REACTION OF THE HALOGENATED PIPERIDINES AND RELATED DERIVATIVES

YOUNG-HO KIM

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REACTION OF THE HALOGENATED PIPERIDINES
AND RELATED DERIVATIVES

BY

YOUNG-HO KIM
B. S., CHOSUN UNIVERSITY, 1953
M. A., BRANDEIS UNIVERSITY, 1960

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This thesis has been examined and approved.

Robert Edle

A. H. Cott

Miyoshi Ikawa

Paul R. Jones

Kenneth K. Anderssen

May 22, 1964

Date
I DEDICATE THIS WORK

TO THE MEMORY OF MY LATE FATHER

AND TO MY MOTHER

WITH BLESSINGS ON HER LONG LIFE
ACKNOWLEDGMENT

It is a great pleasure to express my sincere appreciation to the members of the Faculty and Staff of the Department of Chemistry at the University of New Hampshire for many hours of fruitful discussions and instruction. I would like especially to take this opportunity to acknowledge my indebtedness to my thesis director, Dr. Robert E. Lyle, whose inspirational and enthusiastic direction and guidance made this work possible. I am also grateful to Mrs. Pearl Libby who typed this manuscript. Finally, I wish to thank one of my early instructors in Chemistry at Chosun University, Professor Jung-Kee Choi, for his continued encouragement.

[Signature]
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INTRODUCTION

Recently a number of workers have reported nucleophilic molecular rearrangement reactions of saturated nitrogen heterocyclic systems in which a nucleophile is directly incorporated into the molecule. Especially, this type of reaction of piperidine derivatives has been studied rather extensively in this laboratory (1-5) and less extensively by a few other workers (6-8).

Nucleophilic molecular rearrangements of nonheterocyclic systems have been extensively studied and mechanisms for these reactions have been elucidated during the last half century. Many workers (13a-g) have discussed the relative migratory aptitudes of the substituents, the effect of their electronic character on the stabilization of the transitory intermediate, and the stereochemistry of the reaction.

In the heterocyclic system, the reaction sequences do not follow the pathways postulated for the nonheterocyclic systems. A study of this field is not only of academic interest, but also of synthetic and pharmaceutical applicability. Ortner (9) reported that 4-hydroxy-2,2,6,6-tetramethyl-4-piperidyl dialkyl carbinols on treatment with boiling mineral acid yield only dehydration products and are not converted to rearranged products. On the other hand, Chouvette (5) and Lyle (1) have reported the N-methyl substituted compounds, 4-hydroxy-1,2,2,6,6-pentamethyl-4-piperidyl diphenyl carbinol and 1-methyl-4-hydroxy-4-piperidyl diphenyl carbinol, were
converted to rearranged products on treatment with either
conzentrated sulfuric acid or Lewis acid catalysts. Later,
Leone (3) reported the rearrangement of 1-methyl-4-hydroxy-
4-piperidylmethylphenylecarbinol. Prossianiesc (2) and Warner
(4) studied the reaction of \( \alpha \)-haloketones in the piperi-
dine series. One of these similar types of reaction "the
Quasi-Pesorskii rearrangement reaction" was also reported
by Smissman and Nito (6,7). Brain et al (8) reported that
1-methyl-3-chloropiperidine with nucleophilic reagents, such
as sodium alkoxide or potassium cyanide, resulted in partial
rearrangement to the respective pyrrolidine derivatives.
Smissman also reported hydrolytic rearrangement of ester of
\( N \)-ethyl-3-hydroxy-piperidine to \( N \)-ethyl-2-hydroxymethyl-
pyrrolidine (19). Crop (12) has reported the stereochemistry
of solvolysis reactions of nitrogen heterocyclic compounds,
and Beeconsall (32) has reported the configuration of cyclic
quaternary ammonium salts based on n.r.r. spectroscopic data.

The results to be described here are

1) nucleophilic displacement reactions and an attempted
ring contraction of 1-methyl-3-halo-3-piperidylphenylketones;

2) improved methods of preparation of the starting materials
of 1-methyl-4-halo-4-piperidylphenylketone and 6-methyl-
2-phenyl-1-cxo-6-mespino-[2,5]octane, and their nucleo-
philic molecular rearrangements;

3) preparation of 1-methyl-4-phenyl-4-piperidylcarbinol,
1-methyl-4-phenyl-4-piperidylchloromethane and 1-benzy1-
4-phenyl-4-piperidylaminomethane, and to attempt their nucleophilic molecular rearrangements;

4) synthesis of 1-benzyl-4-α-aminobenzyl-4-phenylpiperidine and its isomer 1-benzyl-4-anilinomethyl-4-phenylpiperidine;

5) preparation and nucleophilic rearrangement reactions of 1-methyl-(1-benzyl)-4-phenyl-4-piperidylphenylcarbinols.

These results suggested that the factors which determine whether or not the nitrogen participates in the solvolysis or rearrangement of these systems are the stereochemistry of the heterocyclic molecule, the nature of the nucleophilic reagent and the solvating power of the solvent. The nature of this last fact is not well investigated. A detailed understanding of the relative importance of these factors would be of significant contribution to the synthetic chemistry and pharmaceutical application.
DISCUSSION

Nucleophilic chemical reactions occur in a molecule when a group leaves with its bonding electrons. The transitory reaction intermediate is classified as carbonium ion or cation pair and will furnish various types of results, such as substitution, elimination and rearrangement depending on the environment and reaction conditions. A general scheme for these reactions can be summarized as follows:

\[ \text{Z} \quad \text{--C--C--Nu} \quad \ldots \ldots (1) \]

\[ \text{Z} \quad \text{--C--C--} \quad \text{--C--C--} \quad \ldots \ldots (2) \]

\[ \text{Z} \quad \text{--C--C--L--} + \text{Nu} \quad \text{--C--C--} \quad \text{or} \quad \text{--C--C--} \quad \text{--C--C--} \quad \text{--C--C--} \quad \ldots \ldots (3) \]

\[ \text{--C--C--} \quad \text{--C--} \quad \text{--C--} \quad \text{--C--} \quad \ldots \ldots (4) \]

In the above equation L at Cα is a leaving group, the Nu is a nucleophile, and Z is an intramolecular nucleophile such as oxygen, nitrogen, sulfur, halogen, carbon or hydrogen.

Recently Lyle and co-workers (1-5) have investigated some of the nucleophilic reactions of piperidyl α-halo-ketones and acid catalyzed dehydrations of related pinacols to compare with the analogous reactions of alicyclic and
cyclic $\alpha$-halo ketones which were reviewed by Tschubar (17, 18), Smissman and Hite (6,7) demonstrated "Quasi-Favorskii rearrangement reactions" on $\alpha$-chloro piperidyl ketones.

It is generally recognised that most chemical reactions take place with minimum structural change; however, some chemical reactions are accompanied by dramatic molecular modification. Substitution, elimination and rearrangement reactions might be listed to illustrate the former while a typical example of the latter is the fragmentation reaction (12). These reactions are clearly the reverse of condensation reactions since the reacting molecule breaks up into fragments. Grob and Baumann (24) proposed the following scheme for the fragmentation reactions:

$$a = b - c - d \rightarrow L + 2Nu$$

$$a = b + c = d + 2L$$

$$a = b - 2Nu$$

$\therefore a = b$

at: alkyl, aryl, $-\overset{\circ}{\sigma} -$; $-\text{OH}, -\text{OR}, -\text{NR}_2$, etc.

$\therefore$ halogen, $-\text{OS}, -\text{H}_{2}$, etc.

The results which are described hereafter involve at least one of the above generalized schemes.
Preparation of the starting materials

With a few minor modifications a number of starting materials, piperidine derivatives which were not commercially available, were prepared by known synthetic methods.

Following the procedures which were developed in this laboratory (2,3,4), the 1-methyl-3-piperidylphenylketone hydrobromides (XXII, XXIII) and 1-benzyl-4-piperidylphenylketone hydrobromide (LII) were synthesized from nicotinic acid and 4-benzoylpyridine. The yields were improved from 62-65% to 72-82% by an improved isolation technique. 1-Methyl-3-(and 4-)bromo-3-(and 4-)piperidylphenylketone hydrobromide (VII, XXIV) and 1-benzyl-4-bromo-4-piperidylphenylketone hydrobromide (LIII) were prepared by the modified methods developed by Troschianiec (2). Chlorination of 1-methyl-3-(and 4-)piperidylphenylketone hydrochloride to the 1-methyl-3-(and 4-)chloro-3-(and 4-)piperidylphenylketone hydrochlorides (IX, XXV) were carried out according to the procedure described by Smith and Hite (6). Sodium borohydride reductions of XXIV, XXV and LIII to 1-methyl-4-bromo-(and chloro)-4-piperidylphenylcarbinol (XXVI, XXVIII) and 1-benzyl-4-bromo-4-piperidylphenylcarbinol (LIV) were performed by the procedure reported by Lyle and Troschianiec (2-c).

The elegant procedure of Lyle and Lyle (1) was used for the preparation of 1-methyl-4-phenyl-4-piperidylphenylketone (XL) from XXI. The phenyllithium reaction of XXI gave

At present, 1-methyl-3-benzoylpyridine also commercially available.
1-methyl-4-piperidyl-4-diphenylcarbinol (XXXVII) followed by dehydration with sulfuric acid produced 1-methyl-4-piperidylidenediphenylmethane (XXXIX). Treatment of the hydrobromide of XXXIX with bromine water, followed by neutralization with potassium hydroxide, yielded 37% of XL along with 38% 1-methyl-4-hydroxy-4-piperidylidenediphenylcarbinol (XLI). 1-Benzyl-4-phenyl-4-piperidylphenoxycarbimol (XVIII) and 1-benzyl-4-phenyl-4-piperidylphenoxycarbimol (XIII) were synthesized from commercially available 1-benzyl-4-cyano-4-phenylpiperidine with phenylmagnesium bromide by modifying Pickard's procedure (23).

\[
\begin{align*}
\text{COOH} & \xrightarrow{\text{SOCl}_2} \text{COCl} \\
R: & -\text{CH}_3, -\text{C}_2\text{H}_5, -\text{CH}_2\text{Ph} \\
X: & \text{Cl}, \text{Br}, \text{I}
\end{align*}
\]
All other piperidines employed in this research were derived from the above starting compounds by standard procedures as indicated in the experimental section.

Physical properties of those known piperidines were in good agreement with the respective data reported by other workers.

Attempt to synthesize anti-radiation agents

According to the present knowledge, protective action against radiation is exhibited by compounds containing the group \( \text{N-O-C-S} \) or \( \text{N-O-C-C-S} \), in which the nitrogen is basic and the sulfur, in fact or potentially, is of mercaptan character. The model compound \( \beta \)-mercaptoethylamine was reported in 1951 to be effective (25) in protecting animal cells against the deleterious effects of ionizing radiation; however, this compound is too toxic for human use (26).

In recent years, therefore, a number of attempts have been made to reduce the toxicity by preparing derivatives which would liberate the \( \beta \)-mercaptoethylamine over a period of time by hydrolysis in vivo, and by synthesizing analogous types of the compounds.

A synthesis was attempted to incorporate the structural moiety of the \( \beta \)-mercaptoethylamine into a piperidine derivative, a compound type known to be pharmaceutically interesting.

The reaction of 1-methyl-3-bromo-3-piperidylphenylketone hydrobromide (VII) with sodium hydrosulfide in anhydrous xylene gave a product which was believed to be 1-methyl-3-
mercapt-3-piperidylphenylketone. Immediately following isolation the product gave a positive color test for the mercapto group (14); however, one hour later it was found that the compound no longer showed a positive test with the reagent. Reduction of the product compound with zinc and hydrochloric acid gave a product which showed a positive color test. These results suggested that a mercapto-disulfide interconversion was involved. A mercapto is susceptible to oxidation to a disulfide by standing in air in an alkaline solution (27).

The elemental analyses of XI-A corresponded to the formula for the 1-methyl-3-mercapto-3-piperidylphenylketone dimers (XI, XII, XIII).

If a lower boiling solvent such as benzene was used for the reaction of VII with sodium hydrosulfide and the product was isolated by the previously described procedure

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only 1-methyl-3-hydroxy-3-piperidylphenylketone (XVI), identified as the hydrochloride (XV), was obtained. The $\alpha$-bromoketone (VII) apparently gave no reaction in the lower boiling solvent and was hydrolyzed to the $\alpha$-hydroxyketone (XVI) during the work-up.

Smiseman (7) attempted the "Quasi-Favorskii reaction" of 1-methyl-3-chloro-3-piperidylphenylketone with sodium hydride in ether or low boiling petroleum ether. The product was the 3-$\alpha$-hydroxyketone (XVI) unlike the product of rearrangement formed in the higher boiling medium.

In polar solvents, such as absolute methanol and ethanol, in which both reactants were soluble, an unexpected product was formed, 1-methyl-3-piperidylphenylketone (V-A). This product was identified by elemental analyses of the hydrochloride (VIII), a mixture melting point with an authentic sample and an identical infrared absorption spectra with that of an authentic sample.

Because of the unexpected result, further structural confirmation was necessitated against a most probable dehydrohalogenation product.

![Chemical Structures](image-url)
If the product was one of dehydrohalogenation, it would produce a different product with phenyllithium and phenylmagnesium bromide. Zimmerman (28), Zaug (29-a) and Krikorian (29-b) demonstrated the analogous reactions as follows:

\[
\text{Reactions}
\]

If the product were 1-methyl-1,2,5,6-tetrahydro-3-pyridyl-phenylketone (A), it should yield 1-methyl-1,2,5,6-tetrahydro-3-pyridyldiphenylcarbinol (B), m.p. 187.5-188.5° (22), with phenyllithium, and 1-methyl-1-phenyl-3-piperidylphenylketone (C) with phenylmagnesium bromide.

The reaction of the ketone with phenyllithium and phenylmagnesium bromide, however, produced in good yield (79-80%) the identical product, 1-methyl-3-piperidynldiphenylcarbinol (XIV), m.p. 148-150°, which was also prepared from an authentic sample of 1-methyl-3-piperidylphenylketone.
The absence of the dehydrohalogenation product is not surprising. Swasman and Hite (7) sought a product of a dehydrohalogenation from the reaction of 1-methyl-3-chloro-3-piperidylphenylketone with sodium hydroxide in xylene, but never detected it among the products. Warnier (4) also never found such a product from the reaction of 1-methyl-3-halo-3-piperidylphenylketone with silver nitrate in an aqueous medium.

The formation of 1-methyl-3-piperidylphenylketone may result from a reduction by sodium hydrosulfide (30). The reaction could be formulated as follows:

\[
\begin{align*}
\text{Br} & \quad \text{C} \quad \text{O} \quad \text{H}_3 \\
\text{C} \quad \text{N} \quad \text{H}_3 & \quad + \text{NaSH} \quad \text{Polar solvents} \\
\end{align*}
\]

Such a reduction with hydroiodic acid has been described by Zimmerman (28) with 2-phenyl-1-bromocyclohexyl-phenylketone.

\[
\begin{align*}
\text{C} \quad \text{O} \quad \text{H}_3 \\
\text{C} \quad \text{Br} & \quad \text{Br} \quad \text{H} \\
\end{align*}
\]
Lyle (2-5) reported that the reaction of 1-methyl-4-bromo-4-piperidylphenylketone with phenyllithium gave 1-methyl-4-piperidylphenylketone.

\[
\text{\textbf{At tempted ring contraction reaction of 1-methyl-3-halo-3-piperidylphenylketone to pyrroolidine derivatives.}}
\]

Brain, Doyle and Mehta (6) have reported that 1-methyl-3-chloropiperidine was converted to a pyrroolidine derivative by nucleophilic reagents such as amine, hydrazine or cyanide, and subsequent thermal rearrangement of 1-methyl-2-chloromethylpyrroloidine to 1-methyl-3-chloropiperidine. Smissman and his co-workers (10) also reported that solvolysis of 1-alkyl-3-halo-piperidine gave a pyrroolidine derivative by ring contraction.
These reactions have been explained by an intermediate azaridinium ion as follows:

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{CH}_3 & \quad \text{CH}_2 & \quad \text{CH}_2 \\
\end{align*}
\]

To determine the effect of a substituent on the rearrangement 1-methyl-3-halo-3-piperidylphenylketones were chosen for the reaction. 1-Methyl-3-halo-3-piperidylphenylketone hydrohalide (VII or IX) was converted to base and, following the procedure of Brain, et al. (8), was treated with potassium cyanide in 95% ethanol, absolute ethanol or isopropyl alcohol. The product from each reaction was characterized as 1-methyl-3-hydroxy-3-piperidylphenylketone (XVI) by comparison of the hydrochloride and picroate with an authentic sample. Similar results were obtained when the hydrohalides (VII or IX) were treated directly with alcoholic potassium cyanide.

\[
\begin{align*}
\text{X: Cl, Br} \\
\end{align*}
\]
The solvolysis with rearrangement of 1-methyl-3-halo-piperidine probably occur with ease due to the favored equatorial conformation of the halogen.

\[
\begin{align*}
\text{CH}_3 & \quad \text{X} \\
\text{CH}_3 & \quad \text{X}
\end{align*}
\]

\(X: \text{Cl}\)

In the case of 1-methyl-3-halo-3-piperidylphenylketone, however, the steric hindrance of the bulky benzoyl group causes the more stable conformation to have an axial halogen (7,31) unfavorable to participation by nitrogen.

\[
\begin{align*}
\text{CH}_3 & \quad \text{X} \\
\text{CH}_3 & \quad \text{X}
\end{align*}
\]

\(\text{VII} - A\)

\(\text{VII} - B\)

In addition, the neighboring carbonyl group can participate in the solvolysis preventing any rearrangement.
The formation of 2-methoxy-6-methyl-2-phenyl-1-oxo-6-aza-
spiro[2,5]octane from the reaction of 1-methyl-4-halo-
piperidylphenylketone with sodium methoxide in methanol (2-c)
and the reaction of α-haloketones with amines (32) illus-
trate the neighboring-group participation of a carbonyl group.

Lyle (2-d) obtained a quantitative yield of the α-hydroxy-
ketone (XXIX) by hydrolysis of 2-methoxy-6-methyl-2-phenyl-
1-oxo-6-azaspiro[2,5]octane, prepared from the α-bromo-
ketone (XXIV) with sodium methoxide. Hite (11) studied the
mechanism of the hydrolysis using isotopically labeled C^18.
The acidic hydrolysis of the epoxide yielded the α-hydroxy-
ketone with total retention of the labeled oxygen at C_3.
Treatment (1) of the \( \alpha \)-hydroxyketone (XXIX) with concentrated sulfuric acid was studied to determine whether a phenyl group migration to form the carboxypiperidine (E), dehydration for form (G), or an acyloin rearrangement product (F) would occur. These reactions, however, gave a quantitative recovery of the starting material (XXIX), which indicated that the hydroxy group was stabilized by the structural environment.

\[
\text{Reaction of 1-methyl-4-halo-4-piperidylphenylcarbinol.}
\]

The pinacol rearrangement in the transformation of a 1,2-diol to an aldehyde or ketone, via the migration of an alkyl or aryl group has been well illustrated on alicyclic and cyclic compounds. The pinacol rearrangements of a number of heterocyclic, piperidine derivatives have been investigated and compared with those of non-heterocyclic pinacols in this laboratory (1,3,5) and others (9). The reaction is generally carried out in a strong acid medium and may be assumed to proceed through at least one carbonium-ion intermediate.
The products of the deamination reaction of amino alcohols with nitrous acid are equivalent to those resulting from the

\[
\begin{align*}
\text{RC} - \text{CH}_2 - \overset{\text{HNO}_2}{\longrightarrow} \text{RC} - \text{CH}_2 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

pinacol rearrangement and one might consider the reaction mechanisms to be very similar except that the location of the initial carbonium ion is determined by the position of the amino group. The reaction of \(\alpha\)-halohydrins with \(\text{Ag}^+\) or \(\text{Hg}^+\) provide a comparable reaction. The silver or mercuric salt acts as an electrophilic catalyst in facilitating the ionization of the halogen leading to reaction having general characteristics of unimolecular heterolysis. The reaction of tertiary \(\alpha\)-iodo alcohols with silver or mercuric salt was reported by Tiffeneau (35) in 1907. He showed that 2-hydroxy-2-phenylpropyliodide was converted to benzylmethyleketone with the migration of phenyl group. In 1914 M. Le-Brazilédo (36) observed an analogous rearrangement from the reaction of 1-methyl-2-iodocylohexanol with an electrophilic
catalyst to give cyclopentylmethylketone by methylene group migration.

\[
\begin{align*}
E = C-C-CH_2- & \quad \text{or } Ag^+ \\
\text{CH}_3 & \quad \rightarrow \quad C-C-CH_2- \\
& \quad \text{CH}_2
\end{align*}
\]

In these cases the direction of rearrangement is fixed by the position of the halogen substituent, for the pinacol rearrangement of analogous \( \alpha \)-glycols with aqueous sulfuric acid, would be expected to proceed through the tertiary carbonium ion formed by loss of the tertiary hydroxyl group.

The pinacol rearrangement of substituted \( \beta \)-hydroxy-\( \beta \)-piperidylcarbinols has been investigated in this laboratory (3). A comparison of the rearrangements of the analogous halo and amino derivatives was attempted to determine any difference in characteristics of the reactions and any possible role the heterocyclic nitrogen might play. The 1-methyl-\( \beta \)-halo-\( \beta \)-piperidylphenylcarbinols were chosen for the investigation of the reactions of heterocyclic halohydrins with silver or mercuric cations. 1-Methyl-\( \beta \)-bromo-\( \beta \)-piperidylphenylcarbinol (XXVI) and 1-methyl-\( \beta \)-chloro-\( \beta \)-piperidylphenylcarbinol (XXVIII) were prepared by the method reported by
Lyle (2-e). The \( \alpha \)-chlorohydrin (XXVIII) was quite stable and, unlike the \( \alpha \)-bromohydrin (XXVI)(2-e), could be purified by recrystallization. The \( \alpha \)-bromohydrin was observed to decompose on heating and on exposure to direct sunlight. The product of decomposition from XXVI was shown to be XXII, and XXII was often found to be a contaminant even when XXVI was prepared by sodium borohydride reduction at ice-bath temperature. The preparation of pure XXVI was best achieved by addition of sodium borohydride at \(-21^\circ\).

The reaction of the bromohydrin (XXVI) with an equimolar amount of silver oxide in aqueous methanol (3:7) at room temperature, or at \(33^\circ\) for 17 hrs., resulted in the
formation of 1-methyl-4-hydroxy-4-piperidylphenylethanol (XXXI) as the major product. A very small amount of a product of rearrangement, believed to be 1-methyl-4-formyl-4-piperidylphenylpiperidine, was detected by an absorption band at 1720 cm\(^{-1}\) in the infrared spectrum of the crude product mixture. This mixture was partially resolved by chromatography over Florisil to obtain fractions which gave positive Tollen's tests.

![Chemical Structures](#)

A minor product having an absorption band at 1675 cm\(^{-1}\) in the infrared spectrum was believed to be 1-methyl-4-piperidylphenylketone (XXI).

Treatment of the bromohydrin (XXVI) with mercuric oxide in aqueous methanol at 33\(^{\circ}\)C for 4.5 hrs. also yielded the diol (XXII) and a very small amount of the starting material. The rearrangement products were not detected in the infrared absorption spectrum.

Unlike the bromohydrin (XXVI) the chlorohydrin (XXVIII) demonstrated stability. Treatment of the chlorohydrin (XXVIII) with silver or mercuric oxide in aqueous methanol, or aqueous acetone, or aqueous silver nitrate solution, gave no reaction.

The reaction of the bromohydrin (XXVI) with silver acetate in aqueous methanol (1:3) was remarkably different from those with silver or mercuric oxide. An immediate reac—
tion with silver acetate was evidenced by the formation of a white emulsion. The mixture was stirred for 17–24 hrs. at 33°C and was worked up the same way as the reaction with silver or mercuric oxides. The product mixture showed an absorption band at 1720 cm⁻¹, as an only carbonyl band, in the infrared absorption spectrum, indicating the formation of 1-methyl-5-formyl-4-phenylpiperidine (XXXII) in 73% yield. The product gave a positive Tollen's test and carbonyl derivatives supported the assignment of structure as

\[
\text{XXXII}
\]

The reaction of the chlorohydrin (XXVIII) with silver acetate, using the same reaction conditions as for XXVI, resulted in only 17% of the rearrangement product XXXII.

Leone (3) observed two carbonyl stretching absorption bands in the infrared absorption spectrum of the product from the reaction of the diol (XXXI) with concentrated sulfuric acid. These compounds could not be separated and purified, but were tentatively identified as XXXII and 1-methyl-5-phenyl-1-aza-4-cycloheptanone.

\[
\text{XXXI} \quad \text{XLIII} \quad \text{XXXII} \quad \text{XLV}
\]
The pinacol rearrangement of 1-methyl-4-hydroxy-4-piperidyl diphenylcarbinol (I) was reported by Lyle (1) to follow a similar reaction sequence to give 1-methyl-4,6-diphenyl-1-aza-5-cycloheptanone (J) and 1-methyl-4-phenyl-4-piperidylphenylketone (XL). In these cases either of two carbonium ions may form and lead to products.

Unlike the pinacol rearrangement the bromohydrin with Ag⁺ produced a definite reactive site followed by migration of phenyl group. The bromohydrin (XXVI) could be an equilibrium of two conformational isomers and in polar medium the reaction may occur largely with conformation XXVIB in which the electron pair on nitrogen may stabilize the carbonium ion by anchimeric assistance, or by providing a molecule of solvent as in XXVIC. Such a reaction sequence would lead to substitution, rather than rearrangement as observed with silver or mercuric oxide in aqueous methanol. In the presence of a strong base and absence of an electro-
philic catalyst, the oxygen of the alcohol function participates, or the neighboring-group leads to epoxide formation.

In acidic solution a pair of electrons on nitrogen is bonded with proton or heavy metal ion to become unavailable for participation in the solvolysis. The product resulting from the reaction of the bromohydrin (XXVI) with silver acetate suggests that the silver cation forms a chelate complex with the basic nitrogen as well as effecting the solvolysis of the bromine at CH₃.
The heterolysis of the C–Br bond is facilitated by the neighboring phenyl group, perhaps to form a phenonium ion, and not by the electron pair on nitrogen which was bound with H⁺ or Ag⁺, or by the hydroxyl oxygen.

The preferred rotational conformation of the complexed bromohydrin seems to be L. This is reasonable since the conformation has the large halogen staggered between the two smaller groups, OH and H, on the adjacent atom. In this conformation the phenyl could assist in the ionization of the bromine and reaction in this conformation rationalizes the absence of the other possible product of rearrangement, 1-methyl-4-piperidylphenylketone (XXI), formed by the hydrogen migration.
1-Methyl-4-formyl-4-phenylpiperidine (XXXII) was rather unstable. When the ether-soluble oily product was allowed to be exposed in air over 48 hrs., the majority of the liquid was no longer soluble in ether and the infrared absorption spectrum of the insoluble material showed bands at 3450, 1680 and 1640 cm\(^{-1}\), while the aldehyde band at 1720 cm\(^{-1}\) was markedly diminished. The oxidized product melted at 305\(^{\circ}\)-309\(^{\circ}\) and was characterized as 1-methyl-4-phenyl-4-carboxypiperidine (E). 1-Methyl-4-formyl-4-phenylpiperidine was characterised by conversion to a series of authentic derivatives.

The oxime of formylpiperidine (XXXIV) was prepared by the conventional method and melted at 144\(^{\circ}\)-146\(^{\circ}\). The typical oxime bands at 3250 and 1510 cm\(^{-1}\) were evident in the infrared absorption spectrum. The reduction of the product (XXXII) with sodium borohydride or lithium-aluminum hydride yielded 1-methyl-4-hydroxymethyl-4-phenylpiperidine (XXXIII). These compounds (XXXII, XXXIII) were prepared by unambiguous routes for comparison with the product of rearrangement of XXVI or XXXIII.
The partial reduction of 1-methyl-4-cyano-4-phenylpiperidine with lithium-aluminum hydride (2:1) in anhydrous ether gave a mixture of the aldehyde (XXXII) (–CHO band at 1720 cm\(^{-1}\)) and the imine (\(>\mathrm{C}=\mathrm{NH}\) band at 1675 cm\(^{-1}\)) as reported by Chiarelli (20). The hydrolysis of the mixture with concentrated hydrochloric acid yielded 1-methyl-4-formyl-4-phenylpiperidine (XXXII) (59%) which had an identical infrared absorption spectrum with that of the rearrangement product.

Reduction of the formylpiperidine, from the above reduction, and ethyl 1-methyl-4-phenyl-4-piperidylcarboxylate,
Demerol, with lithium–aluminum hydride gave identical 4-
hydroxymethylpiperidine (XXXIII), m.p. 134°–135°. The iden-
tity of the products from the rearrangement of the halohydrin
and the authentic compounds was shown by mixture melting
points and identical infrared spectra.

Reaction of 6-methyl( and benzyl–)–2-phenyl-1-oxo-6-asaspiro-

Treatment of the 1-methyl( and benzyl–)–4-halo-4-
piperidylphenylcarbinols (XXVI, XXVIII, LIV) with 10% sodium
hydroxide gave 90–98% of 6-methyl( and benzyl–)–2-phenyl-1-
oxo-6-asaspiro[2,5]octane (XLIII, LV).

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Leone (3) reported that the reaction of the piperidino diol (XXII) with boiling 48% hydrobromic acid in glacial acetic acid, a strong dehydrating combination, followed by neutralization, resulted in the epoxide (XLIII) as a major product. The reaction was explained as resulting from the formation of the bromohydrin hydrobromide (XXVII) as an intermediate which then gave cyclisation to the epoxide or underwent dehydrohalogenation to the phenyllactone (XII) during the work-up with alkali. Leone also observed that treatment of the diol (XXXI) with concentrated sulfuric acid, followed by neutralization, gave the epoxide as a major product (45%). Presumably a monosulfate ester was formed in acid and underwent cyclization on treatment with base. One might anticipate that strong acids might cause a pinacol rearrangement which could result in XXXII and XLV, and Leone found evidence of their presence by infrared spectral analysis.

![Chemical structures](image)

The formation of epoxides XLIII and LV from the reaction of the halohydrins (XXVI, XXVII, LIV) with 10% sodium hydroxide has several analogies in the literature. This procedure is the most efficient method of synthesis of the compounds XLIII, LV and was used for the preparation of these compounds used in further reactions.

The reaction of the epoxide (XLIII) with phenyllithium
and phenylmagnesium bromide was investigated in order to determine the direction of ring opening of the epoxide with these reagents.

In general the Grignard reagents are subject to stereospecific reactions and likewise one would anticipate the phenyllithium to be so, but not always follow the same pattern.

\[
\begin{align*}
R - C - CH_2 & \overset{\text{GrX}}{\longrightarrow} R - C - CH_2\beta \\
\text{major} \\
R - C - CH_2 & \overset{\text{LiAlH}_4}{\longrightarrow} R - C - CH_3 \\
\text{major}
\end{align*}
\]

Inspection of the molecular models reveals that the most plausible stereochemistry of the epoxide would be **XXVIII-C** by the following sequences:

\[
\begin{align*}
\text{XXVI-x, Br} & \overset{\text{OH}}{\longrightarrow} \text{XXVII} \\
\text{XXVIII-x, Cl} & \overset{\text{flip}}{\longrightarrow} \text{XXVIII-C} \\
\text{XXVIII-C} & \overset{\text{OH}}{\longrightarrow} \text{XXVIII-B}
\end{align*}
\]
The direction of ring opening of an epoxide on nucleophilic attack is not easily predicted. Thus Leone (3) obtained the 1-methyl-2-hydroxybenzylpiperidine from the reduction of the epoxide (XLIII) with Raney nickel or lithium-aluminum hydride; however, the reduction of ethylidenecyclohexane epoxide (0) with lithium-aluminum hydride has been reported in one instance to give 1-ethylcyclohexanol (0-a)(37-a), while another investigator reported methylcyclohexylcarbinol (0-b)(37-b) to be the product.

![Chemical Structure](image)

The reaction of the epoxide (XLIII) with phenyl-lithium and phenylmagnesium bromide was investigated to determine the direction of epoxide ring opening. It was anticipated that attack of the nucleophile would occur on the benzilic carbon with cleavage of the benzilic O=C bond of the epoxide.

The reaction of the epoxide (XLIII, 0.021 mole) with a slight excess of phenyllithium (0.025 mole) in ether was run at room temperature under a nitrogen atmosphere for 16 hrs. After hydrolysis with ammonium chloride solution, the reaction mixture was treated so as to separate the basic products. The crude amine fraction showed remarkable bands at 1760 and 1710 cm\(^{-1}\) in the infrared absorption spectrum.
Petroleum ether (30–60°C) fraction

Ether fraction

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The isolation of a product containing a carbonyl function from a reaction with phenyllithium is unusual. These changes in the reaction conditions were made in an effort to determine the source of this product. Hydrolysis of the reaction mixture with water instead of ammonium chloride and elimination of the separation of the basic and neutral components in the product led to no significant change in the infrared spectrum of the product mixture. Chromatographic separation of the oily product on Florisil using petroleum ether (b.p. 30–60°) and anhydrous ether as eluents gave two components. The compound eluted with petroleum ether exhibited a band at 1760 cm⁻¹ in the infrared spectrum and the latter solvent eluted a fraction which showed a band at 1710 cm⁻¹. The compound having the 1760 cm⁻¹ band was converted to a hydrobromide, m.p. 271–272°, with an infrared spectrum identical with 1-methyl-4-piperidylidenadiphenylmethane hydrobromide (XXXIX)(43.5%). The hydrobromide did not depress the melting point of XXXIX (1) on admixing, confirming the identity.

After standing for 85 days, the fraction eluted by petroleum ether no longer showed the band of 1760 cm⁻¹ in the infrared absorption spectrum, which was identical with that of the authentic sample of 1-methyl-4-piperidylidenadiphenylmethane (XXXIII). The source of the absorption band at 1760 cm⁻¹ in the infrared spectrum has not been rationalized.
The fraction eluted with ether was converted to the methiodide (XLIV-B), m.p. 166-168°, which also gave an absorption band at 1710 cm⁻¹ in the infrared spectrum. Sodium borohydride reduction of the base gave an alcohol (XLIV-C) which no longer had a carbonyl absorption band in the infrared spectrum. The elemental analyses of XLIV-B corresponded to the formula C₁₁₄H₂₀NO₅ and the n.m.r. spectrum was consistent with the presence of only one phenyl group. Based on these chemical and physical data, the structure of the compound with the 1710 cm⁻¹ band, eluted from Florisil by ether, was assigned as 1-methyl-4-phenyl-1-aza-5-cyclohepanone (XLIV-A).
(30% yield). The combined products (XXXVIII and XLV-A) accounted for 73.5% of the starting epoxide.

The formation of XLV-A was not expected, and the cause of the rearrangement could not be determined. The absorption band at 1710 cm⁻¹ was present in the infrared spectra of all product mixtures of the reaction of phenyllithium with XLIII. The lithium bromide formed in the preparation of phenyllithium was shown to have no effect on XLIII, for heating the epoxide (XLIII) with lithium bromide freshly prepared from lithium and ethylene bromide in ether gave recovery of XLIII.

\[
2 \text{Li} + \text{BrCH}_2\text{CH}_2\text{Br} \rightarrow 2 \text{LiBr} + \text{CH}_2=\text{CH}_2
\]

The reaction of the epoxide (XLIII) with phenylmagnesium bromide gave a product which on conversion to the hydrobromide gave a small amount of crystalline material, m.p. 294–295°. The infrared spectrum of the salt indicated a hydroxyl compound which most probably had the structure 1-methyl-4-hydroxybenzypiperidine (XXXV). An alternate synthesis of XXXV was attempted to provide an authentic sample for comparison.

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Following the procedure of Gilman (19), diphenylmethyllithium was prepared from n-butyllithium and diphenylmethane, and reaction with 1-methyl-4-piperidone gave a very small amount of XXXV isolated as the hydrobromide, m.p. 260-262°. Zamborski (39) reported the preparation of diphenylmethyllithium from diphenylchloromethane and metallic lithium. Diphenylmethyllithium prepared by this method with 1-methyl-4-piperidone gave 8.5% of 1-methyl-4-hydroxy-4-benzhydryl-piperidine hydrobromide, m.p. 260-262°. Although the melting points of the hydrobromide of XXXV from the two reactions differed, the bases prepared from the salts gave identical infrared spectra.

Rearrangement of the 1-alkyl-4-phenyl-4-piperidylcarbonium-ion.

The method of formation of a carbonium-ion has been shown to affect the product formed. Thus the comparison of the products formed from the 1-alkyl-4-phenyl-4-piperidyl-carbonium-ion prepared as below was attempted.

\[
\text{XXXIII} \quad \text{CH}_2\text{CH} \quad + \quad \text{H} \quad \rightarrow \quad \text{XXXIV} \quad \text{CH}_3
\]

\[
\text{XLVII} \quad \text{CH}_2\text{Cl} \quad \overset{\text{solvolysis}}{\rightarrow} \quad \text{CH}_3
\]

\[
\text{LXIV} \quad \text{CH}_2\text{NH}_2 \quad \overset{\text{HNO}_2}{\rightarrow} \quad \text{CH}_2^+ \quad \text{P}
\]
The preparation of the halide (XLVII) offered an opportunity to study the possible rearrangement (P) of the alcohol XXXIII. Of the available classical chlorination reagents, HX, PX₂, POX₃ and SOX₂, thiomethylchloride was chosen for investigation. This reagent has a broad range of applications, but often gives anomalous reactions such as olefin formation or isomerization. A typical isomerization was reported recently (40) with the chlorination of C¹⁶ labeled 4-methoxy-β-hydroxyethylbenzene by thiomethylchloride. The rearrangement is given in the equations below.

\[
\begin{align*}
\text{CH}_3\text{C} & \text{=CH}_2\text{CH}_2\text{OH} \xrightarrow{\text{SOCl}_2} \text{CH}_3\text{C} & \text{=CH}_2\text{CH}_2\text{Cl} \\
\text{[CH}_3\text{C} & \text{=CH}_2\text{OH} \xrightarrow{\text{S}_2\text{Cl}_2} \text{CH}_3\text{C} & \text{=CH}_2\text{H}_2\text{Cl} \xrightarrow{\text{S}_2\text{Cl}_2} \text{CH}_3\text{C} & \text{=CH}_2\text{Cl} \\
\end{align*}
\]

Depending upon the conformation of the 1-methyl-4-phenyl-4-chloromethylpiperidine obtained from the chlorination ring closure, such as that reported by Krikorian (29-b) with 1-methyl-3-phenyl-4-piperidylphenylcarbinol and 46% of hydrobromic acid could occur.
On the other hand, Hill (41) reported that the reaction of 1-benzyl-2-hydroxymethyl-6-methylpiperidine with thionylchloride occurs with no difficulty to give the expected product.

The reaction of 1-methyl-4-hydroxymethyl-4-phenylpiperidine (XXXIII), with thionylchloride, however, occurred with no difficulty to give a good yield of the hydrochloride (XLVI), m.p. 244-245°.

The base (XLVII) was prepared from XLVI with 10% sodium hydroxide and was dissolved in absolute ethanol. No change in infrared spectrum was observed on heating XLVII under reflux for one or two hours, but after 14 hrs. the spectrum of the product was remarkably different from XLVII. A C-O vibration at 1100 cm⁻¹ had appeared and the C-Cl absorption at 750 cm⁻¹ was decreased. This product gave a weak Beilstein test for halogen, indicating some of the un-
reacted chloromethane (XLVII) was present. On heating XLVII with sodium ethoxide in ethanol, a material was obtained which gave a negative Boilstein test and the infrared spectrum was identical with that of the reaction products with absolute ethanol. The product mixture was separated into two components by chromatography on Florisil with ether and acetone as eluants.

![Chemical structures](image)

The structure of the fraction eluted by ether was assigned as 1-methyl-4-phenyl-4-piperidylmethylethyl ether (XLVIII), based on the infrared absorption spectrum, bands at 1125 (s), 1080 (s) and 1035 (s) cm\(^{-1}\), and the elemental analyses. The hydrobromide melted at 155-157\(^\circ\) and the piperate at 132-134\(^\circ\).

The acetone fraction gave a quite different infrared spectrum from that of the ether fraction. Notable bands were observed between 1080-1200 cm\(^{-1}\) and a shoulder at 720 cm\(^{-1}\).

The ultraviolet absorption spectrum (\(\lambda_{\text{max}}\) 246 m\(\mu\), \(\varepsilon\) = 1100)

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indicated the presence of a conjugated system, such as a styrene type. Based on these physical characteristics and the elemental analyses, the structure was assigned as 1-methyl-4-benzylideneepipipridine (XLIX).

A double-bond exocyclic to a six-membered ring often exhibits a tendency to undergo migration to an endocyclic position. The corresponding isomer of XLIX, 1-methyl-4-benzyl-1,2,5,6-tetrahydroepipipride had been reported by Korlin (21), and the melting point of the picrate was reported to be 134–135°. The product isolated as the acetone eluent gave a picrate, m.p. 159–162°. These facts led to the structural assignment as XLIX, rather than R.

The preparation of the carbonium-ion, P, by the deamination reaction of 1-benzyl-4-phenyl-4-piperidylaminomethane (LXIV) was attempted to determine the nature of the reaction products.

\[ \text{LXIV} \]

\[
\begin{align*}
\text{CH}_2\text{NH}_2 & \rightarrow \text{HNO}_2 \\
\text{N} & \text{CH}_2\phi
\end{align*}
\]

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The aminomethane (LXIV) was prepared from commercial 1-benzyl-4-cyano-4-phenylpiperidine by lithium-aluminum hydride reduction in good yield (74%). The resulting crude, oily product was purified by chromatography on Florisil, using ether as eluant. Crystallization of the oil with ligroin and recrystallization from acetonitrile gave an analytically pure product (LXIV), m.p. 71-72°C.

Treatment of the aminomethane (LXIV) in 10% acetic acid with sodium nitrite at 65°C resulted in 62% of N-nitroso-4-phenyl-4-piperidylcarbinol (LXV), m.p. 204-206°C.

This structural assignment was based on the physical properties, elemental analyses and conversion to a known compound. The N-nitroso compound (LXV) was not soluble in water, 10% acetic acid, or 10% hydrochloric acid, but it was soluble in chloroform and acetone.

![Chemical structures](image-url)
The compound LXV gave a positive Lieberman's test for the N=O group and the infrared absorption spectrum showed a band at 3490 cm\(^{-1}\), assigned as an O-H stretching vibration and a multiple band near 1350 cm\(^{-1}\) for the N-H group. The n.m.r. spectrum was consistent with the presence of only one phenyl group.

The structure of the N-nitroso compound as LXV was confirmed by conversion to the known compound XXXII. Following the procedure of Koelsch (42), the denitrosozation reaction was carried out using concentrated hydrochloric acid and cuprous chloride. The resultant crude intermediate (S), without further purification, was subjected to N-methylation (43) with 44% formaldehyde in formic acid. The product melted at 145-149\(^{\circ}\) and the mixed melting point of the solid with an authentic sample of 1-methyl-4-phenyl-4-hydroxymethylpiperidine (XXXII) melted at 140-145\(^{\circ}\), (c.f., m.p. of the authentic sample 139-141\(^{\circ}\).) The isomeric, 1-methyl-4-benzylhydroxypiperidine (LXVI) was synthesized for comparison. 1-Methyl-4-piperidones was treated with benzyl magnesium chloride to give LXVI, an analytical sample which melted at 83-84.5\(^{\circ}\), and was not identical with the isomeric product from LXV.

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{CH}_3 & \\
\end{align*}
\quad + \quad \text{CH}_2\text{MgBr} \\
\rightarrow \\
\begin{align*}
\text{N} & \quad \text{O} \\
\text{CH}_3 & \\
\end{align*}
\quad \text{LXVI}
\]
The reaction of 1-benzyl-4-phenyl-4-piperidylaminomethane (LXIV) with nitrous acid thus involved attack at the tertiary amine as well as deamination of the primary amine function. The reaction of tertiary amines with nitrous acid has been observed previously and has recently been reviewed (44). This reaction, however, has not received wide attention and many current textbooks indicate stability of tertiary amines toward reaction with nitrous acid.

Smith (45) and his co-workers have provided some mechanistic details of the reaction. The nitroxylation of tertiary amines involves electrophilic attack on the amine nitrogen, similar to the reaction path for primary or secondary amines with the same reagent. The intermediate first formed undergoes loss of a proton if one is available. The reaction of the tertiary amine LXIV, following the mechanism of Smith (45), would be formulated as below:

Primary amine

\[
\text{RNH}_2 + \text{HO}^+ \rightarrow \left[ \text{RNH}_2\text{-NO} \right]^+ \\
\downarrow \text{H}^+ \\
\left[ \text{RNH} - \text{NO} \right] \rightarrow \left[ \text{RN=NOH} \right] \\
\downarrow \\
\left[ \text{RNH}_2^+ \right] \rightarrow \text{etc.}
\]
Secondary amine

\[ R_2\text{NH} + \text{HNO}_3 \rightarrow [R_2\text{NHNO}]^+ \]

\[ \downarrow \text{H}^+ \]

\[ R_2\text{N} - \text{NO} \]

The qualitative observation made by Wegler and Frank (43) indicates that the relative ease of cleavage of a group attached to the tertiary amine nitrogen is benzyl > alkyl > cyclic. Thus the 1-benzyl substituent of LXIV was the group that would have been anticipated to undergo cleavage.

R: either \(-\text{CH}_2\text{NH}_2\) or \(\text{CH}_2\text{OH}\)
It is interesting to note that the carbonium-ion formed by the deamination reaction of the amine methyl group underwent no rearrangement. Displacement reactions without rearrangement are often observed in deamination reactions; however, LXIV is structurally arranged to facilitate a 1,2-shift of the phenyl substituent. The substitution reaction may occur by an intramolecular process, thus competing favorably with a skeletal change.

The reaction of the carbonium-ion \( P \) formed by the acid catalyzed treatment of removal of hydroxyl from 1-methyl-4-hydroxymethyl-4-phenylpiperidine (XXXIII), was not extensively investigated. With concentrated sulfuric acid (1), XXXIII gave a high melting product, m.p. 303-315°, which probably resulted from a sulfonation of the aromatic ring. Other acid catalysts were not used.

\[
\begin{align*}
\text{XXXIII} & \quad \text{CH}_2\text{OH} + \text{H}_2\text{SO}_4 \rightarrow [\text{CH}_2\text{H}] \\
\end{align*}
\]

Reaction of 1-alkyl-4-phenyl-4-piperidylphenylcarbonium-ion.

The nucleophilic displacement of the primary functions occurred with little or no rearrangement. For comparison the comparable reactions were investigated with compounds (XLII, LVIII and LXIII) in which a secondary benzylic substituent would undergo reaction. Any carbonium-ion reaction would then
proceed through intermediates of greater stability.

The compound XLII was prepared by the procedure of Lyle (1) and 1-benzyl-4-phenyl-4-piperidylphenyloxybenzene (LVIII) was synthesized from 1-benzyl-4-cyano-4-phenylpiperidine. 1-Benzyl-4-cyano-4-phenylpiperidine on reaction with phenylmagnesium bromide in toluene gave the ketone LVII in 66% yield. Reduction of the carbonyl was accomplished with sodium borohydride to give LVIII in good yield.
The alcohols (XLII and LVIII) were treated with cold concentrated sulfuric acid following the procedure of Lyle (1). The reaction product from the alcohol in the 1-methyl series (XLII) melted at 188-190°C. The elemental analyses indicated an empirical formula of C_{20}H_{24}N_{2}O and the molecular weight determination by osmometric method showed an average value of 351. The mass spectral data (47), however, revealed that the compound had a molecular weight no greater than that of the starting material. The ultraviolet absorption spectrum, ($\lambda_{\text{max}}$ 253 mp, $\epsilon$ = 427; 258 mp, $\epsilon$ = 632; 263 mp, $\epsilon$ = 446), indicated the presence of a non-conjugated phenyl group, and the n.m.r. spectrum was of little assistance due to the complexity. The infrared absorption spectrum showed bands at 3350 and 1650 cm$^{-1}$ which could be assigned to a secondary amine $\text{NH}$ stretching.
vibration.

A structure consistent with these data was not obvious and further investigation was stopped. The product of reaction of the alcohol in the 1-benzyl series (LVIII) with concentrated sulfuric acid melted at 217-218.5°. The structure, 1-benzyl-1-diphenylmethyl-1,2,5,6-tetrahydropyridine (LX) was assigned to the product isolated in 50% yield as a picrate.

The structure assignment was based on the analytical and spectroscopic data. The infrared absorption spectrum exhibited a band at 855 cm⁻¹ considered to arise from a stretching vibration of a vinyl hydrogen. The ultraviolet absorption spectrum was consistent only with that expected of isolated phenyl rings, (λ_max 252 μ, ε = 770; 257 μ, ε = 1050; 262 μ, ε = 835). Other possible structures could result from ring closure (U for example) and these cannot be
eliminated on the basis of the evidence available.

The amine corresponding to LXIII was prepared from the oxime of LVI by lithium-aluminum hydride. The oxime (LXI) was prepared in very good yield (91%) by the conventional method, and reduction of LXI to 1-benzyl-4-phenyl-4-(α-amino-benzyl)piperidine (LXIII) was attempted with lithium—aluminum hydride. Lithium—aluminum hydride reduction of LXI in ether-tetrahydrofuran or in tetrahydrofuran did not occur and the starting oxime was recovered. Using diglyme, bis(2-methoxy-ethyl) ether, as a solvent, gave a mixture of the primary amine (LXIII) with secondary amine (LXII).

Separation of the mixture was achieved by fractional distillation, giving LXII (42%), b.p. 142-145° at 0.7 mm, and a small amount of LXIII, b. p. 145-185° at 0.7 mm. The rearrangement of aromatic ketoximes on reduction with lithium—aluminum hydride has been described (48-52); however, the reductive rearrangement of a heterocyclic ketoxime under similar con-
ditions has not been reported previously.

The rather high yield of the secondary amine (LXII), compared with the primary amine (LXIII), suggests that the use of the higher boiling solvent may facilitate the rearrangement reaction as does the use of aluminum chloride - lithium-aluminum hydride (51). The primary amine (LXIII) was purified by crystallization and was identified by comparison with an authentic sample of LXIII prepared by the alternate method of Shoppee, et al (53) and Dodgeon, et al (54).

The reduction of oxime LXI with metallic sodium in boiling absolute alcohol gave 63% of the primary amine (LXIII), m.p. 104-105.5°, and a small amount of a compound containing a conjugated carbonyl which was believed to be 1-benzyl-4-phenyl-4-piperidylphenylketone (LVII).

The reaction of 1-benzyl-4-(α-aminobenzyl)-4-phenyl-piperididine (LXIII) with nitrous acid gave an N-nitroso compound as evidenced by a positive Lieberman's test. The product mixture could not be resolved, however, and no positive conclusions can be drawn concerning the nature of the deamination reaction.
The complexity of the reactions observed with the derivative of 4-piperidylcarbinol precludes and generalizes concerning the effect of the heterocyclic nitrogen on displacements at this center. It does not appear, however, that skeletal rearrangements occur easily indicating that the heterocyclic nitrogen may facilitate substitution or stabilize possible ionic intermediates.
EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

Infrared absorption spectra were determined on a Perkin-Elmer Model 137-5 Infracord Spectrophotometer and on a Perkin-Elmer Model 21 Infrared Spectrophotometer equipped with sodium chloride optics. Infrared spectra of liquid samples were determined as film, and solid materials were determined as mulls in Halocarbon oil (from 4000 cm\(^{-1}\) to 1300 cm\(^{-1}\)) and in Nujol (from 1300 cm\(^{-1}\) to 600 cm\(^{-1}\)) unless otherwise indicated. All bands were strong except those indicated as weak (w) or medium (m).

Ultraviolet spectra were determined on a Perkin-Elmer Model 4000 Spectracon Recording Spectrophotometer. Spectra were determined in spectral grade methanol unless otherwise indicated.

Proton magnetic resonance spectra were determined with a Varian Model A-60 proton resonance spectrometer.

Elemental analyses were determined by Schwartzkopf Microanalytical Laboratories, Woodside, New York.
Preparation of 3-Benzoylpyridine (I). The preparation of (I) by the Friedel-Crafts reaction of benzene with nicotinyl chloride as described by Warner (1) was repeated in 75.5% yield; b.p. 150–153°C at 5 mm., Lit. (4) b.p. 143–145°C at 2 mm. The oily product was crystallised by standing overnight at room temperature, m.p. 37–40°C.

Preparation of 1-Ethyl-3-benzoylpyridinium Bromide (II). A mixture of 10 g. (0.055 mole) of 3-benzoylpyridine and 7 g. (0.06 mole) of ethyl bromide in 200 ml. of isopropyl alcohol was tightly stoppered and was allowed to stand for 24 hrs. at room temperature. The white crystalline precipitate which formed was removed by filtration and the filtrate was concentrated under reduced pressure. The product, after crystallization from isopropyl alcohol, was isolated by filtration and washed with ether to give 3 g. (20%) of 1-ethyl-3-benzoylpyridinium bromide, m.p. 160–170°C, which was extremely hygroscopic.

IR spectrum (Nujol mull): 3050(w), 2995(w), 2910(w), 1660(s), 1625(s), 1590(m), 1450(m), 1350(w), 1330(m), 1350(w), 710 cm⁻¹(m).

Anal. calcd. for C₂₃H₂₄BrNO: Br, 27.35.
Found: Br, 27.02, 27.18.

Preparation of 1-Methyl-3-benzoylpyridinium Iodide (III). A solution of 5.5 g. of 3-benzoylpyridine and 4.5 g. of methyl iodide in 200 ml. of acetone was allowed to stand for 24 hrs. at room temperature. The crystals which pre-
cipated were removed by filtration and washed with ether to give 9.5 g. (97%) of 1-methyl-3-benzoylpyridinium iodide (III), m.p. 151-152°C.

IR spectrum (Model 137B, No. 3587): 3000 (w), 1660 (s), 1640 (s), 800 (s), and 720 cm⁻¹ (s).

Anal. calcd. for C₂₃H₂₂I(N): I, 39.03.


Preparation of 1-Methyl-3-benzoylpyridinium Bromide (IV). A solution of 55 g. of 3-benzoylpyridine in 120 ml. of acetone was saturated with anhydrous methyl bromide gas, and the mixture was allowed to stand for 24 hrs. at room temperature in a tightly stoppered flask. The white crystalline solid which precipitated was collected by filtration and was washed with ether to give 75 g. (93%) of 1-methyl-3-benzoylpyridinium bromide (IV), m.p. 146-148°C.; Lit. (4) m.p. 146-148°C.

Preparation of 1-Methyl-3-piperidylphenyl-ketone Hydrobromide (V). A solution of 55 g. (0.306 mole) of 1-methyl-3-benzoylpyridinium bromide (IV) in 650 ml. of methanol was hydrogenated over platinum oxide catalyst, following the procedure of Warner (4). After the catalyst was removed by filtration the solvent was removed by distillation under reduced pressure. Crystallization of the residue from isopropyl alcohol yielded 19 g. of 1-methyl-3-benzoylpiperidine hydrobromide (V), m.p. 126-130°C.; Lit. (4), m.p. 128-131°C.

The solvent was removed from the filtrate above, and
the residue was dissolved in 300 ml. of methanol. Hydrogenation was continued as above an additional 24 hrs. and on treatment of the reduction mixture as above, an additional 11 g. of (V) was obtained giving a total yield of 30 g. (35%).

b. By-product 1-methyl-3-piperidylphenylcarbinol (VI): The alcoholic filtrate from above was concentrated under reduced pressure and the residue was dissolved in water; the solution was made basic and extracted with ether. The ether solution was dried over potassium carbonate and the ether was removed by distillation. Crystallization of the residue from ligroin gave 14.5 g. (23%) of 1-methyl-3-piperidylphenylcarbinol (VI), m.p. 123-125°C; Lit (4), m.p. 122-125°C.

c. Oxidation of 1-methyl-3-piperidylphenylcarbinol (VI): A mixture of 14 g. (0.068 mole) of 1-methyl-3-piperidylphenylcarbinol (VI), 6 g. of chromic acid anhydride, and 300 ml. of acetic acid was heated at 100°C for one hour. The solvent was removed by distillation under reduced pressure, the residue was dissolved in 100 ml. of water, and the solution was made basic with a 25% sodium hydroxide solution. The oily layer which separated was dissolved with ether, and the aqueous layer was extracted with ether. The combined ether extracts were dried over potassium carbonate, and the solvent was removed by distillation. The residue was dissolved in chloroform, and the solution was saturated with anhydrous hydrogen bromide gas. The solution was allowed to stand overnight in a tightly stoppered flask at room temperature. The chloroform was removed by distillation, and the residue was recrystallized
from isopropyl alcohol to give 9.5 g. (69%) of 1-methyl-3-piperidylphenylketone hydrobromide (V), m.p. 129-132°C.

A mixture melting point with the initial product of reduction above was not depressed.

Preparation of 1-Methyl-3-bromo-3-piperidylphenylketone Hydrobromide (VII). A solution of 5.5 g. of 1-methyl-3-piperidylphenylketone hydrobromide (V) in 50 ml. of chloroform was treated with 3 ml. of bromine as described by Warner (4). Recrystallization from isopropyl alcohol and a minimum amount of ethanol gave 6.7 g. (95%) of 1-methyl-3-bromo-3-piperidylphenylketone hydrobromide (VII), m.p. 142-144°C; Lit. (4), m.p. 142-144°C.

Preparation of 1-Methyl-3-chloro-3-piperidylphenylketone Hydrochloride (IX). 1-Methyl-3-benzoypiperidine hydrochloride (VIII) was prepared, by conventional method, in quantitative yield from the base, which in turn was obtained from 10 g. of 1-methyl-3-benzoypiperidine hydrobromide on neutralization with 6% sodium hydroxide solution. The hydrochloride was recrystallized from acetone to give 8.3 g. (99%) of (VIII), m.p. 175-176°C; Lit. (6), m.p. 176-177°C.

The hydrochloride (VIII) from above was dissolved in 150 ml. of glacial acetic acid, and chlorine gas was slowly bubbled into the solution for 10 hrs. at 65°C. After removal of the solvent, 300 ml. of anhydrous ether was added, causing precipitation of a sticky solid. The precipitate was
crystallized from chloroform to give 6.5 g. (87%) of 1-methyl-3-chloro-3-piperidylphenylketone hydrochloride (IX), m.p. 169-170°C.; Lit. (6), m.p. 169.5-170.5°C.

Preparation of D-10-Camphorsulfonic Acid Salt of d,l-methy1-3-bromo-3-piperidylphenylketone. A solution of 1 g. of d,l-methyl-3-bromo-3-piperidylphenylketone hydrobromide (VII) in water at 0°C was neutralized slowly with a saturated sodium bicarbonate solution. The oily 1-methyl-3-bromo-3-piperidylphenylketone was extracted into ether, and the ether solution was dried over anhydrous sodium sulfate. To this ether solution was added an equimolar amount of D-10-camphorsulfonic acid in a minimum amount of ethanol. The solvent was removed by decantation, and the solid was recrystallized from methanol to give the D-10-camphorsulfonic acid salt of d,l-1-methyl-3-bromo-3-piperidylphenylketone (X), m.p. range, 129-136°C.

Reaction of 1-Methyl-3-bromo-3-piperidylphenylketone Hydrobromide with Sodium Hydrosulfide. To a refluxing mixture of 3.36 g. (0.06 mole) of finely powdered dry sodium hydrosulfide in a 100 ml. of anhydrous xylene was added very rapidly 25 ml. of a xylene solution of 4.05 g. (0.0125 mole) of 1-methyl-3-bromo-3-piperidylphenylketone hydrobromide (VII). The reaction mixture was stirred for one min., was cooled in an ice-bath, and was acidified with 10% hydrochloric acid. The aqueous layer was separated, and the organic layer was extracted with water. The combined aqueous solution was
neutralized with a saturated potassium carbonate solution and extracted with chloroform. The chloroform solution gave a positive Grote test \( (*) \) for the \(-\text{SH}\) group. After one hour standing at room temperature the Grote test was negative; however, the solution gave a positive test for sulfur. This implied that compound was probably oxidized to a disulfide.

A hydrochloric acid–sulfuric acid reduction caused the residue to give a positive Grote test again, showing that a mercaptan–disulfide equilibrium was involved.

\( (*) \) Preparation of the Grote Test Solution (14). A solution of 0.5 g. of sodium nitroprusside (sodium nitroferri-
yanide), 0.5 g. of hydroxylamine hydrochloride and 1 g. of sodium bicarbonate was prepared in 10 ml. of water. After evolution of gas had ceased, 2 drops of bromine was added. Excess bromine was removed by passing air into the solution, and the dark greenish or black-brown solution was filtered and diluted to 25 ml. with water. The solution was stable for about two weeks, gradually losing reactivity toward \( \text{C} = \text{S} \). No further purification is necessary for general test use.

Method of testing: A solution of 5 to 20 mg. of the compound to be tested is dissolved in 2 to 3 ml. of water and was buffered by the addition of solid sodium bicarbonate. About 0.5 ml. of the reagent was then added. A purpler–red color given instantly or within 10 minutes indicates \( \text{C} = \text{S} \), while an intense green or blue indicates \( \text{C} = \text{E} \) or \( \text{E} = \text{S} \) (where \( \text{E} \) is any single non–metallic element). Both colors may fade
more or less rapidly, but often reappear upon addition of fresh reagent. If no color appears within 10 minutes, an equal volume of 5% potassium cyanide solution is added, and disulfide \( \text{C-S-S-C} \) gives a pink to purple-red color within 0.5 hr. Ring-linked sulfur compounds of both the \( \text{C-SH} \) and \( \text{C-S-S-C} \) type may fail to react.

a. 1-Methyl-3-mercapto-3-piperidylphenylketone hydrochloride (XI)(dimer): The chloroform solution described above was dried over anhydrous potassium carbonate, and saturated with hydrogen chloride gas immediately. Most of the solvent was removed by distillation under reduced pressure, and ethylacetate was added, causing the precipitation of a solid. The precipitate was removed by filtration and wished with ether to give a crude product, m.p. 85°C. < , complete decomposition at 140-145°C. This compound was very hygroscopic and the infrared absorption spectrum (IR No. 3162, Model 21) showed an hydroxyl, -OH, stretching band at 3400 cm\(^{-1}\) (b). Other bands were evident at 2950 (m), 2680 (s), 1665 (s), cm\(^{-1}\) and monosubstituted benzene ring bands at 765 (s) and 700 cm\(^{-1}\), respectively.

\[ \text{Anal. calcd. for } C_{26}H_{34}N_2O_2S_2Cl_2\cdot4H_2O \text{ (dimer):} \]
\[ C, 50.73; \text{ H, 7.15. Found: } C, 50.43, 50.41; \text{ H, 6.61, 6.34,} \]

b. 1-Methyl-3-mercapto-3-piperidylphenylketone hydrobromide (XII)(dimer): The hydrobromide of 1-methyl-3-mercapto-3-piperidylphenylketone was prepared as described above in (a), and this salt also was very hygroscopic. Re-
crystallization from isopropyl alcohol gave a brownish product which decomposed at 176° without melting. The salt gave a negative Grote test for the —SH, but after reduction with hydrochloric acid—zinc dust gave the product a positive Grote test for —SH. The infrared absorption spectrum was very similar to that of the hydrochloride (XI).

c. 1-Methyl-3-mercapto-3-piperidylphenylketone hydro-
  picrate (XIII) (dimer): The picrate of the 1-methyl-3-mer-
  capto-3-piperidylphenylketone was prepared in ethanol by the
  conventional method and melted at 121-124°(d). This compound
  also gave a negative Grote test for —SH but a positive test
  after reduction with hydrochloric acid—zinc dust. Elemental
  analysis for sulfur gave a positive indication and a mixture
  melting point with picric acid (m.p. 121°) was depressed
  remarkably.

  Anal. calcd. for C₃₈H₃₈N₆O₁₆S₂(dimer):  C, 49.3;
  H, 4.1; N, 12.1; O, 27.6; S, 6.9.
  Found:  C, 49.4; H, 4.40; S, 7.29.

d. Reaction of 1-methyl-3-bromo-3-piperidylphenyl-
  ketone hydrobromide in methanol: A mixture of 5 g. (0.018 mole)
  of 1-methyl-3-bromo-3-piperidylphenylketone hydrobromide and
  4.9 g. (0.088 mole) of finely powdered, dried sodium hydro-
  sulfide in 120 ml. of anhydrous methanol was stirred with
  mechanical stirrer for 10 min. at room temperature and the
  solution was heated under reflux for an additional 10 min. The
  solvent was removed by distillation under reduced pressure,
and the residue was dissolved in water. The aqueous solution, after checking the basicity, was extracted with chloroform. The chloroform solution was dried over potassium carbonate and saturated with anhydrous hydrogen chloride. After removal of the solvent the white solid was recrystallized from ethanol-ethylacetate (1:9) to give 2.5 g. (76%) of 1-methyl-3-benzoyl-piperidine hydrochloride (VIII), m.p. 175-177°, lit. (6) m.p. 176-177°. The infrared spectrum, mixture melting point and reaction described below confirmed the identity of this compound.

Anal. calcd. for C_{13}H_{17}NO\cdot HCl: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79.

Found: C, 65.48, 65.19; H, 7.67, 7.61.

The same product was obtained from the reaction in an absolute ethanolic medium. The reaction mixture in ethanol was shaken for about 2 minutes at room temperature and was treated as described above to give 1-methyl-3-benzoyl-piperidine hydrochloride, m.p. 174-176°.

Anal. calcd. for C_{13}H_{17}NO\cdot HCl: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79.

Found: C, 65.02, 65.18; H, 7.71, 7.59.

Further reactions had been run to confirm the product as follows:

1. With phenyllithium: The base was prepared from 1.5 g. of the hydrochloride of the reaction product by treatment with 10% sodium hydroxide and extraction into ether. The ether solution was dried over potassium carbonate and
added dropwise to an excess of phenyl lithium ether solution. The reaction mixture was heated under reflux for 30 min. with stirring by a magnetic stirrer. The emulsified reaction mixture was hydrolyzed with water, and the product was extracted with ether. After solution was dried, the solvent was removed by distillation under reduced pressure. Crystallization of the residue from 95% alcohol gave 1.3 g. (79%) of 1-methyl-3-piperidylidiphenyl carbinol (XIV), m.p. 148-150°; Lit. (15) m.p. 146.7-147.3°.

ii. With phenyl Grignard reagent: The Grignard reagent was prepared from 0.21 (0.008 mole) of magnesium and 1.32 g. (0.0084 mole) of bromobenzene and was cooled briefly in an ice bath. A solution of 1 g. of the unknown product in ether was added dropwise, the reaction mixture was heated under reflux with stirring for 0.5 hr., and the solution was poured into 30 ml. of 10% sulfuric acid and 25 g. of ice. The organic layer was separated, and the aqueous layer was made strongly basic and extracted with chloroform. The combined organic phases were dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure. Crystallization of the oily residue from absolute alcohol gave 0.6 g. of 1-methyl-3-piperidylidiphenyl carbinol (XIV), m.p. 148-150°. A mixture melting point of this compound with the product of phenyllithium and authentic sample which prepared from 1-methyl-3-piperidylphenylketone and phenyllithium showed no depression.
e. The reaction of 1-methyl-3-bromo-3-piperidylphenylketone hydrobromide with sodium hydrosulfide in benzene. A heterogeneous reaction mixture of 2.09 (0.0055 mole) of 1-methyl-3-bromo-3-piperidylphenylketone hydrobromide (VII) and 1.7 g. (0.03 mole) of sodium hydrosulfide in anhydrous benzene was stirred while heating under reflux for one hour. The reaction mixture was cooled and ether was added. The ether solution was washed with small portions of water until the water extract was neutral. The ether solution was then extracted with 10% hydrochloric acid, and the acidic extracts were made basic with 10% sodium hydroxide solution. The free amine was extracted into chloroform, and the extracts were dried over potassium carbonate. The chloroform solution was saturated with anhydrous hydrogen chloride and allowed to stand for 2 hr. The solvent was removed by distillation under reduced pressure. Elemental analysis of the residue showed that no sulfur was present. Crystallization of the residue from isopropyl alcohol gave 0.5 g. (36%) of 1-methyl-3-hydroxy-3-piperidylphenylketone hydrochloride (IV), m.p. 161-163°; Lit. (6), m.p. 162-163°.

The picrate of 1-methyl-3-hydroxy-3-piperidylphenylketone was prepared by a conventional method, m.p. 174-175°; Lit. (4), m.p. 171-172°.

The Reaction of 1-Methyl-3-bromo-3-piperidylphenylketone with Potassium Cyanide. To attempt a ring contraction to a pyrrolidine derivative; 1 g. of 1-methyl-3-bromo-(3-
(chloro)-3-piperidylphenylketone hydrobromide (-hydrochloride) was converted to the base with 10% sodium hydroxide (or aqueous potassium carbonate) in an ice-bath and the free amine was extracted into ether. The other solution was dried over anhydrous magnesium sulfate, and 2 ml. of 95% ethanol was added and the ether was removed by distillation under reduced pressure.

To the ethanol solution, 0.7 g. of potassium cyanide was added and the reaction mixture was heated under reflux for 30 minutes. An inorganic white salt precipitated was removed by filtration, and the solvent was removed from the filtrate. The residue was triturated with ether, and the solvent was removed by distillation to give an oil. The oily product did not show a $\text{CN}$ stretching band in the infrared absorption spectrum (IR #27, model 137–B). A picrate of the oily product melted at 174–175°C. A mixture melting point with an authentic sample, picrate of 1-methyl-3-hydroxy-3-piperidylphenylketone (XVII), was not depressed; Lit. (4), m.p. 172–172°C. Using absolute ethanol or isopropyl alcohol as the solvent, the reaction mixture was heated under reflux for one hour, gave the same product, 1-methyl-3-hydroxy-3-piperidylphenylketone which was identified as a picrate, m.p. 174–175°C and the hydrochloride, m.p. 162–163°C; Lit. (6), m.p. 162–163°C.

The hydrobromide of 1-methyl-3-bromo-3-piperidyl-phenylketone with potassium cyanide in ethanol or in isopropyl alcohol medium resulted in the same product as above.
Preparation of 1-Methyl-4-benzoylpyridinium Bromide

(XIX). A solution of 183 g. (1 mole) of 4-benzoylpyridine (XVIII) in 700 ml. of acetone was saturated with anhydrous methyl bromide gas. The reaction mixture was allowed to stand for 24 hrs. in a tightly stoppered flask at room temperature. The precipitated white crystals were collected by filtration and washed with ether to give 263 g. (94%) of 1-methyl-4-benzoylpyridinium bromide (XIX), m.p. 165-168°; Lit. (2-5) 165-168°.

Preparation of 1-Methyl-4-piperidylphenylcarbinol

(XX). A solution of 174 g. (0.625 mole) of 1-methyl-4-benzoylpyridinium bromide (XIX) in 1 liter of water was divided into five equal portions and each portion was hydrogenated with 0.25 g. of platinum oxide catalyst with an initial hydrogen pressure of 45 p.s.i. The combined reaction mixture was filtered to remove the catalyst and the solution was made strongly basic with a saturated potassium carbonate solution, causing the precipitation of a semi-solid. The paste slowly crystallized. The crystalline product was removed by filtration, washed several times with water, and was air dried. The yield of 1-methyl-4-piperidylphenylcarbinol (XX) was 125 g. (97%), m.p. 153-156°; Lit. (2-5), m.p. 153-156°.

* Reilly Tar and Chemical Corporation product.
Preparation of 1-Methyl-4-piperidylphenylketone (XXI)

Hydrobromide (XXII) and Hydrochloride (XXIII). Following
the procedure of Leone (2) 15.3 g. (0.08 mole) of 1-methyl-4-
piperidylphenylcarbinol (XX) was converted to 12.9 g. (80%)
of 1-methyl-4-piperidylphenylketone (XXI), b.p., 203 ° at 23
mm; Lit. (3), b.p., 190 ° at 21 mm.

The hydrobromide was prepared by saturation of the
chloroform solution of crude 1-methyl-4-piperidylphenylketone,
without purifying by distillation, from the oxidation product
of 60 g. of 1-methyl-4-piperidylphenylcarbinol with hydrogen
bromide gas, removal of the solvent, and recrystallization
from isopropyl alcohol to give 70 g. (82%) of 1-methyl-4-
piperidylphenylketone hydrobromide (XXII), m.p. 208-209 °;
Lit. (16), m.p. 211-212 °; Lit. (2-b), m.p. 193-204 °.

Saturation of the chloroform solution of crude oxida-
tion product, from the oxidation of 33 g. of 1-methyl-4-
piperidylphenylcarbinol, with anhydrous hydrogen chloride and
treatment as above, gave 28 g. (72%) of 1-methyl-4-piperidyl-
phenylketone hydrochloride (XXIII), m.p. 205-206 °; Lit. (6),
m.p. 208-209 °, Lit. (2-b), m.p. 201-205 °.

Preparation of 1-Methyl-4-bromo-4-piperidylphenyl-
ketone Hydrobromide (XXIV). 1-Methyl-4-bromo-4-piperidyl-
phenylketone hydrobromide (XXIV) was prepared following the
procedure of Troscianiec (2) in 97% yield, m.p. 159-160 ° (d);
Lit. (2), m.p.155-156 °(c).

A mixture melting point with an authentic sample (2)
was not depressed.
Preparation of 1-Methyl-4-chloro-4-piperidylphenylketone Hydrochloride (XXV). Following the procedure which was described in 3-isomer, 26 g. of 1-methyl-4-piperidylphenylketone hydrochloride (XXIII) was converted to 26 g. (87%) of 1-methyl-4-chloro-4-piperidylphenylketone hydrochloride (XXV), m.p. 182-183° (c); Lit (2), m.p. 179-180° (c); Lit (6), m.p. 181-182°.

Reduction of 1-Methyl-4-bromo-4-piperidylphenylketone Hydrobromide (XXIV) with Sodium Borohydride. Following the procedure of Lyle (2-b), 5 g. of (XXIV) was converted to 2.8 g. (72%) of 1-methyl-4-bromo-4-piperidylphenylcarbinol (XXVI), m.p. 103-105°; Lit. (2-b), m.p. 104-105°.

1-Methyl-4-bromo-4-piperidylphenylcarbinol (XXVI) was very sensitive to heat and direct sunlight and, therefore, the compound could not be purified by recrystallization or exposed to direct sunlight. In both cases the product of decomposition was identified as 1-methyl-4-piperidylphenylketone by a mixture melting point of the hydrobromide and infrared absorption spectrum. The reaction mixture in an aqueous or water-methanol medium always gave a mixture of the bromohydrin, the ketone and an unidentified oil.

The hydrobromide salt (XXVII) was prepared and crystallized from chloroform, m.p. 153-154°.

Anal. calcd. for C_{13}H_{19}Br_{2}NO: C, 42.76; H, 5.24; N, 3.83; O, 4.38; Br, 43.77. Found:
Reduction of 1-Methyl-4-chloro-4-piperidylphenylketone Hydrochloride (XXVII) with Sodium Borohydride. A solution of 5 g. of XXVII in 30 ml. of methanol was treated with 1.6 g. of sodium borohydride at 0°C. The reaction mixture was allowed to stand for 2 hrs. at room temperature, and the solvent was removed by distillation under reduced pressure without heating. Hydrolysis of the white residue caused precipitation of 1-methyl-4-chloro-4-piperidylphenylcarbinol (XXVIII) which was contaminated with a boron complex (infrared absorption spectrum showed a boron-hydrogen stretching band at 2450 cm⁻¹, and a flame test indicated the presence of a boron complex and also left an inorganic residue). The impure product was dissolved in ether and the amine was extracted into 10% hydrochloric acid. The hydrochloric acid solution was neutralized with 10% sodium hydroxide, and the free amine was extracted into ether. The ether solution was dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure to give 3.8 g. (86%) of 1-methyl-4-chloro-4-piperidylphenylcarbinol (XXVIII), m.p. 140-141°C; Lit. (2-c), m.p. 140-140.5°C.

The Reaction of 1-Methyl-4-bromo-4-piperidylphenylketone with Sodium Hydroxide in Benzene. To a boiling mixture containing 200 ml. of dry benzene, 16 g. (0.4 mole) of finely powdered sodium hydroxide and 0.5 g. of sodium iodide as catalyst was added 5 g. (0.135 mole) of 1-methyl-4-bromo-4-piperidylphenylketone hydrobromide with stirring during a 30 minute period. The mixture was heated under reflux for an
additional 30 minutes. The mixture was cooled and extracted with ether. The ether extract was washed with water to remove any inorganic material, and was extracted with 10% hydrochloric acid. The aqueous solution was made basic with 10% sodium hydroxide and extracted with chloroform. On evaporation of the chloroform, a yellow powder was obtained. Recrystallization of the solid from acetone gave 2.96 g. (98%) of 1-methyl-4-hydroxy-4-piperidylphenylketone (XXIX), m.p. 131-132°; Lit. (2-b), 131-132°. The methyl iodide salt (XX), m.p. 212-214°, was prepared and recrystallized from ethanol.

The product of rearrangement, 1-methyl-4-phenylcarboxypiperidine, was not detected in the aqueous solution.

The Reaction of 1-Methyl-4-hydroxy-4-piperidylphenylketone with Concentrated Sulfuric Acid. To a chilled (0° C) 2 ml. of concentrated sulfuric acid was added 1.5 g. of 1-methyl-4-hydroxy-4-phenylketone in portions. After standing at 0° C for one hour, the reaction mixture was poured into ice-water and made basic with potassium carbonate. The basic solution was extracted with ether, and the solution was dried over potassium carbonate. Removal of the solvent by distillation under reduced pressure left an oil. The oil exhibited an infrared absorption spectrum (IR #996, model 137-B) identical with that of the starting material. Crystallization of the oil with acetone gave a quantitative recovery of the starting material, 1-methyl-4-hydroxy-4-piperidylphenylketone (XXIX), m.p. 131-132°. A mixture melting point with the authentic starting material was not depressed.
The Reaction of 1-Methyl-4-bromo-4-piperidylphenylcarbinol;

1) With silver oxide

1-Methyl-4-bromo-4-piperidylphenylcarbinol (XXVI), 1.3 g. (0.0046 mole), was dissolved in aqueous methanol (3:7) and to this solution was added an equi-molar amount of silver oxide. The reaction mixture was heterogeneous; a white emulsion was at the top and a dark gray layer was at the bottom. The reaction mixture was stirred for 30 minutes and was allowed to stand for 17 hrs. at room temperature in a tightly stoppered flask. A silver mirror was found on the flask wall. After removing any insoluble material by filtration, the solution was made slightly acidic with 10% hydrochloric acid, and any trace of a silver salt was removed by filtration. The solvent was removed by distillation on the steam bath under reduced pressure, and the pink oily residue which remained was dissolved in a minimum amount of water and was made basic with a concentrated potassium carbonate solution. The solution was extracted with ether, and the solution was dried over anhydrous magnesium sulfate. After removing the solvent, the oily product indicated at least three different functional groups from the infrared absorption spectra; e.g., -OH stretching at 3300 cm⁻¹, >C=O stretching at 1720 cm⁻¹ and 1675 cm⁻¹, respectively, (IR model 21, #3131, #3132, #3142). After 96 hrs. ether insoluble residue was found as a major product from the oil. Recrystallization of the residue from ligroin (60-80°C) benzene gave 1.3 g. of 1-methyl-4-hydroxy-4-piperidylphenyl-
carbinol (XXI), m.p. 146-147\(^\circ\), which was identified by a mixture melting point with an authentic sample, which was obtained from acid hydrolysis of 6-methyl-2-phenyl-1-oxo-6-
azaspiro [2,5] octane and from an identical infrared absorption spectrum (IR \#1224, model 137-B).

\[ \text{Anal. calcd. for } C_{23}H_{16}NO}_2: \ C, 70.5\%; \ H, 8.5\%; \ N, 6.3\%; \ 0, 14.4\%. \text{ Found: } C, 70.9\%; \ H, 8.8\%; \ N, 6.0\%. \]

The ether soluble materials were separated by using a Florisil packed chromatography column. A small amount of petroleum ether fraction showed a 1675 cm\(^{-1}\) band, probably 1-methyl-4-benzoylpiperidine (XXI), and an ether fraction gave 0.9 g. of 1-methyl-4-formyl-4-phenylpiperidine (XXXII), whose structure was assigned, based on the infrared absorption spectra (IR \#3142, model 21, c.f. IR \#2071, model 137-B) and positive Tollens' test.

b) With mercuric oxide

The bromohydrin (XXVI), 3.5 g., was treated with 1.5 g. of mercuric oxide in aqueous methanol. The reaction mixture was stirred with a magnetic stirrer at 33\(^\circ\) for 4.5 hrs. The reaction mixture was treated as described above and a very small amount of the rearrangement product 1-methyl-4-formyl-4-
phenylpiperidine (XXXII) was found. An ether insoluble material, after the ether soluble oil was allowed to stand for 4 hrs., was found to contain 1-methyl-4-hydroxy-4-piperidylphenylearbinol and a bromine containing compound. The bromine containing compound probably was the starting material.
The Rearrangement Reaction of 1-Methyl-4-bromo-4-
piperidylphenylcarbinol with Silver Acetate. 1-Methyl-4-
bromo-4-piperidylphenylcarbinol (XXVI), 3 g. (0.0106 mole),
was dissolved in 100 ml. of aqueous methanol (1:3) and 2.3 g.
(0.014 mole) silver acetate was suspended in the solution.
The reaction mixture was stirred with a magnetic stirrer for
24 hrs. at 33°C. The reaction was noted by the immediate
formation of a white emulsion that soon changed to dark brown
color. After removing the silver salt by filtration, the
solution was acidified with 10% hydrochloric acid to remove
any silver ion. The silver-ion free filtrate was made basis
with 10% sodium hydroxide and extracted with ether. The
ether solution was dried over potassium carbonate, and the
solvent was removed by distillation under reduced pressure.
An infrared absorption spectrum, >C=O stretching at 1720
cm⁻¹, of 1.6 g. (73%) of the oily product, indicated 1-methyl-
4-formyl-4-phenylpiperidine (XXXII) as the product and a posi-
tive Tollens test supported this assignment. The product was
compared with 1-methyl-4-formyl-4-phenylpiperidine prepared by
an unambiguous route. Reduction of the product with sodium
borohydride or lithium-aluminum hydride gave 1-methyl-4-
hydroxymethyl-4-phenylpiperidine (XXXIII).

Preparation of 1-Methyl-4-formyl-4-phenyl-piperidine
(XXXII) from 1-Methyl-4-cyano-4-phenylpiperidine. A
suspension of 0.2 g. (0.005 mole) of lithium-aluminum hy-
dride in 50 ml. of absolute ether was stirred with a magnetic
stirrer in an ice-salt bath. To this suspension a solution of 2.0 g. (0.01 mole) of 1-methyl-4-cyan-4-phenylpiperidine in 40 ml. of absolute ether was added dropwise over a 30-minute period. After being heated under reflux for 1.5 hrs. and cooled, the mixture was hydrolyzed with an aqueous ammonium chloride solution. The basic solution was extracted with ether and the ether solution was dried over potassium carbonate. Removal of the solvent by distillation under reduced pressure left a light colored oil. The infrared absorption spectrum (Model 137-B, #935) of the oil indicated a mixture of the aldehyde (–CHO stretching at 1720 cm⁻¹) and the imine (–C=NH stretching at 1675 cm⁻¹). The oil was dissolved in concentrated hydrochloric acid, and the solution was heated under reflux for one hour. The solution was made basic with 10% sodium hydroxide. The free amino-aldehyde was extracted into ether, and the solution was dried over potassium carbonate. The removal of the solvent by distillation under reduced pressure gave 1.2 g. (overall yield, 59%) of an oil, 1-methyl-4-formyl-4-phenylpiperidine (XXXII), which had an infrared absorption spectrum identical with that of the rearrangement reaction product. The oil gave a positive Tollens’s silver mirror test.

Reduction of the Rearrangememt Reaction Product. 1-
Methyl-4-formyl-4-phenylpiperidine with Sodium Borohydride or Lithium Aluminum Hydride. a. To a solution of 0.5 g. of the aldehyde (XXXII) in 10 ml. of methanol was added slowly 0.5 g. of sodium borohydride in 10 ml. of methanol. The reaction
mixture was allowed to stand for one hour at room temperature, and the solvent was removed by distillation under reduced pressure. The white residue was hydrolyzed with water and the product was extracted into ether. The solvent ether, after being dried over anhydrous magnesium sulfate, was removed by distillation under reduced pressure, and the crude product was recrystallized from absolute ethanol, to give 0.3 g. (60%) of 1-methyl-4-hydroxymethyl-4-phenylpiperidine (XXXIII), m.p. 134-135°; Lit. (3), m.p. 135-136.5°. A mixture melting point with an authentic sample was not depressed and the infrared absorption spectra of the two compounds were identical.

Anal. calc. for C13H19NO: C, 76.05; H, 9.32; N, 6.82; O, 7.79. Found: C, 76.30; H, 9.33.

b. The lithium-aluminum hydride reduction of the rearrangement product gave 1-methyl-4-hydroxymethyl-4-phenylpiperidine, m.p. 134-135°. Reduction of XXXII which, prepared from 1-methyl-4-cyano-4-phenylpiperidine, gave the same product 1-methyl-4-hydroxymethyl-4-phenylpiperidine (XXXIII), m.p. 134-135.5°.

The 1-methyl-4-formyl-4-phenylpiperidine was easily oxidized to 1-methyl-4-phenyl-4-piperidino carboxylic acid by air. After the ether soluble 1-methyl-4-formyl-4-phenylpiperidine was allowed to stand for 48 hrs., the majority of the liquid was no longer soluble in ether. The infrared absorption spectrum (IR #944, model 137-B) of the insoluble material showed bands at 3450, 1680 and 1640 cm⁻¹; on the
other hand, the aldehyde band at 1720 cm⁻¹ was remarkably diminished. The ether insoluble material was identified as 1-methyl-4-phenyl-4-piperidinocarboxylic acid, m.p. 305-309°; Lit. (6), m.p. 309-310°.

Preparation of 1-Methyl-4-hydroxymethyl-4-phenylpiperidine (XXXIII). A suspension of 1.4 g. of Demerol hydrochloride in 50 ml. of anhydrous ether was treated with 1.5 g. (excess) of powdered lithium-aluminum hydride during a 15-min. period at 0° C. The reaction mixture was stirred with a magnetic stirrer for 2 hrs. at 0° C. After hydrolysis of the reaction mixture with water, the product was extracted into ether. The ether extract was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. Recrystallization of the residue from absolute alcohol (or acetonitrile) gave 0.9 g. (90%) of analytically pure 1-methyl-4-hydroxymethyl-4-phenylpiperidine (XXXIII), m.p. 134-135°; Lit. (3), m.p. 135-136.5°.

Preparation of 1-Methyl-4-phenyl-4-piperidylformyl-

oxime (XXIV). To 0.5 g. of the rearrangement product, 1-methyl-4-formyl-4-phenylpiperidine, in 20 ml. of 95% ethanol was added 0.79 g. of hydroxylamine hydrochloride in 10 ml. of 95% ethanol. The mixture was made basic with 10% sodium hydroxide solution. The reaction mixture was heated under reflux on a steam bath for 3 hrs. After cooling, the reaction mixture was diluted with water. The oxime which precipitated was removed by filtration and was washed with water. Recrystal-
lization of the solid from 95% ethanol gave 0.3 g. of the
oxime (XXIV), m.p. 114-116°. The infrared absorption spec-
trum (IR #1172, model 137-B) showed —OH stretching band at
3250 cm⁻¹, C=O stretching band at 1510 cm⁻¹, and the aldehyde
band at 1720 cm⁻¹ was no longer evident.

**Reactions of 1-Methyl-4-chloro-4-piperidylphenylcarbinol**

a. With silver oxide in aqueous methanol: To 2 g.
(0.00845 mole) of 1-methyl-4-chloro-4-piperidylphenylcarbinol
(XXVIII) in 70 ml. of an aqueous methanol solution was added
an equimolar amount of silver oxide. The reaction mixture was
stirred with a magnetic stirrer for 24 hrs. at room tempera-
ture. Unlike the reaction between 1-methyl-4-bromo-4-piperi-
dylyphenylcarbinol and silver oxide, no change was observed at
the early stages of the reaction. Five hours later, however,
a lustrous silver mirror had formed on the flask wall. The
solid was removed by filtration and the filtrate was made
slightly acidic with 10% hydrochloric acid to remove any sil-
ver ion. Evaporation of the solvents under reduced pressure
left an oil. A small amount of water was added to the oil
and the solution was made basic with a saturated potassium
carbonate solution. The free amine was extracted into ether,
and the solution was dried over anhydrous magnesium sulfate.
The solvent was removed, and the residue was no longer soluble
in ether. A Beilstein test indicated chlorine to be present.
Crystallization of the oil from absolute ethanol gave starting
material, m.p. 139-140°. A mixture melting point with authen-
tic starting material was not depressed and the infrared ab-
absorption spectra were identical.

b. With silver oxide in aqueous acetone. To 2 g. of 1-methyl-4-chloro-4-piperidylphenylcarbinol (XXVIII) in 50 ml. of aqueous acetone (1:1) was added equimolar amount of silver oxide. The reaction mixture was stirred and heated under reflux for 4 hrs. The reaction mixture was treated as described above, and an oil was obtained. The solubility and the Fehling test suggested that the oil was starting material. Crystallization from absolute alcohol gave an almost quantitative amount of the starting chlorohydrin, m.p. 139-140°. The negligible amount of oil from mother liquor showed carbonyl bands at 1720 cm⁻¹ and 1680 cm⁻¹ in infrared absorption spectrum.

c. With silver nitrate in aqueous acetone. An aqueous acetone (1:1) solution (50 ml.), containing 2 g. of the chlorohydrin (XXVIII) and an equimolar amount of silver nitrate was stirred for 6 hrs. at room temperature. The reaction mixture was treated as described above and a quantitative amount of the starting material was recovered.

These reactions indicated that 1-methyl-4-chloro-4-piperidylcarbinol was very stable to electrophilic catalyzed solvolysis as compared with 1-methyl-4-bromo-4-piperidylphenylcarbinol.

Rearrangement Reaction of 1-Methyl-4-chloro-4-piperidylphenylcarbinol with Silver Acetate. In a solution of 1.4 g. (0.0059 mole) of 1-methyl-4-chloro-4-piperidylphenylcarbinol
in 50 ml. of an aqueous methanol (1:1) was suspended 1.67 g. (0.01 mole) of silver acetate. The reaction mixture was stirred with a magnetic stirrer for 20 hrs. at 33°C. After removing any insoluble material by filtration, the solution was made slightly acidic with 10% hydrochloric acid and all of the silver chloride was removed by filtration. Evaporation of the solvent by distillation under reduced pressure left an oily residue which was dissolved in a minimum amount of water and was made basic with potassium carbonate solution. The product was extracted into ether, and the solution was dried over anhydrous magnesium sulfate. After removing the solvent, the infrared absorption spectrum showed distinctive bands at 1720 cm⁻¹, 1670 cm⁻¹ and 1610 cm⁻¹. The lithium–aluminum hydride reduction of the oil and crystallization of the product from absolute ethanol by seeding and prolonged standing gave 0.2 g. (17%) of 1-methyl-4-hydroxymethyl-4-phenylpiperidine, m.p. 135-135.5°; lit. (3), m.p. 135-136.5°. The oil from the mother liquor still had bands at 1670 cm⁻¹ and 1610 cm⁻¹.

Preparation of Diphencymethyl lithium (39) and the Reaction with 1-Methyl-4-piperidone. A solution of 10.1 g. (0.05 mole) of diphencychloromethane in 25 ml. of anhydrous tetrahydrofuran was added to a stirred mixture of finely cut lithium wire (1.04 g., 1.15 g. atom) in 15 ml. of tetrahydrofuran. The reaction was carried under dry nitrogen. Reaction was
noted by an initial yellow color that soon changed to a deep red. The mixture was allowed to stir for 22.5 hrs. at room temperature. The organometallic solution was filtered through glass wool and 5.6 g. (0.05 mole) of 1-methyl-4-piperidone in 35 ml. of tetrahydrofuran was added dropwise during a 10-minute period. The reaction mixture underwent a gradual change of color from dark red to yellow. After being stirred for 2 hrs., the reaction mixture was hydrolyzed with a saturated ammonium chloride solution. The tetrahydrofuran layer was washed twice with ammonium chloride solution and the combined aqueous layers were made basic and extracted with ether. The combined tetrahydrofuran and the ether solution were extracted with 10% hydrochloric acid. The aqueous hydrochloride solution was made basic with 10% sodium hydroxide and the free amine was extracted into ether. The ether solution was dried over potassium carbonate, and the solvent ether was removed by distillation under reduced pressure. Florisil column chromatography employing ether elution separated the major product 1-methyl-4-hydroxy-4-diphenylmethylpiperidine (XXXV). The hydrobromide (XXXVI) of XXXV, after recrystallization from methanol gave 1.5 g. (overall yield 8.5%) which melted at 260–262°C.

**Anal. calcd. for C_{19}H_{24}NOBr: C, 62.98; H, 6.63.**

**Found: C, 63.48; H, 6.70.**

The melting point was not depressed on mixing with the product of the following experiment.
An Alternative Preparation of 1-Methyl-4-hydroxy-4-

diphenylmethylpiperidine (XXXV). A solution of 75 ml.

(0.1 mole) of n-butyl lithium (15.06% in n-hexane) was added

rapidly to 16.8 g. (0.1 mole) of diphenylmethane in 50 ml.

of anhydrous ether (19). The reaction mixture was diluted

with 50 ml. of anhydrous ether, and was heated under reflux

for 24 hrs. A color change occurred slowly from yellow to

red.

To the organometallic solution 10 g. (0.088 mole) of

1-methyl-4-piperidone in 25 ml. of absolute ether was added

dropwise during a 10-minute period, and the reaction mixture

was stirred for an additional 2 hrs. After hydrolysis of

the reaction mixture with a saturated ammonium chloride solu-
tion, an ether layer separated and an aqueous layer was made

basic and extracted with ether. The combined ether solution

was washed a few times with a saturated ammonium chloride

solution and extracted with 10% hydrochloric acid. The ether

layer was discarded and the hydrochloride solution was again

made basic and extracted with ether. Evaporation of the sol-

vent, after being dried over potassium carbonate, under re-
duced pressure yielded a very small amount of residue. The

residue was converted to the hydrobromide (XXXVI) by the con-

ventional method and was recrystallized from methanol, m.p.

260-262°C.

Preparation of 1-Methyl-4-piperidylidiphenylcarbinol

(XXXVII). A solution of 4 ml. of bromobenzene in 25 ml. of
absolute ether was added dropwise to a stirred mixture of finely cut 0.4 g. of lithium wire in 20 ml. of ether during a 10-minute period. The reaction was performed under dry nitrogen. The mixture was allowed to stir for 1.5 hrs. at room temperature. After the reaction was completed, the phenyllithium solution was filtered through glass wool and 3.6 g. of 1-methyl-4-benzoylpirperidine in 20 ml. of ether was added dropwise to the mixture during a 10-minute period. The reaction mixture was heated under reflux for 2.5 hrs., was cooled, and hydrolyzed with water in an ice-bath. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether solution was dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure. The crude product was recrystallized from absolute ethanol to give a compound which melted at 123—130°C. Recrystallization from methanol gave 4.5 g. (91%) of 1-methyl-4-piperidylidiphenylcarbinol (XXXVII), m.p. 132—134°C; Lit. (1), m.p. 133—134°C.

Preparation of 1-Methyl-4-piperidylidene-diphenylmethane. Following the procedure of Lyle (1), 10 g. of 1-methyl-4-piperidylidiphenylcarbinol was converted to 9.1 g. (97%) of 1-methyl-4-piperidylidenediphenylmethane (XXXVIII), m.p. 54—56°C; Lit. (1), m.p. 55.0—56.3°C.

A mixture melting point with an authentic sample showed no depression.

The hydrobromide (XXXIX) was prepared in quantitative yield from the base (XXXVIII) by precipitation from a solution

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of hydrogen bromide in ether. Recrystallization from ethanol gave a product melting at 276—277°; Lit. (1), m.p. 264—266°. A mixture melting point with an authentic sample was not depressed and an infrared absorption spectrum was identical with that of the authentic sample. 1-Methyl-4-piperidylidenediphenylmethane hydrobromide is only sparingly soluble in water.

The Reaction of 1-Methyl-4-piperidylidenediphenylmethane Hydrobromide with Bromine Water. Following the procedure of Lyle (1), 4 g. of 1-methyl-4-piperidylidenediphenylmethane hydrobromide was converted to 1.4 g. of petroleum ether soluble oil. The oil was converted to the hydrochloride which did not crystallized even on seeding. A solution of the salt in water neutralized with 10% sodium hydroxide, the free amine was extracted into ether and the solution was dried over magnesium sulfate. Slow removal of the solvent by evaporation caused crystallization to give 1.2 g. of 1-methyl-4-phenyl-4-piperidylphenylketone (XI), m.p. 78—81°; Lit. (1), m.p. 77—78.5°.

The petroleum-ether insoluble residue was recrystallized from acetonitrile to give 1.3 g. of 1-methyl-4-hydroxy-4-piperidyl diphenylcarbinol (XII), m.p. 158—161°; Lit. (1), m.p. 158.5—160.8°. These products accounted for 75% of the starting material.
Preparation of 1-Methyl-4-phenyl-4-piperidylphenylcarbinol (XXIII).

a. The reduction of 1-methyl-4-phenyl-4-piperidylphenylketone with sodium borohydride. A solution of 1 g. of 1-methyl-4-phenyl-4-piperidylphenylketone in 20 ml. of methanol was treated with 0.5 g. of sodium borohydride during a 15-minute period at 0°C. The reaction mixture was allowed to stand for 3 hrs. at room temperature and the solvent was removed by distillation under reduced pressure. The white residue was hydrolyzed with water and the product was extracted into ether. The ether solution was dried over anhydrous magnesium sulfate and the solvent was removed to give a heavy oil. Crystallization from acetonitrile gave 0.78 g. (78%) of 1-methyl-4-phenyl-4-piperidylphenylcarbinol, m.p. 110-111.5°C.

Anal. calcd. for C_{19}H_{23}NO; C, 81.10; H, 8.23; N, 4.97; O, 5.68. Found: C, 80.93; H, 8.27.

b. Phenyllithium reaction with 1-methyl-4-formyl-4-phenylpiperidine. A solution of 0.6 g. of 1-methyl-4-formyl-4-phenylpiperidine, the rearrangement reaction product of 1-methyl-4-bromo-4-piperidylphenylcarbinol (XXVI) with silver acetate, in 10 ml. of anhydrous ether was added dropwise to an excess of phenyllithium ether solution. The reaction mixture was stirred 1.5 hrs. at room temperature and the stirring was continued another hour with heating under reflux. The reaction mixture was cooled and this was hydrolyzed with a saturated aqueous ammonium chloride solution. The product was extracted into ether, and the solvent was removed by distillation under reduced pressure to give a light colored oil.
The oil was caused to crystallize by the addition of a crystalline seed which was obtained from the reaction above to give 0.45 g. (50%) of 1-methyl-4-phenyl-4-piperidylphenylcarbinol (XLII), m.p. 110-112°.

A mixture melting with the above authentic sample was not depressed.

**Preparation of 6-Methyl-2-phenyl-1-oxo-6-azaspiro-[2.5]octane (XLIII).**

**a.** From 1-methyl-4-chloro-4-piperidylphenylcarbinol. A suspension of 5.5 g. of 1-methyl-4-chloro-4-piperidylphenylcarbinol (XXVIII) in 100 ml. of 10% sodium hydroxide was stirred with a magnetic stirrer for 17.5 hrs. at 35° C. The reaction mixture was cooled and was extracted with ether, and the ether solution was dried over potassium carbonate. The solvent was removed by distillation under reduced pressure to give 4.5 g. of an oil epoxide as residue. The distillation of the crude oil under reduced pressure gave 4.2 g. (90%) of 6-methyl-2-phenyl-1-oxo-6-azaspiro-[2.5]octane (XLIII), b.p. 105° at 1.0 mm; Lit. (3), b.p. 126° at 5 mm. The infrared absorption spectrum of the compound was identical with that of the product obtained by Leona (3) from treatment of 1-methyl-4-hydroxy-4-piperidylphenylcarbinol with 48.8% of hydrobromic acid.

**b.** From 1-methyl-4-bromo-4-piperidylphenylcarbinol (XXVI). A suspension of 3 g. of 1-methyl-4-bromo-4-piperidylphenylcarbinol in 40 ml. of 10% sodium hydroxide solution was stirred with a magnetic stirrer for 6.5 hrs. at 35° C. The reaction mixture was treated as described above to give...
2.1 g. (98%) of 6-methyl-2-phenyl-1-oxo-6-azaspiro[2,5]-octane (XXXI), b.p. 108-110° at 1.5 mm.

The colorless crystalline methiodide (XLIV), m.p. 223-225°; Lit. (3), m.p. 223-224, was obtained in quantitative yield from an acetone solution of (XXXI). The identity of the compound was established by comparison of the infrared absorption spectrum and a mixture melting point with an authentic sample.

c. From 1-methyl-4-chloro-(or 4-bromo)-4-piperidyl-phenylcarbinol with sodium methoxide in methanol: A solution of 2 g. of 1-methyl-4-halo-4-piperidylphenylcarbinol in 40 ml. of 10% sodium methoxide solution was stirred with a magnetic stirrer for 5 hrs. The solvent was removed by distillation under reduced pressure and the residue was dissolved in water. The reaction mixture was extracted with ether, and the ether solution was dried over potassium carbonate. The solvent was removed and the oily product showed an infrared absorption spectrum (IR #454, model 137-B) identical with that of the product obtained from the reaction with 10% sodium hydroxide solution as described earlier.

The Hydrolysis of the Epoxide (XXXIII) to 1-Methyl-4-
hydroxy-4-piperidylphenylcarbinol (XXXI). The reaction of 6-methyl-2-phenyl-1-oxo-6-azaspiro[2,5]octane with a 10% hydrochloric acid was heated under reflux for one hour. The reaction mixture was cooled, was made basic with 10% sodium hydroxide solution, and was extracted with ether. The solvent
was removed by distillation, and the residue was recrystal-
ized from intermediate-boiling ligroin-benzene to give a
quantitative yield of 1-methyl-4-hydroxy-4-piperidylphenyl-
carbinol, m.p. 140-141°; Lit. (3), m.p. 139-140°; Lit. (6),
m.p. 134-135°.

Anal. calc. for C₁₃H₁₉NO₂: C, 70.58; H, 8.59;
N, 6.33; O, 14.48. Found: C, 70.98; H, 8.65; N, 6.03.

The Reaction of 6-Methyl-2-phenyl-1-oxo-6-azaspiro
[2,5]octane (XLIII) with Phenyllithium.  a. To a slight
excess of phenyllithium (0.025 mole) in ether was added 4.3
g. (0.021 mole) of 6-methyl-2-phenyl-1-oxo-6-azaspiro[2,5]
Octane (XLIII) in 50 ml. of ether in a 10-minute period,
and the reaction mixture was stirred mechanically for 16 hrs.
at room temperature under dry nitrogen atmosphere. The
reaction mixture was hydrolyzed with a saturated aqueous
ammonium chloride solution in an ice-bath and was extracted
with ether. The ether solution was washed a few times with
the ammonium chloride solution, was extracted with 10% hydro-
chloric acid, and then neutralized with 10% sodium hydroxide.
The free amine was extracted into ether again and dried over
potassium carbonate. After removing the solvent, 4 g. of the
oily product was obtained. The infrared absorption spectrum
gave remarkable bands at 1760 and 1710 cm⁻¹; (IR #2089,
model 137-B; Ir #4145, model 21).

b. A mixture of 0.035 mole of phenyllithium and 5 g.
(0.0246 mole) of 6-methyl-2-phenyl-1-oxo-6-azaspiro[2,5]octane

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(XLIII) in ether was treated as described above. After it was stirred for 5 hrs. at room temperature under dry nitrogen atmosphere, the reaction mixture was allowed to stand overnight and hydrolyzed with water. The reaction mixture was extracted with ether and the ether solution was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure and 5.2 g. of the oily product was obtained. The infrared absorption spectrum (IR #2146, model 137-B) was identical with that of the previous one. The bands were at 3100 (w), 3000, 1760, 1710, 1600 (m), 1500, 1460, 1380, 1290, 1250, 1130 (b), 1080 (m), 995 (w), 930 (w), 770 and 705 cm\(^{-1}\).

The oil was subjected to chromatographic separation on Florisil using petroleum ether and absolute ether as eluents to give two components. The former eluent separated the product exhibiting the 1760 cm\(^{-1}\) band and the latter solvent gave the product with the 1710 cm\(^{-1}\) band (IR #2149, 2151, model 137-B).

**Identification of the Products**

a. The product having the 1760 cm\(^{-1}\) band (IR #2149, model 137-B) was dissolved in ether and converted to 3.7 g. (43.5%) of the hydrobromide, m.p. 271-272°. This salt was identified as 1-methyl-4-piperidylidenediphenylmethane hydrobromide (XXXIX). The mixture melting point with an authentic sample which was prepared from 1-methyl-4-piperidylidiphenyl-carbinol was not depressed and the infrared absorption spectra
of both of these compounds were identical.

Another batch of the fraction of the product having the 1760 cm\(^{-1}\) band in the infrared absorption spectrum was allowed to stand for 85 days in air and dissolved in ether. A negligible amount of ether-insoluble material was discarded and the soluble material was identified as 1-methyl-4-piperidylidenediphenylmethane (XXXVIII). The 1760 cm\(^{-1}\) band completely disappeared and an infrared absorption spectrum, identical with that of an authentic sample of 1-methyl-4-piperidylidenediphenylmethane was obtained. The hydrobromide melted at 269-271\(^\circ\)C. Recrystallization from 95% ethanol gave 1-methyl-4-piperidylidenediphenylmethane hydrobromide, m.p. 271-272\(^\circ\). The mixed melting point showed no depression with the authentic sample of the above.

b. The product having the 1710 cm\(^{-1}\) band (in IR #2151) was dissolved in acetone and converted to the methyl-iodide salt by allowing the reaction mixture to stand overnight at room temperature. The crystalline product which precipitated was recrystallized from methanol to give 2.6 g. (30\%) of an analytical sample of 1-methyl-4-phenyl-1-aza-5-cycloheptanone, (XLV), m.p. 166-168\(^\circ\) (IR #2239, model 137-B).

Anal. calcd. for C\(_{14}\)H\(_{20}\)NO\(_{2}\): C, 48.70; H, 5.84; N, 4.05; O, 4.63; I, 36.76. Found: C, 48.48; H, 6.06.

Sodium borohydride reduction of the product with 1710 cm\(^{-1}\) band fraction gave 1-methyl-4-phenyl-1-aza-5-cycloheptanol and the 1710 cm\(^{-1}\) band completely disappeared (IR #2223-A, model, 137-B).
These products account for 73.5% of the starting material.

**Attempted Reaction Between 6-Methyl-2-phenyl-1-oxo-6-azaspiro[2,5]octane (XLIII) and Lithium Bromide.**  

a. Preparation of the lithium bromide. To a suspension of 0.2 g. (0.3 mole) of a finely cut metallic lithium in 20 ml. of ether, 2.8 g. (0.015 mole) of ethylenes bromide in 10 ml. of ether was added dropwise. The reaction mixture was heated under reflux for 7 hrs. and the white lithium bromide was isolated.

b. A solution of 1.5 g. (0.0074 mole) of 6-methyl-2-phenyl-1-oxo-6-azaspiro[2,5]octane (XLIII) in 40 ml. of ether and the lithium bromide was heated under reflux for 12 hrs. The reaction mixture was treated exactly the same way as described in the above reaction between the epoxide and phenyl lithium and only unreacted starting material (XLIII) was recovered, indicating that the lithium bromide did not catalyze the reaction.

**Chlorination of 1-Methyl-4-phenyl-4-piperidylcarbinol (XXXIII) with Thionyl Chloride.** A solution of 1.5 g. of 1-methyl-4-phenyl-4-piperidylcarbinol (XXXIII) in 30 ml. of thionyl chloride was heated under reflux for 5 hrs., and the excess thionyl chloride was removed by distillation under reduced pressure. The oily residue was crystallized from acetonitrile and an analytical sample of 1-methyl-4-phenyl-4-piperidylchloromethane hydrochloride (XLI), m.p. 244-246° (d), was
obtained. (IR #3283, model 137-B) I.R. spectrum: 3000 (m), 2950 (s), 1500 (w), 1450 (m), 1375 (w), 1270 (m), 1170 (b), 1100 (m), 1070 (m), 1050 (m), 1000 (m), 980 (s), 960 (m), 930 (w), 845 (w), 780 (s), 745 (s), and 715 (s) cm⁻¹.

Anal. calcd. for C₁₅H₁₉Cl₂I: C, 60.06; H, 7.36; N, 5.34; Cl, 27.25. Found: C, 60.17; H, 7.60.

Reaction of 1-Methyl-4-phenyl-4-piperidylchloromethane Hydrochloride (XLVI) with Absolute Alcohol.

1-Methyl-4-phenyl-4-piperidyl chloromethane hydrochloride (XLVI), from the above reaction, was dissolved in a minimum amount of water and was made basic with 10% sodium hydroxide. The solution was extracted with ether, the ether solution was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The infrared absorption spectrum (IR #3290, model 137-B) bands are at 3010 (w), 2950 (s), 2800 (s), 1600 (w), 1500 (m), 1455 (s), 1380 (s), 1295 (s), 1270 (w), 1135 (m), 1100 (w), 1085 (m), 1030 (m), 970 (m), 825 (w), 775 (w), 750 (m) and 700 (s) cm⁻¹.

The oily 1-methyl-4-phenyl-4-piperidylchloromethane (XLVII) was dissolved in absolute ethanol, heated under reflux for 1½ hrs., and was treated in the usual way. The infrared absorption spectrum changed remarkably (IR #3305, model 137-B). The band at 1135 cm⁻¹ had a change in shape, the intensity of 1100 cm⁻¹ band was increased and 750 cm⁻¹ was decreased. The Beilstein test, however, gave a slightly
positive test which indicated some of the unreacted chloro-
methane was present. The oil was dissolved again in absolute
ethanol–sodium ethoxide solution, heated under reflux for 12
hrs. and treated as above to give a material with a negative
Beilstein test but with an identical infrared absorption
spectrum (IR #3323, model 137-B) to that of IR #3305. Chro-
matography using Florisil with ether and acetone as eluants
separated two components. The infrared absorption spectrum
(IR #3330, model 137-B) bands of the ether fraction are
3100 (sh), 2995, 2800, 1600 (w), 1500 (m), 1450, 1380, 1290,
1260 (m), 1200 (w), 1160 (w), 1125, 1080, 1035, 950, 825 (m),
750 and 700 cm⁻¹. The hydrobromide of this fraction, crys-
tallized from acetone, melted at 155–157° and picrate melted
at 132–134°. The structure was assigned as 1-methyl-4-
phenyl-4-piperidylmethyl ethyl ether (XLVIII).

Anal. of the picrate; calcd. for C₂₁H₂₆N₂O₈:
C, 54.54; H, 5.66; N, 12.11; O, 27.67.  Found:
C, 54.65; H, 5.89; N, 12.69.

The infrared absorption spectrum (IR #3331, model
137-B) bands of the acetone fraction are 3400 (b), 3100 (sh),
3000, 2800, 1600 (w), 1500 (m), 1450, 1385, 1285, 1140 (b.s),
1105 (b.s), 1080, 1020 (m), 980, 910 (sh), 850 (sh), 780 (sh),
770 (m), 720 (sh), and 700 cm⁻¹.

The picrate of this melted at 159–162°. The structure
of the latter was assigned as 1-methyl-4-benzilidene-piperidine
(XLIX).

Anal. of the picrate; calcd. for C₁₉H₂₀N₄O₇: C, 54.80;
H, 4.84; N, 13.45; O, 26.89. Found: C, 54.86; H, 5.08; N, 13.56.

c.f. The picrate of 1-methyl-1,2,5,6-tetrahydro-4-benzyl-
pyridine which was prepared from 1-methyl-4-benzylpyridinium
iodide by sodium borohydride reduction melted (21) at 134-
135°.

Preparation of 1-Benzyl-4-benzoylpyridinium Chloride
(L). Following the procedure of Warner (4), a solution of
55 g. (0.3 mole) of 4-benzoylpyridine and 40 g. of benzyl
chloride in 600 ml. of methanol was heated under reflux for
12 hrs. The solution was concentrated on the steam bath by
distillation under reduced pressure, and upon seeding, the
residue crystallized. The crystalline product was removed
by filtration and washed a few times with acetone to give
83 g. (90%), m.p. 185-186°, of 1-benzyl-4-benzoylpyridinium
chloride; Lit. (4), m.p. 186-188°.

The Hydrogenation of 1-Benzyl-4-benzoylpyridinium
Chloride (L) over Platinum Oxide Catalyst. A solution of
82 g. (0.266 mole) of 1-benzyl-4-benzoylpyridinium chloride
(L) in 1 liter of methanol was divided into five equal por-
tions. Each portion was hydrogenated over 0.2 g. of platinum
oxide catalyst with an initial hydrogen pressure of 40 psi.
After the absorption of hydrogen ceased, about 24 hrs., the
catalyst was removed from the solution by filtration and the
filtrate was concentrated under reduced pressure. Addition
of anhydrous ether to this solution caused the precipitation

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of a white crystalline solid which was recrystallized from isopropyl alcohol to give 61 g. (72%) of 1-benzyl-4-piperidylphenylcarbinol hydrochloride (LI), m.p. 184-186°; Lit.(4), m.p. 184-185°.

Preparation of 1-Benzyl-4-piperidylphenylketone Hydrobromide (LI). The oxidation of 61 g. (0.193 mole) of 1-benzyl-4-piperidylphenylcarbinol hydrochloride (LI) by 22.2 g. of anhydrous chromic acid was accomplished in one liter of glacial acetic acid. The reaction mixture was stirred with a mechanical stirrer and was heated at 100° for one hour. The solvent was removed by distillation under reduced pressure, and the residue was diluted with 150 ml. of water and was made basic with 600 ml. of a 25% sodium hydroxide solution. The oily layer which separated was extracted with ether. The combined ether extract was dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure. The oily residue was dissolved in chloroform and the solution was saturated with anhydrous hydrogen bromide. The reaction flask was tightly stoppered and was allowed to stand for 2½ hrs. at room temperature. After the solvent was removed, the residue was recrystallized from isopropyl alcohol to give 48 g. (69.5%) of 1-benzyl-4-piperidylphenylketone hydrobromide (LII), m.p. 237-239°; Lit.(4), m.p. 237-238°.
Preparation of 1-Benzyl-4-bromo-4-piperidylphenylketone Hydrobromide (LIII). A solution of 24 g. (0.06 mole) of 1-benzyl-4-piperidylphenylketone hydrobromide (LIII) in 600 ml. of chloroform was treated with 8 ml. of bromine. The resulting solution was stirred with a magnetic stirrer for 24 hrs. at room temperature. The solvent was removed by distillation under reduced pressure and the residue was dissolved in a solution containing 10 g. of phenol in 200 ml. of methanol. The solution was diluted with anhydrous ether, precipitating 1-benzyl-4-bromo-4-piperidylphenylketone hydrobromide (LIII). Recrystallization of the solid from isopropyl alcohol gave 26 g. (88%) of (LIII), m.p. 164-165°; Lit.(4), m.p. 162-164°.

Reduction of 1-Benzyl-4-bromo-4-piperidylphenylketone Hydrobromide with Sodium Borohydride. A solution of 5 g. of 1-benzyl-4-bromo-4-piperidylphenylketone hydrobromide (LIII) in 200 ml. of methanol was treated with 2.5 g. of sodium borohydride over a 30-minute period at 0°C. The reaction mixture was allowed to stand for 2 hrs. at room temperature. During this period a white precipitate formed and was removed by filtration. Removal of the solvent from the filtrate and addition of water to the residue gave an additional 1.0 g. of the product. Recrystallization of the combined product from ether-methanol gave a total of 3.2 g. (78%) of 1-benzyl-4-bromo-4-piperidylphenylcarbinol (LIV), m.p. 120-121.5°.

Anal. calcd. for C_{19}H_{22}NOBr: C, 63.36; H, 6.11; O, 4.44; N, 3.88; Br, 22.18. Found: C, 63.70; H, 6.04.
Preparation of 6-Benzyl-2-phenyl-1-oxo-6-aza-spiro[2,5]octane (LV). A suspension of 2.8 g. of 1-benzyl-4-bromo-4-piperidylphenylcarbinol (LIV) in 35 ml. of a 10% sodium hydroxide solution was stirred with a magnetic stirrer for 16 hrs. at 35°C. The mixture turned to a gummy mass. The temperature was raised from 35°C to 95°C and stirring was continued for an additional 5 hrs. The organic phase became completely oily. The reaction mixture was cooled, the product was extracted into ether, and the ether solution was dried over potassium carbonate. Removal of the solvent under reduced pressure gave 1.9 g. (88%) of an oily product. A chromatographic purification on Florisil with ether as an eluant gave 1.7 g. (60%) of the pure product 6-benzyl-2-phenyl-1-oxo-6-aza-spiro[2,5]octane (LV).

An infrared absorption spectrum (IR #2479, model 137-B) bands are at 3000, 1600 (w), 1500 (m), 1455, 1375 (m), 1280 (w), 1240 (w), 1200 (w), 1170 (w), 1140 (m), 1060 (m), 1020, 980 (m), 930 (m), 910 (m), 790 (w), 740 and 700 cm⁻¹.

A methyl iodide quaternary ammonium salt, m.p. 223-225°C, was made using a conventional method.

Hydrolysis of the epoxide (LV) with 10% hydrochloric acid under reflux for 15 min. and removal of the solvent left an oil. Crystallization from acetone-methanol yielded quantitatively an analytical sample of 1-benzyl-4-hydroxy-4-piperidylphenylcarbinol hydrochloride (LVII), m.p. 216-219°C.

**Anal. calcd. for C₁₉H₂₄NO₂Cl·1/2H₂O:** C, 66.59; H, 7.35. **Found:** C, 66.08; 66.11; H, 7.44, 7.40.
Preparation of 1-Benzyl-4-phenyl-4-piperidylphenyl- ketone (LVII). To 90 ml. of an ether solution of phenyl-Grignard reagent which was prepared from 30 g. (0.16 mole) of bromobenzene and 5.1 g. (0.213 mole) of metallic magnesium by the conventional method was added 0.09 mole of 1-benzyl-4-cyano-4-phenylpiperidine in 100 ml. of ether during a 15-minute period. The reaction mixture was diluted with 500 ml. of anhydrous toluene and most of the ether was removed by distillation. The reaction mixture was heated under reflux with stirring for 23 hrs. at 95°C. After removal of the solvents by distillation under reduced pressure, the residue was treated with 300 ml. of 10% hydrochloric acid, and the solution was heated under reflux for 22 hrs. for hydrolysis. The reaction mixture, after being cooled, was made basic with a 10% sodium hydroxide solution in ice-bath. The free amine was extracted into ether, and the solution was dried over magnesium sulfate. The solvent was removed under reduced pressure. An infrared absorption spectrum showed that the oil was free of unreacted nitrile and contained a conjugated carbonyl group (band at 1685 cm⁻¹). Crystallization of the oily product from an intermediate boiling ligroin (b.p. 60-90°C) gave 22 g. (66%) of analytically pure product, 1-benzyl-4-phenyl-4-piperidylphenylketone (LVII), m.p. 122-123°C.

Anal. calcd. for C₂₅H₂₅NO: C, 84.45; H, 7.09; N, 3.94; O, 4.50. Found: C, 84.61; H, 7.08.

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The Reduction of 1-Benzyl-4-phenyl-4-piperidylphenylketone (LVII) with Sodium Borohydride. A solution of 2 g. of 1-benzyl-4-phenyl-4-piperidylphenylketone (LVII) in 25 ml. of methanol-ether (the ketone is sparingly soluble in methanol) was treated with 1 g. of sodium borohydride at 0 °C. The reaction mixture was allowed to stand for 1.5 hrs. at room temperature. The solvent was removed by distillation under reduced pressure, the residue was dissolved in water, and the product was extracted into ether. The ether solution was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation. The residue was soluble in most of the organic solvents except low boiling petroleum-ether (b.p., 30-60 °C). Due to the failure of crystallization of the free amine (LVIII) the hydrobromide was prepared to give 1.6 g. (73%) of 1-benzyl-4-phenyl-4-piperidylphenylecarbinol hydrobromide (LIX), m.p. 262-264 °C.

Anal. calcd. for C_{25}H_{28}NOBr: C, 68.49; H, 6.43; N, 3.19; O, 3.64; Br, 18.23. Found: C, 68.64; H, 6.28.

The rearrangement reaction of 1-benzyl-4-phenyl-4-piperidylphenylecarbinol hydrobromide with concentrated sulfuric acid.

To 20 ml. of concentrated sulfuric acid, at -5 °C was added 5.2 g. (0.012 mole) of 1-benzyl-4-phenyl-4-piperidylphenylecarbinol hydrobromide (LIX) in portions. After standing for 3 hrs. at -5 °C, the reaction mixture was poured into ice-water and made basic with potassium carbonate. The reaction mixture was extracted with ether, and the ether solution was
dried over potassium carbonate. After removing the solvent, the oil was crystallized from 95% ethanol. Recrystallization from the same solvent gave 2 g. (50%) of 1-benzyl-4-diphenylmethyl-1,2,5,6-tetrahydropyridine (LX), m.p. 217.5-218.5. The location of the double bond was assigned by the following physical data. The infrared absorption spectrum exhibited a vinyl hydrogen stretching band at 655 cm⁻¹, and the ultraviolet absorption spectrum was consistent only with that of expected isolated phenyl rings, λ_max 252 μμ (E = 770), 257 μμ (E=1050), 262 μμ (E=1130), 267 μμ (E=835). The picrate, m.p. 210-213°C (d) was made by conventional method.

Anal. calcd. for C₃₁H₂₈N₄O₇: C, 65.48; H, 4.96; N, 9.85; 0, 19.69. Found: C, 65.22; H, 4.70.

Preparation of Ketoamine of 1-Benzyl-4-phenyl-4-piperidylphenylketone (LXI). A solution of 20 g. (0.0565 mole) of 1-benzyl-4-phenyl-4-piperidylphenylketone (LXVII) and 4.25 g. (0.0616 mole) of hydroxylamine hydrochloride in 500 ml. of 95% ethanol was treated with 20 g. of potassium hydroxide in 200 ml. of ethanol. The reaction mixture was stirred with a mechanical stirrer for 3 hrs. at 100°C and was allowed to stand overnight at room temperature. A white crystalline solid which precipitated was removed by filtration and water was added to the filtrate to cause more precipitation. The combined product was recrystallized from 95% ethanol to give 18 g. (91%) of an analytical sample of 1-benzyl-4-phenyl-4-piperidylphenylketoxime (LXI), m.p. 210-212°C.
Anal. calcd. for C$_{25}$H$_{26}$N$_2$O: C, 81.08; H, 7.03; N, 7.91; found: C, 81.30; H, 7.32; N, 7.54.

Reduction of 1-Benzyl-$\beta$-piperidylphenylketoxime (LXI) with Lithium Aluminum Hydride.  

a) Ether-tetrahydrofuran medium— A heterogeneous reaction mixture of 1.5 g. (0.004 mole) of the oxime (LXI) and finely powdered 0.2 g. (0.005 mole) of lithium aluminum hydride in 60 ml. of ether-tetrahydrofuran (1:1) was stirred for 16 hrs. at room temperature and heated under reflux for 7 hrs. under a nitrogen atmosphere. After hydrolysis with water, the reaction mixture was extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The solid residue was identified as the unreacted starting material, recovered quantitatively.

b) Tetrahydrofuran medium— A mixture of 5 g. of the oxime (LXI) and 0.7 g. of lithium aluminum hydride in 140 ml. of tetrahydrofuran was heated under reflux for 18 hrs. and treated as above. Almost a quantitative amount of the starting material was recovered.

c) Diglyme, bis(2-methoxyethyl) ether medium— A suspension of 5 g. of the oxime (LXI) and 0.7 g. of lithium aluminum hydride in 140 ml. of diglyme was stirred for 4.5 hrs. at room temperature and heated under reflux for 14 hrs. The reaction mixture was treated by the same method as described above. The resulting oily products were separated by
fractional distillation. The lower boiling fraction, b.p. 142-145° at 0.7 mm. gave 2 g. (42%) of 1-benzyl-4-phenyl-4-
piperidylanilinomethane (LXII). An analytical sample gave
infrared absorption spectrum bands (IR #4404-A, model 21) at
3050, 2910, 280, 1645 (w), 1608, 1575 (w), 1500, 1460, 1395,
1370, 1345, 1265, 1145, 1125, 1070, 1030, 980, 905 (w), 825
(w), 780, 735 and 695 cm⁻¹.

Anal. calc. for C₂₅H₂₈N₂: C, 84.22; H, 7.91;
N, 7.85. Found: C, 84.22; H, 8.10.

A small amount of the higher boiling fraction, b.p. 145-180°, at 0.7 mm., gave a similar infrared absorption
spectrum (IR #4404-B, model 21) to that of 1-benzyl-4-phenyl-
4-(α-amino benzyl)piperidine (LXIII) (c.f. IR #3006, model
137-B). (See following authentic reduction product).

Reduction of 1-Benzyl-4-phenyl-4-piperidylphenyl-
ketoxime (LXI) with Metallic Sodium—absolute Ethanol. A
solution of 1-benzyl-4-phenyl-4-piperidylphenylketoxime (LXI, 5 g.)
in 300 ml. of boiling absolute ethanol was treated with 30 g.
of metallic sodium in portions during a 3-hour period.
Ethanol and water was added to the reaction mixture to destroy
any excess sodium, and the solvents were removed by distilla-
tion under reduced pressure. The residue was dissolved in
water, and the product was extracted into ether. The ether
solution was washed a few times with water and dried over
potassium carbonate. After removal of the solvent, a very
thick oil was obtained. Chromatographic separation of Florisil
separated two components. An ether fraction gave a major product whose infrared absorption spectrum (film) was identical with that of the higher boiling fraction of lithium aluminum hydride reduction in diglyme, (IR #3006, model 137-B) (c.f. IR #4404, model 21) 3450 (w), 3400 (w), 3100, 3000, 2800, 1605, 1500, 1450, 1375, 1350, 1300, 1270, 1120, 1080, 1060, 1030, 1010, 965, 920, 780, 740 and 700 cm⁻¹.

Crystallization and recrystallization from ligroin gave 3 g. (63%) of an analytical sample of 1-benzyl-4-phenyl-4-(α-aminobenzyl)piperidine (LXIII), m.p. 104-105.5°.

Anal. calc'd. for C₂₅H₂₈N₂: C, 84.22; H, 7.91; N, 7.85. Found: C, 84.03; H, 8.04.

IR #3255 (model 137-B, double mull): 3400 (b), 3100 (w), 3000 (w), 2800 (w), 1600 (m), 1500 (m), 1450, 1375, 1270, 1150, 1120, 1080, 1060, 1030, 1010, 970, 940 (m), 925 (m), 860, 850, 800, 780, 750, 740 and 700 cm⁻¹.

The Preparation of 1-Benzyl-4-phenyl-4-piperidyl-aminomethane (LXIV) from 1-Benzyl-4-cyano-4-phenylpiperidyl Hydrochloride. A suspension of 5 g. (0.016 mole) of water insoluble 1-benzyl-4-cyano-4-phenylpiperidyl hydrochloride was neutralized with 10% sodium hydride, and the amine was extracted into ether. The ether solution was dried over anhydrous magnesium sulfate. The solution was concentrated to a volume of 70 ml. and was added slowly to 2 g. (0.0525

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mole) of lithium aluminum hydride which was suspended in 30 ml. of ether. The reaction mixture was stirred for one hour at room temperature with a magnetic stirrer and heated under reflux for 2 hrs. After the reaction mixture was cooled, it was hydrolyzed with water and extracted with ether. The ether solution was dried over potassium carbonate, and the solvent was removed by distillation under reduced pressure. The residual oily product, 3.5 g., was purified by passing through a Florisil packed column, using ether as an eluant. Crystallization and recrystallization from ligroin gave 3.3 g. (74%) of 1-benzyl-4-phenyl-4-piperidylaminomethane (LXIV), m.p. 70-73°. Recrystallization of this solid from acetonitrile gave a colorless analytical sample, m.p. 71-72.5°.


IR #3474 (model 137-B): 3400 (sh), 3100 (m), 3000, 2800, 1600 (w), 1500 (m), 1445, 1375 (m), 1350 (m), 1270 (m), 1140 (m), 1120, 1060 (m), 1040, 980 (m), 930, 880, 770, 745 and 700 cm⁻¹.

The Reaction of 1-Benzyl-4-phenyl-4-piperidylaminomethane (LXIV) with Nitrous Acid. A saturated aqueous solution of 10 g. of sodium nitrite was added slowly with stirring to a solution of 3.3 g. (0.018 mole) of 1-benzyl-4-phenyl-4-piperidylaminomethane (LXIV) in 75 ml. of 10% acetic acid. The reaction mixture was heated and stirred for 2 hrs. at 65° C. An oily material coated the flask wall and was not soluble in
water and 10% hydrochloric acid, but was soluble in chloroform, acetone, and 10% sodium hydroxide. The oily material in the reaction flask was extracted into chloroform and the chloroform solution was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure and the residue, a thick brown oil, was treated with acetonitrile and a crude solid was obtained. The solid was removed by filtration and was dissolved in acetonitrile and treated with activated charcoal (Norite-A). The almost colorless solution was concentrated, on cooling of the solution, to give 1.6 g. (62%) of N-nitroso-4-phenyl-4-piperidylcarbinol (LXV), m.p. 205-208°.

**Anal. calcd. for C_{12}H_{16}N_{2}O:** C, 65.43; H, 7.32; N, 12.71; O, 14.53. **Found:** C, 65.70; H, 7.22.

The structure was assigned based on the following physical and chemical data.

A. 1. The analytical sample gave a positive Lieberman's test for the —NO group.
2. The infrared spectrum (IR #2955, model 137-B) showed —OH stretching band at 3490 cm⁻¹ and a multiple band around 1350 cm⁻¹ for the —NO.
3. The n.m.r. spectrum (#33) was consistent with the presence of only one phenyl group.

B. Conversion of N-nitroso-4-phenyl-4-piperidylcarbinol (LXV) to 1-methyl-4-phenyl-4-piperidylcarbinol (XXXIII): A sample of 100 mg. of the nitroso-compound
(LXV), in 1.5 ml. concentrated hydrochloric acid was treated with 100 mg. of cuprous chloride and the reaction mixture was warmed for 10 min. The reaction mixture was made basic with 10% sodium hydroxide and extracted with ether. The ether solution was dried over potassium carbonate and the solvent was removed by distillation. The oily residue was heated at 100°C for 3 hrs. with 99% formic acid (1.5 ml.) and 44% formaldehyde (1.5 ml.). The reaction mixture was poured into water, was made basic with ammonium hydroxide, and extracted with ether. The ethereal solution was washed with water, and dried over potassium carbonate, and the solvent was removed to yield a compound which melted at 145-149°C. A mixture melting point of this solid with an authentic sample of l-methyl-4-phenyl-4-piperidylcarbinol (XXXIII) melted at 140-145°C. (c.f. m.p. of the authentic sample at 139-140°C).

The Reaction of l-Methyl-4-phenyl-4-piperidylphenylcarbinol with Concentrated Sulfuric Acid. To 15 ml. of concentrated sulfuric acid at -5°C was added 2.3 g. (0.0082 mole) of l-methyl-4-phenyl-4-piperidylphenylcarbinol in portions during a 15-minute period. After the reaction mixture was allowed to stand for 3 hrs. at the same temperature, it was poured into 500 ml. of ice-water and made basic with a saturated potassium carbonate solution. The amine was precipitated immediately along with some of the inorganic salt.
The precipitate was triturated with ether and the filtrate was extracted with ether. The combined ether solutions were dried over potassium carbonate.

The solvent was removed under reduced pressure, and the resulting oil showed significant bands at 3400 and 1650 cm\(^{-1}\) in the infrared absorption spectrum (IR #3084, model 137-3). The oil was dissolved in a minimum amount of ether and was allowed to stand. The slow evaporation of the solvent in air caused crystallization. The crystalline product, m.p. 168-190°, was collected by filtration and washed with ether. The elemental analyses corresponded to an empirical formula, \(\text{C}_{20}\text{H}_{24}\text{O}_{6}\), and molecular weight determination by an Osmonometric method showed an average value, 351. However, the mass spectroscopic result (49) revealed that there was no evidence for the presence of a compound whose molecular weight was greater than that of the starting material. The ultraviolet absorption spectrum \(\lambda_{\text{max}}253\text{ m}\mu (\varepsilon = 427), 258\text{ m}\mu (\varepsilon = 632), 263\text{ m}\mu (\varepsilon = 448)\), a positive bromine water test and the following infrared absorption spectrum strongly suggested a fragmentation reaction might be taking place.

IR #3041: 3350 (w), 2900 (w), 1650 (s), 1550 (s), 1450 (m), 1375 (m), 1295 (s), 1200 (s), 1145 (m), 1125 (m), 1075 (m), 1060 (w), 1030 (w), 1010 (w), 955 (m), 900 (w), 785 (w), 750 (m), 710 (s) and 700 cm\(^{-1}\) (s).

Anal. found: C, 77.96, 77.31; H, 8.12, 8.05; N, 8.38, 8.78.
Preparation of 1-Methyl-4-benzyl-4-hydroxypiperidine (LXXI). To an ether solution of benzylmagnesium bromide (0.04 mole), purified 1-methyl-4-piperidone (4.5 g., 0.039 mole) was added dropwise. The reaction took place very vigorously during a 15-minute period. The reaction mixture was treated by a conventional method and a crude product, m.p. 77-79°, was obtained. Recrystallization of the solid from ligroin gave 1-methyl-4-benzyl-4-hydroxypiperidine (8.3%), m.p. 83-84.5°.

Anal. calcd. for C_{15}H_{20}NO: C, 76.05; H, 9.33; N, 6.82.

Found: C, 75.82; H, 9.22.
The reaction of 1-methyl-3-bromo-3-piperidylphenylketone (VII) with sodium hydrosulfide in a nonpolar high boiling medium gave 1-methyl-3-mercapto-3-piperidylphenylketone, which was very rapidly dimerized (XI-XIII) by air oxidation. In a low boiling solvent this reaction yielded only 1-methyl-3-hydroxy-3-piperidylphenylketone (XVI). In a polar solvent, such as absolute methanol or ethanol, the reaction gave a product of reduction debromination, 1-methyl-3-benzyolpiperidine (VIII).

Treatment of 1-methyl-4-bromo-(and chloro)-4-piperidylphenylcarbinol (XXVI or XXXVIII) with 10% sodium hydroxide gave an excellent yield (90-98%) of 6-methyl-2-phenyl-1-oxo-6-azaspiro[2,5]octane (XLIII). With silver acetate in aqueous methanol medium XXVI or XXVIII yielded 1-methyl-4-formyl-4-phenylpiperidine (XXXII). An authentic sample of XXXII was prepared from 1-methyl-4-phenylisonicotinonitrile for comparison. The chemical and physical properties of the epoxide (XLIII) were described. The hydrolysis of the epoxide (XLIII) with aqueous hydrochloric acid gave a quantitative yield of 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (XXXI), and reaction with phenyllithium gave 1-methyl-4-piperidylidenediphenylmethane (XXXVIII) and 1-methyl-4-phenyl-1-aza-5-cycloheptanone (XLV), a product of ring expansion. The conformation of the halohydrins (XXVI, XXVIII) and the reaction mechanism were
discussed.

Chlorination of 1-methyl-4-hydroxymethyl-4-phenyl-piperidine (XXXIII) with thiouyl chloride followed by treatment with boiling absolute ethanol yielded 1-methyl-4-phenyl-methylethyl ether (XLVIII) and a rearrangement product 1-methyl-4-benzylidene piperidine (XLIX).

The deamination reaction of 1-benzyl-4-aminomethyl-4-phenyl piperidine (LXIV) with nitrous acid in acetic acid involved two reaction centers to give 5-nitroso-4-hydroxymethyl-4-phenyl piperidine (LXV). The structure of the reaction product was proved by physical and chemical methods, and by conversion to a known derivative.

Synthesis of 1-benzyl-4-phenyl-4-piperidyl phenylketoxime (LXI) followed by lithium-aluminum hydride reduction in diglyme gave 1-benzyl-4-anilinomethyl-4-phenyl piperidine (LXII) as a major product accompanied by a small amount of 1-benzyl-4-(α-aminobenzyl)-4-phenyl piperidine (LXIII). The latter product was prepared by reduction of LXI with metallic sodium in boiling absolute ethanol. Treatment of 1-benzyl-4-phenyl-4-piperidyl phenylcarbinol (LXIII) with cold concentrated sulfuric acid gave 1-benzyl-4-diphenyl methyln-1,2,5,6-tetrahydropyridine (LX); however, 1-methyl-4-hydroxymethyl-4-phenyl piperidine (XXXIII) and 1-methyl-4-phenyl-4-piperidylphenylcarbinol (XLII) gave complicated mixtures.
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