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STEREOCHEMICAL STUDIES OF (POS ROT-)-1-METHYL-2,6-DIPHENYL-4-PIPERIDONE OXIME

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STEREOCHEMICAL STUDIES
OF
(+)-1-METHYL-2,6-DIPHENYL-4-PIPERIDONE OXIME

BY

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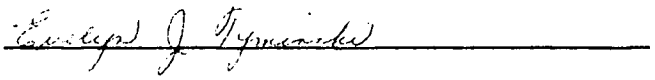

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INTRODUCTION

The absolute configurations of a number of molecules exhibiting optical activity due to atomic asymmetry have been determined. A basis for configurational assignment to molecules exhibiting optical activity due to atomic asymmetry was provided with the establishment of the absolute configuration of D-tartaric acid by the anomalous X-ray technique.[1] The determination of the absolute configuration of molecularly dissymmetric molecules was more difficult due to the absence of an asymmetric center to which correlations with molecules exhibiting atomic asymmetry could be made. A knowledge of the mechanism by which a molecularly dissymmetric compound is either synthesized from materials of known absolute configuration or degraded to molecules of established configuration is necessary in order to establish the absolute configuration of molecularly dissymetric compounds, and relatively few examples of such molecules have been examined in this context. The first compound to be subjected to such analysis involved the conversion of a thebaine derivative to an optically active biphenyl.[2] More recently, correlations of allenes with tetrahedrally asymmetric molecules have been made including configurational assignments by Eliel[3], Landor and co-workers[4,5], and Jones and co-workers.[6]

In 1957, Lyle and Lyle[7], experimentally demonstrated a type of optical isomerism which resulted from the introduction of the elements of geometrical isomerism, centrally, between the two enantiomeric centers of an otherwise meso molecule. The optical activity exhibited by such a molecule is attributed to the molecular dissymmetry created by the

introduction of the elements of geometrical isomerism into a meso form and was therefore designated as geometrical enantiomorphic isomerism by these investigators. The molecule, an oxime, described by Lyle and Lyle[7], possesses two asymmetric centers of mirror image configuration. Introduction of the elements of geometrical isomerism centrally between these two enantiomeric centers leads to two optically active isomers which cannot be superimposed even though the hydroxyl group of the oxime function is directed toward asymmetric carbon atoms of mirror image configuration. The presence of enantiomeric groupings in the molecule provided centers of atomic asymmetry to which the absolute configuration of this otherwise molecularly dissymmetric molecule could be related. Absolute configurational assignments have not yet been demonstrated for molecules exhibiting optical activity due to geometrical enantiomorphic isomerism. Such a study is described in the first section of this Thesis with the unique dextrorotatory isomer of 1-methyl-2,6-diphenyl-4-piperidone oxime.

Stereoisomerism, attributed to atomic or geometrical asymmetry, has been demonstrated to be an important tool for investigating the course of an organic reaction, for the intermediate or transition state of the reaction under consideration may usually be deduced from the optical properties exhibited by the products obtained. The formation of a symmetrical intermediate or transition state during the course of a reaction involving an optically active molecule leads to the isolation of optically inactive products; on the other hand, the isolation of optically active products from such a reaction suggests a stereospecific reaction pathway. An optically active compound of established absolute configuration and whose optical activity is attributed to geometrical enantio-

morphic isomerism would provide a unique tool for studying the reactions of oximes and oxime derivatives in a manner which has heretofore been impossible.

A reaction of oxime tosylates which has recently received wide application in the synthesis of certain acyclic as well as cyclic α-amino ketones is the Neber rearrangement, the base catalyzed rearrangement of an oxime arylsulfonate ester, and some studies have been undertaken to elucidate the mechanism of this rearrangement.[8] In no instance, however, has an optically active oxime having two identical or nearly identical adjacent methylene groups been subjected to such an investigation. In one of his investigations, Neber[9] demonstrated that racemic 1-methyl-2,6-diphenyl-4-piperidone oxime tosylate underwent such a base catalyzed rearrangement to produce a cyclic α-amino ketone which was isolated as its hydrochloride. Hence, the establishment of the absolute configuration of the dextrorotatory isomer of 1-methyl-2,6-diphenyl-4-piperidone oxime afforded a unique method for further investigating the mechanism of the Neber rearrangement for indiscriminate formation of the intermediate or transition state would lead to the isolation of racemic product while preservation of optical activity in the amino ketone would require that the reaction proceeded by a stereospecific pathway. The Neber rearrangement of the para-tolylsulfonate ester of the dextrorotatory isomer of 1-methyl-2,6-diphenyl-4-piperidone oxime is discussed in the second section of this Thesis.

THE ABSOLUTE CONFIGURATION

OF

(+)-1-METHYL-2,6-DIPHENYL-4-PIPERIDONE OXIME

DISCUSSION

The determination of absolute configuration (the actual spatial arrangement) of a molecule is a difficult task to be undertaken only by skilled X-ray crystallographers and limited to suitable crystalline solids containing appropriate atoms. It is fortunate, therefore, that other methods for ascertaining configuration are available, i.e. methods which allow the correlation of the configuration of one molecule with another. Utilization of these methods allows the configuration of any optically active molecule to be related, either directly or indirectly, to (+)- or (-)-tartaric acid of known absolute configuration, and many ingenious methods have been employed to determine the absolute configuration of an optically active compound. One of the most useful of these methods involves the chemical interconversion of one molecule with another by a pathway such that the bonds at the asymmetric center are not disturbed during the interconversion. An extension of this allows the synthesis of desired derivatives from compounds of established configuration to be related to compounds obtained from the degradation of molecules of unknown configuration, usually by simple physical measurements.

The determination of the absolute configuration of molecularly asymmetric molecules requires a knowledge of the mechanism by which the compound is synthesized from materials of known configuration or degraded to compounds of established configuration. The presence of two enantiomeric centers at C-2 and C-6 in (+)-1-methyl-2,6-diphenyl-4-piperidone oxime afforded centers of atomic asymmetry in an otherwise molecu-

larly dissymmetric molecule, to which the configuration of the oximido hydroxyl group could be related.

Synthesis of 1-Methyl-2,6-diphenyl-4-piperidone Oxime

The condensation of dibenzalacetone[10] with methylamine, as described by Lyle and Lyle[7], gave 1-methyl-2,6-diphenyl-4-piperidone (I) whose meso configuration has been adequately demonstrated.[11] Conversion of I to the corresponding mixture of oximes, IIa and IIb, was readily accomplished by the usual procedure. Resolution of the mixture of oxime isomers (IIa and IIb) was accomplished by precipitation of the (+)-10-camphor sulfonic acid salt of the dextrorotatory isomer in an anhydrous ether-methanol medium.[12] Since previous studies indicated that the (+)-10-camphor sulfonate underwent partial racemization in the presence of polar solvents such as methanol and ethanol[13], fractional crystallization was carried out by dissolving the oxime salt in a minimum amount of methanol at room temperature. The immediate addition of anhydrous ether caused precipitation of the salt; cooling the mixture further decreased the amount of racemization and thereby increased the yield of the dextrorotatory salt. Generation of the dextrorotatory isomer of II was then accomplished by neutralization of a water-acetone solution of the (+)-10-camphor sulfonate with a saturated potassium carbonate solution.

The Beckmann Rearrangement of 1-Methyl-2,6-diphenyl-4-piperidone Oxime

Perhaps the most thoroughly investigated reaction of oximes is the Beckmann rearrangement which, if the reaction proceeds by the normal course, produces amides from ketonic

oximes.[14,15] Essentially, the rearrangement proceeds as a stereospecific intramolecular displacement in that the group anti to the oximido hydroxyl function always migrates[15] (Fig. 1). As a result of this stereospecificity, the Beckmann rearrangement has been successfully employed to demonstrate the geometrical isomerism exhibited by unsymmetrically substituted oximes. The configurational assignments of such oximes have been determined on the basis of the structures of the rearrangement products obtained from both oxime isomers.

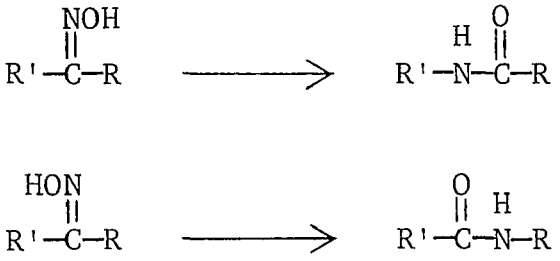


Fig. 1. The Beckmann Rearrangement of Unsymmetrically Substituted Oximes

Due to the high degree of stereospecificity exhibited by the Beckmann rearrangement, an optically active molecularly dissymmetric molecule such as 1-methyl-2,6-diphenyl-4-piperidone oxime (II) should afford an optically active rearrangement product. Further, the optical activity of the Beckmann rearrangement product obtained from such a molecularly dissymmetric molecule should be attributed to atomic asymmetry rather than to molecular dissymmetry. The presence of enantiomeric carbon atoms at the C-2 and C-6 positions in II provides centers of mirror image configuration to which the configuration of the oximido hydroxyl function may be related. Hence, establishment of the stereochemistry of the Beckmann

rearrangement product of (+)-II should not only provide a method for assigning the configuration of the oximido hydroxyl function with respect to one of the enantiomeric centers, but also should provide a method for ascertaining the absolute configuration of the optically active oxime itself. Such a correlation would, in effect, relate the absolute configuration of a molecularly dissymmetric molecule to a molecule whose optical activity was due to atomic asymmetry and thereby provide a method of establishing the absolute configuration of a class of compounds exhibiting optical activity due to the unique type of molecular dissymmetry, geometrical enantiomorphic isomerism.

The well-established mechanism of the Beckmann rearrangement has permitted its application in determining the stereochemistry of many unsymmetrically substituted oximes and has been successfully applied to alicyclic ketoximes.[14,15] Most nitrogen heterocyclic ketoximes[15-17], including II[12], have failed, however, to yield identifiable rearrangement products when subjected to the usual acidic Beckmann rearrangement conditions. On the other hand, under basic rearrangement conditions similar to those described by Brown[18], racemic 1-methyl-2,6-diphenyl-4-piperidone oxime (II) has been demonstrated to undergo a normal Beckmann rearrangement to yield the product expected from a cyclic ketoxime, a cyclic amide, 1,4-diaza-1-methyl-2,7-diphenyl-5-cycloheptanone (III).[13] Employing a modification of the procedure described by Brown[18], (+)-II, $[\alpha]^{24}D$ +28.9°, after treatment with benzene sulfonyl chloride in sodium hydroxide, gave a levorotatory Beckmann rearrangement product, III, $[\alpha]^{24}D$ -6.36°. Since the Beckmann rearrangement requires a migration of the group <u>trans</u> to the oximido hydroxyl function with concomitant migration of the alkyl group, the structure of the Beckmann rearrangement pro-

duct obtained from (+)-II may be represented by IIIa or its mirror image IIIb (Fig. 2).

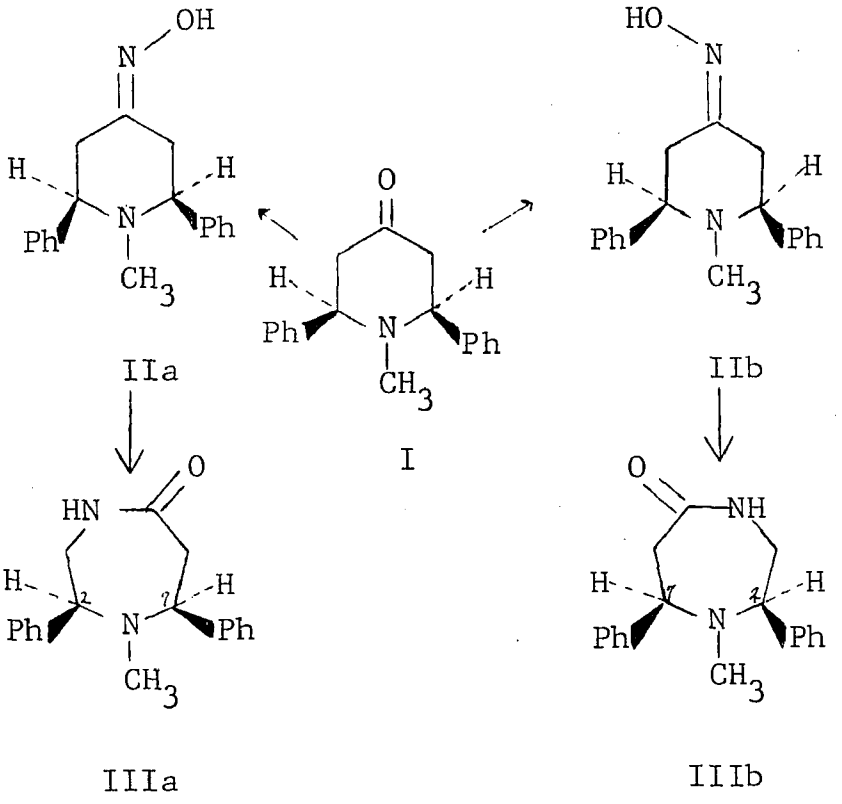


Fig. 2. The Beckmann Rearrangement of 1-Methyl-2,6-diphenyl-4-piperidone Oxime

Degradation of 1,4-Diaza-1-methyl-2,7-diphenyl-5-cycloheptanone

The isolation of a levorotatory lactam (III) from the base catalyzed Beckmann rearrangement of (+)-II, indicated that the rearrangement had proceeded stereospecifically without racemization of the optically active oxime II in the reaction medium. If the stereochemistry of the amide, (-)-III, obtained from the Beckmann rearrangement of (+)-II, were established by a simple degradative procedure, the configuration of the oximido

hydroxyl group of (+)-II could be ascertained. Since the mechanism of the Beckmann rearrangement should not affect the configuration at the enantiomeric centers (C-2 and C-7 in III) of the oxime II, configurational assignment of the oximido hydroxyl group may be designated as either syn or anti with respect to the appropriate enantiomeric center. Degradation of (-)-III should yield an optically active compound whose absolute configuration may be related, by chemical and/or physical methods[19], to a compound of established absolute configuration and, therefore, could possibly be used to establish the absolute configuration of the dextrorotatory isomer of II.

Preliminary studies concerned with the reactivity of II[13] indicated III was resistant to exhaustive methylation and N-oxide formation as a result of the steric hindrance imparted on the free electron pair of the tertiary amino nitrogen by the adjacent bulky phenyl substituents. Due to the lack of reactivity at the tertiary amino nitrogen of III, the Hofmann and Cope procedures[20] normally utilized for the step-wise degradation of nitrogen heterocyclics were unsuitable methods by which a degradation of III could be accomplished. Under acidic conditions, however, hydrolysis of the amide linkage of III had been shown to occur along with cleavage of the C-7, nitrogen bond. The only nitrogen-containing product isolated from this hydrolytic cleavage reaction was identified as β-(N'-methylamino)-β-phenylethylamine (IV)[13], and on this basis it appeared likely that a one-step hydrolytic degradation of (-)-III could possibly be accomplished to yield an optically active compound with which the configuration of the oximido hydroxyl group of (+)-II could be correlated.

Employing a modification of the acidic hydrolysis

conditions described by Dickerman and Lindwall[17], (-)-III, $[\alpha]^{23}D$ -6.36°, after treatment with 20% hydrochloric acid, gave levorotatory β-(N'-methylamino)-β-phenylethylamine (IV), $[\alpha]^{24}D$ -6.77°, along with a high yield of cinnamic acid (Fig. 3). A solid bis-phenylthiourea, which was subsequently demonstrated to be dextrorotatory, was obtained on treatment of (-)-IV with phenyl isothiocyanate. These results suggested that a one-step hydrolytic degradation of the stereospecifically synthesized lactam, (-)-III, could possibly afford a chemical means of ascertaining the absolute configuration of (+)-II, a molecularly dissymmetric molecule.

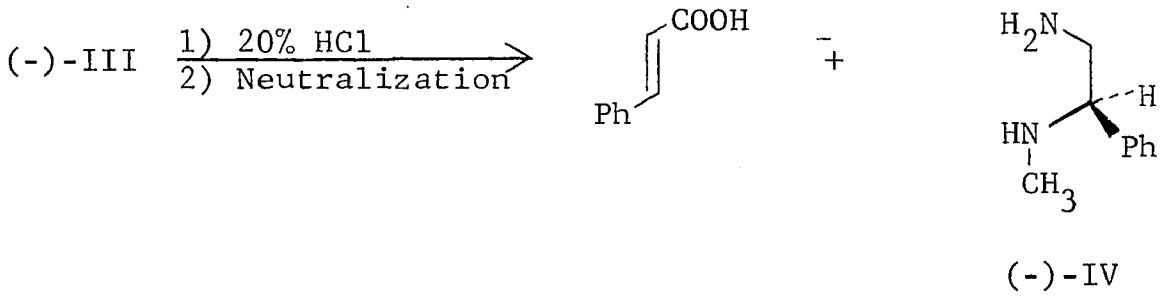
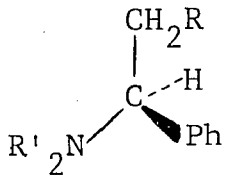


Fig. 3. Acid Hydrolysis of (-)-1,4-Diaza-1-methyl-2,7-diphenyl-5-cycloheptanone

Isolation of levororotatory β-(N'-methylamino)-β-phenylethylamine (IV) from the acid hydrolysis indicated that cleavage of the amide linkage, as well as the C-7, nitrogen bond of (-)-III, had occurred without racemization of one of the asymmetric centers. Since (-)-IV is the N'-methyl derivative of α-phenylethylenediamine, a comparison of the D-line rotation of (-)-IV with the D-line rotations of α-phenylalkylamines of established configuration should theoretically predict the stereochemistry of (-)-IV. Table I indicates that the D-line rotation of (-)-IV, isolated from the hydrolysis of

TABLE I



D-Line Rotations of α-Phenylalkylamines[21,22]

R	R'	[α]D	[α]D, HCl
H	H	-29.3°	-6.0°[a]
OH	H	-	-26.3[b]
Ph	H	+47.9	+128[a]
NH_2	H	-27.5	+17.9
COOH	H	-6.9	-
COOH	CH_3,H	-19.3	+1.7
COOH	CH_3	-8.6	-9.2
$COOC_2H_5$	CH_3	-15.5	-9.4
NH_2	CH_3	-6.77[c]	-

[a] G. G. Lyle, J. Org. Chem., 25, 1779 (1960).

[b] R. Lukes, J. Kovar, J. Kloubek, and K. Blaha, Chem. Listy, 51, 1501 (1957); C.A. 52, 1100 (1958).

[c] This Thesis.

(-)-III, may best be compared with the D-line rotation of β-phenylethylenediamine.[21] Since the D-line rotations of both of these compounds, (-)-IV and α-phenylethylenediamine, are in the same direction, the configuration of these two diamines should be comparable. Further examination of Table I, however, suggests that the introduction of a methyl substituent on an amino nitrogen may alter the D-line rotation, for a change in levorotatory power was noted in the case of β-amino hydrocinnamic acid and its mono and dimethylamino derivatives respectively.[22] Although Arpesella and co-workers[21] have chemically demonstrated the configurational relationships of a number of α-phenylethylenediamine derivatives, failure to include the corresponding N'-methyl analogues in their tabulations necessitated the utilization of a chemical method of establishing, unequivocally, the configuration of the levorotatory β-(N'-methylamino)-β-phenylethylamine obtained from the acid hydrolysis of (-)-III.

Attempted Syntheses of β-(N'-Methylamino)-β-phenylethylamine

Perhaps the most valuable method available for establishing the absolute configuration of an optically active compound of unknown configuration is by a comparison of the D-line rotation of the unknown with the D-line rotation of a compound of established configuration. Generally, this method of determining absolute configuration involves a stereospecific synthesis of the unknown compound from an optically active compound of established configuration. Inspection of the structural formula of IV suggests that the β-(N'-methylamino)-β-phenylethylamine (IV), isolated from the acid hydrolysis of III, may be obtained from an optically active amino acid of established absolute configuration, namely,

α-aminophenylacetic acid (V). A series of reactions which would not destroy the asymmetry of V was proposed and the feasibility of these reactions tested with racemic α-aminophenylacetic acid (V), (Fig. 4).

Attempts to synthesize the diamide VII by a reaction sequence involving initial conversion of the carboxylic acid group to the amide VI followed by formylation of the amino nitrogen of V proved unsuccessful. Attempts to prepare α-aminophenylacetamide (VI) by the usual procedure (thionyl chloride followed by ammonia) resulted only in the isolation of the hydrochloride of V and path A (Fig. 4) was, therefore, abandoned.

Since the diamine (IV) isolated from the acid hydrolysis of III possesses a mono-methylamino as well as a primary amino function, experiments were designed to provide a method of synthesizing α-methylaminophenylacetic acid (VIII) and then converting the carboxylic acid function of VIII to the corresponding amide. Subsequent reduction of α-methylaminophenylacetamide (IX) would yield the stereospecifically synthesized IV. Substitution of the hydrogen atoms of a primary amine by alkyl groups usually leads to the successive formation of secondary and tertiary amines, and the product isolated from such reactions usually consists of a mixture of both types of amines. This difficulty may, however, be overcome by effecting the alkylation on a suitable amine derivative, which after hydrolysis, yields the desired secondary amine. Since benzenesulfonamides have been used for such types of secondary amine syntheses[23,24], it appeared reasonable that the benzenesulfonamide of V could be utilized in a similar manner to yield VIII. The benzenesulfonamide of V was therefore prepared according to the standard procedure[25]

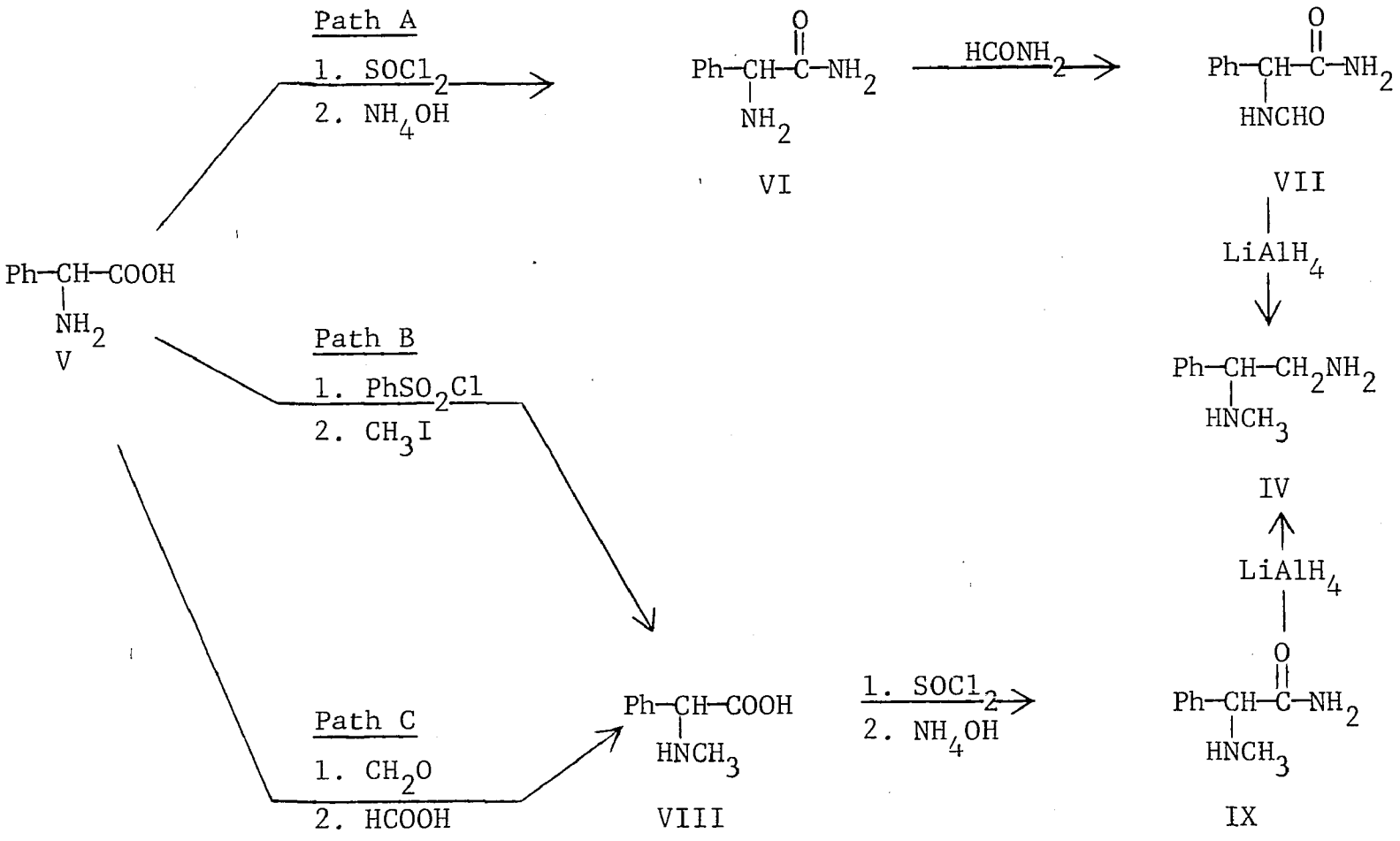


Fig. 4. Proposed Syntheses of β-(N'-Methylamino)-β-phenylethylamine

and subsequently treated with methyl iodide.[23,24] Hydrolysis of the reaction mixture, however, resulted only in the isolation of the hydrochloride of V, and path B (Fig. 4) was abandoned.

A method specifically employed for the synthesis of methylamino compounds is known as the Eschweiler-Clarke procedure.[26] This reaction involves the treatment of an amino compound with a formic acid-formaldehyde mixture, and, depending on the ratio of aldehyde to acid, yields secondary or tertiary amines as products. When V was subjected to Eschweiler-Clarke reaction conditions, only unidentifiable tars and oils were obtained. The absence of infrared absorption bands in the region of 1660-1600 $cm.^{-1}$ along with the appearance of a carbonyl band at 1704 $cm.^{-1}$ in the infrared absorption spectra of the product mixtures obtained from this reaction indicated that decomposition of V had occurred. Clarke and co-workers[27] have observed this type of decomposition with several amines in which the carbon atom bearing the amino function was also attached to polar groups. In the examples reported[27], a mixture of decomposition and condensation products of varying degrees of complexity was usually obtained along with volatile bases. These investigators obtained benzaldehyde as one of the products from the treatment of α-aminophenylacetic acid with a mixture of formaldehyde in acetic acid. The presence of a carbonyl band at 1704 $cm.^{-1}$ in the infrared absorption spectra of the oils obtained when V was subjected to similar treatment with formic acid may be attributed to the presence of benzaldehyde, since this would be the expected non-volatile product if the decomposition of V proceeded as described by Clarke[27] (Fig. 5).

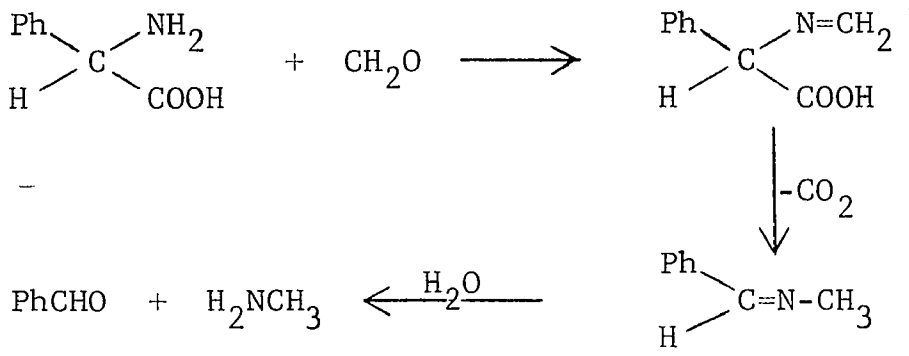
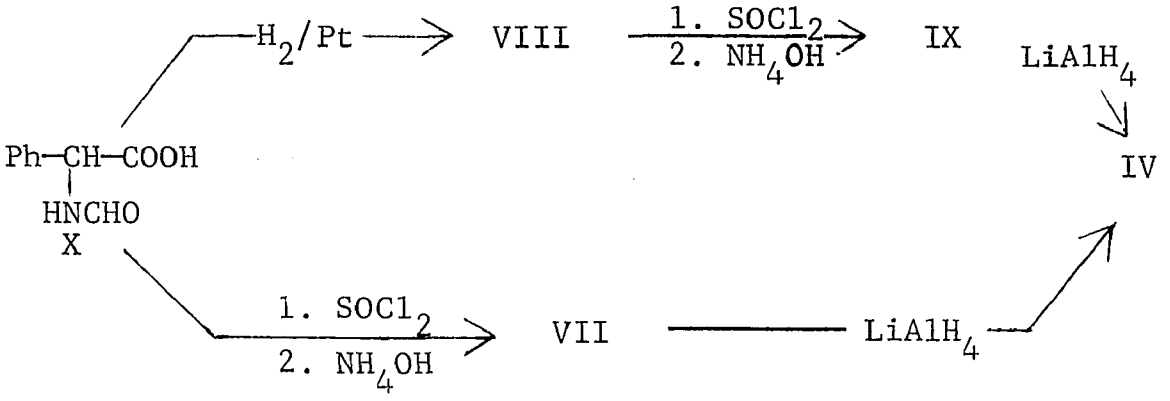


Fig. 5. Mechanism of the Decomposition of α-Aminophenylacetic Acid Under Eschweiler-Clarke Conditions[27]

Formyl derivatives of primary amines are stable substances and may be heated to temperatures in the neighborhood of 200° without undergoing decomposition. Since the N-formyl derivative (X) of α-aminophenylacetic acid had been prepared by Fischer and Weichold[28], a synthetic sequence involving X as an intermediate was designed as an alternate method of obtaining IV. Two possible pathways involving X as intermediate were investigated as possible synthetic routes to β-(N'-methylamino)-β-phenylethylamine (IV). Catalytic reduction of the formyl group of X to the corresponding α-methylamino acid VIII, followed by conversion of VIII to the amide IX and subsequent reduction could possibly lead to IV. Alternatively, reduction of VII which could be obtained from X by the standard procedures for the preparation of amides would also be a plausible route for the synthesis of IV.



Successive treatment of α-aminophenylacetic acid (V) with formic acid, according to the procedure described by Fischer and Weichold[28], gave a solid derivative whose melting point was consistent with that of the N-formyl derivative of V described by these early investigators. The infrared absorption spectrum of the product isolated from this reaction was consistent with X showing absorption bands at 3390 $cm.^{-1}$ characteristic of the NH stretching frequency along with strong absorptions at 1697 $cm.^{-1}$ indicative of the carbonyl stretching frequency of the N-formyl carbonyl, a doublet at 1645 $cm.^{-1}$ characteristic of the carboxylic acid carbonyl stretching frequency of the amino acid, along with the usual absorption bands associated with a mono-substituted phenyl ring.[29] Attempts to reduce catalytically the N-formyl function of X in order to obtain the corresponding α-methylamino acid VIII proved unsuccessful resulting only in the isolation of the starting amino acid V. Successive treatment of X with thionyl chloride and ammonia, an alternate method for the preparation of the amide VII again resulted in quantitative recovery of V. The N-formyl group of X is apparently very sensitive to hydrolysis, for purification of X by recrystallization from water or solvents containing small amounts of water resulted in hydrolysis of the formyl moiety and again

resulted in quantitative recovery of the amino acid V.

Synthesis of β-(N'-Methylamino)-β-phenylethylamine

Because of the experimental difficulties encountered by the introduction of the N-formyl group in the initial steps of the reaction sequence directed towards the synthesis of β-(N'-methylamino)-β-phenylethylamine (IV), a reaction scheme was proposed whereby introduction of the N-formyl substituent would occur in the final steps of the reaction sequence and thereby minimize the possibility of its undergoing hydrolysis, for the final step in this series of reactions required an anhydrous reaction medium (Fig. 6).

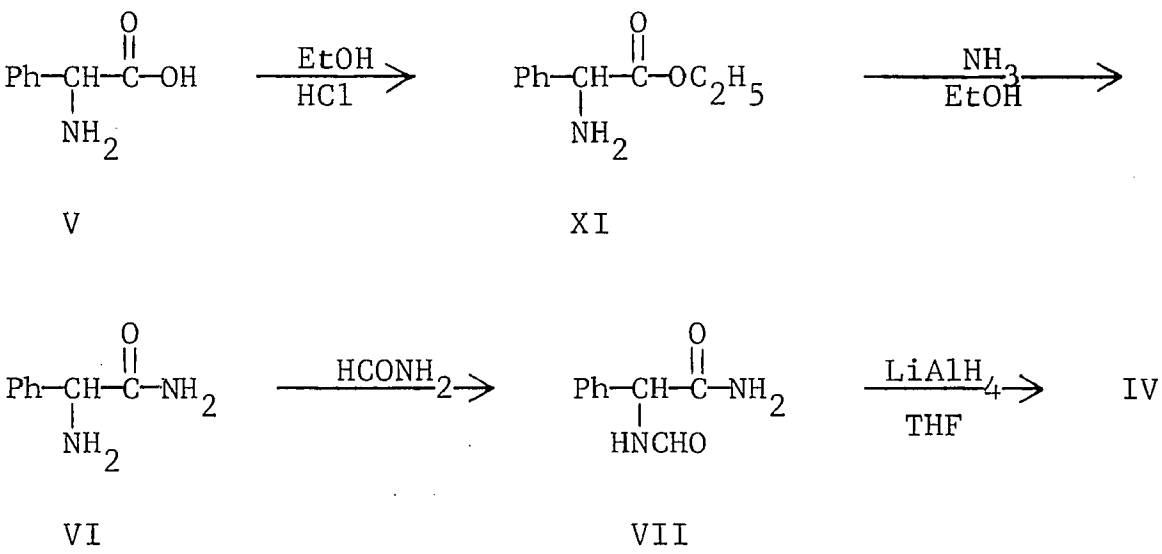


Fig. 6. Synthesis of β-(N'-Methylamino)-β-phenylethylamine

The ethyl ester hydrochloride of V was readily obtained by bubbling an excess of anhydrous hydrogen chloride into an anhydrous suspension of the amino acid V in ethanol, a procedure previously described by Kossel.[30] Neutralization of an aqueous solution of the ester hydrochloride of XI afforded

ethyl α-aminophenyl acetate (XI) which was subsequently converted to the amide VI by treatment with anhydrous ammonia.[31] A modification of the procedure described by Lyle and Lacroix[32] for the formylation of 2-amino-1,2-diphenylethanol led to the isolation of a solid product whose melting point and spectral properties differed from those of any of the starting compounds. The infrared absorption spectrum of the product isolated from this reaction showed bands at 3350, 3275 and 3190 $cm.^{-1}$ characteristic of the NH stretching frequency of primary and secondary amides, two bands in the carbonyl region at 1690 and 1665 $cm.^{-1}$ characteristic of the secondary and primary amide carbonyl stretching vibrations respectively, along with bands associated with a mono-substituted phenyl ring.[29] Mass spectrometric analysis of the isolated product indicated a molecular weight peak at 178 mass units and analysis was consistent with the expected N-formylated product, α-formamidophenylacetamide (VII) (Fig. 7).

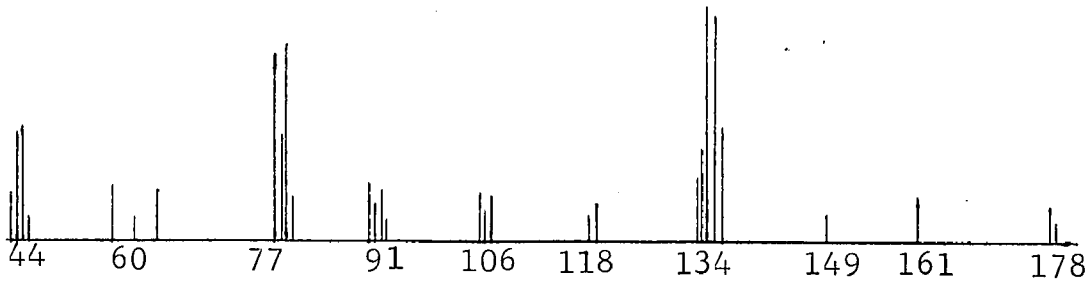


Fig. 7. Mass Spectrum of α-Formamidophenylacetamide

The fragmentation patterns of a number of compounds which have been subjected to mass spectrometric analysis have been determined and general rules established to explain the prominent peaks observed and those expected for certain types of compounds subjected to such analysis.[33,34] Gilpin[35] has studied the mass spectral fragmentation patterns exhibited by a number of aliphatic amides and found that the peak at highest mass corresponded to the molecular weight of the amide. From the data obtained, Gilpin[35] was able to determine the types of fragmentation and rearrangement ions which typified primary, secondary, and teriary aliphatic amides and on this basis established a number of generalizations which could possibly be employed in the characterization of unknown aliphatic amides from their mass spectral data. The mass spectrum of α-formamidophenylacetamide (VII) was expected to exhibit a fragmentation pattern similar to those observed for some of the amides studied by Gilpin.[35] The presence of two different types of amide groups, a primary and a secondary, at the asymmetric carbon atom, coupled with the fact that the asymmetric carbon is also a benzyl carbon atom, complicated the interpretation of the fragmentation pattern observed for VII (Fig. 7).

The presence of a peak at 178 m/e units is consistent with the molecular weight of VII, the expected N-formylated product. The presence of two amide functions at the benzyl carbon atom leads to three possible pathways (Fig. 8) by which fragmentation of VII could occur to lead ultimately to a benzyl ion, m/e 90. Further, since the molecular weights of both amide functions of VII are the same, fragmentation attributed to cleavage of the benzyl-N-formyl bond (Path (c), Fig. 8) cannot be differentiated from a pathway involving cleavage of the benzyl-primary amide bond (Path (b), Fig. 8).

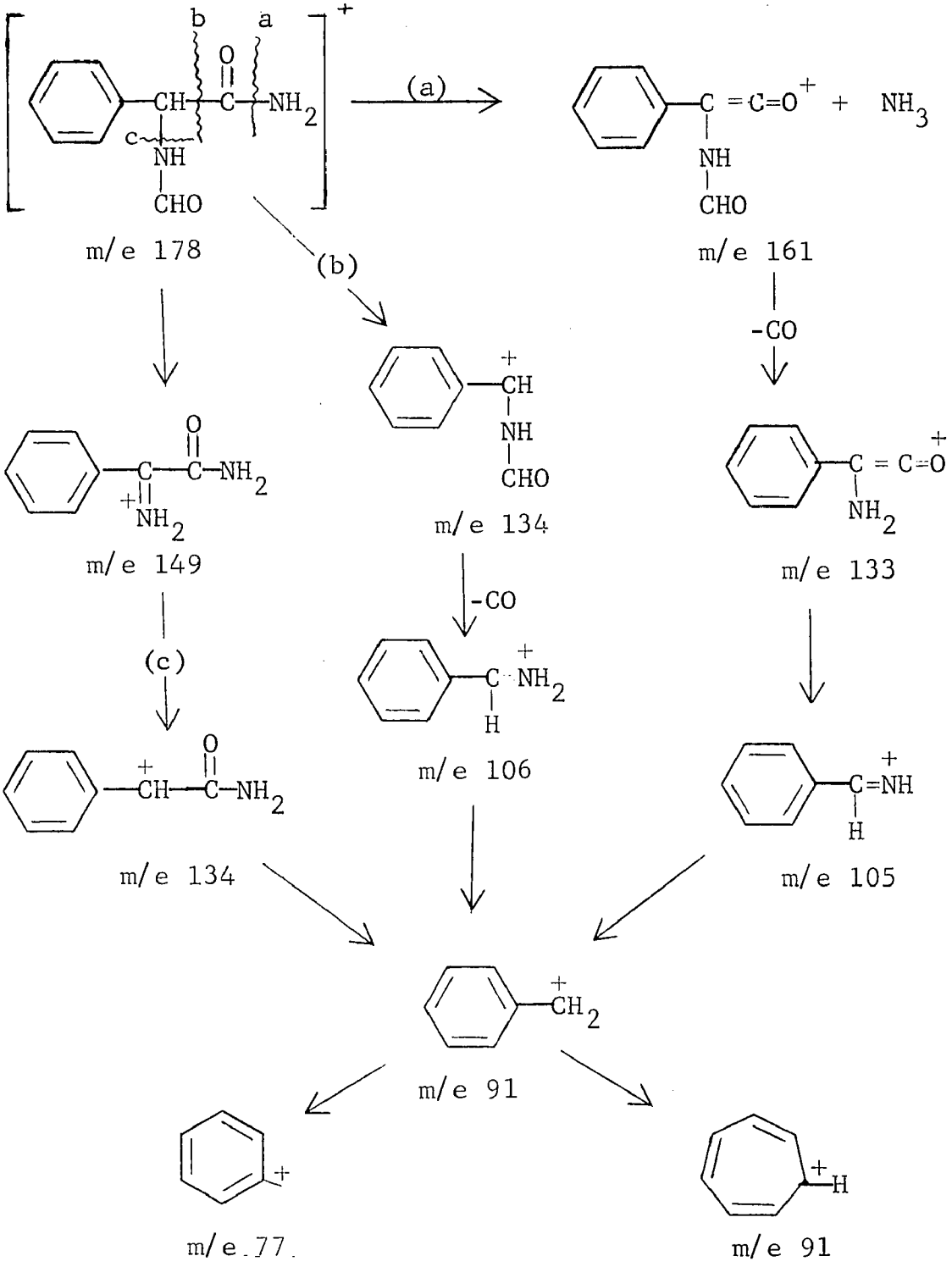


Fig. 8. Mass Spectral Fragmentation Pattern of α-Formamidophenylacetamide

The absence of a peak at M-28 m/e or 150 m/e units suggests that elimination of carbon monoxide does not occur initially, though a relatively weak peak at 149 m/e might indicate some loss of CHO and thereby suggest that some fragmentation of VII occurred by Path (c). On the other hand, the presence of a peak at 161 m/e, consistent with the elimination of ammonia from VII, indicates that fragmentation also occurred by Path (a). The three fragmentation pathways illustrated in Fig. 8 include ions of m/e 133 or 134 which might account for the most intense peaks in the spectrum. These ions would be resonance stabalized and would ultimately undergo further bond cleavage to the benzal ion m/e 91. The presence of a peak at 44 m/e, whose molecular weight corresponds to a $CONH_2$ or HNCOH fragment, could arise by cleavage at either (b) or (c) and does not facilitate the establishment of a definitive fragmentation pattern for VII. Nevertheless, the structure of VII is upheld by the mass spectral data for the peaks, though their origin from VII remains undefined, correspond to ions which would be expected from mass spectrometric analysis of VII.

Synthesis of (-)-β-(N'-Methylamino)-β-phenylethylamine

The series of reactions outlined in Fig. 6 was designed in a manner such that the asymmetric center of V would not be destroyed; hence, use of optically active α-aminophenylacetic acid (V) as starting material, would be expected to yield optically active β-(N'-methylamino)-β-phenylethylamine (IV) of known absolute configuration.

Treatment of an anhydrous suspension of D-(-)-α-aminophenylacetic acid (V) in ethanol, with anhydrous hydrogen chloride resulted in the isolation of the levorotatory ester XI (Fig. 9) which was immediately converted to a levorotatory

amide VI. Formylation of (-)-α-aminophenylacetamide (VI) with formamide afforded a levorotatory N-formyl derivative (VII) whose infrared spectrum and melting point were identical to that of racemic α-formamidophenylacetamide (VII). Subsequent lithium aluminum hydride reduction of (-)-VII afforded a levorotatory diamine which was identical to (-)-β-(N'-methylamino)-β-phenylethylamine (IV) isolated from the acid hydrolysis of (-)-1,4-diaza-1-methyl-2,7-diphenyl-5-cycloheptanone (III). The diamine (IV) obtained from the reaction sequence outlined in Fig. 9, afforded a dextrorotatory bis-phenylthiourea which was identical in every respect to the derivative obtained from the diamine isolated from the acid hydrolysis of (-)-III. The configuration of (-)-IV obtained from the alternate synthesis should be as illustrated by the Fischer projections in Fig. 9.

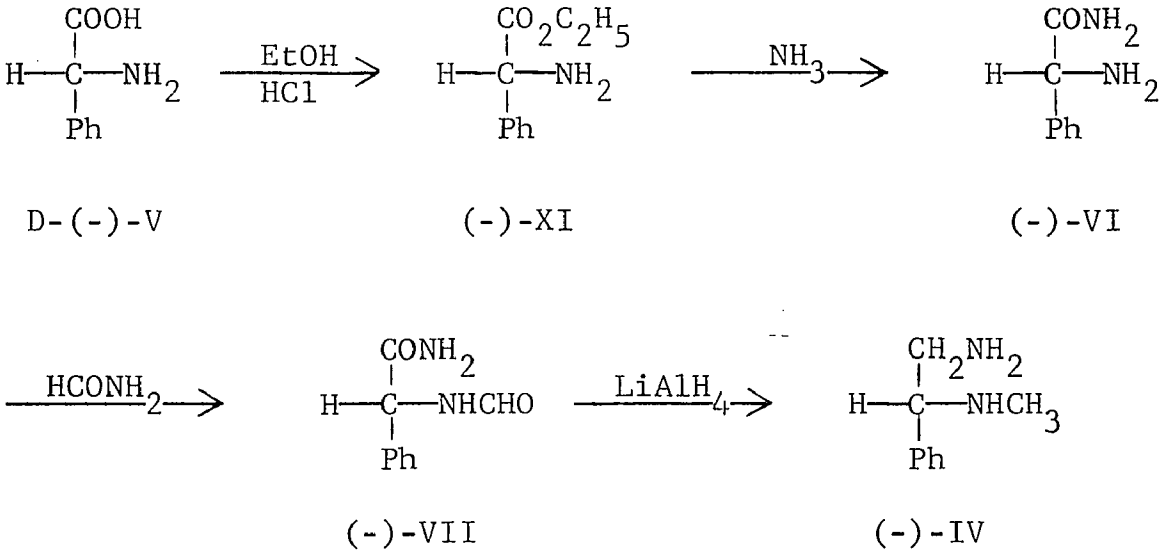


Fig. 9. Synthesis of (-)-β-(N'-Methylamino)-β-phenylethylamine from D-(-)-α-Amino-phenylacetic Acid

The optical rotatory dispersion curves[36] of the derivatives of D-(-)-α-aminophenylacetic acid (V) utilized for the alternate synthesis of (-)-IV are shown in Fig. 10. One of the outstanding features of the optical rotatory dispersion curves of these derivatives is the striking decrease in levorotatory power noted on conversion of the carboxylic acid group of (-)-V to an ester, amide and amine respectively. The optical rotatory dispersion curve of D-(-)-α-aminophenylacetic acid (V) has a molecular rotation of 2,500° at 300 mμ, whereas the molecular rotation of α-aminophenyl acetate (XI), the ethyl ester of V, is of the order of 1900° at this same wavelength. Substitution of the carboxylic acid function of V by an amide group decreases the levorotatory power further for (-)-α-aminophenylacetamide (VI) has a molecular rotation of only 400° at 300 mμ. The most striking decrease in rotatory power observed in this series of amino acid derivatives was the 12° molecular rotation exhibited by α-formamidophenylacetamide (-)-VII at 300 mμ. The relatively weak molecular rotation exhibited by (-)-VII at 300 mμ may be attributed to the fact that a degree of symmetry is imparted on the system by the introduction of the N'-formyl substituent. The presence of two similar, but not identical, amide substituents separated only by the asymmetric carbon atom in (-)-VII may increase the symmetry of the molecule and thus result in a significant decrease in its rotatory power.

The Absolute Configuration of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime

Knowledge of the mechanism by which (+)-II was converted to (-)-III requires that the structure of (-)-III be as indicated in Fig. 2. A comparison of the D-line rotations

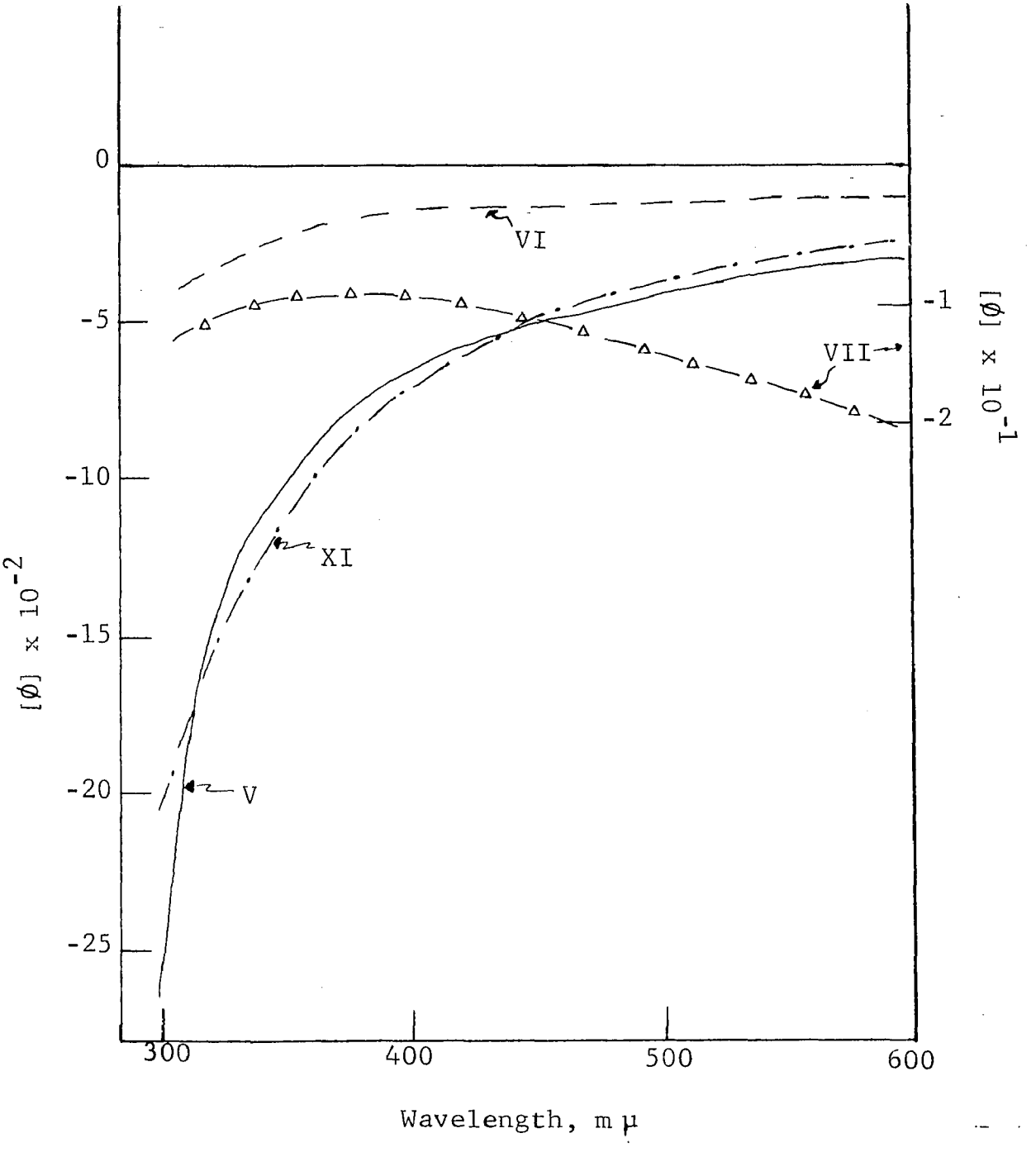


Fig. 10. Optical Rotatory Dispersion Curves of D-(-)-α-Aminophenylacetic Acid (——), Ethyl α-Aminophenyl Acetate (-·-·-), α-Aminophenylacetamide (---), and α-Formamidophenylacetamide (-Δ-Δ-)

of (-)-β-(N'-methylamino)-β-phenylethylamine (IV) isolated from the acid hydrolysis of (-)-III with the D-line rotation of (-)-IV obtained by a stereospecific alternate synthesis from a compound of established configuration chemically establishes the absolute configuration of the amine (-)-IV. These facts then permit the assignment of the absolute configuration of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (II).

The stereospecific synthesis of (-)-β-(N'-methylamino)-β-phenylethylamine (IV) from D-(-)-α-aminophenylacetic acid (V) indicated that the absolute configuration of the diamine (-)-IV isolated from the reaction sequence illustrated in Fig. 9 to be R.[37] The similar rotations exhibited by the diamines obtained from these different reaction sequences suggested that they were of the same absolute configuration. The fact that dextrorotatory bis-phenylthiourea derivatives were obtained from both of these diamines unequivocally establishes the similarity of their stereochemical relationship. On the basis of these results the configuration of the levorotatory lactam (-)-III, obtained from the Beckmann rearrangement of (+)-II, is established to be as illustrated in Fig. 11. Consequently, the asymmetric carbon atom of (-)-III from which the R-diamine, (-)-IV, was derived by acid hydrolysis must be located at C-2 of IIIb (Figs. 2, 11). The mechanism of the Beckmann rearrangement by which the lactam IIIb was prepared, has been demonstrated to proceed by a *trans* migration of the methylene group *anti* to the oximido hydroxyl function and therefore should not affect the configuration at the enantiomeric carbon atoms (C-2 and C-6) of (+)-II. Since the R-diamine (-)-IV has been demonstrated to arise from the C-2 asymmetric center of (-)-IIIb, from a consideration of the mechanism of the Beckmann

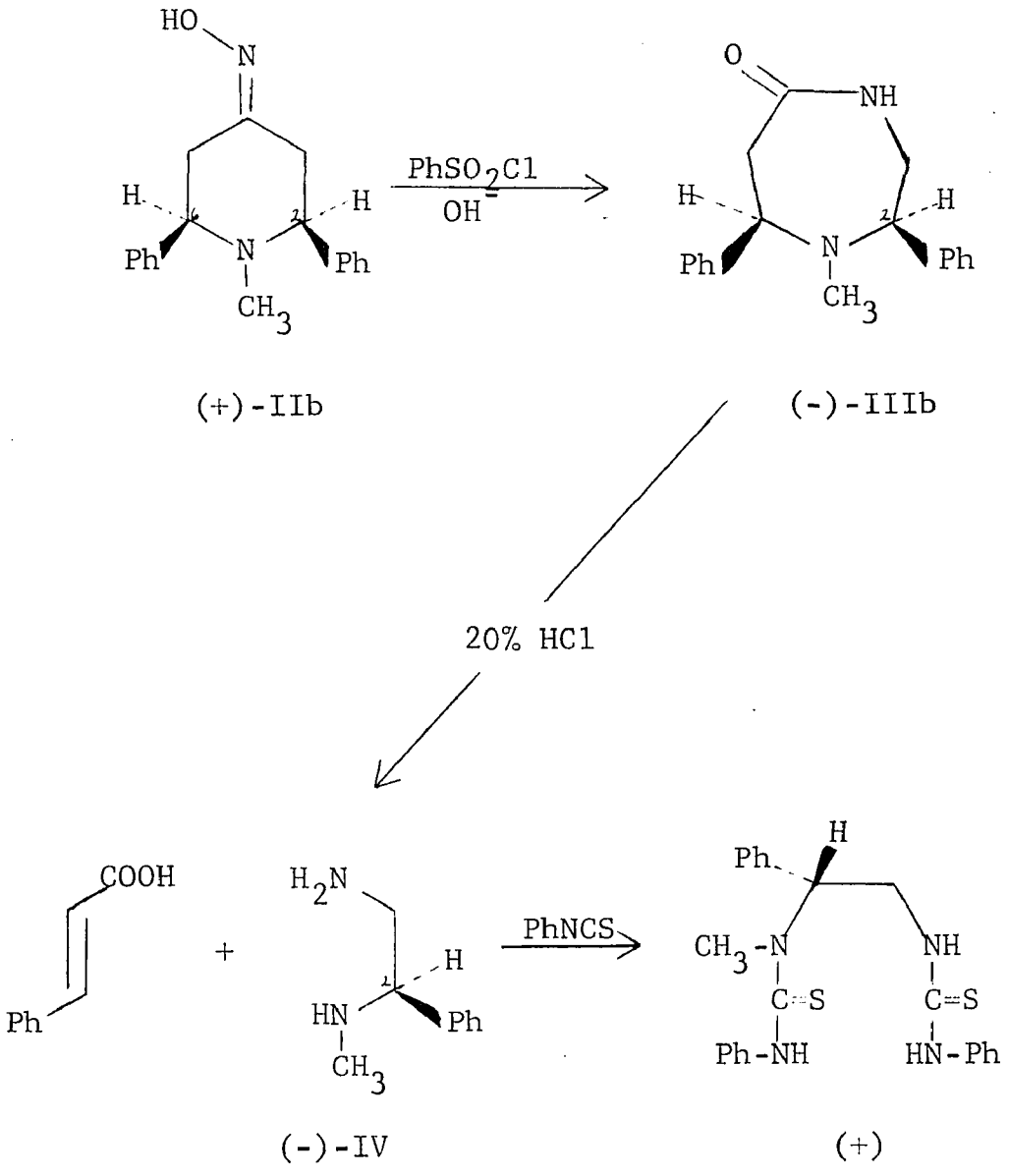


Fig. 11. Configurational Relationship of (-)-β-(N'-Methylamino)-β-phenylethylamine (IV), (-)-1,4-Diaza-1-methyl-2,7-diphenyl-5-cycloheptanone (IIIb), and (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime (IIb)

rearrangement, it follows that this asymmetric center must be located at C-2 of (+)-II. On the basis of the experimental evidence obtained from the stereospecific alternate synthesis of (-)-β-(N'-methylamino)-β-phenylethylamine (IV) (Fig. 12), the Syn-R configuration was assigned to the dextrorotatory isomer of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (IIb) and thus provided the first example of absolute configurational assignment of a molecule exhibiting optical activity due to a unique type of molecular asymmetry, geometrical enantiomorphic isomerism.

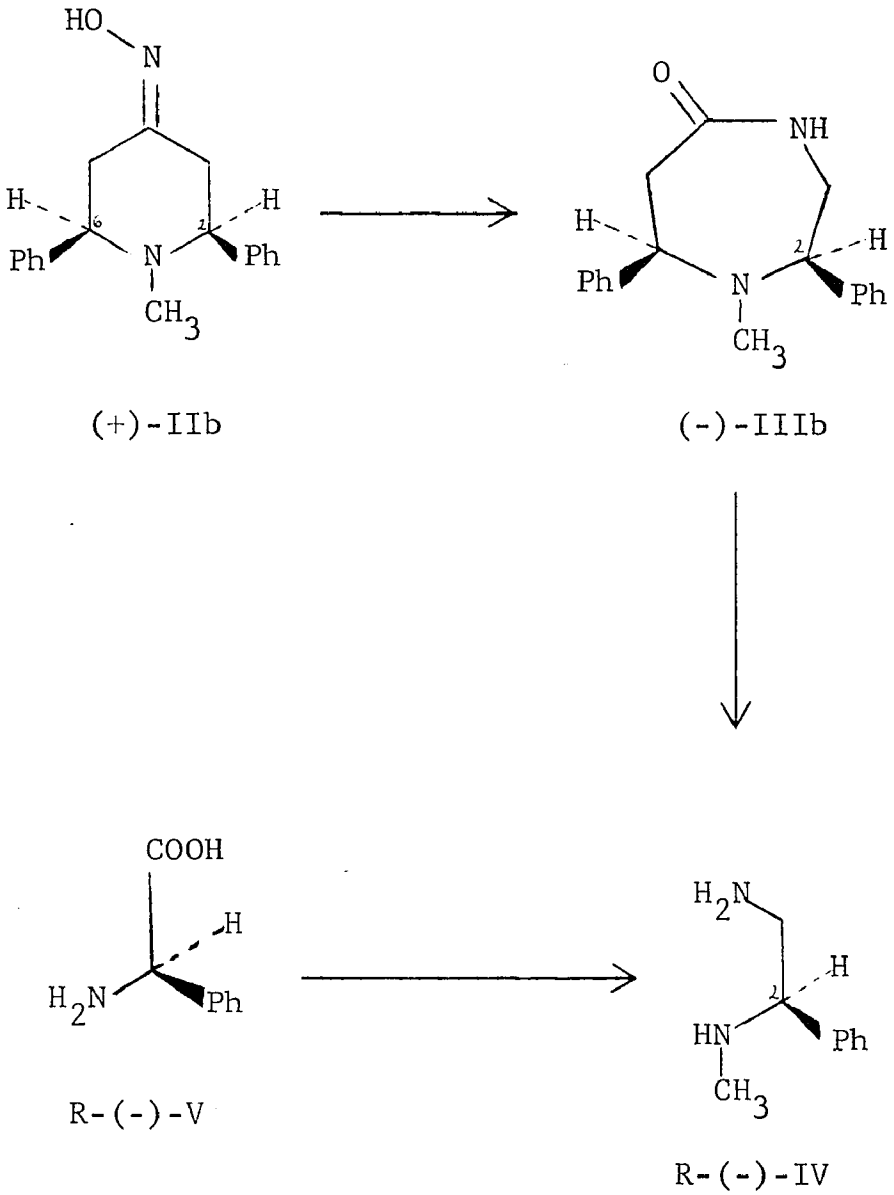


Fig. 12. The Stereochemical Relationship of R-(-)-α-Aminophenylacetic Acid and (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime

THE NEBER REARRANGEMENT

OF

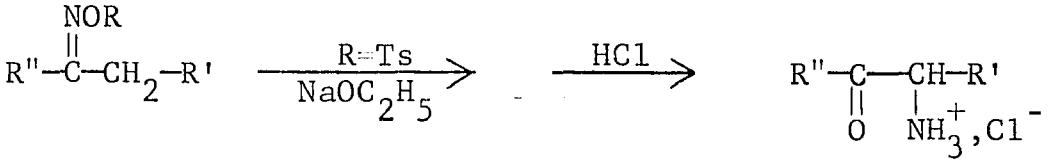
(+)-1-METHYL-2,6-DIPHENYL-4-PIPERIDONE OXIME TOSYLATE

DISCUSSION

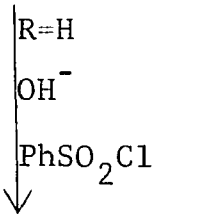
The first report describing the base catalyzed rearrangement of oxime arylsulfonate esters to α-amino ketones, designated the Neber rearrangement after its discoverer, appeared in the literature almost forty years ago.[38] The scope and mechanism of this rearrangement were described during the ten years following this initial report in a series of papers by Neber and his co-workers.[39-42] In general, the reaction may be summarized as the treatment of an alkyl-aryl, heterocyclic or homocyclic oxime arylsulfonate ester with anhydrous base followed by acid hydrolysis to produce an α-amino ketone, isolated as its hydrochloride salt. Conversion of the salt to the free base results in the isolation of pyrazine derivatives which arise from condensation of the primary reaction products. Rediscovery of the reaction in 1953 by Cram and Hatch[43,44] led to further investigation of its mechanism as well as to the recognition of its applicability to the synthesis of α-amino ketones unobtainable by the more conventional methods.

The reaction conditions utilized in effecting the Neber rearrangement are similar, but not identical, to those employed in effecting the Beckmann rearrangement of certain oximes. Brown and co-workers[18] have demonstrated that treatment of an oxime with a catalytic amount of benzenesulfonyl chloride in aqueous base produced an amide, the product of a normal Beckmann rearrangement. Similar reaction conditions have, however, caused a "second order Beckmann" reaction to occur in the case of certain oximes.[45] The Neber rearrangement is effected by initial conversion of the oxime to its

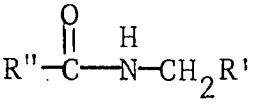
arylsulfonyl ester which on treatment with strong, anhydrous base yields α-amino ketones; the Beckmann rearrangement, on the other hand, occurs in an aqueous medium in the presence of an arylsulfonyl chloride catalyst.

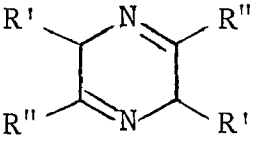


No particular configuration

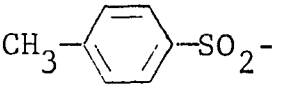


and/or

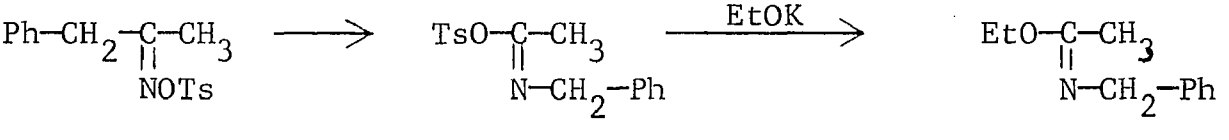




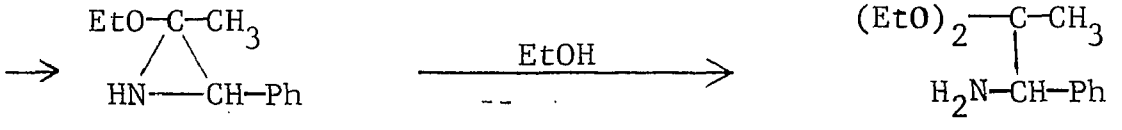
A dihydropyrazine

Ts = 

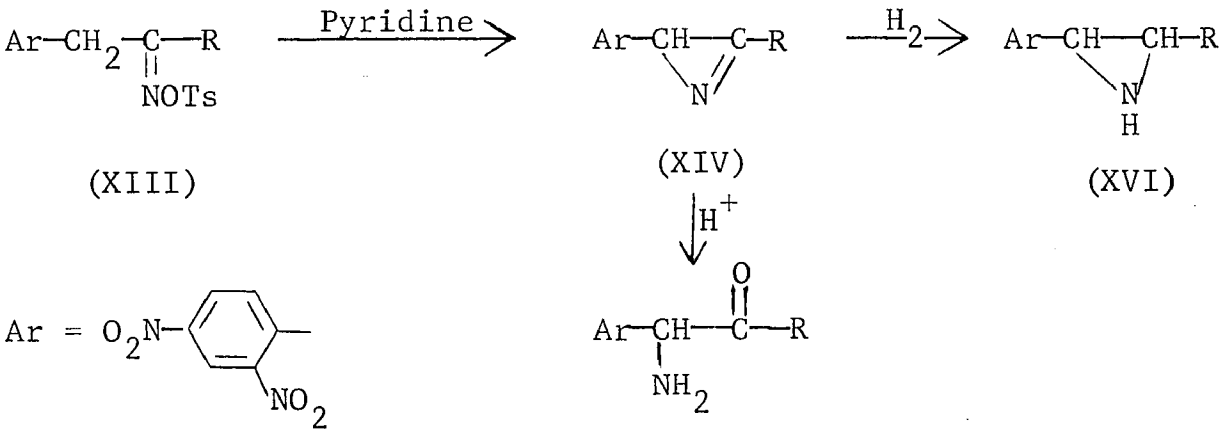
From the results obtained from his investigation of the oxime tosylate of 1-phenyl-2-propanone (XII), Neber[39] suggested that the rearrangement proceeds via a Beckmann type rearrangement.



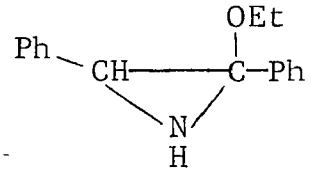
(XII)



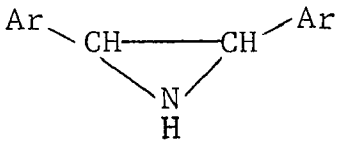
Later investigations[40] which resulted in the isolation of an azirine-pyridine-hydrochloride complex indicated that the rearrangement occurred during the formation of the oxime arylsulfonate esters in the presence of p-toluenesulfonyl chloride in pyridine.[40] The isolation of this complex led Neber and his co-workers to alter their earlier view concerning the mechanism of the reaction and led to the hypothesis that the rearrangement proceeded through an azirine intermediate.[41] In reinvestigating this reaction, Cram and Hatch[43] confirmed the structure of the novel compound isolated by Neber in the following manner: acid hydrolysis of the azirine (XIV) obtained from 2,4-dinitrodesoxybenzoin oxime tosylate (XIII, R=CH_3) gave the corresponding α-amino ketone(XV); reduction of the azirine carbon-nitrogen double bond resulted in the isolation of the corresponding aziridine (XVI), and the position of the double bond in the azirine XIV was confirmed by spectral data.[43]



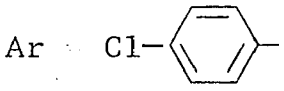
In general, the 2,4-dinitrodesoxybenzoin system should not be considered to be representative of the Neber rearrangement, for the presence of the electron withdrawing nitro substituents increased the acidity of the benzyl hydrogen atoms to the extent that the rearrangement was initiated by the weaker base, pyridine, rather than by an alkali alkoxide. Furthermore, the azirine intermediate XIV of such a system would be expected to exhibit unusual stability due to the resonance stabilization provided by the electron withdrawing nitro substituents. In an attempt to confirm the existence of the azirine intermediate, Hatch and Cram[44] subjected the tosylate of desoxybenzoin oxime to the Neber rearrangement and at low temperatures succeeded in isolating 2,3-diphenyl-2-ethoxy-aziridine (XVII). Further evidence for the existence of the azirine intermediate was obtained by the isolation of 2,3-p,p'-bis(chlorophenyl)-aziridine (XVIII) from the lithium aluminum hydride reduction of the reaction mixture obtained from the Neber rearrangement of p,p'-dichlorodesoxybenzoin oxime tosylate.[44]



(XVII)



(XVIII)



The existence of unsaturated three-membered nitrogen-containing ring systems might seem doubtful due to the strain associated with such a structure; however, such three-membered ring systems have been synthesized and have been demonstrated to undergo acid hydrolysis to α-amino ketones.[46,47] Reaction of phenylmagnesium bromide with oximes has also demonstrated

the occurrence of such three-membered rings as intermediates or products of the reactions of oximes.[48,49]

Cram found that the Neber rearrangement of a ketoxime tosylate having an adjacent methylene group occurred through an unstable ethoxy-aziridine intermediate.[44] The presence of two distinguishable methylene groups adjacent to the oximido function usually resulted in substitution of the amino group for one of the more acidic, alpha protons and, in the majority of cases, the nitrogen of the oximido ester appeared to migrate to the carbon atom <u>trans</u> to the tosylate function. The steric direction of the rearrangement appeared to be <u>cis</u> in those cases in which only one methylene group was available for reactivity. These data led Cram to postulate a "sterically indiscriminate" mechanism[44] for the Neber rearrangement in which the first step could be generalized in terms of a base induced 1,3-elimination reaction (with ring closure) followed by a 1,2-addition reaction, a mechanism similar to that put forth by Neber.[41]

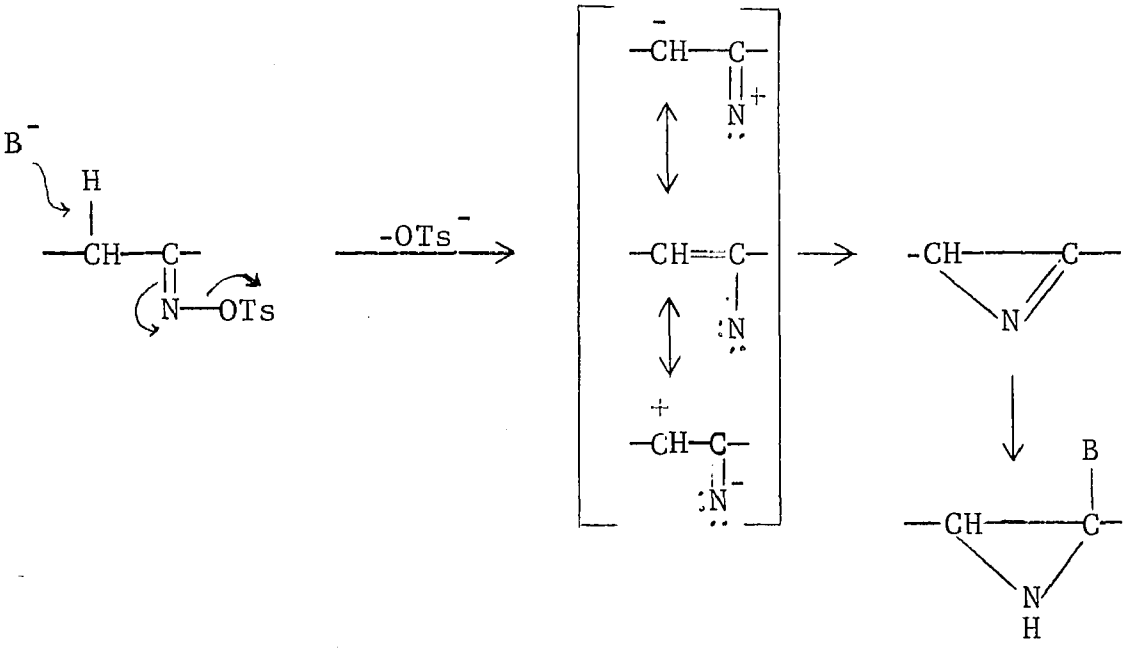
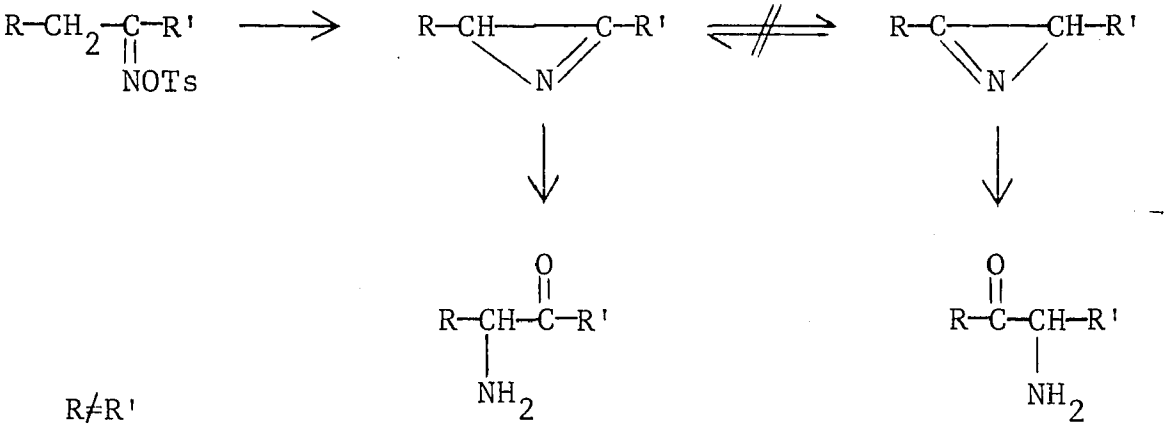


Fig. 13. Mechanism of the Neber Rearrangement Proposed by Cram

During a more recent investigation of the chemistry of oxime derivatives, House and Berkowitz[50] demonstrated the improbability of a symmetrical or a rapidly equilibrating mixture of isomeric azirine intermediates being involved in the rearrangement. The tosylates of several unsymmetrically phenyl-substituted desoxybenzoin oximes of known configuration were prepared and subjected to Neber rearrangement conditions. Isolation of the α-acetamido derivatives of the corresponding ketones from this series of reactions eliminated the possibility that tautomeric equilibration of the azirine intermediate occurred during this rearrangement.



The product usually isolated from the Neber rearrangement of oxime tosylates possessing activated alpha-methylene groups is an α-amino ketone or in some instances an alkoxy aziridine.[44] The possibility of the rearrangement occurring through a saturated nitrene intermediate in cases where the oxime tosylate was adjacent to two methylene groups of different acidity was recently investigated by House.[51] The isomeric tosylates of 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-propanone oximes (XIXA and XIXB) were subjected to the

Neber rearrangement.[51] Isolation of 1-amino-3-(4-methoxyphenyl)-1-(4-nitrophenyl)-2-propanone (XXIA) as the major rearrangement product from both isomeric oxime tosylates indicated to House that the stereochemistry of the tosyloxy function was not involved in determining the product of the Neber rearrangement (Fig. 14). Furthermore, if a saturated nitrene intermediate such as XXII were the intermediate species in the rearrangement, its behavior would be expected to be analogous to the behavior of carbenes.[52] Therefore, XXII should exhibit little selectivity between insertion at either of the benzylic positions; however, if any selectivity was observed, XXIB rather than the isomeric product XXIA which was actually isolated would be expected, for the transition state for hydrogen transfer to a nitrene intermediate should be favored by electron donating substituents.[52] Since the composition of the by-products resulting from a competing Beckmann rearrangement in each reaction appeared to provide evidence that the isomeric oxime tosylates XIXA and XIXB were not being equilibrated prior to undergoing the Neber reaction, House and Berkowitz suggested that the major factor influencing the rearrangement product of such unsymmetrically substituted oximes was the relative acidity of the alpha methylene protons and not the stereochemistry of the oximido function.[51] Thus, the mechanism probably involves an unsaturated nitrene intermediate XX (Fig. 14), which these authors suggest arises through initial removal of a proton alpha to Ar regardless of the stereochemistry of the oxime function.[51]

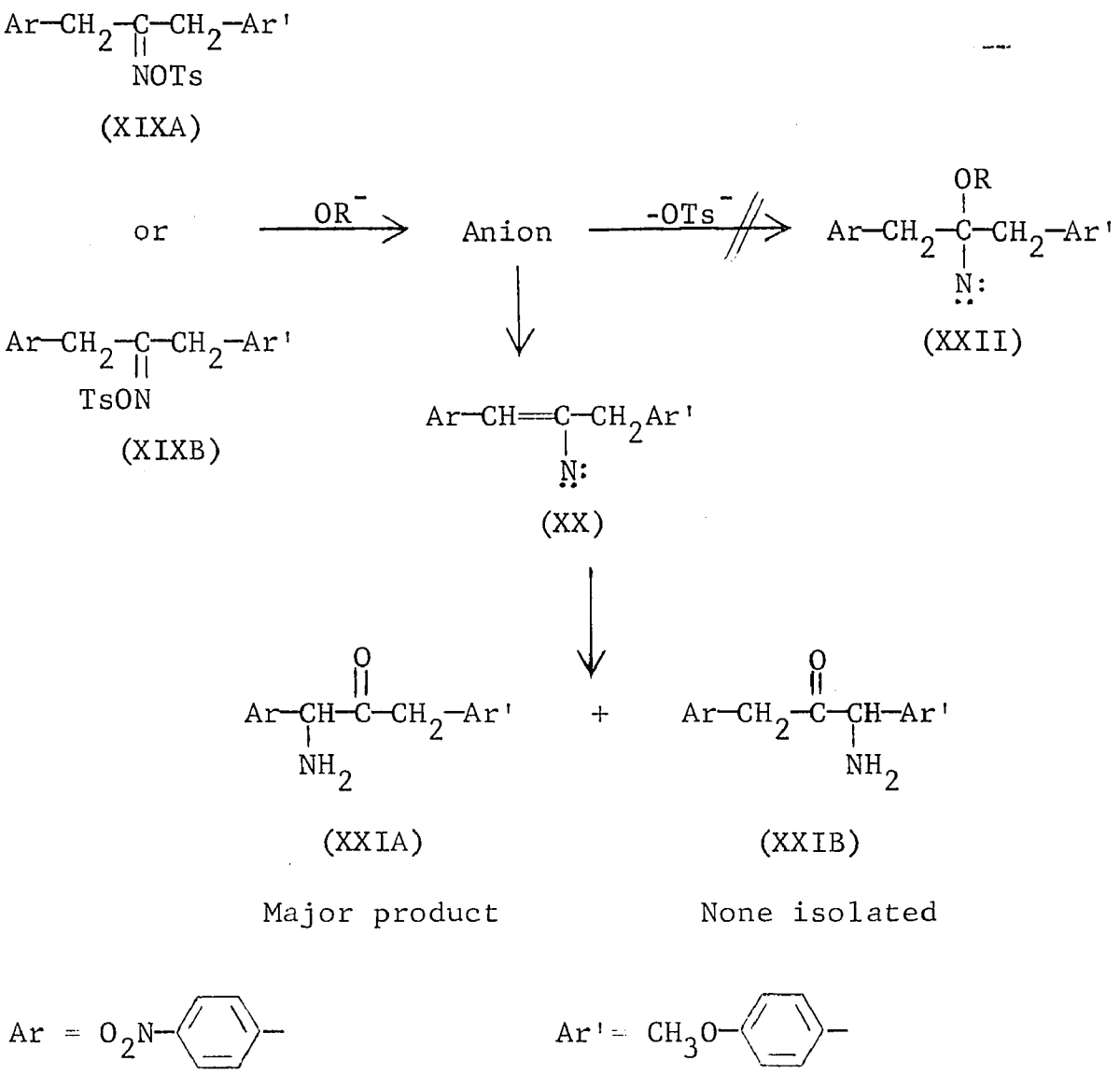
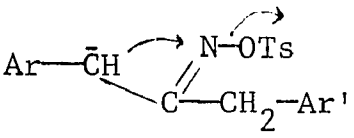


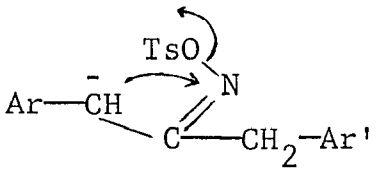
Fig. 14. The Mechanism of the Neber Rearrangement Proposed by House and Berkowitz

Though the present data appear to be consistent with an unsaturated nitrene intermediate, they do not require this species to exist as a discrete intermediate. In spite of the fact that displacements at the carbon-nitrogen double bond appear unlikely[51], a mechanism may be envisioned whereby loss of the tosyloxy function with concomitant formation of an azirine could occur by a concerted

process, XXIII or XXIV. In the case of XXIV, a frontside displacement of the tosyloxy group would be required in order to afford the Neber product obtained and this appears unlikely.[51] However, the possibility of isomerization of XXIV to XXIII before formation of the azirine intermediate cannot be unequivocally eliminated on the basis of the present data.



(XXIII)



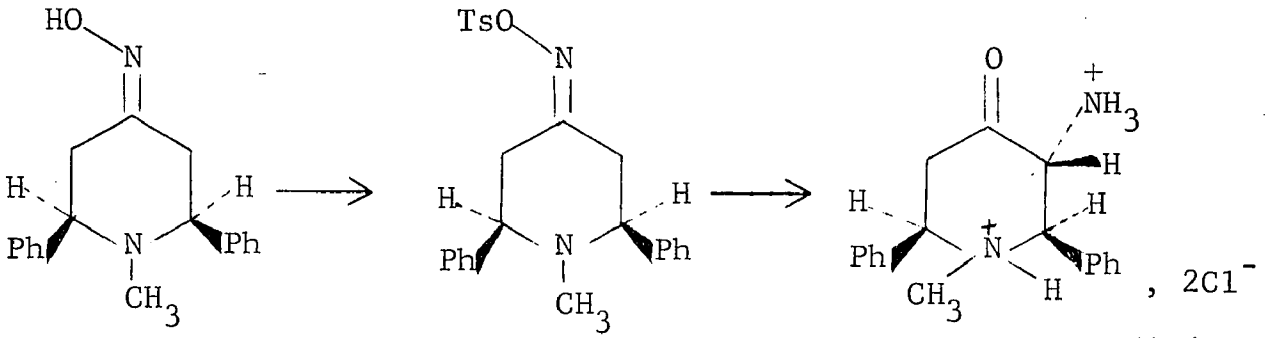
(XXIV)

No correlation of the postulated mechanisms with cyclic α-amino ketones isolated from Neber rearrangements have been made. In no instance was an oxime having identical or nearly identical methylene groups studied to determine the stereochemical consequences or lack of same in this rearrangement. The establishment of the absolute configuration of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (IIb)[53] afforded a unique compound to investigate this question.

The Neber Rearrangement of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate

The p-toluene sulfonate ester of racemic 1-methyl-2,6-diphenyl-4-piperidone oxime (II) has been prepared and its rearrangement to an α-amino ketone described by Neber.[9] The optically active form of the oxime was prepared as described by Tyminski[13] and conversion of the dextrorotatory isomer, IIb, to the corresponding sulfonate ester, according to Cram's

procedure[43], afforded a dextrorotatory oxime tosylate XXV. Modification of Cram's procedure utilizing lower temperatures gave (+)-XXV having a higher degree of optical activity.



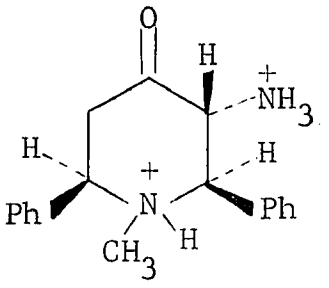
(+)-II (+)-XXV (-)-XXVI

Treatment of an anhydrous alcoholic suspension of (+)-XXV with sodium ethoxide, according to Neber's procedure[9], resulted in the isolation of the α-amino ketone dihydrochloride (XXVI) which was levorotatory in 2N hydrochloric acid. Since the acidity of the protons located on the methylene groups adjacent to the oximido function of XXV should be nearly equivalent, a racemic rearrangement product was expected on the basis of the "sterically indiscriminate" mechanisms put forth for this rearrangement.[44,51] The isolation of a cyclic, optically active α-amino ketone XXVI from this reaction suggested that the stereochemistry of the oximido function was the factor determining the Neber rearrangement product in a molecule in which the relative acidities of the adjacent alpha methylene protons are essentially equivalent.

The Configuration of (-)-3-Amino-1-methyl-2,6-diphenyl-4-piperidone

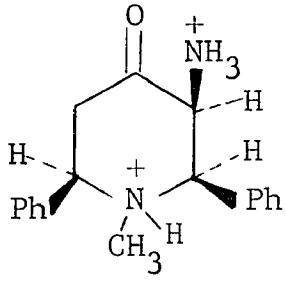
Application of the Neber rearrangement to the stereospecific synthesis of certain α-amino ketones has been described.[54,55] In the cases reported, the amino substituent has been assigned the equatorial configuration, though no unequivocal evidence has been offered to support this assignment.[8,55] The isolation of optically active α-amino ketone dihydrochloride XXVI showed that the Neber rearrangement of (+)-XXV occurred by a stereospecific pathway and should lead to one of the four stereoisomers (XXVIA-XXVID) (Fig. 15). The equatorial configuration of the phenyl substituents of IIb has been adequately demonstrated[11] and the chair conformation, with the bulky phenyl substituents equatorially oriented would be the preferred conformation for this piperidone system; hence, should the amino substituent of XXVI assume the equatorial orientation as has been suggested[8,55], the conformation of the Neber rearrangement product of (+)-XXV may be represented as illustrated in Fig. 15, XXVIA or its mirror image XXVIC.

Optical rotatory dispersion studies have become an important tool for structural elucidation and have been especially useful in the configurational assignment of certain functional groups.[36] Most of the early correlations between structure and/or stereochemistry and optical rotatory dispersion have been achieved with cyclic carbonyl compounds and especially with substituted cyclohexanones. The abundance of experimental data available along with the fact that most cyclohexanones have been shown to prefer the chair conformation led theoretical chemists to establish a set of empirical rules known as the "Octant Rule".[36,56] From a know-



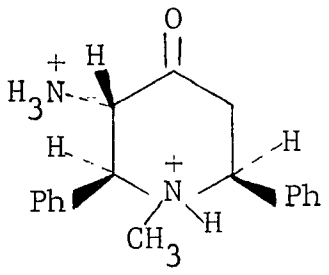
, 2 Cl^-

(XXVIA)



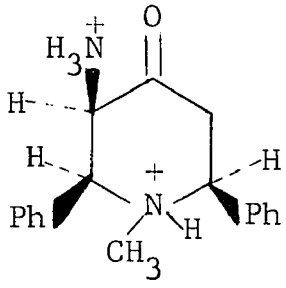
, 2 Cl^-

(XXVIB)



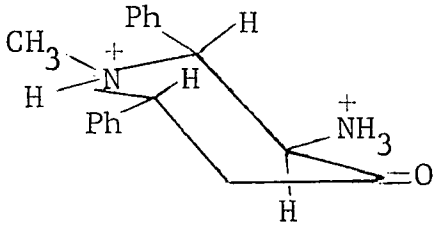
, 2 Cl^-

(XXVIC)



, 2 Cl^-

(XXVID)



, 2 Cl^-

(XXVIA)

Fig. 15. The Stereochemistry of (-)-3-Amino-1-methyl-2,6-diphenyl-4-piperidone Dihydrochloride

ledge of the absolute configuration and conformation of a molecule, this rule permits the prediction of the sign of the Cotton effect. Furthermore, if the conformation of a cyclic ketone has been established or is known, its absolute configuration may be determined by application of the Octant Rule to the optical rotatory dispersion curve of the molecule. If the cyclic α-amino piperidone XXVI may be considered similar to a cyclohexanone ring system, the configuration of the 3-amino substituent should be ascertainable from a consideration of its optical rotatory dispersion curve as well as the optical rotatory dispersion curves of some of its derivatives.

Since 3-amino-1-methyl-2,6-diphenyl-4-piperidone dihydrochloride (XXVI) readily undergoes dimerization to a dihydropyrazine in basic media[9], the derivatives for the optical rotatory dispersion studies were prepared by treating an aqueous solution of the amino ketone dihydrochloride XXVI with the appropriate reagent. Subsequent neutralization of the reaction medium afforded the derivative. Treatment of XXVI with acetic anhydride at steam bath temperatures gave a solid derivative whose physical properties were different from those of the starting material. The infrared absorption spectrum of this derivative showed absorptions at 3300 $cm.^{-1}$ characteristic of the bonded NH stretching frequency of a secondary amide, two carbonyl bands at 1740 and 1650 $cm.^{-1}$ attributed to the carbonyl stretching frequencies of a ketone and secondary amide, respectively, 1550 $cm.^{-1}$ attributed to the amide II band, 1450 $cm.^{-1}$ characteristic of the N-methyl group, along with the usual bands associated with mono-substituted phenyl rings[29]; elemental analysis was consistent with the expected N-acetyl derivative XXVII. Similar treatment of the amino ketone dihydrochloride with benzoyl chloride at room temperature afforded a solid derivative whose analytical

data and infrared absorption spectrum were consistent with the assigned structure XXVIII. The two carbonyl bands in the N-acetyl derivative XXVII occurred at similar frequencies in the N-benzoyl derivative XXVIII, 1740 and 1645 cm.$^{-1}$, respectively. The optical rotatory dispersion curves of the α-amino ketone dihydrochloride (XXVI) and its N-acetyl derivative (XXVII) are illustrated in Fig. 16. The optical rotatory dispersion curve of the amino ketone dihydrochloride shows a trough at 415 mμ with a molecular rotation of +134°. The ultraviolet absorption spectrum of XXVI in 2N hydrochloric acid appeared to be concentration dependent, for a bathochromic shift was noted in the absorption maximum with increasing concentration (Fig. 17). Since the midpoint of the Cotton effect of an optical rotatory dispersion curve should correspond to the point of maximum absorption in the ultraviolet absorption spectrum, and, further, since the concentration employed in determining the optical rotatory dispersion curve of XXVI was considerably greater than that employed for ultraviolet absorption spectra of XXVI, the unusually long wavelength of the midpoint of the Cotton effect of XXVI is not surprising.

The rotatory dispersion curve of the N-acetyl derivative (XXVII) exhibits a negative Cotton effect with its first extremum at 310 mμ and a molecular rotation of -184°. The relatively small rotations shown by the amino ketone XXVI and its derivatives suggest that the amino substituent of XXVI is not axially oriented. Because equatorial substituents adjacent to a carbonyl function apparently lie in one of the nodal planes of the carbonyl group, the contributions made by these substituents to the rotatory dispersion curve have been considered to be negligible.[36,56] Recently, however, it has been demonstrated that an equatorial substituent alpha to the carbonyl function does, in fact, make a small, but

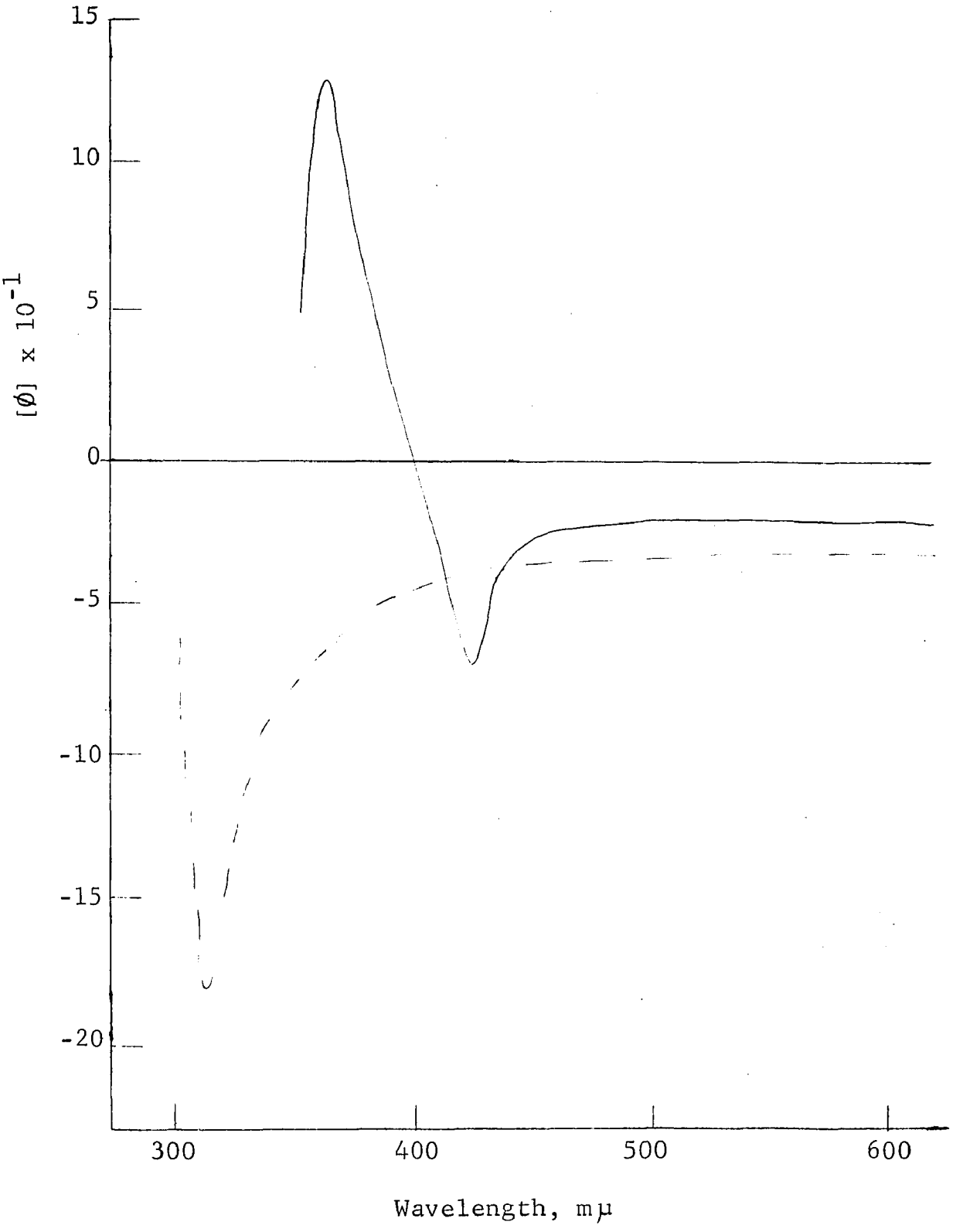


Fig. 16. Optical Rotatory Dispersion Curves of (-)-3-Amino-1-methyl-2,6-diphenyl-4-piperidone Dihydrochloride (——) and (-)-3-Acetamido-1-methyl-2,6-diphenyl-4-piperidone (---)

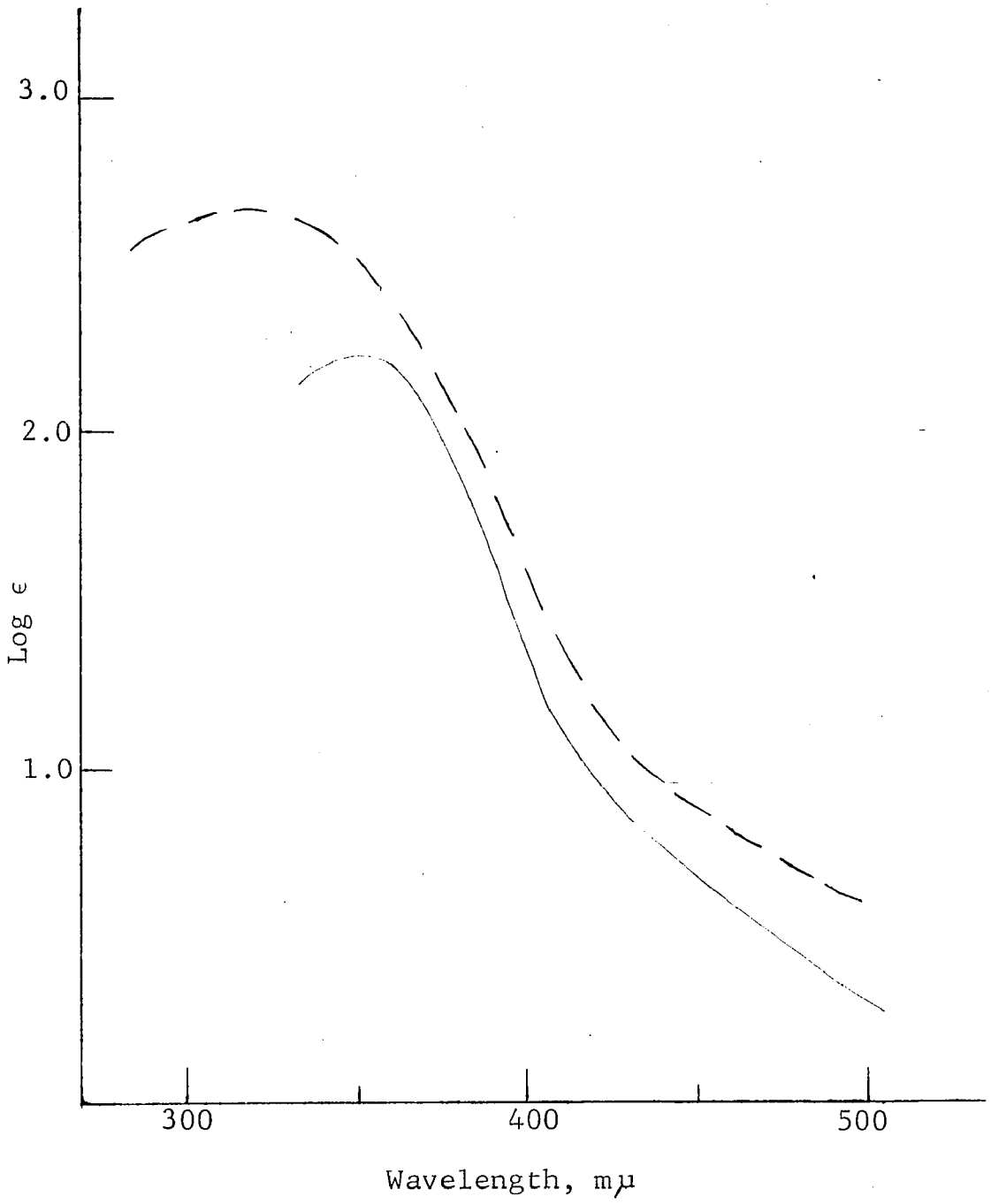
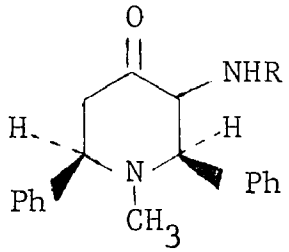


Fig. 17. Ultraviolet Absorption Spectra of 3-Amino-1-methyl-2,6-diphenyl-4-piperidone Dihydrochloride in 2N HCl at C = 10^{-2} M (——) and C = 2.5 x 10^{-3} M (---)

definite, contribution to the amplitude of the Cotton effect due to the fact that it does not lie exactly in the nodal plane of the carbonyl group.[57] The rotatory contribution of the methyl group has been demonstrated to be almost negligible, $\underline{a} < 9$[57], in contrast to the rotatory contribution of more bulky equatorial substituents such as t-butyl[58] or i-propyl[59] ($\underline{a} \backsimeq 33$ and 17 respectively). The small amplitude, $\underline{a}=2.08°$, of the Cotton effect of (-)-3-amino-1-methyl-2,6-diphenyl-4-piperidone dihydrochloride (XXVI) indicates that the amino group is equatorially oriented in the 3-position; this is further supported by the fact that the N-acetyl derivative XXXVII also exhibits a negative Cotton effect of low intensity. Since the molecular rotation of the N-acetyl derivative (XXVII) is somewhat larger compared with the molecular rotation of the α-amino ketone dihydrochloride (XXVI), the slightly larger acetamido group apparently makes a larger contribution to the molecular rotation. Unfortunately, the small rotations and strong ultraviolet absorptions of XXVI and XXVII prevented measurement of the optical rotatory dispersion curves of these compounds farther into the ultraviolet region of the spectrum.



XXVII R = $COCH_3$

XXVIII R = COC_6H_5

The Mechanism of the Neber Rearrangement

Previous investigations indicate that the course of the Neber rearrangement is influenced by the relative acidities of the protons alpha to the oximido function.[44,51] The subsequent removal of the more acidic proton, as was concluded by House and Berkowitz[51], must be ascertained, therefore, by stereoelectronic substituent effects rather than by the stereochemical effect of the oximido configuration. The Beckmann rearrangement, on the other hand, results from the migration of that group anti to the oximido hydroxyl function and is stereochemically controlled.[15]

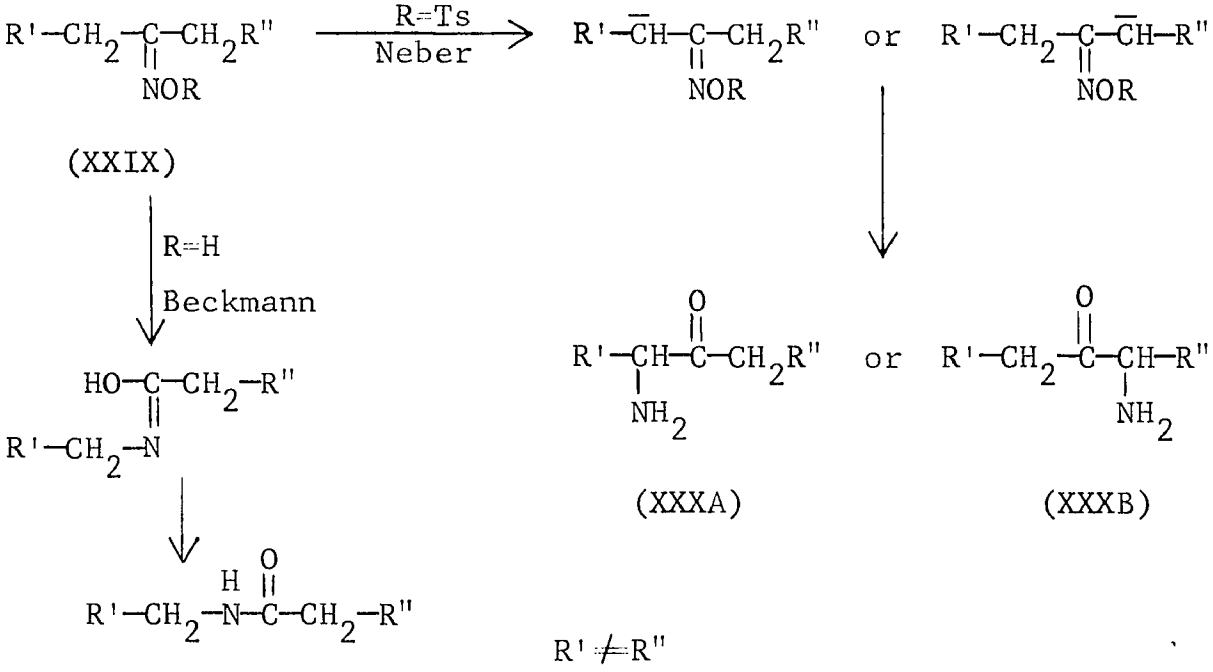


Fig. 18. A Comparison of the Reaction Course of the Neber and Beckmann Rearrangements

Depending on the relative acidities of the alpha methylene protons, the Neber rearrangement should lead to the predominant isolation of either XXXA or XXXB (Fig. 18).

When R' exhibits more electron withdrawing character than R", the Neber rearrangement would be expected to proceed by a trans migration to XXXA. If, however, R" possessed greater electron withdrawing character than R', the proton adjacent to R" and syn to the tosyloxy function would be subject to removal as a consequence of the stereoelectronic influences of the R" substituent and XXXB would be the expected Neber product. Although a pathway involving the removal of the syn tosyloxy substituent would not be expected to be energetically favored, such a possibility cannot be excluded. Furthermore, the fact that the Beckmann rearrangement occurs stereospecifically by a trans migration of the function anti to the oximido hydroxyl group does not preclude the possibility of a cis-migration occurring in the Neber rearrangement, although this possibility seems unlikely.

The isolation of small amounts of esters corresponding to the alcoholic solvolysis of a competing stereospecific Beckmann rearrangement product from the Neber reaction of the isomeric oxime tosylates XIXA and XIXB led House to conclude that equilibration of the tosyloxy function did not occur more rapidly than the Neber rearrangement.[51] However, the trans orientation of the oximido tosylate group with respect to the methylene protons adjacent to the phenyl bearing the electron withdrawing nitro substituent in XIXA should, because of the absence of steric hindrance, enhance the removal of that alpha porton and subsequently increase the rate of its Neber rearrangement to the corresponding α-amino ketone XXIA; consequently, only a small amount of product resulting from the solvolysis of the competing Beckmann rearrangement product would be expected and was obtained (1.8% of XXXI)[51] (Table II). Removal of the alpha proton anti to the tosyloxy function of XIXB would be expected to be more difficult; on the other hand,

removal of the more acidic, syn alpha proton in the isomeric oxime tosylate XIXB should be favored but would result in a sterically unfavorable situation for rearrangement. As a result of the stereochemical considerations, the Beckmann rather than the Neber rearrangement of XIXB should be facilitated and a large amount of product resulting from solvolysis of the competing Beckmann rearrangement product would be expected from this reaction and this is observed (14.3% of XXXII) (Table II).[51] If, however, the tosylates are equilibrated more rapidly than the anion XIXC can undergo rearrangement, the same product mixture should be obtained from XIXB as was obtained from XIXA; and this is in agreement with the data obtained (Table II). Furthermore, the fact that none of the solvolysis product XXXII was obtained from the rearrangement mixture of the tosylate XIXA indicates that the acidity of the proton anti to the tosyloxy group affords a reaction condition such that Neber arrangement occurs more rapidly than isomerization of XIXA to the isomeric tosylate XIXB (Fig. 19).

Table II indicates that the amino ketone to ester ratio obtained from the rearrangement of both isomeric oxime tosylates XIXA and XIXB is essentially the same for both isomers. Furthermore, when the stereochemistry of the oxime tosylate function is such that an anti relationship exists between the more acidic alpha proton and the tosyloxy group, the rate of Neber rearrangement appears to be greater than the rate of isomerization of the tosyloxy function; hence, the data of House and Berkowitz[51] become consistent with a stereochemical factor influencing the Neber rearrangement.

Although the question of the stereochemical influence of the oxime and the possible cis or trans course of the Neber rearrangement are answered, the present investigation cannot

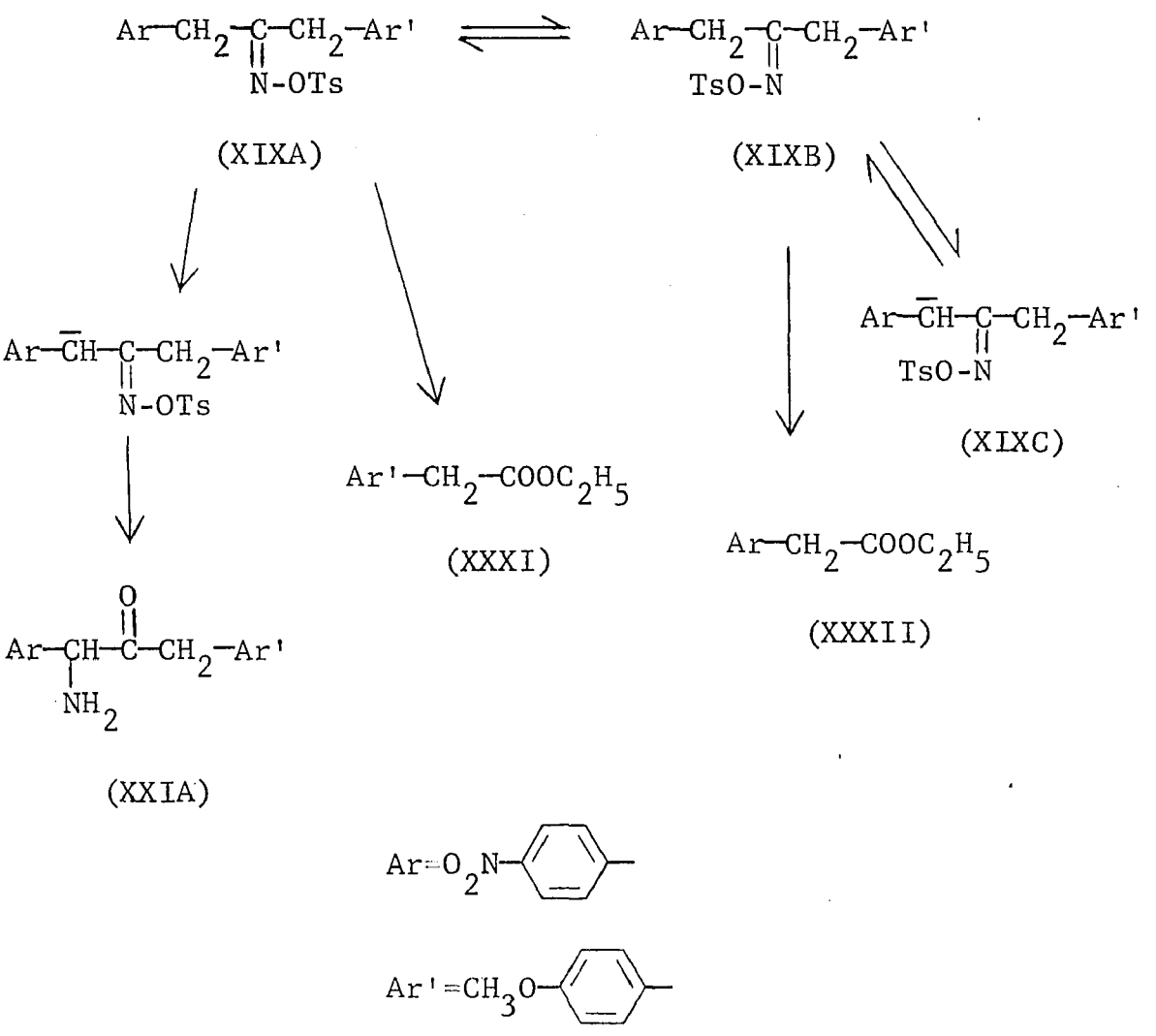


Fig. 19. Mechanism of the Neber Rearrangement

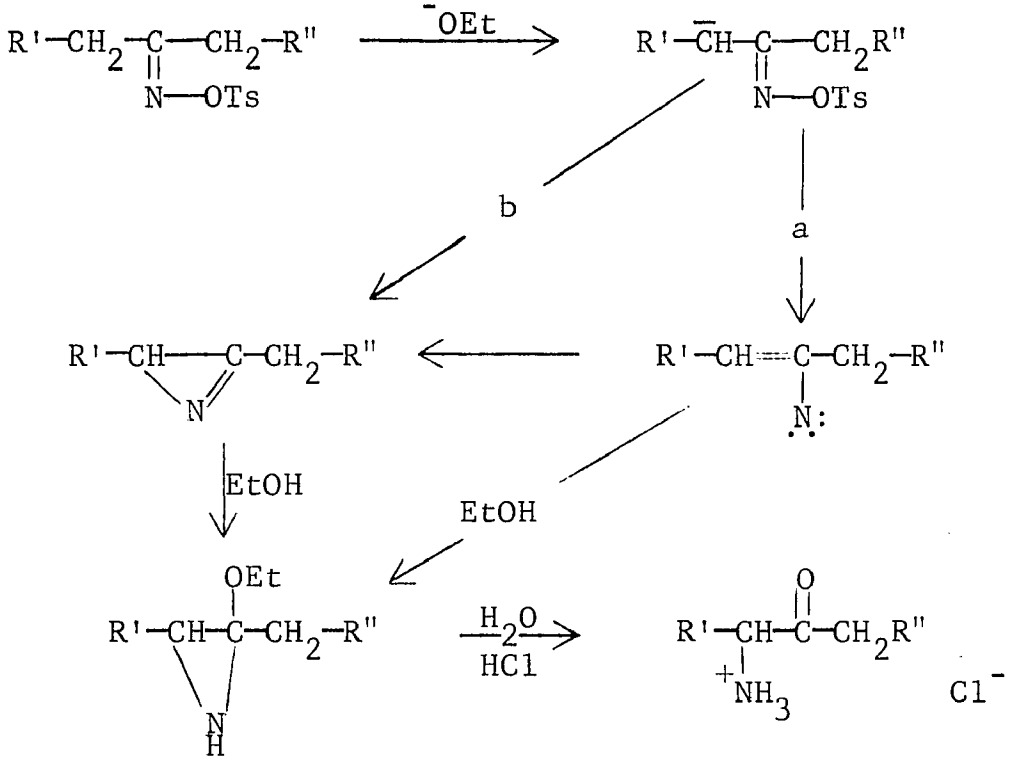
TABLE II

Neber Rearrangement Products from the Isomeric Oxime Tosylates of 1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-2-propanone.[51]

Tosylate	% Amino Ketone[a] XXIA	% Ester XXXI	% Ester XXXII
XIXA	56	1.8	0.0
XIXB	42.5% (plus 5% of product hydrolyzed to amino ketone	1.0	14.3

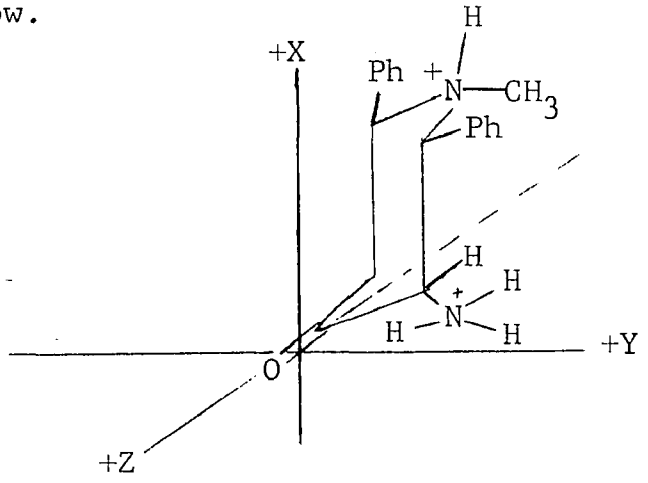
[a] Isolated on the N-acetyl derivative

determine the mechanistic details necessary for the formation of an azirine or aziridine intermediate postulated for this rearrangement. The available data, illustrated below, best fit the pathways by which such three-membered, nitrogen containing heterocyclic intermediates could arise in the course of the Neber rearrangement.



Since the methylene groups alpha to the oximido function of XXV are essentially equivalent, removal of the alpha proton should be free of stereoelectronic effects and the Neber rearrangement of (+)-XXV would be expected, therefore, to yield racemic α-amino ketone XXVI. The isolation of optically active XXVI, therefore, indicated a stereochemical dependence of proton removal on the oxime function; hence, either a cis or trans, but not both, reaction course would result in the retention of optical activity in the rearrangement product. A choice of reaction pathway for this reaction may be deduced on the basis of the absolute configuration of the amino ketone XXVI isolated as the final product of the Neber rearrangement. The relatively small Cotton effect exhibited by the optical rotatory dispersion curve of XXVI indicated that the equatorial conformation of the amino group seems most reasonable (vide supra). Analogous to the numerous examples cited in the literature, a substituent in the equa-

torial position and to the right of the carbonyl substituent of a cyclic ketone may be assumed to spend a large percentage of its time in the upper right octant of a three-coordinate diagram. Consideration of the Octant Rule indicates that such a substituent should make a negative contribution to the Cotton effect; therefore, the absolute configuration 3(R)-amino-1-methyl-2(R),6(R)-diphenyl-4-piperidone (XXVIA) best fits the observed data, as shown in the Octant Rule diagram below.



Since the absolute configuration of the oxime (+)-IIB has been established[53] (Fig. 12) and the optical rotatory dispersion data support the absolute configuration XXVIA for the α-amino ketone dihydrochloride XXXVIA, the mechanistic course which best fits the Neber rearrangement appears to be one involving a <u>trans</u> relationship of the α-proton which is removed by the base and the tosyloxy function of the oxime.

The dependence of the Octant Rule on atomic refractivity has been described by Moffitt and co-workers.[60] Although the atomic refractivity of NH_3^+ has not been ascertained, the atomic refractivity of a secondary amide group has been determined to be 2.27[61]; hence, the Octant Rule is applicable to the optical rotatory dispersion curve of XXVII and the results obtained by application of this rule are therefore valid.

EXPERIMENTAL

EXPERIMENTAL

Melting Points. Melting points were determined using a Kofler hot-stage melting point apparatus equipped with a polarizing microscope and are uncorrected.

Infrared Absorption Spectra. The infrared absorption spectra were determined using a Perkin-Elmer Model 137 B infrared spectrophotometer ("Infracord") equipped with sodium chloride optics and a Perkin-Elmer Model 337 grating infrared spectrophotometer equipped with sodium chloride optics. Those spectra determined on the Model 137 B are indicated by $No._{137}$, while those determined on the Model 337 are indicated by $No._{337}$.

The spectra were determined as mulls in Halocarbon oil from 4000 $cm.^{-1}$ to 1300 $cm.^{-1}$ and in Nujol from 1300 $cm.^{-1}$ to 650 $cm.^{-1}$ unless otherwise indicated. All of the bands listed were strong except those indicated weak (w) or medium (m), and the location of the bands is given in frequency units, $cm.^{-1}$.

Optical Rotation Data. The rotation of optically active compounds was determined using a Franz Schmidt and Haensch polarimeter equipped with a sodium lamp as light source. The solvent and concentration (g. per 100 ml. of solution) are indicated for each determination.

Optical Rotatory Dispersion Data. The optical rotatory dispersion curves of optically active compounds were measured using a Rudolph recording spectropolarimeter Model 260/658/850/810-609 with a 1.0 cm. tube length. The data for each curve are recorded as molecular rotations $[\phi]_\lambda$ in

the solvent and concentrations indicated.

Mass Spectrometric Analysis. The mass spectrum was determined by Applied Physics Corporation on an Atlas CH-4 mass spectrometer equipped with a T04 ion source and a vacuum lock.

Analytical Data. Microanalyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, New York, and by Klaus Weinhardt at the University of New Hampshire, using a F & M Model 180 carbon, hydrogen, nitrogen analyzer. Those analyses determined on the Model 180 are indicated by $Found_{FM}$.

Preparation of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime (IIb)

1-Methyl-2,6-diphenyl-4-piperidone (I). Methylamine (8-10 g.) was bubbled into a suspension of 20.0 g. of dibenzalacetone[10], m.p. 114-115°, in 200 ml. of methanol until solution was effected. The resulting solution was allowed to stand at room temperature for 48 hrs. after which time the solvent was removed by distillation under reduced pressure. The residual brown oil was dissolved in 100 ml. of ether and an equal amount of water was added to the ethereal solution. The product which crystallized at the interface was separated by filtration and recrystallized from 95% ethanol yielding 14-15 g. (62-67%) of 1-methyl-2,6-diphenyl-4-piperidone (I), m.p. 150-151°; lit.[62] m.p. 152-153°.

1-Methyl-2,6-diphenyl-4-piperidone Oxime (II). To a solution of 48.0 g. of potassium hydroxide in 400 ml. of 95% ethanol, 12.0 g. of 1-methyl-2,6-diphenyl-4-piperidone (I) and 12.0 g. of hydroxylamine hydrochloride were added. The resulting mixture was heated on a steam bath under reflux for 3 hrs., cooled, and poured into 900 ml. of water. The solid which precipitated was separated by filtration, washed with water, and dried yielding 13.2 g. of crude oxime. Recrystallization from 95% ethanol gave 10.6 g. (80%) of 1-methyl-2,6-diphenyl-4-piperidone oxime (II), m.p. 190-191°; lit.[9] m.p. 190°.

Resolution of 1-Methyl-2,6-diphenyl-4-piperidone Oxime. A solution of 15.0 g. of (+)-10-camphor sulfonic acid in 150 ml. of anhydrous ether and enough methanol to allow dissolution was added to a stirred solution of 15.0 g.

of racemic 1-methyl-2,6-diphenyl-4-piperidone oxime (II). The solid which was deposited was collected by filtration, dried, and recrystallized from methanol-ether giving 25-26 g. (90-94%) of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (+)-10-camphor sulfonate, m.p. 169-171°, $[\alpha]^{24}D$ +26.0 to 30.86° (95% ethanol, c=2.0); lit.[11] m.p. 167.5-172°, $[\alpha]^{25}D$ +30.08° (95% ethanol, c=2.0).

(+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime (IIb).

A solution of 25.5 g. of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (+)-10-camphor sulfonate, $[\alpha]^{23}D$ +25.5° (95% ethanol, c=2.0), in 500 ml. of water and enough acetone to allow dissolution was neutralized with a saturated aqueous solution of potassium carbonate. The solid which was deposited was collected by filtration and dried giving 12.6 g. (91.8%) of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (IIb). Recrystallization from 95% ethanol gave 12.0 g. of IIb, m.p. 189-193°, $[\alpha]^{23}D$ +29.81° (95% ethanol, c=2.15); lit.[11] m.p. 188-192°, $[\alpha]^{25}D$ +32.63° (95% ethanol, c=2.2).

ORD Curve (No. 8, absolute ethanol, c=2.0): $[\phi]_{700}$ +30.8°, $[\phi]_{589}$ +51.9°, $[\phi]_{304}$ +478°, $[\phi]_{285}$ +439°, $[\phi]_{274}$ +461°, $[\phi]_{269}$ +282°.

Beckmann Rearrangement of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime (IIb)

A mixture of 3.6 g. of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (IIb), $[\alpha]^{24}D$ +28.9° (95% ethanol, c=2.0), 2.34 g. of benzenesulfonyl chloride, 1.8 g. of sodium hydroxide, 18 ml. of water and 72 ml. of acetone was heated under reflux on a steam bath for 6 hrs. After cooling to room temperature, water (180 ml.) was added and most of the acetone removed by distillation under reduced pressure. The resulting mixture was extracted with ether and the combined ethereal extracts dried over potassium carbonate. Evaporation of most of the ether gave a fluffy white solid which was separated by filtration giving 1.25 g. (44.7%) of (-)-1,4-diaza-1-methyl-2,7-diphenyl-5-cycloheptanone (IIIb), m.p. 169.5-170°, $[\alpha]^{23}D$ -6.36° (methanol, c=1.07). The infrared spectrum of the optically active lactam was identical to that of racemic 1,4-diaza-1-methyl-2,7-diphenyl-5-cycloheptanone, lit.[13] m.p. 167-168°.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19. Found: C, 76.83; H, 7.07.

ORD Curve (No. 133, methanol, c=0.765): $[\phi]_{695}$ -73.3°, $[\phi]_{650}$ -91.6°, $[\phi]_{589}$ -88.0°, $[\phi]_{375}$ -176°, $[\phi]_{305} \pm 0.0°$.

Acid Hydrolysis of (-)-1,4-Diaza-1-methyl-2,7-diphenyl-5-cycloheptanone (III)

A mixture of 1.2 g. of (-)-1,4-diaza-1-methyl-2,7-diphenyl-5-cycloheptanone (IIIb), $[\alpha]^{24}D$ -6.36° (methanol, c=1.07), and 50 ml. of 20% hydrochloric acid was heated on a steam bath for 3.5 hrs. After cooling, the solid (0.613 g.) which was deposited was separated by filtration and subsequently identified as cinnamic acid, m.p. 131-132°, mixture melting point 131-132°.

The reaction solution was made basic with aqueous potassium carbonate, extracted with ether, and the combined ethereal extracts were dried over potassium carbonate. Evaporation of the solvent under reduced pressure gave 0.0422 g. of (-)-β-(N'-methylamino)-β-phenylethylamine (IV) as a light yellow oil, $[\alpha]^{24}D$ -6.77° (absolute ethanol, c=3.35); phenylthiourea, m.p. 151-152°, $[\alpha]^{24}D$ +5.0° (95% ethanol, c=0.685). The infrared spectrum of the diamine obtained from this hydrolysis was identical to that of β-(N'-methylamino)-β-phenylethylamine.[13]

ORD Curve (No. 444, absolute ethanol, c=3.35): $[\phi]_{695}$ -6.26°, $[\phi]_{589}$ -6.26°, $[\phi]_{325}$ -21.0°.

Alternate Synthesis of (-)-β-(N'-Methylamino)-β-phenylethylamine (IV)

Ethyl α-Aminophenyl Acetate Hydrochloride. A suspension of 10.0 g. of α-aminophenylacetic acid (V) in 200 ml. of absolute ethanol was treated with anhydrous hydrogen chloride until solution was effected and for 10 minutes longer to insure saturation of the solution with hydrogen chloride. The solution was then concentrated to one-third its original volume and cooled to room temperature. Addition of anhydrous ether (125 ml.) to the concentrated solution followed by cooling in ice gave 10.6 g. (74.5%) of the hydrochloride of ethyl α-aminophenyl acetate XI, m.p. 190-195°; lit.[30] m.p. 200°.

The preparation of optically active ethyl α-amino phenyl acetate (XI) from D-(-)-α-aminophenylacetic acid (V), $[\alpha]^{24}_{-}D$ -157.7° (5% hydrochloric acid, c=1.03), by the method described above gave 5.5 g. (39%) of the hydrochloride of (-)-ethyl α-aminophenyl acetate (XI), m.p. 198°, $[\alpha]^{24}D$ -114.98° (5% hydrochloric acid, c=0.814); lit.[63] m.p. 203°, [α]D -84.6°.

ORD Curve (No. 430, absolute ethanol, c=1.004): $[\phi]_{695}$ -207°, $[\phi]_{589}$ -250°, $[\phi]_{400}$ -651°, $[\phi]_{295}$ -1950°.

Ethyl α-Aminophenyl Acetate (XI). An aqueous solution of 9.6 g. of ethyl α-aminophenyl acetate hydrochloride was neutralized with aqueous sodium hydroxide and the resulting solution was extracted with ether. Removal of the solvent by distillation under reduced pressure gave 5.2 g. (64%) of ethyl α-aminophenyl acetate (XI), which was immediately converted to the corresponding amide.

(-)-Ethyl α-aminophenyl acetate (XI) was obtained from 4.5 g. of (-)-ethyl α-aminophenyl acetate hydrochloride, $[\alpha]^{24}D$ -114.98° (5% hydrochloric acid, c=0.814), by the method described above giving 2.5 g. (66%) of (-)-XI which was immediately converted to the corresponding amide.

α-Aminophenylacetamide (VI). A solution of 3.6 g. of ethyl α-aminophenyl acetate (XI) in 40 ml. of absolute ethanol, which had previously been saturated with anhydrous ammonia, was allowed to stand at room temperature for two weeks. Removal of the solvent by distillation under reduced pressure followed by treatment of the residual semi-solid mass with anhydrous ether gave 2.6 g. (93%) of α-aminophenylacetamide (VI), m.p. 127-129°; lit.[31] m.p. 128-129°.

Optically active α-aminophenylacetamide (VI) was prepared by the method described above from 4.6 g. of (-)-ethyl α-aminophenyl acetate (XI), giving 3.2 g. (92%) of (-)-VI, m.p. 128°, $[\alpha]^{24}D$ -41.98° (95% ethanol, c 0.505). The infrared spectrum of the optically active amide VI was identical to that of racemic α-aminophenylacetamide.

ORD Curve (No. 432, 95% ethanol, c 0.505): $[\phi]_{695}$ -68.4°, $[\phi]_{589}$ -37.0°, $[\phi]_{575}$ -51.3°, $[\phi]_{265}$ -482°.

α-Formamidophenylacetamide (VII). A mixture of 0.94 g. of α-aminophenylacetamide (VI) and 5 ml. of formamide was heated in an oil bath at 150° for 15 minutes. After the reaction mixture was cooled to room temperature, water (30 ml.) was added. The product was salted out by the addition of potassium carbonate and was collected by filtration, washed with cold water, and dried, giving 0.547 g. (49.2%) of α-formamidophenylacetamide (VII), m.p. 264-267°.

IR Spectrum (No.$_{337}$476): 3350 (w), 3270, 3180 (m), 2920 (m), 1690, 1660, 1645, 1525 (m), 1380 (m), 1230 (m), 738, 695.

Optically active α-formamidophenylacetamide (VII) was prepared by the method described above from 2.02 g. of (-)-α-aminophenylacetamide (VI), $[\alpha]^{24}D$ -41.98° (95% ethanol, c=0.505), giving 1.07 g. (45%) of (-)-α-formamidophenylacetamide (VII), m.p. 263-266°, $[\alpha]^{24}D$ -19.25° (methanol, c=0.405). The infrared spectrum of optically active VII was identical to that of racemic α-formamidophenylacetamide.

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.77; H, 5.66; N, 15.72. Found: C, 61.00; H, 5.69; N, 15.77.

ORD Curve (No. 446, methanol, c=1.34): $[\phi]_{680}$ -24.0°, $[\phi]_{589}$ -21.4°, $[\phi]_{375}$ -9.35°, $[\phi]_{350}$ -12.02°, $[\phi]_{270}$ -21.36°.

Mass Spectrum: 178 (parent peak), 161, 149, 134 (base peak), 118, 106, 91, 77, 44.

Lithium Aluminum Hydride Reduction of α-Formamidophenylacetamide (VII). A solution of 0.47 g. of α-formamidophenylacetamide (VII) in tetrahydrofuran was added dropwise with stirring to a slurry of 0.5 g. of lithium aluminum hydride in tetrahydrofuran heated under reflux. The resulting mixture was heated under reflux for 17 hrs., cooled in an ice bath, and the excess lithium aluminum hydride decomposed with 5 ml. of wet ether and 10 ml. of water. The organic layer was decanted, the inorganic salts washed with ether, and the combined organic extracts dried over potassium carbonate. Removal of the solvent by distillation under reduced pressure gave 0.328 g. (82.6%) of β-(N'-methylamino)-β-phenylethylamine (IV) as a yellow oil. The infrared spectrum of the

diamine IV obtained from the above procedure was identical to that of β-(N'-methylamino)-β-phenylethylamine isolated from the hydrolysis of 1,4-diaza-1-methyl-2,7-diphenyl-5-cycloheptanone.[13]

Treatment of this oil with phenyl isothiocyanate gave a solid phenylthiourea, m.p. 151-153°, whose infrared spectrum and melting point were identical to those previously obtained.[13] No depression of melting point was observed in a mixture melting point.

Optically active β-(N'-methylamino)-β-phenylethylamine (IV) was prepared, according to the method described above, from 0.465 g. of (-)-α-formamidophenylacetamide (VII), $[\alpha]^{24}D$ -19.25° (methanol, c=0.405) giving 0.328 g. (84%) of (-)-β-(N'-methylamino)-β-phenylethylamine (IV), $[\alpha]^{24}D$ -6.52° (absolute ethanol, c=0.29); phenylthiourea, m.p. 151-153°, $[\alpha]^{24}D$ +11.52° (95% ethanol, c=0.01).

The Neber Rearrangement of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate

1-Methyl-2,6-diphenyl-4-piperidone Oxime Tosylate (XXV). To a suspension of 10.0 g. of 1-methyl-2,6-diphenyl-4-piperidone oxime (II) in 100 ml. of acetone, 70 ml. of 1.37 N potassium hydroxide was added while the mixture was stirred magnetically. The mixture was cooled to 0° in an ice-salt bath, and 7.0 g. of finely powdered p-toluenesulfonyl chloride was added in portions. A thick white precipitate formed after approximately half the solid was added. After stirring for 0.5 hr. at 0-5°, the reaction mixture was poured into ice-water, and the resulting suspension was stirred vigorously. The solid was collected by filtration and dried in a vacuum desiccator giving 14.2 g. (91.6%) of 1-methyl-2,6-diphenyl-4-piperidone oxime tosylate (XXV), m.p. 100-102°; lit.[9] m.p. 98°.

(+)-1-Methyl-2,6-diphenyl-4-piperidone oxime tosylate (XXV) was prepared at -5°, according to the procedure described above, from 12.0 g. of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (IIb), $[\alpha]^{23}D$ +27.5° (95% ethanol, c=2.13), giving 16.5 g. (84.4%) of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime tosylate (XXV), m.p. 95-97°, $[\alpha]^{24}D$ +8.74 (dioxane, c=2.16); lit.[12] m.p. 96-100°, $[\alpha]^{24}D$ +4.77° to 10.03° (benzene, c=2.3-3.2).

ORD Curve (No. 571, dioxane, c=2.06): $[\phi]_{600}$ +25.3°, $[\phi]_{589}$ +25.3°, $[\phi]_{350}$ +92.9°, $[\phi]_{290}$ +270°, $[\phi]_{288}$ +236°, $[\phi]_{286}$ +261°, $[\phi]_{280}$ +227°.

3-Amino-1-methyl-2,6-diphenyl-4-piperidone Dihydrochloride (XXVI). A solution of sodium ethoxide prepared from 2.0 g. of sodium and 50 ml. of absolute ethanol, was

added to a stirred suspension of 14.8 g. of 1-methyl-2,6-diphenyl-4-piperidone oxime tosylate (XXV) in 150 ml. of absolute ethanol. After stirring at room temperature for 2.5 hrs., anhydrous ether (500 ml.) was added, and the resulting suspension filtered twice through glass wool. The filtrate was washed with water, and the water layer was discarded. The organic layer was extracted with 2 N hydrochloric acid and the combined acidic extracts were evaporated to dryness under reduced pressure leaving a solid residue which was dissolved in chloroform. Addition of anhydrous ether to the chloroform solution caused the precipitation of a yellow solid which was collected by filtration. The solid was dissolved in water, the water solution filtered, and the clear filtrate evaporated to dryness under reduced pressure giving a solid residue. Dissolution of the residual solid in chloroform followed by the addition of anhydrous ether gave 11.4 g. (94.5%) of 3-amino-1-methyl-2,6-diphenyl-4-piperidone dihydrochloride (XXVI), m.p. 127-129° (dec.); lit.[9] m.p. 130° (dec.).

(-)-3-Amino-1-methyl-2,6-diphenyl-4-piperidone dihydrochloride (XXVI) was obtained by the procedure described above from 10.0 g. of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime tosylate (XXV), $[\alpha]^{24}D$ +8.74° (dioxane, c=2.16), giving 8.0 g. (98%) of (-)-3-amino-1-methyl-2,6-diphenyl-4-piperidone dihydrochloride (XXVI), m.p. 128-129° (dec.), $[\alpha]^{25}D$ -5.75° (2N hydrochloric acid, c=2.02); lit.[12] m.p. 118-130° (dec.), $[\alpha]^{25}D$ -4.28° (2N hydrochloric acid, c=2.0).

ORD Curve (No. 572, 2 N hydrochloric acid, c=2.31): $[\phi]_{600}$ -15.4°, $[\phi]_{589}$ -15.4°, $[\phi]_{450}$ -18.4°, $[\phi]_{425}$ -73.0°, $[\phi]_{400}$ ±0.00°, $[\phi]_{365}$ +134°, $[\phi]_{360}$ +122°.

(-)-3-Acetamido-1-methyl-2,6-diphenyl-4-piperidone (XXVII). A suspension of 4.5 g. of (-)-3-amino-1-methyl-2,6-diphenyl-4-piperidone dihydrochloride (XXVI) in 30 ml. of acetic anhydride was heated on a steam bath until solution was effected. After cooling to room temperature, the addition of water (40 ml.) caused the separation of an oil. The mixture was heated until a homogeneous solution was obtained and was allowed to cool to room temperature. Dropwise addition of 5% sodium hydroxide solution caused the precipitation of a light yellow solid which was subsequently collected by filtration giving 2.88 g. of crude product. Recrystallization from methanol-water gave 1.43 g. of (-)-3-acetamido-1-methyl-2,6-diphenyl-4-piperidone (XXVII), m.p. 168-170°, $[\alpha]^{24}D$ -5.51° (95% ethanol, c=2.03).

IR Spectrum ($No._{337}$ 2223): 3300, 3065 (w), 3045 (w), 2965 (m), 2845 (m), 2760 (m), 1745, 1650, 1550, 1450 (m), 1375 (m), 1150, 770 (m), 755, 700.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. $Found_{FM}$: C, 74.20; H, 7.11; N, 8.45.

ORD Curve (No. 575, 95% ethanol, c=2.26): $[\phi]_{605}$ -31.4°, $[\phi]_{589}$ -31.4°, $[\phi]_{350}$ -57.1°, $[\phi]_{318}$ -171°, $[\phi]_{310}$ -140°.

(-)-3-Benzamido-1-methyl-2,6-diphenyl-4-piperidone (XXVIII). To a stirring solution of 4.0 g. of (-)-3-amino-1-methyl-2,6-diphenyl-4-piperidone dihydrochloride (XXVI) in 60 ml. of water, 2.0 g. of benzoyl chloride was added. The resulting suspension was stirred magnetically for 4 hr. after which time it was made basic with aqueous potassium hydroxide and extracted with ether. The combined etheral extracts were dried over anhydrous potassium carbonate. Removal of the solvent by distillation under reduced pressure, gave 1.13 g.

(23.0%) of crude product, m.p. 197-201°. Recrystallization from benzene gave 0.275 g. (6.3%) of (-)-3-benzamido-1-methyl-2,6-diphenyl-4-piperidone (XXVIII), m.p. 216.5-218°. The insolubility of a sufficient amount of XXVIII in the usual organic solvents prevented the determination of its D-line rotation with a polarimeter.

IR Spectrum (No.$_{337}$ 2219): 3365, 3275 (w), 3025 (m), 2975 (m), 2830 (m), 2775 (m), 1745, 1645, 1580 (m), 1520, 1485, 1450, 1155 (m), 955, 795, 785-755, 712, 695.

ORD Curve (No. 578, dimethylsulfoxide, c=0.595): $[\phi]_{605}$ -57.6°, $[\phi]_{308}$ -89.7°, $[\phi]_{275}$ -19.2°.

Anal. Calcd. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29. Found$_{FM}$: C, 77.75; H, 6.32.

SUMMARY

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The absolute configuration of the molecularly dissymmetric dextrorotatory isomer of 1-methyl-2,6-diphenyl-4-piperidone oxime was established by its stereospecific Beckmann rearrangement to (-)-1,4-diaza-1-methyl-2,7-diphenyl-5-cycloheptanone. Acid hydrolysis of the levorotatory Beckmann rearrangement product produced cinnamic acid and (-)-β-(N'-methylamino)-β-phenylethylamine which yielded a dextrorotatory bis-phenylthiourea derivative.

The absolute configuration of the levorotatory diamine was established by an alternate synthesis from D-(-)-α-aminophenylacetic acid. The optically active amino acid was converted successively to (-)-ethyl α-aminophenyl acetate, (-)-α-aminophenylacetamide, and (-)-α-formamidophenylacetamide. Subsequent reduction of (-)-α-formamidophenylacetamide produced levorotatory β-(N'-methylamino)-β-phenylethylamine which on treatment with phenyl isothiocyanate afforded a dextrorotatory bis-phenylthiourea derivative.

The isolation of (-)-β-(N'-methylamino)-β-phenylethylamine from D-(-)-α-aminophenylacetic acid along with the fact that dextrorotatory bis-phenylthiourea derivatives were obtained from the diamines isolated from both reaction sequences established the absolute configuration of (-)-β-(N'-methylamino)-β-phenylethylamine as R. As a result of the trans nature of the Beckmann rearrangement, the syn-R configuration was assigned to (+)-1-methyl-2,6-diphenyl-4-piperidone oxime, thereby providing the first example of absolute configurational assignment to a molecule exhibiting optical activity due to geometrical enantiomorphic isomerism.

The near equivalence of the methylene protons alpha to the oximido function in (+)-1-methyl-2,6-diphenyl-4-piperidone oxime afforded a unique tool for investigating the stereochemical consequences of the Neber rearrangement. Conversion of the dextrorotatory oxime to the corresponding oxime tosylate afforded a dextrorotatory p-toluene sulfonate ester, and Neber rearrangement of this (+)-oxime tosylate produced an optically active α-amino ketone, (-)-3-amino-1-methyl-2,6-diphenyl-4-piperidone dihydrochloride. The methylene protons alpha to the oximido function of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime tosylate are essentially equivalent, and therefore, removal of the alpha proton should be free of stereoelectronic factors. Consequently, isolation of the optically active α-amino ketone from the Neber rearrangement of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime tosylate must be attributed to the stereochemical dependence of proton removal on the oxime function.

Optical rotatory dispersion studies of the (-)-α-amino ketone dihydrochloride and its N-acetyl derivative, (-)-3-acetamido-1-methyl-2,6-diphenyl-4-piperidone, indicate an equatorial orientation for the 3-amino substituent of the Neber rearrangement product and, thereby, suggest the absolute configuration as (-)-3(R)-amino-1-methyl-2(R),6(R)-diphenyl-4-piperidone dihydrochloride. On the basis of the data obtained from the investigation of this rearrangement with a molecularly dissymmetric molecule of established absolute configuration, the mechanistic pathway which best fits the Neber rearrangement most probably involves a trans relationship of the alpha methylene proton and the tosyloxy function.

The results of this study eliminate the possibility of a symmetrical intermediate or transition state being formed during the course of the Neber rearrangement. Furthermore,

contrary to earlier postulations, it is apparent that the Neber rearrangement occurs by a sterically discriminate mechanism.

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