STUDIES OF THE REACTIONS OF ALPHA-BROMO KETONES IN THE PIPERIDINE SERIES

GLENN HOMER WARNER

Follow this and additional works at: https://scholars.unh.edu/dissertation

Recommended Citation
https://scholars.unh.edu/dissertation/762

This Dissertation is brought to you for free and open access by the Student Scholarship at University of New Hampshire Scholars' Repository. It has been accepted for inclusion in Doctoral Dissertations by an authorized administrator of University of New Hampshire Scholars' Repository. For more information, please contact nicole.hentz@unh.edu.
STUDIES OF THE REACTIONS OF ALPHA-BROMO KETONES
IN THE PIPERIDINE SERIES

Keywords
Chemistry, Organic
STUDIES OF THE REACTIONS OF $\alpha$-BROMO KETONES IN THE PIPERIDINE SERIES

BY

GLENN HOMER WARNER

B. S., Bucknell University, 1952
M. S., University of Maine, 1955

A THESIS

Submitted to the University of New Hampshire
In Partial Fulfillment of
The Requirements for the Degree of
Doctor of Philosophy

Graduate School
Department of Chemistry
June, 1959

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
This thesis has been examined and approved.

[Signatures]

May 27, 1959
Date
ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Dr. Robert E. Lyle for suggesting this problem and for his helpful advice which greatly facilitated the completion of this work. Grateful acknowledgement is also due the National Institutes of Health for their financial support, and to Dr. Paul R. Jones and Mr. David A. Nelson who made possible the determination of the infrared and ultraviolet absorption spectra. The author also wishes to thank Dr. Harold A. Iddles for his assistance with the manuscript of this dissertation.
# TABLE OF CONTENTS

I  LIST OF ILLUSTRATIONS 111

II  INTRODUCTION 1

III  DISCUSSION

1. Preparation of the Starting Materials 4

2. Catalytic Hydrogenation of Some Salts of 3-Benzoylpyridine and Related Compounds 5

3. Reactions of the α-Bromopiperidyl Phenyl Ketones 23

4. Reactions of the Epoxyethers 39

IV  EXPERIMENTAL

1. Preparation of the Starting Materials 45

2. Reactions of 1-Benzyl-4-benzoyl-4-bromopiperidine Hydrobromide (XVII) 56

3. Reactions of 1-Methyl-3-benzoyl-3-bromopiperidine Hydrobromide (XIX) 57

4. Reactions of 1,4-Dibenzoyl-4-bromopiperidine (XXII) 59

5. Reactions of 1,3-Dibenzoyl-3-bromopiperidine (XXIII) 61

6. Reactions of 1,1-Dimethyl-4-benzoyl-4-bromopiperidinium Bromide (XX) 63

7. Reaction of 1,1-Dimethyl-3-benzoyl-3-bromopiperidinium Bromide (XXI) with Silver Nitrate 65

8. Reactions of 6-Benzyl-2-methoxy-2-phenyl-1-ox-6-axaspiro (2,5) octane (XXIV) 66

9. Reactions of 2-Methoxy-5-methyl-2-phenyl-1-ox-5-axaspiro (2,5) octane (XXVIII) 69

10. Attempted Rearrangements of Epoxyethers (XXIV) and (XXXI) 73

11. Catalytic Hydrogenation of Some Salts of 3-Benzoylpyridine and Related Compounds 75

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
# List of Illustrations

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A'</td>
<td>Preparation of Some $\text{C} - \text{Br} - \text{3-}$ (and 4) $\text{C} - \text{p}$-piperidyl Phenyl Ketones</td>
<td>6</td>
</tr>
<tr>
<td>1.</td>
<td>Ultraviolet Absorption Spectra of the Catalytic Reduction of 1-Methyl-3-benzoylpyridinium Bromide</td>
<td>10</td>
</tr>
<tr>
<td>2.</td>
<td>Ultraviolet Absorption Spectrum of 1-Methyl-3-benzoylpiperidine Hydrobromide</td>
<td>12</td>
</tr>
<tr>
<td>3.</td>
<td>Ultraviolet Absorption Spectra of the Catalytic Reduction of 3-Phenyldiphenylcarbinol Methobromide</td>
<td>13</td>
</tr>
<tr>
<td>4.</td>
<td>Ultraviolet Absorption Spectra of the Catalytic Reduction of 1-Methyl-3-benzyl-1,4-dihydropyridine</td>
<td>17</td>
</tr>
<tr>
<td>5.</td>
<td>Visible Absorption Spectra of the Catalytic Reduction of 1-Methyl-3-benzoylpiperidine Hydrobromide</td>
<td>19</td>
</tr>
<tr>
<td>6.</td>
<td>Ultraviolet Absorption Spectra of 1-Methyl-3-benzoylpiperidine Hydrobromide and 1-Benzylnicotinamide Bromide in Basic Media</td>
<td>22</td>
</tr>
<tr>
<td>A.</td>
<td>Mechanism of the Quasi Favorski Rearrangement</td>
<td>25</td>
</tr>
<tr>
<td>B.</td>
<td>Effects of Possible Transannular Interaction Upon the Course of the Quasi Favorski Reaction</td>
<td>28</td>
</tr>
<tr>
<td>7.</td>
<td>Ultraviolet Absorption Spectra of 1-Methyl-3-benzylpiperidine and 1-Methyl-3-benzylidene piperidine Methiodides</td>
<td>30</td>
</tr>
</tbody>
</table>

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
INTRODUCTION

The unusual reactivity of α-haloketones has been demonstrated by immeasurable investigations and the chemistry of these compounds was the subject of two excellent review articles by Jacquier (1) and by Tchoubar (2). The utilization of α-haloketones for the synthesis of other compounds therefore has been well established and the type of product which results upon conversion of the α-haloketones (an unsaturated ketone, a hydroxyketone, a halo hydrin, an ethylene oxide or an acid from the Favorški reaction) has been shown to be dependent upon the nature of the nucleophilic initiator and the solvent system. Few investigations, however, have dealt with an α-haloketone system in which aophile is directly incorporated into the molecule; such an arrangement is present in an α-halopiperidyl ketone or in any other heterocyclic system of a similar constitution.

Recently, the mechanistic potential of these heterocyclic α-haloketones and the synthetic application thereof have been realized and concurrently evaluated in this Laboratory (3) and at the University of Wisconsin (4).

The initial studies in this field were conducted by Trosćianiec (3) in this Laboratory and the results of this investigation indicated the desirability of further work, particularly in regard to the pharmaceutical application of the epoxyethers, which were produced upon treatment of an α-haloketone with sodium alkoxide in alcohol, and the quasi
Favorski reaction using heavy metal ion catalysts. The results of pharmacological screening indicated that the ester derivatives of 1-methyl-4-benzoyl-4-piperidinol, which Troscianiec prepared from the corresponding α-bromoketone via the epoxy ether, were quite potent local anesthetics, but of rather limited use due to their high toxicity. In an attempt to eliminate the undesirable side effects while maintaining the anesthetic potency, a new series of ketoesters was prepared by making certain structural variations in the starting material.

As scattered reports (5,6) have shown that the reaction of certain α-haloketones with silver salts results in rearrangements of the Favorski type one phase of the investigation was designed to ascertain whether or not this quasi Favorski reaction could be applied to the synthesis of some acids or esters of the piperidine series. The compounds chosen for the study were derivatives of α-halo-3-(or 4-) benzoylpiperidines which could be related to those ketones employed in the previous work, and whose reaction products possessed the potential of being pharmacologically active.

The preparation of these α-haloketones, some of which were employed in the synthesis of new epoxyethers as well as in the study of the quasi Favorski reaction, required as intermediates the 1-substituted-3- and 4-benzoylpiperidines. The most convenient method of synthesis of the 4-isomers was accomplished by oxidation of the 1-substituted—
4-piperidylphenyl carbinol as described by Sugiomoto and Kugita (7) and modified by Leone (8). The carbinol, in turn, was obtained by catalytic hydrogenation of 4-benzoylpyridinium halides, a reaction which proceeds through the intermediate 4-(α-hydroxybenzyl)pyridinium halide. In the 3-series, however, it was observed that reduction of the heterocyclic ring of 3-benzoylpyridinium halide occurs prior to that of the carbonyl group so that it was possible to isolate the desired 1-substituted-3-benzoylpiperidine directly from the hydrogenation mixture. Although the selective reduction of substituents on the pyridine nucleus is possible, few reactions have been observed in which the reduction of the ring occurred in preference to that of the substituent, and these cases have not been investigated to any extent. The catalytic hydrogenation of the 3-benzoylpyridinium salts was therefore studied in some detail by following the changes in the ultraviolet absorption spectrum during the reaction.
DISCUSSION OF RESULTS

Preparation of the Starting Materials

The preparation of 1-substituted-4-benzoyl-4-bromo-piperidine and 1-substituted-3-benzoyl-3-bromopiperidine was dependent upon the synthesis of the corresponding 1-substituted-3- (and 4-) piperidyl phenyl ketones which could then be converted to the desired starting material by direct halogenation. The methods available for the synthesis of 1-substituted-4-piperidyl phenyl ketones have been reviewed extensively by both Troscianiec (3) and Leone (8) so that no further literature survey will be presented herein.

As the previous investigations in these Laboratories had carefully developed a method of synthesis for the 1-alkyl-4-halopiperidyl phenyl ketones, the compounds employed in this study were readily prepared with only minor deviations in the existing procedures (3,8). The source of 1-benzyl-4-benzoylpiperidine, one of the starting ketones, was the commercially available 4-benzoylpyridine which was converted to the quaternary salt by reaction with benzyl chloride. Catalytic reduction of this salt, followed by neutralization of the resulting hydrochloride, gave a good over-all yield of 1-benzyl-4-piperidylphenylcarbinol (VII). Similarly the low pressure hydrogenation of 4-benzoylpyridine hydrochloride in alcohol gave the corresponding 4-piperidylphenylcarbinol (VIII).

The chromic acid oxidation of these carbinols was
accomplished in the manner previously developed by Leone (8) and resulted in the formation of the hydrobromides of 1-benzyl-4-benzoylpiperidine (XI) and 4-benzoylpiperidine (XII) respectively. The secondary amine, 4-benzoylpiperidine, was benzoylated by means of the Schotten-Baumann method, and this reaction furnished the desired amide, 1,4-dibenzoylpiperidine (XIV) in good yield. Finally, the quaternary salt of 1-methyl-4-benzoylpiperidine was prepared by the reaction of the free base with anhydrous methyl bromide.

Bromination of the amide (XIV) was carried out in glacial acetic acid, while the various salts were brominated in chloroform according to the procedure developed by Troscianiec (3).

The basic compound employed for the synthesis of the corresponding 3-isomers, 3-benzoylpyridine, was prepared by the method of Villiani and King (9). Conversion of this ketone to the 1-substituted-3-benzoyl-3-bromopiperidines could be accomplished by the sequence of reactions previously outlined. However, it was observed that the salts of 3-benzoylpyridine were selectively hydrogenated to yield the 1-substituted-3-benzoylpiperidines directly and thereby rendered the oxidation step unnecessary.

Catalytic Hydrogenation of Some Salts of 3-Benzoylpyridine and Related Compounds.

The catalytic reduction of the several salts of 3-benzoylpyridine carried out in this study has revealed a marked dissimilarity in the reduction of these compounds
Preparation of Some α-Phenyl-Cyclohexyl Ketones

1. H₂O, PdO₂
2. NaOH

R. CH₃: 1. NaOH, CH₂Br

R. CH₃: 2. CH₂Br

3. Series

4. Series

H-X

R. H or CH₃

R. CH₃, CH₂-CH₃, C₆H₅

CH₂-CH₃, HBr, + CH₂Br
and those having the carbonyl group in the 4-position.

Strong and McElvain (10) previously observed a difference in the rates of reduction of 3 and 4-benzoylpyridine, and they report that catalytic hydrogenation of the 4-isomer gave a quantitative yield of 4-piperidylphenylcarbinol. The 3-benzoylpyridine, however, gave only a small yield of the 3-piperidylphenylcarbinol due to the concurrent formation of a hydrogenolysis product, 3-benzylpiperidine. In certain respects, the reduction of the salts of these pyridyl phenyl ketones described herein parallels the observation of Strong and McElvain, for the hydrogenation of 1-benzyl-4-benzoylpyridinium chloride (II) gave an excellent yield of the corresponding 4-piperidylphenylcarbinol (10). Conversely, the reduction of 1-methyl-3-benzoylpyridinium bromide (V) gave a complex mixture from which 1-methyl-3-piperidyl phenyl ketone (X) could be isolated in a sizeable yield. In addition to this ketone (X), 1-methyl-3-piperidylphenylcarbinol (L), a mixture of isomeric 1-methyl-3-piperidylphenylcarbinols (LII) and 1-methyl-3-benzylpiperidine (LIIa) were also isolated from the reduction mixture after neutralization.

The direct isolation of 1-methyl-3-benzylpiperidine (X) from the reduction mixture is surprising as the selective reduction of the pyridine ring in preference to the carbonyl group has been observed in only a limited number of cases. Kuick and Adkins (11) have obtained very interesting results on the reduction of nicotinylacetyl methane over Raney nickel.
catalyst at 150–160°. With butyrylnicotinyl methane this reaction gave 3 different products including a 19% yield of 3—acetylpiperidine in which the pyridine ring is reduced in preference to the ketone, and the isobutyrylnicotinylmethane gave a 33% yield of 3—acetylpiperidine. The benzoylnicotinylmethane gave 18% of the hydrogenolysis product, 1—(3—piperidyl)—3—phenylpropane. The authors assumed that the reduction of the pyridine ring preceded the reduction of the carbonyl group for no products were isolated which contained the pyridine ring. 

The reduction of several benzoyl quinolines over Raney nickel at 20—60° was carried out by Kuhnis and Diebach (12) who observed the selective reduction of the heterocyclic portion of the quinoline ring whenever the benzoyl group was located in the 6 or 8 position. They also established that the corresponding carbinol underwent hydrogenolysis to give 6—tetrahydroquinolylphenylmethane in a reaction similar to that already cited (11).

Sugimoto and Kugita (7) in a study closely related to the present one, reported that the catalytic hydrogenation of 3—pyridylphenylearbinol methochloride in neutral solution gave the same sequence of products, including 1—methyl—3—benzoyl—piperidine (X), as was obtained upon reduction of 1—methyl—3—benzoylpyridinium bromide (V). These authors account for the formation of (X) by air oxidation of the carbinol (L) during vacuum distillation. As neither of the investigations previously cited definitely eliminated the possibility that the
ketones which were isolated were being formed in a similar manner, there still exists a reasonable doubt concerning the selective reduction of the pyridine ring in preference to the carbonyl group. The study of the reduction of 3-benzoylpyridine methobromide (V) and several related compounds was undertaken, therefore, in order to establish conclusively that reduction of the pyridine ring precedes reduction of the ketone. The catalytic hydrogenation of 3-benzoylpyridine methobromide (V) was carried out over platinum oxide at an initial pressure of three atmospheres. Isolation of the ketonic fraction was accomplished by recrystallization of the reduction mixture from isopropyl alcohol and (X) was characterized by comparison with an authentic sample of 1-methyl-3-benzoylpyperidine hydrobromide which was prepared by the oxidation of 1-methyl-3-piperidylphenylcarbinol (L). The hydrogenolysis product, 1-methyl-3-benzylpiperidine (LIA) was separated from the carbinols by distillation under reduced pressure and identified by comparison with an authentic sample prepared by the Wolf-Kishner reduction of 3-benzoylpyridine (I), preparation of the methobromide of this product and subsequent reduction of this salt.

The course of the reduction was followed by observing the variation in the ultraviolet absorption spectra of aliquot samples withdrawn from the reaction mixture after the absorption of various amounts of hydrogen (see Fig. 1). The pure methobromide (V) is characterized by an intense absorption
maximum at 260 mÅ, and as the reduction proceeds, this peak diminished in intensity while a new maximum appears between 315–320 mÅ. This second absorption maximum continues to increase in strength until the reaction has utilized about one-half of the theoretical amount (1.4 moles) of hydrogen. At this point, a third absorption peak becomes apparent, 240 mÅ, and, as the reduction proceeds to 75% completion, this maximum becomes the most prominent with a corresponding abatement in the 315–320 mÅ band. Inspection of the ultraviolet spectrum of 1-methyl-3-benzoylpiperidine (X) (Fig. 2) reveals that this compound absorbs strongly at 240 mÅ and, to a much lesser extent, in the 280 mÅ and 315–320 mÅ regions. Since (X) is obtained directly from the reaction mixture, the absorption at 240 mÅ, which appears during the last stages of hydrogenation, was due to the benzoyl absorption of (X). However, the absorption exhibited by the reduction mixture between 315–320 mÅ was too intense to be attributed to (X), and, as none of the other compounds isolated from the reduction absorb in this region, this band must be assigned to an intermediate product.

This experiment leads to the conclusion that the ketone was one of the main reduction products and was not formed during a secondary reaction of the type proposed by Sugimoto and Kugita to account for the products of a similar reduction. These investigators, however, did not follow the course of their reduction by spectrophotometric methods, and consequently were unable to provide irrefutable evidence to
Figure 2

Ultraviolet Absorption Spectrum of 1-Methyl-3-benzoyclohexidine Hydrobromide (X) in 25% Ethanol

Conc. $1.2 \times 10^{-5}$ m/l $1.2 \times 10^{-4}$ m/l $1.2 \times 10^{-3}$ m/l 0.4

Absorbance

230 nm 260 290 320
support their hypothesis. In order to confirm their results and to establish that the secondary alcohol of 1-methyl-3-piperidylphenylcarbinol (L) was not dehydrogenated to the ketone by catalytic hydrogenation, the reduction of 3-pyridyl-phenylcarbinol methobromide (V) was repeated, and this reaction was followed by the technique previously described. The ultraviolet absorption spectra recorded in (Fig. 3) show how the composition of the reduction mixture changes as the reaction proceeds. The only maximum initially present is that characteristic of the quaternary salt, and as hydrogen is absorbed this band gradually diminishes. No other pronounced maximum appears, except those of the benzene system at 252, 258 and 264 m\(\mu\). Very concentrated samples (10\(^{-2}\) m/l.) displayed an extremely weak absorption band in the 315-320 m\(\mu\) region which would indicate the probability that either 1-methyl-3-benzoylpiperidine (X) or an intermediate is present in the reaction mixture in minute quantities. The only material isolated from the reduction mixture, however, was an inseparable mixture of the isomeric 1-methyl-3-piperidyl-phenylcarbinols (LII). Thus, this evidence supports the proposal of Sugimoto and Kugita (7).

Bohlmann(13) found that either lithium aluminum hydride or catalytic reduction of 3,5-dicyanopyridine gave 3,5-dicyano-1,4-dihydropyridine and postulated that the two electronegative substituents cause polarization of the pyridine ring which increases the probability of hydride addition
at the 2, 4 or 6-position and stabilizes the product of such an attack. This experiment, and reports that acyl pyridines or acyl quinolines could be selectively hydrogenated over Raney nickel (11,12), provoked speculation regarding the role of the quaternary nitrogen atom in the catalytic reduction of 3-benzoylpyridine methobromide. The query as to whether or not the pyridine ring would be reduced in preference to the keto group if the nitrogen atom were not present as a salt was answered by reducing 3-benzoylpyridine (I) in neutral solution. This reaction was conducted in the same manner as the reduction of the salts and gave 3-pyridylphenylcarbinol, exclusively. The reduction of hydrochloride of (I) in methanol, however, gave a reasonable yield of 3-benzoylpiperidine hydrochloride (LIIX) in contrast to the previous report by Crooks and MoElvain (14) that only 3-piperidylphenylcarbinol could be obtained from this reaction. Furthermore, the catalytic hydrogenation of 1-2-phenethyl-3-benzoylpyridinium bromide (IV) over platinum oxide was found to give a 15% yield of the corresponding piperidyl phenyl ketone. These studies indicate that the single electron withdrawing carbonyl group is not capable of decreasing the electron density at the 2, 4 or 6-positions, enough to permit the reaction to take place at these sites. The quaternary salt serves to enhance the polarization of the ring thereby allowing the hydrogenation of the pyridine nucleus to be favored over that of the substituent.

Having once established that the reduction of the
pyridine ring took place before the carbonyl group was attacked, the development of a logical mechanism, to account for the formation of the various products obtained upon catalytic hydrogenation of 3-benzoylpyridine methobromide (V), became the next objective. Bohlmann and Bohlmann (13) have reported that the catalytic hydrogenation of 3,5-dicyanopyridine over platinum oxide gave 3,5-dicyano-1,4-dihydropyridine, an ethanolic solution of which exhibited maximum absorption at 360 m\(\mu\). Berson and Brown (15) prepared a series of 1,4-dihydropyridines by the Hantzsch synthesis and found that those compounds which possessed the chromophoric group present in 3,5-diacetyl-1,4-dihydropyridine displayed maximum absorption between 360 and 385 m\(\mu\). This observation was further supported by the work of Anderson and Berkelhammer (16) who determined the ultraviolet and visible absorption spectra for a number of 1,4-dihydropyridines and found that the maximum absorption of 1-benzyl-3-acetyl-1,4-dihydropyridine occurs at 370 m\(\mu\). The analogous 1-methyl-3-benzoyl-1,4-dihydropyridine which may conceivably be an intermediate in the catalytic reduction of 3-benzoylpyridine methobromide (V) would therefore be expected to absorb in this same region. However, the visible absorption spectrum, (Fig. 4), of several aliquot samples taken from the reaction mixture as the hydrogenation proceeded did not reveal any definite maxima characteristic of a 1,4-dihydropyridine. In order to determine whether or not 1-methyl-3-benzoyl-1,4-dihydropyridine (LXI) was an intermediate stage of this catalytic reduction, the compound was
Figure 4

Ultraviolet Absorption Spectra of the Catalytic Reduction of 1-Methyl-3-benzyl-1,4-dihydropyridine (LXI) in Acidified 95 % Ethanol

<table>
<thead>
<tr>
<th>lts. of Hz</th>
<th>Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$1.4 \times 10^{-5}$ m/l.</td>
</tr>
<tr>
<td>0.1</td>
<td>0.76</td>
</tr>
<tr>
<td>1.25</td>
<td>$1.4 \times 10^{-4}$</td>
</tr>
<tr>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>
prepared by the sodium dithionite reduction of (V) in the manner described by Anderson and Berkelhammer, and was hydrogenated over Adams catalyst in acidic solution. Once again the reaction was followed by observing the change in the ultraviolet absorption spectrum and these results are recorded in (Fig. 5). The 1-methyl-3-benzoyl-1,4-dihydropyridine (LXI) exhibited maximum absorption at 385 mÅ when freshly prepared but after it was exposed to light the absorption band shifted to 317 mÅ. An identical shift in the position of the absorption band occurred when (LXI) was treated with acid, and, as is shown in (Fig. 5), this 317 mÅ peak gradually diminishes as the reduction proceeds with concurrent formation of another maximum at 240 mÅ. The products which were obtained from the reduction of (LXI) in acidic solution were found to be identical to those resulting from catalytic hydrogenation of 3-benzoylpyridine methobromide.

In recent work, Anderson and Berkelhammer (16,17) have studied the reaction of acids with 1,4-dihydropyridines and observed that their so called "primary acid product" exhibited maximum absorption at a wave length 50 to 65 mÅ less than that of the parent 1,4-dihydropyridine. They proposed that a protonation of the 1,4-dihydropyridine occurs in the 5 position, and that this step is followed by attack of the solvent to give a tetrahydropyridine according to the equation:
If this explanation is accepted and applied to the case at hand then (LXI) may be considered as a transient intermediate in the catalytic reduction of 3-benzoylpyridine methobromide, which immediately reacts with the acid generated during its formation; subsequent attack of the solvent then gives the reaction intermediate responsible for the 317 μ absorption bands.

Since the "primary acid product" of 1-methyl-3-benzoyl-1,4-dihydropyridine (LXI) does exhibit maximum absorption at this wave length, this explanation appears to be plausible. The final step, reduction of the "primary acid product" to 1-methyl-3-benzoylpiperidine (X), is similar to the reduction
of the cyanide addition product of 1-methyl-nicotinamide bromide (A) by catalytic hydrogenation to either 1-methyl-hexahydronicotinamide (B) or 1-methyl-1,4,5,6-tetrahydronicotinamide (C) (18).

An alternate mechanism, which would involve initial reduction of a 4,5 double bond and successive reduction around the nitrogen atom to give rise to the tetrahydropyridine having the same chromophore as the "primary acid product" would also be compatible with the spectral data.

To distinguish between these two possible modes of addition, the catalytic reduction of 3-benzoylpyridine methobromide was carried out in a sodium bicarbonate solution in the presence of an immiscible organic liquid which would dissolve the intermediate as soon as it was formed. If the first mechanism were correct, the elimination of the acid should result in the production of a 1,4-dihydropyridine so that the organic layer would show maximum absorption characteristic of this system. On the other hand, the second proposed mechanism is not dependent upon the presence of acid and the tetrahydropyridine which would be formed would absorb at 317 μm. The result of this experiment is depicted in Figure 6 and shows
Ultraviolet Absorption Spectra of the Catalytic Reduction Products of 1-Methyl-3-benzoylpeperidine Hydrobromide (X) and 1-Benzynicotinamide Bromide from Basic Media

Ultraviolet Absorption Spectrum of 1-Methyl-3-benzoyl-1,4-dihydropyridine (LXI) in Acidified 95% Ethanol

Product from (X) in Ether

Product of 1-Benzynicotinamide Bromide in Ether (LXI) in 95% Ethanol and 2 drops of 48% Hydrobromic Acid

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
that reduction of the pyridine ring does not occur by way of a 1,4-dihydropyridine intermediate. This conclusion was supported by an additional experiment in which 1-benzylnicotinamide bromide (LVIII) was reduced in a similar manner, and the organic solution displayed an absorption maximum at 302 m\(\mu\). Karrer (18) has previously established that 1-methyl-(1,4,5,6)-tetrahydronicotinamide (C) absorbs at 295 m\(\mu\), and it would therefore appear that the same chromophore is present in both of these amides. On this basis then, one must conclude that reduction of two of the double bonds of the pyridinium ring occurs by the sequence outlined in the second of the two previously proposed mechanisms.

**Reactions of the \(\alpha\)-Bromopiperidyl Phenyl Ketones.**

In several current investigations it has been established that the reaction of certain \(\alpha\)-haloketones with silver salts in hydroxylic solvents results in a rearrangement of the Favorski type. The relationship of this metal-ion catalyzed, quasi-Favorski reaction with the normal reaction, which is promoted by alkoxide or hydroxide ion, is comparable to that of the hydrolysis of an alkyl halide in which silver or mercuric ions catalyze an \(\text{SN}_1\) displacement with the same reaction occurring via an \(\text{SN}_2\) mechanism. Therefore, the \(\alpha\)-bromoketone was considered more likely to undergo rearrangement than the corresponding \(\alpha\)-chloroketone, and for this reason a group of \(\alpha\)-bromoketones were employed in the study of the applicability of the quasi Favorski reaction to the synthesis of some acids or esters of the piperi-
dine series. The particular derivatives of the α-bromo-3-(or 4)benzoylpiperidines, whose synthesis has been described, were selected because they could be related to the ketones employed in the previous work (3) and because their reaction products possessed the potential of being pharmacologically active.

Cope and Graham (5) found that 1-bromobicyclo-(3,3,1)-nonan-2-one (D) reacted very rapidly with silver nitrate in absolute ethanol to give ethyl bicyclo-(3,3,0)-octane-1-carboxylate (E). They further established that silver nitrate could promote the rearrangement of α-haloketones of a more general structure by showing that α,α-dimethylphenylacetic acid was formed upon reaction of silver nitrate and α-bromo-isobutyrophenone in aqueous alcohol. These reactions were interpreted in terms of a "push-pull" process in which the initial hydration (or hemi-ketal formation) of the carbonyl group is followed by a pinacol type rearrangement.

Tchoubar (6a) has reported that the rearrangement of α-halocyclohexyl phenyl ketone could be achieved by the use of silver oxide or silver nitrate in a variety of aqueous solvents. In addition to the rearrangement product, 1-phenyl-cyclohexanecarboxylic acid, α-hydroxycyclohexyl phenyl ketone was also obtained, and the respective yields of these two
materials was found to be dependent upon the nature of the halogen and the solvent.

Stevens and Farkas introduced some degree of controversy concerning the nature of the products arising from this reaction as they (6b) reported that 1-phenyl cyclohexane-carboxylic acid and 1-cyclohexenyl phenyl ketone were obtained upon treatment of \( \alpha \)-bromo-cyclohexyl phenyl ketone with silver nitrate, but they did not isolate any of the \( \alpha \)-hydroxy-ketone. The mechanisms proposed by these authors, however, are essentially the same and are again similar to the pinacol rearrangement.

**Formation of the Hydroxyketone**

**Mechanism A**

**Formation of the Rearrangement Product**

**Mechanism B**

The requirement for rearrangement is a transition complex in which the migrating group and the departing...
halide are trans and coplanar, and in which free rotation of the carbonyl group about the \( \alpha \)-carbon atom is prohibited. Such a complex would be formed when the four atoms of the carbonyl group and the carbon–bromine bond lie in the same plane and thus permit the maximum coordination of the electronegative oxygen and bromine atoms with the silver ion.

Troscianiec attempted to convert 1-methyl-4-bromo-4-piperidyl phenyl ketone (P) to the analgesic Demerol, ethyl 1-methyl-4-phenyl-4-piperidylcarboxylate, by means of the silver nitrate catalyzed rearrangement of (P) in absolute ethanol, but obtained, instead of the desired ester, a product which he did not characterize, but which he believed to be the result of dehydrohalogenation (3).

A transannular nitrogen–carbonyl interaction, such as Leonard and Oki (19) observed in the cyclic aminoketone, 1-methyl-1-azacyclooctan-5-one, and which was found to occur in other aminoketones whenever a five or six membered ring could be formed provide an adequate explanation for this reaction. Leone (8) has reported that treatment of 1-methyl-4-benzoylpiperidine hydrochloride with hydrogen over Adams catalyst failed to reduce the carbonyl group, and he suggests that the ketone was inert to low pressure hydrogenation because a strong transannular interaction prevents the required orientation of the carbonyl group on the surface of the catalyst. Examination of the infrared absorption spectra of 1-methyl-
4-benzoylpiperidine and its hydrochloride, however, indicates no shift in the carbonyl absorption maxima in going from the free base to the hydrochloride. As a transannular nitrogen carbonyl interaction would result in the shift of the ketonic absorption band to lower frequency, it is apparent that such an interaction does not make an important contribution to the ground state of the molecule. It is conceivable that activation of 1-methyl-4-bromo-4-benzoylpiperidine (F) prior to reaction may allow the molecule to assume the "boat" conformation. In this activated state, transannular interaction may become increasingly important and thereby prevent formation of the transition complex leading to Demerol. The "push" which aids in the displacement of the departing halide therefore is supplied by the electrons of the trans-coplanar carbon-hydrogen bond as is depicted (Figure B), and the subsequent loss of a proton leads to the formation of an α,β-unsaturated ketone.

In recent studies concerned with the reaction of halogenated piperidine derivatives with nucleophilic agents, Smissman and Hite (4,20) and Archer (21) have shown that the overall result of these reactions is retention of configuration. They concluded that the apparent retention is the result of two inversions one of which involves a transannular participation of the nitrogen. Adaptation of this mechanism to the reaction of 1-methyl-4-benzoyl-4-bromopiperidine (F) and silver nitrate might provide additional insight into the reasons why this quasi Favorski reaction fails to produce any
Effect of Possible Transannular Nitrogen-Carbonyl Interaction upon the Course of the Quasi Favoraski Reaction

Effect of Possible Transannular Nitrogen-α-Carbon Interaction upon the Course of the Quasi Favoraski Reaction
rearrangement product. This reaction is depicted in Figure (B) and illustrates one of the possible paths by which 1-methyl-4(4-benzoyl-4-hydroxypiperidine (G) may be formed.

A series of α-bromopiperidyl phenyl ketones was conceived in which both the tranannular nitrogen-carbonyl and the transannular nitrogen-α-carbon interactions were prohibited due either to the restricted availability of the unshared electron pair of the nitrogen atom, or to a limitation in the size of the ring formed as the result of this interaction. These compounds were then subjected to the quasi Favorski reaction to ascertain whether or not transannular nitrogen participation was a definite factor in determining the course of the rearrangement, and to determine if one could utilize this reaction for the synthesis of nitrogen heterocyclic esters when this effect was eliminated.

The 1-benzyl-4-benzoyl-4-bromopiperidine (XVIII) was chosen for this study in hopes that the benzyl group, which could be readily introduced into the molecule as previously described, would provide sufficient steric interference to eliminate the transannular effect. This assumption was based on the investigation of Leonard and Oki (19), who had shown that the possibility of transannular nitrogen-carbonyl interaction diminishes as interference, due to the increasing bulk of the alkyl group attached to the nitrogen atom, increases, and this assumption was questionable only in regard to the actual active bulk of the benzyl group. The compounds of the 3-benzoylpiperidine series including 1-methyl-3-benzoyl-3-
bromopiperidine hydrobromide (XIX) were selected because no transannular nitrogen-carbonyl would be expected to occur in this system since the probability that a four membered ring would form is extremely low.

Both compounds, (XVIII) and (XIX), were allowed to react with sodium methoxide under conditions identical to those employed by Troscianiec (3) for the reaction of 1-methyl-4-benzoyl-4-bromopiperidine (F), and from each reaction mixture there was obtained a substituted azaspirooctane.

The treatment of these α-haloketones with aqueous silver nitrate, however, did not give rise to the formation of an α, β unsaturated ketone such as Troscianiec (3) obtained upon reaction of (F) with silver salts. In each case, the only product which could be isolated and characterized was the corresponding α-hydroxyketone. The extreme susceptibility of these α-bromoketones toward hydrolysis was demonstrated by neutralizing an aqueous solution of either 1-benzyl-4-benzoyl-4-bromopiperidine hydrobromide (XVIII) or 1-methyl-3-benzoyl-3-bromopiperidine hydrobromide (XIX) with sodium bicarbonate and then rapidly extracting the free base into ether and converting it into the quaternary salt by treatment with methyl bromide. Although the free base was exposed to hydrolyzing conditions for an extremely brief period, the quaternary salt which resulted was always that of the α-hydroxy-
ketone. In view of this result, it is not too surprising that the quasi Favorski reaction failed to produce any rearranged material. The hydrolysis of the $\alpha$-bromopiperidyl phenyl ketones in weakly basic media presumably involves the transannular displacement of the bromine by the electron pair of the nitrogen as depicted in Figure (B). When, however, the electron pair of the nitrogen is utilized in salt formation this mechanism becomes inoperative, but the susceptibility of the $\alpha$-carbon toward nucleophilic attack is enhanced due to the presence of another electronegative group in the molecule. Providing the backside of the $\alpha$-carbon is not sterically hindered, the three powerful electron withdrawing groups activate this site for nucleophilic substitution; therefore, treatment of either 1-benzyl-4-benzoyl-4-bromopiperidine hydrobromide (XVIII) or 1-methyl-3-benzoyl-3-bromopiperidine hydrobromide (XIX) with aqueous silver nitrate gave the corresponding $\alpha$-hydroxyketones because Mechanism A (shown in Figure A) is thus highly favored.

The results of these experiments also indicate that the possibility of transannular nitrogen-carbonyl interaction in the 1-benzyl-4-benzoyl-4-bromopiperidine (XVIII) series is quite remote since it does not appear likely that metathesis would occur when the molecule had assumed the bicyclic transition state (T). One could not be sure at this point whether the benzyl group was instrumental in preventing a transannular nitrogen-carbonyl interaction or if this effect just did not
exist in the 4-benzoylpiperidine series.

Two derivatives of 4-benzoyl-4-bromopiperidine were therefore prepared in which transannular interaction was unequivocally excluded: these were 1,4-dibenzoyl-4-bromo- piperidine (XXII) and 1,1-dimethyl-4-dibenzoyl-4-bromo- piperidinium bromide (XX). The corresponding compounds in the 3-benzoyl piperidine series were also prepared for purposes of comparison.

The reaction of (XXII) with silver nitrate in aqueous acetone gave an acidic fraction, which was characterized as the desired Favorski reaction product 1-benzoyl-4-phenyl- isonipecotic acid (XXIX), and an irresolvable mixture.

Repetition of this reaction using mercuric acetate as the catalyst gave a comparable yield of the acid (XXIX) and a mixture of solids from which some starting material could be recovered. When these reaction conditions were applied to 1,3-dibenzoyl-3-bromopiperidine (XXIII) no acidic product was obtained, but an α, β-unsaturated ketone (XXXII) and what appeared to be an isomeric ketone (XXXIIa) were isolated from the reaction mixture. The dehydrohalogenation of 1,3-dibenzoyl-3-bromopiperidine (XXIII) was accomplished by heating (XXIII) with piperidine and afforded an α, β-unsaturated ketone which was identical to the major product.
(XXXII) produced by means of the "modified" Favorski reaction. The infrared absorption spectrum of (XXXII) also suggests an \(\alpha, \beta\)-unsaturated ketone as it exhibited carbonyl absorption at 1663 cm\(^{-1}\) and absorption of a disubstituted amide at 1632 cm\(^{-1}\). Furthermore, this spectrum show medium bands at 1300 cm\(^{-1}\) and at 855 cm\(^{-1}\), frequencies characteristic of a tri-substituted ethylene. The position of the double bond, however, could not be established on the basis of the available evidence. The secondary reaction product (XXXIIa) was not fully characterized as it was formed in minor quantities, but its infrared absorption spectrum suggests that it is an unsaturated ketone isomeric with (XXXII).

Troschianiec (3) concluded that the results of his investigations concerning the reactions of 1-methyl-4-benzoyl-4-bromopiperidine (F) indicated that the preferred conformation of this molecule has the halogen equatorial, the benzoyl group axial and the carbonyl group and the carbon-bromine bond inclined at least 90° to each other so that these four atoms do not all lie in the same plane. Assuming that the replacement of the methyl group by a benzoyl radical, as was done in 1,4-dibenzoyl-4-bromopiperidine (XXII), does not alter the preferred conformation of the piperidine ring, then the success of the silver nitrate catalyzed Favorski reaction with (XXII) would indicate that the carbonyl group and the \(\alpha\)-bromine atom may assume a coplanar orientation. It has been established that the introduction of an \(\alpha\)-bromo substituent shifts the infrared carbonyl absorption to higher frequencies,
If the carbon-oxygen and carbon-bromine bonds are in the same plane, but it has little effect if they are not aligned in this manner (22). Examination of the infrared absorption spectra of the parent piperidyl phenyl ketones and those of the corresponding α-bromo derivatives should therefore establish whether or not the coplanar orientation of the carbonyl group and the bromine atom is possible. Inspection of the infrared absorption spectra of 1,4-dibenzoylpiperidine (XIII) and 1,4-dibenzoyl-4-bromopiperidine (XXII) reveals that carbonyl absorption in (XIII) occurs at 1670 cm⁻¹, and conversion of (XIII) into the α-bromo ketone, (XXII), causes the carbonyl band to shift to 1683 cm⁻¹. A comparison of the infrared absorption spectra of 1,3-dibenzoylpiperidine (XIV) and its α-bromo derivative, (XXIII), however, shows a difference of only 3 cm⁻¹ in the stretching frequencies of the ketonic carbonyl groups in going from (XIV) to (XXIII). Thus the coplanar orientation of the carbonyl group and bromine atom, which gives rise to the transition complex favoring rearrangement, appears to be justified by the comparatively large shift in the carbonyl absorption frequency in the case of the 4-benzoyl-piperidine derivative, but not in the 3-isomer.

The failure of 1,3-dibenzoyl-3-bromopiperidine to give a Favorski rearrangement may be accounted for on the basis of its inability to form the required transition complex, but the fact that no α-hydroxyketone was formed upon reaction of 1,3-dibenzoyl-3-bromopiperidine (XXIII) with aqueous silver nitrate requires some further explanation. The ease with
which (XXIII) is dehydrohalogenated leads to the conclusion that this molecule must possess a conformation in which the \( \alpha \)-bromine and adjacent hydrogen are both axial and coplanar. Such a spatial arrangement favors a bimolecular elimination in preference to a nucleophilic substitution, and would also account for the production of two isomer \( \alpha, \beta \)-ethylenic ketones as there are two axial hydrogens adjacent to the \( \alpha \)-bromine which may participate in a trans elimination. However, 1-methyl-3-benzoyl-3-bromopiperidine hydrobromide (X), which would be expected to have identical orientation of the \( \alpha \)-bromine and neighboring hydrogen, gave only the \( \alpha \)-hydroxyketone in a similar reaction. It must be assumed, therefore, that (XXIII) does not yield any \( \alpha \)-hydroxyketone because the two electron rich carbonyl oxygen atoms effectively screen the backside of the \( \alpha \)-carbon atom so that the displacement of the bromine by the nucleophile is prohibited.

The rearrangement of \( 4 \)-aryl-4-piperidinecarboxylic acid betaines has been reported to give an excellent yield of \( 4 \)-aryl-4-piperidinecarboxylic acid esters (23). In view of the success of the modified Favorski reaction in promoting the rearrangement of (XXII), it would seem reasonable to assume that this reaction, and subsequent thermal rearrangement of the expected betaine, could be applied to quaternary salts of \( \alpha \)-bromo-3-(and 4-)benzoylpiperidines and would provide a convenient synthesis of the corresponding piperidinecarboxylic acid esters.
The reaction of 1,1-dimethyl-4-benzoyl-4-bromopiperidinium bromide (XX) with aqueous silver nitrate produced a high melting solid (XXXIV) whose infrared absorption spectrum displayed intense absorption at 1640, 1370 and 1375 cm\(^{-1}\); frequencies which were interpreted as being characteristic of an ionized carboxyl group (24). A similar reaction with the 3-isomer (XXI) gave a sharp melting solid (XXXVII) whose infrared absorption spectrum was very nearly identical to that of (XXXIV). The attempted thermal rearrangement of these salts at 200–250\(^\circ\) led to almost complete carbonization of the material. In one instance, heating the product from the reaction of 1,1-dimethyl-4-benzoyl-4-bromopiperidine bromide (XX) with silver nitrate gave a very small amount of yellow oil which when recrystallized from ligroin melted in the range reported for methyl 1-methyl-4-phenylisonipecotate. However, the infrared absorption spectrum revealed that this material was 4-benzoylpyridine, and this was confirmed by a mixed melting point with an authentic sample. The mechanism by which 4-benzoylpyridine was formed defies explanation, but the significant fact of these experiments is the failure of the silver nitrate catalyzed rearrangement to occur with either of the quaternary salts.

Re-examination of the infrared absorption spectra of
both (XXXIV) and (XXXVII) indicates that both compounds are \( \alpha, \beta \)-unsaturates ketones. The 1640 cm\(^{-1}\) band displayed by both compounds may be assigned to the ketone and the shift in the frequency attributed to conjugation with the double bond. Although no absorption characteristic of a trisubstituted ethylene appears in the double bond stretching region, which is probably due to masking by the carbonyl group \((25)\), a sharp absorption band indicative of such an ethylene occurs in both spectra at 835 cm\(^{-1}\). The pronounced absorption at 1370 and 1325 cm\(^{-1}\) which is exhibited by both spectra and which was originally attributed to an ionized carboxyl, may be ascribed to an inorganic nitrate which is probably the anionic part of the quaternary salt \((24)\).

No shift in the carbonyl infrared absorption frequency is noted upon examination of the infrared spectra of either 1-methyl-4-benzoylpiperidine methobromide (XVI) and its \( \alpha \)-bromo derivative (XX) or those of the corresponding pair of 3 isomers, (XVII) and (XXI). It would appear, therefore, that the transition complex which would lead to the formation of a betaine is not favored in either case, so that the only modes of reaction available are dehydrohalogenation or nucleophilic substitution. In both (XX) and (XXI) the preferred orientation would appear to be that in which the \( \alpha \)-bromine is axial and the benzoyl group is equatorial. This spatial arrangement of the \( \alpha \)-bromine and the adjacent hydrogen atoms is one which favors a trans elimination. Conceivably the axial methyl group, the axial hydrogen atoms and the oxygen
atom of the carbonyl group could screen the backside of the \(\alpha\)-carbon against attack by the nucleophile and thereby prevent metathesis from occurring in either case. The boat conformation is depicted for 1,1-dimethyl-3-benzoyl-3-bromo-piperidinium bromide (XXI) because it seems reasonable to assume that the steric interference, which occurs between the groups located in the 1,3 positions, would be less pronounced in this arrangement than it would be in the normally strainless chair conformation.

\[
\begin{align*}
\text{Consideration of all these results prompted a re-examination of the reduction which led Leone (8) to propose that transannular nitrogen-carbonyl interaction may occur in the 4-benzoylpiperidine series. Repetition of the reduction of either the hydrochloride or the methobromide of 1-methyl-4-benzoylpiperidine by low pressure hydrogenation over Adams catalyst established that the carbonyl group was being reduced, although sluggishly, to the corresponding carbinol. Based on this consideration, it must be concluded that the existence of a transannular nitrogen-carbonyl interaction is extremely doubtful in the case of the \(\alpha\)-halo piperidyl phenyl ketones as this interaction does not appear to exert any influence upon the reactions of the parent, non-halogenated 4-benzoylpiperidines. Any interpretation of the}
\end{align*}
\]
reaction of the various α-bromopiperidyl phenyl ketones with aqueous silver nitrate based upon this effect, as was done 1-methyl-4-benzoyl-4-bromopiperidine (F), does not appear to be justifiable. The ease with which 1-benzyl-4-benzoyl-4-bromopiperidine hydrobromide (XVIII) or 1-methyl-3-benzoyl-3-bromopiperidine hydrobromide (XIX) is hydrolyzed upon conversion to the free base indicates that a transannular nitrogen-α-carbon interaction of the type proposed by Archer (20) is quite influential in determining the course of the reaction of α-bromopiperidyl phenyl ketones with nucleophilic reagents. When this effect was eliminated by limiting the availability of the electron pair of the nitrogen through salt or amide formation, the α-bromopiperidyl phenyl ketone derivatives were found to react, generally, in the manner of the analogous alicyclic compounds. Rearrangement of the various α-bromopiperidyl phenyl ketone could not be promoted by the use of silver nitrate except in the case of 1,4-dibenzoyl-4-bromopiperidine (XXII), and presumably the success of this quasi Favorski depends mainly upon the geometrical arrangement of the carbon-bromine and carbon-oxygen bonds (6a). The utilization of this rearrangement for the synthesis of heterocyclic esters of the Demerol type does not appear to be profitable in view of the impractically small yield of the intermediate acid that was obtained.

Reactions of the Epoxyethers

The facile conversion of either 1-benzyl-4-benzoyl-
4-bromopiperidine hydrobromide (XVIII) or 1-methyl-3-benzoyl-3-bromopiperidine hydrobromide (XIX) to the corresponding axaspirooctane provided a reactive intermediate which could be cleaved by organic acids to yield either 4,4 or 3,3 disubstituted piperidines, respectively. Previously, 2-methoxy-6-methyl-2-phenyl-1-azaspiro[2,5]octane (H) had been converted by reaction with various carboxylic acids into a series of esters of 1-methyl-4-benzoyl-4-hydroxypiperidine (I) which contained the same grouping, and aromatic acid esterified with a tertiary amino alcohol, that is present in the cocaine molecule and which is believed to be the anesthesiphoric center (26,27). Furthermore, these esters were similar in structure to derivatives of 4-piperidinol such as 1-methyl-4-hydroxy-4-phenylpiperidyl propionate which are known to have a high analgesic potency (26).

Consequently, interest developed in the potential pharmaceutical activity of this class of compounds and led to a series of tests to determine the extent of their local
anesthetic action. Although some of the compounds tested were relatively inactive, certain of them displayed potent local anesthetic activity. Interest in this class of compounds, and the availability of the intermediate, 6-benzyl-2-methoxy-2-phenyl-6-axaspiro [2,5] octane (XXIV) therefore prompted the synthesis of a second series of 4-piperidinol esters. The ring opening of this epoxyether was accomplished in the manner previously employed and led to the formation of 4,4-disubstituted piperidines.

The preparation of 1-methyl-3-benzoyl-3-hydroxy-piperidine (XLIII) was accomplished by treatment of 5-methyl-2-methoxy-2-phenyl-5-azaspiro [2,5] octane (XXVII) with dilute hydrochloric acid. As esterification of this tertiary

\[ \text{HCl} \quad \text{H}_2\text{O} \]

3-piperidinol would lead to the formation of the same anesthesiophoric group present in cocaine or in the esters previously prepared, two esters of this alcohol were prepared and were submitted for preliminary screening along with the hydroxyketone (XLIII). The results of these tests indicated that 1-methyl-3-benzoyl-3-piperidyl benzoate hydrochloride (XLV) was effective as a hypotensive agent as well as a local anesthetic. A crude comparison of the structure of (XLV) with that of 1-phenyl-1-benzoyloxy-2-diethylaminopropane (J)
and 2-(N-methyl-N-propyl)-aminopropiophenone (K) may provide some insight into the overlapping pharmacological properties exhibited by this 3-piperidyl benzoate (26,27).

Each of these compounds may be considered as a derivative of β-phenylethylamine and on this basis could be related to (-) ephedrine, a known vasopressor (25). Benzoylation of the alcoholic hydroxyl group of the β-phenyl-ethanol amine as was done to give (J), the local anesthetic Allocaine, destroys this pressor activity. In (K) the secondary alcohol has been oxidized to a ketone and this compound has been reported to show hypertensive activity. Examination of (XLV) indicates that both of these structural features have been incorporated in this molecule with only
minor variation so that one might expect both pharmacological effects.

As one of the most effective potent hypotensive agents, \( \alpha-(\text{isopropylaminomethyl})-3,4\text{-dihydroxybenzyl alcohol} \) has hydroxyl groups meta and para to the side chain, it was interesting to speculate what effect the introduction of a phenolic group would produce on the activity of \( 1\text{-methyl-3-benzoyl-3-piperidyl benzoate (XLV).} \) Since the preparation of a group of esters having the phenolic hydroxyl on the ketonic ring was too laborious to contemplate, a sequence of compounds was produced by varying the position of the hydroxyl group in the acid used to cleave the epoxyether. The results of the pharmacological screening of the compounds thus prepared were not available at the time of this writing.

One of the characteristic reactions of epoxyethers observed by Stevens (28) is the acid catalyzed rearrangement which results in the formation of the corresponding methoxy ketone. Presumably this rearrangement would also take place when \( 1\text{-benzyl-2-methoxy-2-phenyl-1-ox-6-axaspiro (2,5) octane (XXVIII), a nitrogen heterocyclic analog of (L), was allowed} \)
to react with anhydrous magnesium bromide under similar conditions. It is of interest to note that these reaction conditions caused the precipitation of the epoxyether (XXVIII) as an ether insoluble salt and that the only product which could be isolated from the resulting mixture was 1-benzyl-4-benzoyl-4-hydroxypiperidine (XXXVIIIa). Repetition of this reaction using boron trifluoride etherate as the catalyst and nitromethane as the solvent did not give rise to any precipitate, but even though the reaction mixture was decomposed under reasonably anhydrous conditions, the product was, once again, the hydroxyketone (XXXVIIIa).

These results are in agreement with the observations Troscianiec made concerning the acid catalyzed ring opening of an epoxyether containing a basic nitrogen: coordination of the basic nitrogen with the Lewis acid does not prevent, as Stevens had postulated for the amino epoxyether, 1-phenyl-1-(2-dimethylamino)-ethoxy-2-methyl-1,2-epoxypropane, further approach of a proton to catalyze the ring-opening reaction.
EXPERIMENTAL

Infrared Absorption Spectra. The infrared absorption spectra were determined using a Perkin-Elmer Model 21 infrared spectrophotometer with sodium chloride optics at settings of: resolution, 927; response, 1; gain, 5; speed, 4.6; suppression, 0; scale, standard. The spectra of solids were determined as mulls in series 11-14 Halocarbon oil from 1300-4000 cm\(^{-1}\) and in Nujol from 650 to 1300 cm\(^{-1}\), or as a single mull in Nujol alone unless designated otherwise. All bands were strong except those indicated weak (W) or medium (M), and the location of the bands is given in frequency units, cm\(^{-1}\).

Ultraviolet Absorption Spectra. The ultraviolet absorption spectra were determined using a Perkin-Elmer Model 4000 recording spectrophotometer. The spectra were determined in 95% ethanol, and the wavelength is given in millimicrons (\(\text{mm}\))

Analytical Data. Microanalyses were determined by Dr. G. Weiler and Dr. F. B. Strauss of Oxford, England, and by Galbraith Microanalytical Laboratory, Knoxville, Tennessee.

Preparation of the Starting Materials

Benzoylpyridines.

(a) 4-Benzoylpyridine. This ketone was obtained from the Reiley Tar and Chemical Company.

(b) 3-Benzoylpyridine (I). To 123 g. (1 mole) of nicotinic acid in a three-necked apparatus was added 500 ml.
of thionyl chloride over a period of 30 minutes. The mixture was heated under reflux for 2 hours, and then the excess thionyl chloride was removed by distillation. After most of the thionyl chloride had been removed by distillation, 200 ml. of anhydrous benzene was added, the mixture was cooled in an ice–water bath, and 330 g. of aluminum chloride was added with stirring over a period of 1 hour. The reaction mixture was heated under reflux for 6 hours and then was poured into a 4 liter beaker filled with crushed ice and 200 ml. of concentrated hydrochloric acid. The resulting mixture was poured into a 4 liter separatory funnel, and the aqueous layer was withdrawn and extracted with ether. The combined ether extracts and the benzene layer were discarded, and the aqueous layer was made strongly basic with sodium hydroxide. The oil which separated was removed by decantation and distilled under reduced pressure to give 141 g. (77.2%) of 3–benzoylpyridine (I), b.p. 143–145°/2mm, lit. (9) 141–145°/2mm.

The picrate and hydrochloride (II) of 3–benzoylpyridine were prepared by standard procedures to give solid derivatives, m.p. 160–162°, lit. (9) 162–163°; and m.p. 166–169°, lit. (19) 165–166° respectively.

Preparation of 3 and 4–Benzoylpyridine Quaternary Salts.

(a) Preparation of 1 Benzyl–4–benzoylpyridinium Chloride (III). A solution of 18.3 g. (0.1 mole) of 4–benzoylpyridine and 12.6 g. of benzyl chloride in 200 ml. of methanol was heated under reflux for 12 hours. The solution was concentrated on the
steam bath and on standing crystallized to give 24.6 g. (82%) of 1-benzyl-4-benzoylpyridinium chloride, m.p. 186-188°.

Anal. Calcd. for C_{13}H_{16}ClNO: Cl, 11.45. Found: Cl, 11.73, 11.00.

(b) Preparation of 1-β-Phenethyl-3-benzoylpyridinium Bromide (IV). In the manner described previously, 18.3 g. of 3-benzoylpyridine (I) and 20 g. of β-phenethyl bromide gave 33 g. of 1-β-phenethyl-3-benzoylpyridinium bromide (IV), m.p. 147-149°.


(c) Preparation of 1-Methyl-3-benzoylpyridinium Bromide (V). A mixture of 182.2 g. of 3-benzoylpyridine (I) and 100 g. of methyl bromide in 350 ml. of isopropyl alcohol was allowed to stand at room temperature for 24 hours in a tightly stoppered flask. The precipitated solid was collected by filtration and washed with ether to give 271 g. (96%) 1-methyl-3-benzoylpyridinium bromide (V), m.p. 146-148°.

UV spectrum (λ max. (log Ε)): 266(3.57).

Anal. Calcd. for C_{13}H_{15}BrNO: Br, 28.73. Found: Br, 28.69, 28.85.

Preparation of 3 and 4-Piperidylphenylcarbinols.

(a) Preparation of 1-Benzyl-4-piperidylphenylcarbinol Hydrochloride (VI). A solution of 15 g. (0.049 mole) of 1-benzyl-4-benzoylpyridinium chloride (III) in 200 ml. of methanol was shaken with 0.3 g. of platinum oxide at an initial hydrogen pressure of 50 p.s.i. After the absorption
of hydrogen ceased, the filtrate was concentrated under reduced pressure. Addition of anhydrous ether caused the precipitation of a white, crystalline solid which was recrystallized from isopropyl alcohol to give 14.8 g. (90%) of 1-benzyl-4-piperidylphenylcarbinol hydrochloride (VI), m.p. 184–185°.

Anal. Calcd. for C_{19}H_{24}ClNO: Cl, 11.20. Found: Cl, 11.75, 11.77.

Neutralization of an aqueous solution of (VI) gave a quantitative yield of 1-benzyl-4-piperidylphenylcarbinol (VII), m.p. 114–115.5°.

Anal. Calcd. for C_{19}H_{23}NO: C, 81.2; H, 8.19. Found: C, 80.98; H, 8.32.

IR spectrum (mull, No. 740): 3480, 1380, 973, 785, 762, 693.

(b) **Preparation of 4-Piperidylphenylcarbinol (VIII).** Similarly, the reduction of 10 g. of 4-benzoylpyridine hydrochloride, m.p. 194–197°, lit. (14) 195–197°, gave 9.1 g. (86%) of 4-piperidylphenylcarbinol hydrochloride (VIIIa), m.p. 190–193°, lit. (14) 191–193°. An aqueous solution of (VIIIa) which was basified by the addition of solid sodium hydroxide quantitatively furnished 4-piperidylphenylcarbinol (VIII), m.p. 162–164°, lit. (24) 166–167°.

(c) **Catalytic Hydrogenation of 1-Methyl-2-benzoylpyridinium Bromide (V).** A solution of 54 g. (0.2 mole) of (V) in 300 ml. of methanol was shaken with 0.6 g. of platinum oxide at an initial hydrogen pressure of 50 p.s.i. After the
absorption of hydrogen ceased, about 24 hours, the catalyst was removed from the solution by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residual solid was dissolved in water, and the resulting solution basified by the addition of solid sodium hydroxide and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, and after evaporation of the ether, a yellow oil remained. Distillation of this oil gave 27 g. of product (IX) b.p. 146-152°/4mm. This material was oxidized directly without further purification.

Preparation of 3 and 4-Benzoylpiperidines.

(a) Preparation of 1-Methyl-3-benzoylpiperidine Hydrobromide. To 25 g. (0.122 mole calculated on the basis of 1-methyl-3-piperidylphenylcarbinol) of the oil (IX) dissolved in 200 ml. of glacial acetic acid was added a solution of 9 g. (0.09 mole) of chromium trioxide in 100 ml. of 80% acetic acid. The resulting solution was heated on the steam bath for 1 hour, and then the solvent was removed by distillation under diminished pressure. The residue was dissolved in 400 ml. of chloroform, and this solution was saturated with anhydrous hydrogen bromide. After removal of the chloroform, the residue was recrystallized twice from isopropyl alcohol to give 22.6 g. (39.6% overall) of 1-methyl-3-benzoylpiperidine hydrobromide (X), m.p. 128-131°.


IR spectrum (mull, No. 296): 3490, 3430, 2940, 2640,
2770, 1675, 1475, 1455, 1280(m), 775(m), 700.

UV spectrum (λmax. (log e)): 248(4.01), 279(3.42), 317(3.06).

Neutralization of an aqueous solution of (X) quantitatively furnished the base, 1-methyl-3-benzoylpiperidine, (Xa), b.p. 160–165°/4mm.; N\text{D} 1.5410; lit. (9) b.p. 107–109°/1mm.; N\text{D} 1.5418. The picrate of (Xa) was prepared by standard methods and melted at 192–194°; lit. (22) 193–194°. Treatment of (Xa) with phenyl lithium gave 1,1-diphenyl-3-(1-methylpiperidyl)methanol, m.p. 145–146°; lit. (9) 145–146°.

IR spectrum (film, No.299): 3080(w), 3030(w), 2920, 1675, 1470, 1455, 1265, 770(m), 705.

(b) Preparation of 1-Benzyl-4-benzoylpiperidine Hydrobromide (XI). The oxidation of 17 g. (0.062 mole) of 1-benzyl-4-piperidylphenylcarbinol (VII) by 4.1 g. (0.04 mole) of chromium trioxide was accomplished in glacial acetic acid in the manner previously described. The reaction proceeded to give 15 g. (68.7%) of 1-benzyl-4-benzoylpiperidine hydrobromide (XI), m.p. 237–238°.

Anal. Calcd. for C\textsubscript{19}H\textsubscript{22}BrNO: Br, 22.18. Found: Br, 21.84, 22.05.

UV spectrum (λmax. (log e)): 245(4.14), 278(2.96).

(c) Preparation of 1,4-Dibenzoylpiperidine (XIII). A 4 g. (0.02 mole) sample of 4-piperidylphenylcarbinol (VIII) was oxidized in glacial acetic acid with 1.5 g. (0.015 mole) of chromium trioxide in the manner described for the synthesis of (X). The reaction gave 3.2 g. (59.2%) of 4-benzoylpiperi-
dine hydrochloride (XII), m.p. 227–228°. The free base, 4-benzoylpiperidine, was obtained by neutralizing an aqueous solution of (XII).

UV spectrum (λmax. (log ε)): 241(4.10), 276(3.12).
Anal. (XII) Calcd. for C10H16ClNO: Cl, 15.70.
Found: Cl, 15.48, 15.67.

A 42 g. (0.185 mole) sample of 4-benzoylpiperidine hydrochloride (XII) was dissolved in 200 ml. of water, and this solution was basified by the addition of 20 g. (0.5 mole) of solid sodium hydroxide. To the stirred mixture 25 g. (0.18 mole) of benzoyl chloride was added over a period of 30 minutes. The resulting mixture was stirred at high speed for 3 hours, and then the precipitated solid was collected by filtration and recrystallized from aqueous alcohol to give 38.2 g. (64.5%) of 1,4-dibenzoylpiperidine (XIII), m.p. 105–108°.

Anal. Calcd. for C10H16ClNO: C, 77.64; H, 6.49
Found: C, 76.95; H, 6.56.

IR spectrum (mull, No. 494): 1670, 1635, 1470, 1452, 1380, 1280, 1265, 1215, 790(m), 750(m), 717(m), 700.

(d) Preparation of 1,3-Dibenzoylpiperidine (XIV).
An 8 g. (0.035 mole) sample of 3-benzoylpiperidine hydrochloride (1a) was benzoylated in the same manner as was described for the 4- isomers. The crude solid obtained from the reaction was recrystallized from ligroin to give 7.1 g. (71%) of 1,3-dibenzoylpiperidine (XV), m.p. 92–94°.
Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{NO}_2$: C, 77.84; H, 6.49.

Found: C, 77.33; H, 6.78.

IR spectrum (double mull, No. 491): 2940, 2870, 1670, 1635, 1450, 1310, 1275, 1218, 1092, 770, 748, 706, 700.

(e) Preparation of 1,1-Dimethyl-4-benzoylpiperidinium Bromide (XVI). A solution containing 20 g. (0.07 mole) of 1-methyl-4-benzoylpiperidine hydrobromide*, m.p. 208–210°, was made alkaline by the addition of solid sodium hydroxide and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, cooled by means of an ice-bath and saturated with anhydrous methyl bromide. This solution was allowed to stand in a tightly stoppered flask for 24 hours, and then the precipitated salt was collected by filtration and recrystallized from isopropyl alcohol to give 16.7 g. (79.5%) of 1,1-dimethyl-4-benzoylpiperidinium bromide (XVI), m.p. 206–212°.

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{BrNO}$: Br, 26.91. Found: Br, 27.13, 27.70.

IR spectrum (double mull, No. 549): 1678, 1580(m), 1260, 792(w), 775(w), 712(m), 702.

(f) Preparation of 1,1-Dimethyl-3-benzoylpiperidinium Bromide (XVII). In the same manner 10.2 g. (0.036 mole) of 1-methyl-3-benzoylpiperidine hydrobromide (X) was converted to 10.8 g. (94%) of 1,1-dimethyl-3-benzoylpiperidinium bromide (XVII), m.p. 108–111° (resolidifies and melts again 201–203°).


* Supplied by S. A. Leone
Bromination of 3 and 4-Benzoylpiperidines.

(a) Preparation of 1-Benzyl-4-benzoyl-4-bromo-piperidine Hydrobromide (XVIII). To a solution of 12 g. (0.03 mole) of 1-benzyl-4-benzoylpiperidine hydrobromide (XI) in 200 ml. of chloroform was added 4 ml. (0.06 mole) of bromine. The resulting solution stood at room temperature for 24 hours, and then the solvent was evaporated under reduced pressure. The residue was dissolved in methanol and treated with phenol to destroy any excess bromine or perbromide. The addition of ether to the alcoholic solution caused the precipitation of a white solid which was collected by filtration and recrystallized from isopropyl alcohol to give 13 g. (88%) of 1-benzyl-4-benzoyl-4-bromopiperidine hydrobromide (XVIII), m.p. 162-164°.

Found: Br, 18.29.

(b) Preparation of 1-Methyl-3-benzoyl-3-bromo-piperidine Hydrobromide (XIX). A solution of 15.1 g. (0.055 mole) of 1-methyl-3-benzoylpiperidine (Xa) in 150 ml. of chloroform was treated with 8 ml. (0.13 mole) of bromine and was allowed to stand overnight at room temperature. Isolation of the product in the manner described for (XVIII) gave 15.3 g. (56.2%) of 1-methyl-3-benzoyl-3-bromopiperidine hydrobromide (XIX), m.p. 142-144°.
Anal. Calcd. for C₁₈H₁₇Br₃NO: Br, 22.22 (ionic).

Found: Br, 22.38, 22.18.

(c) Preparation of 1,1-Dimethyl-4-benzoyl-4-bromo-
piperidinium Bromide (XX). A 15 g. (0.05 mole) sample of
1,1-dimethyl-4-benzoylpiperidinium bromide (XVI) and 6 ml.
(0.11 mole) of bromine were dissolved in 300 ml. of chloro-
form, and the resulting solution was allowed to stand at room
temperature for 24 hours. In the manner previously cited, 1,
1-dimethyl-4-benzyl-4-bromopiperidinium bromide (XX), m.p. 168-
169°, was isolated from the reaction mixture in 84% yield
(16.1 g.).

Anal. Calcd. for C₁₄H₁₈Br₃NO: Br, 21.2 Found:  
Br, 21.27, 21.53.

IR spectrum (mull, No. 549): 1678, 1260, 712, 702.

(d) Preparation of 1,1-Dimethyl-3-benzoyl-3-bromo-
piperidinium bromide (XXI). A chloroform solution of 9.86 g.
(0.032 mole) of 1,1-dimethyl-3-benzoylpiperidinium bromide
(XVII) and 6 ml. of bromine was allowed to stand at room
temperature for 24 hours. From this reaction there was ob-
tained, as before, 5.4 g. (48%) of 1,1-dimethyl-3-benzoyl-3-
bromopiperidinium bromide (XXI), m.p. 128-130°.

Anal. Calcd. for C₁₄H₁₈Br₃NO: Br, 21.2. Found:
Br, 20.81, 21.20.

IR spectrum (mull, No. 643): 1675, 1350, 1260, 763,
707.

(e) Preparation of 1,4-Dibenzoyl-4-bromopiperidine
(XXII). A suspension of 42 g. (0.14 mole) of 1,4-dibenzoyl-
piperidine (XIII) in 300 ml. of chloroform was treated with 15 ml. of bromine, and the resulting mixture was allowed to stand at room temperature overnight. The solvent was removed by evaporation under reduced pressure, and the residue was dissolved in 300 ml. of ether. The ethereal solution was washed with sodium thiosulfate solution and then with water. After drying the solution over anhydrous calcium sulfate, the solvent was removed by evaporation, and the residue was re-crystallized from isopropyl alcohol to give 27 g. (52%) of 1,4-dibenzoyl-4-bromopiperidine, m.p. 108–109.5°.


IR spectrum (mull, No. 755): 1682, 1380, 1285(m), 1250(m), 705, 695.

(f) Preparation of 1,3-Dibenzoyl-3-bromopiperidine (XXIII). A solution of 7 g. (0.023 mole) of 1,3-dibenzoyl-piperidine (XIV) in 100 ml. of glacial acetic acid was treated with 4 ml. of bromine, heated on the steam bath for 4 hours, and then poured into 200 ml. of water. The aqueous solution then was extracted with chloroform, and the chloroform extract was washed with a solution of sodium thiosulfate and then with water. After drying the chloroform solution over anhydrous calcium sulfate, the solvent was removed by evaporation under reduced pressure, and the residue was re-crystallized from ligroin to give 3.8 g. (47%) of 1,3-dibenzoyl-3-bromopiperidine (XXIII), m.p. 106–109°.

IR spectrum (mull, No. 756): 1672, 1605, 1385(m),
1285(m), 1250(m), 710, 703.

Reactions of 1-Benzyl-4-benzoyl-4-bromopiperidine Hydro-
Bromide (XVIII).

(a) With Silver Nitrate. To a solution of 3.5 g.
(0.08 mole) of (XVIII) in 100 ml. of water was added 4 g. of
silver nitrate. This mixture was heated on the steam bath 4
hours, and the insoluble salts were removed by filtration.
The filtrate was acidified by the addition of concentrated
hydrochloric acid. After removal of the insoluble silver
chloride, the filtrate was evaporated to dryness under
pressure, and the residue was recrystallized twice from iso—
propyl alcohol to give 1.8 g. (72%) of 1-benzyl-4-benzoyl-4—
hydroxypiperidine hydrochloride, m.p. 185-187°. The melting
point of this material was not depressed when mixed with an
authentic sample of 1-benzyl-4-benzoyl-4—hydroxypiperidine
(XXXVIII).

IR spectrum (mull, No. 663): 3240, 2650, 2570, 1678,
1380, 1265(m), 725(m), 700.

(b) With Sodium Methoxide in Methanol. To a solution
of 13.5 g. (0.25 mole) of sodium methoxide in 150 ml. of
methanol was added 11 g. (0.027 mole) of (XVII) dissolved in
350 ml. of hot methanol. The stirred mixture was heated under
reflux for 4 hours, and the solvent was partially removed by
distillation. The residue was dissolved in water, and this
solution was extracted with three 75 ml. portions of ether.

After drying the ether extracts over anhydrous calcium sulfate, the solvent was removed by evaporation, and the residue was distilled under pressure to give 3.5 g. (45%) of 6-benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2,5]octane, b.p. 170-175°/2 mm., \( \Delta^0 \) 1.5560.

Anal. Calc. for C\(_{20}\)H\(_{24}\)NO: C, 77.7; H, 7.46.

Found: C, 77.60, 77.78; H, 7.39, 7.53.

Reactions of 1-Methyl-3-benzoyl-3-bromopiperidin Hydrobromide (XIX).

(a) With Silver Nitrate. To a solution of 7.2 g. (0.02 mole) of (XIX) in 50 ml. of methanol was added 7 g. of solid silver nitrate and 20 ml. of water. The mixture was heated under reflux for 4 hours, and the insoluble salts then were removed by filtration. After the alcohol had been removed by evaporation under reduced pressure, the residue was dissolved in water, and this solution was acidified with concentrated hydrochloric acid. The insoluble silver chloride was removed by filtration; the filtrate was basified and extracted with ether. After drying the ether extract over anhydrous calcium sulfate, the solvent was removed by evaporation, and the residue was distilled at reduced pressure to give 2.2 g. of (XXV), b.p. 135-140°/2 mm.; equivalent weight 210±5 by titration with 1/10 N sodium hydroxide.

The picrate of (XXV) was prepared by conventional methods and melted at 171-172°. This melting point was not depressed when (XXV) was mixed with the picrate of an
authentic sample of 1-methyl-3-benzoyl-3-hydroxypiperidine.

IR spectrum (film, No. 255): 3500(b), 2930, 2760, 1675(m), 1470, 1455, 1270, 1230, 1150, 1140, 1070, 780, 705.

(b) With Sodium Methoxide in Benzene. An aqueous solution of 7.2 g. (0.02 mole) of (XIX) was basified by the addition of solid sodium carbonate and extracted with two 50 ml. portions of benzene. The benzene extract, after drying over anhydrous sodium sulfate, was treated with 10 g. of sodium methoxide, and this mixture was heated under reflux for 3 hours. The insoluble salts were removed by filtration, and the solvent was removed by distillation. The residue was distilled under reduced pressure to give 3.2 g. of oil (XXVI), b.p. 135-140°/2mm. The picrate of (XXVI) was prepared by standard methods and melted 171-172°. The melting point of this derivative was not depressed when it was mixed with the picrate of an authentic sample of 1-methyl-3-benzoyl-3-hydroxypiperidine (XLIII).

IR spectrum (film, No. 254): 3500(b), 2930, 2760, 1675(m), 1470, 1455, 1270, 1230, 1150, 1075, 780(m), 745(m), 705.

(c) With Methyl Bromide. An ethereal solution of the base from (XIX) was obtained as described previously, and, after drying, it was diluted with 100 ml. of isopropyl alcohol. The resulting solution was cooled in an ice-bath, and an excess of anhydrous, liquid methyl bromide was added. This mixture was allowed to stand at room temperature for 12 hours,
and then the crystalline solid was collected by filtration
and recrystallized from isopropyl alcohol to give 2.5 g.
(42%) of 1,1-dimethyl-3-benzoyl-3-hydroxy-piperidinium bromide
(XXVII), m.p. 186–188°.

Anal. Calcd. for C_{16}H_{16}BrNO_{3}: Br, 25.50. Found:
Br, 24.97, 25.43.

IR spectrum (mull, No. 519): 3440, 3200, 1665, 1255,
1187, 995, 775(m), 705, 660.

(d) With Sodium Methoxide in Methanol. A solution
of 20.5 g. (0.056 mole) of (XIX) was added to a hot solution
of 13.5 g. (0.25 mole) of sodium methoxide in 150 ml. of
methanol. This mixture was heated under reflux with mechanical
stirring for 6 hours, and the solvent was partially removed by distillation. To the residue was added 200 ml. of
water, and the resulting solution was extracted with three
100 ml. portions of ether. After drying the ether over anhydrous calcium sulfate, the solvent was removed by evaporation, and the residue was distilled at reduced pressure to
give 4.2 g. (33%) of 2-methoxy-5-methyl-2-phenyl-1-ox-5-aza-
spiro 2,5 octane (XXVIII), b.p. 117–119°/2mm.

Anal. Calcd. for C_{16}H_{16}NO_{3}: C, 72.07; H, 8.21.
Found: C, 72.14, 72.21; H, 8.30, 8.18.

IR spectrum (film, No. 404): 2935, 2770, 1465, 1450,
1275, 1225, 1145, 1135, 1100, 1075, 780, 778, 700.

Reactions of 1,4-Dibenzoyle-4-bromopiperidine (XXII).

(a) With Silver Nitrate in Aqueous Acetone. To a
solution of 3 g. (0.009 mole) of (XXII) in 50 ml. of acetone was added 2 g. of silver nitrate and 50 ml. of water, and the resulting mixture was heated under reflux for 12 hours. After the insoluble salts were removed by filtration, the filtrate was poured into 150 ml. of water, and this solution was extracted with four 50 ml. portions of ether. The ethereal solution then was extracted with two 125 ml. portions of a saturated sodium carbonate solution, and this basic extract was neutralized by the addition of dilute hydrochloric acid. The precipitated solid was collected by filtration and recrystallized from ligroin to give 0.4 g. (15%) of 1-benzoyl-4-phenylisonicotinic acid (XXIX), m.p. 191-193°, neutral equivalent 320 ± 5.

Anal. Calcd. for C_{19}H_{18}N_{3}O_{3}: C, 73.8; H, 6.15.
Found: C, 74.21; H, 6.32.

IR spectrum (mull, No. 204): 3200(b), 2800(b), 1715, 1610, 1590, 1578, 1305, 1232, 782(w), 750(m), 722(m), 695(m).

This reaction was repeated using 3.7 g. (0.01 mole) of (XXII) dissolved in 40 ml. of t-butyl alcohol and 10 ml. of water. To this solution was added 2 g. of solid silver nitrate. Isolation of the product in the manner described previously gave 0.7 g. (23%) of (XXIX), m.p. 191-193°. The reaction of 2.0 g. (0.009 mole) of (XXII) with 2.5 g. of mercuric acetate in 50 ml. of aqueous acetate gave 0.35 g. (12%) of (XXIX), m.p. 191-193°.

(b) With Sodium Methoxide in Methanol. A solution of 25 g. of (XXII) in 200 ml. of methanol was added to 40 g.
of sodium methoxide dissolved in 350 ml. of methanol. This mixture was heated under reflux for 5 hours, and then the solvent was removed partially by distillation. The residue was dissolved in water, and this mixture was extracted with three 100 ml. portions of ether. After drying the ether extract over anhydrous calcium sulfate, the solvent was removed by evaporation, but all attempts to distill the residue under reduced pressure failed. Finally the residue was dissolved in hot petroleum ether, and the insoluble material was collected by filtration, to give 7.2 g. (34.6%) of 1,4-dibenzoyl-4-hydroxypiperidine, m.p. 186-188° (XXX).

Anal. Calcd. for C_{l0}H_{16}N_{0.5}: C, 73.80; H, 6.15.

Evaporation of the filtrate from (XXX) gave 14 g. of red oil (XXXI) which did not crystallize. It was used without further purification.

Reactions of 1,3-Dibenzoyl-3-bromopiperidine (XXIII).

(a) With Silver Nitrate in Aqueous Acetone. To a solution of 3.8 g. (0.01 mole) of (XXIII) in 100 ml. of 60% acetone was added 2 g. of silver nitrate in 10 ml. of water. This solution was heated under reflux for 12 hours, and then the insoluble material was removed by filtration. The filtrate was poured into 250 ml. of water. This solution was extracted with three 50 ml. portions of ether, and the ethereal solution in turn was extracted with two 75 ml. portions of a saturated sodium carbonate solution. Neutralization of this basic solution failed to yield any material.
The ethereal solution, after drying, was evaporated to dryness and the residue was recrystallized from ligroin to give 1.3 g. (44.5%) of 1,3-dibenzoyl-(1,4,5,6)-tetrahydropyridine (XXXII), m.p. 125–128°.

Anal. Calcd. for C_{14}H_{14}NO: C, 78.40; H, 5.85.

Found: C, 77.85, 78.00; H, 5.86, 5.78.

IR spectrum (double mull, No. 14-07): 1663(m), 1632(m), 1602, 1575(m), 1383(m), 1300, 1265, 1255, 1175, 1105, 715, 700, 698.

The ligroin filtrate from (XXXII) was evaporated, and the residue was recrystallized from isopropyl alcohol to give 0.3 g. of (XXXIIa), m.p. 198–201°.

IR spectrum (mull, No. 509): 1680(sh), 1658, 1568, 1300(m), 1270(m), 750(w), 720(w), 702(m).

(b) With Piperidine in Benzene. A 1.5 g. (0.004 mole) sample of (XXIII) was dissolved in 50 ml. of benzene and to this solution was added 5 ml. of piperidine. This solution was heated under reflux for 4 hours, and then the insoluble material was collected by filtration to give 0.52 g. (79%) of piperidine hydrobromide, m. p. 232–234°, lit. (29) 234–235°.

The benzene filtrate was washed with water, and the solvent was removed by distillation. Recrystallization of the residue from ligroin gave 0.6 g. (60%) of (XXXII), m. p. 125–128°. The melting point of this material was not depressed when mixed with (XXXII).

(c) With Sodium Hydroxide in Benzene. To a solution of 2 g. of (XXIII) in 50 ml. of benzene was added 4 g. of
powdered sodium hydroxide, and this mixture was heated under reflux for 4 hours and then was poured into 50 ml. of water. The benzene layer was separated, and the solvent was removed by distillation. The residue was triturated with a saturated sodium bicarbonate solution, and the insoluble layer was decanted from the basic solution.

The bicarbonate layer was acidified and then was extracted with two 50 ml. portions of ether. After drying the ether extract over anhydrous sodium sulfate, the solvent was removed, and the waxy, brown residue was recrystallized from ligroin to give 0.3 g. of white solid (XXXIII), m.p. 106—107°. The melting point of (XXXIII) was depressed when mixed with a sample of (XXIII).

Anal. Calcd. for C₁₈H₁₀N₅O₇:  C, 73.8;  H, 6.15.
Found:  C, 69.67, 69.83;  H, 5.34, 5.25.

IR spectrum (double mull, No. 507):  3200—2800(b), 1725, 1625(b), 1458, 1425, 1325, 1300—1275(b), 705, 668.

All attempts to crystallize the bicarbonate insoluble oil were unsuccessful.

Reactions of 1,1-Dimethyl-4-benzoyl-4-bromopiperidinium Bromide (XX).

(a) With Silver Nitrate. A 12 g. (0.03 mole) sample of (XX) and 6 g. of silver nitrate were dissolved in 200 ml. of water, and this solution was heated under reflux for 4 hours. The insoluble salts were removed by filtration, and the filtrate was evaporated to dryness. The yellow residue
was recrystallized from isopropyl alcohol to give 6.8 g. of white solid (XXXIV), m.p. 180–200° decomposes.

IR spectrum (mull, No. 600): 1640, 1370, 1330, 1270(m), 835(m), 775(w), 705.

(a—1) Attempted Thermal Rearrangement of (XXXIV). A 6 g. sample of (XXXIV) was placed in a 50 ml. distilling flask equipped with a side arm test tube and a thermometer. The flask was evacuated (20 mm.) and heated by means of a Woods metal—bath to 200–230°. A small amount of yellow distillate was collected, but the majority of the material in the flask carbonized. Recrystallization of the distillate (XXV) from petroleum ether gave 0.6 g. of (XXVa), m.p. 63–65°.

IR spectrum (double mull, No. 605): 3040(w), 1662, 1570(m), 1435, 1300, 765(m), 710.

The melting point of (XXXVa) was not depressed when mixed with an authentic sample of 4-benzoylpyridine, and the infrared absorption spectrum, No. 417, of 4-benzoylpyridine is identical to that of (XXXVa).

(b) With Silver Oxide in Aqueous Ethanol. A 4 g. sample of (XX) was dissolved in 100 ml. of 95% ethanol, and to this solution was added 2 g. of silver oxide. The mixture was stirred at room temperature for 1 hour, and then a solution of 1 g. of silver nitrate in 10 ml. of water was added. The mixture was heated under reflux for 4 hours, and the insoluble salts were removed by filtration. The filtrate was evaporated under reduced pressure, and recrystallization of the residue from isopropyl alcohol gave 1.2 g. of a hygroscopic solid.
(XXXVb), m.p. 80-110°. Repeated recrystallization from chloroform or isopropyl alcohol did not improve the melting point range.

IR spectrum (mull, No. 547): 3260, 1720(m), 1687(m), 1660, 1390-1370(b), 1360-1330(b), 1265, 1206, 791.(m), 712.

(c) With Sodium Methoxide in Methanol. A 4 g. sample of (XX) was dissolved in 100 ml. of methanol, and to this solution was added 8 g. of sodium methoxide. The reaction mixture was stirred at room temperature for 4 hours, and the methanol was concentrated under reduced pressure. The residue was dissolved in water, and this solution was acidified and then was evaporated to dryness. The residue was triturated with 75 ml. of hot isopropyl alcohol, and the insoluble salts were removed by filtration. Cooling the filtrate in an ice bath yielded 2.4 g. (81%) of 1,1-dimethyl-4-benzoyl-4-hydroxypiperidinium bromide (XXXVI), m.p. 185-188°, lit. (3) 190-191°.

IR spectrum (double mull, No. 546): 3210, 3020(m), 1675, 1263, 1185, 1162, 770(w), 725(w), 707.

Reaction of 1,1-Dimethyl-3-benzoyl-3-bromopiperidinium Bromide (XXI) With Silver Nitrate.

A 3 g. sample of (XXI) was dissolved in 100 ml. of water, and 4 g. of silver nitrate was added. The mixture was heated on the steam bath for 6 hours, and the insoluble salts were removed by filtration. After evaporation of the solvent, a yellow, oily solid remained which was twice recrystallized
from isopropyl alcohol to give 1.2 g. of (XXXVII), m.p. 178–180.5°.

IR spectrum (mull, No. 585): 1635, 1370, 1345, 1332, 1320, 1270(m), 835(m), 775(w), 705.

UV spectrum (λ max. (Abs.)): 252(97% at 2.8 x 10^-4).

The attempted thermal rearrangement of (XXXVII) resulted in the complete carbonization of this product.


(a) With Dilute Hydrochloric Acid. A 3 g. (0.01 mol) sample of (XXIV) was treated with 100 ml. of dilute hydrochloric acid, and the resulting mixture was warmed on the steam bath for 30 minutes. On cooling the solution, a pink solid precipitated, was collected by filtration, and was recrystallized from water to give 2.5 g. (78%) of 1–benzyl–4–benzoyl–4–hydroxypiperidine hydrochloride (XXXVIII), m.p. 190–191.5°.

Anal. Calcd. for C19H23ClN02: Cl, 10.68. Pound: Cl, 10.10.

IR spectrum (mull, No. 97): 3330(m), 2800, 2620(m), 2540(m), 1675, 1375(m), 1265(m), 762(m), 725(m), 705(m).

An aqueous solution of (XXXVIII) was basified by the addition of sodium hydroxide to give a quantitative yield of 1–benzyl–4–benzoyl–4–hydroxypiperidine (XXXVIIIa), m.p. 68–70°.


Found: C, 77.33; H, 6.78.

IR spectrum (chloroform, No. 205): 3620(w), 3480(m),
2940(m), 2830(m), 1668, 1280, 1155, 1060, 695(m).

(b) **With Acetic Acid.** A solution of 3 g. (0.01 mole) of (XXIV) in 100 ml. of absolute ether was added to 100 ml. of absolute ether containing 2 ml. of acetic acid. The resulting solution was allowed to stand overnight at room temperature, was washed with a saturated sodium carbonate solution, and was dried over anhydrous calcium sulfate. The solvent was removed by evaporation, and the residue was recrystallized from ether to give 2 g. (60%) of 1-benzyl-4-benzoyl-4-piperidyl acetate (XXXIX), m.p. 91–93°.

An ethereal solution of (XXXIX) was saturated with anhydrous hydrogen chloride, and the precipitated solid was collected by filtration and recrystallized from chloroform-ether to give 1.3 g. (39%) of (XXXIX) hydrochloride, m.p. 265–267°.

**Anal. Calcd. for C_{31}H_{36}ClNO_{8}:** Cl, 9.49. **Found:** Cl, 9.53.

(c) **With Propionic Acid.** The reaction of 3 g. (0.01 mole) of (XXIV) with 2 ml. of propionic acid was carried out as in (b), but no solid was obtained on treatment of the reaction mixture with ether. The ethereal solution, therefore, directly was saturated with hydrogen chloride, and the precipitated solid was collected by filtration and recrystallized from isopropyl alcohol to give 0.8 g. (20%) of 1-benzyl-4-benzoyl-4-piperidyl propionate hydrochloride, (XL), m.p. 230–233°.

**Anal. Calcd. for C_{31}H_{36}ClNO_{8}:** Cl, 9.22. **Found:** Cl, 9.72.
(d) **With Benzolic Acid.** The reaction of 3 g. (0.01 mole) of (XXIV) with 3 g. of benzolic acid was carried out as described previously in (b), and gave 2.5 g. (61.7%) of 1-benzyl-4-benzoyl-4-piperidyl benzoate (XLI), m.p. 121-123°. Conversion of (XLI) to the hydrochloride by the usual method gave, after recrystallization from isopropyl alcohol, 1.2 g. (27.2%) of (XLI) hydrochloride, m.p. 220-222°.


(e) **With p-Aminobenzoic Acid.** A 3 g. sample of (XXIV) was dissolved in 50 ml. of anhydrous ether, and the solution was added to 100 ml. of pyridine in which 3.6 g. (0.026 mole) of p-aminobenzoic acid had been dissolved. This solution stood overnight at room temperature, and then the solvents were removed by evaporation under reduced pressure. The residue was washed with three 100 ml. portions of a saturated sodium carbonate solution and then was dissolved in 150 ml. of ether. The ethereal solution was washed with water and dried over anhydrous calcium sulfate. After drying, the solvent was removed by evaporation, and the residue was recrystallized from petroleum ether to give 3 g. (72.3%) of 1-benzyl-4-benzoyl-4-piperidyl p-aminobenzoate (XLII), m.p. 173-174°.

Anal. Calcd. for C₈₆H₆₆N₂O₃: C, 75.40; H, 6.28. Found: C, 75.13; H, 6.27.

(a) With Hydrochloric Acid: A sample of 4.35 g. (0.019 mole) of (XXVIII) was treated with 100 ml. of dilute hydrochloric acid, and the resulting solution was allowed to stand at room temperature for 12 hours and then was basified by the addition of sodium hydroxide. The mixture was extracted with ether, and the ether extract was dried over anhydrous calcium sulfate. After removal of the solvent by evaporation, a brown semi-solid remained, and this material was recrystallized from ligroin to give 2 g. (48%) of 1-methyl-3-benzoyl-3-hydroxy-piperidine (XLIII), m.p. 52-54°.

Anal. Calcd. for C_{13}H_{17}NO: C, 71.2; H, 7.76.
Found: C, 71.65; H, 7.37.
The picrate of (XLIII) was prepared by standard methods and melted 168-171°.

An ethereal solution of (XLIII) was saturated with anhydrous hydrogen chloride to give (XLIII) hydrochloride, m.p. 161-164°.

Anal. Calcd. for C_{13}H_{16}ClNO: Cl, 13.92. Found: Cl, 13.70.

IR spectrum (double mull, N°. 463): 3040(w), 1673, 1464, 1450, 1275, 1240, 1160, 1015, 740, 720.

(b) With Acetic Acid. A solution of 2.5 g. (0.01 mole) of (XXVIII) in 50 ml. of anhydrous ether was added to 50 ml. of ether containing 3 ml. of glacial acetic acid, and the resulting solution was allowed to stand at room temper—
ature for 12 hours. The ethereal solution then was washed with a saturated solution of sodium carbonate and dried over anhydrous calcium sulfate. The solvent was removed by evaporation, and the resi­dues was recrystallized from petroleum ether to give 2.1 g. (81%) of 1-methyl-3-benzoyl-3-piperidyl acetate (XLIV), m.p. 88–89°.

Anal. Calcd. for C_{18}H_{18}NO_{3}: C, 69.00; H, 7.28. Found: C, 68.80; H, 6.95.

IR spectrum (double mull, No. 406): 2960(m), 2780(m), 1730, 1675, 1375, 1295, 1225, 785(m), 708.

An ethereal solution of 2.5 g. of (XLIV) was saturated with anhydrous hydrogen chloride, and the solid which precipitated was collected by filtration and recrystallized from isopropyl alcohol to give 2.0 g. (70.5%) of (XLIV) hydro­chloride, m.p. 248–250°.

Anal. Calcd. for C_{18}H_{18}ClNO_{3}: Cl, 11.95. Found: Cl, 11.68.

(c) With Benzoic Acid. The reaction of 4.35 g. (0.019 mole) of (XXVIII) with 5 g. (0.041 mole) of benzoic acid in the manner described in (b) gave, after recrystallization from ligroin, 4.1 g. (66%) of 1-methyl-3-benzoyl-3-piperidyl benzoate (XLV), m.p. 114–115°.

Anal. Calcd. for C_{18}H_{18}NO_{3}: C, 74.30; H, 6.50. Found: C, 74.32, 74.38; H, 6.57, 636.

IR spectrum (mull, No. 580): 1715, 1680(m), 1305(m), 1268(m), 775(w), 705.

The hydrochloride of (XLV) was prepared in the usual
manner and melted 201–202°.

Anal. Calcd. for C₉₆H₉₀ClNO₆: Cl, 9.85. Found: Cl, 10.17, 10.43.

(d) With m-Hydroxybenzoic Acid. A 4.35 g. (0.019 mole) sample of (XXVII) in 50 ml. of anhydrous ether was added to 5.5 g. (0.04 mole) of m-hydroxybenzoic acid in 100 ml. of anhydrous ether, and, after a period of 12 hours, the reaction product was isolated as described in (b). The crude material was recrystallized from 400 ml. of methanol to give 3.2 g. (51%) of 1-methyl-3-benzoyl-3-piperidyl m-hydroxybenzoate (XLVI), m.p. 214–216°.

A solution of 2 g. (0.059 mole) of (XLVI) was dissolved in 400 ml. of boiling methanol and to this solution was added 1.5 g. of maleic acid. After cooling, the solution was concentrated, and solid separated on standing to give 2.1 g. (78.5%) of the maleic acid salt of (XLVI), m.p. 208–209°.


IR spectrum (double mull, No. 714): 3280(m), 1720(B,s), 1684(m), 1380(m), 1304(m), 1278(m), 1175(m), 708(m), 706.

(e) With o-Hydroxybenzoic Acid. A 4.25 g. (0.0185 mole) sample of (XXVIII) was treated with 5.5 g. (0.04 mole) of o-hydroxybenzoic acid in 100 ml. of ether, and, after standing overnight, the reaction mixture was treated as described in (b). The impure material thus obtained was recrystallized from ligroin to give 2.0 g. (34%) of 1-methyl-3-benzoyl-3-piperi-
Dyl o-hydroxybenzoate (XLVII), m.p. 128–130°.

Anal. Calcd. for C_{20}H_{19}NO_{4}: C, 70.7; H, 6.21.
Found: C, 70.5, H, 6.35.

IR spectrum (mull, No. 738): 3220(m), 1680, 1615(m), 1598(m), 1487(m), 1342(m), 1260, 1205, 1152, 1090, 705, 695.

An ethereal solution of (XLVII) was saturated with anhydrous hydrogen chloride, and the precipitated solid was collected by filtration and recrystallized from isopropyl alcohol to give 2 g. of (XLVII) hydrochloride, m.p. 196–200°.

Anal. Calcd. for C_{20}H_{19}ClNO_{4}: Cl, 9.32. Found: Cl, 8.92.

(f) With p-Hydroxybenzoic Acid. A 4.25 g. (0.0185 mole) sample of (XXVIII) was allowed to react with 5.5 g. of p-hydroxybenzoic acid in 100 ml. of ether, and the reaction mixture was treated as described in (b). The crude ester was then recrystallized from aqueous alcohol to give 1.9 g. (33%) of 1-methyl-3-benzoyl-3-piperidyl p-hydroxybenzoate (XLVIII), m.p. 212–214°.

Anal. Calcd. for C_{20}H_{19}NO_{4}: C, 70.7; H, 6.21.
Found: C, 69.32, 69.52; H, 6.66, 6.78.

IR spectrum (mull, No. 737): 2600–2400(b), 1700, 1680(m), 1625, 1590, 1300, 1278, 1220, 1095, 755(m), 710.

An ethanolic solution of (XLVIII) was saturated with anhydrous hydrogen chloride, and the solvent was removed by evaporation under reduced pressure. Addition of ether to the residue gave 1.7 g. (80%) of 1-methyl-3-benzoyl-3-piperidyl
p-hydroxybenzoate hydrochloride (XLVIIIa), m.p. 188–189°.

Anal. Calcd. for C\textsubscript{10}H\textsubscript{9}ClNO\textsubscript{4}: Cl, 9.33. Found: Cl, 9.44.

(g) With Furanoic Acid. A 4.25 g. sample of (XXVIII) was treated with 5 g. (0.045 mole) of 2-furanoic acid in the manner described previously, and gave, after recrystallization from ligroin, 3 g. (50.5%) of 1-methyl-3-benzoyl-3-piperidyl 2-furanooate, (XLIX), m.p. 127-128°.

Anal. Calcd. for C\textsubscript{16}H\textsubscript{19}N\textsubscript{3}O\textsubscript{4}: C, 69.00; H, 6.06. Found: C, 69.20; H, 6.08.

IR spectrum (mull, No. 736): 1720, 1673, 1390(m), 1315, 1275(m), 1175, 762, 702.

An ethereal solution of 3.4 g. of (XLIX) gave 3.5 g. of 1-methyl-3-benzoyl-3-piperidyl furanoate hydrochloride (XLIXa), m.p. 210-212°.

Anal. Calcd. for C\textsubscript{18}H\textsubscript{20}ClNO\textsubscript{4}: Cl, 10.60. Found: Cl, 10.31.

Attempted Rearrangements of Epoxyethers (XXIV) and (XXXI).

(a) Reaction of 6-Benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2,5]octane (XXIV) with Boron Trifluoride Etherate.

To a stirred solution of 5.1 g. (0.017 mole) of (XXIV) in 100 ml. of anhydrous nitromethane was added 10 ml. of freshly distilled boron trifluoride etherate, and the resulting solution was heated under reflux for 12 hours. After cooling, a methanolic potassium hydroxide solution was added to the reaction mixture, and the precipitated solids were removed by filtration.
The solvent was removed by distillation under reduced pressure, the residue was dissolved in anhydrous ether, and treatment of the ethereal solution with anhydrous hydrogen chloride gave 4.2 g. (73.4%) of 1-benzyl-4-benzoyl-4-hydroxypiperidine hydrochloride (XXXVIII), m.p. 191–193°. The melting point of this material was not depressed when mixed with an authentic sample of (XXXVIII).

(b) **Reaction of 6-Benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]octane (XXIV) with Anhydrous Magnesium Bromide.**

Into 100 ml. of n-butyl ether was placed 2 g. (0.08 g.-atom) of magnesium turnings, and to this mixture was added 4.5 ml. (0.08 mole) of bromine over a 30 minute period. After the bromine color disappeared, the stirred mixture was heated to 100°, and a solution of 5.1 g. (0.017 mole) of (XXIV) in 100 ml. of n-butyl ether was added causing the precipitation of a red-orange solid. The mixture was heated under reflux for 12 hours, cooled and treated with 10 ml. of dioxane, but the precipitate did not dissolve. The solvents were removed by decantation, the solid was dissolved in water, and this solution was extracted with ether. After the ethereal solution had been dried, the solvent was removed by evaporation and the residue recrystallized from alcohol to give 4.0 g. of yellow solid (XXXVIIIa), m.p. 68–71°. A mixed melting point of this material with an authentic (XXXVIIIa) sample of 1-benzyl-4-benzoyl-4-hydroxypiperidine was not depressed.

(c) **Reaction of 6-Benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]octane (XXXI) with Boron Trifluoride Etherate.**

A 8.4 g. sample of (XXXI) was dissolved in 250 ml. of
nitromethane and to this solution was added 10 ml. of freshly distilled boron trifluoride etherate. The reaction was carried out as previously described, (a), and recrystallization of the crude product from isopropyl alcohol gave 4 g. of 1,4-dibenzoyl-4-hydroxypiperidine (XXX), m.p. 186–188°. The melting point of this material was not depressed when mixed with an authentic sample of (XXX).

**Catalytic Hydrogenation of Some Salts of 3-Benzoylpyridine and Related Compounds**

**(a) Reduction of 3-Benzoylpyridine Methobromide (V).**

A solution of 75 g. (0.288 mole) of (V) in 600 ml. of methanol was divided into three equal portions and each portion was shaken with 0.3 g. of platinum oxide under an initial hydrogen pressure of 50 p.s.i. In each case, the reaction stopped after the absorption of three moles of hydrogen per mole of (V); the catalyst was removed by filtration, and the combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in 300 ml. of hot isopropyl alcohol, and, on cooling, there was obtained 17.2 g. of 1-methyl-3-benzoylpiperidine hydrobromide (X), m.p. 131–133°.

The solvent was removed from the filtrate by distillation; the residue was dissolved in 300 ml. of methanol, and upon further hydrogenation in the manner described above gave an additional 14.9 g. of (X), making the total yield (40.5%). The melting point of this material was not depressed when mixed with an authentic sample of 1-methyl-3-benzoylpiperidine hydro-
bromide. The piorate, prepared from the free base of (X), melted 192–194° and had M.W. 435 ± 5; lit. (22) m.p. 193–194°, theoretical M.W. 433.

(a–1) Isolation and Identification of 1-Methyl-3-piperidylphenylcarbinol (L). The alcoholic filtrate from the recrystallization of (X) was evaporated to dryness under reduced pressure, and the residue was then dissolved in water. Neutralization of this solution caused the separation of a dark brown oil which was dissolved in 100 ml. of ether, and was then separated from the aqueous phase. After drying the ethereal solution of anhydrous sodium carbonate, the solvent was evaporated, and the residue was recrystallized from ligroin to give 6.1 g. of one isomeric form of 1-methyl-3-piperidylphenylcarbinol (L), m.p. 122–125°, lit. (22) 122–125°.

IR spectrum (double mull, No. 482): 3400, 2940, 2790, 1145, 1080, 1045, 763, 705.

Oxidation of 5 g. (0.025 mole) of (L) by 1.7 g. (0.017 mole) of chromic anhydride was accomplished in glacial acetic acid in the same manner as previously described for (IX), and gave 3.8 g. (54.1%) of 1-methyl-3-benzoyl-piperidine hydrobromide (X), m.p. 131–133°.

(a–2) Isolation and Identification of 1-Methyl-3-benzylpiperidine (LIa). The filtrate from the recrystallization of 1-methyl-3-piperidylphenylcarbinol (L) was evaporated, and the oily residue was distilled under reduced pressure to give 10.2 g. of crude 1-methyl-3-benzylpiperidine (LI), b.p. 105–130°/2mm., 5.7 g. of the mixture of isomeric 1-methyl-3-piperi-
diphenylcarbinols (LII), b.p. 130-140°/2mm. and 2.4 g. of residue (LIII).

The infrared absorption spectrum of (L) showed absorption due to the carbonyl stretching of an aliphatic ketone at 1705 cm.\(^{-1}\) and absorption of the carbonyl stretching of an aromatic ketone at 1675 cm.\(^{-1}\). Repeated distillations of (L) under reduced pressure gave 8.8 g. of colorless 1-methyl-3-benzylpiperidine (LIIa), b.p. 110-113°/2mm.

Anal. Calcd. for \(\text{C}_{13}\text{H}_{18}\text{N}\): C, 82.50; H, 10.05. Calcd. for \(\text{C}_{13}\text{H}_{17}\text{N}\): C, 83.4; H, 10.80. Found: C, 79.60; H, 10.28.

IR spectrum (film, No. 348): 3080(w), 3430(w), 2940, 2840, 2770, 1705(vw), 1680(vw), 1470, 1455, 775, 705.

The molecular weight of the picrate of (LIIa), m.p. 148-150°, was 412 ± 5.

The methiodide of (LIIa) was prepared by the conventional method and melted at 111-115°.

Anal. Calcd. for \(\text{C}_{14}\text{H}_{20}\text{IN}\): I, 38.61. Calcd. for \(\text{C}_{14}\text{H}_{22}\text{IN}\): I, 38.38. Found: I, 37.79.

UV spectrum - See Figure 7.

This salt was then compared with an authentic sample of 1-methyl-3-benzylidenepiperidine methiodide (LIV), which was prepared as described below:

A 5.4 g. sample of (L) was dissolved in 40 ml. of 48% hydrobromic acid and 25 ml of glacial acetic acid, and the resulting solution was heated under reflux for 4 hours, cooled and poured onto 50 g. of crushed ice. The acidic portion was
neutralized and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and treated with excess methyl iodide to give 1-methyl-3-benzylidene piperidine methiodide (LIV), m.p. 168-172°.

The hydrobromide of (LIIa) was prepared by conventional methods and melted 122-124°. This salt was compared with an authentic sample of 1-methyl-3-benzylpiperidine hydrobromide which was prepared as described below.


IR spectrum (double mull, No. 480): 2920, 2460, 1460, 1450, 755, 705.

To a solution of 18 g. (0.1 mole) of 3-benzoylpyridine and 100 ml. of diethylene glycol was added 12.3 g. (0.22 mole) of potassium hydroxide and 11 g. (0.22 mole) of 95% hydrazine hydrate. The resulting mixture was gently heated to 115-125° by means of a paraffin-bath and maintained at this temperature for 2 hours. The mixture was then heated to 180-190° and maintained at this temperature until the evolution of the gas ceased. The reaction product was then removed from the mixture by distillation, and the distillate was extracted with ether. The ether extract, after drying, was cooled by means of an ice bath and saturated with methyl bromide. After standing at room temperature for 12 hours, the crystalline precipitate was collected by filtration and recrystallized from isopropyl alcohol to give 12.2 g. (45.6%) of 1-methyl-3-benzylpyridinium bromide (LV), m.p. 65-67°.
Anal. Calcd. for C_{13}H_{14}BrN.H_{2}O: Br, 28.30.

Found: Br, 28.08, 28.08.

IR spectrum (double mull, No. 477): 3500, 3433, 1460, 1440, 1245, 1215, 770, 742, 710, 705.

A 5 g. (0.017 mole) sample of (LV) was dissolved in 100 ml. of methanol and shaken with 0.2 g. of platinum oxide at an initial hydrogen pressure of 50 p.s.i. After the absorption of hydrogen ceased, the catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was recrystallized from isopropyl alcohol and gave 3.2 g. (67%) of 1-methyl-3-benzylpiperidine hydrobromide (LVa), m.p. 122-124°. A mixture of (LVa) and the hydrobromide of (Lla) was found to melt 122-124°.

Anal. Calcd. for C_{13}H_{20}BrN: Br, 29.60. Found: Br, 29.32, 29.63.

IR spectrum (double mull, No. 476: 2920, (2480—2440), 1465, 1458, 760, 706.

The yield of (Lla) resulting from the catalytic hydrogenation of 3-benzoylpyridine methobromide was 16.8%.

(a-3) Comparison of the Mixture of Isomeric 1-Methyl-3-piperidylphenylcarbinols (LII) with 1-Methyl-3-(1,2,5,6)-tetrahydropyridylphenylcarbinol (LVI). The second fraction from the distillation, (LII), crystallized when it was tritutrated with petroleum ether and gave an irresolvable mixture of the isomeric 1-methyl-3-piperidylphenylcarbinols which melted at 80-95°, lit. (7) m.p. 80-101°. All attempts to separate this mixture into its components by either vacuum sublimation
or by recrystallization (7) were unsuccessful.

IR spectrum (double mull, No. 482): 3400, 2940, 2790, 1455, 1160, 1080, 1045, 763, 705.

A 25 g. (0.092 mole) sample of 3-benzoylpyridine methobromide (IX) was dissolved in 300 ml. of methanol, and this solution was cooled by means of an ice-bath and treated with 16 g. (0.4 mole) of sodium borohydride in small portions. After the addition of the hydride was complete, 300 ml. of water was added, and the methanol was removed by distillation. The resulting mixture was extracted with ether; the ethereal solution was dried, and the solvent was removed by evaporation. Distillation of the residue under reduced pressure gave 11 g. of red oil, b.p. 175-190°/4mm. which was recrystallized from ligroin. In this manner, there was obtained 4.2 g. (22.6%) of 1-methyl-3-(1,2,5,6)-tetrahydropyridylphenylcarbinol (LVII), m.p. 116-117°.

Anal. Calcd. for C_{15} H_{17} NO: C, 76.8; H, 8.36.
Found: C, 77.33; H, 7.77.

IR spectrum (double mull, No. 481): 2920, 2880, 2835, 1500, 1335, 1118, 765, 710, 700, 680(m).

(b) Catalytic Reduction of 3-Pyridylphenylcarbinol Methobromide (LVIII).

A solution of 17 g. (0.06 mole) of 3-benzoylpyridine (I) and 100 ml. of methanol was cooled by means of an ice-bath, and to this stirred solution was added 4.6 g. (0.12 mole) of sodium borohydride in small portions. After the
addition was complete, the solvent was removed by distillation under reduced pressure, water was added to the residue, and the resulting mixture was extracted with ether. The ether extract was dried, and then evaporation of the solvent left a clear, heavy oil which was distilled under reduced pressure to give 12.2 g. (85.6%) of 3-pyridylphenylcarbinol (LVII), b.p. 180-184°/4mm., lit. (30), b.p. 180-182°/2.5mm.

This carbinol was also prepared by the catalytic reduction of 3-benzoylpyridine. The picrate of (LVII) melted at 154-157°, lit. (31), 156.5-157°.

A solution of 11.8 g. (0.065 mole) of 3-pyridylphenylcarbinol in 100 ml. of isopropyl alcohol was treated with excess methyl bromide and this mixture was allowed to stand at room temperature for 12 hours. The crystalline methobromide was collected by filtration and recrystallized from isopropyl alcohol to give 16.1 g. (93.6%) of 3-pyridylphenylcarbinol methobromide, (LVIII), m.p. 145-148°.


A solution of 14 g. (0.05 mole) of (LVIII) in 100 ml. of 95% ethanol was shaken with 0.2 g. of platinum oxide at an initial hydrogen pressure of 50 p.s.i. The change in the ultraviolet absorption spectrum as the reduction proceeded was followed by withdrawing aliquot samples and determining the ultraviolet spectrum at various times. These spectra are recorded in Figure 2.

After the reaction mixture ceased to absorb hydrogen,
the catalyst was removed by filtration, the solvent was evaporated under reduced pressure, and the residue was dissolved in 100 ml. of hot isopropyl alcohol. Cooling this solution, however, did not cause the formation of any crystalline product. The alcohol was then removed by distillation, the residue was dissolved in water, and this solution basified by the addition of sodium carbonate. The brown oil which separated was extracted into ether and recovered from the dried ethereal solution by evaporation of the solvent. Distillation of this oil under reduced pressure gave 5.8 g. of the mixture of isomeric 1-methyl-3-piperidylphenylcarbinols (LII), m.p. 82-93°. The melting point range of this material was neither increased nor depressed when mixed with (LII).

(c) **Reduction of 3-Benzoylpyridine Hydrochloride.** A 44 g. (0.2 mole) sample of 3-benzoylpyridine (I) hydrochloride was dissolved in methanol and shaken with 0.6 g. of platinum oxide at an initial hydrogen pressure of 50 p.s.i. The reaction was discontinued when the absorption of hydrogen ceased, and the reduction mixture was filtered in order to remove the catalyst. The solvent was removed by evaporation under reduced pressure, and recrystallization of the residue from isopropyl alcohol gave 10.4 g. of 3-benzoylpiperidine hydrochloride (LIX), m.p. 187-189°. Removal of the solvent from the alcoholic filtrate by distillation left a brownish-red residue which was dissolved in 200 ml. of methanol and rehydrogenated. The reduction product was isolated in the
manner already described and in this way an additional 5.8 g. of (LIX) was obtained.

Anal. Calcd. for C₁₆H₁₆ClNO: Cl, 15.71. Found: Cl, 15.81, 15.80.

IR spectrum (double mull, No. 349): 2940, 2750, 2690, 2600, 2560, 1675, 1450, 1272, 1212, 770 (M), 698.

The alcoholic filtrate from the recrystallization of (LIX) was concentrated by distillation and the last vestiges of solvent were removed by evaporation under reduced pressure. The residual material was then dissolved in water and this solution was basified by the addition of sodium hydroxide and extracted with ether. After drying the ether extracts over anhydrous calcium sulfate, the solvent was evaporated and the residue was distilled under reduced pressure to give the following fractions:

(LIXa) b.p. 104–108°/4mm., IR spectrum (film, 499): 1635 (M), 1497 (M), 1465 (M), 1450 (M), 1354 (M), 765, 745, 695.

(LIXb) b.p. 108–138°/4mm., IR spectrum (film, 500): 3400 (B), 2920, 1660, 1450, 1280, 750, 715, 700.

(LIXc) b.p. 138–141°/4mm., IR spectrum, (film, 501): 3400 (B), 2920, 2860, 1660, 1455, 1280 (M), 1265 (M), 750, 715, 700.

(d) Catalytic Hydrogenation of 1-β-phenethyl-3-
benzoylpyridinium Bromide (IV). A 97 g. (0.28 mole) sample of (IV) was dissolved in 600 ml. of methanol and hydrogenated in 2 portions as previously described for (X). Isolation of the
reduction product was carried out in an identical manner and there was obtained 23.5 g. (16%) of 1-phenethyl-3-benzoyl-piperidine hydrobromide (LX), m.p. 200-202°.

Anal. Calcd. for C_{20}H_{14}BrNO: Br, 21.4%. Found: Br, 20.70.

IR spectrum (mull, No. 759): 2600, 2540, 1670, 1378, 1295 (M), 1275 (M), 765 (M), 732 (M), 698.

(e) Catalytic Hydrogenation of 1-Methyl-3-benzoyl-1,4-dihydropyridine. A stirred solution of 27 g. (0.1 mole) of 3-benzoylpyridine methobromide and 49 g. of sodium bicarbonate in 500 ml. of water was treated with 69.5 g. of sodium dithionate in small portions over a period of several minutes. The solution evolved carbon dioxide and a yellow solid precipitated. After stirring for 4 hours, the product was collected by filtration and recrystallized from 50% alcohol. There was obtained 15.1 g. (76%) of 1-methyl-3-benzoyl-1,4-dihydropyridine (LXI), m.p. 67-69°, which in an ethanol solution exhibited maximum absorption at 385 m\(\mu\).

Anal. Calcd. for C_{18}H_{15}NO: C, 78.49; H, 6.54.

Found: C, 78.39; H, 6.58.

IR spectrum (double mull, No. 577): 3080(m), 2940(m), 2860(m), 2820(m), 1678, 1590-1565, 1390, 1330, 1295, 720.

A solution of 14 g. (0.07 mole) of (LXI) and 250 ml. of methanol was treated with 11.4 g. of 48% hydrobromic acid, and the resulting acidic solution hydrogenated over 0.2 g. of platinum oxide at a hydrogen pressure of 3 atmospheres. When the pressure remained constant over a 30 minute period, the
catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from isopropyl alcohol and gave 3.4 g. (18.4%) of 1-methyl-3-benzoylpiperidine hydrobromide (X). The melting point of this material was not depressed when mixed with an authentic sample of (X).

Neutralization of the residue resulting from the evaporation of the alcoholic filtrate gave a heavy brown oil. This oil was dissolved in hot ligroin, and the crystalline material which separated on cooling was collected by filtration to give 1.6 g. (11.5%) of 1-methyl-3-piperidylphenylcarbinol, m.p. 122–124°. The identity of this sample was established by a mixed melting point with (L); there was no depression in the melting point range.

The filtrate was allowed to evaporate and the residue was triturated with warm petroleum ether. The insoluble material was collected by filtration, washed with petroleum ether and dried. In this manner there was obtained 0.9 g. of the mixture of isomeric 1-methyl-3-piperidylphenylcarbinols, m.p. 81–93°.

The petroleum ether soluble material was collected by evaporation of the solvent and was dissolved in 20 ml. of 95% ethanol. Treatment of this solution with an alcoholic solution of picric acid gave a picrate, m.p. 148–151°. A mixture of this picrate and that of 1-methyl-3-benzylpiperidine was found to melt 148–151°.

A solution of 14 g. (0.07 mole) of (LXI) in 100 ml. of methanol was hydrogenated over Adams catalyst at a hydrogen...
pressure of 50 p.s.i. Aliquot samples were withdrawn after the absorption of various amounts of hydrogen and the ultraviolet absorption spectra of these samples were determined and recorded in Figure 4.

Catalytic Reduction of 3-Benzoylpyridine Methobromide in Basic Solution.

A 15 g. (0.05 mole) sample of (V) was dissolved in 150 ml. of saturated sodium bicarbonate solution and the resulting pale yellow solution was hydrogenated over 0.3 g. of platinum oxide at a hydrogen pressure of 3 atmospheres. When the solution developed a deep orange color, the reaction was halted and 100 ml. of ether was introduced into the reduction bottle. The reduction was then continued for 30 minutes and the ethereal layer was then separated and dried over anhydrous potassium carbonate for 12 hours. The ultraviolet absorption spectrum of this solution was determined and is recorded in Figure 5.

This experiment was repeated with one minor variation: the time that the ethereal solution was dried over anhydrous potassium carbonate was reduced to 1 hour.

The reduction of 1-benzylnicotinamide bromide (supplied by David A. Nelson) was carried out in the same way and the ultraviolet absorption curve of the resulting ethereal solution is recorded in Figure 5.

Hydrogenolysis of the Carbinols (L) and (LVI).

(a) With 1-Methyl-3-piperidylphenyloarbinol. A
solution of 2 g. (0.01 mole) of (L) and 100 ml. of methanol was treated with anhydrous hydrogen bromide for about 2 minutes and 0.1 g. of platinum oxide was added to the resulting acidic solution. This mixture was shaken for 12 hours under an initial hydrogen pressure of 45 p.s.i.; then the reaction was terminated and the catalyst was removed by filtration. The alcohol was removed from the filtrate by evaporation under reduced pressure and the resulting solution was basified by the addition of solid sodium hydroxide. The yellow oil which separated was extracted with ether, and the ethereal solution was dried over anhydrous potassium carbonate. Evaporation of the solvent left a yellow oil which partially crystallized and was then triturated with petroleum ether. The insoluble (L) was collected by filtration and melted 122–125°. The petroleum ether soluble material was obtained by evaporation of the solvent and a picrate of this material, prepared by conventional methods, melted 149–152° after recrystallization from alcohol. A mixture of this picrate and that of 1-methyl-3-benzylpiperidine (Lia) also melted 149–152°.

(b) With 1-Methyl-(1,2,5,6)-tetrahydropyridylphenylcarbinol (LVI). A 0.2 g. (0.01 mole) sample of (LVI) was treated with hydrogen by a procedure identical to that described in (a). From this reaction there was obtained 0.6 g. of 1-methyl-3-piperidylphenylcarbinol, m.p. 122–125°, and a yellow oil whose picrate melted 149–151°. A mixture of this picrate and the picrate of 1-methyl-3-benzylpiperidine also melted 148–152°.
Catalytic Reduction of Salts of 1-Methyl-3( and 4-)benzoylpiperidine.

(a) **Hydrogenation of 1,1-Dimethyl-3-benzoylpiperidine* Bromide (XXXVII).** A 2 g. sample of (XVII) in methanol was hydrogenated over platinum oxide for 4 hours to give 1-methyl-3-piperidylphenylcarbinol methobromide, m.p. 202–204°.

IR spectrum (mull, No. 657): 3280, 1382 (M), 1058 (M), 710 (M), 700.

(b) **Hydrogenation of 1,1-Dimethyl-4-benzoylpiperidine* Bromide (XVI).** A 2 g. sample of (XVI) was similarly reduced to give 1-methyl-4-piperidylphenylcarbinol methobromide, m.p. 210–211°.

IR spectrum (mull, No. 656): 3260, 1500 (Sh), 1382, 1020 (M), 920 (M), 772 (M), 765 (M), 710.

(c) **Hydrogenation of 1-Methyl-3-benzoylpiperidine Hydrobromide (X).** A 4 g. sample of (X) was hydrogenated over platinum oxide for 12 hours to give after neutralization 1-methyl-3-piperidylphenylcarbinol (L), m.p. 122–125° and a mixture of the isomeric carbinols.

(d) **Hydrogenation of 1-Methyl-4-benzoylpiperidine Hydrobromide.** A 4 g. sample of this hydrobromide was prepared by conventional methods and the infrared absorption spectrum, No. 761, exhibited a strong band at 1683 cm.⁻¹. Catalytic hydrogenation of this salt over platinum oxide gave, after neutralization, 1-methyl-4-piperidylphenylcarbinol, m.p. 153–155°, lit. (15), 157–158°.

This sample was supplied by S. A. Leone.
SUMMARY

A series of α-bromopiperidyl phenyl ketones, in which the possibility of any interaction between the nitrogen atom and the carbonyl group was either minimized or completely excluded were prepared by procedures previously developed in these Laboratories. Attempts to convert these α-haloketones to piperidinecarboxylic acids by means of the Favorski rearrangement catalyzed by silver ion were generally unsuccessful, but 1-benzoyl-4-phenylisonipeptic acid was formed as the result of the rearrangement of the carbon skeleton of 1, 4-dibenzoyl-4-bromopiperidine. Most frequently, however, these reaction conditions were found to favor a trans elimination so that an α, β-unsaturated ketone was the primary product usually obtained upon treatment of these α-bromoketones with aqueous silver nitrate. In other cases when neither rearrangement nor dehydrohalogenation occurred, the product, an α-hydroxyketone, was one in which simple replacement of the bromine atom had transpired. These results are best explained on the basis of the geometry of each particular α-bromopiperidyl phenyl ketone; and it may be concluded, as has been done by several previous investigators, that rearrangement occurs only when the α-bromine atom and the carbonyl group are capable of assuming a specific spatial orientation.

Two of the α-bromoketones, 1-methyl-3-benzoyl-3-bromopiperidine hydrobromide and 1-benzyl-4-benzoyl-4-bromopiperidine hydrobromide, were converted to the corresponding
azaspiro (2,5) octanes by treatment with sodium methoxide in anhydrous methanol. These epoxyethers were transformed into a series of 3- (or 4-) piperidinol esters respectively by means of the acid catalyzed ring opening reaction which was prompted by a variety of carboxylic acids. Since these esters were similar in structure to certain piperidinol derivatives known to be potent analgesics they were submitted for pharmacological screening.

By the use of controlled conditions it was possible to hydrogenate selectively the pyridinium ring of 3-benzoylpyridine methobromide, (X), so that 1-methyl-3-benzoyl-piperidine could be obtained in reasonable yield. The identity of this ketone and the other products of the reduction, 1-methyl-3-piperidylphenylcarbinol and 1-methyl-3-benzyl-piperidine, was established by either an alternate synthesis or through their physical and chemical properties. The mode of formation of 1-methyl-3-benzoylpiperidine was determined by following the course of the catalytic hydrogenation of (X) and that of two model compounds, 3-pyridylphenylcarbinol methobromide and 1-methyl-1,4-dihydropyridine, spectrophotometrically. The data thus obtained established that reduction of the pyridinium ring of (X) precedes the reduction of the carbonyl group, and indicates the presence of a transitory stage which absorbs strongly at 317 m\(\mu\) and which may well be a tetrahydropyridine. Two mechanisms are presented to account for the formation of the intermediate responsible for the 317 m\(\mu\) band and they are examined in the light of addi-
tional evidence obtained upon the catalytic reduction of (X)
and 1-benzylnicotinamide bromide in basic solution.
BIBLIOGRAPHY

6. (a) B. Tohoubar, Comp. rend. 235, 720 (1952).
    77, 444 (1955).
    80, 992 (1958).
    23, 1109 (1958).
    Acta, 39, 1451 (1956).
    74, 5352 (1952).
20. E. E. Smissman and G. Hite, Abstract of Papers, 135th
    Meeting, American Chemical Society, 18 N (1959).
    77, 5418 (1955) and preceding papers.
23. H. Kaegi and K. Miescher, U.S. Patent 2,486,795:
    C. A., 44, 7887 (1950), Swiss Patent 259,442: C.A.,
    44, 5920 (1950).
24. L. J. Bellamy, The Infrared Absorption Spectra of
    Complex Molecules, 1st edition, J. Wiley and Sons, Inc.,
    N. Y., 1956.
25. K. Dobriner, E. R. Katzenellenbogen and R. Jones,
    Infrared Absorption Spectra of Steroids, Interscience
26. A. Burger, Medicinal Chemistry, Interscience Publishers,


BIOGRAPHICAL DATA

Name in Full               Glenn Homer Warner
Date of Birth       December 15, 1930
Place of Birth      Easton, Pennsylvania
Collegiate institutions attended

<table>
<thead>
<tr>
<th>Institution</th>
<th>Dates</th>
<th>Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bucknell University</td>
<td>1948-1952</td>
<td>B.S.</td>
</tr>
<tr>
<td>University of Maine</td>
<td>1953-1955</td>
<td>M.S.</td>
</tr>
</tbody>
</table>

Publications