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A STUDY OF THE STEREOCHEMISTRY OF 1-METHYL-3-PHENYL-4-BENZOYLPIPERIDINE

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BY

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Robert L. Krikorian

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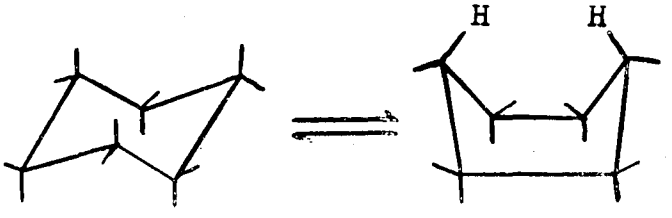
INTRODUCTION

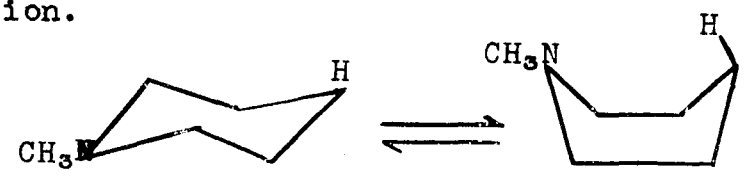
Conformational analysis and the stereoisomerism of cyclohexane derivatives are the subjects of two excellent review articles by Barton and Cookson[32] and by Orloff[33]. The conclusion by Sachse[34] and by Mohr[35] that cyclohexane can exist in only two conformations free from angle strain has long been accepted by chemists. That the chair conformation (A) is more stable than the boat (B) is attested to by much physical evidence, including infrared[36] and Raman[37] spectroscopy and electron diffraction[38], and by thermodynamic considerations[39,40]. Derivatives of cyclohexane always tend to take up the chair conformation whenever this is stereochemically possible.



A B

The substitution of a hetero-atom such as nitrogen for one of the carbon atoms of a cyclohexane ring causes only slight distortion of the ring. The presence of a trigonal nitrogen atom should reduce the difference in thermodynamic stability between the chair and boat forms of the piperidines as compared to cyclohexanes due to the lack of a "flagstaff" substituent on the nitrogen. The unshared pair

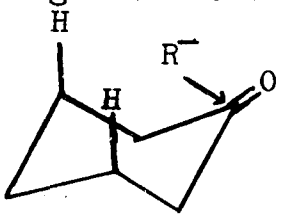
of electrons of the nitrogen atom, by interaction with appropriately located substituents, may affect the relative thermodynamic stability of various possible conformational isomers. The position of greatest interaction appears to be the 4-position.



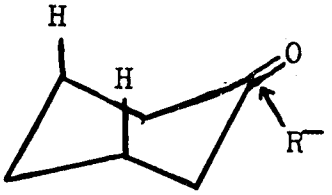
The factors controlling the stereochemistry of addition reactions with the carbonyl group of alicyclic ketones have been explained in terms of thermodynamic and kinetic contributions in the reaction. Jackman et al[42] considered that steric hindrance about the carbonyl group was the chief factor determining the relative amounts of isomers obtained in the reduction of alkylcyclohexanones. Barton[41] emphasized the thermodynamic factor in pointing out that the equatorial isomer was predominant in the product of reductions of alicyclic unhindered ketones.

The rate-controlling step in the nucleophilic addition to a carbonyl is considered to be an attack of the R^- on the carbon of the carbonyl group. In cyclohexanones, there can be a substantial steric effect in the approach of the nucleophilic reagent to the carbonyl carbon atom. If the reagent approaches as depicted in C, there is considerable steric interference by the axial hydrogens, whereas in D there is no such interference. Such factors as these play important roles

in determining the stereochemical course of a reaction.



C



D

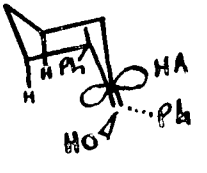
Zimmerman investigated the stereochemistry of the ketonization reaction to determine the possibility of similar effects in the conversion of the trigonal enol carbon to the tetrahedral carbon alpha to the carbonyl. He found that the major product from the reaction of phenylmagnesium bromide with 1-benzoylcyclohexene was a ketone, m.p. 117°, whose identity with 1-phenyl-2-benzoylcyclohexane was established by infrared comparison and mixture melting point determination. A minor product was a stereoisomer which melted at 124° and depressed the melting point of the major product[1].

Subsequently, it was shown that the ketone, m.p. 117°, was <u>cis</u>-1-phenyl-2-benzoylcyclohexane and the ketone, m. p. 124°, was the <u>trans</u> isomer. This was demonstrated by the quantitative conversion of the former to the latter compound by treatment with sodium ethoxide in ethanol, and the rapid bromination of the <u>cis</u> ketone gave 1-phenyl-2-bromo-2-benzoylcyclohexane. Under similar conditions, the <u>trans</u> ketone was recovered unchanged. Repeated experiments indicated that whereas the <u>cis</u> isomer was brominated readily under very mild

conditions, the other was extremely resistant to bromination. Since it is very likely that the ease of bromination depends on the rates of enolization of the two isomers, the contrasting behavior can be attributed to a much greater rate of enolization of the cis isomer than that of the trans.

The fact that in the Grignard reaction the less stable isomer, cis-1-phenyl-2-benzoylcyclohexane, is the major product signifies that of the two possible ketonization processes occurring on acidifying the magnesium enolate, the process leading to the less stable ketone has the greater rate. This difference in the rate of ketonization has been attributed by Zimmerman to a steric effect which comes into play during the acidification process.

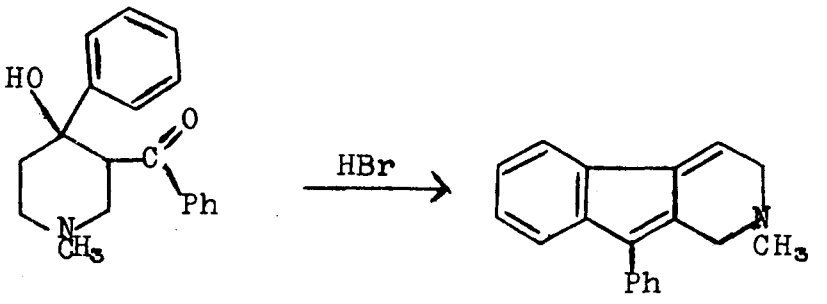
Zimmerman has explained that there are two possible approaches to the enol carbon atom which undergoes attack by a proton donor. One approach (that which is from the underside of the six-membered ring) is much more hindered than the other (that which is from the topside of the six-membered ring). Assuming that the phenyl substituent (because of its bulkiness) is equatorial, the proton donor, in the former approach, would be interfered with by the beta-axial hydrogens. Thus, the preferred approach of the proton donor would be that which leads to the kinetic product rather than that which leads to the thermodynamic product.



Zaugg[2] reported similar results in the analogous piperidine series. When methyl 1-methyl-1,2,5,6-tetrahydronicotinate (arecoline) was treated with excess phenylmagnesium bromide, a ketone, m.p. 115-116°, was isolated in 36% yield. Elemental and infrared analysis indicated that it was 1-methyl-4-phenyl-3-benzoylpiperidine which must have resulted from both simple and conjugate addition of the Grignard reagent to the α,β -unsaturated ester linkage.

In an attempt to cyclodehydrate this ketone to the corresponding indenopyridine, treatment with refluxing 48% hydrobromic acid gave an isomeric ketone, m.p. 62-63°, in 72% yield. All other attempts to cyclodehydrate the higher-melting isomer with acidic reagents were unsuccessful and led only to the thermodynamically more stable isomer, m.p. 62-63°. The thermodynamically less stable ketone decolorized bromine in hot glacial acetic acid whereas the more stable isomer did not. Thus, the higher-melting isomer was assigned the cis-configuration and the lower-melting isomer the trans-configuration. Another significant difference appears in the infrared absorption spectra of the two ketones. Carbonyl absorption of the cis isomer appears at 1701 $cm.^{-1}$ (5.88 μ), whereas the trans isomer absorbs at 1689 $cm.^{-1}$ (5.92 μ).

When 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine is subjected to the action of 48% hydrobromic acid at the reflux temperature, 2-methyl-9-phenyl-2,3-dihydro-1H-indeno-[2,1,c] pyridine was obtained in excellent yield[3,14].



Plati and Wenner devised another method for the synthesis of indenopyridines. By this method they hoped that they would be able to prepare a larger number of derivatives. From the reaction of phenylmagnesium bromide with arecoline at -10° the two racemates of methyl 1-methyl-4-phenylnipecotate were separated and isolated. This product resulted from the conjugate addition of one mole of the Grignard reagent to the α,β -unsaturated ester linkage. Hydrolysis of the esters gave the corresponding acids. Both of the stereoisomeric acids were converted by means of thionyl chloride into their respective acid chlorides which were then cyclized by means of aluminum chloride in tetrachloroethane. The same keto-indenopyridine was obtained from either racemate [4].

It was of interest to this Laboratory to determine the effect, if any, of the location of the heterocyclic nitrogen on the ketonization process of the enol formed during the Grignard reaction, and to compare the results with those reported by Zaugg[2] and Plati and Wenner[4] in the isomeric 3-substituted series. When the present investigation was undertaken, it was fairly certain that only one product could

be isolated from the Grignard reaction. Our immediate goal was to establish the stereochemistry of 1-methyl-3-phenyl-4-benzoylpiperidine (III) and to study the reactions of III and its derivatives comparing them to the reactions of 1-methyl-4-phenyl-3-benzoylpiperidine.

DISCUSSION

This research required the preparation of methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (II) as the major intermediate in this study; however, the synthesis of several other 1,2,3,6-tetrahydropyridines were also required. These preparations ultimately necessitated the preparation of a number of substituted pyridine quaternary salts which are reduced more readily than the pyridines and are the most satisfactory intermediates for the synthesis of partially reduced pyridines.

Preparation of quaternary salts.- The 4-substituted and 3,4-disubstituted pyridine quaternary salts used in this investigation were prepared by standard procedures. The preparation of quaternary salts of pyridines containing an electron-withdrawing group such as -CN or -COPh in the 3-position was more difficult than pyridines with these same groups in the 4-position. Whereas the methobromide and the methiodide of isonicotinonitrile precipitated in yields of 85% and 80%, respectively, and the methiodide of 4-benzoylpyridine precipitated in 88% yield, the quaternary salts of the 3-substituted pyridines can be obtained in yields of only 50-60% even with prolonged reaction times.

The methobromide of 3-phenyl-4-benzoylpyridine (XX) was prepared in 60% yield by saturating a solution of the pyridine in methanol with methyl bromide, allowing the

solution to stand overnight and concentrating the solution to obtain the crystalline salt in 30% yield. Repetition of this process gave an additional 30% of the methobromide. This quaternization process is not comparable to the quaternization of 3-benzoyl-4-phenylpyridine carried out by Nelson[9] who reported 80-90% yields of the quaternary salt. It seemed desirable, therefore, to somehow circumvent this particular quaternization process. 3-Phenyl-4-benzoylpyridine (XX), which was obtained in 57% yield from the sulfur dehydrogenation of 1-methyl-3-phenyl-4-benzoylpiperidine (III), was reduced with sodium borohydride to give 3-phenyl-4-pyridyl-phenyl carbinol (XXIII) in 80% yield. Allowing a solution of XXIII in acetone saturated with methyl bromide to stand for one hour caused the precipitation of the methobromide of XXIII in 93% yield.

Preparation of tetrahydropyridines.- Tetrahydropyridines have been prepared in a variety of ways. Certain cyclization reactions, such as the Mannich[10b] and Hantzsch syntheses[10b], lead directly to tetrahydropyridines or to piperidols which can be dehydrated easily to tetrahydropyridines. The reductions of pyridines by sodium in alcohol[6] and of pyridinium salts by hydrogen over Adams' catalyst[5] have been shown to produce tetrahydropyridines but are not the best methods available. The method which is most extensively used in the production of tetrahydro derivatives is the reduction of pyridine quaternary salts by sodium or potassium borohydride[10a]. It has been established by

Panouse[10a], by Leonard[11] and by Lyle[7] that the reduction of the methiodides of pyridine derivatives with sodium or potassium borohydride gives 1-methyl-1,2,3,6-tetrahydropyridines in good yields[10a,11] and that the double bond is in the 3,4-position[7]. Recently, however, Schenker and Druey[12] showed that the reduction of the methiodide of nicotinonitrile by sodium borohydride gave 1-methyl-1,2,5,6-tetrahydronicotinonitrile and 1-methyl-1,6-dihydronicotinonitrile in equal amounts. Using the method of Lyle, et al[7], methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (II) was obtained in 70-75% yield from the methiodide of methyl isonicotinate (I).

In the course of this investigation it seemed desirable to study the reaction of phenylmagnesium bromide with 1-methyl-1,2,3,6-tetrahydroisonicotinonitrile (XXIX) as a possible method for the synthesis of the stereoisomeric 1-methyl-3-phenyl-4-benzoylpiperidine. The only feasible route to this tetrahydro derivative seemed to be the reduction of the methobromide of isonicotinonitrile by sodium borohydride. A yellow oil, which decomposed rapidly, was obtained. Infrared analysis of this oil showed weak nitrile absorption at 2230 cm.$^{-1}$, medium nitrile absorption at 2215 cm.$^{-1}$, strong C = C absorption at 1642 cm.$^{-1}$ and medium absorption at 1592 cm.$^{-1}$. Due to the fact that the composition of the product obtained from this reaction was uncertain and the yield of ketonic material from its subsequent reaction with phenylmagnesium bromide was

very poor, this particular reaction scheme was not investigated further.

As another possible method for the preparation of the cis- and trans-1-methyl-3-phenyl-4-benzoylpiperidines, the reaction of phenylmagnesium bromide with 1-methyl-1,2,3,6-tetrahydropyridylphenyl ketone (XXXIII) in the presence of cuprous chloride was explored. The preparation of XXXIII was accomplished by the sodium borohydride reduction of 1-methyl-4-benzoylpyridinium bromide (XXXI) and subsequent oxidation of the tetrahydroalcohol to XXXIII. The yield (50-60%) of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenyl carbinol (XXXII) was comparable to that obtained by Kerlin[13].

In the final phase of this research, difficulties were encountered with the catalytic hydrogenations of 1-methyl-3-phenyl-4-benzoylpyridinium bromide (XXI) and 3-phenyl-4-pyridylphenyl carbinol methobromide (XXIV). In an attempt to circumvent this problem, the quaternary salt XXIV was reduced with sodium borohydride in the usual manner to give, in 84% yield, 1-methyl-3-phenyl-1,2,5,6-tetrahydro-4-pyridylphenyl carbinol (XXV).

Reaction of phenylmagnesium bromide with methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (II).- The preparation of 1-methyl-3-phenyl-4-benzoylpiperidine (III) by treatment of II with excess phenylmagnesium bromide at room temperature was essentially the method used by Zaugg (2) to prepare 1-methyl-4-phenyl-3-benzoylpiperidine. The yield of III was very poor (15-30%) and could not be improved, III was obtained

pure by vacuum distillation of the oil(Fig. 1).

Infrared analysis of the remaining tarry residue indicated that it contained at least four components. Absorption maxima appeared at 3600 cm.$^{-1}$ (B,W), 1740 cm.$^{-1}$ (M), 1710 cm.$^{-1}$ and 1683 cm.$^{-1}$ (S). The band at 3600 cm.$^{-1}$ is due to the diphenyl carbinol (V) which results from the reaction of excess Grignard reagent with III. The infrared spectrum of an authentic sample of V shows the -OH stretching absorption at 3572 cm.$^{-1}$. The 1,4-addition of phenylmagnesium bromide to the tetrahydroester (II) gives methyl 1-methyl-3-phenylisonipecotate (IV), the infrared spectrum of which has the carbonyl stretching absorption at 1740 cm.$^{-1}$. Thus, some IV appears to be present in the residue. The 1710 cm.$^{-1}$ band is at the frequency expected for the carbonyl stretching of the starting ester II. The pure ketone, III, absorbs at 1678 cm.$^{-1}$ which probably corresponds to the band at 1683 cm.$^{-1}$ in the residue. Thus, the poor isolated yield of III can be attributed to the formation of two other products, the saturated ester IV and the carbinol V, and the difficulty in recovering all of III from the product mixture.

The initial phase of this reaction definitely involves the conjugate addition of the Grignard reagent to the α,β - unsaturated ester II. The above discussion on the infrared analysis of the residue supports this hypothesis. This is also supported by the work of Plati and Wenner[4] who obtained in 73% yield a mixture of the stereoisomeric racemates of

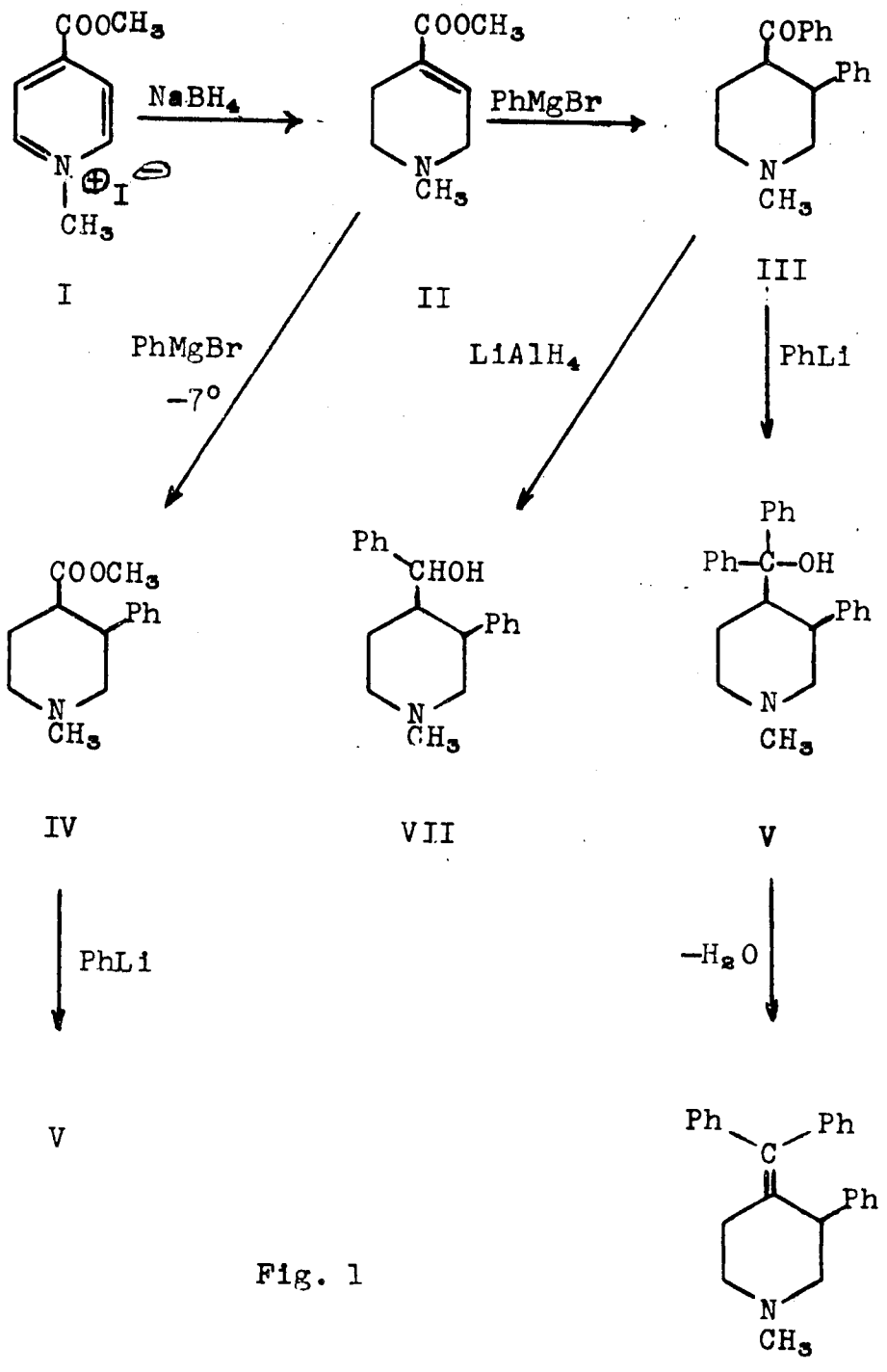
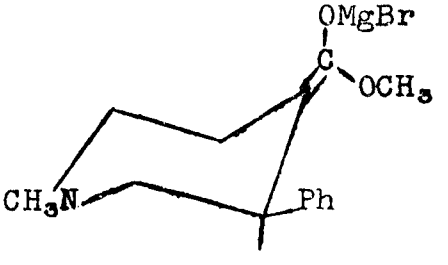

COOCH3
NaBH4
N ⊕ I ⊖
CH3
I
COOCH3
N
CH3
II
PhMgBr
COPh
Ph
N
CH3
III
PhMgBr
−7°
LiAlH4
PhLi
COOCH3
Ph
N
CH3
IV
Ph
CHOH
Ph
N
CH3
VII
Ph
Ph—C—OH
Ph
N
CH3
V
PhLi
V
−H2O
Ph
Ph
C
Ph
N
CH3
VI

Fig. 1

methyl 1-methyl-4-phenylnipecotate when arecoline was treated with one mole of the Grignard reagent at -10°. This research added further support to this hypothesis. The reaction of phenylmagnesium bromide with methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (II) at -7° gave methyl 1-methyl-3-phenylisonipecotate (IV) in good yield. The procedure for this preparation was essentially that used by Plati and Wenner[4] who isolated both the cis and trans racemates of methyl 1-methyl-4-phenylnipecotate from the reaction of phenylmagnesium bromide with arecoline. Proof that only one stereoisomeric racemate of IV was obtained is evident from the reactions with phenyllithium(see p.19).

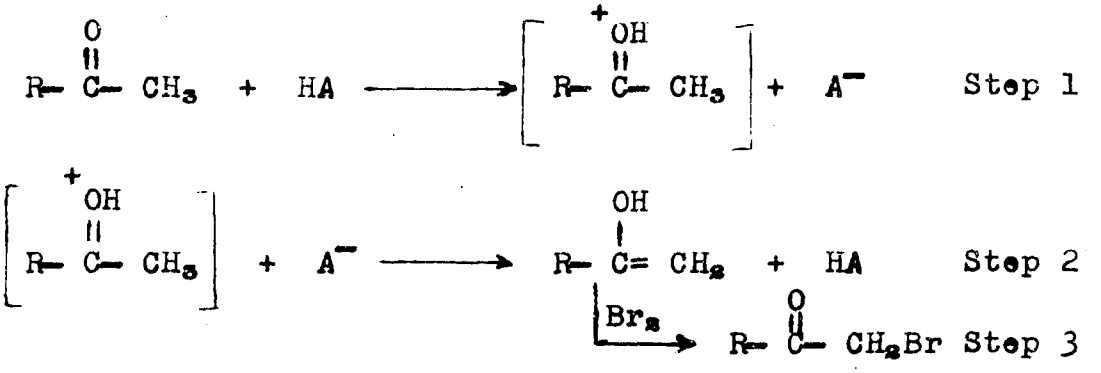
In the second phase of the reaction, one mole of the Grignard reagent may react with the magnesium enolate of the ester, IV, by a displacement of the $-OCH_3$ grouping by the phenyl radical to give the final product, III. The stereochemistry of IV or III would not be determined until the hydrolysis step.



The initial objective of this investigation was to determine the stereochemistry of the ketonic product from this reaction. Bromination and acidic or basic isomerization reactions were anticipated to be instrumental in establishing

the correct stereochemistry.

It has been determined that the rate of bromination is independent of the concentration of bromine and dependent on the rate of enolization[18]. Thus, acid-catalyzed bromination presumably takes place in three steps in which step 2 is rate-determining.



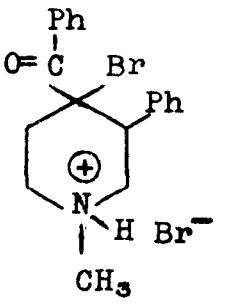
The first step is the addition of a proton to the carbonyl oxygen. The addition of the proton displaces the electronic system toward the proton and, therefore, away from the α-carbon. This results in the facile dissociation of the proton from the α-carbon. The rate-determining step is the removal of the proton and the formation of the enol[19]. These considerations would also apply for the epimerization of the ketone, since the formation of the enol is required for this reaction also.

The bromination reactions were carried out in chloroform and glacial acetic acid at room temperature and at reflux temperatures. These reactions led only to the recovery of the starting material.

The bromination of III was accomplished using radical conditions. When the reaction mixture was illuminated for 9

hours with an incandescent lamp, hydrogen bromide was evolved copiously. A white solid (XIX) was obtained in good yield. The elemental analyses of XIX agreed with those of an α-bromoketone hydrobromide. The infrared absorption spectrum of XIX showed strong carbonyl absorption at 1666 $cm.^{-1}$ which represents a shift of -14 $cm.^{-1}$ from the hydrobromide of III. The ultraviolet absorption spectrum of XIX showed absorption at λ max. 252 mμ ($\log \epsilon$ 3.92) and at λ max. 334 mμ ($\log \epsilon$ 3.25). The former maximum represents a bathochromic shift of 7 mu with a slight decrease in intensity compared with the spectrum of III, and the latter represents a bathochromic shift of 14 mu with an increase in intensity. After neutralization, the crystalline free base gave a positive Beilstein test. The infrared absorption spectrum of the free base showed two broad -OH bands at 3340 $cm.^{-1}$ and 3380 $cm.^{-1}$, a weak band at 1642 $cm.^{-1}$ and a medium band at 1615 $cm.^{-1}$. The ultraviolet absorption spectrum showed absorption at λ max. 238 mμ (weak), λ max. 260 mμ (weak) and λ max. 336 mμ (medium).

Since upon conversion of XIX into the free base the carbonyl absorption disappears and hydroxyl absorption appears, some other reaction must have occurred during the bromination or the neutralization step, or the carbonyl is involved in a transannular interaction with the basic nitrogen. Since the analysis of the salt agreed with the empirical formula $C_{19}H_{21}Br_2NO$, it is fairly certain that the structure of XIX is XIXa.



XIXa

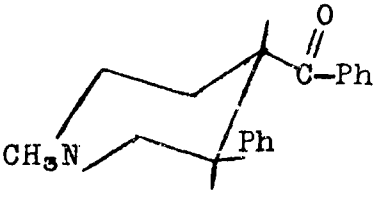
Upon neutralization of XIXa, any number of reactions could occur, but the formation of such secondary reaction products as epoxy alcohol, α,β -unsaturated ketone, carboxylic acid, hydroxy ketone is disproved by the presence of halogen in the base and by inspection of the infrared and ultraviolet spectra of the free base. One other possibility which is suggested by the infrared spectrum is the transannular interaction between the carbonyl and the nitrogen. Leonard has investigated the properties of cyclic aminoketones and aminoacyloins[43-45], and he found that indeed there was interaction between nitrogen and carbonyl in some medium-sized ring compounds.

The epimerization of III was attempted using both acidic and basic conditions. The hydrobromide of III was recovered unchanged after treatment with refluxing 48% hydrobromic acid for seven hours. Heating a solution of III in vinyl acetate and a trace of sulfuric acid for three hours led to the recovery of III. Treatment with sodium ethoxide in refluxing 95% ethanol or with sodium hydride in refluxing

xylene did not affect III. Evidently, the enol of III is very resistant to formation. These facts alone suggest that the α-hydrogen is axial.

In a six-membered ring system, an axial position is more hindered sterically than an equatorial one. Thus, if III is the trans isomer with the phenyl and benzoyl groups equatorial, the α-hydrogen is axially-oriented. A basic reagent (e.g. A^-) would be hindered in its approach to the α-hydrogen, and since the removal of the proton to form the enol is the rate-determining step, the extent of enolization would be negligible[19].

The combined results from the bromination and isomerization studies seem to indicate that III is the trans isomer in which both the phenyl and the benzoyl substituents are equatorial, whereas the bromination under drastic conditions suggests possibly that it is cis.



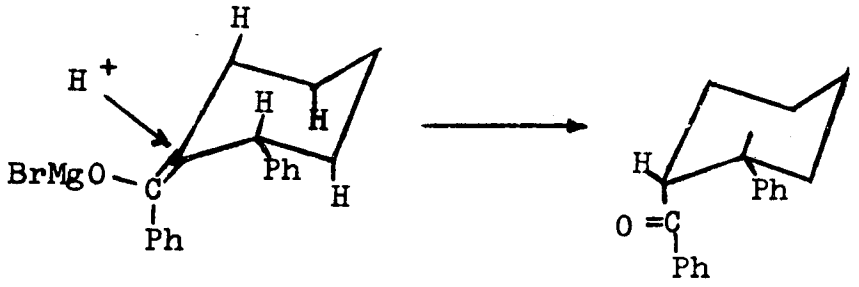
The formation of the thermodynamically more stable trans ketone as the sole product can be rationalized. Zimmerman[1] has shown that cis-1-phenyl-2-benzoylcyclohexane forms on hydrolysis of the Grignard reaction mixture, because the proton donor necessary for the conversion of the magnesium enolate (present before hydrolysis) to the ketone approaches by the least hindered route (equatorial). In our system, as

opposed to that of Zimmerman and of Zaugg[2], there is a proton donor incorporated in the molecule, and the necessary geometry is present for an intramolecular transfer. Thus, the amino group could be hydrated in water or, perhaps, protonated in ammonium chloride or acid, and if the molecule shifted into the boat form with the phenyl substituent in the pseudo-equatorial conformation, the transfer could occur to give the thermodynamically more stable trans isomer (Fig. 2). This intramolecular proton transfer could not occur with the other compounds studied[1,2].

In order to test the hypothesis that the electron pair of the nitrogen is actually involved during the hydrolysis of the Grignard reaction, a Grignard reaction with the methiodide of methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate was attempted, but due to the insolubility of the quaternary salt in ether no reaction occurred. Since the electron pair in the salt would not have been available for a transannular interaction, the product was anticipated to be the salt of the isomeric 1-methyl-3-phenyl-4-benzoylpiperidine.

Also, to test this hypothesis, the possible formation of the second isomeric ketone was investigated. A material balance was sought to determine the maximum amount of the ketone, m.p. 107°, which was formed. The reactions which were crucial in checking this point were:

1) The reaction of phenyllithium with the crude Grignard reaction mixture to give 1-methyl-3-phenyl-4-piperidyldiphenyl carbinol (V) in 54% yield.



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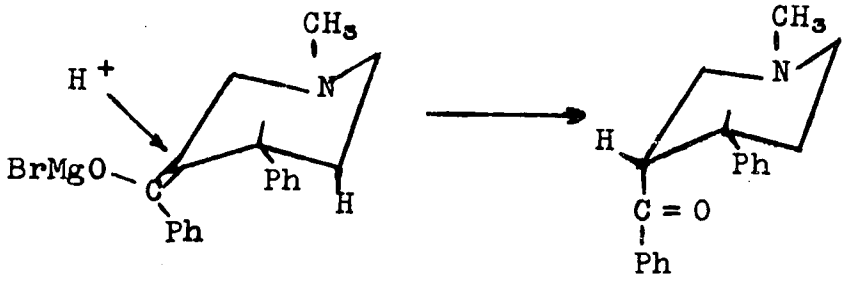


Ref. 2

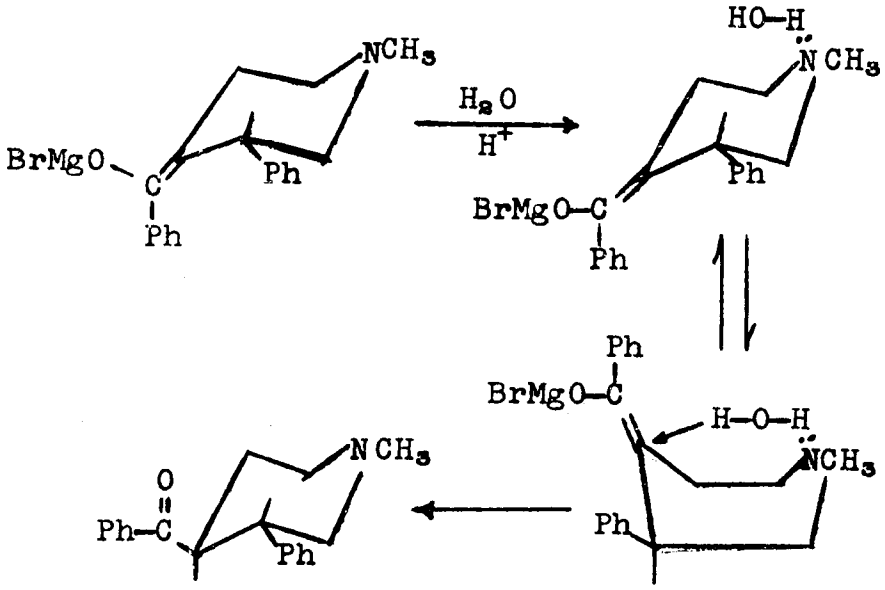


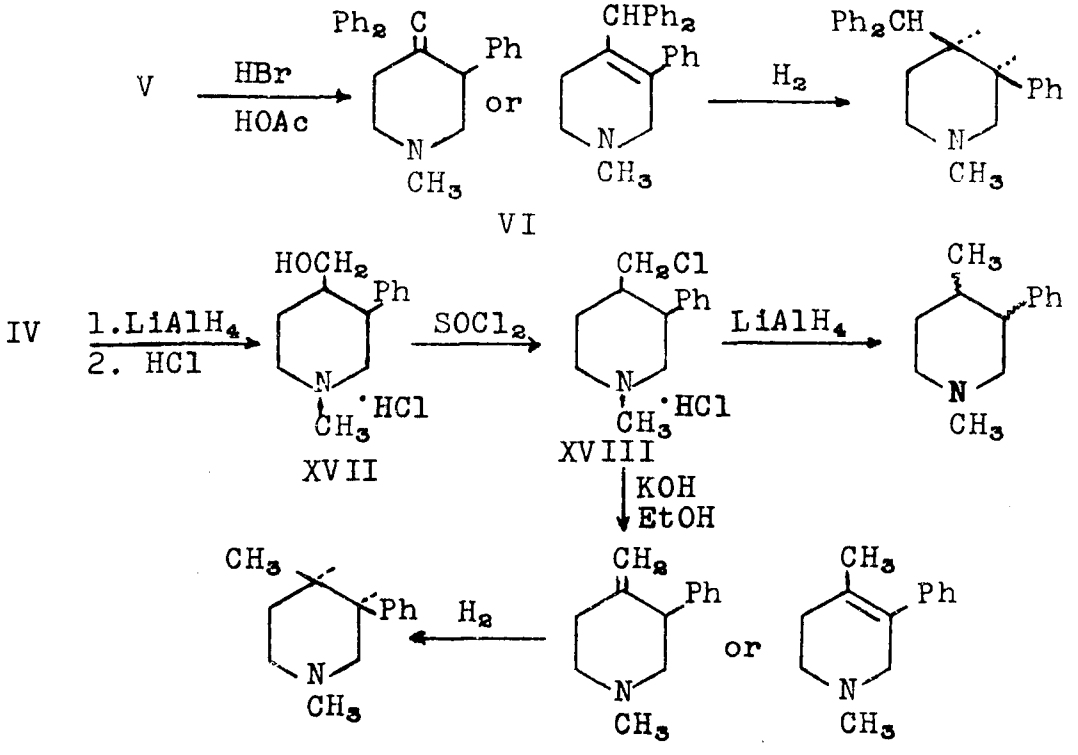
Fig. 2

2) The reaction of phenyllithium with pure 1-methyl-3-phenyl-4-benzoylpiperidine (III) to give V in 80% yield.

3) The reaction of phenyllithium with pure methyl 1-methyl-3-phenylisonipecotate (IV) to give V in 80% yield.

Since all the above reaction gave the same isomer of the carbinol V, III and IV must have the same configuration, and any stereochemical information obtained from one must be applicable to the other. Thus, it is quite certain that only one isomer of 1-methyl-3-phenyl-4-benzoylpiperidine is formed in the Grignard reaction.

Since the bromination and epimerization reactions with III were unsuccessful, it seemed desirable to destroy one of the centers of asymmetry and then introduce it again by a reaction whose stereochemical requirements are known. Two of these proposed reaction schemes are shown below.



The dehydration of 1-methyl-3-phenyl-4-piperidyldiphenyl carbinol (V) using 48% hydrobromic acid and glacial acetic acid proceeded smoothly in 45% yield to give 1-methyl-3-phenyl-4-piperidylidenediphenyl methane (VI). The infrared absorption spectrum showed no -OH stretching absorption and a weak band at 1616 $cm.^{-1}$. In the ultraviolet region an absorption maximum was observed at 238 mμ (log ε 4.18). Lyle et al[22] reported that benzhydrylidenecyclohexane showed an absorption maximum at 246 mμ (log ε 4.17). 2-Benzhydrylidenecyclohexanol exhibits one absorption maximum at 240 mμ (log ε 4.12)[46]. The hypsochromic shift of 6 mμ as compared with benzhydrylidenecyclohexane can be explained in terms of steric interference of the -OH group with the coplanarity of the benzene rings with the double bond. If the structure of VI is the one with the exocyclic double bond, then steric interference of the 3-phenyl substituent with the benzhydryl system should cause either a hypsochromic or a hypochromic shift, or both[28]. Thus, the hypsochromic shift of 8 mμ observed with VI as compared with benzhydrylidenecyclohexane seems to verify the assignment of the exocyclic double bond to VI. If the structure of VI had been the one with the endocyclic double bond, it would be analogous to a substituted 1-phenylcyclohexene. A study of the ultraviolet absorption spectra of the phenylcyclohexenes revealed that methyl groups substituted in either ring diminished the absorption band in the ultraviolet which is associated with conjugation of side-chain unsaturation with that of the aromatic ring[47]. The observations of the

effects of methyl substitution on the spectra of the phenylcyclohexenes have been explained in terms of steric interference by the methyls with the coplanarity of the ethylenic system with the aromatic ring. Since the bulky benzhydryl group would force the 3-phenyl substituent out of coplanarity with the double bond, the ultraviolet spectrum of VI should approach that of a non-conjugated benzene ring.

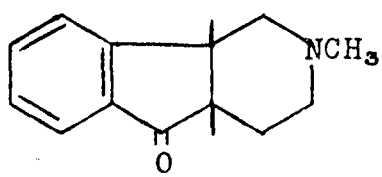
In view of the failure to effect hydrogenation of 1-methyl-3-phenyl-1,2,5,6-tetrahydro-4-pyridylphenyl carbinol (XXV)(see below), the catalytic hydrogenation of VI was not attempted. In order to avoid the problems of steric hindrance in the hydrogenation, the second approach was attempted.

In the second approach, methyl 1-methyl-3-phenylisonipecotate (IV) was reduced with lithium aluminum hydride to give 1-methyl-3-phenyl-4-piperidine methanol as a thick oil whose infrared absorption spectrum showed broad, medium hydroxyl absorption at 3410 $cm.^{-1}$ and no carbonyl absorption. All attempts to crystallize the oil failed, but the hydrochloride was obtained as a solid. The elemental analysis did not agree with the structure XVII; however, the reaction of thionyl chloride with the hydrochloride gave a solid whose elemental analysis agreed with that of structure XVIII. The infrared absorption spectrum of XVIII showed no hydroxyl absorption and showed the characteristic hydrochloride bands in the vicinity of 2500 $cm.^{-1}$. The ultraviolet absorption spectrum showed only maxima characteristic of benzene rings. The discrepancy in the analysis of the hydrochloride from the reduction of IV

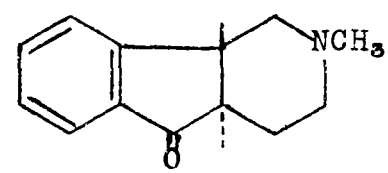
might have been due to the presence of impurities in the analytical sample.

The dehydrohalogenation of XVIII was attempted using potassium hydroxide in absolute ethanol. A red oil was obtained. Infrared analysis of the oil showed broad, medium absorption at 3420 $cm.^{-1}$ (probably due to the presence of a trace of ethanol) and a broad, strong carbonyl absoprtion at 1670 $cm.^{-1}$. Due to the apparent anomalous nature of the products from this reaction this particular sequence of reactions was halted.

Preparation of 2-methyl-5-keto-1,2,3,4,4a,9b-hexahydro-1H-indeno [1,2,c] -pyridine (X) and derivatives. It was of interest to this laboratory to prepare X, in order to help clarify this question of stereochemistry. The ketone X has



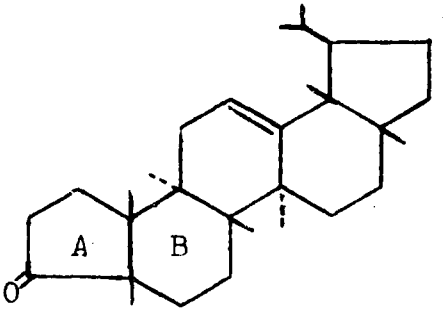
dl



dl

two asymmetric carbon atoms and, therefore, can exist as 2 dl pairs or as a cis or trans racemate; that is to say, the ring junction between the five-membered ring and the piperidine ring can be cis or trans fusion. It has been determined that for a structure containing a five-membered ring fused to a six-membered ring and a ketone function adjacent to one of the fused carbon atoms the cis isomer is more stable than the trans. For example, it has been shown for compound E that rings A and

B are cis-fused[27]. Compound E was recovered unchanged after treatment with alkali, thus proving that rings A and B are fused in the more stable form.

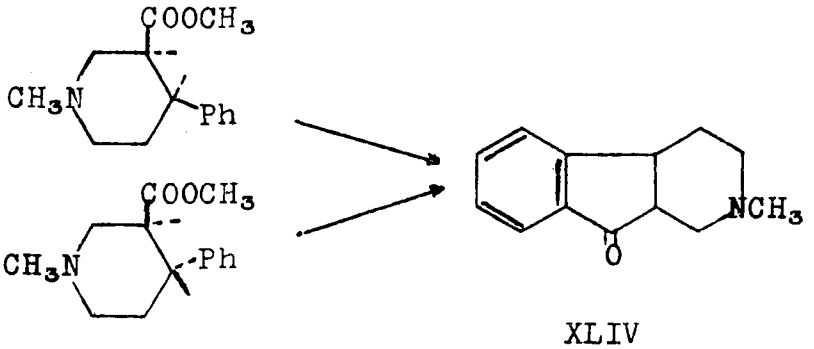


E

Thus, it is certain that X has a cis ring-fusion. Supporting evidence for this was obtained from a test run of the bromination of X. Since hydrogen bromide was evolved during the reaction, it was assumed that bromination did occur. This would necessitate the conformation of the hydrogen alpha to the ketone to be equatorial and X to be the more stable cis form.

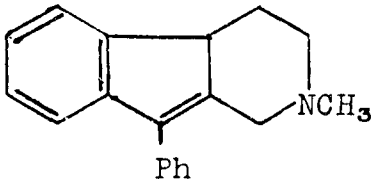
It might be argued that since X undoubtedly has a cis ring-fusion, then methyl 1-methyl-3-phenylisonipecotate (IV) must be the cis-racemate and consequently, 1-methyl-3-phenyl-4-benzoylpiperidine (III) must be the cis-racemate; however, Plati and Wenner[4] found that the same keto-indeno-pyridine (XLIV) was obtained from either the cis- or the trans-racemate of methyl 1-methyl-4-phenylnipecotate. This suggests that at some time during the conversion of IV to X (probably during the Friedel-Crafts cyclization) an isomerization of the

trans- to the cis-isomer occurs.



XLIV

Derivatives of X were also of interest with respect to their physiological activity. Plati and Wenner[4] found that some tetrahydroindenopyridines of the type shown below were potent anti-histamines. None of the derivatives of X exhibited any outstanding activity.



Methyl 1-methyl-3-phenylisonipecotate (IV) was hydrolyzed with hydrochloric acid in 96% yield to the acid VIII which was then converted by thionyl chloride to the acid chloride IX (Fig. 3). IX was cyclized by means of aluminum chloride to give 2-methyl-5-keto-1,2,3,4,4a,9b-hexahydro-1H-indeno [1,2,c]-pyridine (X) in 64% overall yield from IV. The infrared absorption spectrum of X exhibited strong carbonyl absorption at 1710 cm.$^{-1}$. Bands of medium intensity appeared at 782 cm.$^{-1}$, 766 cm.$^{-1}$, 762 cm.$^{-1}$ and 739 cm.$^{-1}$. A very weak intensity band appeared at 715 cm.$^{-1}$. Bellamy[20]

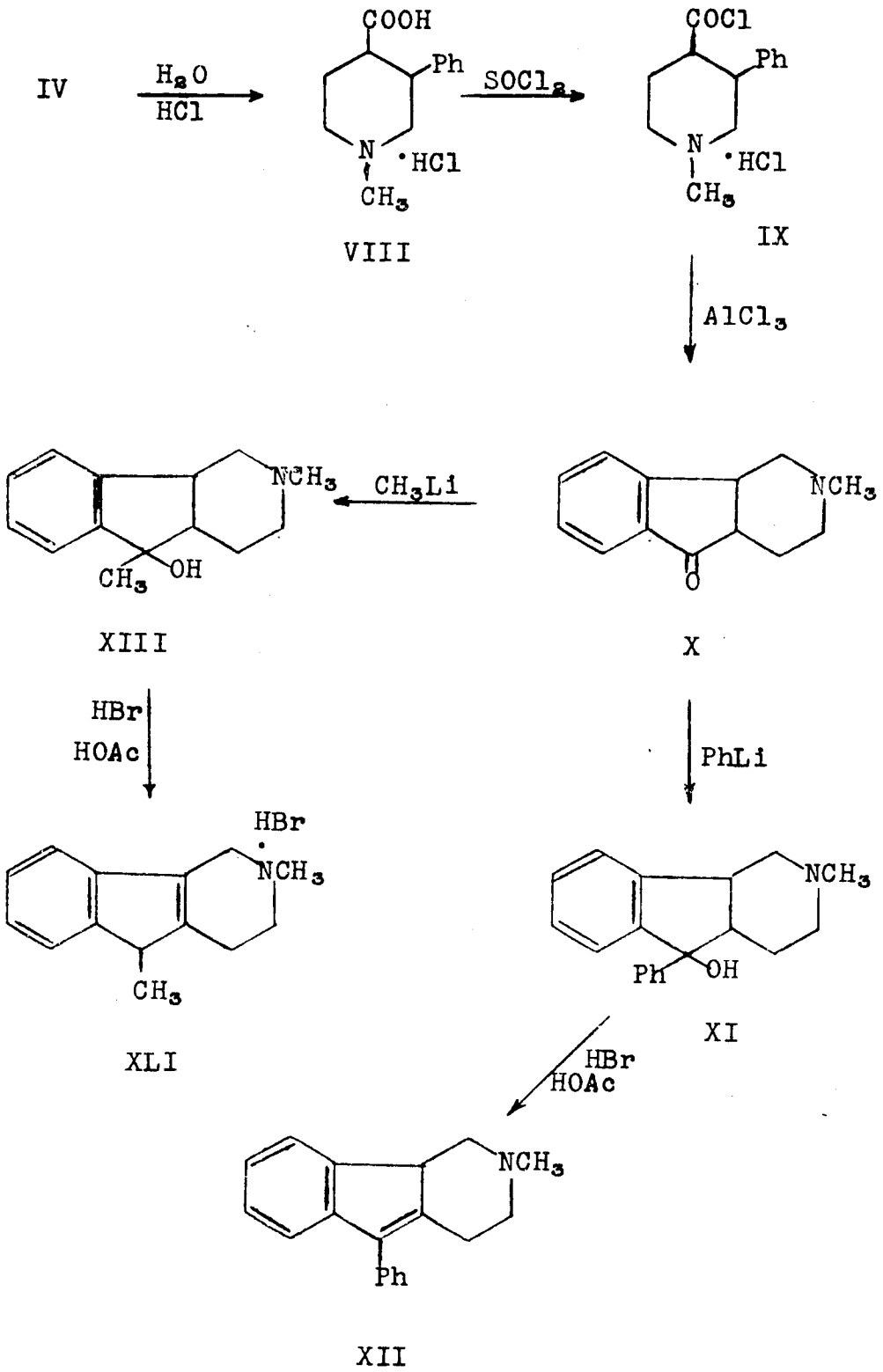

IV
H2O
HCl
COOH
Ph
N
·HCl
CH3
VIII
SOCl2
COCl
Ph
N
·HCl
CH3
IX
AlCl3
NCH3
CH3Li
CH3
OH
XIII
NCH3
O
X
HBr
HOAc
PhLi
HBr
NCH3
CH3
XLI
NCH3
Ph
OH
XI
HBr
HOAc
NCH3
Ph
XII

Fig. 3

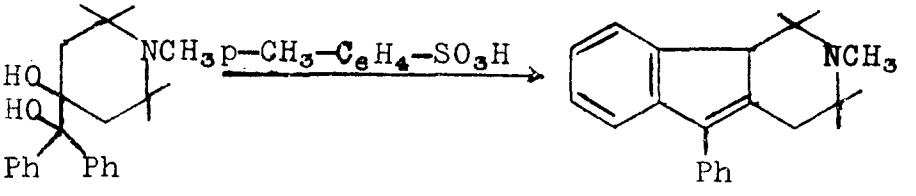
states that the absence of a band within the range 700±10 cm.$^{-1}$ is strong evidence for the absence of a mono-substituted benzene ring. The spectrum of X is devoid of a strong band in this region. Ortho-disubstituted benzene rings show strong absorption in the range 770-735 cm.$^{-1}$[20] and sometimes weak absorption in the range 725-680 cm.$^{-1}$. It seems likely that the medium-strong intensity absorption at 766 cm.$^{-1}$ and the weak absorption at 715 cm.$^{-1}$ can be attributed to the presence of an ortho-disubstituted benzene ring.

The reaction of phenyllithium with X gave 2-methyl-5-hydroxy-5-phenyl-1,2,3,4,4a,9b-hexahydro-1H-indeno [1,2,c] - pyridine (XI) in 72% yield. The infrared absorption spectrum of XI showed no bands in the carbonyl or hydroxyl stretching regions. The absence of -OH absorption is probably due to a weak mull. The presence of a mono-substituted benzene ring was shown by strong absorption at 744 cm.$^{-1}$ and 700 cm.$^{-1}$. Two bands of medium intensity appeared at 769 cm.$^{-1}$ and 752 cm.$^{-1}$, and a very weak intensity band appeared at 720 cm.$^{-1}$. The presence of the ortho-disubstituted benzene ring is shown by one of the medium bands and by the band at 720 cm.$^{-1}$. The ultraviolet absorption spectrum showed absorption at λ max. 253 mμ (log ϵ 2.66), λ max. 258 mμ (log ϵ 2.82), λ max. 265 mμ (log ϵ 2.90) and λ max. 272 mμ (log ϵ 2.81). This absorption is characteristic of a non-conjugated benzene ring.

Using a mixture of 48% hydrobromic acid and glacial acetic acid, XI was dehydrated to 2-methyl-5-phenyl-2,3,4,9b-

tetrahydro-1H-indeno [1,2,c] pyridine (XII) in 52% yield. The infrared absorption spectrum of XII showed no absorption in the -OH stretching region. Sharp, strong absorption appeared at 775 cm.$^{-1}$, 715 cm.$^{-1}$ and 704 cm.$^{-1}$ and medium absorption appeared 754 cm.$^{-1}$ and 745 cm.$^{-1}$. These bands account for the presence of both a mono- and an ortho-disubstituted benzene ring. The ultraviolet absorption spectrum showed an absorption maximum at 265 mμ (log ε 4.08) and shoulders at 289 mμ (log ε 3.49) and 298 mμ (log ε 3.16).

Chauvette[21] studied the pinacol rearrangement of 1,2,2,6,6-pentamethyl-4-hydroxy-4-piperidyldiphenyl carbinol (XXXIV) using various acid catalysts. With p-toluenesulfonic acid he found that the product was the indenopyridine XXXV which has been postulated to form via a cyclodehydration following a dehydration and allylic rearrangement.

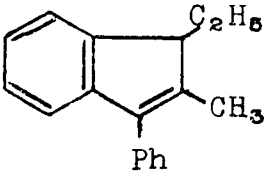


XXXIV XXXV

1,1,2,3,3-Pentamethyl-5-phenyl-2,3,4,9b-tetrahydro-1H-indeno [1,2,c] pyridine (XXXV) exhibited an absorption maximum at 268 mμ (log ε 3.90) and shoulders at 289 mμ (log ε 3.49) and 299 mμ (log ε 3.18). The superimposability of the spectrum of XII on that of XXXV confirms Chauvette's assignment of structure. The possibility of the double bond being

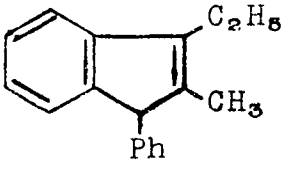
endocyclic to the piperidine ring is not as likely, since this would require the shifting of the double bond out of conjugation with two benzene rings into conjugation with only one benzene ring. Evidently, the effect of maximum conjugation with an exocyclic double bond overcomes the effect of minimum conjugation with an endocyclic double bond.

Of interest, in connection with this research, is the work of Zanden and De Vries[23]. They found that the ultraviolet absorption spectrum of 1-ethyl-2-methyl-3-phenylindene (XXXVI) resembles that of 1,1-diphenylethylene, whereas the spectrum of 3-ethyl-2-methyl-1-phenylindene (XXXVII) resembles that of styrene.



$\lambda^{alc.}_{max.}$ 275 (log ϵ 3.95)

XXXVI



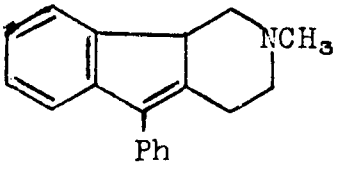
$\lambda^{alc.}_{max.}$ 263 (log ϵ 4.10)

XXXVII

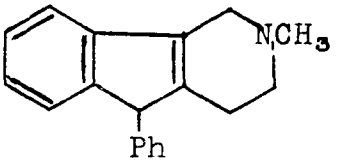
From this correlation it seems that the ultraviolet absorption spectrum of the product obtained from the dehydration of XI resembles the spectrum of XXXVII.

However, the assignment of structure XII rather than XXXVIII can be confirmed by the work of Plati and Wenner[14]. They reported that the ultraviolet absorption spectrum of XXXIX in 0.1 N hydrochloric acid showed a maximum at 267 mμ (log ϵ 3.98), whereas XL showed a maximum at 260 mμ (log ϵ

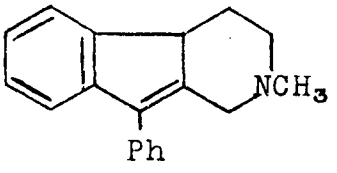
3.97). The product from the dehydration of XI showed an absorption maximum at 265 mμ (log ε 4.08).



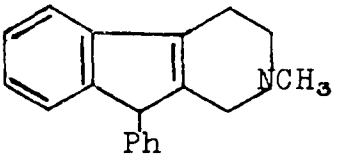
XII



XXXVIII



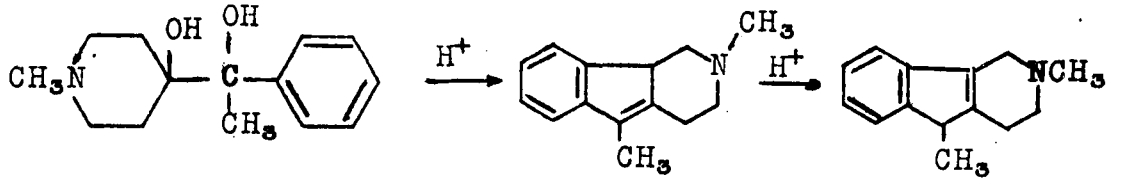
XXXIX



XL

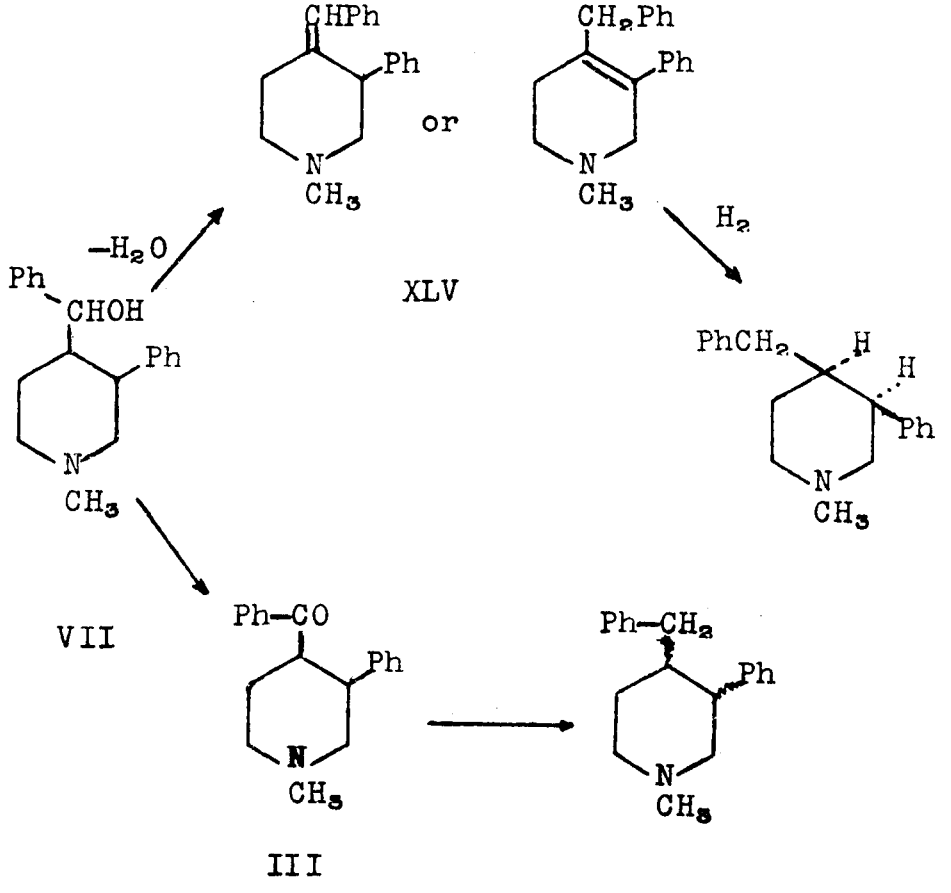
2,5-Dimethyl-5-hydroxy-1,2,3,4,4a,9b-hexahydro-1H-indeno [1,2,c] pyridine (XIII) was prepared by treatment of X with methyllithium. XIII was dehydrated with 48% hydrobromic acid and glacial acetic acid to give presumably, 2,5-dimethyl-1,2,3,4-tetrahydro-1H-indeno [1,2,c] pyridine (XLI). The hydrobromide melted at 235-237° and showed strong absorption in the infrared region at 762 cm.$^{-1}$. Leone(24) reported that, under the influence of boron trifluoride-acetic acid, 48% hydrobromic acid or 32% sulfuric acid, 1-methyl-4-hydroxy-4-piperidylphenylmethyl carbinol (XLII) rearranged and cyclized to give the indenopyridine XLIII whose piperidyl exocyclic double bond might isomerize to furnish the end product, XLI. The hydrobromide melted at 230°—233°. The infrared absorp-

tion spectra of the two hydrobromides were essentially identical.



XLII XLIII XLI

Reactions of 1-methyl-3-phenyl-4-piperidylphenyl carbinol (VII). The reaction scheme illustrated below was another series proposed to shed some light on the stereochemistry of III and IV.



III

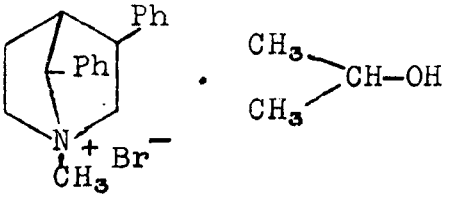
1-Methyl-3-phenyl-4-piperidylphenyl carbinol (VII) was obtained in quantitative yield from the reduction of 1-methyl-3-phenyl-4-benzoylpiperidine (III) with lithium aluminum hydride. The dehydration of VII was attempted using glacial acetic-48% hydrobromic acid, concentrated sulfuric acid and phosphorous pentoxide.

Concentrated sulfuric acid and phosphorous pentoxide gave extensive decomposition and intractable oils. The glacial acetic-48% hydrobromic acid mixture had been used successfully as a dehydrating agent several times during the course of this research. However, three different products have been isolated from three different reactions of VII with this reagent.

When a mixture of VII, glacial acetic acid and 48% hydrobromic acid was heated at 100° for four hours, the only product obtained was a crystalline solid XIV, m.p. 209-211°, which was insoluble in ether, soluble in water and gave a positive silver nitrate test. Neutralization of XIV did not cause the precipitation of a free base, therefore it was not a hydrobromide. Its infrared absorption spectrum showed strong bands at 3395 $cm.^{-1}$, 765 $cm.^{-1}$, 734 $cm.^{-1}$ and 698 $cm.^{-1}$ and medium intensity bands at 2980 $cm.^{-1}$, 1140 $cm.^{-1}$, 959 $cm.^{-1}$ and 715 $cm.^{-1}$. The band at 3395 $cm.^{-1}$ indicates the presence of an -OH function. The bands appearing below 800 $cm.^{-1}$ seem to suggest the presence of something more complex than a mono-substituted benzene ring, since for this system only two strong bands should appear in the vicinity of 750 $cm.^{-1}$ and 700 $cm.^{-1}$.

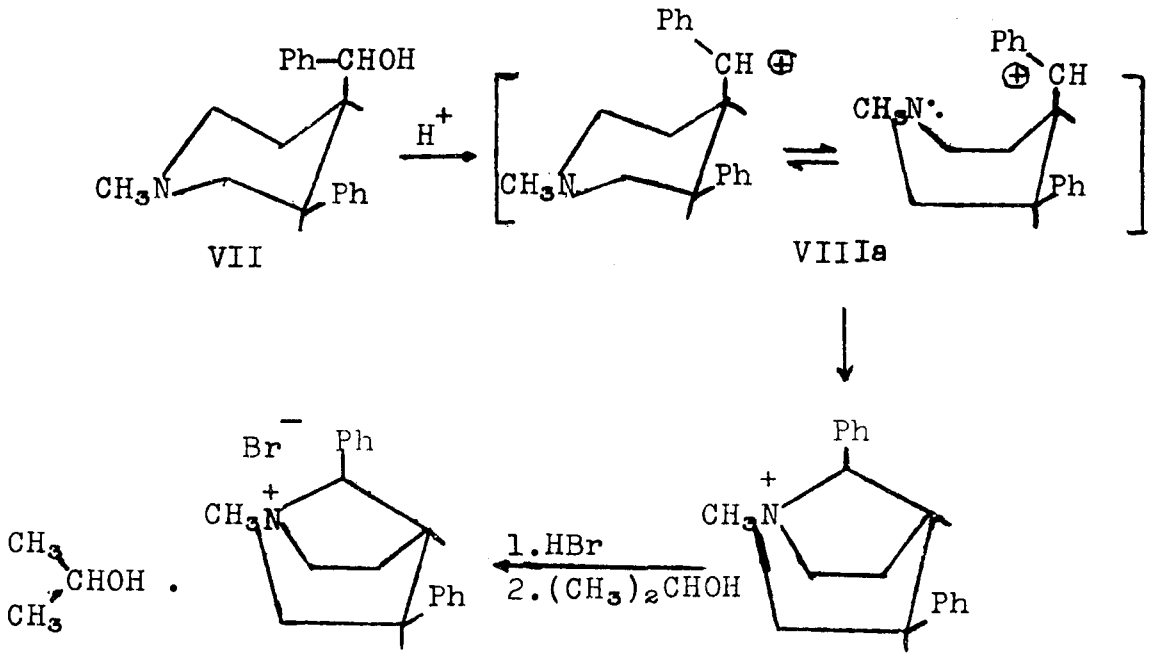
In the ultraviolet spectrum absorption maxima were observed at 252 mμ (log ε 2.48), 258 mμ (log ε 2.59, 263 mμ (log ε 2.57) and 269 mμ (log ε 2.42). This absorption is characteristic of a non-conjugated benzene ring.

Since the infrared absorption spectrum showed intense absorption in the -OH stretching region, it was possible that XIV had incorporated an isopropyl alcohol molecule into its structure. XIV had been recrystallized from isopropyl alcohol. Also, its infrared spectrum was devoid of the characteristic absorption of a 1-methylpiperidine in the 2800-3000 cm.$^{-1}$ region. These bands are masked in the spectra of salts of piperidines. Elemental analyses agreed with the empirical formula, $C_{16}H_{22}BrN \cdot C_3H_8O$. All of this evidence, in conjunction with its high melting point, its solubility in water and its insolubility in ether, suggests that XIV is probably a quaternary salt. If this assumption were correct, then XIV could have a structure of this type



If the ketone III and the alcohol VII were of the <u>cis</u> configuration, then the formation of the quaternary salt can

be easily rationalized as shown.



Upon treatment of VII with acid, the carbonium ion, VIIIa, would be formed. If the molecule shifted into the boat form, the location of the nitrogen atom and the benzylic carbonium ion is favorable for a transannular interaction. The carbonium ion could then easily undergo a nucleophilic attack by the electron-pair on the nitrogen atom to form the bicyclic quaternary salt. Examples of a similar type of transannular reaction are available in the literature (25,26).

The attempted dehydration of VII under the same conditions, without the use of isopropyl alcohol at any time during the work-up of the reaction, gave a solid product (XV), m.p. 221-224°. XV was soluble in water, insoluble in ether and gave a positive silver nitrate test. As was the case with XIV, XV could not be converted to a free base. Elemental

analysis agreed with the empirical formula $C_{19}H_{22}BrN$. Its infrared absorption spectrum was identical with that of XIV with the exception of two bands. Bands of weak-medium intensity appeared at 1160 cm.$^{-1}$ and 959 cm.$^{-1}$ in the spectrum of XIV which were absent in the spectrum of XV. Absorption appeared at 3395-3400 cm.$^{-1}$ for both compounds. The presence of -OH or -NH in the structure of XV can not be explained. Oxygen analysis was not run on either compound. These results are best explained by the bicyclic quaternary salt structure.

The third product which was obtained from an attempted dehydration of VII was an isomeric alcohol, m.p. 195-199°. The work-up of the reaction mixture was the same as before except that, upon concentration of the ether, a solid, XVI, precipitated. Its infrared absorption spectrum was identical with that of VII except that the -OH stretching absorption for XVI appeared at 3150 cm.$^{-1}$, whereas that for VII appeared at 3420 cm.$^{-1}$. Their melting points were significantly different. Thus, XVI is one of the other racemates which is epimeric at the carbinol carbon atom.

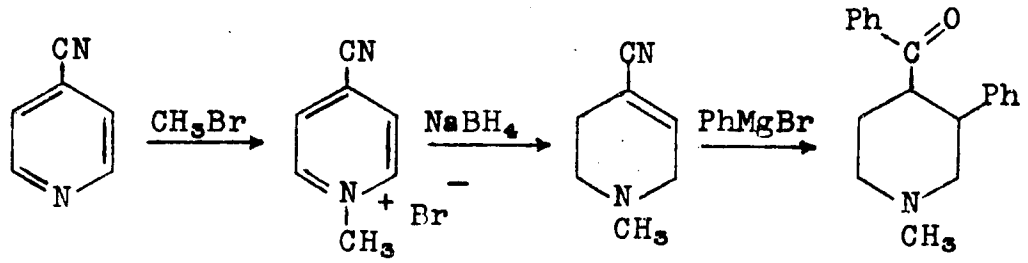
Attempts to prepare the isomeric 1-methyl-3-phenyl-4-benzoylpiperidine. In an attempt to prepare a mixture of the stereoisomers of 1-methyl-3-phenyl-4-benzoylpiperidine, three other reaction schemes were proposed and explored. The first of these was the reaction of phenylmagnesium bromide with 1-methyl-1,2,3,6-tetrahydroisonicotinonitrile (XXIX) which was prepared by the sodium borohydride reduction of 1-

methyl-4-cyanopyridinium bromide (XXVIII)(Fig. 4). XXVIII was prepared in 85% yield from isonicotinonitrile (XXVII).

The reduction of XXVIII with sodium borohydride was carried out in the usual manner to give an oil in 70% yield. As discussed earlier (p.10), the infrared absorption spectrum of this oil indicated that it was actually a mixture of at least two nitriles. Absorption maxima appeared at 246 mμ in the ultraviolet region and at 397 mμ in the visible ultraviolet region. It was expected that XXIX would have an absorption maximum at 210-215 mμ due to the α,β -unsaturated nitrile system. It is evident that the product is actually a mixture. However, the reaction of the impure product with the Grignard reagent was carried out anyway.

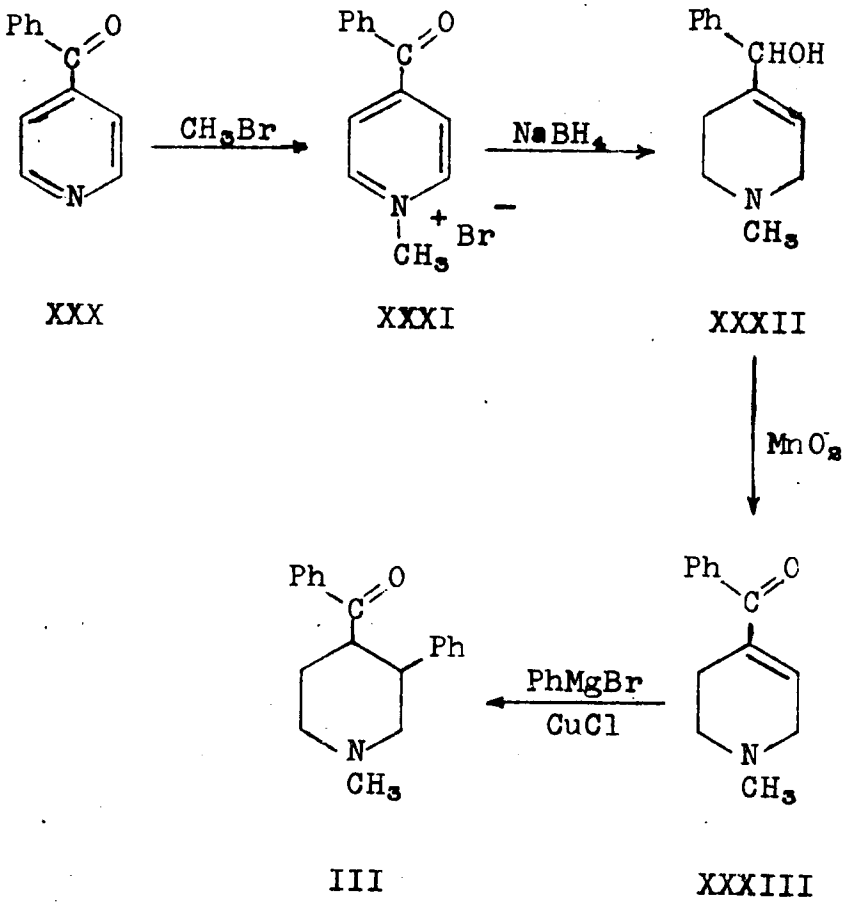
The procedure for the Grignard reaction was essentially the same as that used to prepare 1-methyl-3-phenyl-4-benzoyl piperidine (III). The dark red oil which was obtained was collected in two fractions. The infrared absorption spectrum of the first fraction showed a weak nitrile band at 2210 $cm.^{-1}$, strong carbonyl absorption at 1661 $cm.^{-1}$ and characteristic mono-substituted benzene absorption in the vicinity of 750 $cm.^{-1}$ and 700 $cm.^{-1}$. The second fraction showed sharp, weak nitrile absorption at 2210 $cm.^{-1}$, broad, strong carbonyl absorption at 1680 $cm.^{-1}$ and the characteristic mono-substituted benzene absorption.

Fraction 1 appears to be a mixture of an α,β -unsaturated aldehyde or ketone and 1-methyl-3-phenylisonipecotonitrile. The infrared absorption band at 1161 $cm.^{-1}$



XXVII XXVIII XXIX III

Fig. 4



XXX XXXI XXXII

III XXXIII

Fig. 5

might be due to the presence of some 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenyl ketone (XXXIII) which could form by the 1,2-addition of phenylmagnesium bromide to the nitrile XXIX. The carbonyl absorption for XXXIII would be expected to appear at about 1665 $cm.^{-1}$ due to the extended conjugation of the benzoyl group with the double bond. The formation of 1-methyl-3-phenylisonipecotonitrile can occur by the 1,4-addition of the Grignard reagent to the α,β -unsaturated nitrile system. This type of addition has previously been shown to occur in the preparation of 1-methyl-3-phenyl-4-benzoylpiperidine (III) by the Grignard reaction.

Fraction 2 appears to be a mixture of III, and the product of 1,4-addition, 1-methyl-3-phenylisonipecotonitrile. Since this particular reaction scheme did not show any promise in preparing the isomeric 1-methyl-3-phenyl-4-benzoylpiperidine, it was not investigated further.

The second proposed reaction scheme which was carried out in hopes of preparing the isomeric ketone is illustrated in Fig. 5. 1-Methyl-1,2,3,6-tetrahydro-4-pyridylphenyl carbinol (XXXII) was prepared by the sodium borohydride reduction of 1-methyl-4-benzoylpyridinium bromide (XXXI), according to the procedure of Kerlin[13]. XXXII was then oxidized by activated manganese dioxide to give 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenyl ketone (XXXIII) which was analyzed via its picrate. XXXIII could not be isolated in a pure state, since it darkened and decomposed rapidly upon heating.

Following the procedure of Zimmerman[1], impure XXXIII

was treated with phenylmagnesium bromide in the presence of cuprous chloride. Usual work-up gave an oil whose infrared absorption spectrum showed strong carbonyl absorption at 1678 $cm.^{-1}$. The infrared absorption spectrum of authentic III showed strong carbonyl absorption at 1678 $cm.^{-1}$ also. All attempts to crystallize the oil failed; consequently, a picrate of the oil was made. The infrared absorption spectra of this picrate and the picrate of III were identical. Mixture melting points of the two picrates did not depress, so they must be one and the same.

The last and most promising attempt at an independent synthesis of cis-1-methyl-3-phenyl-4-benzoylpiperidine involved the catalytic hydrogenation of a pyridine quaternary salt. It was felt that if the corresponding pyridine derivative could be made, then catalytic hydrogenation of its quaternary salt would give the piperidine with the cis configuration or at least a mixture of the two isomers.

Dehydrogenations of 1-substituted piperidines using palladium-on-charcoal are available in the literature and usually proceed in good yields[29-31]. 1-Alkylpiperidines have been dehydrogenated to pyridine using this catalyst[29,30]. Quinuclidine and 1-azabicyclo [2,2,1] heptane have been dehydrogenated to 4-ethylpyridine and 4-picoline, respectively[31]. The dehydrogenation of 1-methyl-3-phenyl-4-benzoylpiperidine (III), using 5% palladium-on-charcoal, was attempted at 240° and in boiling naphthalene. The only product isolated, in either case, was a red oil whose infrared absorption spectrum

showed bands at 2980 cm.$^{-1}$ and 2770 cm.$^{-1}$ which are due to aliphatic —CH stretching vibrations. Carbonyl absorption appeared at 1672 cm.$^{-1}$ and absorption due to the N—CH_3 group appeared at 1380 cm.$^{-1}$. It is quite evident that the dehydrogenation was unsuccessful.

Baliah and Ekambaram[17] encountered success in dehydrogenating substituted piperidines and piperidinols, using sulfur which is a more active catalyst than palladium. By modifying their procedure somewhat, it was possible to obtain 3—phenyl—4—benzoylpyridine (XX) in 57% yield by heating III in the presence of sulfur to about 180° (Fig. 6). The infrared absorption spectrum of XX showed no aliphatic C—H bands in the region of 2800—3000 cm.$^{-1}$ and no N—CH_3 absorption in the vicinity of 1375 cm.$^{-1}$. Carbonyl absorption appeared at 1672 cm.$^{-1}$ and strong absorption was observed at 783 cm.$^{-1}$, 757 cm.$^{-1}$ and 700 cm.$^{-1}$. Its ultraviolet absorption spectrum showed maxima at 248 mμ (log ϵ 4.36) and at 290 mμ (log ϵ 3.70).

1—Methyl—3—phenyl—4—benzoylpyridinium bromide (XXI), which was obtained in 60% yield from XX, was hydrogenated over a platinum oxide catalyst at low pressure for 19 hours. Infrared analysis of the oily product indicated a mixture of an alcohol and a ketone. All attempts to crystallize the oil failed. Chromatography over Florisil and elution with chloroform gave an oil which crystallized. The infrared absorption spectrum of the solid material (XXII) showed —OH stretching absorption at 3260 cm.$^{-1}$ and no carbinol absorption. Aliphatic

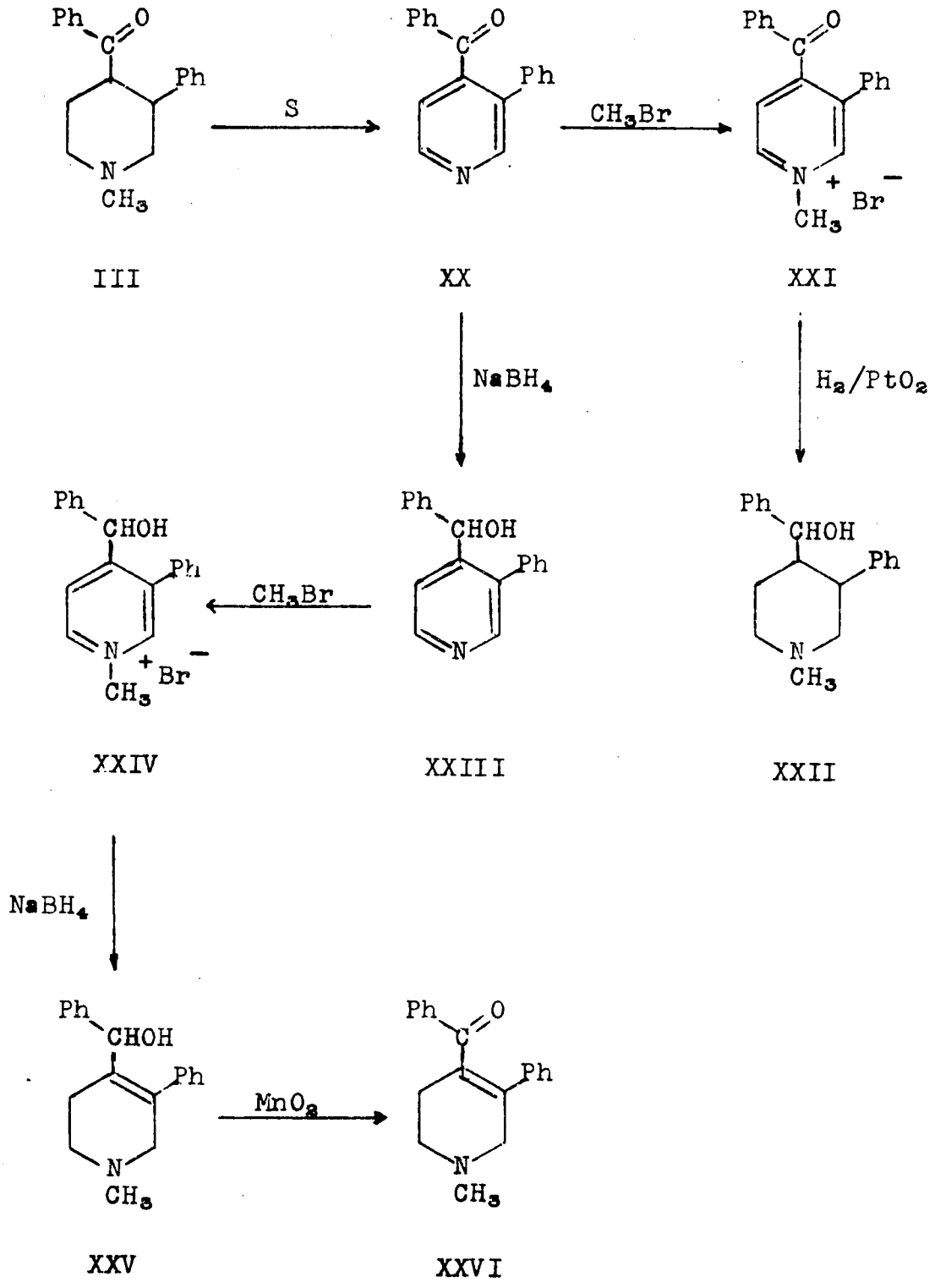

Ph
O
Ph
N
CH3
S
CH3Br
Br
III
XX
XXI
NaBH4
H2/PtO2
CHOH
XXIV
XXIII
XXII
XXV
XXVI
MnO2

Fig. 6

–CH absorption appeared in the region 2700–3000 cm.$^{-1}$. Elemental analysis agreed with the empirical formula, $C_{19}H_{23}NO$. Its melting point (119.5–121°) was significantly different from the two other isomeric alcohols, VII and XVI. Treatment of XXII with the CrO_3–pyridine reagent and activated manganese dioxide resulted in only incomplete oxidation, whereas the oxidation of VII or XVI proceeds readily. This observation seems to lend support to the hypothesis that VII and XVI are of the trans configuration differing only in the configuration of the carbinol carbon atom and that XXII is the cis isomer. It might be expected that the oxidation of the cis alcohol would be more difficult, since the axial –CHOH group is more sterically hindered than the equatorial alcohol (trans). No pure product could be isolated from the oxidation.

Since the catalytic hydrogenation of XXI gave incomplete reduction, another approach was taken. XX was reduced with sodium borohydride in the usual manner to give 3–phenyl–4–pyridylphenyl carbinol (XXIII) in 80% yield. Quaternization of XXIII with methyl bromide proceeded smoothly in 93% yield. The pyridinium salt, XXIV, could not be reduced catalytically. In the hydrogenations of XXI and XXIV, the finely–dispersed catalyst became clumped as soon as a methanol solution of the compound was added to the catalyst. The only explanation available for this clumping is that there were traces of sulfur present which poisoned the catalyst and so inhibited the hydrogenation.

In order to circumvent this difficulty, XXIV was reduced with sodium borohydride to give 1-methyl-3-phenyl-1,2,5,6-tetrahydro-4-pyridylphenyl carbinol (XXV) in 84% yield. The weak infrared absorption spectrum showed a broad, weak band at 3070 cm.$^{-1}$. Its ultraviolet absorption spectrum showed no maxima above 230 mμ. There was no uptake of hydrogen, when XXV was subjected to catalytic hydrogenation. Adsorption of the double bond on the surface of the catalyst would be inhibited by interference of axial hydrogens and of the bulky phenyl and benzoyl groups. Thus, the catalytic hydrogenation of a 3,4-disubstituted pyridine or pyridinium salt appears to be inhibited for steric reasons.

In hopes that reduction with sodium amalgam in alcohol might give a mixture of stereoisomers, XXV was oxidized with activated manganese dioxide. A yellow oil was obtained. Its infrared absorption spectrum showed a broad, medium band at 3440 cm.$^{-1}$ and a broad, strong band at 1655 cm.$^{-1}$. Its ultraviolet absorption spectrum showed shoulders at 250 mμ, 288 mμ and 345 mμ. Complete oxidation using activated manganese dioxide was not possible.

In conclusion, the available evidence does not definitely establish the stereochemistry of 1-methyl-3-phenyl-4-benzoylpiperidine (III). Certainly the attempted epimerization and bromination reactions indicate strongly that III is the <u>trans</u>-isomer. On the other hand, the formation of the bicyclic quaternary salt, XIV, in the attempted dehydration of 1-methyl-3-phenyl-4-piperidylphenyl carbinol (VII) strongly suggests that III is the <u>cis</u>-isomer.

EXPERIMENTAL

Infrared Absorption Spectra.- The infrared absorption spectra were determined using a Perkin-Elmer Model 21 infrared spectrophotometer with sodium chloride optics at settings of: resolution, 927; response, 1; gain, 5; speed, 4-6, suppression, 0; scale, standard. The spectra of solids were determined as mulls in series 11-14 Halocarbon oil from 1300-4000 $cm.^{-1}$ and in Nujol from 650-1300 $cm.^{-1}$. All bands were strong except those indicated weak (W) or medium (M), and the location of the bands is given in frequency units, $cm.^{-1}$.

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

Analytical Data.- Microanalyses were determined by Galbraith Microanalytical Laboratory, Knoxville, Tennessee, and by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Preparation of the Starting Materials

Methyl Isonicotinate.- This ester was obtained from the Reilly Tar and Chemical Corporation.

Preparation of Methyl Isonicotinate Methiodide (I).- The methiodide of methyl isonicotinate precipitated in 87%

yield over a period of 10 hr. from a solution of 0.67 mole of methyl isonicotinate and 0.70 mole of methyl iodide in 300 ml. of acetone. After recrystallization from a water–ethanol mixture, I melted at 177–179° (dec.); lit. m.p. 179° (8).

Preparation of Methyl 1–Methyl–1,2,3,6–tetrahydroisonicotinate (II).– To a solution of 120 g. (0.43 mole) of methyl isonicotinate methiodide (I) in 350 ml. of methanol, 20 g. of sodium borohydride was added in small portions. The vigorous reaction was moderated by external cooling. After being stirred at room temperature for 0.5 hr., the methanol solution was evaporated to dryness on the steam bath. The semi–solid residue was dissolved in water, saturated with anhydrous potassium carbonate, and extracted several times with ether. After drying over potassium carbonate, the ether was removed, and the residual oil was distilled under 10 mm. of pressure to give 47 g. (71%) of methyl 1–methyl–1,2,3,6–tetrahydroisonicotinate (II), b.p. 99–102°/10 mm., lit. b.p. 95–100°/7 mm (7).

The hydrobromide of II was prepared and melted at 190–191° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_8H_{14}NO_2Br$: Br, 39.90. Found: Br, 39.99.

The methiodide of II was prepared and after recrystallization from isopropyl alcohol melted at 205–208°; lit. m.p. 210–212° (7).

Preparation of 1–Methyl–3–phenyl–4–benzoylpiperidine (III).– To a stirred solution of approximately 128 g. (0.71

mole) of phenylmagnesium bromide in 500 ml. of dry ether was added dropwise, 49.1 g. (0.32 mole) of methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (II). The mixture was stirred and heated under reflux for 1 hr. To the stirred reaction mixture, cooled in an ice bath, was added dropwise an aqueous solution of ammonium chloride. The ether layer was then separated and extracted with dilute hydrochloric acid. The acid extract was cooled in ice and made alkaline with 40% aqueous potassium carbonate. The oil which precipitated was taken up in ether, and the ether extract was dried over anhydrous potassium carbonate. Filtration and distillation of the ether solution gave an oily residue. The residue was distilled at reduced pressure to yield 34 g. of a viscous orange liquid, b. p. 180-230°/20 mm. Trituration with and recrystallization from petroleum ether gave 18 g. (21%) of 1-methyl-3-phenyl-4-benzoylpiperidine (III), m. p. 107.5-108°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57. Found: C, 81.30; H, 7.47.

IR spectrum (Nujol mull No. 138): 1678, 757 (M), 700.

UV spectrum (λmax. (log ϵ)): 245(4.26), Sh 276(3.81), Sh 320(2.15).

The methiodide of III, m.p. 153-155°, was prepared by the addition of excess methyl iodide to a solution of III in acetone and recrystallization of the resulting precipitate from isopropyl alcohol.

Anal. Calcd. for $C_{20}H_{24}INO$: I, 30.15. Found: I, 30.43.

The hydrobromide and the hydrochloride of III were pre-

pared by standard procedures and were purified by recrystallization from isopropyl alcohol to give solids, m.p. 243–244° and 269–270°, respectively.

Anal. Calcd. for (hydrobromide) $C_{16}H_{22}BrNO$: Br, 22.18. Found: Br, 22.10.

Anal. Calcd. for (hydrochloride) $C_{16}H_{22}ClNO$: Cl, 11.24. Found: Cl, 11.06.

The picrate of III was prepared and after two recrystallizations from an ethanol–water mixture melted at 225–234°.

Preparation of Methyl 1–Methyl–3–phenylisonipecotate (IV).– About 100 ml. of dry ether and 3 g. (0.123 g–atom) of magnesium turnings were placed in a 500–ml. three–necked flask. A solution of 22.4 g. (0.143 mole) of bromobenzene in 100 ml. of dry ether was added in the course of 1 hr. to maintain gentle reflux. After being stirred for 0.5 hr., the mixture was cooled to −5°, and 65 ml. of an ether solution of 15 g. (0.097 mole) of methyl 1–methyl–1,2,3,6–tetrahydroisonicotinate (II) was added during the course of 1 hr. The mixture was stirred for 20 min. longer at the same temperature. The reaction mixture was hydrolyzed with an aqueous solution of ammonium chloride. The ether layer was separated and extracted with dilute hydrochloric acid. The acid extracts were cooled in ice and made alkaline with 40% aqueous potassium carbonate. The precipitated oil was taken up in ether. After drying over potassium carbonate, the ether was removed and the residual oil was distilled under reduced pressure to give

14.2 g. (67%) of methyl 1-methyl-3-phenylisonipecotate (IV), b.p. 172°/18 mm., $n_D^{26.3}$ 1.5217.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.20; H, 8.35.

IR spectrum (film, No. 684): 1740 (B,S), 788 (M), 759 (M), 719 (W), 701.

Preparation of 1-Methyl-3-phenyl-4-piperidyldiphenylcarbinol (V).- A solution of 4.6 g. (0.017 mole) of 1-methyl-3-phenyl-4-benzoylpiperidine(III) in anhydrous ether was added dropwise to a 0.05 mole phenyllithium solution prepared from 0.7 g. of lithium and 7.5 g. of bromobenzene in 200 ml. of anhydrous ether. After the addition was complete, the mixture was heated under reflux for 45 min. and then decomposed with water. The ether layer was separated, dried over anhydrous potassium carbonate, and the ether was removed by distillation. The remaining oil solidified, and the solid was recrystallized from isopropyl alcohol to give 4.7 g. (80%) of 1-methyl-3-phenyl-4-piperidyldiphenylcarbinol(V), m.p. 136-137.5°.

Anal. Calcd. for $C_{25}H_{27}NO$: C, 83.99; H, 7.61. Found: C, 83.92, 84.08; H, 7.87, 7.70.

IR spectrum (Mull No. 667): 3572 (M), 1600 (W), 1493 (M), 767 (M), 749 (M), 739 (M), 703, 695.

The hydrochloride was prepared and melted at 237-238° after recrystallization from isopropyl alcohol.

Reaction of Phenyllithium with the Room Temperature Grignard Reaction Mixture. Preparation of V.- An ether solution of 11.8 g. of the crude mixture from the room-

temperature Grignard reaction was added dropwise to a phenyllithium reagent prepared from 3.5 g. (0.51 g-atom) of lithium and 39 g. (0.25 mole) of bromobenzene in 200 ml. of anhydrous ether. After the addition was complete, the mixture was allowed to cool. The reaction mixture was then decomposed with water. The ether layer was separated, dried over anhydrous potassium carbonate and the ether was distilled. The resulting dark red oil was dissolved in isopropyl alcohol, and the solution was allowed to stand for a few hours. Scratching the sides of the flask with a glass rod caused the precipitation of 8.1 g. (54%) of V, m.p. 134-136°. This material did not depress the melting point of an authentic sample of 1-methyl-3-phenyl-4-piperidyldiphenyl carbinol (V).

Preparation of 1-Methyl-3-phenyl-4-piperidylidenediphenylmethane (VI).- The reaction of 10 g. of 1-methyl-3-phenyl-4-piperidyldiphenylcarbinol (V) with 50 ml. of 48% hydrobromic acid and 50 ml. of glacial acetic acid was heated on the steam bath for 2 hr. and then allowed to stand overnight. The acetic acid was removed by distillation under reduced pressure, and the remainder of the mixture was made alkaline with potassium carbonate solution. The brown oil which precipitated was taken up in ether. The ether extracts were dried over potassium carbonate, and the ether was distilled yielding 4.3 g. (45%) of 1-methyl-3-phenyl-4-piperidylidenediphenylmethane (VI). The material was crystallized and recrystallization from isopropyl alcohol gave pale yellow crystals, m. p. 121-123°.

Anal. Calcd. for $C_{26}H_{25}N$: C, 88.45; H, 7.43; N, 4.13. Found: C, 88.75; H, 7.54; N, 4.03.

IR spectrum (Mull No. 828): 1616 (W), 1600 (W–M), 1497, 772, 763, 747 (M), 733, 697.

UV spectrum (λmax. (log ϵ)): 238(4.18).

Preparation of 1–Methyl–3–phenyl–4–piperidyldiphenylcarbinol (V) from Methyl 1–Methyl–3–phenylisonipecotate (IV).– An ether solution of 17.5 g. (0.075 mole) of methyl 1–methyl–3–phenylisonipecotate (IV) was added dropwise to a phenyllithium reagent prepared from 4.6 g. (0.665 g–atom) of lithium and 52.3 g. (0.333 mole) of bromobenzene in 300 ml. of anhydrous ether. After the addition was complete, the mixture was heated under reflux for 1 hr., and then decomposed by the addition of water. The ether layer was separated, dried over anhydrous potassium carbonate and the ether was distilled yielding 18.8 g. (65%) of 1–methyl–3–phenyl–4–piperidyldiphenylcarbinol (V). Recrystallization from isopropyl alcohol gave pure material, m.p. 121–123°. Mixed melting point with authentic V did not depress the melting point. The infrared absorption spectrum was identical with that of an authentic sample of V prepared from III.

Preparation of 2–Methyl–5–keto–1,2,3,4,4a,9b–hexahydro–1H–indeno [1,2,c] pyridine (X).–

a. Hydrolysis of Methyl 1–Methyl–3–phenylisonipecotate to 1–Methyl–3–phenylisonipecotic Acid Hydrochloride (VIII).– To 21 g. of methyl 1–methyl–3–phenylisonipecotate (IV) were added

40 ml. of water and 65 ml. of concentrated hydrochloric acid. The mixture was distilled slowly until the temperature of the distillate remained constant at 108°. The solvent was then removed by distillation under reduced pressure yielding 22.1 g. (96%) of impure 1-methyl-3-phenylisonipecotic acid hydrochloride (VIII).

b. 1-Methyl-3-phenylisonipecotyl Chloride Hydrochloride (IX).- To 22.1 g. of impure VIII was added 100 ml. of thionyl chloride, and the mixture was allowed to stand overnight. The thionyl chloride was then removed by distillation under reduced pressure, and to the residue was added 150 ml. of anhydrous dichloroethane. The resulting solution was subjected to distillation at reduced pressure until 50 ml. of distillate was collected. To the residual solution 50 ml. of dichloroethane again was added, and the distillation was repeated until 50 ml. of distillate was collected. Again 50 ml. of dichloroethane was added.

c. Intramolecular Friedel-Crafts Acylation of 1-Methyl-3-phenylisonipecotyl Chloride Hydrochloride to 2-Methyl-5-keto-1,2,3,4,4a,9b-hexahydro-1H-indeno [1,2,c] pyridine (X).- To the above solution of IX in dichloroethane was added 30 g. of anhydrous aluminum chloride. A vigorous evolution of hydrogen chloride began. The mixture was stirred for 0.5 hr. after the evolution of hydrogen chloride ceased, and then poured into 350 g. of ice and 50 ml. of concentrated hydrochloric acid. After standing overnight, the aqueous and organic layers were separated, and the aqueous layer was extracted twice with

ether. The aqueous layer was cooled in ice and made alkaline with sodium hydroxide solution. The resulting mixture was extracted several times with ether. The combined ether extracts were treated with Norite, dried over anhydrous potassium carbonate and the ether was distilled, yielding 11.5 g. (64% overall yield from IV) of 2-methyl-5-keto-1,2,3,4,4a,9b-hexahydro-1H-indeno[1,2,c]pyridine, m.p. 90-92.5°. Two recrystallizations from petroleum ether gave pure X, m.p. 93-94°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.53; H, 7.67.

IR spectrum (Mull No. 907): 1709, 1606 (M), 1585 (W), 782 (M), 766 (M), 762 (M), 739 (W-M), 715 (W).

The oxime of X was obtained in quantitative yield by the potassium hydroxide method (16). After one recrystallization from 95% ethanol the oxime melted at 195-200°.

Preparation of 2-Methyl-5-hydroxy-5-phenyl-1,2,3,4,-4a,9b-hexahydro-1H-indeno[1,2,c]pyridine (XI).- To a 0.05 mole phenyllithium solution prepared from 0.7 g. of lithium and 9.7 g. of bromobenzene in 100 ml. of anhydrous ether was added 4.6 g. of the keto-indenopyridine X in anhydrous ether. After the addition was complete, the mixture was heated under reflux for 5 hr. and then decomposed by the addition of water. The ether layer was separated, and the aqueous layer was extracted twice with ether. The combined ether extracts were dried over anhydrous potassium carbonate and the ether was distilled yielding 4.5 g. (72%) of 2-methyl-5-hydroxy-5-phenyl-1,2,3,4,4a,9b-hexahydro-1H-indeno[1,2,c]pyridine (XI).

Recrystallization from isopropyl alcohol gave pure XI, m.p. 188–190°.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 81.68; H, 7.57. Found: C, 80.86; H, 7.29.

IR spectrum (Mull No. 911): 1603 (W), 1493 (W), 769 (W), 752 (M), 744, 720 (W), 700 (M).

UV spectrum (λ max. (log ϵ)): Sh 253(2.66), 258(2.82), 265(2.90), 272(2.81).

The hydrochloride of XI was prepared by standard procedures and melted at 208–210° (dec.).

Anal. Calcd. for $C_{18}H_{22}ClNO$: Cl, 11.23. Found: Cl, 11.61; 11.43.

Preparation of 2-Methyl-5-phenyl-2,3,4,9b-tetrahydro-1H-indeno[1,2,c]pyridine (XII).- A solution of 3.1 g. of 2-methyl-5-hydroxy-5-phenyl-1,2,3,4,4a,9b-hexahydro-1H-indeno-[1,2,c]pyridine (XI) in 50 ml. of 48% hydrobromic acid and 50 ml. of glacial acetic acid was heated on the steam bath for 2 hrs. The acetic acid was removed by distillation under reduced pressure on a steam bath. The remaining solution was made alkaline with aqueous potassium carbonate, and the oil which precipitated was taken up in ether. The combined ether extracts were dried over anhydrous potassium carbonate, and the ether was removed by distillation yielding 1.5 g. (52%) of a waxy solid. Two recrystallizations from petroleum ether gave pure 2-methyl-5-phenyl-2,3,4,9b-tetrahydro-1H-indeno-[1,2,c]pyridine (XII), m.p. 111–112.5°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.33; H, 8.81. Found: C, 77.47; H, 9.03.

IR spectrum (Mull No. 1006): 3100 (B,M), 755 (M), 745.

Preparation of 1-Methyl-3-phenyl-4-piperidylphenyl-carbinol (VII).- An ether solution of 5 g. (0.018 mole) of 1-methyl-3-phenyl-4-benzoylpiperidine (III) was added dropwise to a slurry of 2 g. (0.053 mole) of lithium aluminum hydride in 300 ml. of anhydrous ether. There was no visible reaction during the addition. After the addition was complete, the mixture was heated under reflux for 23 hr. and then decomposed by the cautious addition of water. The precipitate was removed by filtration, and the aqueous and organic layers were separated. The aqueous layer was extracted once with ether. The combined ether extracts were dried over anhydrous potassium carbonate, and the ether was removed by distillation yielding 5 g. (100%) of 1-methyl-3-phenyl-4-piperidylphenyl-carbinol (VII). Two recrystallizations from isopropyl alcohol gave pure VII, m.p. 159-160.5°.

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24. Found: C, 81.41; H, 8.27.

IR spectrum (Mull No. 1157): 3409 (W), 757 (M), 699.

The hydrochloride was prepared and melted at 245-247° after recrystallization from isopropyl alcohol.

Reactions of 1-Methyl-3-phenyl-4-piperidylphenyl-carbinol (VII).

a. With 48% Hydrobromic Acid and Glacial Acetic Acid. Pre-

paration of XIV.- A solution of 5 g. of 1-methyl-3-phenyl-4-piperidylphenylcarbinol (VII) in 50 ml. of 48% hydrobromic acid and 50 ml. of glacial acetic acid was heated on the steam bath for 4 hr. After standing overnight, the acetic acid was removed by distillation under reduced pressure. The remaining acidic solution was cooled in an ice bath and made alkaline with aqueous potassium carbonate. The mixture was extracted several times with ether. The combined ether extracts were dried over anhydrous potassium carbonate and treated with Norite, and the ether was removed by distillation. A pasty product remained, and after treatment with petroleum ether yielded 2.4 g. (39%) of a solid material. Recrystallization from isopropyl alcohol gave pure XIV, m.p. 209-211°.

Anal. Calcd. for $C_{19}H_{22}BrN \cdot C_3H_8O$: C, 65.34; H, 7.48; Br, 19.76. Found: C, 65.13, 65.16; H, 7.51, 7.37; Br, 19.95.

IR spectrum (Mull No. 1287): 3395, 765 (M), 734, 715, (M), 698.

UV spectrum ($\lambda_{max.}$ (log ϵ)): Sh 252(2.48), 258(2.59), 263(2.57), 269(2.42).

b. With 48% Hydrobromic Acid and Glacial Acetic Acid. Preparation of XVI.- A solution of 5 g. of 1-methyl-3-phenyl-4-piperidylphenylcarbinol (VII) in 50 ml. of 48% hydrobromic acid and 50 ml. of glacial acetic acid was heated on the steam bath for several hours. After the mixture stood overnight, the acetic acid was removed by distillation under reduced pressure. The remaining acidic solution was made alkaline with aqueous potassium carbonate and extracted with ether.

The combined ether extracts were treated with Norite and dried over anhydrous potassium carbonate, and the ether was removed by distillation. Upon concentration of the ether solution a solid began to precipitate. The precipitate was collected and washed with anhydrous ether yielding 1 g. (20%) of an isomeric alcohol, XVI, m.p. 196–208°. XVI gave a negative Beilstein test, was soluble in ether and insoluble in water. Two recrystallizations from ligroin (b.p. 60–90°) gave pure XVI, m.p. 195–199°.

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24. Found: C, 81.00; H, 8.18.

IR spectrum (Mull No. 1338): 3150 (B,M), 760, 700.

UV spectrum ($\lambda_{max.}$ (log ϵ)): 247(2.46), 251(2.55), 257(2.63), Sh 260(2.57), 263(2.54), 267(2.44).

c. With 48% Hydrobromic Acid and Glacial Acetic Acid. Preparation of XV.- A solution of 17.1 g. of 1-methyl-3-phenyl-4-piperidylphenylcarbinol (VII) in 60 ml. of 48% hydrobromic acid and 60 ml. of glacial acetic acid was heated on the steam bath for 1 hr. The mixture was allowed to stand overnight. The acetic acid was removed by distillation under reduced pressure, and the remaining acidic solution was made alkaline with aqueous potassium carbonate. The mixture was extracted with ether. The combined ether extracts were dried over anhydrous potassium carbonate, and the ether was removed by distillation. The residue was triturated with petroleum ether yielding 5.9 g. (30%) of a solid material. Washing the solid with ligroin (b.p. 60–90°) gave pure XV, m.p. 221–224°.

XV was soluble in water, insoluble in ether and gave a positive silver nitrate test.

Anal. Calcd. for $C_{18}H_{22}BrN$: C, 66.28; H, 6.44. Found: C, 66.19; H, 6.63.

IR spectrum (Mull No. 1393): Identical with that of XIV.

Oxidation of XVII with Activated Manganese Dioxide to 1-Methyl-3-phenyl-4-benzoylpiperidine (III).- A solution of 0.5 g. of XVII in 50 ml. of chloroform was stirred for 6 hr. with 10 g. of manganese dioxide which was prepared by the method of Attenburrow et al[15]. The reaction mixture was allowed to stand overnight, and the manganese dioxide was collected by filtration through a fine sintered glass funnel. The yellow chloroform solution was concentrated leaving 0.5 g. (100%) of crystals. Two recrystallizations from isopropyl alcohol gave a solid, m.p. 108-110°. This material did not depress the melting point of an authentic sample of 1-methyl-3-phenyl-4-benzoylpiperidine (III). The infrared absorption spectrum of the product obtained from this reaction was identical with that of authentic III.

Reduction of Methyl 1-Methyl-3-phenylisonipecotate (IV) with Lithium Aluminum Hydride. Attempted Preparation of 1-Methyl-3-phenyl-4-piperidylmethanol Hydrochloride (XVII).- A solution of 21.3 g. (0.09 mole) of IV in anhydrous ether was added dropwise to a slurry of 2 g. (0.053 mole) of lithium aluminum hydride in 300 ml. of anhydrous ether. When the

addition was completed, the mixture was heated under reflux for 45 min. The excess hydride was decomposed by the cautious addition of water. The ether layer was separated and dried over anhydrous potassium carbonate. After removal of the carbonate by filtration, anhydrous hydrogen chloride was passed through the ether solution precipitating 22.1 g. (77%) of a hydrochloride. Two recrystallizations from isopropyl alcohol gave a pure hydrochloride, m.p. 295–298°.

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34. Found: C, 71.07, 71.33; H, 7.74, 7.67.

IR spectrum (Mull, No. 1795): 3278 (B,W), 747 (W), 710 (W–M).

Reaction of XVII with Thionyl Chloride. Preparation of 1–Methyl–3–phenyl–4–piperidylmethyl Chloride Hydrochloride (XVIII).– XVII (7.9 g.) was added to 30 ml. of thionyl chloride cooled in an ice bath, and the mixture was allowed to stand overnight. The thionyl chloride was removed by distillation under reduced pressure on a steam bath. Anhydrous benzene (30–40 ml.) was added, and the benzene was removed by distillation under reduced pressure. The process was repeated with 35 ml. more. A tan solid (3 g., 37%) was collected. Two recrystallizations from isopropyl alcohol gave pure 1–methyl–3–phenyl–4–piperidylmethyl chloride hydrochloride (XVIII), m.p. 174–176°.

Anal. Calcd. for $C_{13}H_{19}Cl_2N$: C, 60.00; H, 7.36. Found: C, 60.52, 60.24; H, 7.54, 7.60.

IR spectrum (Mull, No. 1560): 780 (W), 751, 734 (W–M), 695.

Attempted Reactions of 1–Methyl–3–phenyl–4–benzoyl–piperidine (III).

a. With Bromine.– A solution of 0.3 g. of the hydrobromide of III in 25 ml. of chloroform was treated with 0.17 g. of bromine, and the mixture was heated gently under reflux for 30 min. The solvent was removed by distillation under reduced pressure, and methanol was added. Phenol was added to destroy any excess bromine or perbromide. Upon addition of ether an orange oil precipitated. A chloroform–ether mixture was used to effect crystallization. 0.1 g. of white needles, m.p. 243–244°, was the only product isolated. The product was shown to be identical with the hydrobromide of III by infrared analysis and by a mixed melting point with an authentic sample of the hydrobromide of III.

b. With Bromine in Glacial Acetic Acid.– The hydrobromide of III (2.1 g.) was treated with 1 ml. of bromine in 60 ml. of glacial acetic acid, and the mixture was illuminated for 9 hr. with a 150–watt incandescent lamp. Hydrogen bromide gas was evolved, and the solution changed from dark red to orange. The mixture was allowed to stand for 30 hr. Most of the acetic acid was removed by distillation under reduced pressure on the steam bath. The residue was dissolved in methanol, and phenol was added to destroy any excess bromine or perbromide. The oil which precipitated crystallized upon addition of a few

drops of isopropyl alcohol. 1.57 g. (62%) of a white solid (XIX), m.p. 169–171°, was obtained.

Anal. Calcd. for $C_{10}H_{21}Br_2NO$: C, 51.95; H, 4.82. Found: C, 51.37: H, 4.77.

IR spectrum (Mull, No. 1590): 1666, 1595 (W), 751 (M), 701.

UV spectrum ($\lambda_{max.}$ (log ϵ)): 252(3.92), 334(3.25).

A small amount of XIX was converted to the free base. The solid obtained in this manner gave a positive Beilstein test.

IR spectrum (Mull, No. 1886): 3440 (B,M), 3380 (B,S), 1642 (W), 1615 (M), 1595 (M), 765 (M), 702 (M).

UV spectrum ($\lambda_{max.}$): 238, 260, 336.

c. Unsuccessful Isomerization with 48% Hydrobromic Acid.– III (0.3 g.) was treated with 20 ml. of 48% hydrobromic acid, and the solution was heated under reflux for 7 hr. The mixture was then poured into cold water, made alkaline with aqueous potassium carbonate, and extracted with ether. The combined ether extracts were dried over anhydrous potassium carbonate. Removal of the ether by distillation gave an oil which crystallized upon trituration with petroleum ether. One recrystallization from petroleum ether gave white needles, m.p. 108–110°, which did not depress the melting point of an authentic sample of III.

d. Unsuccessful Isomerization with Sodium Ethoxide. III (0.5 g.) was added to a sodium ethoxide solution prepared

from 50 ml. of absolute ethanol and sodium metal (0.10 g.). The clear solution was heated under reflux for 24 hr. The ethanol was removed by distillation leaving an oily residue which crystallized upon trituration with petroleum ether. Recrystallization from petroleum ether gave fine, flowery needles, m.p. 108–109°. Mixed melting point of this product with an authentic sample of III did not depress. Infrared analysis of this product showed it to be identical with the infrared spectrum of III.

e. Unsuccessful Isomerization with Sodium Hydride in Refluxing Xylene.– A solution of III (0.5 g.) in xylene (40 ml.) was treated with sodium hydride (0.065 g.), and the mixture was heated under reflux for 24 hr. After cooling the reaction mixture, glacial acetic acid (0.16 g.) was added followed by the addition of water. The organic layer was extracted with dilute hydrochloric acid, and the acid extracts were made alkaline with aqueous sodium carbonate. The oil which precipitated was taken up in ether. The ether solution was dried over anhydrous potassium carbonate, and the ether was distilled leaving a solid material. Recrystallization from petroleum ether gave white needles, m.p. 107–108°. Mixed melting point of this product with an authentic sample of III did not depress.

f. Unsuccessful Isomerization with Vinyl Acetate and Sulfuric Acid.– III (1.0 g.) was treated with vinyl acetate (8.8 ml.) and sulfuric acid (0.01 ml.). The mixture was heated under reflux for 3 hr. The solution was concentrated to one–half

its original volume, and the solution was cooled. When ether was added, a gummy substance precipitated. Aqueous potassium carbonate was added, and the mixture was extracted with ether. The ether was dried over anhydrous potassium carbonate, and the ether was distilled. The residue was heated with petroleum ether and then cooled, whereupon fine, flowery needles, m.p. 107–109°, were obtained. Mixed melting point of this product with an authentic sample of III did not depress.

Sulfur Dehydrogenation of 1–Methyl–3–phenyl–4–benzoylpiperidine (III). Preparation of 3–Phenyl–4–benzoylpyridine (XX).– 1–Methyl–3–phenyl–4–benzoylpiperidine (III) (12.3 g.; 0.044 mole) and sulfur (4.5 g.; 0.141 g–atom) were heated in a 100 ml. round–bottomed flask in a Wood's metal bath. The temperature of the bath was gradually increased, and at about 120° the evolution of hydrogen sulfide began. The temperature was increased and kept constant at 180°. After 45 minutes of heating the evolution of hydrogen sulfide had ceased. Heating was continued for 15 minutes longer. The dark red mixture was cooled to room temperature and extracted with ether. The dark red ethereal solution was filtered, and then extracted 5 times with 50–ml. portions of dilute hydrochloric acid. The acid extract was made alkaline with aqueous sodium carbonate. The red oil which precipitated was taken up in ether. The combined ether extracts were treated with Norite, dried over anhydrous potassium carbonate and filtered. After removal of

the ether by distillation, an oil (6.5 g.; 57%) remained. Treatment of the oil with petroleum ether (b.p. 30–60°) gave 5.3 g. of crystalline material, m.p. 110–113°. Recrystallization from ethyl ether gave 4.9 g. of pure 3–phenyl–4–benzoylpyridine (XX), m.p. 114–115°.

Anal. Calcd. for $C_{18}H_{13}NO$: C, 83.37; H, 5.05. Found: C, 83.07; H, 5.14.

IR spectrum (Mull, No. 2739): 3040 (W), 1672, 1480 (W), 1450 (M), 1402 (W), 1314 (M), 940, 927 (M), 846, 801 (W), 783, 765 (W), 757, 707, 700.

UV spectrum ($\lambda_{max.}$ (log ϵ)): 248(4.36), 290(3.70).

Preparation of 1–Methyl–3–phenyl–4–benzoylpyridinium Bromide (XXI).– A solution of 6.5 g. of impure 3–phenyl–4–benzoylpyridine (XX) in 40 ml. of acetone was saturated with methyl bromide. The flask was tightly stoppered and allowed to stand overnight. The flask was cooled, and the stopper was removed. The solution was concentrated on the steam bath. Upon cooling a crystalline solid (2.5 g.) precipitated. The mother liquor was saturated again with methyl bromide, and the foregoing procedure was repeated yielding an additional 2.8 g. of solid. The total yield of 1–methyl–3–phenyl–4–benzoylpyridinium bromide (XXI) was 5.3 g. (60%). Recrystallization from acetone gave pure XXI, m.p. 224.5–226°.

Anal. Calcd. for $C_{19}H_{16}BrNO$: C, 64.42; H, 4.55. Found: C, 64.53; H, 4.68.

IR spectrum (Mull, No. 2759): 2965 (M), 2920 (M), 1670, 1636 (W), 1450 (M), 770 (W), 755 (W), 724 (W),

710 (M), 695 (M).

Catalytic Hydrogenation of 1-Methyl-3-phenyl-4-benzoylpyridinium Bromide (XXI). Preparation of 1-Methyl-3-phenyl-4-piperidylphenyl Carbinol (XXII).- A solution of 5.3 g. of 1-methyl-3-phenyl-4-benzoylpyridinium bromide (XXI) in 50 ml. of methanol was reduced with hydrogen at low pressure over 0.2 g. of platinum oxide for 19 hours. The catalyst was collected by filtration, and the solvent was removed by distillation. The residue was dissolved in water, and the solution was made alkaline with aqueous sodium carbonate. The white solid which precipitated was taken up in ether. The ethereal solution was dried over anhydrous potassium carbonate, filtered and the ether was removed by distillation. A pasty oil (3.5 g.; 75%) remained.

The oil was subjected to chromatography over a column (22 cm. x 3 cm.) of Florisil (100/200 mesh). A solution of the oil in ligroin (b.p 60-90°) was placed on the Florisil. Fractions 1-4 were collected using ligroin (b.p. 60-90°) as the eluent and contained nothing. Fractions 5-8 were collected using benzene as the eluent and contained nothing. Fractions 9-12 were collected using chloroform as the eluent. Fraction 9 was blank. Fractions 10-12 yielded a total of 1.5 g. (32%) of a solid, m.p. 114-118°. Fractions 14-16 were collected using methanol as the eluent. Fraction 14 contained only a trace of oil. Fraction 15 contained an oil whose infrared spectrum (smear, No. 8 (Infracord)) showed broad

hydroxyl absorption at 3300 cm^{-1} and broad carbonyl absorption at about 1665 cm^{-1}.

The solid obtained from fractions 10–12 was recrystallized from petroleum ether (b.p. 30–60°) yielding 0.6 g. of colorless needles of 1-methyl-3-phenyl-4-piperidylphenyl carbinol, m.p. 119.5–121°.

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24. Found: C, 81.32; H, 8.35.

IR spectrum (Mull, No. 2835): 3260, 3040 (W), 3005 (W), 2910 (M), 2855 (W), 2820 (W), 2750 (M), 2710 (W), 765 (M), 704, 696.

Sodium Borohydride Reduction of 3-phenyl-4-benzoylpyridine (XX). Preparation of 3-Phenyl-4-pyridylphenyl Carbinol (XXIII).- Sodium borohydride (1 g.; 0.026 mole) was added in small portions with stirring to a solution of 2.1 g. (0.008 mole) of 3-phenyl-4-benzoylpyridine (XX) in 50 ml. of methanol. After the addition was complete, stirring was continued for 0.5 hr. The solvent was removed by distillation, water was added and the mixture was extracted with chloroform. Upon removal of the solvent an oil remained. Crystallization of the oil was effected with petroleum ether (b.p. 30–60°) to give 1.7 g. (80%) of 3-phenyl-4-pyridylphenyl carbinol (XXIII). Recrystallization from petroleum ether gave pure XXIII, m.p. 142–143°.

Anal. Calcd. for $C_{18}H_{15}NO$; C, 82.73; H, 5.79. Found: C, 82.82; H, 5.73.

IR spectrum (Mull, No. 3058): 3100 (B,S), 2840 (B,M), 1080 (W), 1053 (M), 760 (M), 755, 695.

Preparation of 3-Phenyl-4-pyridylphenyl Carbinol Methobromide (XXIV).- A solution of 1.7 g. of 3-phenyl-4-pyridylphenyl carbinol (XXIII) in acetone was saturated with methyl bromide. After standing for 1 hour, colorless crystals precipitated to give 2.15 g. (93%) of 3-phenyl-4-pyridylphenyl carbinol methobromide (XXIV), m.p. 221-223°. Recrystallization from an acetone-isopropyl alcohol mixture did not raise the melting point.

Anal. Calcd. for $C_{19}H_{18}BrNO$: C, 64.05; H, 5.09. Found: C, 64.32; H, 5.33.

IR spectrum (Mull, No. 3076): 3180, 3010 (M), 2930 (W), 1635 (M), 1055 (M), 769 (M), 750 (M), 735, 720, 704, 696.

Sodium Borohydride Reduction of 3-Phenyl-4-pyridylphenyl Carbinol Methobromide (XXIV). Preparation of 1-Methyl-3-phenyl-1,2,5,6-tetrahydro-4-pyridylphenyl Carbinol (XXV).- To a solution of 2 g. of 3-phenyl-4-pyridylphenyl carbinol methobromide (XXIV) in 50 ml. of methanol was added in small portions, 3 g. of sodium borohydride. After being stirred at room temperature for 30 min., the methanol solution was evaporated to dryness on the steam bath. The solid residue was dissolved in water, and the aqueous solution was extracted several times with ether. After drying the extracts over anhydrous potassium carbonate, the ether was removed by distillation yielding 1.3 g. (84%) of a solid material, m.p. 153-155°. Recrystallization from an ethanol-water mixture gave 1.1 g. of pure 1-methyl-3-phenyl-1,2,5,6-tetrahydro-4-pyridyl-

phenyl carbinol (XXV), m. p. 154.5–156°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.67; H, 7.58. Found: C, 81.66; H, 7.56.

IR spectrum (Mull, No. 3099): 3070 (B,W), 776 (W–M), 759, 715, 696.

UV spectrum: No absorption maxima above 230 mu.

Oxidation of 1–Methyl–3–phenyl–1,2,5,6–tetrahydro–4–pyridylphenyl Carbinol (XXV) with Activated Manganese Dioxide. Attempted Preparation of 1–Methyl–3–phenyl–1,2,5,6–tetrahydro–4–pyridylphenyl Ketone (XXVI).– A solution of 0.375 g. of 1–methyl–3–phenyl–1,2,5,6–tetrahydro–4–pyridylphenyl carbinol (XXV) in 50 ml. of chloroform was stirred for 3 hr. with 8 g. of activated manganese dioxide. The manganese dioxide was removed by filtration through a fine, sintered glass funnel. To the chloroform solution 8 g. of manganese dioxide again was added, and the mixture was stirred for 3 hr. The filtration was repeated. Again 8 g. of manganese dioxide was added, and the mixture was stirred for 4.5 hr. The filtration was repeated. The chloroform solution was treated with Norite and filtered, and the chloroform was removed by distillation. The residue was taken up in ether, and the ether solution was treated with Norite. Concentration of the colorless ether solution gave 0.19 g. of an oil which could not be crystallized.

IR spectrum (Film, No. 3181): 3440 (B,M), 3030 (M), 1655 (B,S), 1175 (M), 1072 (M), 940 (M), 764 (B,S), 700 (B,S).

UV spectrum ($\lambda_{max.}$): Sh 250, Sh 288, Sh 345.

Preparation of 1-Methyl-4-cyanopyridinium Bromide (XXVIII).- A solution of 20 g. of 4-cyanopyridine (XXVII) in 75 ml. of acetone was saturated with methyl bromide. The flask was tightly stoppered and allowed to stand for 2 days, whereupon 32.5 g. (85%) of 1-methyl-4-cyanopyridinium bromide (XXVIII), m.p. 219-220°, were collected. Recrystallization of the solid from isopropyl alcohol gave pure XXVIII, m.p. 225-227° (dec.).

Anal. Calcd. for $C_7H_7BrN_2$: Br, 40.15; Found: 40.23.

IR spectrum (Mull, No. 2092): 3080 (M), 2975, 2240 (W), 1631 (M), 858, 717 (W).

Sodium Borohydride Reduction of 1-Methyl-4-cyanopyridinium Bromide (XXVIII). Preparation of 1-Methyl-1,2,3,6-tetrahydroisonicotinonitrile (XXIX).- To a solution of 20 g. (0.10 mole) of 1-methyl-4-cyanopyridinium bromide (XXVIII) in 125 ml. of methanol was added 4.65 g. (0.12 mole) of sodium borohydride portionwise. The exothermic reaction was moderated by external cooling with an ice bath. After being stirred at room temperature for 15 min., the methanol solution was evaporated to dryness on the steam bath. The semi-solid residue was dissolved in water, saturated with anhydrous potassium carbonate, and the mixture was extracted several times with ether. After drying over potassium carbonate, the ether solution was concentrated, and the residual oil was distilled under 0.7 mm. of pressure. 1-Methyl-1,2,3,6-tetrahydroisonicotinonitrile (XXIX) was collected in two fractions: b.p. 85-

88°, n_D^{29}1.4967; and b.p. 88–90°, n_D^{29} 1.4967. The total yield of XXIX was 8.7 g. (70%).

An analysis of this product was not obtained, since the oil decomposed rapidly and the infrared absorption spectrum indicated that other products were present.

IR spectrum (Film, No. 2085): 3040 (W), 2935, 2835 (M), 2780, 2235 (W), 2215 (M), 1642, 1592 (M), 1380 (M).

UV spectrum ($\lambda_{max.}$): 246, 397.

Reaction of 1-Methyl-1,2,3,6-tetrahydroisonicotinonitrile (XXIX) with Phenylmagnesium Bromide.- To a stirred solution of phenylmagnesium bromide (0.214 mole) prepared from 5.2 g. (0.214 g.-atom) of magnesium and 34 g. (0.215 mole) of bromobenzene in 300 ml. of anhydrous ether was added dropwise 8.7 g. (0.072 mole) of 1-methyl-1,2,3,6-tetrahydroisonicotinonitrile (XXIX). The mixture was stirred and heated under reflux for 2 hr. and allowed to stand overnight. To the stirred reaction mixture, cooled in an ice bath, was added dropwise an aqueous solution of ammonium chloride. The ether layer was separated and extracted with hydrochloric acid (20%). The acid extract was cooled in ice and made alkaline with 40% aqueous potassium carbonate. The oil which precipitated was taken up in ether, and the ether extracts were dried over anhydrous potassium carbonate. Filtration and concentration of the ether solution gave a dark red oil. The oil was distilled under reduced pressure to give two fractions: 5.9 g., b.p. 165–170°/20 mm.; and 2.6 g., b.p. 170–204°/20 mm.

Fraction 1

IR spectrum (Film, No. 2102): 3040 (W), 2917 (M), 2825 (W), 2770 (M), 2210 (W), 1660, 1595 (M), 755 (M), 745 (M), 719 (W), 696.

UV spectrum ($\lambda_{max.}$): 252, Sh 330–335.

Fraction 2

IR spectrum (Film, No. 2103): 3040 (M), 3010 (M), 2920, 2825, 2770, 2230 (W), 1681 (B,S), 758, 698.

Sodium Borohydride Reduction of 1-Methyl-4-benzoylpyridinium Bromide (XXXI). Preparation of 1-Methyl-1,2,3,6-tetrahydro-4-pyridylphenyl Carbinol (XXXII).- A solution of 32 g. (0.115 mole) of 1-methyl-4-benzoylpyridinium bromide (XXXI) in 150 ml. of methanol was treated with 8 g. (0.21 mole) of sodium borohydride in essentially the same manner as that of Kerlin[13]. In this way, 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenyl carbinol (XXXII) was prepared in 50–55% yields.

Oxidation of 1-Methyl-1,2,3,6-tetrahydro-4-pyridylphenyl Carbinol (XXXII) with Activated Manganese Dioxide. Preparation of 1-Methyl-1,2,3,6-tetrahydro-4-pyridylphenyl Ketone (XXXIII).- A solution of 9 g. of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenyl carbinol (XXXII) in 125 ml. of chloroform was stirred for 14 hr. with 65 g. of activated manganese dioxide. The manganese dioxide was removed by filtration through a sintered glass funnel which was packed with Filter-cel. The filtrate was concentrated on a steam bath using a Rinco evaporator. It was necessary to control

the steam so that the temperature of the flask remained close to room temperature, otherwise extensive decomposition occurred. A dark red oil (8.5 g.) was obtained. All attempts at crystallization were unsuccessful.

IR spectrum (Film, No. 2122): 3040 (W), 2920 (M), 2825 (W), 2770 (M), 1645 (B,S), 1375 (M), 775 (W), 750 (M), 700.

A picrate of the oil was prepared in the usual manner. The yellow solid was recrystallized twice from 95% ethanol giving the picrate of 1-methyl-1,2,3,6-tetrahydro-4-pyridyl-phenyl ketone (XXXIII), m.p. 159-161° (dec.).

Anal. Calcd. for $C_{13}H_{15}NO \cdot C_6H_3N_3O_7$: C, 53.02; H, 4.22. Found: C, 53.03; H, 4.37.

IR spectrum (Mull, No. 2130): 2940 (B,W), 1640 (W), 1625 (M), 1608 (M), 1360 (M), 781 (W), 740 (W), 700 (M).

Reaction of 1-Methyl-1,2,3,6-tetrahydro-4-pyridyl-phenyl Ketone (XXXIII) with Phenylmagnesium Bromide in the Presence of Cuprous Chloride.- To a stirred solution of phenylmagnesium bromide (0.032 mole) prepared from 0.77 g. (0.032 g-atom) of magnesium and 5.1 g. (0.033 mole) of bromobenzene in 200 ml. of anhydrous ether was added 0.03 g. of cuprous chloride. The mixture was stirred for 15 min. A solution of 3.2 g. of impure 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenyl ketone (XXXIII) in 50 ml. of ether was added dropwise. After the addition was complete, the mixture was stirred and heated under reflux for 2 hr. To the stirred reaction mixture, cooled in an ice bath, was added dropwise an aqueous solution of ammonium chloride. The ether layer

was separated and extracted with hydrochloric acid (20%). The acid extract was cooled in ice and made alkaline with 40% aqueous potassium carbonate. The oil which precipitated was taken up in ether, and the ether extracts were dried over potassium carbonate. Removal of the ether by distillation gave a dark red oil which could not be crystallized.

IR spectrum (Film, No. 2363): 3340 (B,M), 3070 (M), 3040 (M), 1678, 1595, 1495, 753, 737 (M), 695.

A picrate of the oil was prepared in the usual manner. The yellow solid was recrystallized twice from 95% ethanol giving bright yellow plates, m.p. 223–227°. Mixture melting with an authentic sample of the picrate of 1–methyl–3–phenyl–4–benzoylpiperidine (III), m.p. 225–234°, did not depress. The infrared absorption spectra (Nujol mulls, Nos. 2367 and 2371) of the two picrates were identical.

SUMMARY

The reaction of phenylmagnesium bromide with methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate (II) at room temperature gave 1-methyl-3-phenyl-4-benzoylpiperidine (III). In order to establish the stereochemistry of III, equilibration reactions with acid and base were attempted. It was found that in every case, no reaction occurred and III was recovered. Attempted bromination of III gave only the hydrobromide of III. On the basis of these preliminary results, III was assigned the trans-configuration, since the failure of III to equilibrate indicates that the hydrogen alpha to the carbonyl is axially-oriented.

The reaction of phenylmagnesium bromide with II at -7° gave methyl 1-methyl-3-phenylisonipecotate (IV). III and IV were found to have the same stereochemistry, since the reaction of phenyllithium with III and IV gave one and the same carbinol, 1-methyl-3-phenyl-4-piperidyldiphenyl carbinol (V). The ester, IV, was successfully converted to 2-methyl-5-keto-1,2,3,4,4a,9b-hexahydro-1H-indeno[1,2,c]pyridine (X). Although X undoubtedly has a cis ring-fusion, the stereochemistry of IV does not necessarily have to be cis. Plati and Wenner[4] found that either racemate of methyl 1-methyl-4-phenylnipecotate gave the same indenopyridine. Isomerization of the trans to the cis racemate probably occurs during the Friedel-Crafts cyclization. Several compounds derived

from X were prepared.

Lithium aluminum hydride reduction of III gave 1-methyl-3-phenyl-4-piperidylphenyl carbinol VII in quantitative yield. The stereochemistry of VIII should be the same as that of III and manganese dioxide oxidation of VII gave III. In an attempt to dehydrate the carbinol VII, a glacial acetic acid 48% hydrobromic acid mixture, which had been used previously with success, was employed. It was found that from three different attempted dehydrations three different products were isolated.

In the first, a solid which had been recrystallized from isopropyl alcohol was isolated. Its high melting point, solubility in water, insolubility in ether and positive silver nitrate test gave strong evidence in favor of a quaternary salt. Elemental analyses agreed with the empirical formula, $C_{19}H_{22}BrN \cdot C_3H_8O$. Structure XIV is the only one which accounts for all of the experimental facts.

In the second reaction, the use of isopropyl alcohol was avoided. A solid differing from XIV only in melting point and only slightly in the infrared spectrum was obtained. Elemental analysis agreed with the empirical formula, $C_{19}H_{22}N$. Structure XV accommodates all the experimental facts. If the assigned structures are correct, then their formations can be rationalized only if it is assumed that VII is the <u>trans</u> carbinol.

In the third reaction, an isomeric alcohol, $C_{19}H_{23}NO$, was obtained. The position of -OH stretching absorption in

its infrared absorption spectrum was different than that of VII. It also differed in melting point. Manganese dioxide oxidation of this carbinol, XVI, to III suggests that the two alcohols differ only in the configuration of the carbinol carbon atom.

Bromination of III under forcing conditions gave a solid hydro-bromide (XIX) whose elemental analysis agreed with the empirical formula, $C_{19}H_{21}Br_2NO$. The infrared absorption spectrum of XIX showed a carbonyl bond at 1666 $cm.^{-1}$, and the ultraviolet absorption spectrum showed maxima at 252 mμ ($\log \epsilon = 3.92$) and 334 mμ ($\log \epsilon = 3.25$). Conversion of XIX to the free base gave a solid whose infrared absorption spectrum showed -OH stretching absorption at 3440 $cm.^{-1}$ (B,M) and 3380 $cm.^{-1}$ (B,S) and a weak band at 1642 $cm.^{-1}$. Its ultraviolet absorption spectrum showed maxima at 238 mμ, 260 mμ, and 336 mμ. The structure of the free base has not been determined. Compound XIX is 1-methyl-3-phenyl-4-bromo-4-benzoylpiperidine hydrobromide.

1-Methyl-3-phenyl-4-benzoylpiperidine (III) was successfully dehydrogenated with sulfur to give 3-phenyl-4-benzoylpyridine (XX). Catalytic hydrogenation of 1-methyl-3-phenyl-4-benzoylpyridinium bromide (XXI) gave a mixture of products from which a small amount of 1-methyl-3-phenyl-4-piperidylphenyl carbinol (XXII) was isolated. XXII was found to be different from VII and XVI by melting point and by infrared analysis. Catalytic hydrogenations of 3-phenyl-4-pyridylphenyl carbinol methobromide (XXIV) and 1-methyl-3-

phenyl-1,2,3,6-tetrahydro-4-pyridylphenyl carbinol (XXV) were unsuccessful. The failure of these hydrogenations may be due to catalyst poisoning by a trace of sulfur.

Thus, the results of this research have not produced conclusive evidence for either the cis or the trans configuration for 1-methyl-3-phenyl-4-benzoylpiperidine (III) and related compounds. Most of the experimental evidence points to the trans configuration, but this is countered by the results obtained from the attempted dehydration reactions of VII.

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