 g. of the second fraction with dry hydrogen bromide in ether
produced an oil from which no solid could be isolated. This oily hydrobromide turned dark brown on standing a few hours. The 0.15 g. of the colorless first fraction was similarly observed to change to a dark brown oil on standing several days.

(c) **With Potassium Hydroxide in Methanol.** To 1.0 g. of LII dissolved in 40 ml. of methanol was added 10 g. of potassium hydroxide, and the mixture was heated under reflux for 7 hours. The methanol solution then was evaporated to dryness under reduced pressure, and the residue was triturated with ether. The ether triturate was filtered, and the ether was removed by distillation leaving an oil as a residue. Addition of petroleum ether to the oil gave 0.9 g. (90% recovery) of crude LII, m.p. 45-99°. Recrystallization from ether-petroleum ether gave 0.55 g. of pure LII, m.p. 106-107.5°.

(d) **With Methyl Iodide.** A 0.3 g. sample of LII was treated with a slight molar excess of methyl iodide in methanol, and after standing for several hours the solution was concentrated to dryness under reduced pressure. The solid residue that remained was washed with acetone to give 0.5 g. of LII methiodide, m.p. 144-146°. Recrystallization from acetone gave 0.3 g. of LII methiodide, m.p. 144-146°.

(e) **With Aqueous Hydrogen Bromide.** A 0.3 g. sample of LII was dissolved in 10 ml. of a 1:1 48% hydrobromic acid solution. The acid solution was concentrated under reduced pressure on a steam bath leaving a dark oily residue. No crystalline hydrobromide could be isolated from this oil.
(f) Distillation.—A 0.5 g. sample of LII was heated under reduced pressure in a side arm test tube. After melting, the liquid condensate proceeded up the sides of the tube where it resolidified on cooling.
TABLE I

![Chemical structure](https://via.placeholder.com/150)

XXI

<table>
<thead>
<tr>
<th>Epoxyether</th>
<th>Acid</th>
<th>Solvent Medium</th>
<th>Reaction Product</th>
<th>% Yield</th>
<th>M.P.&quot;C</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXIa</td>
<td>Hydrochloric</td>
<td>Water</td>
<td>XVIIIa, R=H</td>
<td>100</td>
<td>130-132</td>
</tr>
<tr>
<td>&quot;</td>
<td>Propionic</td>
<td>Ether</td>
<td>XXIVa, R=H, R'=C2H5</td>
<td>85 (a)</td>
<td>254-255 dec. (b)</td>
</tr>
<tr>
<td>&quot;</td>
<td>Benzoic</td>
<td>Ether</td>
<td>XXIVb, R=H, R'&quot;=C6H5</td>
<td>92</td>
<td>112.5-114.5</td>
</tr>
<tr>
<td>&quot;</td>
<td>Diphenylacetic Ether</td>
<td>XXIVc, R=H, R'&quot;=(C6H5)2CH</td>
<td>35</td>
<td>122-124</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>Hippuric</td>
<td>Ether-Methanol</td>
<td>XXIVd, R=H, R'&quot;=C6H5CONHCH2</td>
<td>58</td>
<td>104-111</td>
</tr>
<tr>
<td>&quot;</td>
<td>Mandelic</td>
<td>Ether-Methanol</td>
<td>XVIIIa, R=H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>p-Aminobenzoic Ether</td>
<td>XVIIla, R=H</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>p-Acetamidobenzoic Ether-Methanol (c)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>p-Nitrobenzoic Ether</td>
<td>XXIVe (d), R'&quot;=p-NO2C6H5, R=H</td>
<td>95</td>
<td>164-168</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>p-Aminobenzoic Pyridine</td>
<td>XXIVf, R=H, R&quot;=p-NH2C6H5</td>
<td>97</td>
<td>179-180</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>Isonicotinic</td>
<td>Pyridine</td>
<td>XXIVg, R=H, R&quot;=l-C5H4N</td>
<td>95</td>
<td>126-128</td>
</tr>
<tr>
<td>XXIc</td>
<td>Hydrochloric</td>
<td>Water</td>
<td>XXIVb, R=CH3</td>
<td>95</td>
<td>156-158</td>
</tr>
<tr>
<td>&quot;</td>
<td>Propionic</td>
<td>Ether</td>
<td>XXIVh, R=CH3, R'&quot;=C2H5</td>
<td>90</td>
<td>231-233 (b)</td>
</tr>
<tr>
<td>&quot;</td>
<td>Benzoic</td>
<td>Ether</td>
<td>XXIVi, R=CH3, R&quot;=C6H5</td>
<td>72</td>
<td>255-256 (b)</td>
</tr>
</tbody>
</table>

(a) The per cent yield was calculated from the quantity of product isolated as the hydrochloride
(b) Melting point of hydrochloride
(c) No structure could be deduced from the analytical data of the hydrochloride
(d) This compound was not analyzed
TABLE II
LOCAL ANESTHETIC ACTION OF
CH₃N[O⁻][C-=O]R
Corneal Irrigation
(Rabbit) Infiltration
(Guinea Pig)

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>X</th>
<th>Conc.</th>
<th>Anesthesia</th>
<th>Irritation</th>
<th>Conc.</th>
<th>Anesthesia</th>
<th>Irritation</th>
</tr>
</thead>
<tbody>
<tr>
<td>XVIIIa(a)</td>
<td>H</td>
<td>H</td>
<td>HCl</td>
<td>1</td>
<td>0(b)</td>
<td>0.25</td>
<td>Slight(c)</td>
<td></td>
</tr>
<tr>
<td>XVIIIb</td>
<td>CH₃</td>
<td>H</td>
<td>HCl</td>
<td>1</td>
<td>23</td>
<td>0.25</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>XXIVa</td>
<td>H</td>
<td>CH₃CH₂CO</td>
<td>HCl</td>
<td>1</td>
<td>2(b)</td>
<td>0.25</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>XXIVb</td>
<td>CH₃</td>
<td>CH₃CH₂CO</td>
<td>HCl</td>
<td>1</td>
<td>8</td>
<td>0.1</td>
<td>Negligible(c)</td>
<td></td>
</tr>
<tr>
<td>XXIVc</td>
<td>CH₃</td>
<td>C₆H₅CO</td>
<td>HCl</td>
<td>0.4</td>
<td>25</td>
<td>0.05</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>XXIVd</td>
<td>H</td>
<td>C₆H₅CONHCH₂CO</td>
<td>HCl</td>
<td>1</td>
<td>60(b)</td>
<td>0.25</td>
<td>Slight(c)</td>
<td></td>
</tr>
<tr>
<td>XXIVe</td>
<td>H</td>
<td>C₆H₅CO</td>
<td>HCl</td>
<td>1</td>
<td>15</td>
<td>0.25</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>XXIVf</td>
<td>H</td>
<td>p-NH₂C₆H₄CO</td>
<td>(g)</td>
<td>1</td>
<td>0</td>
<td>0.25</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>XXIVg</td>
<td>H</td>
<td>4-C₆H₄N-CO</td>
<td>(g)</td>
<td>2</td>
<td>0</td>
<td>0.25</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>XXIVh</td>
<td>H</td>
<td>(C₆H₅)₂CHO</td>
<td>(h)</td>
<td>1</td>
<td>0</td>
<td>0.25</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

(a) The hydrochloride and methobromide were also tested for antispasmodic, the methobromide for analgesic,
and the hydrochloride for hypothermic activity, but in all cases were found to be inactive. However,
the hydrochloride was found to produce definitive reduction of blood pressure under certain conditions,
and the methobromide transient but definitive depressor activity when tested for hypertensive activity.
(b) The corneal irrigation was determined using guinea pig’s eye.
(c) The irritation was determined on rabbit skin.
(d) At greater concentrations irritation was evident.
(e) Also tested as an analgesic but found to be inactive.
(f) Greater concentration produced necrosis at the site of ingestion.
(g) Since the analyses of the salts indicated incomplete conversion to the dihydrochloride, the esters
were isolated and characterized as the base.
(h) Not tested for local anesthetic activity; the hydrochloride and methobromide however when tested as
antispasmodics were found to be inactive.
SUMMARY
SUMMARY

Direct bromination or chlorination of l-methyl-4-piperidyl aryl ketones (IX) was found to proceed smoothly to give l-methyl-4-halo-4-piperidyl aryl ketone hydrohalides (XII). The l-methyl-4-piperidyl aryl ketones (IX) were prepared by either of two synthetic routes. One method utilized l-methylisonipecotic acid chloride which was prepared by either of two methods from methyl isonicotinate (I). In the first method, methyl isonicotinate (I) was methylated by conversion to the quaternary methyl salt which then was reduced catalytically to methyl l-methylisonipecotate (IV). In the other, methyl isonicotinate (I) was hydrogenated and reductively methylated with formaldehyde to the methyl l-methylisonipecotate (IV). Conversion of the methyl l-methylisonipecotate (IV) to the acid chloride by hydrolysis and reaction with thionyl chloride, followed by the Friedel-Crafts acylation of benzene then afforded the l-methyl-4-piperidyl aryl ketones (IX). The second method of synthesis of IX consisted of reduction of l-methyl-4-benzoyl-pyridinium halide (XV) to l-methyl-4-piperidylphenylmethanol (XVII) and oxidation of the latter to l-methyl-4-piperidyl phenyl ketone (IX).

The l-methyl-4-halo-4-piperidyl phenyl ketone hydrohalides (XII) were found to be unstable as the base if the halogen was bromine but stable if the halogen was chlorine. The reactions of the l-methyl-4-halo-4-piperidyl phenyl ketone hydrohalides (XII) with sodium hydroxide or alkoxide
in ether led to 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (VIIIa), while in alcohol 6-methyl-2-alkoxy-2-phenyl-1-ox-6-azaspiro(2.5)octane (XXI) was formed. Since the latter, an epoxyether, was produced in excellent yield, it proved to be a useful intermediate for the synthesis of a series of compounds for pharmacological screening. These compounds were prepared by the facile reaction of the epoxyether with organic acids to give 1-methyl-4-acyloxy-4-piperidyl aryl ketones (XXIV). By reaction of the epoxyether with mineral acids 1-methyl-4-hydroxy-4-piperidyl aryl ketones (XVIII) were prepared and also tested for pharmacological activity.

The reaction of phenyllithium with 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) gave 1-methyl-4-piperidyl phenyl ketone (IXa), 30%, and 1-methyl-4-piperidyl-diphenylmethanol (XXV), 32%. Isolation of these products suggested that metal halogen interchange rather than addition occurred and confirmation of this organometallic intermediate was obtained by adding benzoyl chloride to the reaction mixture before hydrolysis to give 1-methyl-4-piperidylidene-α-benzoyloxy-α-phenylmethane (XXVII). The structure of the latter, XXVII, was proved by ultraviolet and infrared absorption spectra, and by quantitative hydrolysis of XXVII to 1-methyl-4-piperidyl phenyl ketone (IXa) and benzoic acid. The formation of the 1-methyl-4-piperidyl diphenylmethanol (XXV) was shown to arise by the reaction of excess phenyllithium with 1-methyl-4-piperidyl phenyl ketone (IXa) produced during the hydrolysis of the reaction mixture.
The reaction of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) with phenylmagnesium bromide gave a complex mixture of products. From one reaction the ketonic products were isolated by distillation of the product mixture to give 36\% of 1-methyl-4-piperidyl phenyl ketone (IXa) and 34\% of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX). The slight solubility of 1-methyl-4-phenyl-4-piperidyl-diphenylmethanol (XXX) hydrobromide in water led to its isolation in about 18\% yield from several reactions. 1-Methyl-4-piperidyl-diphenylmethanol (XXV) was also found in several reactions, but the amount of this compound present was dependent on the method of hydrolysis used and thus the yield varied considerably. The yield of 1-methyl-4-phenyl-4-piperidyl-diphenylmethanol (XXX) did not appear to be dependent on the hydrolysis procedure. The latter is suggested to arise by reaction of phenylmagnesium bromide with 1-methyl-4-phenyl-4-piperidyl phenyl ketone (XXIX) formed in the reaction medium by a rearrangement of the 1,2-addition product of the 1-methyl-4-chloro-4-piperidyl phenyl ketone (XIIIc) with the Grignard.

Catalytic hydrogenation of 1-methyl-4-halo-4-piperidyl phenyl ketone (XIII) demonstrated the influence of the halogen atom on the reactions of the carbonyl group. 1-Methyl-4-piperidyl phenyl ketone (IXa) was not reduced over platinum catalyst in methanol; whereas, 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIIa), as the base or hydrobromide, and 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIIb) under these conditions gave 1-methyl-4-piperidylphenylmethanol (XVII). If the catalyst was changed to palladium-charcoal or
the solvent to chloroform, 1-methyl-4-piperidyl phenyl ketone (IXa) was formed. Other polar substituents such as hydroxy or acyloxy in the C-4 position of 1-methyl-4-piperidyl phenyl ketone (IXa) were found to enhance carbonyl reduction over platinum catalyst in methanol while a bulky non-polar phenyl substituent had little effect on carbonyl reduction.

Reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone (XIIa) with sodium borohydride produced a product which appears to have been formed by way of a novel rearrangement. The product, compound XXXVIII, isolated as the hydrobromide, had an analysis which indicated the molecular formula to be C13H17Br2N. XXXVIII was found to be unstable as the base; as the hydrobromide, both of the halogens were titrated by aqueous silver nitrate. On reaction with lithium aluminum hydride, XXXVIII suffered loss of the bromine substituent giving a new product, XXXIX. The ultraviolet absorption spectra of XXXVIII, XXXVIII hydrobromide, XXXIX and its hydrobromide and methiodide derivatives, all indicated the presence of a double bond in conjugation with a benzene ring. The infrared absorption spectra gave no indication of the presence of hydroxyl or carbonyl groups in these compounds. XXXIX methiodide on hydrogenation over platinum catalyst produced a saturated compound which was shown not to be identical with 1-methyl-4-benzylpiperidine (LIV). Since the parent compound, XXXVIII, does not appear to contain the 4-substituted piperidine skeletal system, a phenyl-substituted azacycloheptane skeletal system is proposed. Thus XXXVIII is considered to be a 1-methyl azacycloheptane containing a double bond in conjugation.
with a benzene ring and a bromine atom in an allyl position. A possible mechanism for the rearrangement required is offered.

As with sodium borohydride, reaction of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIIa) with lithium aluminum hydride led to products other than those usually expected from the reaction of an α-haloketone with lithium aluminum hydride. The products isolated were found to be 1-methyl-1,2,3,6,-tetrahydro-4-pyridylphenylmethanol (LII), 55%, 1-methyl-4-benzylidenepiperidine (LIIIA), 34%, and 1-methyl-4-piperidylphenylmethanol (XVII), trace. The 1-methyl-1,2,3,6,-tetrahydro-4-pyridylphenylmethanol (LII) was characterized by comparison with an authentic sample, by mixture melting point determination, by observation of its facile decomposition, and by analysis. The characterization of 1-methyl-4-benzylidenepiperidine (LIIIA) was complicated by the fact that it had not been reported previously and attempts to prepare this compound had always led to 1-methyl-4-benzyl-1,2,3,6,-tetrahydropyridine. In addition, since the alcohols LII and XVII were also products, the isolation of pure LIIIA was greatly impaired. However, the structural assignment of LIIIA is considered to be consistent with the ultraviolet absorption and infrared absorption spectra and elemental analysis of LIIIA and its hydrobromide and methiodide; and with the fact that the 4-substituted piperidine skeletal system had remained intact, for LIIIA methiodide gave 1-methyl-4-benzylpiperidine (LIV) methiodide on catalytic reduction.
Considerable evidence showing that LIIIA was not formed from 1-methyl-4-benzyl-1,2,3,6-tetrahydro-4-pyridyl-phenylmethanol (LII) was found by subjecting the LII to a wide variety of reaction conditions. A mechanism suggesting the possible method of formation of LIIIA and LII is offered.
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8 Compare 6c with 2a


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BIOGRAPHICAL DATA

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