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THE ACID-CATALYZED REACTIONS OF SOME UNSYMMETRICAL PIPERIDINE GLYCOLS

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BY

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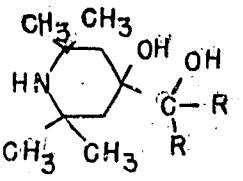
TABLE OF CONTENTS

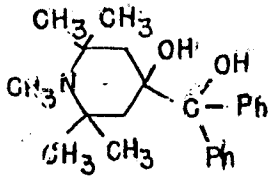
INTRODUCTION

The elucidation of the mechanism of the pinacol rearrangement has been the object of several excellent researches during the past fifty years. As a result, data have been compiled and classified embracing many important features of the reaction (1) (2) (3) (4). Formerly much was written concerning both the relative migratory aptitudes of the glycol substituents and the effect of their electronic character on the stabilization of the transitory carbonium ion. Today these are still mentioned occasionally; however, more important aspects have been investigated such as the effect of stereochemistry on the migrating group and the stability of the intermediates. The influence of various acids on the course of the transformation has also been noted. The products of the rearrangement often defy predictions when examined by older postulates.

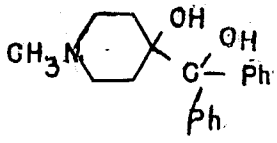
The study of these facets of the rearrangement has received little attention in the nitrogen heterocyclic field (5) (6). A beginning, however, has been realized in the piperidine series. Orthner (7) reported that the 4-hydroxy-2,2,6,6-tetramethyl-4-piperidyldialkylcarbinols (I) underwent dehydration on reaction with boiling mineral acid and were not converted by rearrangement into carbonyl compounds. On the other hand 4-hydroxy-1,2,2,6,6-pentamethyl-4-piperidyldiphenylcarbinol (II) and 1-methyl-4-hydroxy-4-piperidyldiphenylcarbinol (III) were converted to carbonyl compounds using both protonic and other Lewis acid catalysis (8) (9).



I, R= CH_3, C_2H_5

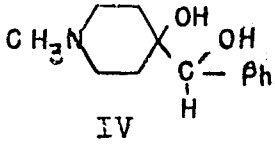


II

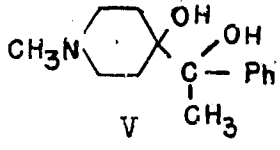


III

Since the behavior of 4-hydroxy-4-piperidylcarbinols containing an alkyl or hydrogen substituent attached to the carbon bearing an aryl grouping has not been determined, and in view of the complete and interesting information existing with the analogous carbocyclic glycols, it seemed desirable to bridge this gap by studying the pinacol rearrangement of 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (IV) and 1-methyl-4-hydroxy-4-piperidylphenylmethylcarbinol (V) under the influence of various protonic and other Lewis acids.



IV



V

Thus with parallel studies available in both the cyclohexane and piperidine series, any similar or dissimilar behavior characterized by differences in the products from these series when subject to the action of protonic and Lewis acids might indicate conformational differences or polarity effects due to the presence or absence of the N-hetero atom (10). Furthermore, in this light the study of the rearrangement of the glycol (IV) would be of special interest, for this glycol represents the first example of the acid catalyzed reaction of a heterocyclic "hydrobenzoin" potentially possessing the alternative of phenyl versus hydrogen migration. The

pinacol rearrangement among such 1,2-diols is somewhat unsettled (11) because of ambiguity in the mechanism (3). The glycol (V), on the other hand, would represent a sort of hybrid of all the piperidyl glycols studies, having structural features which would allow dehydration on the side chain to occur, a feature which is not available in glycols II, III and IV, and possessing at the same time an aryl substituent not present in the glycols (1).

DISCUSSION

The Pinacol Rearrangement and Related Work

Since its discovery in 1860, the pinacol-pinacolone rearrangement named after the original transformation of tetramethylethylene glycol to methyl tert-butyl ketone, has been applied to a wide variety of 1,2-diols and their derivatives. A true pinacol rearrangement comprises an acid-catalyzed monodehydration of an alpha glycol resulting in the formation of ketonic or aldehydic products which usually possess a rearranged carbon skeleton. The rearranging aspect of the reaction is the transfer of a group from one carbon atom to the adjacent carbon. When the shifting group is hydrogen, the carbon skeleton remains unchanged. Some glycols, depending on the structure or conformation of the molecule and the reaction conditions, give, in addition to the pinacol rearrangement, dehydration to dienes, cyclodehydration (double dehydration), epoxidation or in rare cases bimolecular dehydration to form dioxanes. The earliest postulates concerning the nature of the intermediate in the pinacol rearrangement centered on three-membered rings. Although one of these, a cyclopropane, has long since been disproved, Cram (12) recently has cited evidence for a discrete bridged phenonium ion intermediate occurring in the related Wagner-Meerwein rearrangement, Fig. 1.

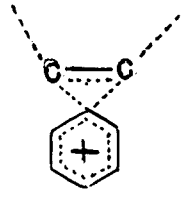
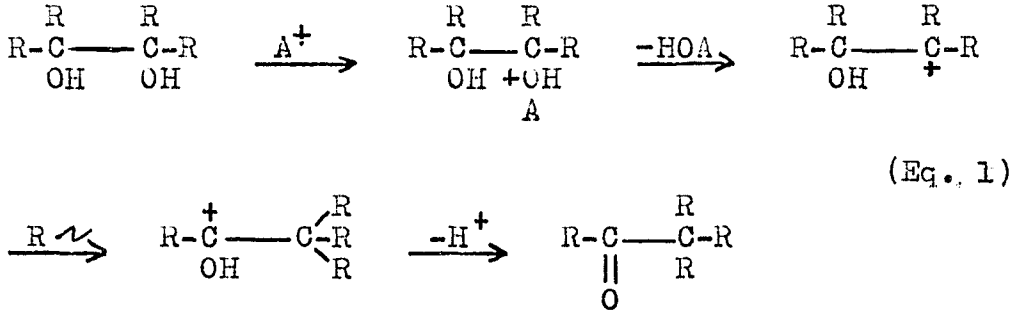


Fig. 1

The epoxide intermediate was also postulated since some epoxides isomerize to the same products as the pinacol rearrangement under the same reaction conditions. However, this is not generally true and in cases which can accommodate an epoxide intermediate, the isomerization, on acidic ring opening would probably reduce to a Whitmore 1,2-shift mechanism (2) (13), which is the currently accepted pathway of the pinacol and allied rearrangements. The acid species, A^+, effects the ionization of one of the hydroxyl groups leading to the formation of an electron deficient carbon atom, a carbonium ion; this is followed by an intramolecular 1,2-shift of a group, R, with its electrons (migration) to the carbonium ion. This results in the formation of another carbonium ion which is the resonance-stabilized hybrid of the protonated carbonyl function. The entire process may be wholly concerted and probably does not occur stepwise as depicted in Equation 1.



(Eq. 1)

It is immediately obvious that with this mechanism, the course of the transformation in glycols containing dissimilar groupings will be largely determined by which of the two hydroxyl groups is ionized and secondly which of the two groups will migrate. The predictability of these features

of the rearrangement have enjoyed a certain measure of success when removed from any stereochemical factors. Thus by the appropriate choice of some symmetrical glycols, Fig.2, in which the ionization of either hydroxyl offers the same migrational alternative between R and R' it has been found, in general, that the order of mobility increased with nucleophilic character, i.e.... p-anisyl⟩ phenyl⟩ methyl; hydrogen⟩ methyl.

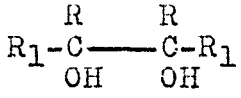


Fig. 2

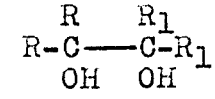
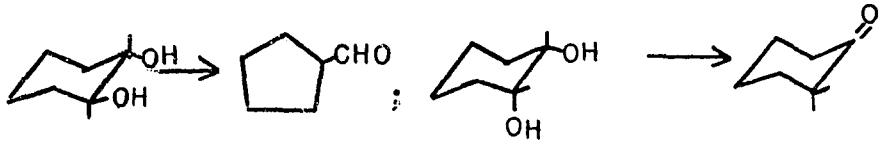


Fig. 3

This has been borne out by similar studies of symmetrical heterocyclic analogs of benzopinacol, which revealed that phenyl migrated to the complete exclusion of 2-or 3-pyridyl groups while the reverse was true for the 2-furyl and 2-thienyl substituents (5). The furyl and thienyl nuclei contain unshared pairs of electrons at the hetero atom which are capable of resonating with the π-electrons of the carbons in the five-membered ring (14). The resulting high nucleophilic character of these systems, which is not present in the unsubstituted phenyl or pyridyl nuclei, thus enables these systems to possess a relatively high migratory aptitude. The pyridyl nucleus, judging from its reluctance to undergo electrophilic substitution, would be expected to exhibit negligible migrational tendency even without the added deactivation which can result by protonation of the ring by the acidic medium. In this regard, recently it has been suggested that in protonic medium a weakly basic group exists in equilibrium with the protonated

form and as a consequence the para-aminophenyl group rearranges to the exclusion of methyl regardless of the protonic medium. Presumably the migration occurred when the equilibrium was favorable, i.e., in the unprotonated form. Thus it is probable that acid media would only influence the rate of the reaction and not which group migrates (15).

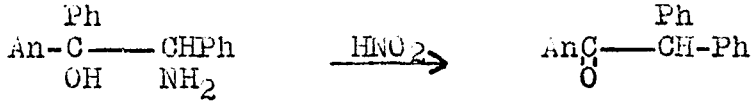
When a "symmetrical" glycol such as 1,2-cyclohexanediol is subjected to the conditions of the pinacol rearrangement, the products of the reaction depend on the geometrical isomer employed (16). The cis modification furnishes cyclohexanone almost exclusively while the trans compound gives only formylcyclopentane, Equation 2. This sequence suggests that a 1,2-shift of a grouping should be favored by that conformation of the molecule in which the migrating group is trans and coplanar with respect to the departing hydroxyl.



(Eq. 2)

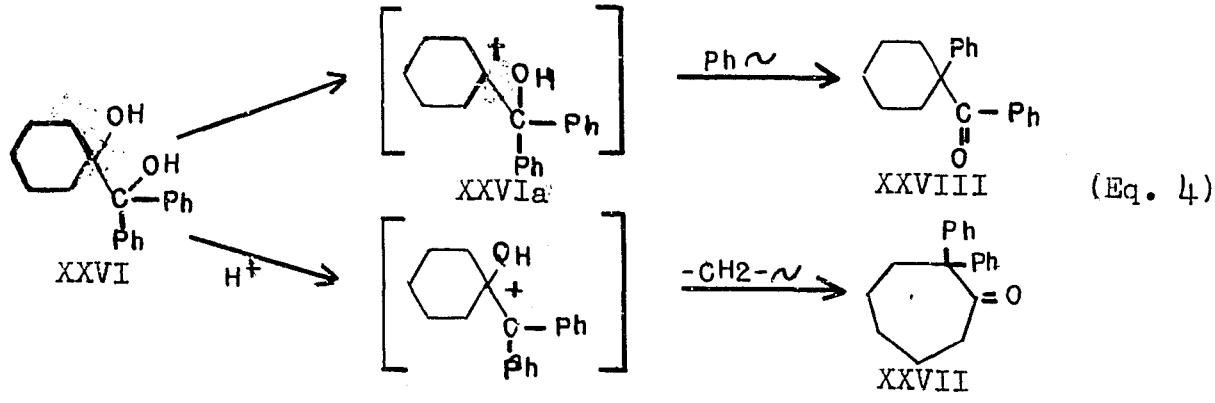
By a study of appropriate unsymmetrical glycols, Fig. 3, it has been found in general that the order of stability of a carbonium ion decreases from tertiary to primary. If both carbonium ions that are possible are tertiary a diaryl carbonium ion forms in preference to a dialkyl. Approximately the same stabilization of a carbonium ion results with two alkyl groups as with one aryl substituent. However, it has been pointed out that in unsymmetrical pinacols one group may migrate by one mechanism and a second group by another, and the product formed is dependent on which mechanism

is the more energetically feasible, not necessarily which possible carbonium ion is more stable or which group has the greater migratory aptitude (4). Stereochemical requirements dictate the course of the reaction to such an extent that previously established migrational rules have been upset. Thus phenyl (Ph) migration occurs with the virtual exclusion of migration of p-anisyl (An) in the semi-pinacolic deamination of the α-racemate of 1,2-diphenyl-1-p-anisyl-2-aminoethanol, Equation 3, (17).



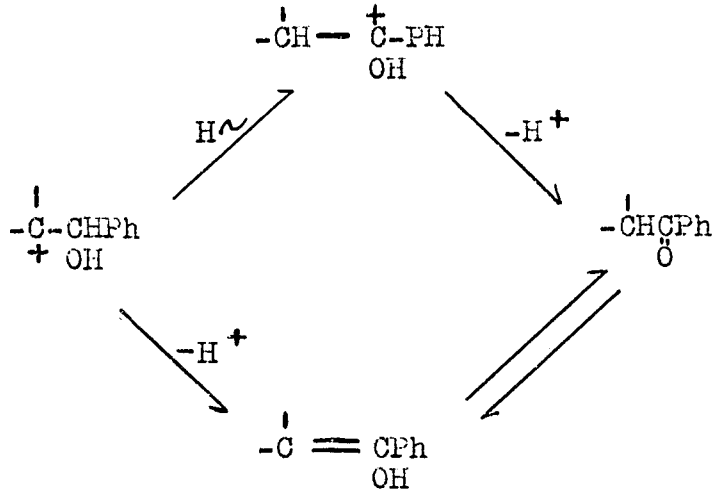
(Eq. 3)

A preferential rearrangement has been described in which the pinacol rearrangement of 1-(1-hydroxycyclohexyl)-diphenylcarbinol (XXVI) in protonic media furnishes the expected 2,2-diphenylcycloheptanone (XXVII) while in the absence of any protons, the rearrangement apparently proceeds via the dialkyl carbonium ion (XXVIa) furnishing 1-(1-phenyl-cyclohexyl) phenyl ketone (XXVIII) exclusively (18), Equation 4. A similar selectivity also has been observed with the N-methyl-4-piperidine analog (III) (9).



(Eq. 4)

The relative ease of migration of hydrogen and phenyl has not been clearly established. When a glycol presents the possibility of a phenyl versus hydrogen migration such as hydrobenzoin, the ketonic product could conceivably arise by an intramolecular hydrogen migration or by dehydration of the "hydrobenzoin" to the enolic tautomer of the finally formed phenyl ketone, Equation 5.



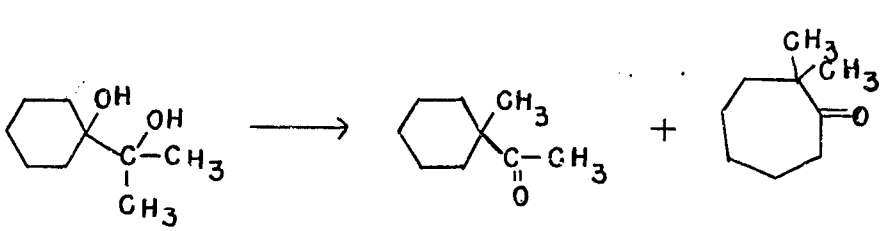
(Eq. 5)

A further complication arises from this "hydrobenzoin" rearrangement for the product of phenyl migration, an aldehyde, can itself undergo rearrangement under the reaction conditions to give a ketone (3). This reaction appears to be the result of one migration but actually the product is formed by three overall migrations, only one of which can be credited to hydrogen. The use of optically active glycols has revealed the necessity of postulating some intramolecular hydrogen migration because retention of optical activity was observed at the carbon losing the oxygen (migration terminus) (19).

An excellent study was made by Collins (11) in an effort to determine the contributions of the aldehyde to ketone rearrangement by employing chain and ring labeled carbon-14 in the

triphenylethylene glycol system. The reactions of the labeled glycol were studied under the influence of five acidic catalysts differing in their ability to cause ionization of the hydroxyl. The extent of carbon-14 migration in the benzhydryl phenyl ketone obtained by the rearrangement of the labeled glycol indicated that the ratio of phenyl/hydrogen migration may vary by a factor of 180, depending on the catalyst. In the reaction medium assumed to favor classical or open carbonium ions (cold concentrated sulfuric acid) the ratio was highest, 7.33, while in the reaction medium assumed to favor a concerted process (refluxing dilute hydrochloric acid-dioxane) the ratio was as low as .0406. The relative contribution, if any, of the tautomeric enol intermediate could not be distinguished by this technique, and the use of hydrogen isotopes has been proposed as a possible method for solving this question by both Ingold (3) and Collins (11).

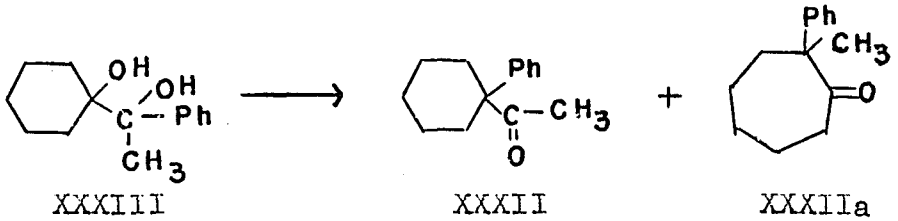
The application of the pinacol rearrangement to alicyclic systems has given interesting results of both synthetic and theoretical significance. In 1913 Meerwein (20) reported that the rearrangement of 1-(1-hydroxycyclohexyl)-dimethylcarbinol did not proceed smoothly and that ketone formation was accompanied by dehydration giving olefins. The ketones were obtained in a 2:1 ratio of methyl migration to ring enlargement respectively, Equation 6.



(Eq. 6)

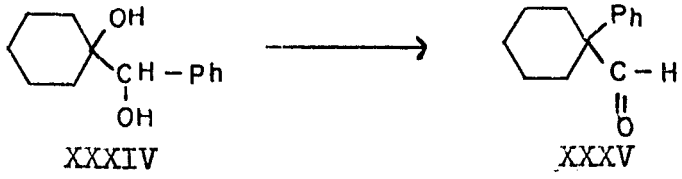
The pinacol rearrangement of the diphenyl analog (XXVI) was postulated by Meerwein to undergo dehydration to the epoxide. This rearrangement was reinvestigated in 1951 by Lyle and Lyle, who observed the selective rearrangements already mentioned with no evidence of epoxide formation (18).

The pinacol rearrangement of the mixed analog, 1-(1-hydroxycyclohexyl)-methylphenylcarbinol (XXXIII), was first studied by Russell (21) and Lyle (22) and later by Cauqil (23). In protonic medium, cold concentrated sulfuric acid, about 72% of ring expansion to methylphenylcycloheptanone (XXXIIa) was observed (22) (23); the remaining 28% of the product was the result of phenyl migration, XXXII, Equation 7. This corresponds to a 3:1 ratio of the relative stabilities of the two possible carbonium ions. Boiling 50% sulfuric acid gave only a 31% yield of XXXII; the remainder of the product was not identified (21). Employing non-protonic media, French workers (24) obtained the methyl ketone (XXXII). The fact that a methyl group has replaced a phenyl substituent apparently no longer exclusively furnished one carbonium ion in protonic medium.



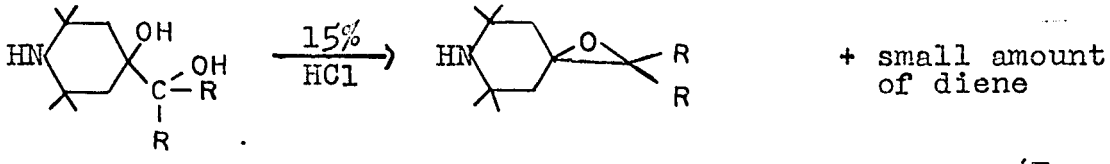
XXXIII XXXII XXXIIa (Eq. 7)

Felkin and Tchoubar (25) have stated, without the benefit of experimental details, that 1-(1-hydroxycyclohexyl)-phenyl carbinol (XXXIV) underwent dehydration to form 1-formyl-1-phenylcyclohexane (XXXV), Equation 8.

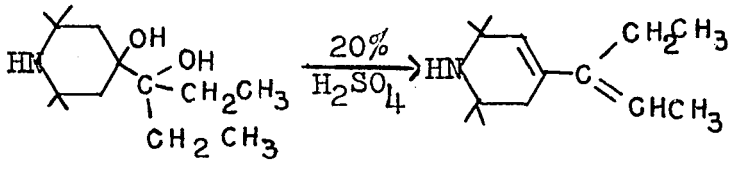


XXXIV XXXV (Eq. 8)

In 1927, Orthner (7) attempted to cause the pinacol rearrangement of some 2,2,6,6-tetramethyl-4-hydroxy-4-piperidyldialkylcarbinols (I). Like Meerwein's dimethyl carbocyclic analog, Equation 6, olefins were formed but carbonyl compounds could not be detected, Equation 9.



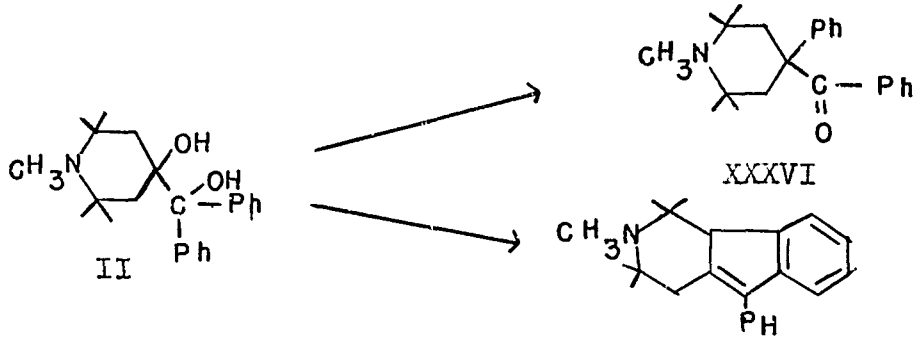
I (Eq. 9)



These results led Orthner to the conclusion that in ditertiary glycols which have one hydroxyl group attached to a piperidine ring, dehydration is the rule with no rearrangement, because the formation of the piperidinium ion would inhibit the formation and reactivity of the carbonium ion, presumably by a field effect. However, the highly substituted piperidine ring used by Orthner introduces an added conformational factor (10) which possibly would prevent the migration of alkyl groups or ring carbon. The availability of hydrogen in alkyl groups then probably directs the reaction to dehydration.

Chauvette (8), employing the diphenyl analog of Orthner's

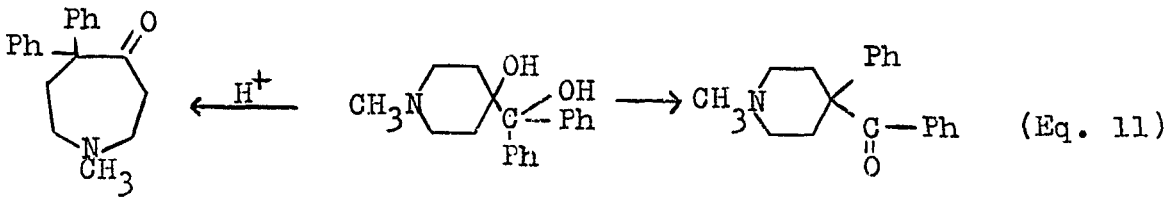
glycols, studied the pinacol rearrangement of 1,2,2,6,6-pentamethyl-4-hydroxy-4-piperidyldiphenylcarbinol (II) and found that the product of phenyl migration (XXXVI) was obtained using a boiling protonic medium, Equation 10. The reaction of II with cold concentrated sulfuric acid, however, gave a disulfonated form of a monodehydrated product and a trace of what was believed to be the ketonic product resulting from ring enlargement. The use of p-toluenesulfonic acid, which might be expected to catalyze the rearrangement in the same fashion as sulfuric acid, without sulfonation, furnished the cyclodehydrated indeno pyridine (XXXVII), Equation 10.



(Eq. 10)

Lyle and Lyle (18) have studied the pinacol rearrangement of 1-methyl-4-hydroxy-4-piperidyldiphenylcarbinol (III) under conditions comparable to their study of the analogous carbocyclic compound XXVI. With cold concentrated sulfuric acid 79% of the product of ring expansion was obtained as evidenced by the isolation of 1-methyl-5,5-diphenyl-1-aza-4-cycloheptanone (XXXVIII). Although the yield (40%) was poorer, and the hydrochloride salt was necessary for smooth rearrangement, the product obtained from non-protonic medium

was the phenyl ketone (XXXIX), Equation 11. Thus the piperidine glycol (III) gave reactions paralleling the type of rearrangements noted for the carbocyclic compound (XXVI), although the yields were not identical.



(Eq. 11)

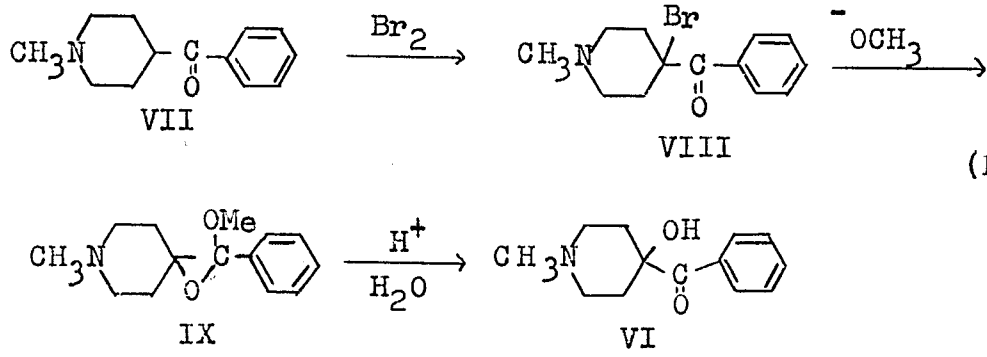
XXXVIII III XXXIX

The behavior of 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (IV) and 1-methyl-4-hydroxy-4-piperidylphenylmethylcarbinol (V) comprises the subject of this work. Their reactions under the conditions of the pinacol rearrangement used with the aforementioned piperidine glycols and the corresponding carbocyclic glycols are described in detail.

Preparation of the Starting Materials

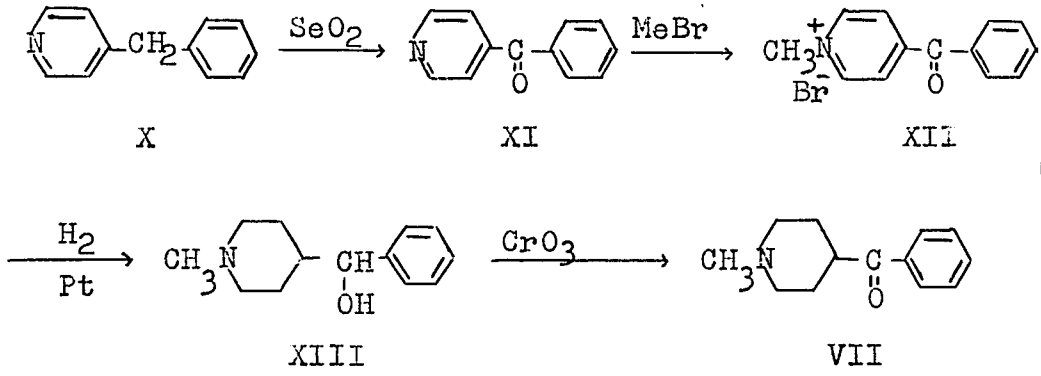
The preparation of 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (IV) and 1-methyl-4-hydroxy-4-piperidylphenylmethylcarbinol (V) was dependent on the synthesis of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (VI) which had been prepared in This Laboratory (26) by the procedure shown in Equation 12. The bromination of VII hydrobromide in chloroform solution furnished the hydrobromide-perbromide of VIII, which, after treatment with phenol to remove the perbromide linkage, was converted to the epoxyether (IX) by reaction with alcoholic sodium methoxide. The desired hydroxy ketone (VI) was obtained by the treatment of IX with dilute mineral acid. These reactions proceeded in high yield, and the problem of

preparation of the starting material thus was reduced to a satisfactory method of synthesis of 1-methyl-4-piperidyl phenyl ketone (VII).



(Eq. 12)

The original procedure for obtaining VII in This Laboratory was the acylation of benzene by 1-methylisonipecotyl chloride hydrochloride using Friedel-Crafts reaction conditions (27). Although this reaction consistently gave good yields, 90% of VII, the mechanical operations were tedious and time consuming. This difficulty in conjunction with the commercial availability of 4-benzylpyridine (X), suggested the study of alternate routes of the synthesis of VII starting with X. The procedure illustrated in Equation 13 was ultimately adopted and served as the method of choice.



(Eq. 13)

The oxidation of X to 4-pyridyl phenyl ketone (XI) with either neutral or acidic permanganate as reported in the literature (28) (29) was repeated in yields of about 65%. Better yields (92%) of 4-pyridyl phenyl ketone (XI) were obtained by the Friedel-Crafts acylation of benzene by isonicotinyl chloride (27); however, this synthesis suffered the same disadvantages as the previously mentioned Friedel-Crafts acylation.

Since the methylene group to be oxidized is activated by two aromatic rings, selenium dioxide appeared to be a logical reagent for this purpose (30). The investigation of this reaction showed that XI consistently could be prepared in yields of 80% or better. Also, the reaction presented a minimum of mechanical difficulties. Later during this work, 4-pyridyl phenyl ketone (XI) became available commercially from Reilly Tar and Chemical Corp.

The quaternary methiodide (XIIa) or methobromide (XII) of XI was prepared readily by the reaction of XI with the appropriate methyl halide in methanol solution. The methiodide XIIa was yellow colored and had a limited solubility in methanol or water. The extent of reduction of XIIa at pressures of 3-4 atmospheres over platinum at room temperature was governed by the solubility of XIIa, the degree of purity of XIIa, the amount of catalyst, and the length of the reduction period. Incomplete reductions were characterized by a purple coloration which appeared when the reduction mixture was neutralized with base. Little or no carbinol (XIII) was isolated from such reactions. This undesirable feature

could be avoided by the use of more catalyst, or better, by employing the colorless and less sensitive quaternary methobromide (XII). When the hydrogenation was substantially complete, the carbinol (XIII) precipitated quantitatively on neutralization of the reaction mixture, and no color change was observed.

The preparation of XIII hydrobromide by the conventional procedure of passing dry hydrogen bromide gas into an ethereal solution of the base failed to give a crystalline product. This difficulty was overcome by employing the catalytic reduction of XII in methanol and subsequent evaporation of the filtered solution. The XIII hydrobromide prepared in this way also was hygroscopic, and recrystallization of the product failed to give a sharp melting solid.

For this synthesis it was desired that the catalytic hydrogenation of XII and XIIa would not reduce the carbonyl group first but would primarily attack the ring and furnish directly the desired ketone (VII). The investigation of the hydrogenation, however, indicated that the carbonyl was the first functional group to undergo reduction and 4-pyridyl phenyl carbinol (XIV) was an intermediate in this reduction. Conversely, there is no evidence that VII hydrohalide is an intermediate in the catalytic reductions of XII and XIIa. The following experimental observations lend support to these statements:

a. A reduction of XIIa in methanol, conducted with insufficient catalyst (50:1 by weight), furnished a methiodide, different from XIIa, which did not

depress the melting point of the methiodide of authentic 4-pyridyl phenyl carbinol (XIV).

b. A reduction of the pure methobromide (XII) in chloroform, using excess catalyst (20:1 by weight), was immediately interrupted after only a small initial uptake of hydrogen by a tarry precipitate on the surface of the catalyst. The hydrogenation ceased, presumably, when the catalyst was deactivated by a coating of the chloroform-insoluble intermediate, the methobromide of XIV.

c. The phenyl ketone (VII) in methanol or dilute acid was recovered unchanged when subjected to conditions which cause the hydrogenation of either the quaternary or hydrohalide salts of XI. This failure of VII to undergo reduction on catalytic hydrogenation might be explained on the basis of a strong intramolecular interaction between the carbonyl linkage and the amino nitrogen which would exist in both neutral and acidic media, Fig. 4, thus preventing a required orientation of the carbonyl on the surface of the catalyst. The quaternary or hydrohalide salts of XI are planar, and reduction of the carbonyl proceeds readily.

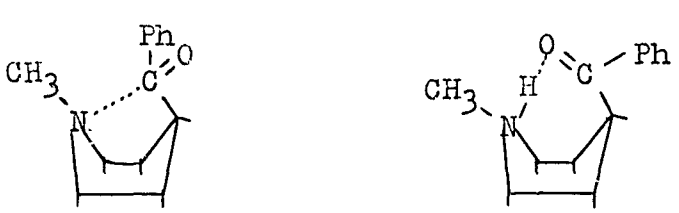


Fig. 4

The oxidation of the carbinol (XIII) was attempted employing nitric acid, potassium permanganate, hypohalite and aqueous potassium dichromate-sulfuric acid. Only the latter oxidation produced any ketone (VII), as shown by a positive oximation reaction. Sugimoto (31) reported that the oxidation of XIII to VII proceeded in 70% yield by the use of chromic anhydride in acetic acid at 90°. A modification of this procedure, employing a reaction temperature of 100°, gave an improved yield (85%) of VII.

The isolation of VII was complicated by the necessity of extracting the base from an alkaline medium, thus causing the precipitation of the interfering chromic hydroxide. This gelatinous solid caused the formation of a stable emulsion on extraction with organic solvents. To avoid this difficulty, a continuous extraction of the water insoluble solids in a Soxhlet extractor was attempted; however, the ether failed to penetrate the gel and dissolve the entrapped VII. Also the volume of the extraction chamber was too small to allow large scale runs. The filtration of the gelatinous mass was extremely slow, and frequently the filter clogged before the operation was completed. Filter aids such as asbestos were ineffective. To avoid extraction and filtration entirely the isolation was attempted by steam distillation, but the desired ketone (VII) was not volatile with steam.

A satisfactory method of isolation was finally achieved by removing acetic acid, the solvent of the oxidation, by distillation under reduced pressure, dissolving the dark green residue in chloroform, and saturating the resulting solution

with hydrogen bromide gas. The chloroform was removed by distillation, and the green residue was dissolved in hot isopropyl alcohol. On cooling VII hydrobromide precipitated in a form satisfactory for the subsequent bromination reaction.

Because of the successful use of selenium dioxide and chromium trioxide as oxidants, an even shorter route to the phenyl ketone (VII) was possible if either of these reagents could effect the oxidation of 1-methyl-4-benzylpiperidine (XV) to 1-methyl-4-piperidyl phenyl ketone (VII) in satisfactory yield. Villani (27) reported the isolation of 18.5% of VII from the oxidation of XV with chromic acid in boiling acetic acid.

The 1-methyl-4-benzylpiperidine (XV) used for this oxidation study was prepared by the low pressure catalytic hydrogenation of X methobromide following the procedure for the reduction of XII. The catalytic hydrogenation was superior to the sodium-alcohol reduction and methylation synthesis (13), for the catalytic reduction was rapid and afforded a high yield of XV in a pure state (32). Unfortunately, no reaction occurred on treatment of XV with either selenium dioxide or chromium trioxide, using conditions identical to the oxidation of X and XIII, respectively, for the infrared absorption spectrum of XV was not changed by these treatments.

Thus the most satisfactory method for the synthesis of 1-methyl-4-piperidyl phenyl ketone (VII) was found to be that represented by Equation 13. VII hydrobromide was then converted to 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (VI) by the procedure of Troscianiec (26), illustrated by Equation 12.

By operating on the carbonyl group of VI, the desired glycol could be prepared readily. Thus the reaction of VI with methyl lithium in absolute ether was performed several times, and the yields of 1-methyl-4-hydroxy-4-piperidylphenylmethylcarbinol (V) were always over 90%. The corresponding reactions of VI with ethyllithium and isopropyllithium, however, furnished the glycols (LIX and LX) in 27% and 45% yields, respectively.

The reduction of the carbonyl group of VI to give the desired 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (IV) was attempted using complex metal hydrides and catalytic hydrogenation. The reduction of the hydroxy ketone VI with sodium borohydride in aqueous methanol apparently effected the desired reduction, but the formation of boron complexes, as evidenced by the occurrence of pronounced color changes, complicated the isolation of the product. Only 15% of the expected amount of glycol (IV) was obtained even after treatment of the reduction product with hot alkali, which should hydrolyze any complex present. On the other hand, quantitative yields of the glycol (IV) were obtained in excellent purity by the action of ethereal lithium aluminum hydride on the hydroxy ketone (VI). Catalytic hydrogenation of VI was attempted at low pressure over Raney nickel or Adams' catalyst in methanol or acidified aqueous methanol, respectively. These reductions, however, did not give satisfactory yields of IV, and there were indications that the aromatic ring was being reduced in the acid media over platinum oxide. A quantitative yield of VI hydrochloride was obtained

from the attempted catalytic reductions of VI over Adams' catalyst in chloroform. Similar unexplained observations have been cited in the literature from time to time (33). The superior yield and purity of product led to the exclusive use of lithium aluminum hydride for the preparation of glycol (IV).

As expected, the hydrochloride of IV could not be crystallized when it was prepared by the conventional procedure. On the basis of previous experience, the catalytic reduction of VI hydrochloride in methanol appeared to be a logical method for the isolation of crystalline IV hydrochloride, for this technique allowed the successful preparation of crystalline XIII hydrobromide. Reduction of VI hydrochloride, however, also failed to furnish a crystalline product. The base which formed on neutralization of the reduction product appeared to be impure IV. Several recrystallizations of this mixture from ligroin gave a sharp melting unknown solid. This unknown gave no reaction with ethereal lithium aluminum hydride, and the infrared absorption spectrum of the unknown showed no absorption in the carbonyl stretching region. Thus the carbonyl group of VI had been reduced. The unknown, however, appeared to have suffered hydrogenation of the benzene ring as well as the carbonyl as shown by the following data:

a. The percentage of hydrogen in this product was greater than that in IV.

b. The ultraviolet absorption spectrum exhibited maxima at the same wavelengths as in pure IV, but the absorption was much less intense, Fig. 5. Calculations

based on pure IV as a standard revealed that 73% of the unknown solid was non-aromatic (34).

c. The infrared absorption spectrum indicated the presence of hydroxyl, causing absorption at 3570 cm^{-1}, and the absorption resulting from a monosubstituted benzene ring at 700 cm^{-1} and 750 cm^{-1} (35) was very weak compared to the absorption of pure IV in the same region.

d. An attempted high pressure hydrogenolysis of the pure glycol (IV) with Raney nickel at 100° C, conditions more favorable to benzene ring reduction, performed by Troscianiec (26) in an effort to obtain 1-methyl-4-hydroxy-4-benzylpiperidine (XVI), instead furnished this same unknown solid. Identity was established by melting point and mixed melting point in addition to the essentially superimposable infrared absorption spectra.

It is interesting to note that the platinum catalyzed hydrogenation of 4-benzylpyridine (X) in dilute hydrochloric acid solution has been reported by Veer and Goldschmidt (36) to result in reduction of the benzene ring. The corresponding reduction with the 2-isomer however fails to hydrogenate the benzene ring.

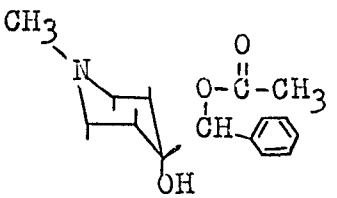
Reactions of 1-Methyl-4-hydroxy-4-piperidylphenylcarbinol (IV)

1-Methyl-4-hydroxy-4-piperidylphenylcarbinol (IV) when heated under reflux with p-toluenesulfonic acid in glacial acetic acid gave a thick viscous oil which resisted purification by

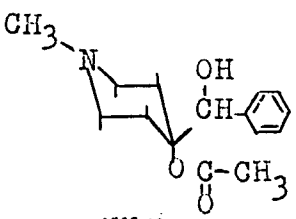
crystallization and distillation under reduced pressure. The reaction of the crude product with ethereal lithium aluminum hydride gave only IV. The oil was characterized by conversion to the picrate. The molecular weight of the picrate, as determined by the spectrophotometric method of Cunningham (37), and the elemental analysis of this derivative corresponded to the diacetate of IV, 1-methyl-4-acetoxy-4-piperidylphenylmethyl acetate (XXIX). Pure XXIX picrate was decomposed with hot alcoholic alkali to regenerate the glycol (IV). These results indicate that the medium, p-toluenesulfonic acid in boiling glacial acetic acid, does not cause dehydration of the glycol (IV) but rather results in acylation of IV to give the diacetate (XXIX).

When the glycol (IV) was treated with boron trifluoride-etherate in boiling glacial acetic acid, again acetylation resulted, and both a crystalline and an oily material were isolated in a ratio of about 2:1 respectively. The minor product, a viscous oil, resembled XXIX obtained from the aforementioned p-toluenesulfonic acid reaction and was shown to be the diacetate (XXIX) by the melting point and mixed melting point of the picrate derivative. The solid product (XXX) was quantitatively converted to IV by ethereal lithium aluminum hydride or saponification with warm alcoholic potassium hydroxide. The infrared spectrum of XXX showed absorption due to the hydroxyl group (3140 cm^{-1}) and acetate carbonyl (1730 cm^{-1}), and the elemental analysis confirmed the structure to be the monoacetate of IV.

It would be reasonable to assume that the secondary hydroxyl of IV was acetylated in preference to the tertiary (perhaps axial) hydroxyl resulting in the hydroxy ester (XXXa) (38). This assumption would receive considerable support if the isomeric tertiary acetate XXXb could be synthesized unambiguously and a definite non-identity established by comparison with XXXa.



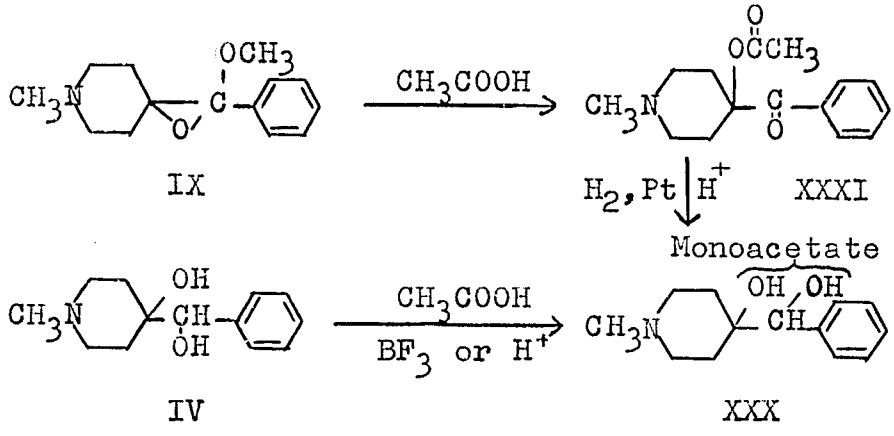
XXXa



XXXb

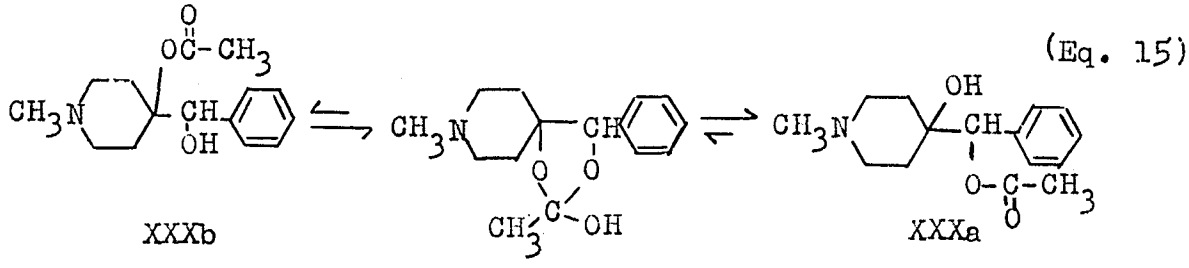
Since epoxy ethers are readily cleaved by various carboxylic acids to give the corresponding alpha keto ester (26) (39), IX was treated with glacial acetic acid to furnish 1-methyl-4-acetoxy-4-piperidyl phenyl ketone (XXXI) in high yield. The structure was in accord with both the infrared absorption spectrum and elemental analysis. Although the carbonyl group of 1-methyl-4-piperidyl phenyl ketone (VII) failed to undergo catalytic hydrogenation, the catalytic reduction of XXXI was not anticipated to be difficult in view of the facile reduction of the carbonyl group of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (VI). However, it was found that the carbonyl group of XXXI was unaffected by hydrogen over Adams' catalyst at low pressures and Raney nickel at both low and high pressures in neutral medium. After an attempted selective reduction of XXXI using sodium borohydride at 0° C. failed and XXXI was recovered, the reaction was repeated at room temperature. An intractable polymeric material was obtained. This product was reminescent

of the material resulting from the action of sodium borohydride on 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (VI) from which little or no solid could be isolated. Catalytic reduction in acid medium appeared somewhat precarious because the hydrolysis of the acetate linkage in XXXI could occur and also because the aromatic ring could undergo hydrogenation as mentioned earlier with VI. However, since no alternative remained for the reduction of XXXI, the acid catalyzed reduction of XXXI with platinum oxide was attempted. The reaction was found to be successful at either low or high pressures. The crystalline product, obtained in low yields, was found to be identical to XXX prepared from IV, Equation 14. The identity was established by melting point, mixed melting point and infrared absorption spectrum.



In view of the fact that the catalytic reduction of XXXI was carried out in acid medium and gave only a small yield of XXX, the synthesis was not confirmatory for the structure of XXXb. A reversibly formed cyclic intermediate could exist thus allowing an intramolecular ester interchange similarly to that observed to occur at very mild conditions by Stevens (39). Thus this glycol monoacetate as well as the glycol monoacetate resulting

from the esterification of IV may be the expected structure XXXa. The driving force of the acetate interchange during the reduction would be the relief of the steric interference of the tertiary (perhaps axial) acetoxy grouping in XXXb gained by shifting to the sterically more favorable position on the side chain in XXXa, Equation 15.



(Eq. 15)

XXXb XXXa

The differentiation of XXXa and XXXb by chemical methods does not appear to be a simple matter, and the existing spectral techniques (40) are complicated by shifts in the absorption maxima due to hydrogen bonding.

The same monoacetate (XXX) also was obtained as the only product from the reaction of IV with a boiling mixture of concentrated sulfuric acid and glacial acetic acid. It is interesting to note that sulfuric acid in a diluted state is without action in promoting dehydration of the glycol (IV). When acetic acid is the solvent, sulfuric acid catalyzes the acetylation, as does boron trifluoride and p-toluenesulfonic acid. If, however, water or methanol are employed as solvents, the glycol (IV) is recovered quantitatively. In addition, the following conditions led to the isolation of substantial amounts of unchanged glycol (IV), a) five hours heating with 90% formic acid

b) boron trifluoride and acetic acid at 95-100°C and c) four days standing in ether-methanol saturated with hydrogen chloride.

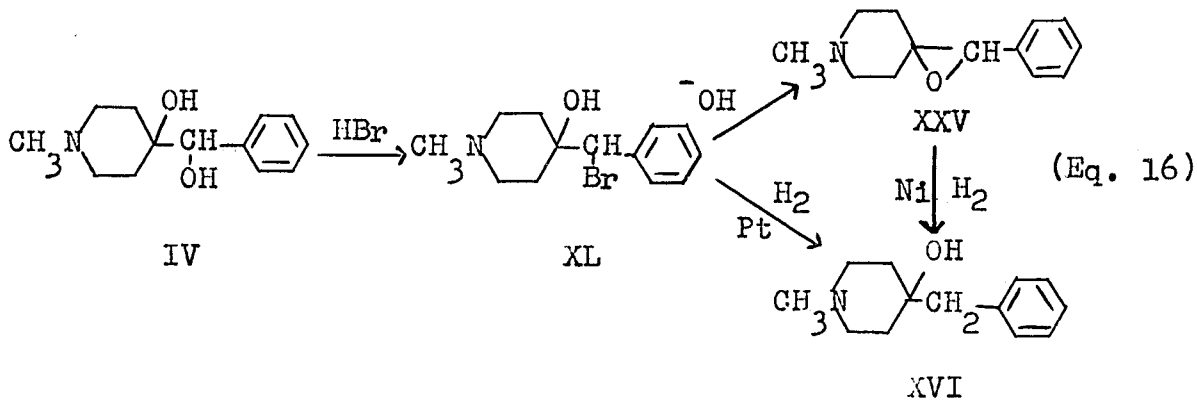
Thus in an effort to cause the rearrangement of IV, more rigorous conditions were attempted. From the reaction of IV with boiling 48.8% hydrobromic acid, 20% of the glycol (IV) was recovered, but the predominant product was an oil, whose elemental analysis was in perfect agreement with that calculated for a monodehydrated product, $C_{13}H_{17}NO$. The infrared absorption spectrum indicated that a small amount of at least two, and possibly three carbonyl containing compounds were present, for weak absorption bands were evident at 1719 and 1675 cm^{-1}, and a sharp inflection at 1700 cm^{-1}. The 3600-3100 cm^{-1} region was devoid of any bands, indicating the absence of hydroxyl groups. The ultraviolet absorption spectrum of the methiodide of the oil showed only the maxima characteristic of an isolated benzene ring. The small amount of carbonyl compounds obviously could not account for the analytical data. On the basis of this information and subsequent reactions there remained little doubt that the major product isolated was the epoxide, 6-methyl-2-phenyl-1-ox-6-azaspiro [2,5] octane (XXV).

The key reaction that led to the determination of this structure was the Raney nickel catalyzed hydrogenolysis of XXV to give the tertiary alcohol, 1-methyl-4-hydroxy-4-benzyl-piperidine (XVI), consequently excluding any possibility that the major product XXV contained a carbonyl. The epoxide ring was not entirely cleaved by hydrogen over Adams' catalyst in neutral medium nor by heating under reflux for two hours with a slight excess of lithium aluminum hydride in ether. The

latter reduction, however, did lead to the isolation of a small amount of impure 1-methyl-4-piperidylphenylcarbinol (XIII) which was purified and characterized as the methiodide. The carbinol (XIII) does not arise by reduction of the epoxide. The isolation of XIII chemically confirmed the suspicion that the stronger carbonyl absorption band at 1675 cm^{-1} was due to 1-methyl-4-piperidyl phenyl ketone (VII). From this incomplete reaction, both XVI and unchanged epoxide (XXV) were also isolated and identified as the methiodides. In another experiment, the presence of the phenyl ketone (VII) was further confirmed by fractionation of the reaction product. The higher boiling fraction was richer in the phenyl ketone (VII) and gave VII methiodide, shown by melting point and mixed melting point to be identical to authentic VII methiodide. The yield of VII methiodide corresponded to the formation of VII in about 5% yield.

Although boiling 48.8% hydrobromic acid might be anticipatated to cause a concerted intramolecular hydrogen migration (11) forming the phenyl ketone VII, one could hardly expect the epoxide (XXV) to form and survive this vigorous acidic condition. Orthner similarly has reported an epoxide to be the major product of the reaction of the piperidyl glycol (I) with boiling 15% hydrochloric acid. In view of the fact that a neutralization is required in the isolation procedure, a plausible explanation for the origin of the epoxide XXV seemed to be dehydrohalogenation of the halohydrin during the neutralization. The postulation of the formation of the bromohydrin, in this work, is in keeping with the notable inertness of glycol IV and could be verified

by the isolation and characterization of the intermediate bromohydrin. When the solvent was removed from the reaction mixture by distillation under reduced pressure, however, the red, oily residue could not be crystallized. This oily mixture of hydrobromides was dried thoroughly and traces of hydrogen bromide were removed by heating under reduced pressure in an Abderhalden "pistol" charged with potassium hydroxide. The bromine determination on this material was made using a modification of the Volhard method. The weighed sample first was treated with alkali, paralleling the workup procedure, and then acidified following the requirements of the Volhard titration. Due to contaminants, the bromine content was slightly lower than the value calculated for the pure bromohydrin hydrobromide (43.77%), but the experimental value was sufficiently high (39.72%) to indicate the presence of two potentially ionic bromides and approximately 90% of bromohydrin. Without using the modification mentioned above the Volhard method indicated 36.36% bromine. This would indicate that the covalent bromine was labile in the presence of silver ions. These data are in accord therefore with structure XL for the bromohydrin hydrobromide. Further evidence in support of XL as intermediate in the formation of XXV was obtained by hydrogenation of the crude hydrobromide in water over platinum oxide at 3-4 atmospheres to furnish, after neutralization, 1-methyl-4-hydroxy-4-benzylpiperidine (XVI), characterized as the methiodide. No evidence for the formation of the isomeric 1-methyl-4-piperidylphenylcarbinol (XIII) was obtained. This sequence is illustrated in Equation 16.



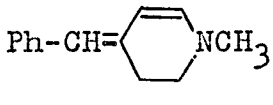
(Eq. 16)

The reaction of the glycol (IV) with boiling 48.8% hydrobromic acid in glacial acetic acid, a strong dehydrating combination, also furnished predominately the epoxide (XXV) after the usual neutralization procedure. The infrared absorption spectrum of XXV, No. 29, was essentially the same as that of the product of IV and boiling hydrobromic acid. The former product, however, showed an absorption maximum at 1730 cm^{-1}, attributed to acetate, which may have obscured the band at 1719 cm^{-1} found in the spectrum of the latter product. An inflection was present at 1700 cm^{-1} as well as a sharp band at 1675 cm^{-1}, due to contamination by the phenyl ketone (VII). That the epoxide structure XXV was correct for the major product of this reaction was shown by the Raney nickel hydrogenolysis of the reaction product to 1-methyl-4-hydroxy-4-benzylpiperidine (XVI). This XVI gave a methiodide identical to that obtained previously.

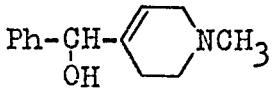
It is surprising that the glycol (IV) resisted substantial dehydration in view of the available tertiary axial hydroxyl group which is stereochemically in a favorable conformation for a trans elimination.

The ultraviolet absorption spectrum of the distilled product, Fig. 6, revealed that some very highly absorbing impurity was present, since the broad absorption maximum at 332 mμ (ε, 258), cannot be attributed to the ketone impurities indicated by the infrared absorption spectra 27,29. Absorption in this region could result only from the presence of an impurity having a phenylbutadiene system in conjugation with amino nitrogen. Such a compound could be formed by dehydration of the tertiary hydroxyl of IV to give 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylcarbinol (XLII), which on allylic rearrangement and dehydration would lead to the highly conjugated 4-benzal-1-methyl-1,2,3,4,-tetrahydropyridine (XLI). This reaction is similar to the reaction previously reported, formation of 4-benzhydrlyidene-1-methyl-1,2,3,4,-tetrahydropyridine (XLIII) from 1-methyl-1,2,3,6-tetrahydro-4-pyridyldiphenylcarbinol (LVII) (41). The diene XLI, possessing a phenylbutadiene system with an enhanced conjugation, because of the participation of the free electrons of the nitrogen atom, would be in accord with the ultraviolet absorption spectrum. If the presence of diene is responsible for the broad maximum at 332 mμ, it can be assumed on the basis of the ultraviolet spectrum for XLIII (338 mμ, ε = 19,000), that the ϵ_{max} for the pure diene XLI might be at least 13,000. Consequently, the amount of XLI present as an impurity in the epoxide XXV as indicated by the ϵ_{max} 258, amounts to less than 2%. As expected, the ultraviolet spectrum of pure XXV methiodide exhibits only absorption maxima at 260 and 266 mμ, characteristic of unconjugated phenyl. The maximum at 258 mμ, normally expected in the spectrum of a benzene

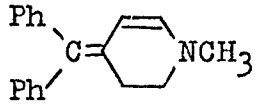
derivative, is present only as an inflection due to the intense absorption of iodide ion in this region (Fig. 7).



XLI



XLII



XLIII

The attempt to synthesize the diene XLI by the reaction of XLII with boiling 48.8% hydrobromic acid in glacial acetic acid apparently failed, for only a polymeric material could be isolated.

The hydrogenolysis of the epoxide (XXV) or the methiodide was incomplete at high or low pressure over Adams' catalyst in neutral medium. The infrared absorption spectrum, No. 46, of the product of the reduction was identical with that of XXV except for a small absorption at 3100-3400 cm^{-1} indicating the presence of some hydroxyl containing contaminant, probably XVI. This mixture resulting from the incomplete hydrogenolysis was converted completely to XVI by further reaction with hydrogen over Raney nickel at high pressure.

The use of cold concentrated sulfuric acid to induce the pinacol rearrangement of 1-methyl-4-hydroxy-4-piperidylphenyl-carbinol (IV) was attempted and abandoned early in this research due to extensive sulfonation or incomplete reaction. Thus on standing three hours in the cold acid, the glycol (IV) was destroyed to the extent of about 80% apparently due to sulfonation. A shorter reaction period of 0.5-1 hour gave only 25% of oily product. The failure of the other acid catalysts to effect

a rearrangement of IV led to a reinvestigation of this reaction. By limiting the reaction time of IV with concentrated sulfuric acid at 0° to five minutes, an isolatable product was obtained in good yield. The liquid product contained considerable epoxide (XXV), for treatment of the reaction product with excess lithium aluminum hydride in boiling ether for six hours gave only 1-methyl-4-hydroxy-4-benzylpiperidine (XVI). Also the reaction of the oily product with methyl iodide gave only XXV methiodide which could be converted to XVI methiodide by hydrogenation over Raney nickel.

The infrared absorption spectrum of the product of the reaction of IV with sulfuric acid indicated the presence of some carbonyl containing compounds, for bands at 1719 cm^{-1} and 1700 cm^{-1} were superimposed on the spectrum of XXV. The oily product also was found to give a positive Tollens' test. These results indicate the formation of 1-methyl-4-formyl-4-phenylpiperidine (XLIV), in small yield, from the rearrangement of IV. Attempts to isolate the suspected aldehyde (XLIV) or its derivatives failed. Oximation of the reaction mixture furnished only polymeric material, and treatment with semicarbazide or methyllithium gave no reaction, since the recovered substance still reduced Tollens' reagent. The formyl group of XLIV, because of its attachment to a tertiary carbon, undoubtedly is very hindered, but this functional group can be reduced with lithium aluminum hydride, since the oily product from this reduction failed to give a positive Tollens' test. In view of subsequent knowledge, this reaction undoubtedly reduced the small amount of carbonyl compounds, but also gave only

partial ring opening of the epoxide (XXV). The oil from the reduction possessed essentially the same boiling point and refractive index as observed prior to the reduction. The crystalline hydrobromide of the reduction product was obtained in 20% yield only after the oily salt was triturated with isopropyl alcohol. The possibility that this salt was the hydrobromide of 1-methyl-4-phenyl-4-piperidylcarbinol (XLVI), due to the reduction of the aldehyde (XLIV), was disproven when XLVI, prepared independently by the lithium aluminum hydride reduction of 1-methyl-4-carbethoxy-4-phenylpiperidine hydrochloride (Demerol), did not give a crystalline hydrobromide. Also, the infrared absorption spectrum of the unknown hydrobromide was shown to be devoid of absorption due to hydroxyl. The salt was shown to be identical by melting point, mixed melting point and infrared absorption spectrum, to the hydrobromide produced by Troscianiec in This Laboratory by the inverse addition of sodium borohydride to 1-methyl-4-bromo-4-piperidyl phenyl ketone (VIII). This salt also was isolated from the reduction of VIII by lithium aluminum hydride, and Troscianiec has reported (26) that the salt contains two bromine atoms and a substituted styrene system. The structure of this hydrobromide has not yet been elucidated.

During this work Chiavarelli (42) reported the synthesis of 1-methyl-4-formyl-4-phenylpiperidine (XLIV). The infrared absorption spectrum of XLIV in 10% solution in carbon tetrachloride showed an absorption band at 1729 cm^{-1} attributed to the carbonyl group. This value could not be considered positive evidence for or against the structure XLIV for the aldehyde from the sulfuric acid reaction since the infrared absorption

spectra of this and other reaction mixtures were all determined as liquid smears. However, because of intermolecular bonding, compounds in condensed phases exhibit absorption maxima at lower frequency than when in solution, and usually these bonding forces are minimized by using dilute solutions in carbon tetrachloride (35). Thus the frequencies of the carbonyl absorption maxima for various ketones determined by Campbell (43) averaged about 10 cm^{-1} higher when measured as carbon tetrachloride solutions, than when determined as nujol mulls or as liquid smears. This correlation would indicate that XLIV as a liquid smear would have the absorption maximum due to the carbonyl group at about 1719 cm^{-1}. This is in agreement with one of the absorption bands found in the infra-red absorption spectrum of the product from the sulfuric acid reaction of glycol (IV). The presence of XLIV in the reaction mixture could only be based on the infrared absorption spectrum and positive Tollens' test. Due to the failure to isolate or derivatize XLIV from the reaction mixture, the synthesis of XLIV was attempted in order to obtain a sample for comparison of these two properties.

It is well known that the inverse addition of lithium aluminum hydride to nitriles gives only small yields of the corresponding aldehydes (44). The customary procedure involves the addition of one-quarter mole of the hydride to one mole of the nitrile at low temperatures (45). Thus the Italian workers (42) obtained 7% of the Schiff's base (XLIX) by the reduction of 1-methyl-4-cyano-4-phenylpiperidine (XLVIII) with lithium aluminum hydride at -15°; hydrolysis of XLIX by acid gave the

aldehyde, XLIV, in about 3% overall yield. The same Schiff's base (XLIX) was obtained in a 10% yield from the hydrogenation of the nitrile (XLVIII) over Raney nickel at 100° and 90 atmospheres. The remainder of the product from both reductions was the diamino compound (LVIII) resulting from the complete hydrogenation of the cyano group.

When the reduction of the nitrile (XLVIII) was attempted by the inverse addition of one-quarter mole of lithium aluminum hydride at Dry Ice temperature, the nitrile was recovered as shown by the infrared absorption spectrum No. 248. Surprisingly, the aldehyde (XLIV) was detected mixed with unchanged nitrile (XLVIII) from the reaction at 0° of 2.5 moles of lithium aluminum hydride to one mole of nitrile. The mixture was analyzed by means of the infrared absorption spectrum; the nitrile (XLVIII) gave the characteristic absorption of the nitrile function at 2240 cm^{-1}, and the carbonyl of the aldehyde caused absorption at 1720 cm^{-1}. After acid hydrolysis, the 1720 cm^{-1} band was somewhat stronger and sharper. Presumably a trace of imine or Schiff's base (XLIX) in the reduction product caused a minute band at 1663 cm^{-1} which disappeared after hydrolysis by acid. The Schiff's base (XLIX) was reported to exhibit an absorption maximum at 1665 cm^{-1}, but the Schiff's base was also reported to be absent from the product of the reduction when the temperature was zero or higher (42). The Tollens' test was positive with the aldehyde-nitrile mixture, and a blank performed on the pure nitrile (XLVIII) was negative. This sequence establishes that the 1719 cm^{-1} band, present in the infrared absorption spectra of the products from the cold

concentrated sulfuric acid or boiling hydrobromic acid, results from absorption of 1-methyl-4-formyl-4-phenylpiperidine (XLIV). The data obtained from the 1600-1750 cm^{-1} region of the infrared absorption spectra of the reaction products of IV offered the only means of determining the course of the pinacol rearrangement of glycol (IV). The bands at 1719 and 1700 cm^{-1} indicated that two unconjugated carbonyl compounds were formed by the rearrangement of IV. The absorption maximum at 1719 cm^{-1} was attributed to the presence of the aldehyde (XLIV), and since unconjugated alkyl aldehydes exhibit the carbonyl absorption bands at slightly higher frequencies than the corresponding ketones (35), the 1700 cm^{-1} maximum, present in the infrared absorption spectrum of the product of the sulfuric acid reaction, therefore could be attributed to the carbonyl absorption of the isomeric, 1-methyl-4-phenyl-1-aza-4-cycloheptanone (XLV). This value is in agreement with the relatively low frequency of the carbonyl absorption band, 1690 cm^{-1}, reported for 2-phenylcycloheptanone (46). In order to confirm the presence of the azacycloheptanone (XLV), an attempt was made to synthesize this seven-membered ring ketone by the semi-pinacolic rearrangement of α-(1-methyl-4-hydroxy-4-piperidyl)-benzyl amine (LVI). The α-amino alcohol could not be prepared by the catalytic reduction of the oxime of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (VI) using Raney nickel in alcohol-dioxane or Adams' catalyst in aqueous acetic acid at room temperature and high pressure. These conditions failed to cause the absorption of a significant amount of hydrogen, and 83% of VI oxime was recovered from these reactions. Of necessity the

reduction of VI oxime with lithium aluminum hydride was used although the possibility existed that a rearranged, isomeric product might be formed along with the desired amino alcohol (LVI) (47). From this reduction about 7% of unreacted oxime was isolated, and the remaining oily product could not be crystallized*. The material was not amenable to distillation, and thus the crude mixture was used directly in the nitrous acid deamination in cold 50% acetic acid. This reaction gave predominantly the glycol (IV) with a small amount of oily material which contained an acetate ester, as evidenced by the absorption band at 1729 cm^{-1} in the infrared absorption spectrum. The remainder of the infrared absorption spectrum was substantially identical to that of the epoxide (XXV). That the oil contained XXV was chemically confirmed by the isolation of the methiodide shown to be identical with XXV methiodide.

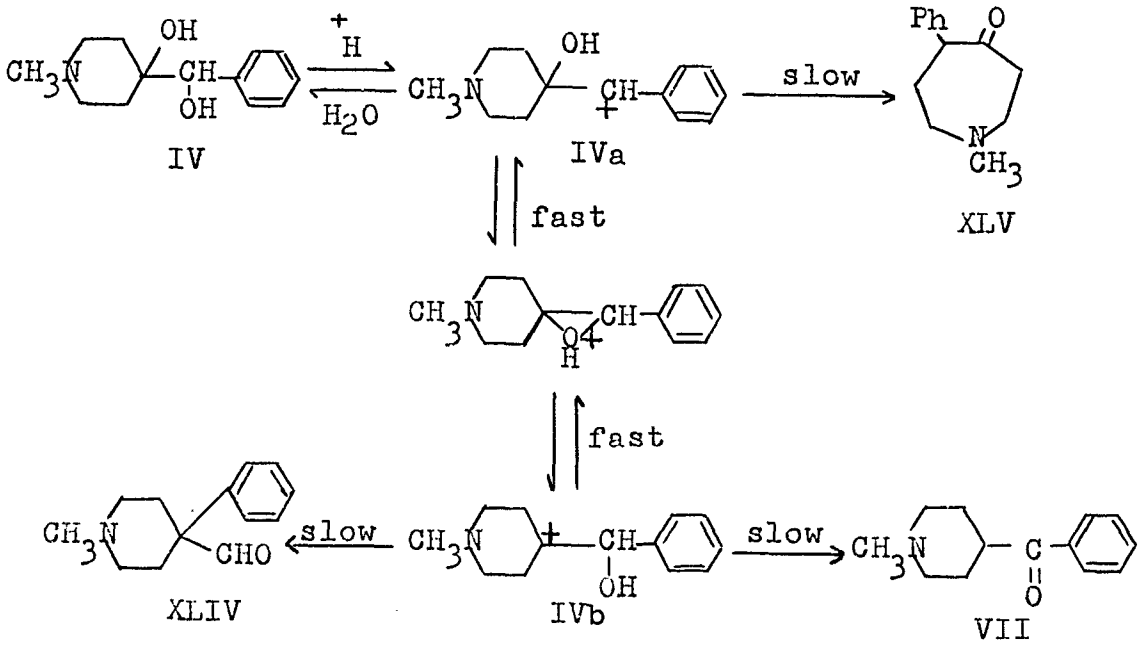
The results of the deamination reaction of (LVI) parallel closely the observations made by Felkin and Tchoubar (49) with the analogous carbocyclic amino alcohol. These workers stated that such aryl-cyclic, α-amino alcohols in aqueous acetic acid do not undergo intramolecular rearrangement to form α-arylcycloheptanones under the influence of nitrous acid, but

*An intractable oil was also obtained by Troscianiec (26) from the reduction of VI oxime with lithium aluminum hydride. Petrarca (48) has indicated that the similar VII oxime, after a prolonged reaction with lithium aluminum hydride, gave 82% total reduction. The ratio of normal product to rearranged product, found by a titrimetric procedure, was about 3:2 respectively.

instead yield glycols and small amounts of the corresponding acetate. The epoxide, however, also has been reported to be formed in semipinacolic deaminations (50). The failure of the ring expansion to occur in these deamination reactions may be attributed to the lack of a truly trans ring bond which by migration could compete with water or acetate for reaction with the carbonium ion. Unlike the reaction of the glycol,IV, with cold concentrated sulfuric acid this process is irreversible. Although 1-methyl-5-phenyl-1-aza-4-cycloheptanone (XLV) could not be prepared by the deamination procedure for comparison of the infrared absorption spectrum, there is little doubt that the 1700 cm^{-1} absorption band is due to the presence of XLV in the reaction product.

The mechanism of the formation of the epoxide, XXV, in the reaction of IV with 48.8% hydrobromic acid was established as proceeding via a dehydrohalogenation of the bromohydrin (XL) as a result of neutralization. Thus the formation of 1-methyl-4-piperidyl phenyl ketone (VII) could not be due to the isomerization of the epoxide (XXV). Furthermore, the presence of VII was not detected in the product of the reaction of glycol (IV) with cold concentrated sulfuric acid; although this reaction also furnished the same epoxide XXV as the major product. Acidic conditions would be expected to promote readily and quantitatively the isomerization of the epoxide (XXV) to carbonyl compounds. The isomerization of the carbocylic epoxide related to XXV was reported (59) to give 1-formyl-1-phenylcyclohexane (XXXV) along with the product of ring expansion but no phenyl ketone comparable to (VII). This

suggests that the formation of 1-methyl-4-formyl-4-phenyl-piperidine (XLIV) and 1-methyl-5-phenyl-1-aza-4-cycloheptanone (XLV), present in about equal amounts in the product of the cold sulfuric acid reaction, may be the result of a slow, irreversible isomerization of the epoxide (XXV). If this were not true one would expect that more of the carbonyl compounds, XLIV and XLV would have formed. Thus it must be concluded that either the epoxide (XXV) is stable in acid and is in equilibrium with the glycol (IV) as well as with its two open classical carbonium ions (11), so that XLIV and XLV probably are formed slowly and irreversibly, or the two carbonium ions (IVa and IVb) which give XLV and XLIV respectively are formed in small amounts independently of the epoxide. The former alternative appears to be the more likely. The formation of the epoxide (XXV) as the major product of the cold sulfuric acid reaction is in accord with the observations that in general the glycol (IV) is extremely inert to acid. Cold concentrated sulfuric acid, as did hot hydrobromic acid, most likely operated by ionization of the more reactive, side-chain benzylic hydroxyl, and since the ring carbon apparently is not situated in a position stereochemically favorable for a ring expansion, as shown by the deamination reaction of LVI, the aryl carbonium ion yields products by attack of the axial and truly trans 4-hydroxyl group to form the epoxide. The probable behavior of glycol (IV)is depicted by the following illustration:



The presence of a small amount of the phenyl ketone (VII) accompanied by a lesser amount of the aldehyde (XLIV) in the product of the hydrobromic acid reaction appears to stem from the conventional carbonium ion mechanism. This medium favors an intramolecular concerted hydrogen migration (11), thus explaining the relative amounts of phenyl ketone (VII) and the aldehyde (XLIV). There is little or no indication of the product of ring expansion, the isomeric ketone (XLV), indicating that the carbonium ion (IVb) was the intermediate leading to carbonyl containing products. The isomeric carbonium ion (IVa) probably led exclusively to the bromohydrin (XL).

Reactions of 6-Methyl-2-phenyl-1-ox-6-azaspiro [2,5] octane (XXV)

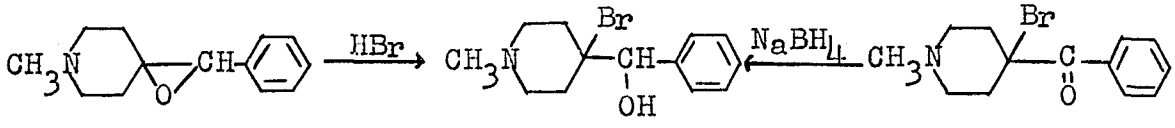
The reactions of the glycol IV with acids gave as the predominant product the epoxide (XXV). This necessitated an investigation of the properties of this epoxide (XXV). The hydrogenolysis of XXV has been mentioned above. Thus catalytic hydrogenation with Raney nickel at high pressure and room temperature or prolonged heating with excess lithium aluminum hydride in ether convert XXV to 1-methyl-4-hydroxyl-4-benzylpiperidine (XVI). The identity of XVI was established by comparison of melting point, infrared absorption spectrum and mixed melting point determination with the product obtained in This Laboratory by the action of benzyl magnesium chloride on 1-methyl-4-piperidone (26). The catalytic hydrogenolysis of XXV to XVI is in agreement with the observed tendency of aryl-substituted ethylene oxides to undergo cleavage of the oxygen bond to the carbon atom bearing the most aryl groups. Thus indene oxide (51) and styrene oxide (52) are ruptured by hydrogen in the presence of Raney nickel to β-indanol and 2-phenylethanol respectively. The ring opening of XXV by ethereal lithium aluminum hydride is in accord with the steric requirements of the reagent (53) in opening an unsymmetrical epoxide by attack of the reactive species at the least substituted carbon to furnish the most highly substituted alcohol (54) (55).

The epoxide (XXV) underwent cleavage with anhydrous hydrogen halides in absolute ether solution, a rather general reaction for epoxides (56). In this way a 14% yield of chlorohydrin (XLVIIa) was obtained by the reaction of XXV with hydrogen

chloride. The chlorohydrin (XLVIIa) was stable, and was purified and characterized by analysis. The analytical data of the picrate of XLVIIa also were in agreement with this structure. The corresponding bromohydrin (XLVIIb), obtained in 12% yield as a crude solid, resisted purification and on standing for one month had decomposed to a dark brown oil. Analytical data, however, obtained on the stable picrate confirmed the structure to be XLVIIb.

The mechanism of the acid-catalyzed ring opening of epoxides is not certain and, on the basis of present knowledge (57), one would predict that with unsymmetrical epoxides both possible halohydrins are formed by cleavage with hydrogen halide. In the case of XXV, the halohydrin actually isolated was suspected to be the tertiary halide XLVII. This suspicion was based on the fact that a bromohydrin was isolated even though a neutralization was required. The isomeric bromohydrin (XL) was shown to form the epoxide (XXV) on treatment with base. The structure of the bromohydrin (XLVIIb) was confirmed by establishing the identity of its picrate with the picrate of the bromohydrin obtained from the inverse addition of sodium borohydride to 1-methyl-4-bromo-4-piperidyl phenyl ketone (VIII) (58), Equation 17.

(Eq. 17)



XXV XLVIIb VIII

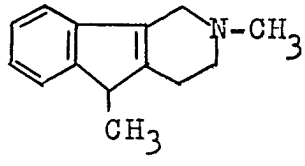
Tiffeneau (59) reported that the iodohydrin obtained from the ring opening of the analogous carbocyclic epoxide rearranged under the influence of mercurous ion to give 1-formyl-1-phenylcyclohexane (XXXV). The iodine atom was heterolyzed from the tertiary position, and the resulting dialkyl carbonium ion was then stabilized by a phenyl migration to give XXXV.

Reactions of 1-Methyl-4-hydroxy-4-piperidylphenylmethylcarbinol (V)

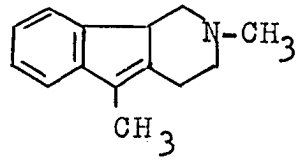
The reaction of 1-methyl-4-hydroxy-4-piperidylphenylmethylcarbinol (V) with boron trifluoride in boiling glacial acetic acid furnished a small amount of a ketone, corresponding to about 6% yield based on an assumed molecular formular $C_{14}H_{19}NO$ isolated as the semicarbazone derivative. The major product, however, contained no carbonyl group, for the oil could be recovered unchanged after treatment with ethereal lithium aluminum hydride. The elemental analyses of the oil totaled 99.48% and corresponded to an empirical formula of $C_{14}H_{17}N$, showing that the glycol (V) had undergone a double dehydration. The ultraviolet absorption spectrum of the oil, Fig. 8, exhibited a maximum at 261 mμ (log ε 4.16) and a minimum at 235 mμ (log ε 3.70) which is indicative of methyl indene structure (60). The ultraviolet absorption spectrum of the hydrobromide of this oil was identical with that of the base thus excluding an enamine type structure (64). The infrared absorption spectra recorded, Nos. 15 and 16, represent a strong and normal spectrum respectively of the base. In the strong spectrum the carbonyl region contained a small band at 1732 cm^{-1},

indicative of acetate, while a sharp medium band was present at 1700 cm^{-1}. This latter band, as well as the isolation of the semicarbazone indicated a small yield of one of the two unconjugated ketones predicted to arise from the pinacol rearrangement of glycol (V) namely, the product of phenyl migration, 1-methyl-4-phenyl-4-piperidyl methyl ketone (XVII) or the product resulting from ring enlargement, 1,5-dimethyl-5-phenyl-1-aza-4-cycloheptanone (XIX). In the normal spectrum the carbonyl bands were hardly noticeable. The spectra contained a strong band at 756 cm^{-1} but were devoid of bands near 700 cm^{-1} showing the product to contain an ortho-disubstituted benzene ring. The infrared spectrum of the hydrochloride of this oil also indicated the presence of an ortho-disubstituted benzene and was lacking all the bands in the carbonyl region but retained the band assignable to carbon-carbon double bond stretching at 1640 cm^{-1}. The structure most likely complying with the available evidence was the product of cyclodehydration, 2,5-dimethyl-1,2,3,4-tetrahydro-5-indeno[1,2-c] pyridine (XVIII). Although the position of the double band is not certain, independent evidence obtained from the acid catalyzed dehydration of 1-methyl-4-piperidyl phenyl carbinol (XIII) suggested that the position of the double band may be as depicted in XVIII. Thus XIII on dehydration furnished 1-methyl-4-benzyl-1,2,3,4-tetrahydropyridine (L) and not 1-methyl-4-benzalpiperidine (LI) possessing the exocyclic double bond, which would be expected to be more stable due to the added resonance stabilization by the conjugation with the phenyl group. In the carbocyclic series numerous examples are known for the acid catalyzed isomerization

of cycloalkylidenes to alkyl cyclenes; the reaction appears to be perfectly general and independent of the ring size (61). A striking example of this behavior is the isomerization of 1-benzhydrylidene indane to 3-benzhydrylindene in which the double bond is changed from conjugation with three phenyl groups in the exocyclic position to conjugation with only one aromatic ring in the endocyclic position (63). By analogy, in the indeno pyridine product (XVIII) the double bond is endocyclic to the piperidine ring but still is in conjugation with the aromatic ring. In the alternate structure (LII), the conjugation interaction still exists but the double b nd would be exocyclic to the piperidine ring, a situation which probably does not survive in the piperidine ring system as well as in the carbocyclic series.



XVIII



LII

In order to identify definitely the small amount of ketonic product responsible for the semicarbazone and for the absorption at 1697-1700 cm^{-1}, an authentic sample of the product of phenyl migration, 1-methyl-4-phenyl-4-piperidyl methyl ketone (XVII), was prepared from 1-methyl-4-cyano-4-phenylpiperidine (XLVIII) by a modification of Eisleb's procedure (62). The ketone (XVII) readily furnished a semicarbazone, which was different in melting point and mixed melting point, from the semicarbazone isolated from the reaction

mixture; and further, XVII contained sharp bands at 1704 cm^{-1} and 1500 cm^{-1} in the infrared absorption spectrum. With the exclusion of XVII as a possibility, it is safe to assume that the ketone formed by the rearrangement of V is the result of ring expansion, XIX, and is not the product of methyl migration, 1,4-dimethyl-4-piperidyl phenyl ketone (LIII). The carbonyl of LIII is conjugated with a phenyl group, and thus would be expected to exhibit an absorption maximum in the infrared spectrum well below 1690 cm^{-1}, more specifically near 1675 cm^{-1}. On the other hand α-phenyl cycloheptanones are reported to show absorption just below 1700 cm^{-1} (18) (46). The latter absorption is more nearly related to that observed in the absorption spectra of the carbonyl products from the rearrangements of both glycols (IV) and (V). A pathway for an independent synthesis of the azacycloheptanone (XIX) is not immediately obvious, and final conclusive proof of structure must await such a synthesis for both the confirmation of the carbonyl absorption band in the infrared at 1697-1700 cm^{-1} and the melting point of the semicarbazone.

The reaction of glycol (V) with boiling 48.8% hydrobromic acid also was found to furnish predominantly the cyclodehydrated indeno pyridine (XVIII) as shown by comparison of the methiodide with the methiodide obtained from the reaction product of V with boron trifluoride in acetic acid. The ultraviolet absorption spectrum likewise contained a maximum at 261 mμ, log ϵ 3.99 and a minimum at 234 mμ, log ϵ 3.55; however, an additional maximum was present at 310 mμ, ϵ 1400; Fig. 9. The infrared absorption spectrum differed slightly

in the carbonyl region; otherwise it was essentially similar to that using XVIII obtained from the boron trifluoride reaction. Since no acetic acid was employed in the reaction, the absence of a carbonyl band of acetate near 1730 cm^{-1} was understandable. There were no bands near 1700 cm^{-1}, but a small absorption occurred at 1663 cm^{-1}. An additional intense maximum near 1610 cm^{-1} was evident on the low wavelength side of the main phenyl band.

The product of the reaction of glycol, V, with hot 32% sulfuric acid gave an infrared absorption identical to that of the product of the reaction of V with heated hydrobromic acid. The bands present at 1663 cm^{-1} and 1610 cm^{-1} could not be assigned definitely but were suggestive of an olefinic bond, the former band possibly being an overtone of the olefinic deformation band near 830 cm^{-1}. These infrared bands and the maximum at 310 mμ in the ultraviolet spectrum were not found in the spectrum of the product of the reaction of glycol V with boron trifluoride in acetic acid. These bands probably indicate the presence of an isomeric, conjugated diene contaminating the major product, XVIII. The salt of XVIII did not have these bands in its spectrum; however, the prevalent double bond stretching absorption near 1640 cm^{-1} was present in the spectra of the salt and amine.

The reaction of glycol (V) with p-toluenesulfonic acid in boiling glacial acetic acid also gave a didehydrated product; however, the elemental analyses of the product totaled only 97.90%. The presence of acetate containing contaminant was detected in the infrared absorption spectrum by showing a band

at 1735 cm^{-1}. This oxygenated contaminant accounts for the remaining 2.1% in the analysis. Thus the empirical formula of the product XXa was $C_{14}H_{17}N$. The presence of a strong band at 700 cm^{-1} in the infrared absorption spectrum of (XXa) indicated a monosubstituted phenyl. The ultraviolet absorption spectrum of XXa, Fig. 10, exhibited two maxima, 225 mμ (4.16) and 310 mμ (2.87). The ultraviolet absorption spectra of the methiodide or methobromide of XXa retained only the low wavelength absorption maxima, 221 mμ (4.42) and 223 mμ (4.12) respectively, Fig. 10. The unassigned bands at 1662 cm^{-1} and 1610 cm^{-1} present in the infrared absorption spectrum of this reaction product are likewise absent in the spectrum of the recrystallized methobromide salt. On the basis of the weak infrared absorption bands at 1662-1663 cm^{-1} and the low intensity of the absorption maximum at 310 mμ in the ultraviolet, it would seem that the same conjugated diene which contaminated the indeno pyridine (XVIII) resulting from the reactions of boiling hydrobromic and sulfuric acid was also formed as a by-product from the reaction of p-toluenesulfonic acid with glycol (V). The possibility that XXa might be the highly conjugated diene, 4-α-methylbenzylidene-1-methyl-1,2,3,4-tetrahydropyridine (XXIV) was ruled out because the extended conjugation of the "phenyl butadiene" system with the available electrons on the nitrogen would be expected to exhibit a maximum around 335 mμ in the ultraviolet absorption spectrum (64) (65).

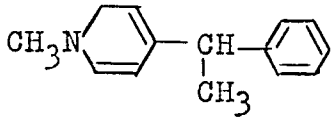
Because of the persistence of the intense maximum at 222 mμ in the ultraviolet absorption spectrum of the quaternary salt, indicative of a conjugated butadiene system, 1-(1-methyl-

1,2-dihydro-4-pyridyl)-1-phenyl ethane (XX) appeared to be the most likely structure which can be assigned. However, this does not eliminate the initial formation of other dienes, for during the purification or on reaction with methyl halide they could have isomerized to XX. This would be expected to occur readily with 1-(1-methyl-1,4-dihydro-4-pyridyl)-1-phenyl ethane (XXI), since the conjugation involving the electrons on the nitrogen would not be present in the quaternary salt; the molecule could gain stability by the shift of one of the double bonds into the 3,4-position and into conjugation with the other double bond forming XX.

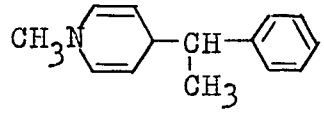
That the action of p-toluenesulfonic acid and acetic acid on glycol (V) has not furnished a rearranged or cyclized product has been further shown by the hydrogenation of the methiodide of XXa at high pressure over Raney nickel to the corresponding saturated system namely, the methiodide of 1-(1-methyl-4-piperidyl)-1-phenyl ethane (XXIII). This saturated methiodide did not cause a depression of the melting point of XXII methiodide when mixed with an authentic sample of XXII methiodide and the infrared absorption spectra of the two methiodides were found to be superimposable.

The authentic sample of XXII methiodide was made by the catalytic hydrogenation of 1-(4-pyridyl)-1-phenylethylene (LIV) methobromide over platinum oxide at low pressure and room temperature, neutralization of the resulting XXII hydrobromide, and reaction of XXII with methyl iodide. The ethylenic compound LIV was made by a modification of the procedure described by Villani (27). The synthesis of the diene which would result

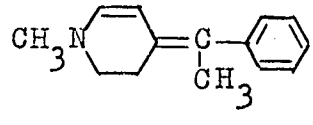
from the dehydration of glycol (V) without rearrangement, 1-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-1-phenylethylene (XXIII), seemed equally promising by the reduction of LIV methobromide, since the action of sodium borohydride on quaternary salts of pyridine derivatives has been reported to form the corresponding 1,2,3,6-tetrahydropyridines (44) (65) (66). The physical properties of the product obtained from the sodium borohydride reduction of LIV methobromide did not agree with those of the product of dehydration of glycol (V). The ultraviolet absorption spectrum of the reduction product exhibited no maximum or minimum but merely gave a shoulder at 241 mμ (ε 5000). The structure of this material was not investigated further, but was hydrogenated in dilute acid over platinum oxide to XXII. The methiodide obtained from this reduction was shown, by mixed melting point determination, to be identical with XXII methiodide prepared directly by the catalytic hydrogenation of LIV methobromide.



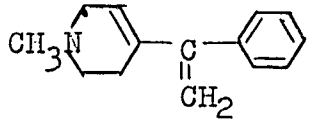
XX



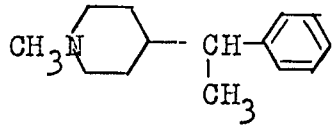
XXI



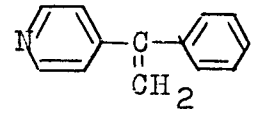
XXIV



XXIII



XXII

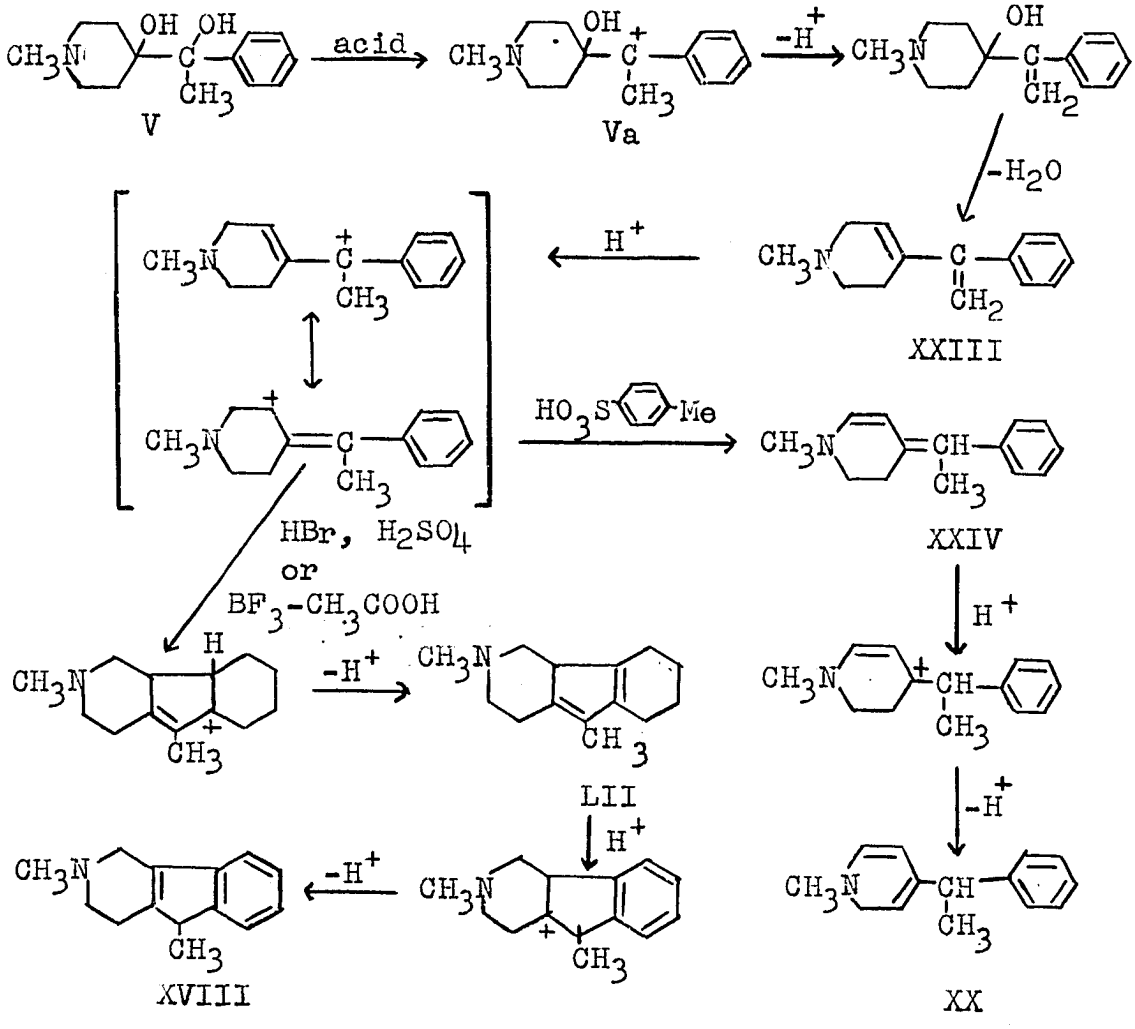


LIV

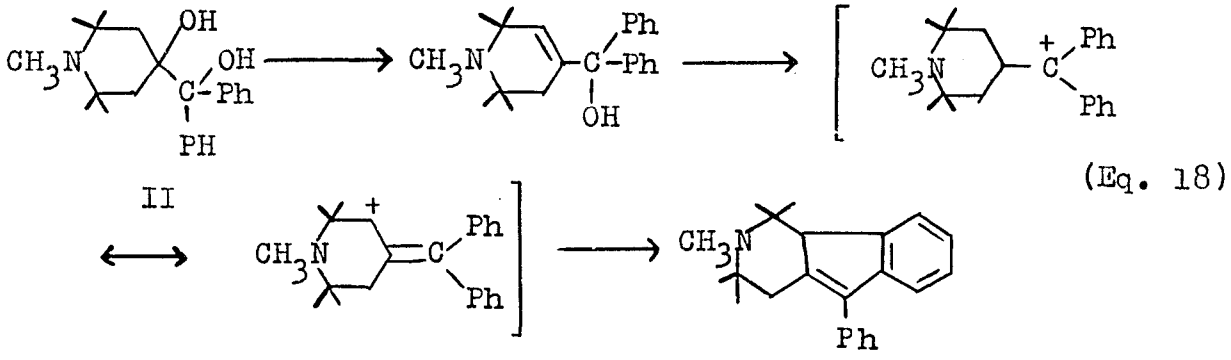
The diene (XXIII) by analogy with other formulations reported in the literature (67) (68) appears to be the most likely intermediate in the formation of the indeno pyridine (XVIII). On the basis of the extreme stability observed for the axially oriented hydroxyl in the glycol (IV), one might expect the same degree of inertness under identical reaction conditions for the similarly disposed non-benzylic hydroxyl of the glycol (V). No cyclized product was ever isolated from the reactions of glycol (IV). The obvious difference with glycol (V) is the dehydration pathway allowed by the methyl group. This structural feature is not available in glycol (IV). Thus it seems reasonable to assume that the first step for the formation of the intermediate diene (XXIII) was the dehydration of the side chain hydroxyl group and the hydrogen of the methyl substituent. Again ring migration does not seriously compete as a reaction of the carbonium ion (Va) and in this case the methyl phenyl carbonium ion (Va) was converted to products by ejection of a proton forming the monodehydrated intermediate which contains a terminal methylene group. The remaining hydroxyl would now be a more reactive allylic alcohol, and consequently dehydration could occur readily to give the diene (XXIII). Under the influence of boron trifluoride-acetic acid, 48.8% hydrobromic acid, or 32% sulfuric acid the diene (XXIII) cyclized to give the indeno pyridine (LII) whose piperidyl exocyclic double bond, as already explained, might isomerize to furnish the end product, 2,5-dimethyl-1,2,3,4-tetrahydro-5-indeno [1,2-c] pyridine (XVIII).

If it is assumed further that the sequence leading to

the diene XXIII was common to the p-toluenesulfonic acid catalysis as well, then proton ejection of the protonated diene XXIII occurred to give XXIV rather than cyclization. In this regard it might be pointed out that very few cyclizations have been reported to occur with p-toluenesulfonic acid. The resulting diene (XXIV) contains an exocyclic double bond which is isomerized in acid to give the likely product of the reaction, 1-(1-methyl-1,2-dihydro-4-pyridyl)-1-phenyl ethane (XX). The stepwise dehydration of glycol (V) is summarized by the following illustration:



The indeno pyridine (XXXVII) reported by Chauvette (8) as the product of the reaction of p-toluenesulfonic acid with glycol (II) has been postulated to form via a cyclodehydration following a dehydration and allylic rearrangement. However, it is to be noted that glycol (II) cannot give normal dehydration because a hydrogen atom is not available on the 2- or 6-positions, Equation 18.



(Eq. 18)

XXXVII

The behavior of 1-methyl-4-hydroxyl-4-piperidylphenylmethylcarbinol (V) in cold concentrated sulfuric acid could not be studied because of the occurrence of sulfonation. Attempts to effect the reversal of the sulfonation reaction by prolonged heating with either dilute or concentrated hydrochloric acid apparently failed for sulfur was qualitatively (sodium fusion) detected in the recovered material. Sulfonation of (V) was noted after only two minutes of contact with the cold sulfuric acid. It is interesting to note that Orthner (7) reported that glycol (I) undergoes complete resinification in concentrated sulfuric acid at -10°, while Chauvette (8) employing glycol (II) at -5°C isolated 65% of a disulfonated product which was inert to superheated steam at 330°. When Orthner employed boiling 20% sulfuric acid with glycol (I)

the "butadiene" compound was obtained as the main product; Equation 9; indeno pyridine formation, was of course impossible since an aryl grouping was lacking. The dehydration of the carbocyclic glycol (XXXIII) analogous to glycol (V), by boiling 50% sulfuric acid, conditions closely approximating those used herein with glycol (V), was studied by Russell (21), who reported only a 31% yield of 1-phenyl-1-cyclohexyl methyl ketone (XXXII) isolated as the oxime. The remainder of material which failed to undergo oximation was not identified and in all probability was the indene product comparable to XVIII obtained in this work.

EXPERIMENTAL

Most of the infrared absorption spectra of the compounds reported in this work were recorded with a Perkin-Elmer Model 21, double beam infared spectrophotometer using a standard scale and sodium chloride optics, operated at a resolution of 927, a response of 1, a speed of 4-6, and a gain of 5.5 with no suppression. These spectra are filed with the Department of Chemistry, University of New Hampshire. The remainder of the infrared absorption spectra were measured by S. P. Sadtler and Son Inc., Philadelphia 2, Pa., and are so designated.

The ultraviolet absorption spectra were measured using a Beckman Model DU quartz spectrophotometer with a photomultiplier attachment employing matched silica cells of 0.999 cm. thickness. All of these spectra were determined using 95% ethanol as solvent.

Carbon, hydrogen and nitrogen microanalyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England. Halides were analyzed by the Volhard method. Melting points are uncorrected.

Preparation of the Starting Materials

4-Pyridyl Phenyl Ketone (XI)

a) Literature Methods-----The preparation of XI by the acylation of benzene with isonicotinyl chloride as described by Villani (27) was repeated in 92% yield. The product melted at 73-75°; reported by Villani, 70-71°. The oxidation of 4-benzylpyridine (X) with neutral (28) and acidic permanganate (29) gave (XI) in yields of 63% and 65% respectively.

b) Oxidation of 4-Benzylpyridine (X) with Selenium Dioxide-----A suspension of 26.0 g. (0.235 mole) of selenium dioxide in a solution of 31.2 g. (0.184 mole) of 4-benzylpyridine (X) in 125 ml. of glacial acetic acid was heated carefully until a highly exothermic reaction commenced. After the reaction subsided, the mixture was heated under reflux for 0.5 hour. When cooled to room temperature, the selenium was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in about 100 ml. of water, and the solution was treated with Norit and filtered to remove additional amounts of deposited selenium. The chilled filtrate was neutralized with sodium hydroxide solution, and the liberated solid was collected by filtration and washed thoroughly with water. Recrystallization of the solid from aqueous ethanol furnished 27.5 g. (81%) of 4-pyridyl phenyl ketone (XI), m.p. 69-75°, lit. (5) m.p. 72-75°. The picrate of XI obtained in the usual manner melted at 160°; reported (29) m.p. 160°.

4-Pyridyl Phenyl Ketone Methiodide (XIIa)

A solution of 32.9 g. (0.180 mole) of 4-pyridyl phenyl ketone (XI) and 52 g. (0.36 mole) of methyl iodide in 150 ml of dry methanol was heated gently under reflux for two hours and then was allowed to stand for two days at room temperature. The salt which precipitated, about 15 g., was collected by filtration. The solvent was removed from the filtrate by distillation under reduced pressure, and the residue crystallized on treatment with acetone. The combined solids, m.p. 174-176°, weighed 56 g. (96%). Recrystallization of the solid from methanol-ethyl acetate gave XIIa as glistening yellow crystals, m.p. 177-179°, lit. (31) m.p. 80-180°.

Anal. Calcd. for $C_{13}H_{12}INO$: I, 39.03

Found: I, 39.08, 39.15

4-Pyridyl Phenyl Ketone Methobromide (XII)

a) A solution of 34.2 g. (0.187 mole) of commercial XI in 40 ml. of methanol and 80 ml. of benzene was saturated with methyl bromide. After standing at room temperature for 24 hrs., the solution was concentrated by evaporation under diminished pressure. Some chloroform was added, and the solution was filtered to remove any solid impurities. Dry ethyl acetate (100 ml.) was added, and the walls of the flask were scratched with a glass stirring rod to induce crystallization. The precipitated salt was collected by filtration and dried at 105°C.* The product, XII, weighed 47 g. (90%) and melted at 168-171°.

*Failure to dry the salt gave a solid with a low melting point, 116-122°; or with a broad melting range, 113-165°. In either case the bromine analysis was always about 5% low.

b) To a solution of 3.0 g. (0.0164 mole) of XI in 15 ml. of acetone contained in a 50 ml. Erlemmeyer flask was added about 5 ml. of liquified methyl bromide, and the flask was stoppered tightly and swirled occasionally. The precipitated salt, 3.8 g. (82%), was collected by filtration and melted at 116-122°. Recrystallization of the solid from acetone, followed by prolonged drying at reduced pressure in an Abderhalden pistol, gave XII, m.p. 165-168°.

Anal. Calcd. for $C_{13}H_{12}BrNO$: Br, 28.73

Found: Br, 28.93, 28.61

Preparation of 1-Methyl-4-piperidylphenylcarbinol (XIII)

a) Reduction of 4-Pyridyl Phenyl Ketone Methiodide (XIIa)-----A solution of 9.6 g. (.0295 mole) of XIIa in 50 ml. of water and 40 ml. of methanol was shaken in a low pressure bottle with hydrogen at 45.5 p.s.i. and 0.25 g. of platinum oxide. In six hours 10 pounds of hydrogen were absorbed, and the clear colorless solution was filtered to remove the catalyst. The filtrate was neutralized with potassium hydroxide solution, and the solid which precipitated was collected by filtration and was found to melt at 153-158°. Recrystallization from dilute ethanol gave 5.6 g. (93.5%) of colorless XIIa, m.p. 155-160°; lit. (31) m.p. 157-159°.

b) Reduction of 4-Pyridyl Phenyl Ketone Methobromide (XII)-----A solution of 15.9 g. (.0572 mole) of XII in 55 ml. of water was shaken with hydrogen and 0.3 g. platinum oxide at an initial pressure of 47.9 p.s.i. for twenty four hours; after which time, 20 pounds of hydrogen were absorbed. The catalyst was removed by filtration, and the filtrate was

neutralized with 50 ml. of 20% potassium hydroxide solution. The liberated oil crystallized on short standing, and the solid was collected by filtration, giving 11.0 g. (94%) of 1-methyl-4-piperidylphenylcarbinol (XIII), melting point, after two recrystallizations from 95% ethanol or benzene, 155-160°. The infrared absorption spectrum of XIII, No. 225, was determined in carbon disulfide solution.

The methiodide of XIII was prepared by the usual method, and after recrystallization from ethanol melted at 212-214°.

Anal. Calcd. for $C_{14}H_{22}INO$: I 36.55

Found: I, 36.67

Preparation of XIII Hydrobromide

a) Low Pressure Reduction of 4-Pyridyl Phenyl Ketone Methobromide (XII)-----A solution of 10 g. (.036 mole) of XII in 40 ml. methanol was treated with 0.2 g. of platinum oxide and was agitated in a low pressure bottle with hydrogen at an initial pressure of 23.6 p.s.i. The hydrogenation was stopped after 4.25 hours, after which time, 10.8 p.s.i. of hydrogen had been absorbed. Removal of the catalyst by filtration and distillation of the methanol under diminished pressure gave an oil, which on treatment with dry ether and petroleum ether at Dry Ice temperatures crystallized to give 8.8 g. (85.5%) of a waxy solid, m.p. 120-140°. Recrystallization of XIII hydrobromide from isopropyl alcohol-ethyl acetate raised the melting point to 133-141°.

Anal. Calcd. for $C_{13}H_{20}BrNO$; Br, 27.92

Found: Br, 27.35, 27.39

Neutralization of an aqueous solution of XIII hydrobromide quantitatively furnished the base, XIII, m.p. 160°; lit. (17), m.p. 157-159°.

b) High Pressure Reduction of 4-Pyridyl Phenyl Ketone Methobromide (XII)-----A solution of 2.0 g. (.0072 mole) of XII in 30 ml. of methanol was subjected to hydrogenation with 0.1 g. of 5% palladium on charcoal and hydrogen at 58 atmospheres. The pressure dropped 1.5 atms. in 20 minutes and no further decrease was noted after 3 hrs. The solution was filtered, and after evaporation of the solvent, 2.0 g. (97%) of XIII hydrobromide, m.p. 128-136°(frothing) was obtained. This product did not depress the melting point of the XIII hydrobromide obtained in a) above. Neutralization of a solution of XIII hydrobromide with potassium carbonate solution gave a quantitative yield of XIII, m.p. 153-157°.

Partial Reduction of 4-Pyridyl Phenyl Ketone Methiodide (XIIa)

A suspension of 10.8 g. (.0332 mole) of XIIa in 200 ml. of methanol and 0.2 g. of platinum oxide was shaken in a low pressure bottle with hydrogen at 39 p.s.i. After three pounds of hydrogen were absorbed, requiring three hours, the yellow colored solution was filtered to remove the catalyst, and the filtrate was concentrated under reduced pressure. Treatment of the residue with anhydrous ether caused partial crystallization, and after removal of the gummy precipitate by filtration, the filtrate was heated with ethyl acetate in the presence of Norit and filtered. On cooling 1.8 g. of a yellow solid, m.p. 138-139°, was obtained. Recrystallization of the XIV methiodide from methanol-ethyl acetate raised the melting

point to 143-144°. On admixture with the methiodide of XIV prepared from an authentic sample of 4-pyridylphenylcarbinol (XIV) (5) the melting point was 148-153°. Pure XIV methiodide melts at 150-154° after recrystallization from isopropyl alcohol-ethyl acetate.

Anal. Calcd. for $C_{13}H_{14}INO$: I, 38.79

Found: I, 38.94

Preparation of 1-Methyl-4-piperidyl Phenyl Ketone (VII)

To a solution of 32.5 g. (0.158 mole) of 1-methyl-4-piperidylphenylcarbinol (XIII) in 650 ml. of glacial acetic acid containing 5-10 ml. of acetic anhydride was added 13.3 g. (0.133 mole) of chromium trioxide. The mixture was stirred mechanically for 0.5 hour at 90°C and 0.5 hour at 100°C. The acetic acid was removed by distillation under diminished pressure, and the dark green residue was diluted with 100 ml. of water. The resulting acidic solution was made alkaline by the addition of 400 ml. of 25% sodium hydroxide solution. The green gelatinous mixture was repeatedly extracted with ether, and after filtration of the mixture, the filtrate was extracted further while the gel was triturated with ether. The combined ethereal extracts were dried over potassium carbonate, filtered, and concentrated. The residual red oil was distilled to give 27.5 g. (85%) of VII, b.p. 190° at 21 mm.

The hydrobromide of VII melted at 202-206° after a recrystallization from isopropyl alcohol; lit. m.p. 211-212° (69) and 204-206° (26).

Preparation of VII Hydrobromide Without Isolation of VII

The oxidation of XIII was run with 33 g. (0.161 mole) of XIII and 13.5 g. (.135 mole) of chromium trioxide in 650 ml. of glacial acetic acid containing 10 ml. of acetic anhydride, as described above in a) up to the point of the removal of the acetic acid. The dark green residue was dissolved in chloroform, and the solution was saturated with anhydrous hydrogen bromide. The chloroform was removed by distillation under diminished pressure, the residue was taken up in hot isopropyl alcohol, and the solution was filtered while hot. The solid which precipitated on cooling the solution was collected by filtration and washed with isopropyl alcohol and petroleum ether, to give 29.3 g. (65%) of VII hydrobromide, m.p. 198-204°. This product showed no depression of melting point on mixing with an authentic sample prepared by the conventional procedure.

Neutralization of VII hydrobromide with potassium carbonate solution gave pure VII, b.p. 144° at 4.5 mm, in quantitative yield. The infrared absorption spectrum, No. 78, and the ultraviolet absorption spectrum Fig. 11, were obtained. The latter, at concentrations of 6.026×10^{-3}, 10^{-4} and 10^{-5} m./l., exhibited the typical maxima for conjugated ketones at 244, 279 and 316 mμ with the corresponding logϵ values of 4.03, 2.95 and 1.91. The methiodide was made in the usual manner and precipitated from ethanol as shining white plates, m.p. 226-229°.

Anal. Calcd. for $C_{14}H_{22}INO$: I, 36.76

Found: I, 36.97

Preparation of 1-Methyl-4-Benzylpiperidine (XV) from 4-Benzylpyridine (X)

A solution of 12.9 g. (.0765 mole) of 4-benzylpyridine (X) in 30 ml. of dry methanol and 80 ml. of absolute ether was saturated with methyl bromide, and the solution was allowed to stand for a few days. The solvents were removed by distillation under diminished pressure, and the residue crystallized on trituration with acetone or by cooling in dry ether surrounded by a Dry Ice-acetone bath. The yields of X methobromide, m.p. 79-83°, from two separate runs averaged 18.4 g. (91%). Recrystallization of X methobromide from methanol-ether followed by recrystallization from ethanol-ethyl acetate gave an analytical sample, m.p. 87.5-89°; lit. (32) m.p. 84-87°. The infrared absorption spectrum has been determined by Sadtler and is numbered 9447.

Anal. Calcd. for $C_{13}H_{14}BrN$: Br, 30.25
Found: Br. 30.36

Catalytic Reduction of 4-Benzylpyridine (X) Methobromide

A solution of 12.1 g. (.046 mole) of X methobromide in 25 ml. of methanol and 80 ml. of water was treated with 0.1 g. of platinum oxide and hydrogen at an initial pressure of 41.0 p.s.i. The hydrogenation was complete in 6.5 hours; after which time, 15 pounds of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was basified with potassium hydroxide solution. The resulting mixture was extracted three times with ether, and the extracts were dried over sodium sulfate. After filtration, the solution was distilled fractionally giving 8.1 g. (93%) of 1-methyl-4-

benzylpiperidine (XV), b.p. 168° at 45 mm. Redistillation gave XV as a colorless oil, b.p. 113-115° at 6 mm., $n_D^{27.5}$ 1.5191; lit. (32), b.p. 100-103° at 3.5 mm., n_D^{26} 1.5189. The infrared absorption spectrum, No. 13, has been determined.

The picrate of XV was prepared in methanol to give a yellow solid, m.p. 182-185°, which after one recrystallization from ethanol melted at 184-185°; lit. (32) m.p. 185-186°.

The methiodide of XV was prepared in ethanol-ether and melted at 205-207°. After recrystallization from ethanol the melting point was raised to 208-209°.

Anal. Calcd. for $C_{14}H_{22}IN$: I, 38.31

Found: I, 38.16

Attempted Oxidation of 1-Methyl-4-Benzylpiperidine (XV)

Selenium dioxide, 5.7 g. (.042 mole), suspended in a solution of 6.35 g. (.0335 mole) of XV in 25 ml. of glacial acetic acid was treated as previously described for the oxidation of X. The only organic material isolated was 5.8 g. (92%) of recovered XV.

A portion, 2.4 g. (.0127 mole), of the XV recovered from the above oxidation was treated with 2.0 g. chromium trioxide in 40 ml. of acetic acid under the conditions as described for the preparation of VII. Again XV was recovered unchanged in quantitative amounts and boiled at 110° at 5 mm., $n_D^{27.5}$ 1.5194. The infrared absorption spectrum, No. 08, was identical with that of pure XV, No. 13.

Preparation of 1-Methyl-4-hydroxy-4-piperidyl Phenyl Ketone (VI)

The sequence of reactions from VII hydrobromide leading to VI were carried out according to the procedure employed by Troscianiec (26). Thus 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (VIII), m.p. 158-160°, was obtained in 90% yield by the bromination of VII hydrobromide in chloroform. The epoxidation of VIII by methanolic sodium methoxide furnished a quantitative yield of 6-methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]-octane (IX), b.p. 177-180° at 30 mm. The epoxyether, IX, on treatment with dilute hydrochloric acid and subsequent neutralization with excess potassium carbonate gave a 97% yield of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (VI), m.p. 131-133°. The hydrochloride of VI melted at 171-172°.

Preparation of 1-Methyl-4-hydroxy-4-piperidylphenylcarbinol (IV)

1. Metal Hydride Reduction of VI

a) With Lithium Aluminum Hydride-----To a stirred boiling slurry of 3.0 g. (.079 mole) of lithium aluminum hydride in 150 ml. of absolute ether in a 500 ml. round-bottomed, three-necked flask, equipped with a reflux condenser, mercury sealed stirrer, and an addition funnel, was added portion-wise 4.0 g. (.0183 mole) of VI suspended in 80 ml. of dry ether. The addition required one half hour. The mixture was then maintained at the boiling point for 2.5 hours, after which time the reaction mixture was cautiously hydrolyzed by the dropwise addition of about 20 ml. of water. The ether was filtered to remove the aluminum hydroxide, which was thoroughly triturated with chloroform before being discarded. The combined ether

and chloroform solutions were concentrated on the steam bath, and the residue was taken up in hot benzene. On cooling and adding petroleum ether, 4.0 g. (98.9%) of 1-methyl-4-hydroxy-4-piperidyl phenyl carbinol (IV), m.p. 138-139°, was obtained. An analytical sample, m.p. 139-141°, was obtained by recrystallization of IV from benzene-intermediate boiling ligroin. The infrared absorption spectrum was determined as 0.5% in a potassium bromide wafer by Sadtler and is numbered 9445. The ultraviolet absorption spectrum was determined at a concentration of 5.617×10^{-3} m./l., exhibiting maxima at 252, 258, and 264 mμ, the corresponding log ε being 2.18, 2.28, 2.15, Fig. 5, curve A.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65
Found: C, 70.56; H, 8.75

The methobromide of IV after recrystallization from ethanol-ether melted at 180-181°.

Anal. Calcd. for $C_{14}H_{22}BrNO_2$: Br, 25.27
Found: Br. 25.12, 25.27

b) With Sodium Borohydride-----A solution of 0.7 g. (.0185 mole) of sodium borohydride in 30 ml. of aqueous methanol was added over a period of five minutes to a magnetically stirred solution of 2.0 g. (.00915 mole) of VI in 25 ml. of methanol. The resulting solution was slowly heated to boiling and maintained at this temperature for two hours. The solution was concentrated under reduced pressure, and the residue was heated with dilute sodium hydroxide. The cooled alkaline mixture was extracted twice with chloroform, and the extract was dried over potassium carbonate and was filtered.

The solvent was removed by distillation, to give 0.3 g. (15%) of 1-methyl-4-hydroxy-4-piperidyl phenyl carbinol (IV), m.p. 136-138°. There was no depression of the melting point of IV on admixture with the product obtained from the lithium aluminum hydride reaction in a) above.

2. Catalytic Reduction of VI

a) With Raney Nickel-----A solution of 1.5 g. (.00685 mole) of VI in 40 ml. of methanol in the presence of Raney nickel and hydrogen at an initial pressure of 40.1 p.s.i. was shaken in a low pressure bottle for five hours. The absorption of 0.6 pounds of hydrogen occurred during the first hour. The solution was filtered to remove the active catalyst, and the filtrate was concentrated by heating under reduced pressure. The residue was made alkaline with sodium carbonate solution and was extracted with chloroform. The chloroform was removed from the dried extract by distillation, and the residue was crystallized from benzene. The product, 1.2 g. (80%), melted at 137-140° and did not depress the melting point of the product obtained in 1. a) above.

b) With Adams' Catalyst-----A solution of 2.0 g. (.00915 mole) of VI in about 40 ml. of 50% aqueous methanol containing four drops of concentrated hydrochloric acid was shaken for about four hours with hydrogen (36.4 p.s.i. initial pressure) in the presence of 0.1 g. of platinum oxide. At the end of this time 1.2 p.s.i. of hydrogen had been absorbed. Most of the methanol was removed by distillation, and the remaining acidic layer was neutralized with sodium carbonate. The mixture was extracted with chloroform and treated as in

2. a) above to give 1.65 g. (82%) of 1-methyl-4-hydroxy-4-piperidyl phenyl carbinol (IV), m.p. 138-141°. Further work up furnished 0.3 g. of impure IV, m.p. ca. 120°, which resembled the product of phenyl-ring reduction; cf. subsequent reduction with VI hydrochloride.

c) With Adams' Catalyst in Chloroform-----A solution of 1.0 g. (.00455 mole) of VI in 50 ml. of chloroform was treated with hydrogen (39.9 p.s.i. initial pressure) at room temperature over 53 mg. of platinum oxide. The hydrogen absorption (0.9 p.s.i.) occurred within 45 minutes, and continued reaction for four hours gave no further drop in pressure. The solution was treated with a few drops of methanol to dissolve some suspended material and then filtered to remove the catalyst. The filtrate was concentrated by distillation, and addition of petroleum ether gave a water soluble product, m.p. 90-162°. After recrystallization from benzene-chloroform mixture containing a trace of methanol, 1.15 g. of long white needles, m.p. 168-170° were obtained. This represented a quantitative recovery of VI as the hydrochloride; no depression of melting point occurred on admixture with authentic VI hydrochloride. Neutralization of the salt with potassium carbonate solution gave the base VI m.p. 129-131°, which also showed no depression in melting point when mixed with authentic VI.

Attempted Preparation of IV Hydrochloride by Catalytic Reduction of VI Hydrochloride

A solution of 1.65 g. (.0064 mole) of VI hydrochloride, m.p. 171-172°, in 60 ml. of dry methanol with 0.1 g. of platinum oxide was subjected to hydrogenation at room temperature. After 0.5 hours 1.1 p.s.i. of hydrogen had been absorbed, and further shaking of the solution for three hours effected no additional hydrogen uptake. The solution was filtered from the pyrophoric catalyst and the solvent in the filtrate evaporated on standing. Treatment of the residue with dry ether at Dry Ice temperature failed to cause crystallization of the residue, and the salt was converted to the base by neutralization with sodium carbonate. The mixture was extracted with chloroform, the extract was dried over sodium sulfate and filtered, and the solvent was removed by distillation. The residue was crystallized from benzene to give 1.05 g. of substance, m.p. 112-118°. After treatment with ethereal lithium aluminum hydride the solid was recovered essentially unchanged. Two recrystallizations of the compound from petroleum ether-intermediate boiling ligroin gave m.p. 115-116°. No depression in melting point occurred on admixture with the compound obtained by the hydrogenation of pure VI performed at 100° in the presence of Raney nickel by Troscianiec (26). The infrared absorption spectrum of this substance is filed as No. 229 and the ultraviolet absorption spectrum, determined at a concentration of 0.463 g./l. exhibited the following maxima; 252 mμ (log ε 1.56), 258 mμ (log ε 1.72) and 264 mμ (log ε 1.61), Fig. 5, curve B.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33
$C_{13}H_{25}NO_2$: C, 68.68; H,11.08; N, 6.16
$C_{13}H_{25}NO$: C, 73.88; H,11.92; N, 6.63
Found: C, 71.61, 71.53; H, 9.75, 9.82; N, 5.1

Preparation of 1-Methyl-4-hydroxy-4-piperidyl-phenylmethylcarbinol (V)

To 3.1 g. (.447 g. at.) of small lengths of lithium wire in 100 ml. of absolute ether was added 9.2 ml. (21 g. .147 mole) of methyl iodide in 50 ml. of dry ether during a 0.5 hour period. When the addition was complete, a suspension of 11.1 g. (.053 mole) of VI in about 90 ml. of dry ether was added in portions. Stirring and heating were continued for four hours, after which time the unreacted lithium was removed by decantation through a fine wire screen. The reaction mixture was hydrolyzed by the cautious addition of cold water. The ether layer was separated, and the aqueous layer was extracted with chloroform. The combined organic layers were dried, and the solvent was removed by distillation. The residue was 11.0 g. (92%) of 1-methyl-4-hydroxy-4-piperidyl-phenylmethylcarbinol (V), m.p. 145-147°. Two recrystallizations of the solid from intermediate boiling ligroin furnished an analytical sample of V, m.p. 147-149°. The infrared absorption spectrum is listed in the Sadtler catalogue as No. 9444.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.47; H, 9.00
Found: C, 71.64: H, 9.05

The methobromide was prepared by the standard procedure,

and after recrystallization from alcohol-ethyl acetate, melted at 211-213°.

Anal. Calcd. for $C_{15}H_{24}BrNO_2$: Br, 24.20

Found: Br. 24.41

1-Methyl-4-hydroxy-4-piperidylphenylethylcarbinol (LIX)

The reaction of 4.8 g. (.0219 mole) of VI with .07 mole of ethyllithium prepared from 7.6 g. of ethyl bromide and 1.0 g. of lithium in absolute ether furnished 3.8 g. (69%) of impure 1-methyl-4-hydroxy-4-piperidylphenylethylcarbinol (LIX), m.p. 154-159°. Recrystallization of the solid from benzene gave 1.5 g. (27.4%) of glycol (LIX), m.p. 163-164°. An analytical sample was prepared by recrystallization from ethanol-water or benzene and melted at 164-165°.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30

Found: C, 71.77; H, 9.44

1-Methyl-4-hydroxy-4-piperidylphenylisopropylcarbinol (LX)

The reaction of 3.6 g. (.0164 mole) of VI with .10 mole of isopropyllithium prepared from 7.8 g. of isopropyl chloride and 1.0 g. of lithium in absolute ether gave 2.5 g. (45%) of glycol (LX), m.p. 155-161.5°. Two recrystallizations from benzene-intermediate boiling ligroin furnished an analytical sample of 1-methyl-4-hydroxy-4-piperidylphenylisopropylcarbinol (LX), m.p. 160.5-162.5°. The infrared absorption spectrum has been catalogued by Sadtler as No. 9446.

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57

Found: C, 72.72, 72.83; H, 9.12, 9.36

Reactions of 1-Methyl-4-hydroxy-4-piperidylphenylcarbinol (IV)

a) With p-Toluenesulfonic Acid-Acetic Acid-----A mixture containing 2 g. (.009 mole) of glycol, IV, 2 g. of p-toluenesulfonic acid monohydrate, 5 ml. of acetic acid anhydride dissolved in 40 ml. of glacial acetic acid was heated under reflux for six hours. After cooling, the solution was neutralized with cold sodium hydroxide solution and extracted with several portions of chloroform. The extracts were dried over anhydrous potassium carbonate and filtered. The chloroform was removed by distillation, and the residue was triturated in the cold with petroleum ether. The residual 0.3 g. of impure IV was collected by filtration and recrystallized from benzene to give 0.28 g. of IV, m.p. 139-140°. This solid gave no depression on admixture with authentic IV. The filtrate was concentrated by distillation to give 1.86 g. of viscous undistillable residue of 1-methyl-4-acetoxy-4-piperidylphenylmethyl acetate (XXIX). The yield of XXIX was 80% based on the recovered starting material.

Preparation of the Picrate of XXIX

An ethanolic solution of 0.7 g. (.00229 mole) of crude oil from a) was treated with a saturated ethanolic solution of picric acid to give 1.0 g. (82%) of a picrate, m.p. 166.5-167.5°. One recrystallization of the picrate from isopropyl alcohol (Norit) raised the melting point to 167-168.5°. Employing the method of Cunningham (37) the molecular weight was found to be 533.5, determined on a concentration of 2.225 mg./100 ml. ethanol. The calculated molecular weight for XXIX is 534.5.

Anal. Calcd. for $C_{23}H_{26}N_4O_{11}$; C, 51.68; H, 4.90; N, 10.48

Found: C, 51.74; H, 4.99; N, 10.37

Decomposition of XXIX Picrate

About 0.5 g. of XXIX picrate was heated on the steam bath for twenty minutes with 50% potassium hydroxide solution. The darkened mixture was cooled to room temperature and extracted with chloroform. The extracts were dried over potassium carbonate and filtered. The solution was concentrated on the steam bath to a small volume and diluted with petroleum ether. The resulting glycol (IV) 0.1 g., melted at 131-136°. Recrystallization from benzene (Norit) gave a purer sample, melting at 137-139°, and this sample gave no depression when mixed with authentic IV.

Reaction of XXIX with Lithium Aluminum Hydride

A solution of 1.0 g. (.00328 mole) of crude oil from a) was heated under reflux for a few hours with an ethereal solution of excess lithium aluminum hydride (ca. 1.5 g.). The usual work up, similar to that used in the preparation of IV from VI, gave 0.7 g. (96%) of pure IV, as shown by melting point and mixed melting point determination.

b) With Boron Trifluoride-Acetic Acid-----A solution of 3.85 g. (.0174 mole) of glycol, IV, in 25 ml. of glacial acetic and 2 ml. of acetic anhydride containing 10 ml. of 45% boron trifluoride-etherate was heated under reflux for two hours. After cooling, the solution was diluted with an equal volume of water, chilled, and neutralized with sodium hydroxide solution. The liberated material was extracted with several portions of chloroform. The combined extracts were dried over anhydrous potassium carbonate and filtered. The filtrate was evaporated on the steam bath, and the residue was taken up in

hot benzene. On cooling and adding petroleum ether, 2.2 g. (46%) of monoacetate, XXX, separated as a solid, m.p. 137-144°. The mother liquor was saved for isolation of the diacetate, XXIX. Two recrystallizations of XXX from benzene raised the melting point to 144-147°. An analytical sample of XXX prepared by recrystallization from intermediate ligroin melted at 145-147°. The infrared absorption spectra obtained from this monoacetate XXX are filed as Nos. 28 and 104.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04
Found: C, 68.75; H, 8.00

The mother liquor from the isolation of XXX was concentrated, and the residual oil, 1.4 g. (24.8%) started to distill at 175° at 4.5 mm. The distillation was interrupted when the side arm became obstructed with the viscous distillate. The picrate derivative was made in the usual manner, and after two recrystallizations from methanol, the picrate melted at 166-168.5°. There was no depression in melting point on admixture with XXIX picrate obtained in a) above.

Reactions of the Monoacetate (XXX)

1) With Ethereal Lithium Aluminum Hydride-----A solution of 0.45 g. (.00171 mole) of XXX in absolute ether was added dropwise to a boiling ethereal solution containing a suspension of 0.65 g. of lithium aluminum hydride. After heating under reflux for two hours, the solution was cooled and cautiously decomposed with water, to give 0.4 g. (a quantitative yield) of glycol, IV, m.p. 133-135°, isolated

in the manner already described for the preparation of IV. No depression (m.p. 138-139°) in melting point was observed when mixed with authentic IV.

2) With Alcoholic Alkali-----A small quantity of monoacetate, XXX, was saponified by warming with an aqueous alcoholic solution of potassium hydroxide for twenty minutes. The glycol IV, obtained melted at 136-140° and did not depress (138-141°) the melting point of pure IV on admixture.

Saponification of the Diacetate (XXIX)

The reaction of the viscous oily XXIX treated as in 2) above furnished IV, m.p. 137-138°, which on recrystallization from benzene gave pure IV, m.p. 139-140°. This solid gave no depression on mixing with authentic IV.

c) With Sulfuric Acid-Acetic Acid-----A solution of 2.5 g. (.0113 mole) of IV in a mixture of 30 ml. of glacial acetic acid and 3 ml. of concentrated sulfuric acid was heated under reflux for two hours. The solution was chilled and neutralized with cold sodium hydroxide solution, and the resulting mixture was extracted with ether and once with chloroform. The combined extracts were dried over anhydrous potassium carbonate and filtered, and the solvent was removed by distillation. The residual, red oil was triturated with petroleum ether, and the polymeric material which formed was removed by filtration. The addition of more petroleum ether caused the solution on standing to deposit 0.65 g. (21.9%) of monoacetate XXX, m.p. 141-145°. Recrystallization from intermediate ligroin-benzene gave 0.42 g. (14.2%) of pure monoacetate XXX, m.p. 145-147°. No depression of melting point was observed

on admixture with XXX obtained from the boron-trifluoride-acetic acid reaction, b) above.

Preparation of 1-Methyl-4-acetoxy-4-piperidyl Phenyl Ketone (XXXI)

A solution of 1.8 g. (.00773 mole) of 6-methyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2,5]octane (IX) in 20 ml. of absolute ether was added all at once to a magnetically stirred solution of 11 ml. of glacial acetic acid in 15 ml. of dry ether. The reaction mixture was allowed to remain at room temperature for two hours. The ether was removed by distillation, and the residue was diluted with 25 ml. of water. The solution was chilled by immersion in an ice-bath and gradually was neutralized with potassium carbonate. The precipitated ketoester (XXXI), 1.85 g. (92.5%), was collected by filtration, and after air drying melted at 98-101°. An analytical sample, m.p. 103.5-105°, was obtained by two recrystallizations from absolute ether. The infrared absorption spectrum has been recorded and filed as No. 117.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33

Found: C, 68.90; H, 7.09

Preparation of the Hydroxy-acetate (XXX) by the Reduction of the Ketoacetate (XXXI)

1) Low Pressure-----A solution of 0.7 g. (.00268 mole) of the ketoester (XXXI) in 20 ml. of distilled water containing twelve drops of concentrated hydrochloric acid was subjected to reduction by shaking for four hours in the presence of hydrogen at 41.2 p.s.i. over 0.05 g. of platinum oxide. The

uptake of hydrogen after this time was 0.4 p.s.i. The catalyst was removed by filtration, and the filtrate was neutralized with potassium carbonate. The alkaline mixture was extracted with several portions of ether, and the combined extracts were dried over potassium carbonate, and were filtered, and were concentrated by distillation. The residue was treated with petroleum ether, and after standing a short while in a Dry Ice-Acetone bath, 0.15 g. (21.4%) of hydroxy-acetate (XXX), m.p. 138-143°, was obtained as thin needles. After recrystallization from intermediate ligroin 0.1 g. (14.2%), of pure XXX, m.p. 145-146.5°, was obtained. There was no depression in melting point on admixture with the hydroxy-acetate (XXX) obtained by the boron trifluoride-catalyzed acetylation of the glycol (IV).

2) High Pressure-----The ketoacetate (XXXI) obtained by the reaction of 2.8 g. (.012 mole) of epoxyether (IX) and 10 ml. of glacial acetic acid in absolute ether was not isolated; but the ether was removed by distillation, 20 ml. of water was added, and the acidic solution was directly subjected to hydrogenation over 0.1 g. of platinum oxide in the presence of hydrogen at 1660 p.s.i. The hydrogen absorbed in about three hours amounted to 60 p.s.i. The catalyst was removed by filtration, and the filtrate was neutralized in the cold with potassium carbonate. The alkaline mixture was extracted with ether, and the extract was separated and dried over potassium carbonate. The filtered extract was concentrated by distillation, and the residue was treated with petroleum ether at Dry Ice-Acetone temperature to precipitate 0.24 g.,

overall yield of 7.6%, of hydroxyacetate (XXX), m.p. 140-143.5°. Recrystallization from intermediate boiling ligroin furnished 0.2 g. of pure XXX as thin needles, m.p. 145-147°. The infrared absorption spectrum, No. 162, compared favorably to that obtained by acetylation of glycol IV. The melting point of XXX was not depressed on admixture with this sample nor with that of the low pressure reduction 1) above.

d) With 48.8% Hydrobromic Acid-----A solution of 50 ml. of 48.8% hydrobromic acid containing 5.0 g. (.0226 mole) of glycol, IV, was heated under reflux for three hours. The reaction mixture was cooled and neutralized with potassium carbonate liberating an oil which was extracted into ether. The aqueous layer was extracted once with chloroform. The combined extracts were dried over anhydrous potassium carbonate, filtered, and concentrated by distillation. The residual oil was triturated with petroleum ether, inducing the crystallization of 1.0 g. (20%) of glycol, IV. After filtration and recrystallization from benzene (Norit), the melting point of the solid was 138-140° with no depression on admixture with the authentic glycol, IV. The petroleum ether filtrate was concentrated, and the residual oil, 2.6 g., was fractionally distilled under diminished pressure to furnish 2.1 g. (57%, based on recovered IV) of 6-methyl-2-phenyl-1-ox-6-azaspiro [2,5] octane (XXV), b.p. 126° at 5 mm., n_D^{27} 1.5341.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89
Found: C, 76.63; H, 8.53; N, 7.08

The methiodide of XXV obtained in the usual manner melted at 190-191° after two recrystallizations from isopropyl alcohol. The infrared absorption spectrum, No. 73, of this salt has been recorded. One recrystallization from acetone furnished pure XXV methiodide, m.p. 223-224°.

Anal. Calcd. for $C_{14}H_{22}INO$: I, 36.76

Found: I, 36.86; 37.14

The reaction d) above was repeated employing 3.0 g. of glycol (IV) and 30 ml. of 48.8% hydrobromic acid to give 42% of XXV. The infrared absorption spectrum, No. 66, was determined on the fraction, b.p. 120° at 4.5 mm., $n_D^{24.7}$ 1.5363.

The XXV methiodide was made in acetone, and, after recrystallization from the same solvent, melted at 223-226°.

Isolation of 1-Methyl-4-piperidyl phenyl ketone (VII)

A second, high boiling fraction, b.p. 130-160° at 4 mm., 0.5 g. contained mostly 1-methyl-4-piperidyl phenyl ketone (VII) and gave 0.15 g. of crude VII methiodide. After recrystallization from acetone, the methiodide melted at 223-227°, with no depression (226-230°) on admixture with authentic VII methiodide. A considerable depression, (193-203°), however, was observed when mixed with the above XXV methiodide.

Catalytic Hydrogenolysis of XXV Methiodide

A solution of 0.5 g. of XXV methiodide in methanol was subjected to hydrogenation in the presence of hydrogen at 1350 p.s.i. over 0.2 g. of platinum oxide for 5.3 hours. The uptake of hydrogen (30 p.s.i.) was complete in less than three hours. The catalyst was removed by filtration, and the solution was concentrated to a small volume by distillation.

The addition of absolute ether with scratching by means of a glass stirring rod gave 0.45 g. of incompletely reacted substance, m.p. 155-198°. This material was combined with a further quantity of XXV methiodide, comprising a total of 0.95 g. (.00274 mole) of starting material, and hydrogenated over excess Raney nickel in 150 ml. of ethanol in the presence of hydrogen at 1225 p.s.i. The absorption of hydrogen (45 p.s.i.) was complete in less than three hours, and the pyrophoric nickel was removed by filtration. The clear solution was concentrated by distillation to a volume of about 20 ml., and 0.6 g. (63%) of 1-methyl-4-hydroxy-4-benzylpiperidine (XVI) methiodide, m.p. 197-199° was obtained by the addition of dry ether. After recrystallization from ethanol, XVI methiodide melted at 199-200.5°. The infrared absorption spectrum, No. 91, was exactly superimposable on that of XVI methiodide, No. 92, prepared from the product of the reaction between 1-methyl-4-piperidone and benzylmagnesium chloride (26). There was also no depression in melting point on admixture with the authentic XVI methiodide. The ultraviolet absorption spectrum was determined using a concentration of 1.265×10^{-3} m./l. and exhibited maxima at 258 mμ log ε 2.30, and 264 mμ log ε 2.17.

Anal. Calcd. for $C_{14}H_{22}INO$: I, 36.55

Found: I, 36.87

Characterization of 1-Methyl-4-hydroxy-4-piperidyl benzyl bromide Hydrobromide (XL)

A solution of 1.0 g. of glycol, IV, in 15 ml. of 48.8% hydrobromic acid was heated for 1.5 hours. The cooled reaction mixture was filtered and evaporated to dryness by heating under diminished pressure. The resulting thick red oil resisted all efforts at crystallization.

a) Reaction of XL with Catalytic hydrogen-----About one-half of this oil was diluted with water and subjected to hydrogenation in the presence of hydrogen at 3-4 atmospheres over platinum oxide. The catalyst was removed by filtration, and the solution was neutralized with potassium carbonate. The mixture was extracted with ether and the extract was dried and the solvent removed by distillation. The addition of petroleum ether failed to precipitate any solid, and so the petroleum ether was removed by distillation. The residue was treated with methyl iodide in alcohol, and the methiodide which formed melted at 193-195° after two recrystallizations from acetone. There was no depression in melting point on admixture with the methiodide of 1-methyl-4-hydroxy-4-benzyl-piperidine (XVI). Significant depression of melting points were observed, however, with the methiodide of both XIII and XXV.

b) Analytical Data-----The residual oily hydrobromide mixture was thoroughly dried by heating under reduced pressure in an Abderhalden pistol which was charged with potassium hydroxide.

Anal. Calcd. for $C_{13}H_{19}Br_2NO$: Br, 43.77;

$C_{13}H_{18}BrNO$: Br, 28.12

Found: Br, 39.72*, 36.36

Reaction of Epoxide (XXV) from d) with Lithium Aluminum Hydride Partial Ring Opening and Detection of the Phenyl Ketone (VII)

A suspension of about 1.5 g. of lithium aluminum hydride in 100 ml. of boiling absolute ether was treated dropwise with 0.9 g. (.0044 mole) of distilled product from d), containing mostly epoxide (XXV), dissolved in absolute ether. The solution was maintained at gentle boiling for about two hours, and after the usual work up, the residual oil was triturated with petroleum ether to precipitate a very small amount of impure 1-methyl-4-piperidylphenylcarbinol (XIII), m.p. 125-142°, which was isolated by filtration and characterized as the methiodide, m.p. 209-211°. There was no depression of melting point (210-214°) on admixture with authentic XIII methiodide. The filtrate remaining after removal of XIII was concentrated, and the residual oil was distilled under diminished pressure. The fraction boiling in the range of 125-143° at 8 mm. was collected to give 0.7 g., (77%) of XXV, which was treated with methyl iodide in methanol solution. On the addition of dry ether and scratching the sides of the glass vessel with a stirring rod, 0.7 g. of crude XXV methiodide was collected by filtration. On recrystallization from

*This determination was made by the Volhard method subsequent to reaction with hydroxide and corresponds to about 91% of bromohydrin (XL).

isopropyl alcohol 0.57 g. of XXV methiodide, m.p. 215-218°, was obtained. The mother liquor and filtrate were combined and heated until a clear solution resulted and then allowed to cool undisturbed. Two crystalline forms of solid were obtained after about twenty-four hours standing. These solids were well defined individual rods and rosette clusters; the weight of solids totaled 0.25 g. The two kinds of crystals were separated manually; the rods were recrystallized from isopropanol furnishing 0.05 g. of XXV methiodide melting at 216-220°. After combining the total yield of XXV methiodide, 0.62 g., corresponding to 25% XXV, it was recrystallized from acetone to give pure XXV methiodide, m.p. 224.5-226.5°, which showed no depression of melting point on admixture with authentic XXV methiodide. The rosette clusters, obtained directly, melted at 184-191° and, after recrystallization from ethanol-ether, gave 0.15 g. of XVI methiodide, m.p. 195-197°. There was no depression of melting point (197-200°) when this methiodide was mixed with authentic XVI methiodide. The isolation of 0.15 g. of XVI methiodide under these conditions accounts for 9.8% of ring opening of the epoxide (XXV).

e) With 48.8% Hydrobromic Acid-Glacial Acetic Acid----A solution of 45 ml. of 48.8% hydrobromic acid and 20 ml. of glacial acetic acid containing 3.5 g. (.0158 mole) of glycol, IV, was heated under reflux for two hours. The reaction mixture was cooled and neutralized with sodium hydroxide solution, and then was extracted with several portions of chloroform. The combined extracts were dried over potassium carbonate, filtered, and concentrated to a small volume. The addition of

petroleum ether precipitated 0.5 g. (14%) of glycol, IV, which was collected by filtration and, after recrystallization from benzene (Norit), melted 138-140°. The remaining petroleum ether filtrate was concentrated by distillation, and the residual oil was fractionally distilled giving an oil which represented 56% of XXV, based on recovered glycol. The main fraction, 1.30 g., distilled at 114-115 at 4.5 mm, n_D^{26} 1.5342 and was used to determine the infrared absorption spectrum, No. 27. The ultraviolet absorption spectrum, determined at a concentration of 0.1167 and 1.167 g./l. or 5.74×10^{-4} and 10^{-3} m./l. exhibited maxima at 238 mμ (log ε 2.79), 243 mμ (log ε 2.80), 247 mμ (log ε 2.80), 266 mμ (log ε 2.52) and 332 mμ (log ε 2.41), Fig. 6.

The higher boiling fraction, 0.50 g. was collected at 120-125° at 4 mm., n_D^{26} 1.5422, and was used for the stronger infrared spectrum, No. 29.

Hydrogenolysis of 6-Methyl-2-phenyl-1-ox-6-azaspiro[2,5]octane (XXV)

The same reaction as described in e) was repeated to give 0.6 g. (17%) of glycol, IV, and 2.4 g. (90%) of undistilled crude epoxide XXV. The latter oil was dissolved in ethanol and was treated with hydrogen at 850 p.s.i. over freshly prepared Raney nickel at room temperature. The reduction was complete in less than 3.5 hours during which time ten p.s.i. of hydrogen were absorbed. The catalyst was removed by filtration, and the solvent was distilled. The residue was triturated with an ether-petroleum ether mixture and was filtered from some insoluble polymeric material. The filtrate

was concentrated by distillation, and on standing with added petroleum ether the residue gradually crystallized to give 0.9 g. of solid m.p. 69-77°. After two recrystallizations from hot petroleum ether (Norit), this solid gave 0.3 g. of pure 1-methyl-4-hydroxy-4-benzylpiperidine (XVI), m.p. 79-81°, which showed no depression of melting point on admixture with an authentic sample of XVI (26). The remaining mother liquors were combined and concentrated to give .85 g. oily (XVI), which was quaternized with methyl iodide in ethanol yielding, after isolation and recrystallization from ethanol (Norit), 0.45 g. of XVI methiodide, m.p. 196-197°. No depression of melting point occurred on admixture with authentic XVI methiodide.

Preparation of 1-Methyl-1,2,3,6-tetrahydro-4-pyridylphenylcarbinol (XLII)

A solution of 4.0 g. (.0144 mole) of 4-pyridyl phenyl ketone methobromide (XII) in 50 ml. of methanol was treated dropwise with constant stirring with a solution of 2.0 g. (.053 mole) of sodium borohydride in 50 ml. of methanol. When the reaction subsided, the mixture was heated under reflux for 0.75 hour. The methanol was removed by distillation under reduced pressure, and 25 ml. of water was added. The resulting mixture was extracted with several portions of ether, and the combined ethereal extract was dried over anhydrous sodium sulfate, filtered and concentrated by distillation. The residual oil was taken up in hot intermediate boiling ligroin and on cooling, 1.43 g. (49%) of dark colored crystals, m.p.

104-107°, were collected by filtration. After the recrystallization of 1.13 g. from intermediate ligroin (Norit), 1.0 g. (44%) of colorless carbinol (XLII), m.p. 107-108°; (lit. (67) m.p. 108-109°, (26) 107-108.5°) was obtained. The carbinol, XLII, tends to decompose on standing.

The treatment of XLII in ether with either anhydrous hydrogen chloride or hydrogen bromide gave oily salts, and on neutralization, XLII, m.p. 107°, was recovered quantitatively.

After two hours of boiling in 48.8% hydrobromic acid-glacial acetic acid mixture according to the conditions of the reaction with glycol (IV) in e) above, XLII furnished intractable polymeric material.

f) With Cold Concentrated Sulfuric Acid-----To 50 ml. of concentrated sulfuric acid maintained at 0-5°, was added 7.3 g. (.033 mole) of glycol, IV, in small portions with stirring over a .75 hour period. After standing for five minutes the clear red solution was poured onto 200 g. of ice and neutralized with cold sodium hydroxide solution. The alkaline mixture was extracted with chloroform, and the extracts were dried over potassium carbonate, filtered, and concentrated by distillation. The residue, on treatment with petroleum ether, solidified to give a small amount of tacky substance, which after warming with concentrated hydrochloric acid for 1.5 hours, furnished .05 g. of glycol (IV). The petroleum ether filtrate was concentrated, and the residual oil was distilled to give 3.0 g. (45%) of XXV, b.p. 119-121° at 5 mm., n_D^{26} 1.5271. The infrared absorption spectrum, No. 153, was obtained, and the substance was found to cause reduction of

Tollens' reagent.

The methiodide was made in acetone, and after recrystallization from the same solvent, melted at 223-225°. The methiodide was shown by mixed m.p. determination to be identical to XXV methiodide obtained from d) above. The ultraviolet absorption spectrum exhibited maxima at 260 mμ (log ε 2.34) and 266 mμ (log ε 2.21) at a concentration of 8.43×10^{-4} m./l., Fig. 7. The infrared absorption spectrum, No. 163, was determined.

Hydrogenolysis of XXV Methiodide

A solution of 0.45 g. (.0013 mole) of pure XXV methiodide (m.p. 223-225°) obtained from f) in 30 ml. of methanol was subjected to hydrogenation by hydrogen at 43.0 p.s.i. over excess Raney nickel for 1.5 hour at room temperature. During this time a negligible amount of hydrogen was absorbed. The catalyst was removed by filtration, and the methanol was evaporated on the steam bath to give 0.4 g. of partially reacted XXV methiodide, m.p. 150-185°. This material was combined with an additional quantity of pure XXV methiodide, comprising a total of 0.7 g. (.002 mole), and hydrogenated over excess Raney nickel in ethanol in the presence of hydrogen at 1075 p.s.i. After the absorption of hydrogen (35 p.s.i.) that occurred in fifteen minutes, the reaction was complete. The catalyst was removed by filtration, and the filtrate was concentrated to a small volume by distillation. The addition of dry ether precipitated 0.6 g. (84%) of pure 1-methyl-4-hydroxy-4-benzylpiperidine (XVI) methiodide, m.p. 198-200°. There was no depression in melting point when this methiodide

was mixed with authentic XVI methiodide.

Reaction of XXV With Lithium Aluminum Hydride

A solution of 0.55 g. (.0027 mole) of epoxide (XXV) from f) in absolute ether was gradually added to a suspension of 1.5 g. (.0400 mole) of lithium aluminum hydride in 50 ml. of absolute ether in the conventional, three-necked apparatus. The solution was maintained at the boiling temperature for six hours. Following the usual work up, the residual oil was derivatized with methyl iodide in acetone giving 0.35 g. (63%) of XVI methiodide, m.p. 188-194°. After recrystallization from acetone 0.23 g. (41.5%) of pure XVI methiodide m.p. 198-199° was obtained, and the melting point was not depressed on admixture with an authentic sample of XVI methiodide.

g) A repetition of f), allowing the reactants to stand for 15 minutes, gave 25% of epoxide (XXV) as an oil, b.p. 115-117° at 4.5 mm., n_D^{25} 1.5331, which gave a positive Tollens' test.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43

Found: C, 75.93; H, 8.66

The aldehyde present could not be derivatized with semicarbazide or methyl lithium. Oximation by the pyridine method gave a polymeric substance.

Reaction of XXV With Lithium Aluminum Hydride

To a suspension of 0.95 g. of lithium aluminum hydride in 25 ml. of boiling absolute ether was added 0.8 g. (.00394 mole) of XXV, from g) above, dissolved in 5 ml. of dry ether. Heating was continued for 2.5 hours, and the cooled mixture was decomposed with water. After filtration, the ether layer

was dried over potassium carbonate and evaporated leaving 0.75 g. of colorless oil, which did not reduce Tollens' reagent. On distillation under diminished pressure, 0.5 g. of unchanged epoxide, XXV, was collected as a fraction boiling at 130-132° at 12 mm, n_D^{23} 1.5336.

The hydrobromide, made in the usual manner, crystallized with difficulty, and after trituration with isopropyl alcohol gave 95 mg. of hydrobromide, m.p. 161-162.5°. The infrared absorption spectrum of the salt, No. 160, was obtained and was found to be identical with that of the hydrobromide of the product of the reaction of lithium aluminum hydride and 1-methyl-4-bromo-4-piperidyl phenyl ketone (VIII) performed by Troscianiec (26). Mixed melting point determination showed no depression.

Reaction of XXV With Hydrogen Chloride

Dry hydrogen chloride was passed into an ethereal solution of 1.86 g. (.00915 mole) of XXV from g) above. The gummy mass could not be crystallized and on neutralization with potassium carbonate .3 g. (14%) of the precipitated chlorohydrin (XLVIIa) was collected by filtration. After washing with ether XLVIIa melted at 135-137°. Recrystallization from benzene-petroleum ether raised the melting point to 138-139. A mixed melting point determination with authentic glycol, IV, showed a considerable depression of melting point (119-126°). The substance gave a positive Beilstein test for halogen. An analytical sample, after recrystallization from intermediate ligroin melted at 140-140.5°. The infrared absorption spectra,

Nos. 87 and 227 were obtained. The ultraviolet absorption spectrum, determined with a solution of a concentration of 0.1788 g./l. showed maxima at 257 mμ (log ε 2.33) and 264 mμ (log ε 2.22).

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.12; H, 7.57; N. 5.84
Found: C, 65.12, 64.72; H, 7.06, 7.17; N, 5.26

The picrate was obtained in the usual manner and melted at 200.5-202.5° after recrystallization from ethanol. The molecular weight determined spectrophotometrically (37) was 467, using a solution of a concentration of 1.885 mg./100 ml. ethanol. The calculated molecular weight is 472.

Anal. Calcd. for $C_{19}H_{24}ClN_4O_8$: N, 11.87
Found: N, 12.1

Reaction of XXV With Hydrogen Bromide

An ethereal solution of 0.9 g. (.0044 mole) of XXV from g) was saturated with dry hydrogen bromide. The resulting precipitate could not be crystallized and was neutralized with potassium carbonate in aqueous solution. The yellow oil liberated was extracted with ether, and the extract was dried, filtered and concentrated. The addition of petroleum ether, aided by scratching the glass vessel with a stirring rod, caused the residual oil to crystallize slowly and 0.15 g. (12%) of crude bromohydrin (XLVIIb), m.p. 95-105°, was obtained. After recrystallization from benzene and trituration with petroleum ether, the solid started melting at 95° and remained cloudy up to 125°. Within one month's standing XLVIIb liquefied to a dark brown oil.

The picrate prepared in ethanol melted at 176-176.5°. There was no depression of melting point on admixture with the picrate of the product of the inverse addition of sodium borohydride to 1-methyl-4-bromo-4-piperidyl phenyl ketone (VIII) (58).

Anal. Calcd. for $C_{19}H_{24}BrN_4O_8$: C, 44.20; H, 4.68; N, 10.85

Found: C, 44.93, 45.14; H, 4.09, 4.22; N, 10.8

Preparation of 1-Methyl-4-phenyl-4-piperidylcarbinol (XLVI)

To a boiling solution of 150 ml. of absolute ether containing a suspension of 4.0 g. (0.105 mole) of lithium aluminum hydride in the conventional three-necked flask, was gradually added, by means of a solids addition flask attached to a neck, 5.0 g. (.0176 mole) of Demerol (1-methyl-4-carbethoxy-4-phenylpiperidine hydrochloride)* The addition required about 0.5 hour, and the solution was maintained at boiling temperature with stirring for five hours. After standing at room temperature overnight the excess hydride was decomposed by the cautious addition of water. The hydrolyzed mixture was filtered, and the ethereal filtrate concentrated by distillation. The crystalline residue of the carbinol (XLVI) weighed 3.5 g. (97%) and melted at 135-136.5°, lit. (70) m.p. 136.8-137.4°. Recrystallization from ligroin or chloroform-ether did not alter the melting point. The infrared absorption spectrum, No. 141, was obtained in carbon disulfide solution.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33

Found: C, 76.19; H, 9.60

*Obtained from Sterling Winthrop Co.

The hydrobromide of XLVI was made by passing anhydrous hydrogen bromide into an ethereal solution of the base, but the material resisted crystallization.

Identification of 1-Methyl-4-formyl-4-phenylpiperidine (XLIV)

To a magnetically stirred solution of 2.0 g. (.01 mole) of 1-methyl-4-cyano-4-phenylpiperidine (XLVIII)* in 50 ml. of absolute ether, maintained at 0° by means of an ice-bath, was added dropwise a solution-suspension of 1.0 g. (.025 mole) of lithium aluminum hydride in 40 ml. of absolute ether; the usual precautions for an anhydrous atmosphere were observed throughout the addition which required approximately two hours. After short standing, the mixture was hydrolyzed with water and was filtered. The ethereal filtrate was dried over potassium carbonate, was filtered, and was concentrated by distillation under diminished pressure leaving a light colored oil which reduced ammoniacal silver nitrate, depositing a lustrous silver mirror. The infrared absorption spectrum, No. 257, contained a small band at 1720 cm^{-1}, indicative of the presence of the aldehyde (XLIV). The band was sharpened and somewhat intensified by treatment of the oil with dilute hydrochloric acid.

Oximation of 1-Methyl-4-hydroxy-4-piperidyl Phenyl Ketone (VI)

To a solution of 5.0 g. (.0228 mole) of phenyl ketone (VI) in 25 ml. of 95% ethanol and 30 ml. of water was added 5.0 g. (.072 mole) of hydroxylamine hydrochloride and 5.0 g. of anhydrous sodium acetate, and the reaction was heated under

*Sterling Winthrop Co.

reflux for 2.5 hours. The solution was cooled and neutralized with potassium carbonate, and the VI oxime, 5.1 g. (95%) which precipitated was collected by filtration and found to melt at 204-206°. The melting point, after recrystallization from ethanol, was 206-208°; lit. (26) m.p. 204-205°. The infrared absorption spectrum is filed as No. 105.

Lithium Aluminum Hydride Reduction of VI Oxime

To a refluxing ethereal solution (200 ml.) containing a suspension of 2.0 g. (.053 mole) of lithium aluminum hydride in a conventional three-necked flask, equipped with a mercury sealed stirrer, and a reflux condenser, was added 2.5 g. (.0107 mole) of VI oxime via a solids addition flask. Heating under reflux was continued for two hours, and after short standing, the excess hydride was carefully decomposed with water, and the mixture was filtered. The ethereal filtrate was concentrated by distillation, and the residue was treated with petroleum ether to precipitate 0.45 g. of unreacted oxime which was removed by filtration. The filtrate was concentrated to give 1.9 g. (80%) of reduction products which could not be crystallized. An attempt to purify this material failed when the distillate at 170° at 8 mm. clogged the side arm and prevented any further fractionation of the product. The infrared absorption spectrum, No. 125, of this partially distilled material was obtained.

In a similar reaction, employing 5.8 g. (.0248 mole) of VI oxime with excess lithium aluminum hydride, 5.15 g. (94%) of oily reduction products was obtained and was used directly in the subsequent deamination reaction.

Attempted Preparation of 1-Methyl-5-phenyl-1-aza-4-cycloheptanone (XLV) Deamination of α-(1-Methyl-4-piperidyl) benzylamine (LVI)

A solution of 4.0 g. of crude reduction product, containing the amino alcohol (LVI), in 120 ml. of 50% aqueous acetic acid was stirred vigorously and was maintained at 0° by an ice-bath while simultaneously from different funnels a solution of 50 ml. of 50% acetic acid and a solution of 3.7 g. of sodium nitrite in 45 ml. of water were added. The sodium nitrite solution was added about half as fast as the acetic acid, and the tip of the funnel was immersed beneath the surface of the reaction mixture. After four hours of stirring at 0°, the solution was warmed to room temperature and concentrated by distillation under reduced pressure. Water was added, and the solution was neutralized with potassium carbonate. The alkaline mixture was extracted with ether and chloroform; the extracts were dried over potassium carbonate, were filtered, and concentrated to a small volume. The addition of benzene and petroleum ether precipitated 1.53 g. of glycol (IV), m.p. 133-136°, which was collected by filtration, and after recrystallization from benzene 1.1 g. of IV, m.p. 138-139° was obtained. This solid gave no depression of melting point on mixing with pure IV. The filtrate was concentrated, and the residue was distilled under diminished pressure to give 0.3 g. of oil, b.p. 160° at 9 mm., n_D^{27} 1.5355, comprising a mixture of monoacetate (XXX) and epoxide (XXV) as shown by

the infrared absorption spectrum, No. 137. The methiodide was prepared in acetone and after one recrystallization from acetone, 25 mg. of XXV methiodide, m.p. 219-222°, was isolated. There was no depression in melting point on admixture with authentic XXV methiodide.

Reactions of 1-Methyl-4-hydroxy-4-piperidyl-methylphenylcarbinol (V)

a) With Boron Trifluoride-Acetic Acid-----A solution of 5.3 g. (.0226 mole) of glycol, V, in 40 ml. of glacial acetic acid, 2.5 ml. acetic anhydride, and 13 ml. of 45% boron trifluoride-etherate was heated under reflux for two hours. After cooling to room temperature, the dark solution was diluted with an equal volume of water and was neutralized with cold sodium hydroxide solution. The alkaline mixture was extracted with several portions of ether and finally with chloroform. The combined extracts were dried over potassium carbonate, filtered and concentrated by distillation. The residual oil was treated with petroleum ether and filtered from a trace amount of dark polymeric material. After concentration, the residual oil, 4.2 g., was distilled under reduced pressure giving an average yield of 3.3 g. (73%) of 2,5-dimethyl-1,2,3,4-tetrahydro-5-indeno [1,2-c] pyridine (XVIII) in three separate runs, b.p. 91-93° at 1.5 mm., n_D^{26} 1.5742; 125-127° at 4 mm., n_D^{27} 1.5732; 137-138° at 5.5 mm. The infrared absorption spectra numbered 15 and 16 were obtained with the sample n_D^{27} 1.5732. The ultraviolet absorption spectrum was determined with a solution of a concentration of 4.576×10^{-5} m./l. and exhibited a maximum at 261 mμ, (log ε 4.16), the minimum occurred at 235 mμ, (log ε 3.70), Fig. 8. A sample for analysis was redistilled to give XVIII, b.p. 103° at 2 mm., n_D^{24} 1.5742.

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.38; H, 8.60; N, 7.03

Found: C, 83.42; H, 9.11; N, 6.95

The hydrobromide of XVIII was obtained in the usual manner and was found to melt at 223-223.5° after recrystallization from methanol-ether. The ultraviolet absorption spectrum was determined using a solution of a concentration of 5.68×10^{-5} m./l. and showed a maximum at 259 mμ (log ε 4.18), and a minimum at 233 mμ (log ε 3.63), Fig. 8. Recrystallization from ethanol-acetone was found to raise the melting point to 230-233°. The XVIII hydrobromide is difficultly soluble in water or alcohol.

Anal. Calcd. for $C_{14}H_{18}BrN$: Br, 28.52

Found: Br, 28.72

The hydrochloride of XVIII was also obtained by the usual procedure and melted at 197.5-199° (dec.), after recrystallization from isopropyl alcohol. The infrared absorption spectrum, No. 79, was recorded. Recrystallization from acetone-isopropyl alcohol was found to raise the melting point to 203-204.5° (dec.).

Anal. Calcd. for $C_{14}H_{18}ClN$: Cl, 15.04

Found: Cl, 14.99, 15.10

The methiodide of XVIII was made in acetone and melted at 205-209°. After recrystallization from the same solvent, XVIII methiodide melted at 211-213°.

Anal. Calcd. for $C_{15}H_{20}IN$: I, 37.19

Found: I, 36.88, 36.98

Isolation of 1,5-Dimethyl-5-phenyl-1-aza-4-cycloheptanone (XIX) Semicarbazone

A solution of 3.0 g. (.01275 mole) of glycol (V) in 22 ml. of glacial acetic acid, 1.5 ml. acetic anhydride, and 7 ml. of 45% boron trifluoride-etherate was heated under reflux for two hours and worked up in the manner described for a) above up to the point of treatment of the residual oil with petroleum ether. The solution was immersed in a Dry Ice-acetone bath to precipitate a dark oily substance. After standing at room temperature for a few minutes, the petroleum ether was decanted for the subsequent isolation of 1.9 g. of indeno pyridine (XVIII) as mentioned in a) above, and the residue was treated with semicarbazide hydrochloride in the customary manner. After heating on the steam bath for 1.5 hours and cooling, the mixture was neutralized, and the liberated base was extracted with ether. The dried and filtered extract was concentrated, and the addition of petroleum ether precipitated 0.2 g. (5.7% yield based on glycol V) of XIX semicarbazone, m.p. 170-175°. Recrystallization from chloroform-intermediate boiling ligroin raised the melting point to 173-176.5°. An analytical sample, m.p. 175-177.5°, was obtained after a further recrystallization from methanol-water.

Anal. Calcd. for $C_{15}H_{22}N_4O$: C, 65.66; H, 8.08

Found: C, 42.25, 42.08; H, 8.13, 8.17

Preparation of 1-Methyl-4-phenyl-4-piperidyl Methyl Ketone (XVII)

To a magnetically stirred and refluxing solution of methyllithium,, prepared by passing gaseous methyl bromide into 150 ml. of ether containing 1.2 g. (.173 g.at.) of short lithium wire, was added dropwise a solution of 3.95 g. (.0197 mole) of 1-methyl-4-cyano-4-phenylpiperidine (XLVIII)* in 50 ml. of absolute ether. Heating was continued for 3 hours, and the solution was allowed to stand overnight at room temperature. The mixture was hydrolyzed by the portion-wise addition of 25 ml. of water, and the ether layer was separated and dried over anhydrous sodium carbonate. The filtered ethereal solution was concentrated, and the residual oil was distilled under diminished pressure furnishing 3.3 g. (78%) of XVII ketimine, as indicated by the infrared absorption spectrum, No. 157, b.p. 143-145° at 2 mm., $n_D^{24.5}$ 1.5487.

Acidic Hydrolysis of the Ketimine-----A solution of 2.5 g. (.0116 mole) of the imine was warmed on the steam bath for 10 minutes with 25 ml. of 1 : 1 hydrochloric acid and neutralized with potassium carbonate liberating copious amounts of ammonia. The alkaline mixture was extracted with ether, and the ether was dried over potassium carbonate. The filtered ethereal solution was concentrated and the residual methyl ketone (XVII) was fractionally distilled under reduced pressure to give 1.9 g. (76%) of pure XVII, b.p., 145-148° at 9 mm., n_D^{22} 1.5389; lit. (62) b.p. 143° at 3.5 mm. and (71) 156-157° at 10 mm. The infrared absorption spectrum, No. 196,

*Sterling Winthrop, redistilled, b.p. 130-133° at 3.5 mm., n_D^{24} 1.5348

exhibited a strong carbonyl band at 1704 cm.$^{-1}$ and was devoid of bands near 1635 cm.$^{-1}$ (imine).

Reduction of XVII to the carbinol derivative was effected in 60% yield by employing ethereal lithium aluminum hydride according to the procedure described by Morrison (72) for this reduction. After one recrystallization from intermediate boiling ligroin the carbinol melted at 119-120°, lit. (72) m.p. 123.5-124°. Further recrystallization did not alter the melting point of this derivative.

Semicarbazone of 1-Methyl-4-phenyl-4-piperidyl Methyl Ketone (XVII)

A solution of 1.05 g. (.0049) of the methyl ketone (XVII) in 30 ml. of water containing 1.0 g. of semicarbazide hydrochloride and 1.5 g. of anhydrous sodium acetate was warmed on the steam bath for one hour. After cooling to room temperature, the solution was neutralized with potassium carbonate, and the precipitated semicarbazone, 1.05 g. (79%) was collected by filtration and was found to melt at 181-191°. Recrystallization of the derivative from chloroform-ethyl acetate raised the melting point to 200-201°.

Anal. Calcd. for $C_{15}H_{22}N_4O_2$: N, 20.42

Found: N, 19.9

b) With 48.8% Hydrobromic Acid-----A solution of 3.0 g. (0.0128 mole) of the glycol (V) in 35 ml. of 48.8% hydrobromic acid containing 1 ml. of glacial acetic acid was heated to boiling over a two hour period. After cooling to room temperature and diluting with an equal volume of water, the solution was neutralized with potassium hydroxide solution and solid

potassium carbonate. The orange-colored oil which separated was taken up in ether and the aqueous layer was extracted thoroughly with ether. The combined ether extracts were dried over potassium carbonate and filtered, and the ether was evaporated on the steam bath. The resulting crude oil was dissolved in petroleum ether and allowed to stand overnight. Filtration removed a small amount of dark gum, and the filtrate was concentrated by distillation. The residual oil was distilled under reduced pressure to give 1.3 g. (51.2%) of indeno pyridine (XVIII) b.p. 135-137° at 4 mm., n_D^{24} 1.5770, infrared absorption spectrum, No. 204. The ultraviolet absorption spectrum was determined on a solution of a concentration 9.03×10^{-5} m./l. and showed a maximum at 261 mμ (log ε 3.99) and a minimum at 234 mμ (log ε 3.55), Fig. 9.

The methiodide of XVIII was prepared in the usual manner in acetone solution yielding a solid, m.p. 208-210°, which, after recrystallization from a large volume of acetone, melted at 209-212°. No depression in melting point was observed on admixture with XVIII methiodide obtained in a) above.

c) With 32% Sulfuric Acid-----A solution of 2.5 g. (0.0106 mole) of the glycol, V, in 45 ml. of (32%) sulfuric acid, made by mixing two parts by weight of water and one part by weight of 96% sulfuric acid (sp.gr. 1.84) was heated under reflux for four hours. The cooled solution was neutralized with 50% sodium hydroxide solution. The resulting mixture was extracted with ether and finally with chloroform, and the extracts were dried over potassium carbonate. The drying agent was removed by filtration, the filtrate was concentrated by

distillation, and the residue was triturated with petroleum ether to give a dark brown tacky substance which was removed by filtration. The filtrate was concentrated, and the residual yellow oil was distilled under diminished pressure to give 1.3 g. (61.4%) of XVIII, b.p. 141-143° at 3 mm., n_D^{23} 1.5798. The infrared absorption spectrum, No. 210, has been recorded.

After refluxing for three hours with ethereal lithium aluminum hydride, the indeno pyridine (XVIII) was recovered and treated with methyl iodide in acetone solution. The resulting XVIII methiodide melted at 213-214° after recrystallization from acetone. No depression in melting point was observed on admixture of XVIII methiodide obtained from either a) or b) above.

Acid-Catalyzed Dehydration of 1-Methyl-4-piperidylphenylcarbinol (XIII)

A solution of 3.0 g. (.0146 mole) of XIII in 25 ml. of 48.8% hydrobromic acid and 10 ml. of glacial acetic acid was heated under reflux for one hour. The solution was cooled, neutralized with potassium carbonate, and extracted with several portions of ether. The combined extracts were dried over potassium carbonate, filtered and concentrated by distillation. Fractionation under diminished pressure furnished 2.1 g. (77%) of 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine (L), b.p. 165-170° at 45 mm., n_D^{23} 1.5368, reported (66) b.p. 278-279°. The infrared absorption spectrum, No. 59, was obtained.

The methiodide of L was crystallized and recrystallized from ethanol-ether and melted at 163-165°. No depression of the melting point was observed when L was mixed with the sample,

m.p. 162-164°, prepared by the sodium borohydride reduction of 4-benzylpyridine (X) methiodide (66). Further recrystallization from acetone-ethanol was found to raise the melting point to 167-169°.

The isomeric 1-methyl-4-benzalpiperidine (LI) methiodide has been characterized and was reported to melt at 212-214° (26).

d) With p-Toluenesulfonic Acid-Acetic Acid------A mixture of 3.0 g. (.0129 mole) of V and 3.0 g. of p-toluenesulfonic acid monohydrate was dissolved in 50 ml. of glacial acetic acid containing 7 ml. of acetic anhydride, and the solution was heated under reflux for 2-3 hours. The cooled solution was diluted with an equal volume of water and was neutralized with cold potassium hydroxide solution. The mixture was extracted with ether and then chloroform, and the combined extracts were dried, filtered and concentrated. The residual oil was distilled under reduced pressure, furnishing a yield of 1.68 g. (66%) of diene (XXa) as an average of three separate runs. The infrared absorption spectrum, No. 179, was obtained on a sample which distilled at 138° at 6.5 mm., n_D^{25} 1.5687. The ultraviolet absorption spectrum also was determined on this specimen, using solution of concentration .09145 and .009145 g./l.; the two maxima observed were at 225 mμ (log ε 4.16) and 310 mμ (log ε 2.87), Fig. 10. The analytical sample boiled at 121-124° at 4 mm., n_D^{28} 1.5643.

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.38; H, 8.60; N, 7.03

Found: C, 83.48; H, 8.34; N, 6.10

The methiodide of XXa prepared in 70% yield from acetone solution melted at 170-174°, and after recrystallization from acetone, melted at 176-178°. The ultraviolet absorption spectrum was determined with solutions having concentrations of .02880 g./l. and 1.713 g./l., and only one maximum occurred, at 221 mμ (log ε 4.42), Fig. 10.

Anal. Calcd. for $C_{15}H_{20}IN$: I, 37.19

Found: I, 37.36

The methobromide was prepared in acetone solution to give quantitative yields of a solid, m.p. 168-172°. After recrystallization from acetone-ethyl acetate, 68% of XXa methobromide m.p. 170-172°, was obtained pure. The infrared absorption spectrum, No. 215, was recorded for this diene methobromide, while the ultraviolet absorption spectrum, determined using solutions of concentration .0739 and .00739 g./l., exhibited a maximum at 223 mμ (log ε 4.12), Fig. 10.

Anal. Calcd. for $C_{15}H_{20}BrN$: Br, 27.20

Found: Br, 27.16, 26.96

Catalytic Hydrogenation of XXa Methiodide

A solution of 0.58 g. (.0017 mole) of XXa methiodide obtained from d) in 50 ml. of methanol was subjected to reduction in the presence of hydrogen at 730 p.s.i. over Raney nickel for nine hours. The hydrogen absorption in 10 p.s.i. was, however, complete after the first few minutes. The catalyst was removed by filtration, and the methanol solution was evaporated to a small volume by warming in a current of air. On the addition of ethyl acetate 0.1 g. (17%) of XXII methiodide, m.p. 170-171°, precipitated (accidental losses incurred

during hydrogenation). Recrystallization from acetone-ethyl acetate afforded a purer sample of XXII methiodide, m.p. 174-175.5°. There was a considerable depression of the melting point of XXII methiodide on admixture with the starting XXa methiodide; however, no depression of melting point occurred when mixed with a sample of authentic XXII methiodide. The infrared absorption spectrum, No. 255, is superimposable on that of authentic XXII methiodide.

Preparation of Methylphenyl-4-pyridylcarbinol (LV)

A solution of 18.3 g. (.10 mole) of 4-pyridyl phenyl ketone (XI) in 100 ml. of dry benzene was added dropwise to a magnetically stirred, refluxing ethereal solution of .15 mole of methyllithium,, prepared by the reaction of small lengths of lithium (2.3 g., 0.33 g.at.) with 9.5 ml. (22 g., 0.15 mole) of methyl iodide in 200 ml. of absolute ether. After the addition of XI was complete, the mixture was maintained at reflux temperature for three hours and allowed to stand overnight at room temperature. The mixture was decomposed with water, and the precipitated (8.0 g.) methylphenyl-4-pyridylcarbinol (LV) was collected and combined with that obtained from the work up of the ether layer to give a total of 18.2 g. (83%) of crude LV, m.p. 143-144°. The pure carbinol (LV) is reported (27) to melt at 146-147°.

Preparation of 1-(4-pyridyl)-1-phenylethylene (LIV). Dehydration of Methylphenyl-4-pyridylcarbinol (LV)

a) With 32% Sulfuric Acid-----A solution of 3.0 g. (.015 mole) of the carbinol (LV) in 45 ml. of 32% sulfuric acid was heated under reflux for three hours. After cooling, the solution was neutralized with sodium carbonate and extracted with ether. The combined extracts were dried over potassium carbonate, filtered and concentrated by distillation. The residual oil was fractionally distilled under diminished pressure to give 1.1 g. (41%) of colorless LIV, b.p. 134-135° at 3 mm., n_D^{23} 1.6097 (lit. (27), b.p. 113-114° at 1 mm., n_D^{22} 1.6100).

The infrared absorption spectrum, No. 224, was recorded. The picrate of LIV was obtained in quantitative yield by the usual procedure, and after recrystallization from acetone, melted at 196-197°.

Anal. Calcd. for $C_{19}H_{14}N_4O_7$: C, 55.61; H, 3.44

Found: C, 56.23, 55.94; H, 3.32, 3.58

The reaction a) was repeated using 8.0 g. (.04 mole) of LV in 125 ml. of 32% sulfuric acid and 5.5 hours of heating to give 3.8 g., (53%) LIV, b.p. 141-143° at 5 mm.

b) With 48.8% Hydrobromic acid-Acetic Acid-----A solution of 7.2 g. (.36 mole) of the carbinol (LV) in 50 ml. of 48.8% hydrobromic acid and 25 ml. of glacial acetic acid was heated under reflux for four hours. The solution was concentrated to about one half the original volume by heating under reduced pressure and then was neutralized with potassium hydroxide solution. The alkaline mixture was extracted with

chloroform; the extracts were dried, filtered and concentrated by distillation. The residual oil was fractionally distilled under diminished pressure to give 3.0 g. (46%) of colorless LIV, b.p. 143° at 5 mm., n_D^{24} 1.6080, lit. (27) b.p. 113-114° at 1 mm., n_D^{22} 1.6100.

Preparation of 1-(1-Methyl-4-piperidyl)-1-phenyl ethane (XXII) Methiodide

a) Methobromide of 1-(4-pyridyl)-1-phenylethylene (LIV)-----A solution of 3.7 g. (.0204 mole) of LIV in 10 ml. of methanol containing excess methyl bromide was allowed to stand in a closed system for one week. The methanol was removed by distillation under reduced pressure, and the residual LIV methobromide resisted all attempts at crystallization.

b) Catalytic Reduction of LIV Methobromide-----The oily methobromide was dissolved in 40 ml. of water. Five drops of concentrated hydrochloric acid was added, and the solution subjected to reduction in the presence of hydrogen at 42 p.s.i. for eleven hours over 0.2 g. of platinum oxide. The hydrogen uptake was five p.s.i. The catalyst was removed by filtration, and the filtrate was neutralized with potassium carbonate. The alkaline solution was extracted thoroughly with ether; the combined ethereal extracts were dried and filtered. The filtrate was concentrated by distillation, and the residual oil was distilled under diminished pressure to give 2.2 g. (53%) of 1-(1-methyl-4-piperidyl)-1-phenyl ethane (XXII), b.p. 112° at 1.5 mm., n_D^{24} 1.5205.

c) Quaternization of XXII with Methyl Iodide-----A solution of 2.15 g. (.0106 mole) of XXII in 20 ml. of methanol-acetone mixture was treated with an excess (ca.3 ml.) of methyl iodide with cooling and swirling. The addition of ethyl acetate precipitated 3.3 g. (90%) of XXII methiodide, m.p. 177-179°. Two recrystallizations from acetone-ethyl acetate gave pure XXII methiodide, m.p. 180-181°. The infrared absorption spectrum, No. 276, of XXII methiodide was superimposable on that of the catalytic reduction of XXa methiodide. There was no depression in a mixed melting point determination between these two methiodides.

Anal. Calcd. for $C_{15}H_{24}IN$: I, 36.75

Found: I, 37.12

d) Reduction by Sodium Borohydride and Catalytic Hydrogen-----A chilled and magnetically stirred solution of about 4.0 g. (.014 mole) of LIV methobromide, as the non-crystalline modification, in 100 ml. of 50% aqueous methanol was gradually treated with 2.0 g. (.053 mole) of sodium borohydride and stirred in the cold for one hour further. After standing at room temperature for a few days the solution was concentrated to about one-half the original volume by distillation under reduced pressure, and the mixture was extracted with ether. The ethereal extract was dried over potassium carbonate, filtered, and concentrated by distillation. The residual oil was fractionally distilled under diminished pressure to give 1.0 g. (ca. 36%) of partially reduced substance, b.p. 110° at 1 mm., $n_D^{26.5}$ 1.5457, whose ultraviolet absorption

spectrum was determined using solutions of concentrations of 1.099, 0.1099 and .01099 g./l. from 220 mμ-350 mμ. The ultraviolet absorption spectrum exhibited only a shoulder at 241 mμ (log ε 5000). This oil, which rapidly darkened on short standing, was dissolved in 20 ml. of dilute hydrochloric acid and was reduced by hydrogen at three atmospheres pressure over platinum oxide and then treated as described in b) and c) to give 0.75 g. (44%) of XXII methiodide, m.p. 164-166°. After one recrystallization from acetone-ethyl acetate, the melting point of XXII methiodide was raised to 177-178°. There was no depression of melting point of XXII methiodide obtained in c) on admixture with this methiodide and likewise no depression of melting point of this methiodide on admixture with the product from the catalytic reduction of XXa methiodide.

SUMMARY

An improved procedure leading to 1-methyl-4-piperidyl phenyl ketone (VII) hydrobromide has been developed. The oxidation of 1-methyl-4-piperidylphenylcarbinol (XIII) by chromic anhydride in acetic acid and subsequent precipitation of VII as the hydrobromide from the spent oxidant in isopropyl alcohol proved to be a superior method to those previously reported. The carbinol (XIII) was readily produced by the catalytic hydrogenation of 1-methyl-4-benzoylpyridinium bromide (XII). As evidence was obtained indicating that the reduction of the carbonyl group in (XII) occurred prior to the complete hydrogenation of the pyridinium ring, the direct synthesis of the phenyl ketone (VII), which is unaffected by similar treatment, was thus precluded.

Following a previously explored pathway, VII hydrobromide was converted in high yield to 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (VI). A quantitative yield of 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (IV) was obtained by the reduction of VI with lithium aluminum hydride, while the reaction of VI with methyllithium afforded 1-methyl-4-hydroxy-4-piperidylphenylmethylcarbinol (V).

The acid-catalyzed reactions of the glycol (IV) were characterized by acetylation when glacial acetic acid was employed as solvent. With boron trifluoride catalyst, a 2:1 ratio of monoacetate (XXX) to diacetate (XXIX) was obtained. The monoacetylated product (XXX) was the only substance

isolated when the reaction of the glycol (IV) was catalyzed by concentrated sulfuric acid. The identical monoacetate (XXX) could be obtained in low yield by the catalytic hydrogenation in acid medium of 1-methyl-4-acetoxy-4-piperidyl phenyl ketone (XXXI). The diacetate, 1-methyl-4-acetoxy-4-piperidylphenylmethyl acetate (XXIX), was isolated alone from the reaction with p-toluenesulfonic acid catalysis.

Dilute sulfuric acid failed to cause the dehydration of the glycol (IV); however, cold concentrated sulfuric acid, with short reaction times to avoid extensive sulfonation, produced a mixture containing as the major component 6-methyl-2-phenyl-1-ox-6-azaspiro[2,5]octane (XXV). The presence of a small amount of 1-methyl-4-formyl-4-phenylpiperidine (XLIV) in the mixture was confirmed by a positive Tollens' test and by a small carbonyl infrared absorption band at 1719 cm^{-1}. Similar characteristics were found with the small amount of authentic aldehyde (XLIV) obtained from the inverse addition of lithium aluminum hydride to 1-methyl-4-cyano-4-phenylpiperidine (XLVIII). The presence of small carbonyl band at 1700 cm^{-1} in the infrared absorption spectrum of the reaction mixture indicated the presence of a small quantity of 1-methyl-5-phenyl-1-aza-4-cycloheptanone (XLV). The attempted preparation of an authentic sample of XLV by the semipinacolic deamination of α-(1-methyl-4-hydroxy-4-piperidyl)-benzylamine (LVI) failed; the reaction produced the glycol (IV) and small amounts of the corresponding acetate (XXX) and epoxide (XXV).

The reaction of the glycol (IV) with boiling 48.8% hydrobromic acid gave a mixture of products composed largely of the epoxide (XXV), formed from the bromohydrin, 1-methyl-4-hydroxy-4-piperidyl benzyl bromide (XL), on neutralization. A 5% yield of 1-methyl-4-piperidyl phenyl ketone (VII) was isolated and characterized. The infrared spectrum of the reaction mixture established the presence of trace amounts of the aldehyde (XLIV) and the azacycloheptanone (XLV). The reaction of IV with hydrobromic acid in glacial acetic acid produced an additional compound, which was detected by ultraviolet spectroscopy and was thought to be the highly conjugated diene, 1-methyl-4-benzal-1,2,3,4-tetrahydropyridine (XLI).

The reactions of 6-methyl-2-phenyl-1-ox-6-azaspiro 2,5 octane (XXV) with hydrogen halide or catalytic hydrogen led to 1-methyl-4-halo-4-piperidylphenylcarbinol (XLVII) or 1-methyl-4-hydroxy-4-benzylpiperidine (XVI) respectively. The latter alcohol (XVI) was also formed from the reaction of XXV with excess lithium aluminum hydride. The identity of XVI was established by comparison with an authentic specimen.

The acid-catalyzed reactions of glycol (V) were chiefly characterized by cyclodehydration to form 2,5-dimethyl-1,2,3,4-tetrahydro-5-indeno[1,2-c]pyridine (XVIII). XVIII was isolated as the major product from the reactions of V with boron trifluoride-acetic acid, 48.8% hydrobromic acid or 32% sulfuric acid catalysis. Evidence for the structural assignment of XVIII is considered to be consistent with both ultraviolet and infrared absorption determinations and elemental analysis of XVIII and its derivatives. Evidence that the

indenyl double bond of XVIII is endocyclic to the piperidine ring is presented.

The boron trifluoride-acetic acid catalyzed reaction of glycol (V) furnished, in addition to XVIII, a small quantity of ketonic material as evidenced by the isolation of a semicarbazone, and the presence of a medium carbonyl band near 1700 cm^{-1} in the infrared spectrum of the reaction mixture. Both the infrared carbonyl absorption band and the melting point of the semicarbazone obtained from an authentic sample of 1-methyl-4-phenyl-4-piperidyl methyl ketone (XVII) eliminated XVII as the structure and supported the assignment of 1,5-dimethyl-4-phenyl-1-aza-4-cycloheptanone (XIX) as the structure for the carbonyl compound present in the reaction product.

The action of boiling 32% sulfuric acid or 48.8% hydrobromic acid failed to transform the glycol (V) into carbonyl containing compounds. Instead the infrared absorption spectra revealed bands at 1663 and 1610 cm^{-1} which indicated the presence of some olefinic product. The glycol (V) apparently underwent immediate and extensive sulfonation when subjected to the influence of cold concentrated sulfuric acid.

The reaction of the glycol (V) with p-toluenesulfonic acid in glacial acetic acid furnished a substance (XXa) whose molecular formula corresponded to $C_{14}H_{17}N$ but which was different from the indeno pyridine (XVIII). Further, XXa was shown by catalytic hydrogenation to possess intact, the parent skeletal system of the glycol (V) for the 1-(1-methyl-4-piperidyl)-1-phenyl ethane (XXII) which was produced, was identical with an authentic sample. On the basis of the

ultraviolet absorption spectrum the most probable composition for XXa was postulated as 1-(1-methyl-1,2-dihydro-4-pyridyl)-1-phenyl ethane (XX) and/or 1-(1-methyl-1,4-dihydro-4-pyridyl)-1-phenyl ethane (XXI); whereas for the quaternary methyl halide of XXa, the structure XX was suggested.

A mechanism for the acid-catalyzed reactions of the glycol (V) was presented suggesting that the formation of both the indeno pyridine (XVIII) and the diene (XXa) proceeded through a common intermediate, 1-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-1-phenylethylene (XXIII).

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APPENDIX

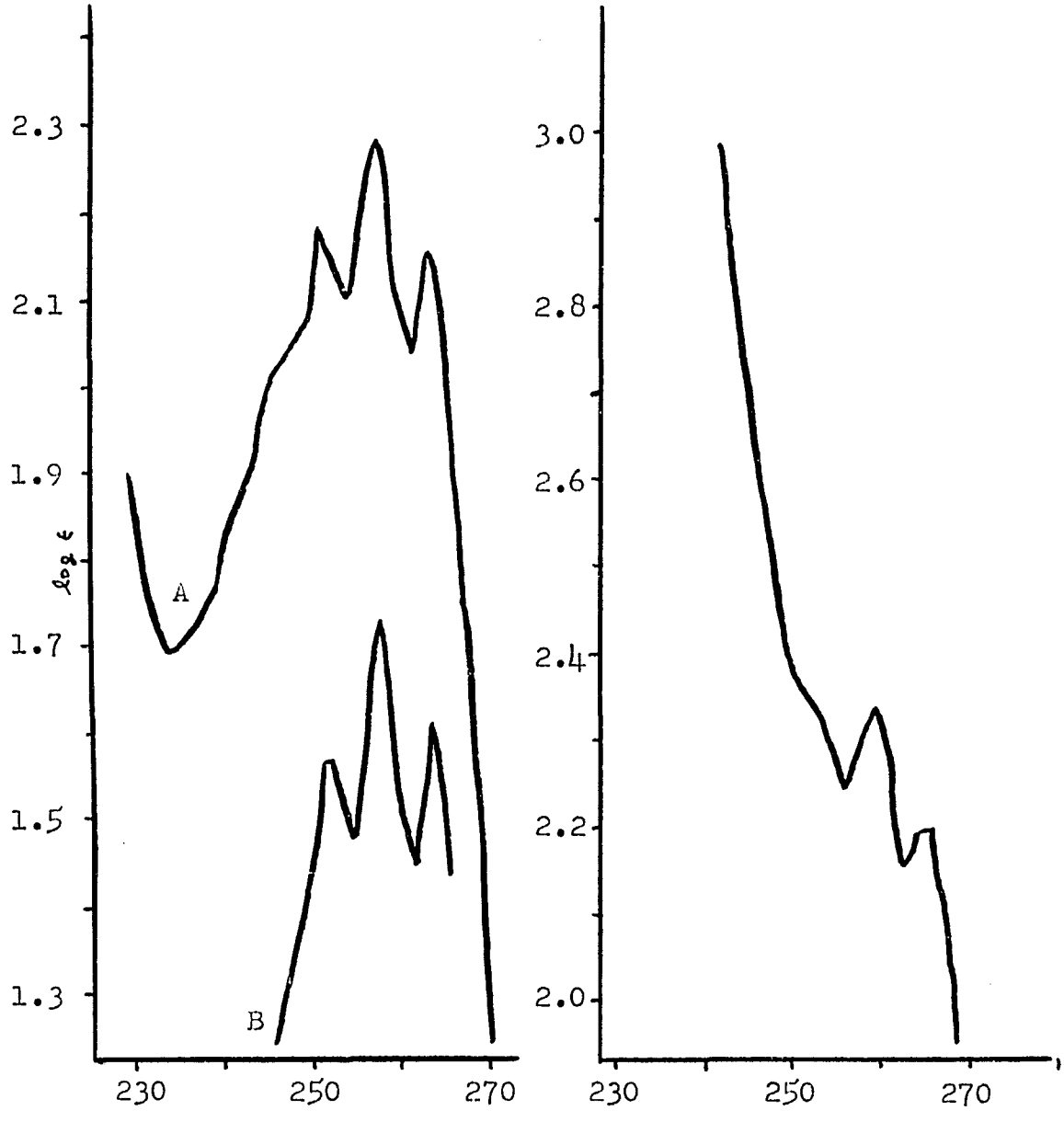

Fig. 5.-Ultraviolet absorption curves for 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (IV) (curve A), and the hydrogenated derivative of IV (curve B).

Fig. 7.-Ultraviolet absorption spectrum for the methiodide of 6-methyl-2-phenyl-1-ox-6-azaspiro [2,5] octane (XXV).

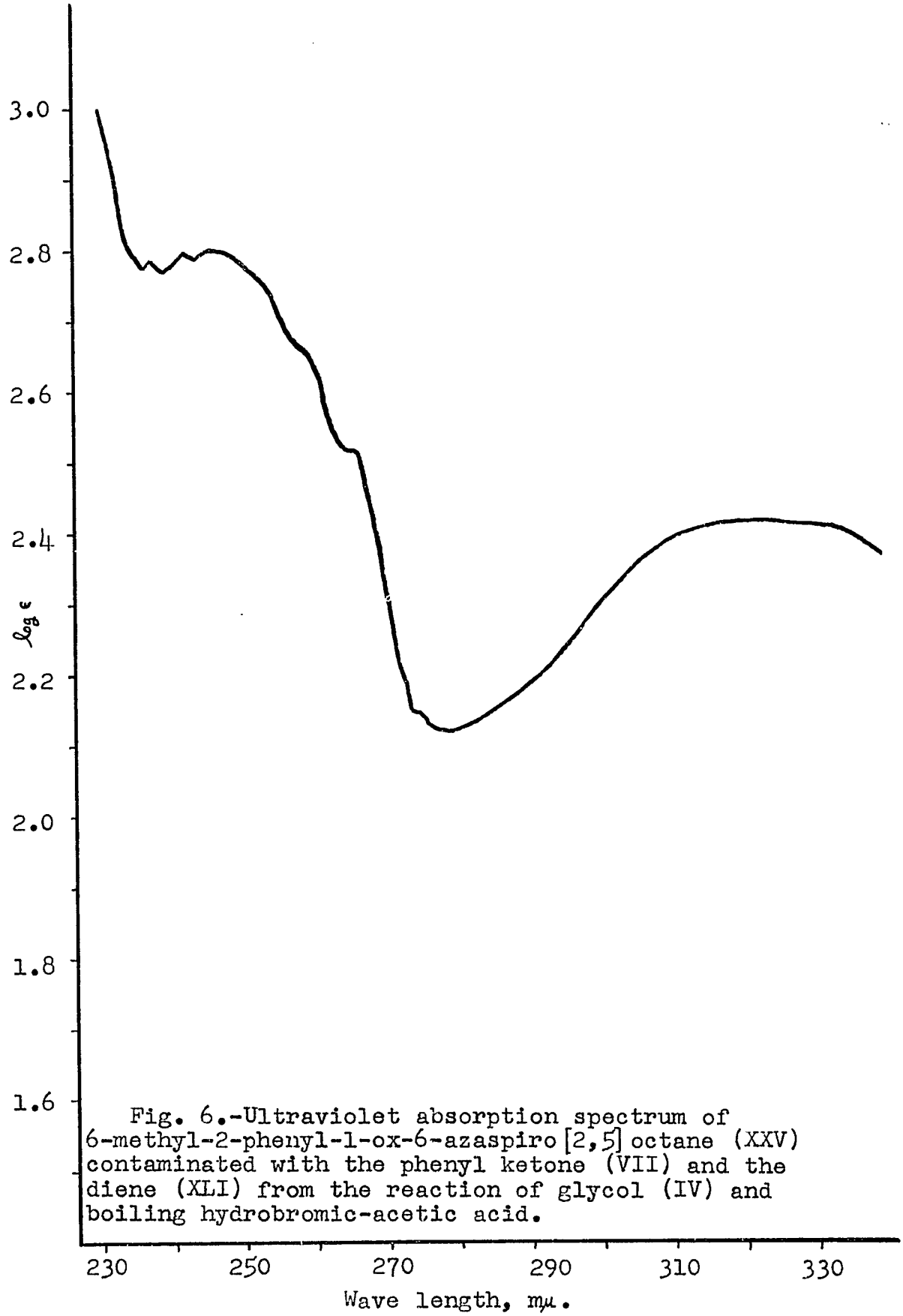

Fig. 6.-Ultraviolet absorption spectrum of 6-methyl-2-phenyl-1-ox-6-azaspiro[2,5]octane (XXV) contaminated with the phenyl ketone (VII) and the diene (XLI) from the reaction of glycol (IV) and boiling hydrobromic-acetic acid.

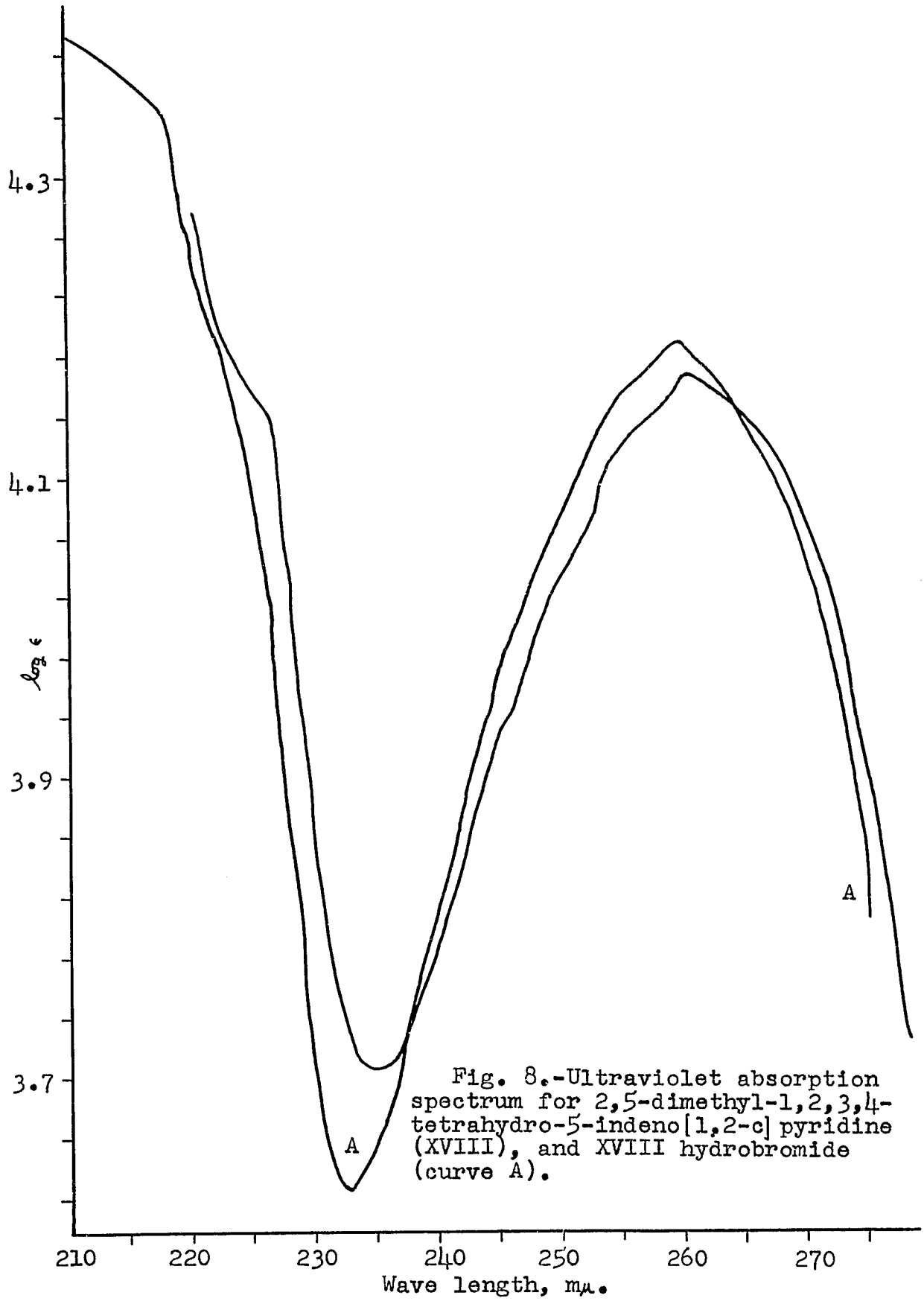

Fig. 8.-Ultraviolet absorption spectrum for 2,5-dimethyl-1,2,3,4-tetrahydro-5-indeno[1,2-c] pyridine (XVIII), and XVIII hydrobromide (curve A).

Fig. 9.-Ultraviolet absorption spectrum of 2,5-dimethyl-1,2,3,4-tetrahydro-5-indeno [1,2-c] pyridine (XVIII) from the reaction of glycol (V) and boiling 48% hydrobromic acid.

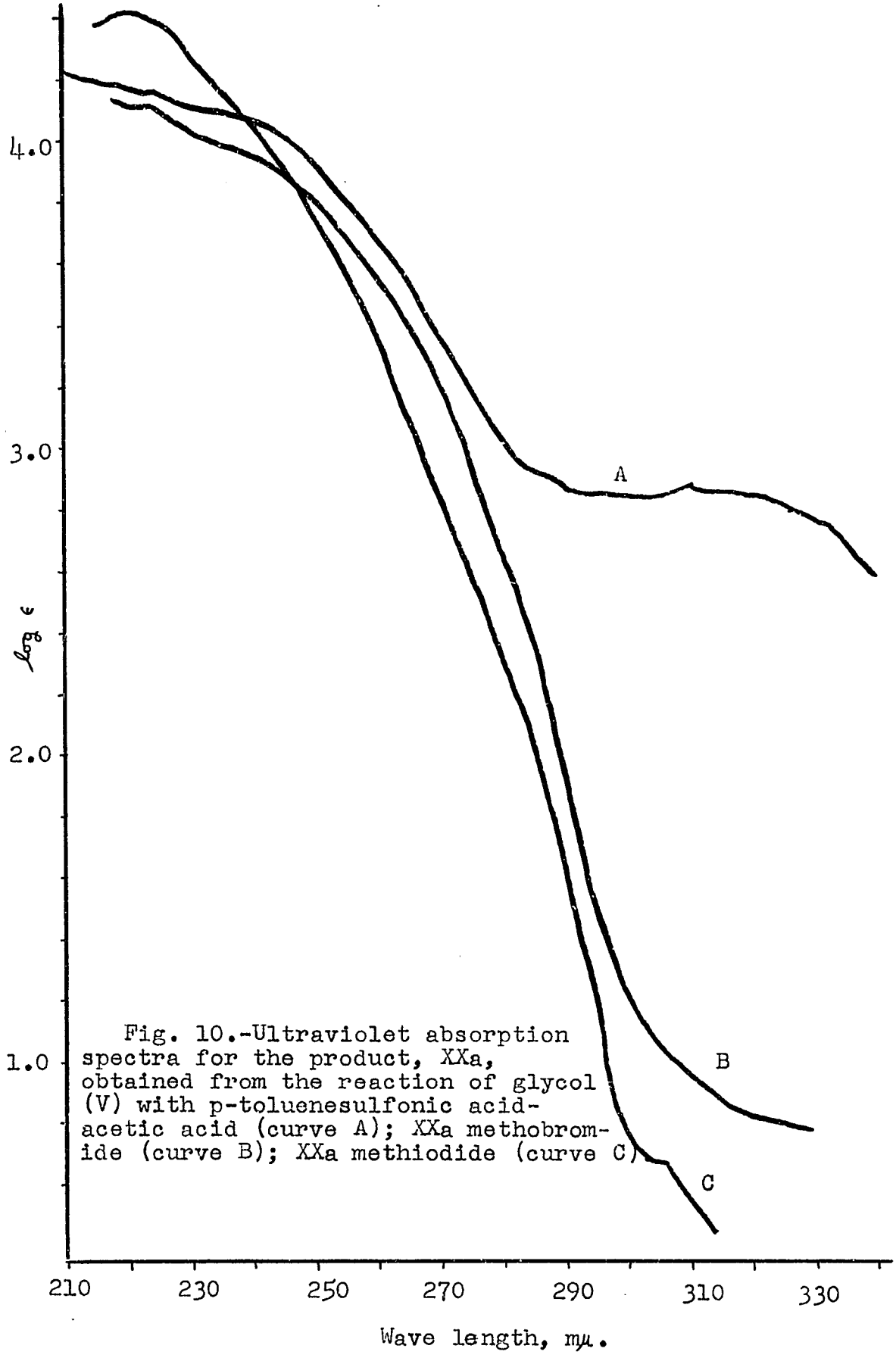

Fig. 10.-Ultraviolet absorption spectra for the product, XXa, obtained from the reaction of glycol (V) with p-toluenesulfonic acid-acetic acid (curve A); XXa methobromide (curve B); XXa methiodide (curve C).

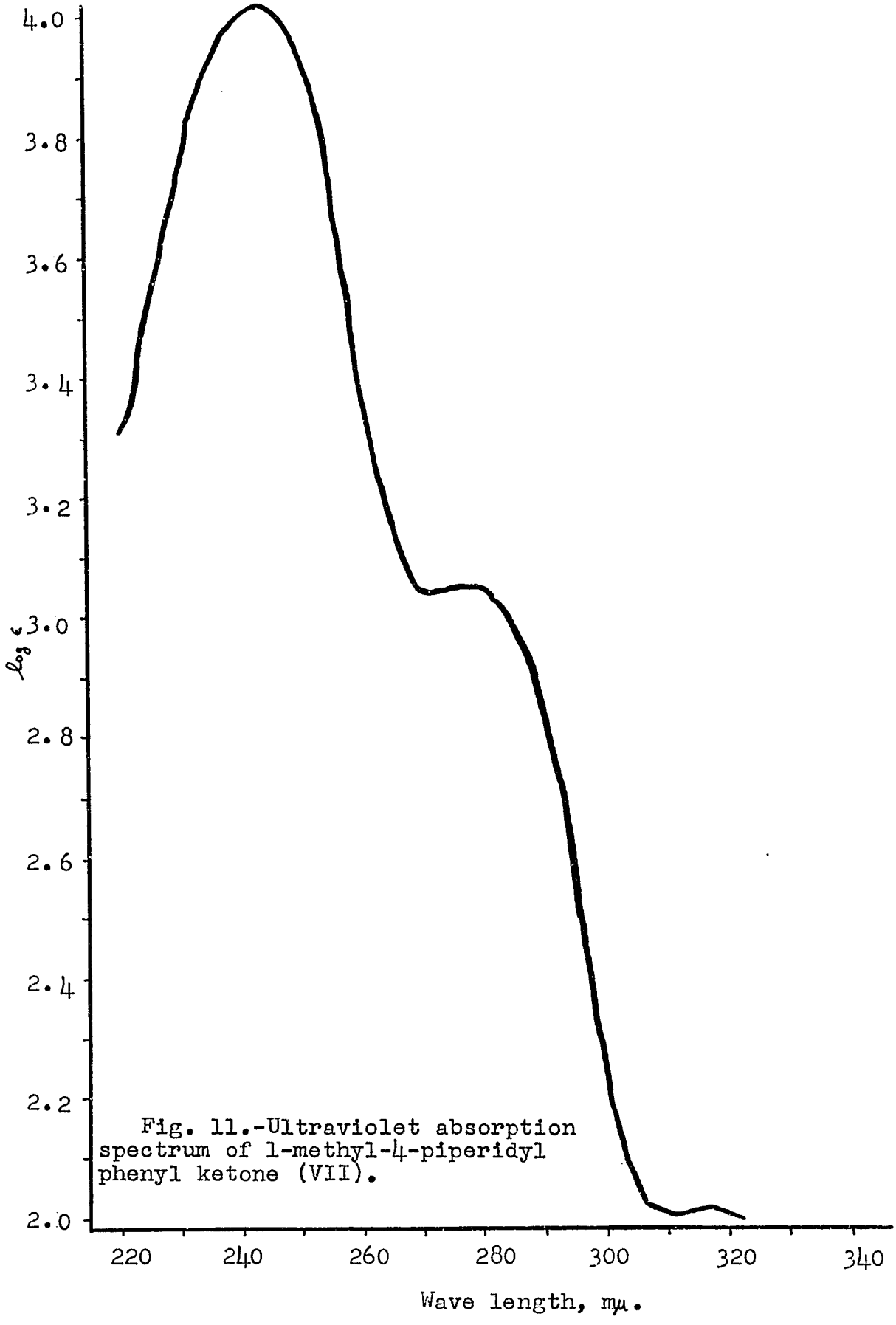

Fig. 11.-Ultraviolet absorption spectrum of 1-methyl-4-piperidyl phenyl ketone (VII).

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