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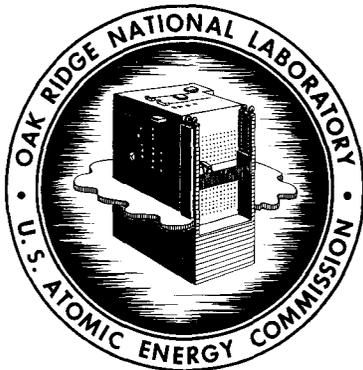
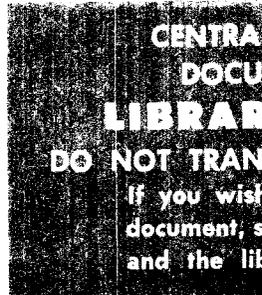
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THE DEAMINATION AND REARRANGEMENT
OF erythro-1-AMINO-1-PHENYL-2-o-
TOLYL-2-PROPANOL

M. M. Staum



OAK RIDGE NATIONAL LABORATORY

operated by

UNION CARBIDE CORPORATION

for the

U. S. ATOMIC ENERGY COMMISSION

Printed in USA. Price \$2.00. Available from the
Office of Technical Services
Department of Commerce
Washington 25, D. C.

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CHEMISTRY DIVISION

THE DEAMINATION AND REARRANGEMENT OF erythro-

1-AMINO-1-PHENYL-2-o-TOLYL-2-PROPANOL

M. M. Staum

DATE ISSUED

Aug. 2, 1961

Submitted as a Thesis to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

OAK RIDGE NATIONAL LABORATORY
Oak Ridge, Tennessee
operated by
UNION CARBIDE CORPORATION
for the
U. S. ATOMIC ENERGY COMMISSION



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ACKNOWLEDGMENTS

The author expresses sincerest appreciation to Dr. Clair J. Collins of the Oak Ridge National Laboratory for his valuable guidance and assistance in the research problem and to Professor Werner M. Lauter of the University of Florida for his encouragement and help.

The author acknowledges the contributions of each member of his Graduate Supervisory Committee: the late Professor C. B. Pollard, Professors L. G. Gramling, C. E. Reid, A. H. Gropp and W. A. Gager of the University of Florida and Dr. S. W. Peterson of the Oak Ridge National Laboratory.

Grateful thanks are given to Drs. B. M. Benjamin and V. F. Raaen of the Organic Group of the Oak Ridge National Laboratory for their practical advice which they have always offered unstintingly.

The author is indebted to the American Foundation for Pharmaceutical Education and the Oak Ridge Institute of Nuclear Studies for the fellowships which supported graduate studies and research.

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INTRODUCTION

In the nitrous acid deamination and rearrangement of α -aminoalcohols, it has been shown by Curtin and Crew that the products are formed stereospecifically.¹ Using dl-diastereomers of 1-p-anisyl-1-phenyl-2-amino-1-propanol, they found that the dl-erythro compound yielded a ketone with about 90 per cent phenyl migration, whereas the dl-threo compound yielded a ketone of correspondingly predominant p-anisyl migration. The amount of each ketone produced was determined by ultraviolet absorption spectroscopy. The equations shown on Charts 1 and 2 illustrate the erythro and threo configurations specified by Curtin and demonstrate the mechanism leading to the observed products.

The authors proposed that the observed migration ratio is due solely to the differences in free energy of two transition states which they designate as cis and trans. These are also illustrated on Charts 1 and 2.

Chart 1 illustrates p-anisyl migration through the trans-transition state (II \rightarrow IV) and phenyl migration through a cis-transition state (V \rightarrow VII). The cis-transition states, according to Curtin, have the bulky, nonmigrating groups eclipsing each other with larger activation energies.

In the absence of the steric factor, the electronic

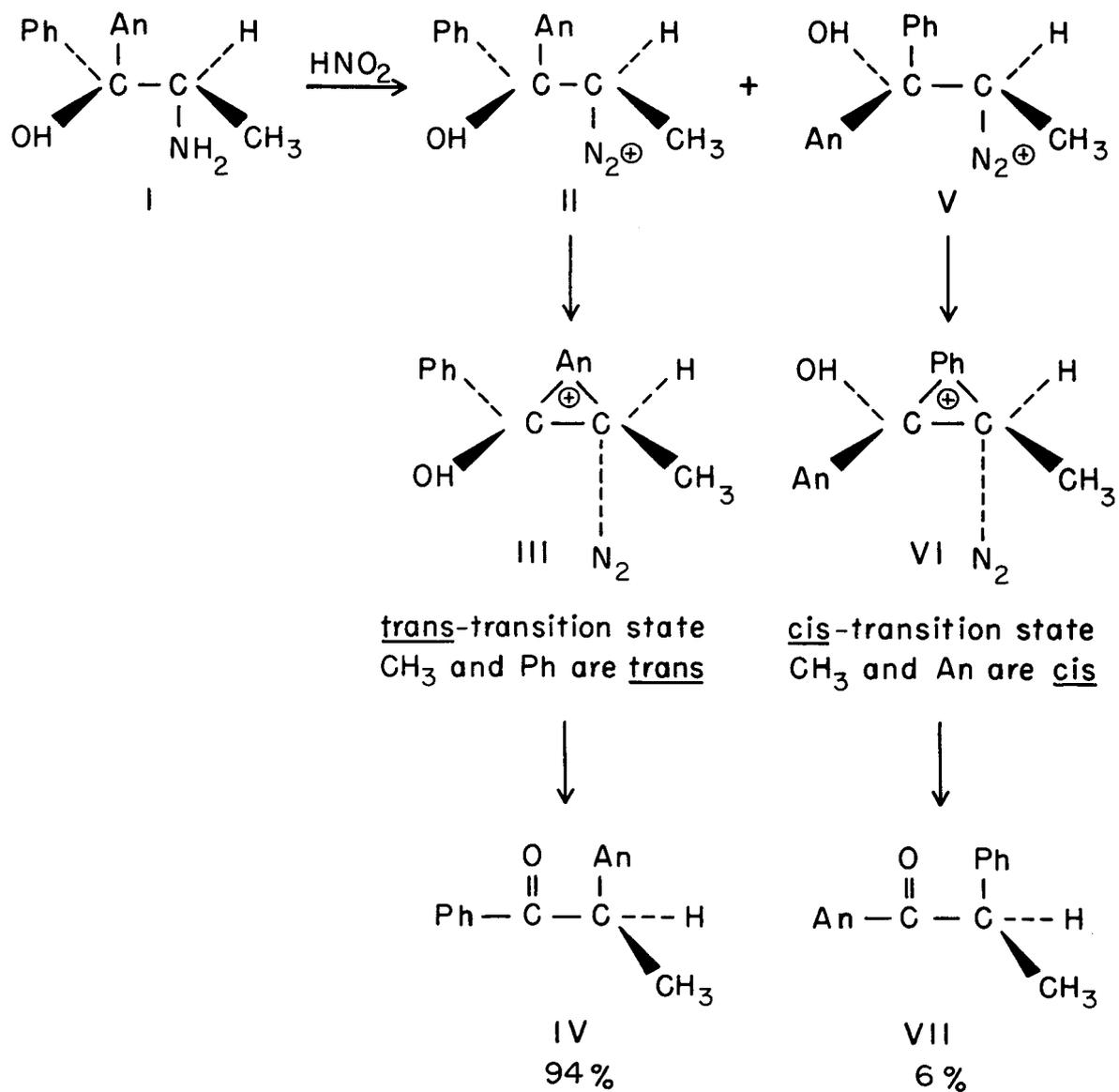


Chart 1.—Deamination of threo-1-p-anisyl-1-phenyl-2-amino-1-propanol.

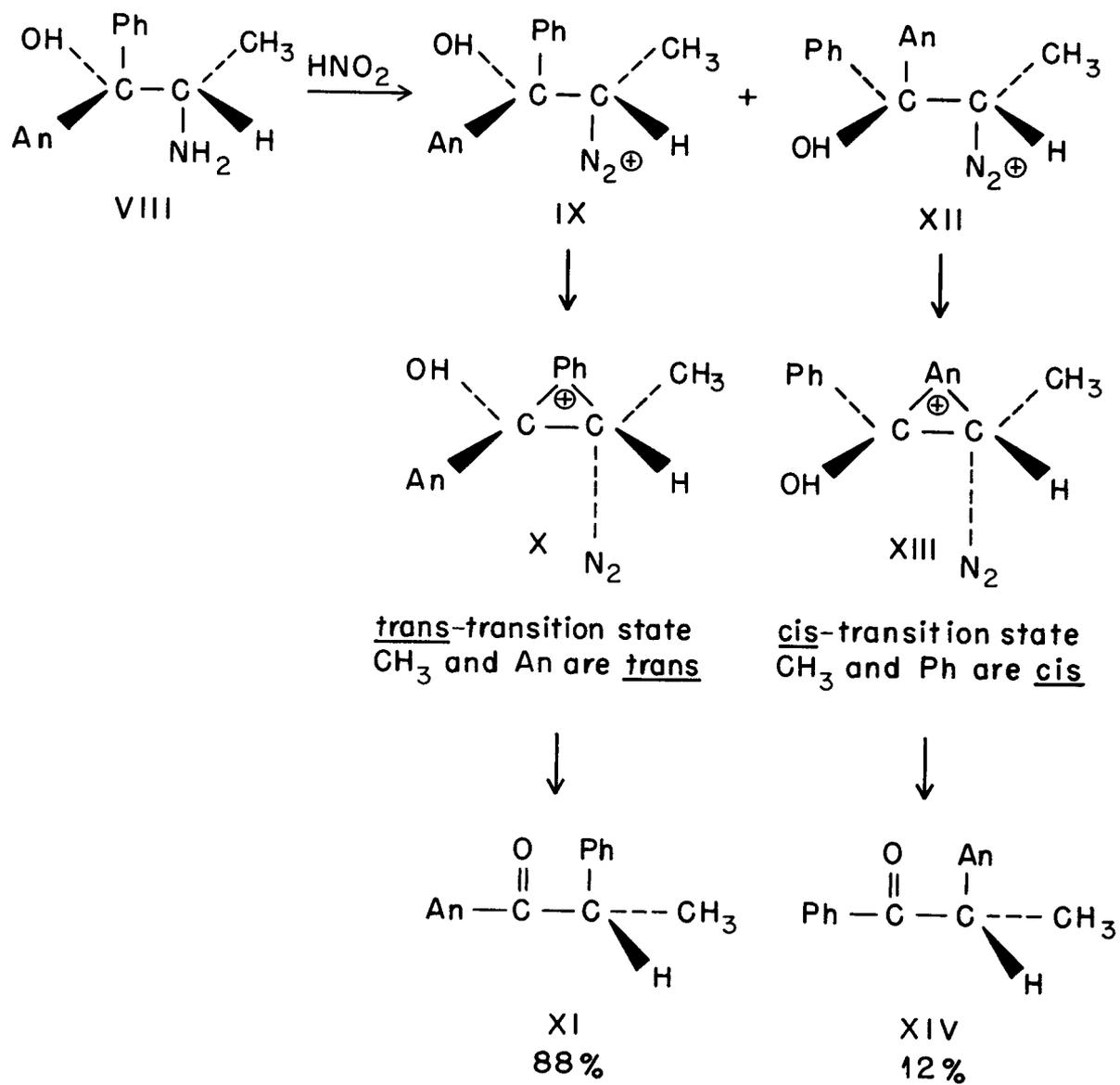


Chart 2.—Deamination of erythro-1-p-anisyl-1-phenyl-2-amino-1-propanol.

factor alone would have decided the migration ratio of p-anisyl and phenyl groups. The electronic effect is not altogether missing in this case and is used to explain the somewhat better p-anisyl migration in the threo compound (94 per cent) compared to the phenyl migration in the erythro compound (88 per cent). It should be emphasized that, according to Curtin's explanation, the ratio of products formed is based on differences in free energies of the cis- and trans-transition states, which are postulated as alternate intermediates, and that the actual mechanism of transfer is an intramolecular bridging of the migrating group from its origin to its terminus. Such bridging groups have been mentioned previously as possible intermediates.^{2,3} With either p-anisyl or phenyl groups migrating, such bridging in the aminoalcohol should cause inversion at the migration terminus. Since Curtin and Crew employed racemic reactants however, the configurations of products could not be determined.

The mechanism of aminoalcohol deamination was further elucidated by Benjamin, Schaeffer and Collins,⁴ who prepared (+)- and (-)-1,1-diphenyl-2-amino-1-propanol stereospecifically labeled in one of the phenyl groups.^{1,5-7}

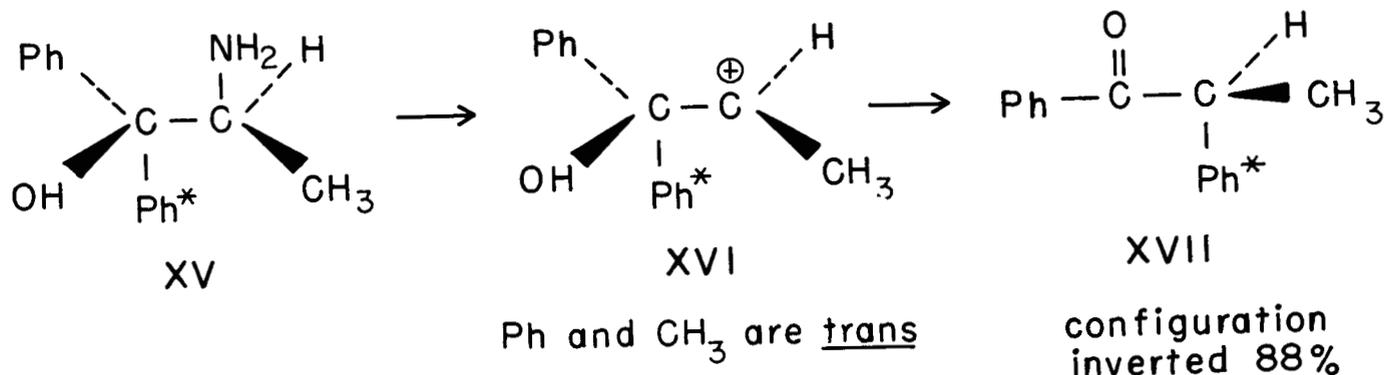
Resolution of the optically active products and radiochemical examination of the chemically degraded α -phenylpropiophenone produced by rearrangement indicated:

(1) that 88 per cent of the product was produced by

inversion of configuration and 12 per cent by retention, and (2) that the inverted product was produced entirely by labeled-phenyl migration, whereas the retained product resulted entirely from nonlabeled-phenyl migration. Thus both enantiomers of α -phenylpropiophenone had been formed through intermediates which allowed phenyl migration through trans-transition states (Chart 3). If rotation about the C-C \oplus bond was very rapid compared to the rate of phenyl migration, as has been suggested by Curtin,¹ the product would have been a racemic ketone produced by an equal amount of labeled- and nonlabeled-phenyl migration, both going through an intermediate trans-transition state. Chart 4 illustrates this with Newman projections of the same reactions shown on Chart 3.

The results of the deamination reactions mentioned thus far in this dissertation have shown that it would be enlightening to study further how much control the ground state conformation does exert. An aminoalcohol containing an o-tolyl group, erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol, XXI, was chosen for this study. The o-tolyl group has a high migration ratio⁸ compared to $-\text{CH}_3$ and $-\text{H}$. In a system in which these three groups are in a migrating position, the o-tolyl group might be considered the predominant one to migrate. The o-tolyl group occasionally exhibits anomalous behavior,⁹ and in aminoalcohol XXI, because of its size, may decrease the amount of free

Labeled-Phenyl Migration



Nonlabeled-Phenyl Migration

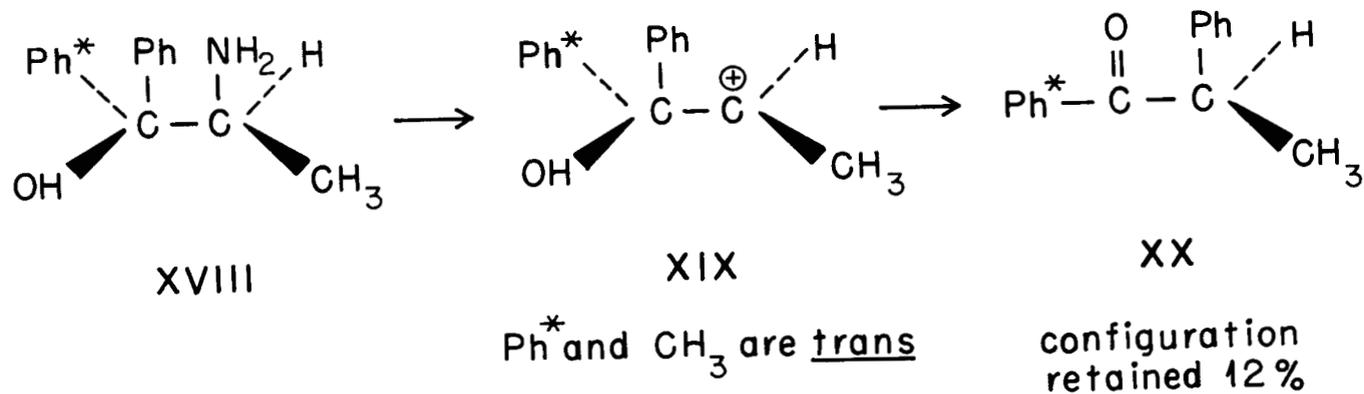


Chart 3.—Deamination of 1,1-diphenyl-2-amino-1-propanol-phenyl- C_1^{14} .

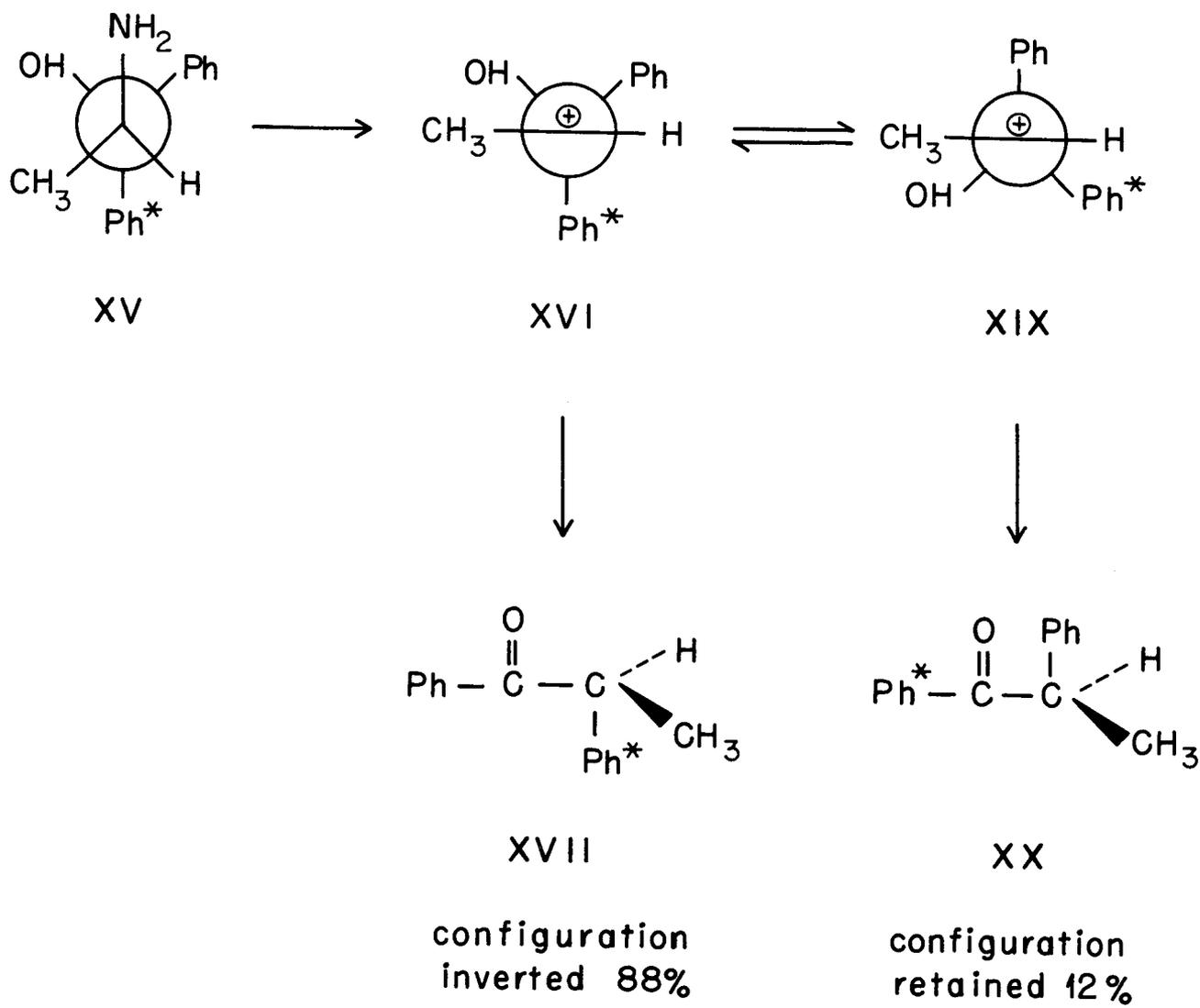


Chart 4.—Deamination of 1,1-diphenyl-2-amino-1-propanol-phenyl-C₁₄; Newman projections.

rotation about the C-C bond and alter the ratio of products which could be expected, based on the deaminations of corresponding phenyl members of the aminoalcohol series.⁴

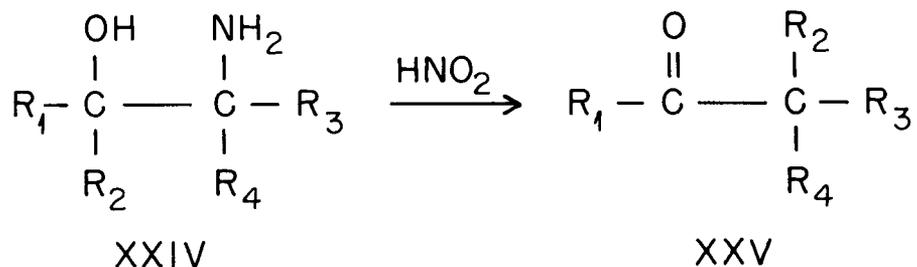
The deamination of one enantiomer of XXI produced almost entirely 1-phenyl-1-o-tolylpropanone, XXIII, a product of o-tolyl migration. Examination of the enantiomeric nature of this ketone by isotope-dilution analysis showed that it consisted of 96.5 per cent of one enantiomer.

One may then deduce that the aminoalcohol in its ground state and carbonium ion conformations exists largely in the steric positions indicated by XXI and XXII on Chart 5.

These results indicate the importance of the ground state conformation in determining the identity and direction of the migrating group in this aminoalcohol.

HISTORICAL BACKGROUND

When a substituted α -aminoalcohol, as XXIV, is treated with nitrous acid, deamination is accompanied by rearrangement with formation of a ketone or an aldehyde.⁹ In some cases, the glycol corresponding to the aminoalcohol is produced in varying quantity.

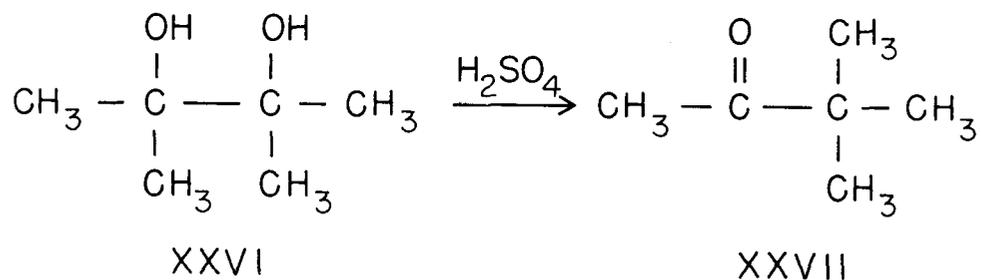


R = H, alkyl, aryl, or part of saturated cyclic system

Closely related reactions followed by similar rearrangements are described in the literature.

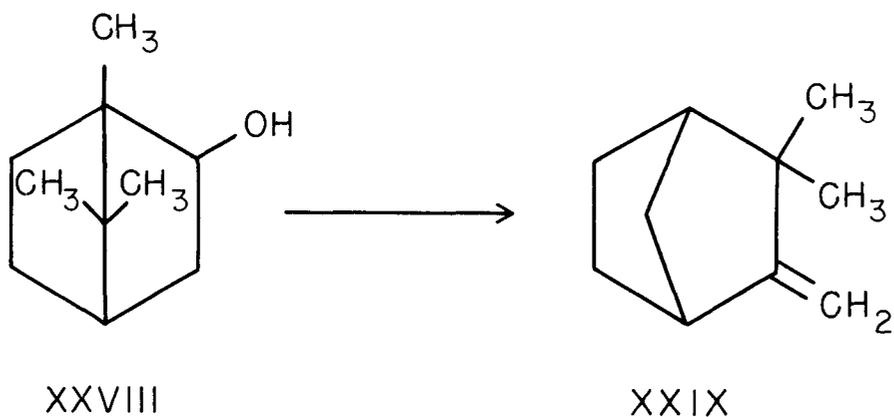
Pinacol Rearrangement. Fittig,¹⁰ in 1860, discovered that pinacol, XXVI, a glycol, was converted to the ketone, pinacolone, XXVII, on treatment with concentrated sulfuric acid.

Subsequently this reaction has been shown to be quite widely applicable to various substituted α -glycols.



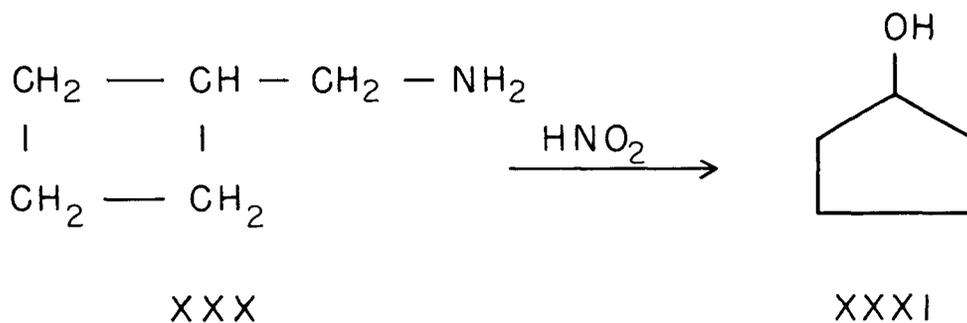
The products are aldehydes or ketones, depending on the reagent or solvent, and the structure of the glycol.^{9,11} A variation of this reaction, the Aldehyde-Ketone Rearrangement, takes place under similar conditions and produces ketones from aldehydes in the presence of concentrated sulfuric acid.^{9,12}

Wagner-Meerwein Rearrangement. The conversion of isoborneol, XXVIII, to camphene, XXIX, was the first in a series of intramolecular rearrangements described by Wagner.¹³ When applied to cyclic compounds, these rearrangements produced changes in ring size.



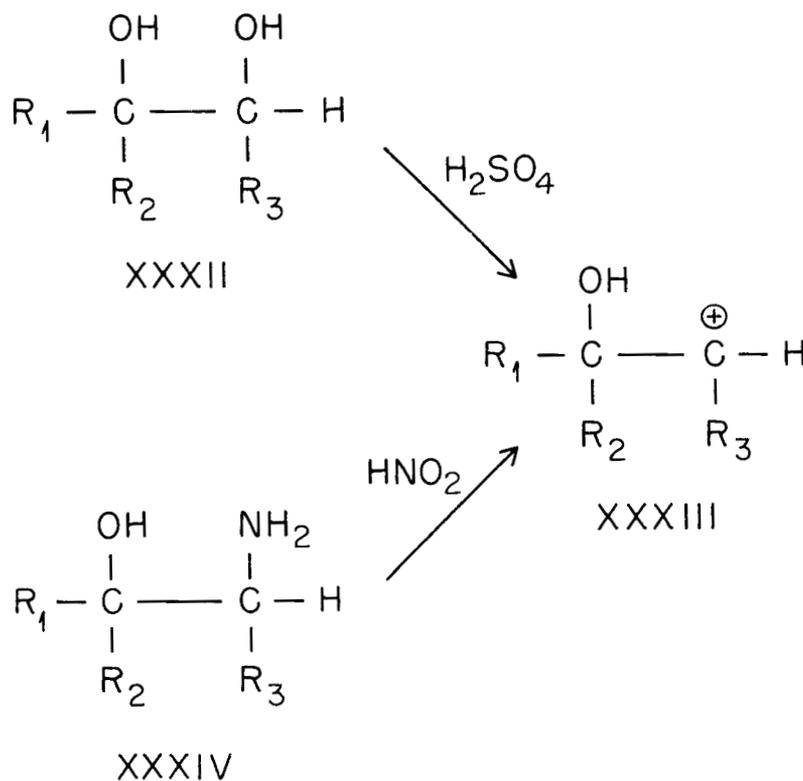
Subsequently other reactions of this type, leading to ring expansion or contraction, were observed.¹⁴ These rearrangements could be initiated by the action of concentrated sulfuric acid or phosphoric acid on a monohydric alcohol or by heavy metal ions, as Ag^+ , on a halide.¹³⁻¹⁵ The Nametkin Rearrangement is the name given to reactions of the same kind in which rearrangement occurs without changes in ring size.¹⁵

Demjanov Rearrangement. Rearrangement which produces enlargement of ring size as a result of nitrous acid deamination of a cyclic aliphatic primary amine, as XXX, was first described by Demjanov.¹⁶



Semipinacolinic Deamination. At the beginning of this section, there is mentioned the reaction in which α -aminoalcohols, under the influence of nitrous acid, rearrange to form carbonyl compounds. The special case in which deamination of an aminoalcohol, as XXXIV, produces a

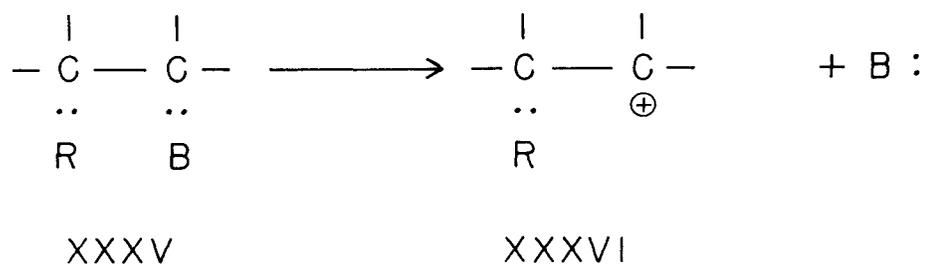
carbonium ion intermediate XXXIII similar to that produced by removing the secondary hydroxyl of a trisubstituted pinacol, as XXXII, has been called the Semipinacolinic Deamination by McKenzie⁶ because of its analogy to the Semipinacolinic Rearrangement. The latter name, as a variation of the Pinacol Rearrangement, was first used by Tiffeneau.¹⁷



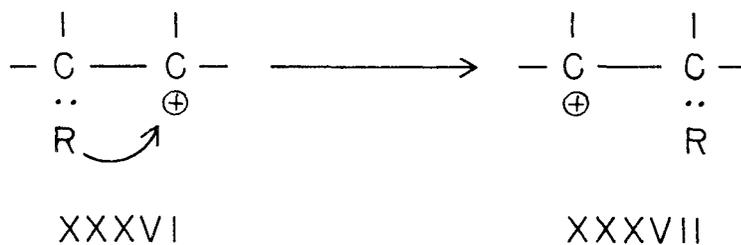
Under the title of "1,2-Shifts," numerous rearrangements of the type just discussed are described and examined in the literature.^{9,12} In offering theories to

explain the "1,2-Shifts," most investigators are in agreement with the following basic stages:⁹

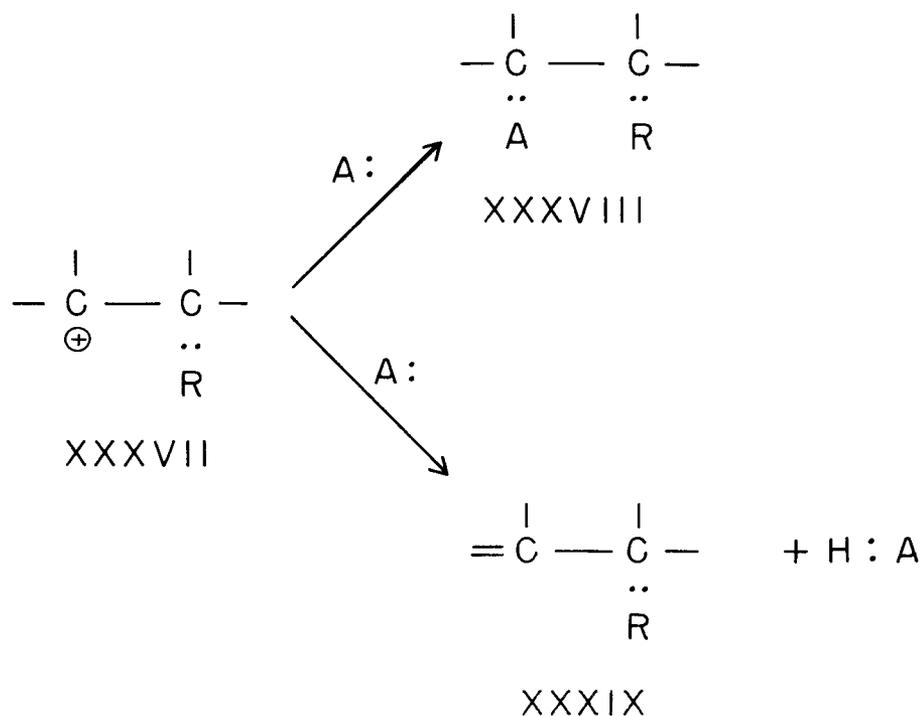
(1) A group or atom, as -OH, -NH₂, or halide, together with its electrons, is removed from its bond with carbon and leaves within the molecule a positively charged carbon atom XXXVI.



(2) A neighboring group, attached to an adjacent carbon atom, migrates with its shared electron pair and becomes bonded to the positively charged carbon atom. This neutralizes the charge on the electron-deficient carbon atom but leaves another carbon atom, XXXVII, with a positive charge.



(3) This positive charge is immediately removed either by bonding with a negatively charged fragment present in the reaction medium or by loss of a positively charged particle such as a proton.



In postulating a mechanism which is consistent with the qualitative and quantitative nature of the products which have been isolated, many factors have been considered by research workers in this field.^{9,12,18} Among these are:

- (1) Location at which the carbonium ion is formed.
- (2) Stability of the carbonium ion.
- (3) Rotation about the C-C[⊕] bond.
- (4) Migratory aptitudes of substituents on adjacent carbon atoms.

- (5) Steric properties of the molecule.
- (6) Control by the ground state conformation of the molecule during deaminations.
- (7) Reversibility of the rearrangement due to open equilibrating carbonium ions.
- (8) Neighboring group participation.
- (9) Cis-effect.
- (10) Free energy change in the transition state.
- (11) Bridged ions and other intermediates in the transition state.
- (12) Effect of solvent, temperature or reagent.

Some of these factors have greater application to a particular reaction than to others. For example, the following three pertain mainly to the mechanism of the Pinacol Rearrangement:

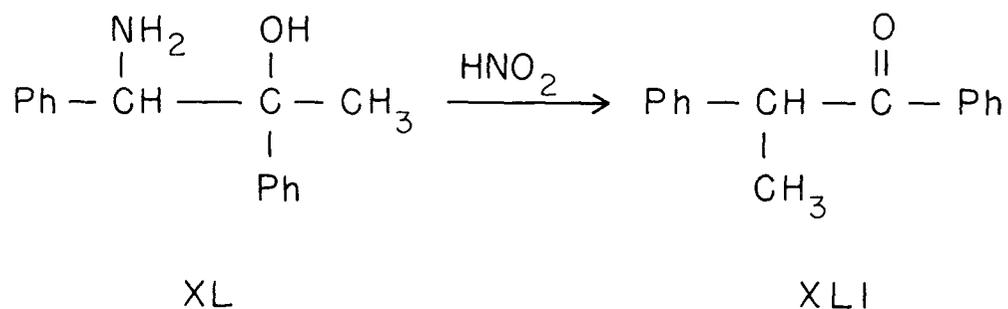
(1) The site of initial formation of the carbonium ion is a factor applicable to glycols since either of the two hydroxyl groups can be removed to start the reaction.

(2) The reagent initiating the reaction has been shown to have an effect on the type of product isolated or their ratio if more than one is produced.¹¹

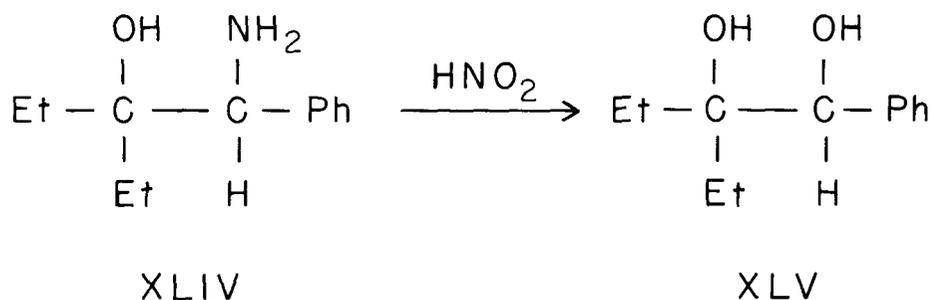
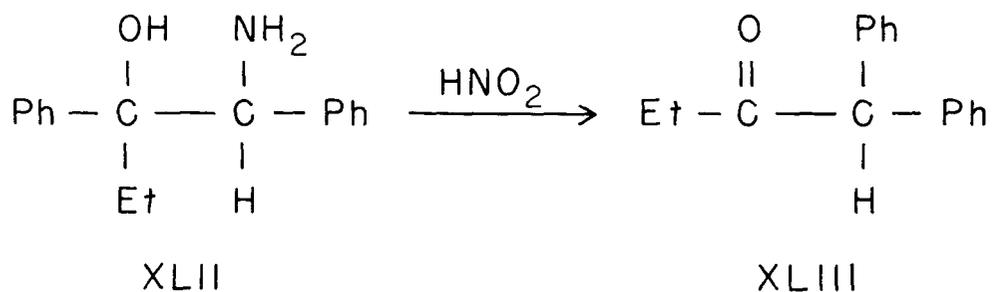
(3) The reversibility of the reactions which form intermediates has explained the variety of products in several rearrangements and has also been used to interpret anomalies observed in the Aldehyde-Ketone Rearrangement.¹⁹

The remaining factors mentioned have applications to proposed mechanisms of deaminations. Their role in the deamination of α -aminoalcohols, which is the specific subject of this paper, will be discussed in this section.

McKenzie, one of the early workers in this field, studied the Walden Inversion and expected such inversion to occur during glycol formation in the nitrous acid deamination of 1-amino-1,2-diphenyl-2-propanol.²⁰ Instead of a glycol, he isolated a ketone XLI. After further experi-

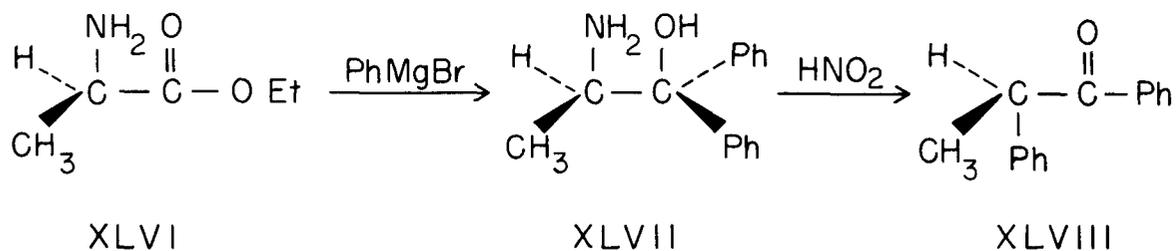


ments with other aminoalcohols, he became convinced of the generality of this reaction and compiled a list of his own work and that of others who reported finding ketones after aminoalcohol deaminations.²¹ McKenzie noted differences in migratory aptitude of phenyl and alkyl groups (XLII \rightarrow XLIII), and recognized that when alkyl groups are attached to the carbinol-carbon atom, glycols are formed predominantly (XLIV \rightarrow XLV). This accumulation of data on aminoalcohol

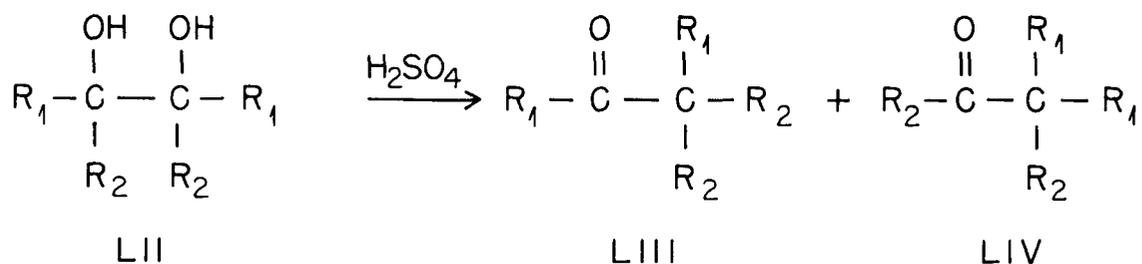
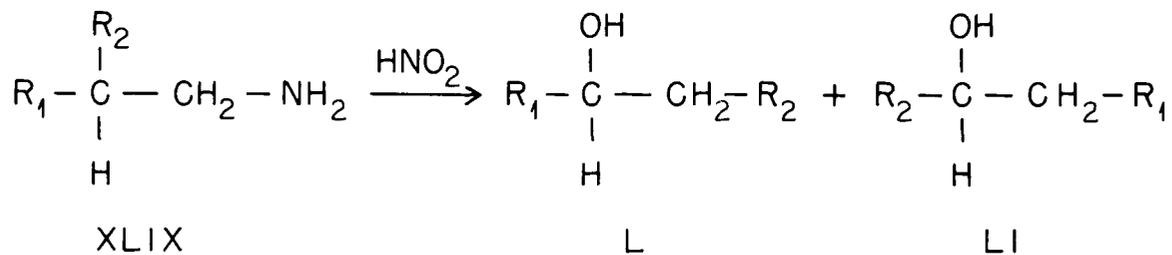


deaminations was the first step towards the proposal of a suitable mechanism.^{21,22}

In addition to the basic recognition of the rearrangement and the qualitative differences in migratory aptitudes, McKenzie found it "remarkable that optical activity (was) preserved in spite of the molecular rearrangement which (was) involved."⁶ He had prepared (-)-2-amino-1,1-diphenyl-1-propanol XLVII from (+)-alanine ethyl ester hydrochloride XLVI and phenyl magnesium bromide, treated it with nitrous acid and isolated (+)-methyldesoxybenzoin XLVIII. McKenzie noted a similar stereospecificity with the same reaction sequence starting with phenylalanine: (-)-phenylalanine ethyl ester \rightarrow (-)-1,1,3-triphenyl-2-amino-1-propanol \rightarrow (+)-benzyldesoxybenzoin



There must also have been some racemization in these reactions, since the observed rotation of the total ketones of the deamination reaction was not as high as the purified optically active ketone isolated from the reaction mixture. Likewise, McKenzie observed a difference in the migratory aptitude of various substituent groups.²¹ Subsequently, other investigators have measured and expressed migratory aptitudes as ratios referred to phenyl.²³ Migratory aptitudes were readily determined in rearrangements of compounds in which both groups in question have an equal opportunity to migrate, so that any differences in the quantities of rearranged products would be the result solely of differences in the electronic nature of the moving group. Symmetrically aryl-substituted pinacols²⁴⁻²⁶ or 2,2-diaryl-substituted ethylamines²⁷ appear to be examples of compounds of the type which permit direct measurement of migratory aptitude, at least when no ortho-substituents are present in the aryl moieties.



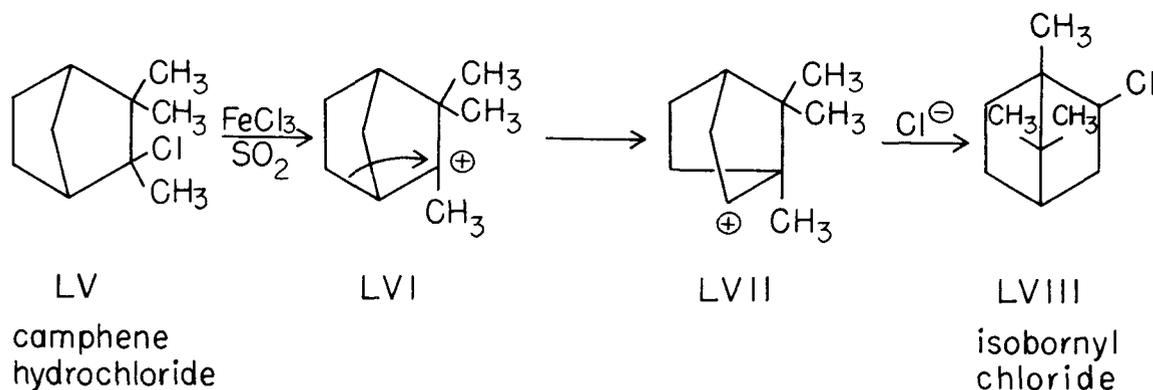
Where steric requirements of the molecule predominate,²⁵ or if some substituent participates so as to influence the site of formation of the carbonium ion,^{23,28} the situation becomes more complicated. In the Semipinacolinic Deamination, the influence of the electronic nature of the migrating group is often completely overshadowed by the steric requirements of the molecule.¹ In a 1,1-diaryl aminoalcohol, for example, the ratio of products of deamination is a consequence mainly of the relative positions of the two aryl groups, not of their migratory aptitudes.

Listings of migratory aptitudes may be found in many texts. These values are approximately in the order of the nucleophilic nature of each group.^{29,30} A knowledge of migratory aptitude values permits prediction of the

expected relative yields of products where more than one group is in a position to migrate. If the relative order is not qualitatively adhered to in a given reaction of this type, an alternate mechanism may be suspected.^{1,29,31}

In addition to determinations of stereospecificity and migratory aptitudes in deaminations, investigators in this field have been interested in the exact mode of transfer of the migrating group to its migration terminus.¹² It was proposed by an early theory that an ethylene oxide structure was an intermediate in the rearrangement.³² In support of this theory were experiments showing: (1) that oxides are occasionally isolated in the Pinacol Rearrangement,³³ and (2) that some oxides are known to rearrange under conditions of the Pinacol Rearrangement to produce ketones.⁹ However, it has been shown that oxides can form the glycol first and then rearrange.³⁴ Also arguing against this theory is the failure to isolate an oxide during reactions when the expected oxide is stable and could have been isolated were it present.³⁵⁻³⁷ Oxide formation does not explain the migration itself, and its role as an intermediate is not fully understood yet. Cycloalkane structures were once proposed as intermediates during "1,2-Shifts"³⁸ and then rejected by the evidence that the point of attachment of substituted aryl groups was not changed during migration.³⁹ In the Wagner-Meerwein Rearrangement of isoborneol to camphene, tricyclene

corresponds to the postulated cyclopropane intermediate. Synthesized independently, tricyclene, under the conditions of the experiment, could not be converted to camphene.⁴⁰ A free radical hypothesis advocated at one time by Tiffeneau⁴¹ and McKenzie,⁹ was similarly unsupported by the facts. The existence of an electron-deficient carbon atom, now called a carbonium ion, was proposed by Meerwein and van Emster as a result of their observations on the kinetics of the rearrangement of camphene hydrochloride to isobornyl chloride.⁴⁰ The rate of rearrangement increased when the experimental conditions were changed to increase the amount of ionization of camphene hydrochloride. Coordinating metal halides, as HgCl_2 , FeCl_3 , and SnCl_4 , known to form additive compounds with triphenylmethyl chloride, also acted as strong catalysts for the camphene hydrochloride rearrangement. The idea of an electron-deficient carbon atom

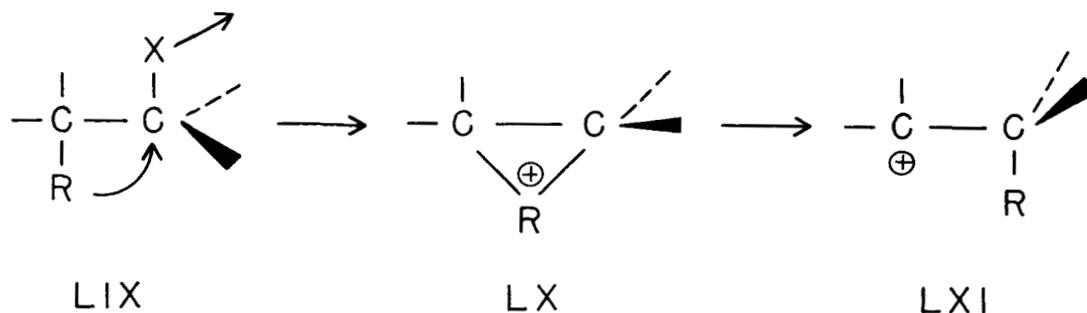


received further experimental support by Meerwein and others⁹ and was developed as a general theory by Whitmore.⁴² Whitmore⁷ used the idea of an electron-deficient carbon atom to explain a rearrangement which had been performed earlier by McKenzie.⁶ In this reaction, the starting compound was the aminoalcohol, (-)-1,1-diphenyl-2-amino-1-propanol XLVII synthesized from (+)-alanine ethyl ester XLVI. Using the data of McKenzie for the deamination of XLVII, Whitmore calculated that the reaction produced 94 per cent of (+)-methyldesoxybenzoin. This calculation was based on a crude ketone yield of 1.9 gms. from 2.2 gms. of aminoalcohol. The unpurified ketone had a specific rotation of $+158^{\circ}$ in chloroform. After purification, the ketone was found to have a specific rotation of $+207^{\circ}$ in chloroform which corresponds to 88 per cent inversion and 12 per cent retention, in good agreement with the results of deamination of the same phenyl-labeled aminoalcohol reported by Benjamin and Collins.⁴

By relating the configuration of starting aminoalcohol and ketonic product, Whitmore showed clearly that inversion had taken place.⁷ The argument in favor of a carbonium ion followed in his discussion, with the stipulation that the carbonium ion did not exist independently, else "racemization would seem inevitable." The large yield of optically active ketone led him to conclude that migration had taken place with Walden Inversion. These

results were additional evidence for a simultaneous rearward attack on the migration terminus by the migrating group at the moment of removal of the leaving group. The mechanism for this reaction did not take into account the 12 per cent of ketone produced with retention of configuration.

The idea of a concerted rearward attack on the migration terminus led many investigators to the concept of a bridged ion as an intermediate in these rearrangements.^{30,43} This bridged-ion theory differs from the cyclopropane theory once proposed³⁸ and to which it seems similar. In bridging, no hydrogen atom is lost, and the cyclic intermediate has a positively charged fragment partially bonded between the migration origin and terminus. The bridged-ion mechanism clearly indicates how the migrating group participates in the rearrangement to result



in inversion of configuration at the site of the leaving group. Participation of the neighboring group, leading to bridging, controls the steric configuration of the molecule

during a subsequent reaction--as elimination, solvolysis, halogenation or rearrangement--and increases the reaction rate if the participation occurs in the rate-determining step.⁴³ The idea of "neighboring group participation" or "anchimeric assistance"⁴⁴ was developed by Winstein and Lucas⁴⁵ and used very admirably to explain the observed configuration of the intermediates and final products in the transformation of meso- and racemic-2,3-acetoxybutane to the racemic- and meso-dibromide, respectively, with fuming hydrobromic acid.⁴⁵ The existence of a bridged "bromonium" ion prevents a second inversion which would have restored the original configuration. The ability of bromine to engage in bridging is explained on the basis of its unpaired electrons in proximity to an electron-deficient carbon atom. The nucleophilic character of aryl groups had led to theories of aryl participation by bridging, in a similar manner.⁴³

Evidence for a bridged "phenonium" ion derives from its use in explaining the acetolysis of the stereoisomers of the tosylate of 3-phenyl-2-butanol.⁴⁶ A "phenonium" ion intermediate is consistent with the observation that the acetolysis of an optically pure threo-tosylate produces dl-threo-acetate, whereas the optically pure erythro-tosylate is converted to the erythro-acetate with retention of configuration. It should be noted that such bridging precludes formation of the classical open carbonium

ion with free rotation about the central C-C bond, but it also causes, if it occurs in rearrangements, inversion of configuration at the migration terminus. Although these intermediate bridged forms are used in explaining solvolytic stereospecificity, they cannot be used to account for that portion of aminoalcohol rearrangements which occurs with retention of configuration, as shown previously,^{4,6} and as will be mentioned subsequently in this dissertation.

The Semipinacolinic Deamination has also been explained by using another mechanism utilizing bridged intermediates. In this theory there is the requirement that intermediate stages have the nonmigrating groups trans to each other.^{1,47-51} This theory was first stated by Curtin in reference to a reaction in which the formation of trans-stilbene is preferred to that of cis-stilbene, and was named the "cis-effect" because of the total destabilization of the transition state leading to the cis product compared to that leading to the trans product. The ". . . cis-effect is . . . a composite . . . (result) . . . of steric strain, steric inhibition of resonance, dipole interactions and selective restriction of motion in one isomer."^{52,53}

The reactions which illustrate the cis-effect as applied to deaminations are shown in Charts 1 and 2. According to the theory, unrestricted rotation is permitted about the C-C bond, just prior to bridging and migration,

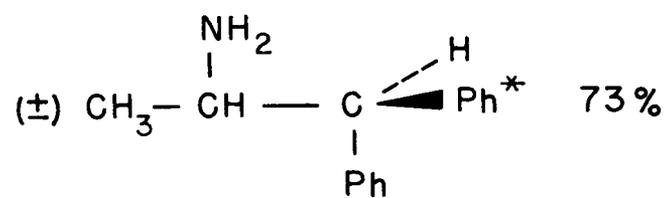
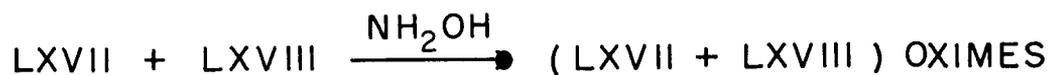
with the choice of migrating group being a function of the trans placement of the nonmigrating groups and the smaller difference in free energy associated with that transition state.¹ As mentioned in the introduction to this dissertation, Curtin's use of racemic diastereoisomers obscured the stereospecific nature of the rearrangements that were observed. His theory, therefore, did not take into account the possibility of retention of configuration.

Since 1953, Collins and co-workers have been examining the results of Pinacol Rearrangements, deaminations and solvolyses of optically pure alcohols, amines and esters in the 1,2,2-triphenylethyl system.^{8,54-56} Using carbon-14-labeling and isotope-dilution techniques, the identities of the migrating groups and the amounts of inversion and retention in these rearrangements were accurately determined. The mechanism that was postulated to account for these results required open, equilibrating, classical carbonium ions. In reference to the deamination reaction, the identity and direction of attack of the migrating group was expressed as a dependence on the steric conformation of the ground state, with migration occurring quickly compared to the rotation about the C-C[⊕] bond.

An open carbonium ion, with a possible rotation of 60° about the C-C[⊕] bond, is postulated as an intermediate leading to formation of ketone of 88 per cent inverted and 12 per cent retained configuration in the deamination⁴ of

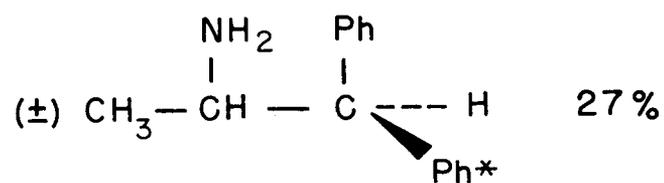
1,1-diphenyl-2-amino-1-propanol (Chart 3). The carbonium ion intermediates leading to rearrangement with inversion and retention in the deamination of the aminoalcohol are shown in Newman projections on Chart 4.

More rigorous dependence on an open carbonium ion is required by the sequence of reactions shown on Chart 6, in which L-(+)-1,2-diphenyl-1-amino-2-propanol-1-phenyl-C¹⁴, LXII, is deaminated and rearranged to 1,1-diphenyl-propanone-phenyl-C¹⁴.⁵⁷ Only the nonlabeled-phenyl group migrated, but the amount migrating with inversion, LXVII, or retention, LXVIII, as shown on Chart 6, had to be determined by the subsequent reactions shown on Charts 7 and 8. The ketone LXVII + LXVIII is converted to the oxime, and the oxime is reduced to 1,1-diphenyl-2-amino-propane, LXIX + LXX, a molecule in which the labeled-phenyl group is distributed in accordance with the products of deamination shown on Chart 6. By a resolution of the amine LXIX + LXX, it is possible to separate the dextrorotatory molecules of LXIX + LXX, from the levorotatory molecules of LXIX + LXX. Compounds LXIX + LXX are indistinguishable chemically, but their different stereoselective label can be used to differentiate them. Deamination of each of these enantiomers, followed by degradative study of the labeled-phenyl distribution (Chart 8), yielded the results shown before on Chart 6 for the distribution of radioactivity in the phenyl groups. The configurations as shown



(±) - LXIX

+



(±) - LXX

Chart 7.—Synthesis of 1,1-diphenyl-2-amino-propane-phenyl-C⁴ from benzhydryl-phenyl-C⁴ methyl ketone of Chart 6.

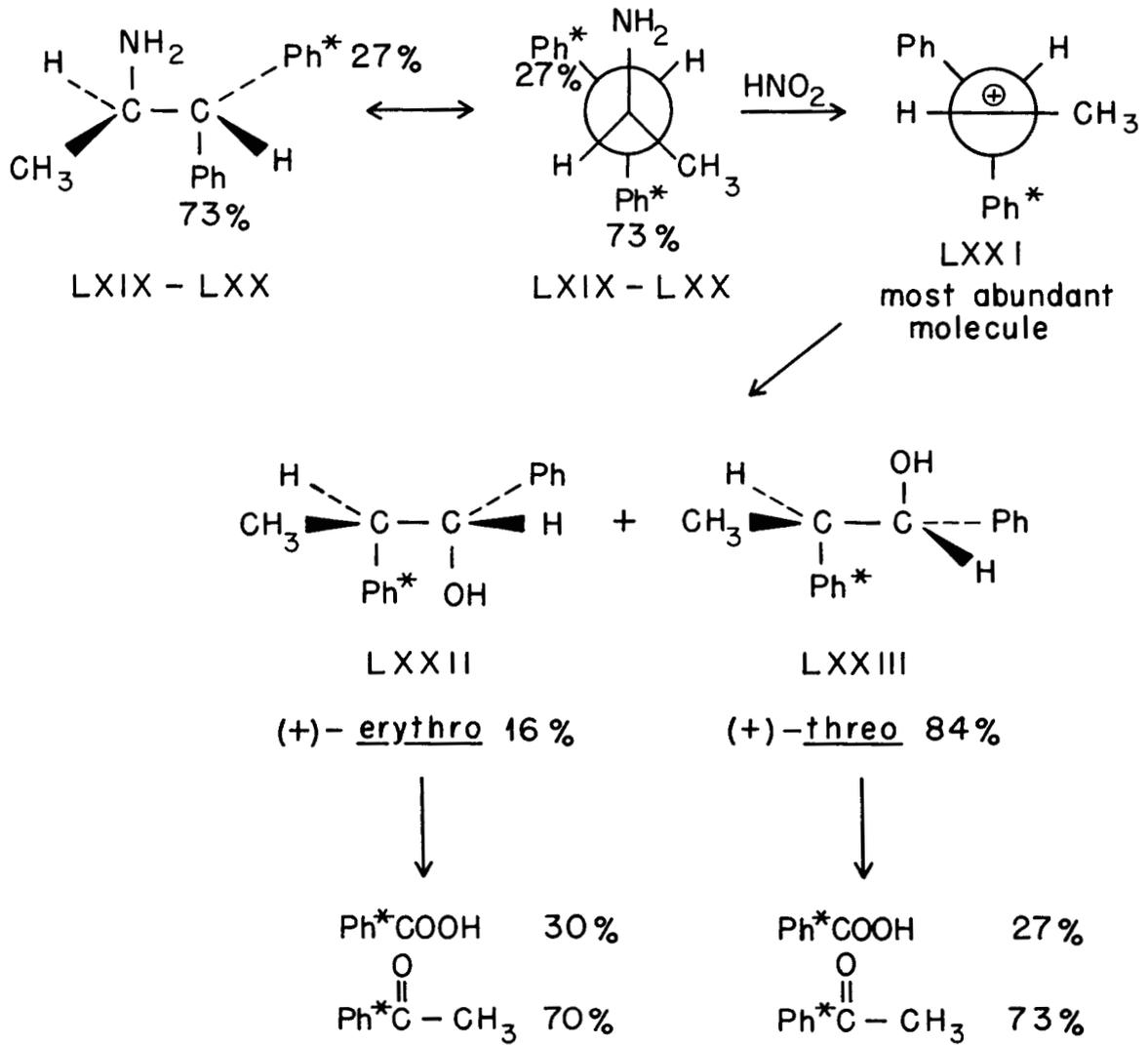
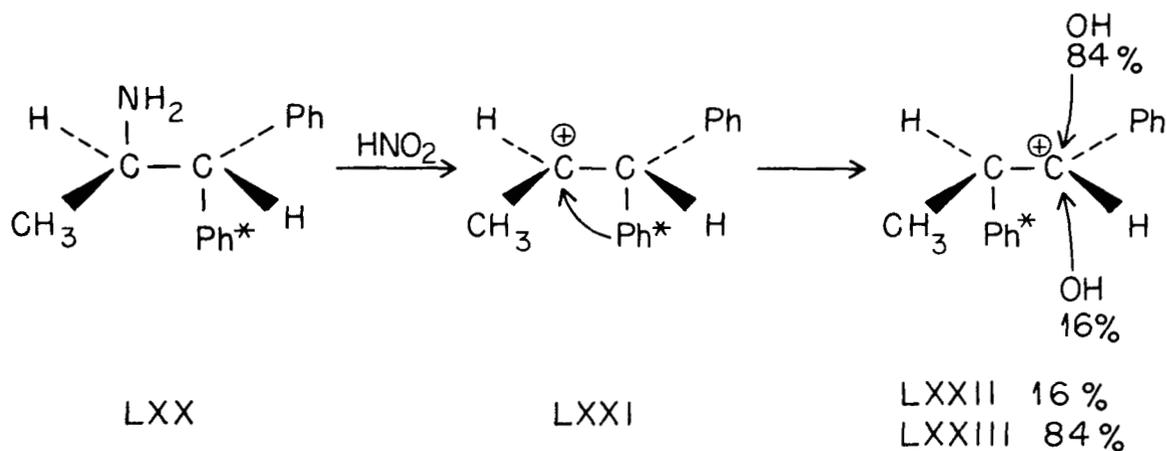


Chart 8.—Deamination of 1,1-diphenyl-2-amino-propane-phenyl-C₁¹⁴ with analysis of radioactivity distribution by degradation study.

on Chart 8 for the compounds in this reaction are in accordance with their proven relationship to D-(-)- and L-(+)-phenylglycine.

In the deamination shown on Chart 8, not more than 1 per cent racemic product was formed. The absence of racemic product indicated that rearrangement occurred completely with inversion and through a trans-transition state. If the migration had occurred with bridging, as might be inferred from the observed 100 per cent inversion at the migration terminus, the hydroxyl group could come in only on the side opposite the migrating group and no erythro diastereomer could form. The erythro form LXXII was found to the extent of 16 per cent. The existence of LXXII and LXXIII indicates that a short-lived carbonium ion is formed at the migration origin after the migrating group leaves.



The reaction sequence shown on Chart 8 was repeated with the labeling reversed, that is, starting with D-(-)-1,2-diphenyl-1-amino-2-propanol-2-phenyl-C₁⁴. Oxidative degradation of the final threo carbinol of the series gave substantially the same, but inverted, ratio of distribution of the phenyl label in the benzoic acid and acetophenone fractions, 74:26, as expected.⁵⁷

Another reaction performed by Collins, et al., involved the deamination of enantiomers of erythro- and threo-1-amino-1-phenyl-2-p-tolyl-2-propanol. The rearrangement produced (+)- and (-)-1-phenyl-1-p-tolylpropanone in amounts which cannot be justified by a bridged-ion theory.⁵⁷ The threo and erythro aminoalcohols LXXIV and LXXIX have been related to D-(-)-phenylglycine, and their absolute configurations are shown in the deamination sequences on Charts 9 and 10.

Chart 10 indicates clearly that more retention than inversion of configuration had taken place on deamination of the threo compound. Examination of the ground state conformation leading to inversion, LXXIXb, shows that a close steric position is required for the three bulkiest groups in the molecule, and that migration would require a cis-transition state. These results, therefore, demand an open classical carbonium ion with migration of groups in the order and direction governed by the most favorable ground state conformations.

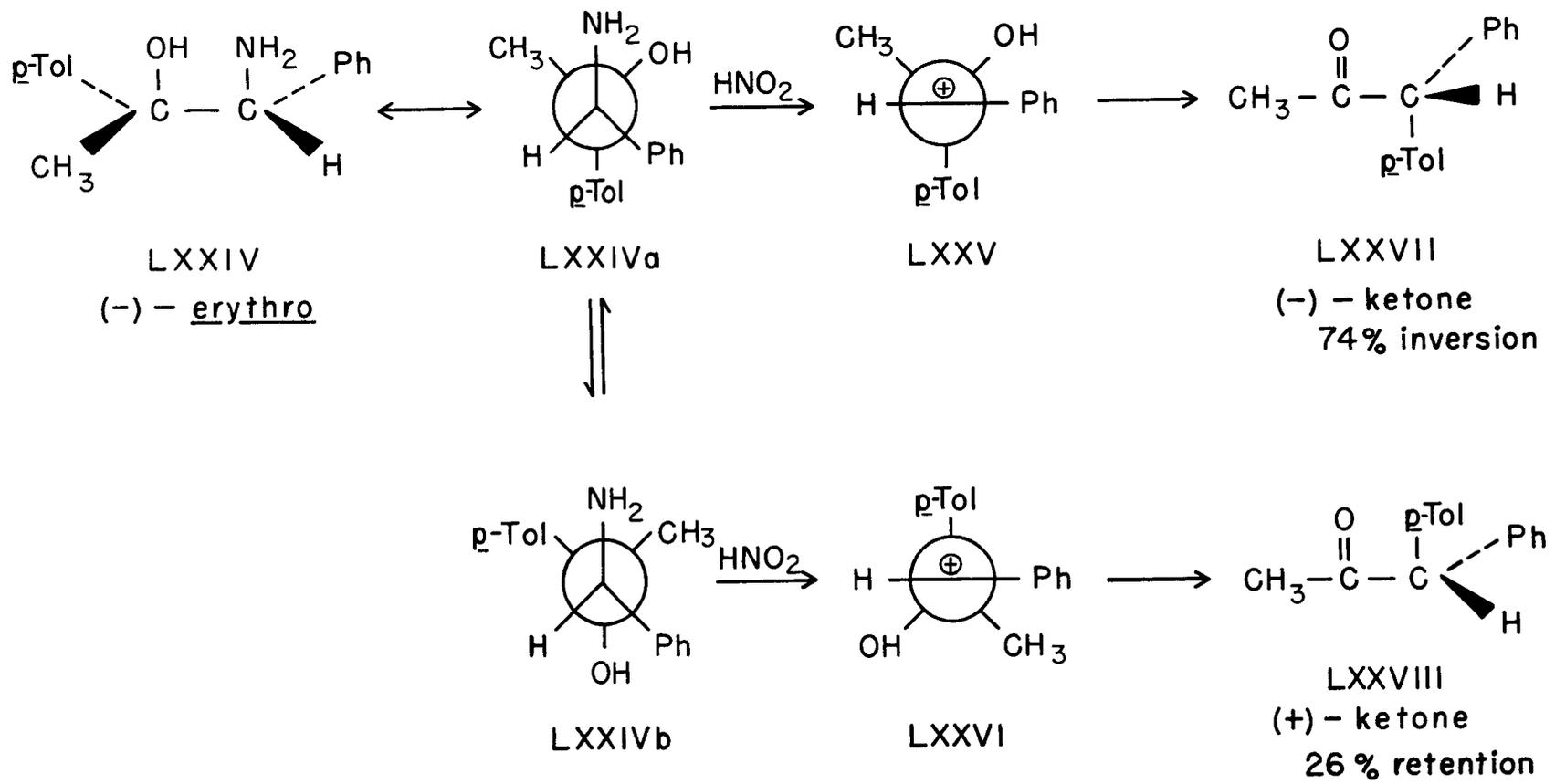


Chart 9.—Deamination and rearrangement of erythro-(-)-1-amino-1-phenyl-2-p-tolyl-2-propanol.

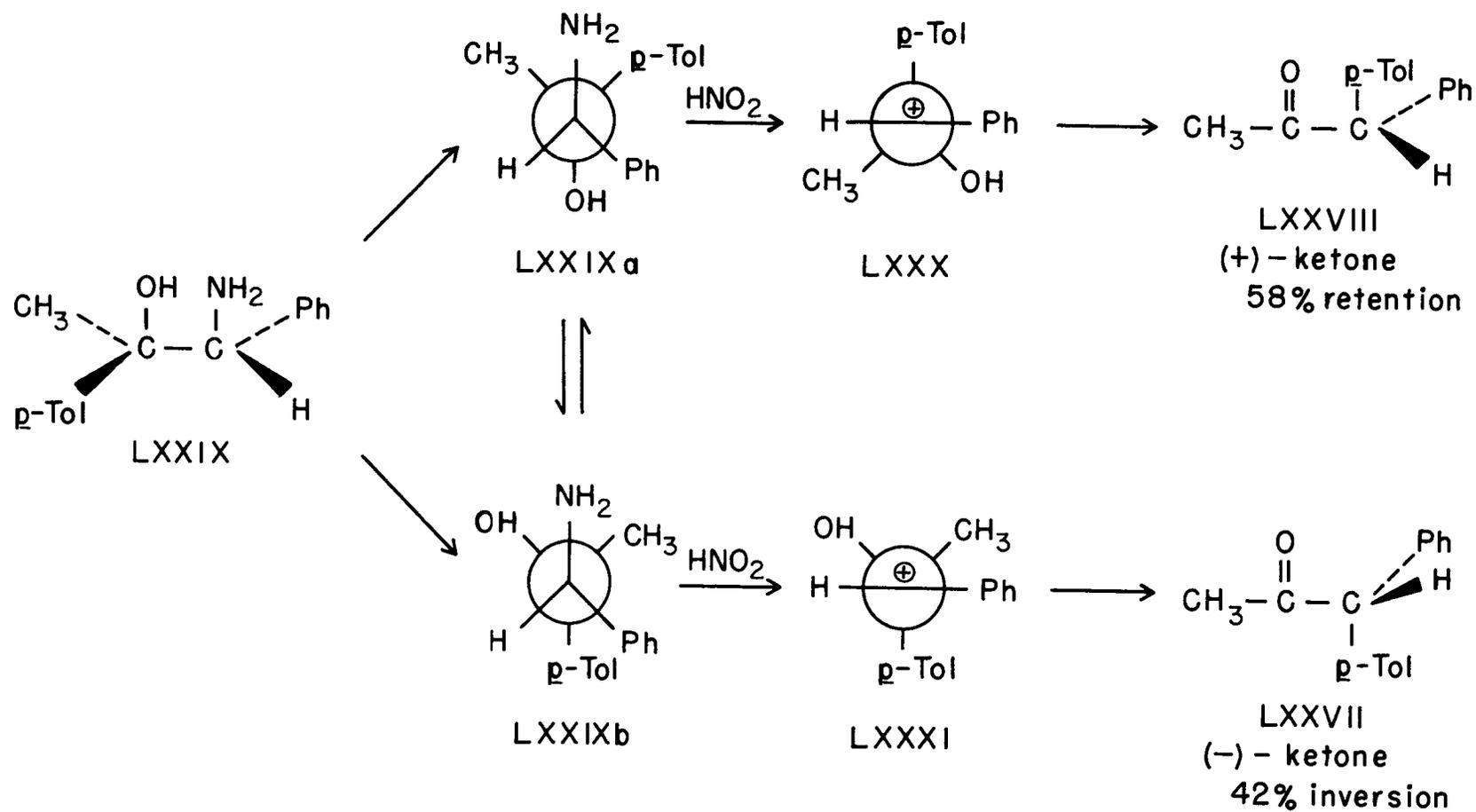


Chart 10.—Deamination and rearrangement of threo-(+)-1-amino-1-phenyl-2-p-tolyl-2-propanol.

Further information about this theory will be sought by the deamination and rearrangement of the enantiomers of the sterically hindered erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol and by examination of these results in relation to deaminations of similar compounds of this series.

METHODS AND RESULTS

The synthesis of erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride XXI was accomplished according to the sequence of reactions shown on Chart 11, in which the addition of methyl magnesium bromide to the aminoketone LXXXVIII follows a well-established rule of stereospecificity to produce the erythro compound.^{1,5-7}

The nomenclature describing the erythro and threo diastereomeric pairs containing two adjacent asymmetric centers relates these compounds arbitrarily to erythrose and threose. Oxidation of erythrose produces meso-tartaric acid, whereas oxidation of threose produces dl-tartaric acid. By analogy, when the same or similar substituent groups (-OH and -NH₂ in aminoalcohols) attached to each of the two asymmetric centers of diastereomers are aligned in one plane, the erythro designation refers to the configuration of the molecule if the two larger, or specifically designated groups of approximately equal constitution, are on the same side of the plane; threo, if they are on opposite sides.⁵⁸

The enantiomers of the erythro aminoalcohol XXI were separated by resolution with d-tartaric acid and with d-10-camphorsulfonic acid. The d-tartaric acid salt of $[\alpha]_D^{25} = -37.5^{\circ}$ (water) yielded the aminoalcohol

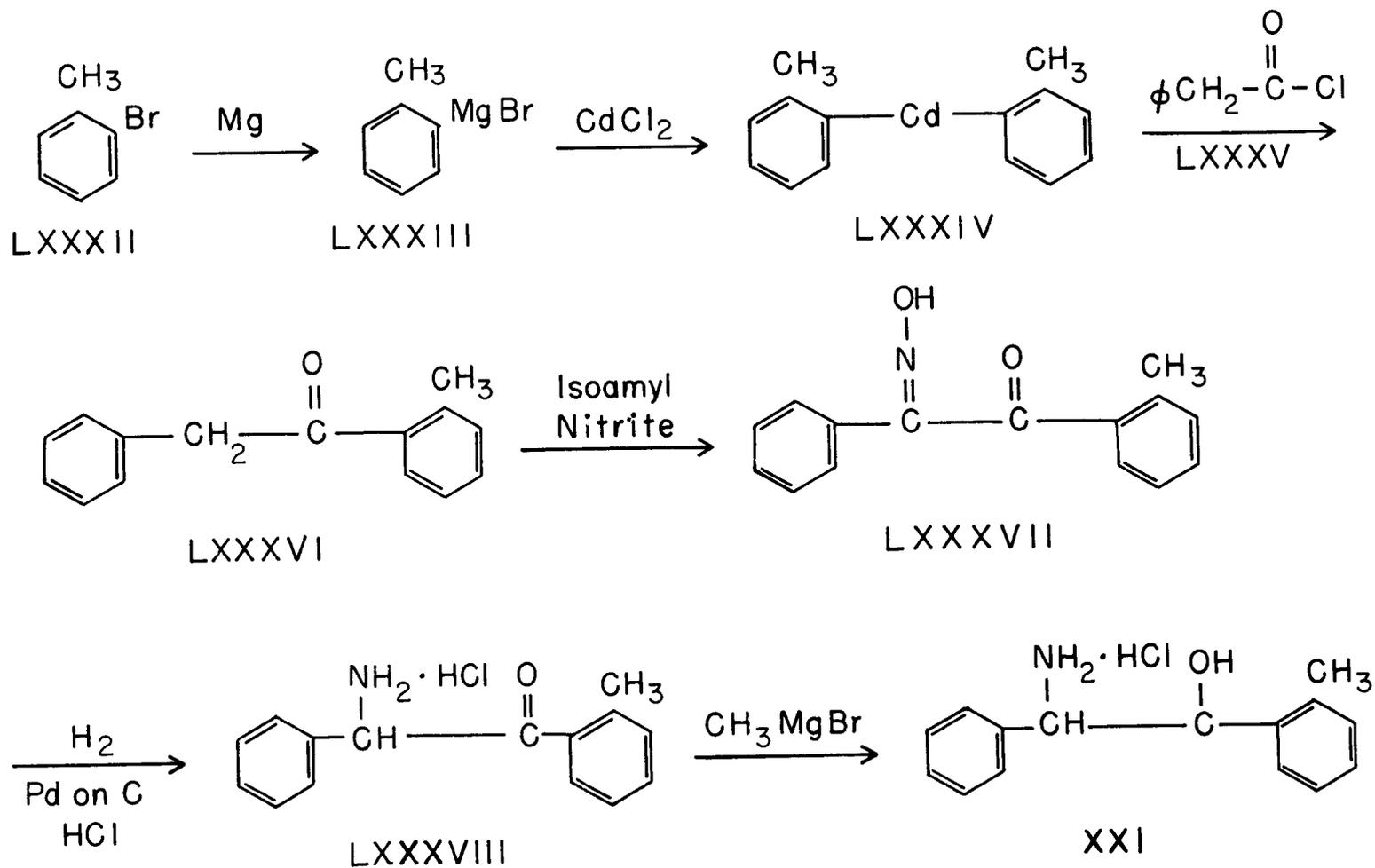


Chart 11.—Synthesis of erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride.

hydrochloride of $[\alpha]_D^{25} = -83^\circ$ (ethanol). The other d-tartaric acid salt was very soluble and could not be crystallized. Hydrolysis of the mother liquors did not produce optically pure aminoalcohol. The d-10-camphor-sulfonic acid salts of the aminoalcohol were separated by fractional crystallization into diastereomers of $[\alpha]_D^{25} = -28.4^\circ$ (ethanol) and $+72^\circ$ (ethanol), which yielded, upon hydrolysis, aminoalcohol hydrochlorides of $[\alpha]_D^{25} = -83^\circ$ (ethanol) and $+83^\circ$ (ethanol), respectively.

In a preliminary test, a small sample of erythro-(-)-aminoalcohol hydrochloride was deaminated. The oily extract, after being washed and dried, had a specific rotation in ethanol of $+79^\circ$. This crude extract was dissolved in hexane and passed through a column of alumina. The infrared absorption curve exhibited by the concentrated eluate was characteristic of the o-tolyl migration product, 1-phenyl-1-o-tolylpropanone XXIII. To analyze exactly for the amount of this ketone, as racemate and as excess of the (+)-enantiomer, the techniques of the isotope-dilution methods, as modified by Berson,⁵⁹ have been employed. This required the synthesis, shown on Chart 12, of 1-phenyl-1-o-tolylpropanone-3- C^{14} . Since the position of the radioactive label was unimportant for isotope-dilution purposes, the carbon-14 was incorporated during the last step. The synthesis of dimethyl- C^{14}_2 cadmium XCIV is shown on Chart 13.

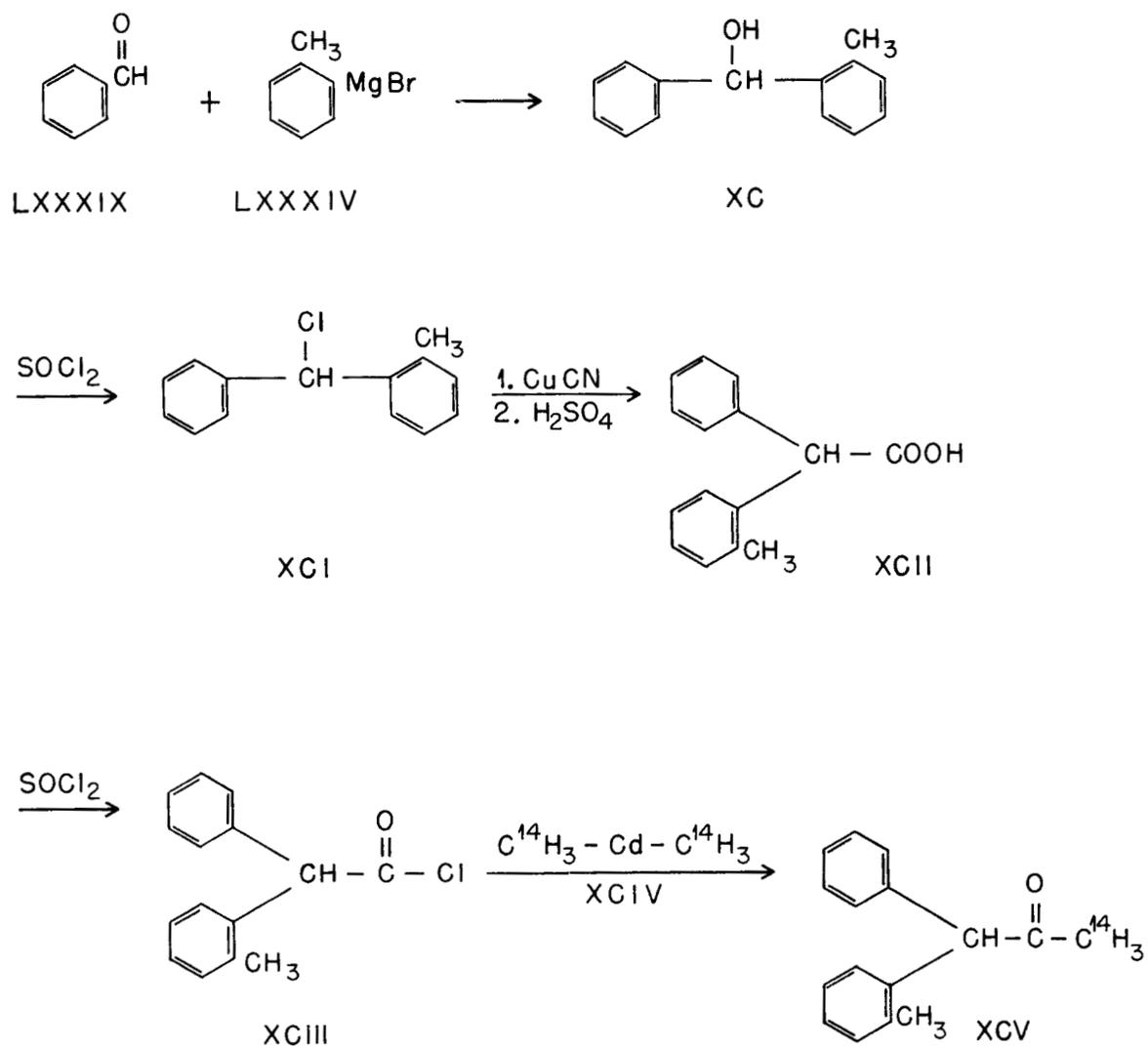


Chart 12.—Synthesis of 1-phenyl-1-o-tolylpropanone-3- C^{14} .

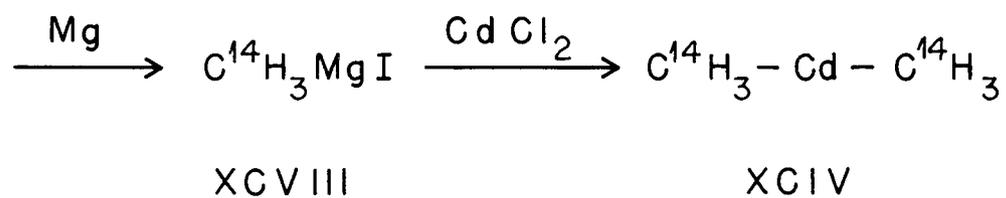
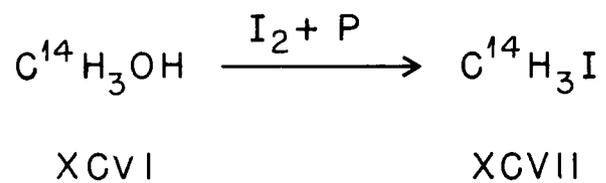


Chart 13.—Synthesis of dimethyl-C¹⁴ cadmium.

A synthesis of optically active ketone was first attempted in order that the isotope-dilution analysis could be carried out with the more familiar and simpler mathematical treatment of results.⁶⁰ This procedure called for the resolution of phenyl-o-tolylacetic acid XCII, one of the intermediates in the reaction sequence of Chart 12, and then a continuance of the synthetic procedure with the individual enantiomers. Since the reactions involved in converting the acid to the ketone do not occur directly on the asymmetric center, it was thought that this procedure would produce an optically active ketone. The acid was resolved using cinchonidine, which produced a salt of $[\alpha]_D^{25} = -46.5^\circ$ (methanol), yielding (+)-phenyl-o-tolylacetic acid upon hydrolysis. The mother liquors of the cinchonidine salt yielded the other enantiomer of the acid upon hydrolysis.

However, the final step in the reaction leading to the ketone produced almost completely racemic product. It may be possible, by using gentler reaction conditions, to prepare the enantiomeric 1-phenyl-1-o-tolylpropanone-3- C^{14} . This was not done because the racemic, radioactive ketone which was isolated was satisfactory for the isotope-dilution analysis.

As shown on the accompanying Tables 1 and 2, the yield of 1-phenyl-1-o-tolylpropanone XXIII consisted of 96.5 per cent of the (+)-enantiomer and 3.5 per cent of the (-)-enantiomer.

TABLE 1

EXPERIMENTALLY MEASURED DATA OF THE
 DEAMINATION OF erythro-(-)-1-AMINO-
 1-PHENYL-2-o-TOLYL-2-PROPANOL

	Experiment I	Experiment II
Specific rotation of sample	-82.0 ^o	-80.2 ^o
Weight of sample of aminoalcohol hydrochloride	3.41 gms.	3.53 gms.
Total yield of deamination	2.75 gms.	2.87 gms.
Amount of hot racemic ketone diluent	2.75679 gms.	2.98433 gms.
Molar radioactivity of racemic ketone diluent	2.9679 mc./mole	2.9649 mc./mole
Molar radioactivity of racemic ketone reisolated from deamination experiment	2.0474 mc./mole	2.0425 mc./mole
Molar radioactivity of racemic ketone reisolated after racemization	1.7505 mc./mole	1.7524 mc./mole

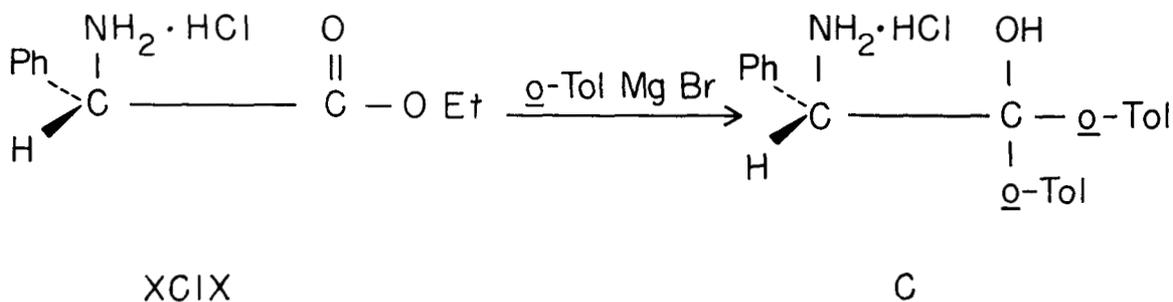
TABLE 2

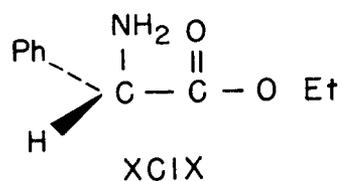
DETERMINATION OF THE RATIO OF ENANTIOMERS OF 1-PHENYL-1-
o-TOLYLPROPANONE IN THE DEAMINATION OF erythro-(-)-
1-AMINO-1-PHENYL-2-o-TOLYL-2-PROPANOL

	Experiment I	Experiment II
Theoretical yield	70%	72%
Total ketones	1.9175 gms.	2.0649 gms.
Yield of excess (+)-enantiomer of ketone	1.7803 gms.	1.9028 gms.
Yield of racemic ketone	0.13720 gms.	0.16213 gms.
Total (+)-enantiomer	1.8489 gms.	1.9838 gms.
Total (-)-enantiomer	0.0686 gms.	0.0811 gms.
Per cent of (+)-enantiomer	96.42%	96.07%
Per cent of (-)-enantiomer	3.58%	3.93%

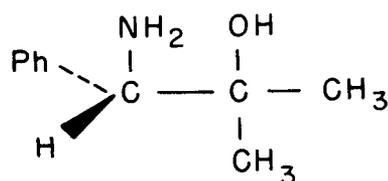
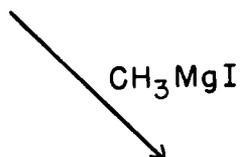
In relating the absolute configuration of the aminoalcohol XXI to compounds of known configuration, several methods were tried. Most of them failed, presumably because of the severe steric conditions which were imposed by these methods on the hydroxy-carbon atom of the aminoalcohol. The configuration was established ultimately by relating the erythro to the threo aminoalcohol through a common derivative. The absolute configuration of the threo compound has been established by Benjamin⁶¹ with the series of reactions shown on Chart 14. The configurational relationship of erythro and threo aminoalcohols is shown on Chart 15 and is based on the identity of the dehydrated products.

To relate the configuration of the erythro aminoalcohol to phenylglycine by a method similar to that shown on Chart 14, it was necessary: (1) to resolve the amino-ketone, 2-amino-2-phenyl-2'-methylacetophenone LXXXVIII, and (2) to prepare the corresponding di-o-tolyl aminoalcohol, C, from the resolved ketone as well as from an enantiomer



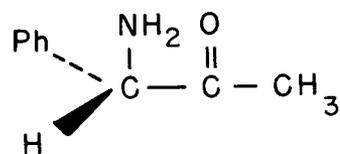
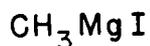


L-(+)-Phenylglycine
Ethyl Ester
 $[\alpha]_D^{25} = +156^\circ$ (ethanol)



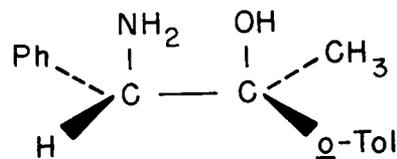
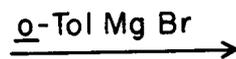
CI

$[\alpha]_D^{25} = +11.2^\circ$ (ethanol)



LXXXVIII a

$[\alpha]_D^{25} = +360^\circ$ (ethanol)



CII

L-(-)-Threo-1-Amino-1-Phenyl-
2-o-Tolyl-2-Propanol

$[\alpha]_D^{25} = -64.5^\circ$ (ethanol)

Chart 14.—Relationship of configuration of
L-(-)-threo-1-amino-1-phenyl-2-o-tolyl-2-propanol to
L-(+)-phenylglycine.

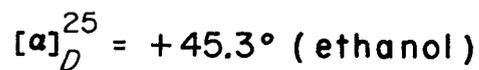
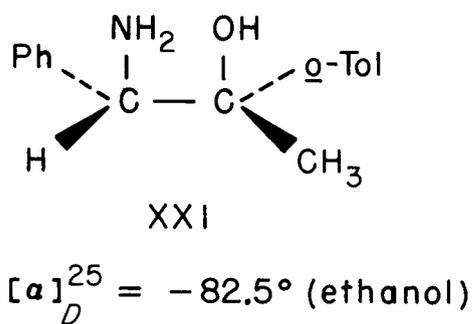
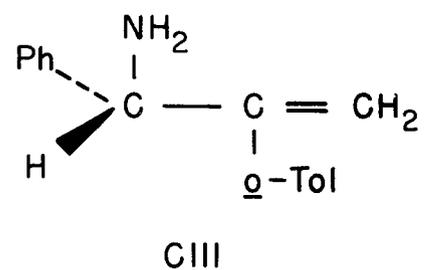
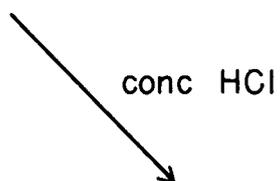
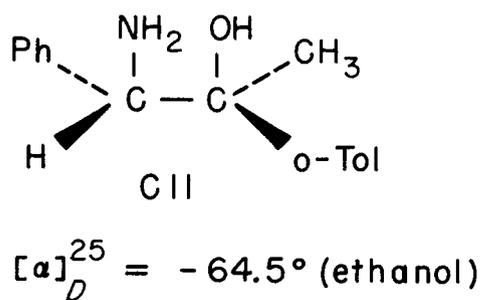
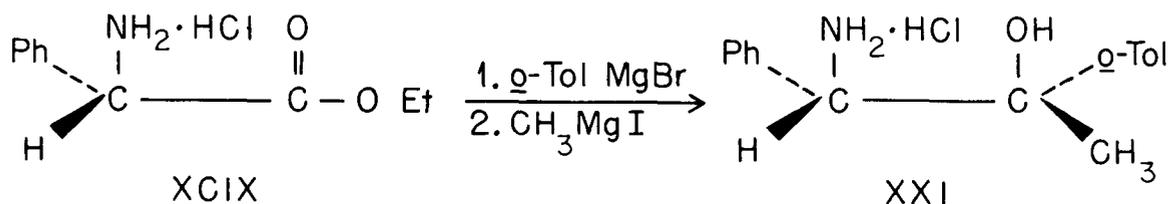


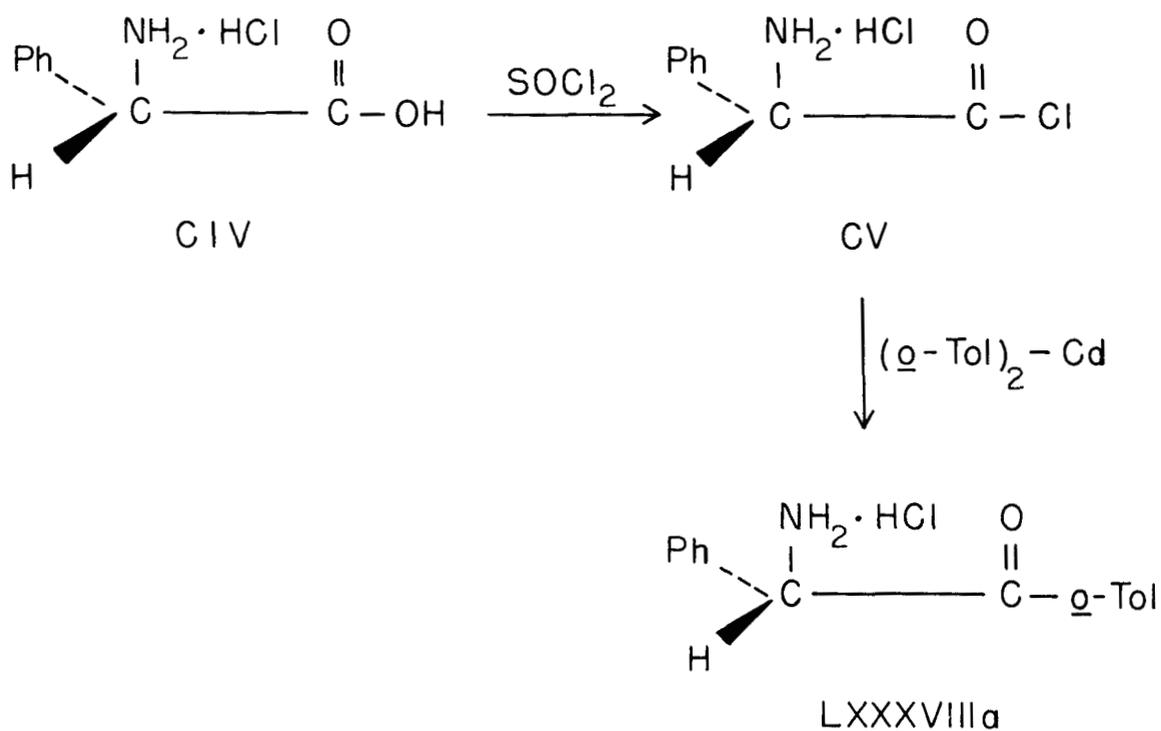
Chart 15.—Relationship of configuration of L-(-)-erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol to L-(-)-threo-1-amino-1-phenyl-2-o-tolyl-2-propanol.

of phenylglycine ethyl ester. The reaction XCIX \rightarrow C was performed several times following usual techniques, but no aminoalcohol hydrochloride could be isolated. The infrared absorption spectrum of the product was indicative of a ketone rather than a carbinol. Therefore, it was attempted to prepare an enantiomer of the erythro aminoalcohol XXI through a double Grignard addition, XCIX \rightarrow XXI. This was also unsuccessful.

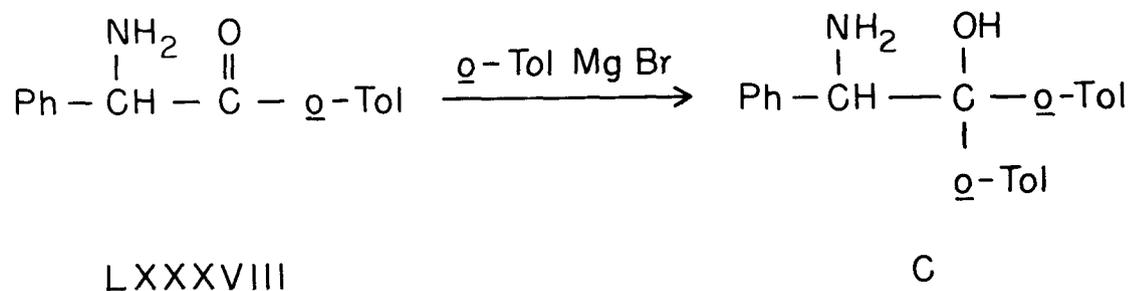


The resolution of the aminoketone was attempted with the (+)-tartrate, (+)-10-camphorsulfonate and (-)-mandelate salts. All of the salt solutions underwent gradual decomposition to a brown, oily liquid. Compounds recovered from these salts did not resemble the original aminoketone in physical properties. The aminoketone LXXXVIII has thus far been found stable only as the hydrochloride. This difficulty corroborates the observations of others on the instability of certain α -aminoketones⁶² and the ease with which the optically active aminoketone undergoes racemization.

An unsuccessful attempt was also made to prepare an enantiomer of the aminoketone by the addition of di-o-tolyl cadmium to the acid chloride of known configuration (CIV → LXXXVIIIa). Finally, the attempt to prepare



dl-1-amino-1-phenyl-2,2-di-o-tolyl-2-propanol, C, from the corresponding racemic aminoketone LXXXVIII with prolonged refluxing of the Grignard reaction was also unsuccessful.



Methods for effecting transformations of erythro to threo aminoalcohols, and vice versa, have been demonstrated recently⁶³ with racemic diastereomers of 1-amino-1,2-diphenyl-2-propanol CVI. A partial scheme of the chemical relationships between these diastereomers is shown on Chart 16.

The methods shown on Chart 16 were employed in attempting to relate an enantiomer of the erythro o-tolyl aminoalcohol XXI of this research to a corresponding enantiomer CII of its threo series. An enantiomer of the erythro aminoalcohol would have the same configuration about the amino-carbon as the threo did, if the trans-oxazolines derived from each of them had the same optical rotation. The compounds isolated after ring closure reactions in the 1-phenyl-2-o-tolyl series were not oxazolines as shown by elemental analysis.

With the exception of the addition of methyl magnesium bromide, all attempts to increase the amounts of aryl substitution on the carbonyl-carbon of the o-tolyl

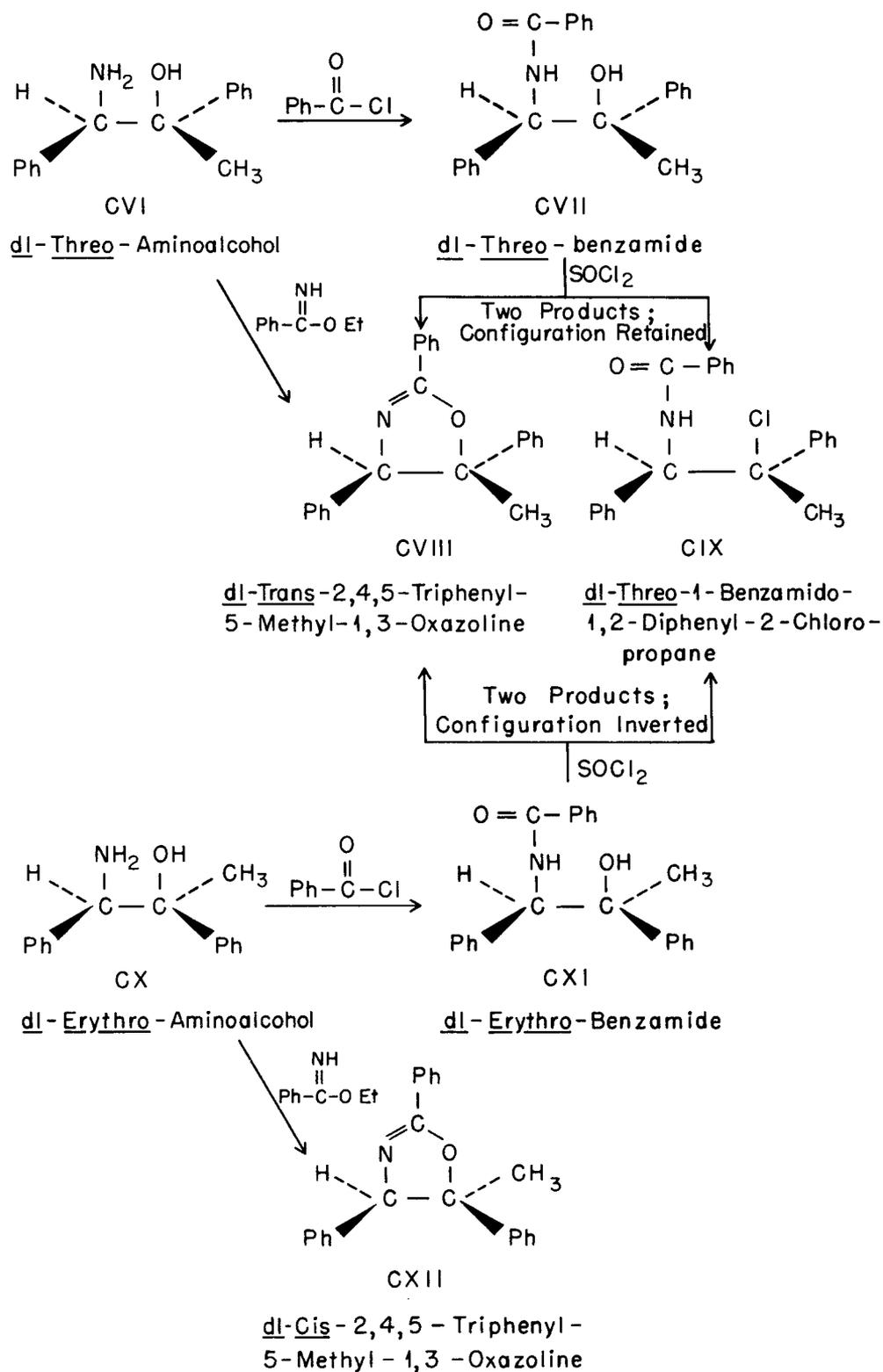


Chart 16.—Transformations of erythro- to threo- 1-amino-1,2-diphenyl-2-propanol.

ketone LXXXVIII have not been successful. The configurational relationship of erythro to threo in this series was done, as shown on Chart 15, by converting a sample of each of the erythro and threo aminoalcohols to the same compound through an elimination reaction.

DISCUSSION

Examination of the data from the deamination of the erythro aminoalcohol XXI indicates that the rearrangement step was 96 per cent stereospecific. With the information gained from the configurational relationship to phenylglycine, Charts 14 and 15, and by analogy with the known course of other reactions of erythro and threo aminoalcohols,^{1,4,48-53} it is consistent to deduce that this reaction has proceeded with predominant inversion of configuration about the migration terminus. Chart 17 shows the conformations and possible pathways of this rearrangement, with the intermediate stages represented by open carbonium ions, as XXII. The almost complete absence of ketone product with retained configuration must then be a consequence of the large population of molecules in conformation XXIIa and of the negligible amount of rotation about the C-C[⊕] bond of ion XXIIa. The small amount of such rotation is a result of the steric requirements of the highly hindered o-tolyl system. Because of the almost complete inversion that occurs, these results are not inconsistent with bridged-ion intermediates. In addition, rearrangement occurs with the nonmigrating methyl and phenyl groups in a trans-transition state. The deamination of the erythro aminoalcohol is, therefore, equally consistent with

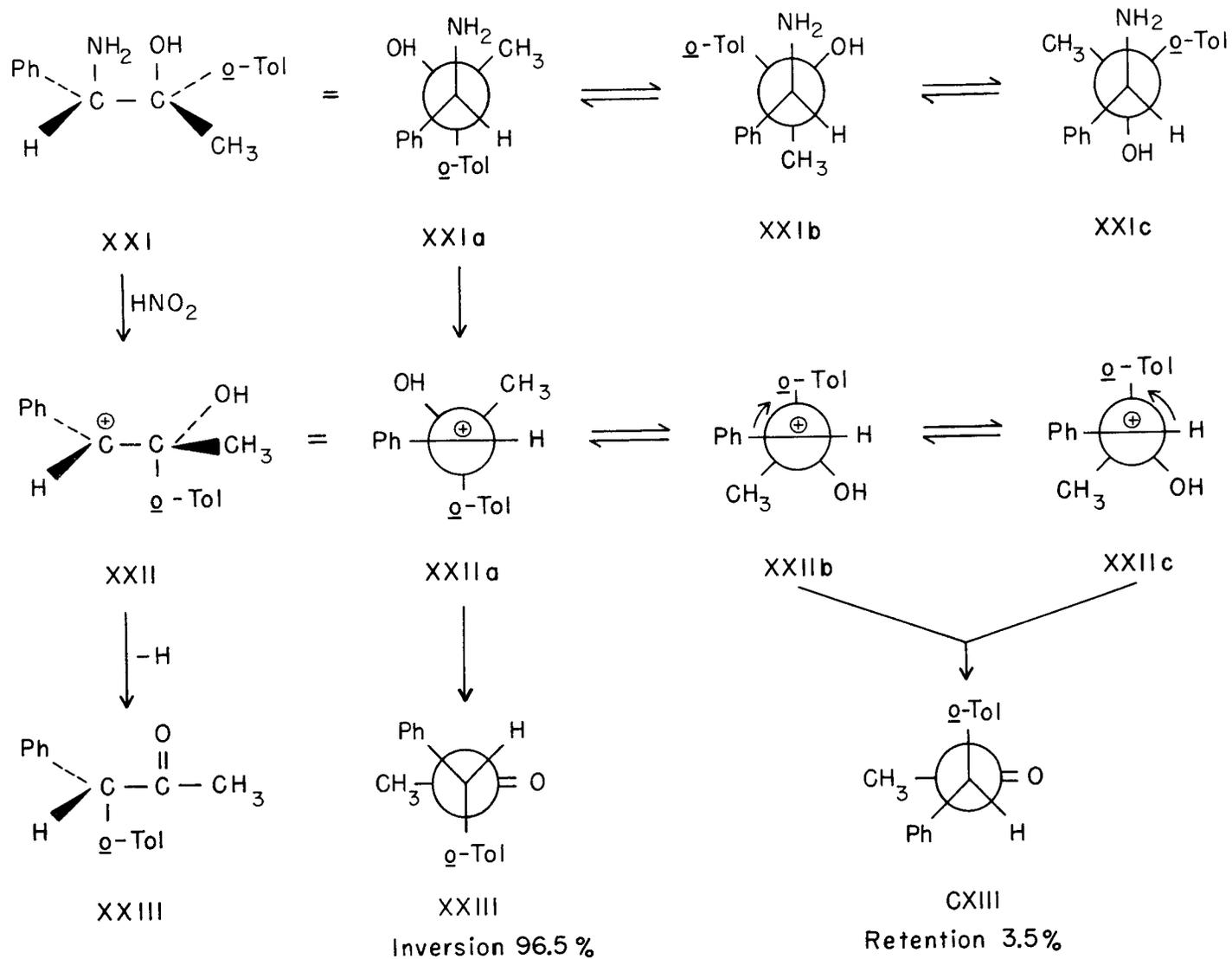


Chart 17.—Proposed pathways for the deamination and rearrangement of L-(-)-erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol.

bridged or open carbonium ion intermediates. However, the p-tolyl member of this aminoalcohol series⁵⁷ undergoes deamination with results which are not consistent with bridged-ion intermediates (Chart 9). A much simpler explanation is provided by the open carbonium ion intermediates LXXV and LXXVI, with restricted rotation about the C-C[⊕] bond. A concerted reaction with bridged ions and participation would not permit the formation of product LXXVIII with retained configuration.

The deamination of the erythro o-tolyl aminoalcohol XXI (Chart 17) can be explained with the added consideration of greater limitation of rotation about the C-C[⊕] bond. The ground state conformation possessed by the largest number of molecules would be one in which no more than two large groups (phenyl, o-tolyl or methyl) are in adjacent or eclipsing positions and would have two large groups trans to each other. Two such conformations are XXIa and XXIc. Deamination of molecules in any of the three possible ground state conformations of XXI should cause rearrangement; inversion results from XXIa, accounting for the bulk of the product; the other two, XXIb and XXIc, require 60° rotation for the o-tolyl group to migrate with retention, accounting for the small amount of ketone of retained configuration. Emphasis must then be placed on the ground state conformation of XXI as controlling in large part the identity and direction of the migrating group.

Also illuminating this reaction mechanism are the results of deamination of the other diastereomer of this o-tolyl series, threo-1-amino-1-phenyl-2-o-tolyl-2-propanol,⁶¹ shown on Chart 18. Examination of the ground state conformations of this molecule shows that there is a conformation of least strain CXIVa comparable to the one of the erythro aminoalcohol XXI from which the bulk of the rearrangement took place. The stereoselective synthesis of the threo aminoalcohol from the corresponding ketone LXXXVIIb places the group previously attached to the carbonyl-carbon of the ketone in a position to migrate with inversion. From conformation CXIVa, a methyl group is in position to migrate with inversion; the o-tolyl group is not in a position to migrate at all. Here it must be argued, the carbonium ion CXVa must exist for a sufficient length of time to allow rotation about the C-C[⊕] bond so that the o-tolyl group can move into position CXVb or CXVc to migrate to the topside or bottomside of the carbonium ion. From the analytical data, it may be deduced that the o-tolyl group has undergone rotation to produce a ketone of inverted configuration CXIII in a slightly larger amount than ketone of retained configuration XXIII.

By analogy, the erythro p-tolyl member of this series rearranged with an inversion to retention ratio of 74:26, as shown on Chart 9. The threo diastereomer is rearranged⁵⁷ with retention favored over inversion by a ratio of 58:42, as shown on Chart 10.

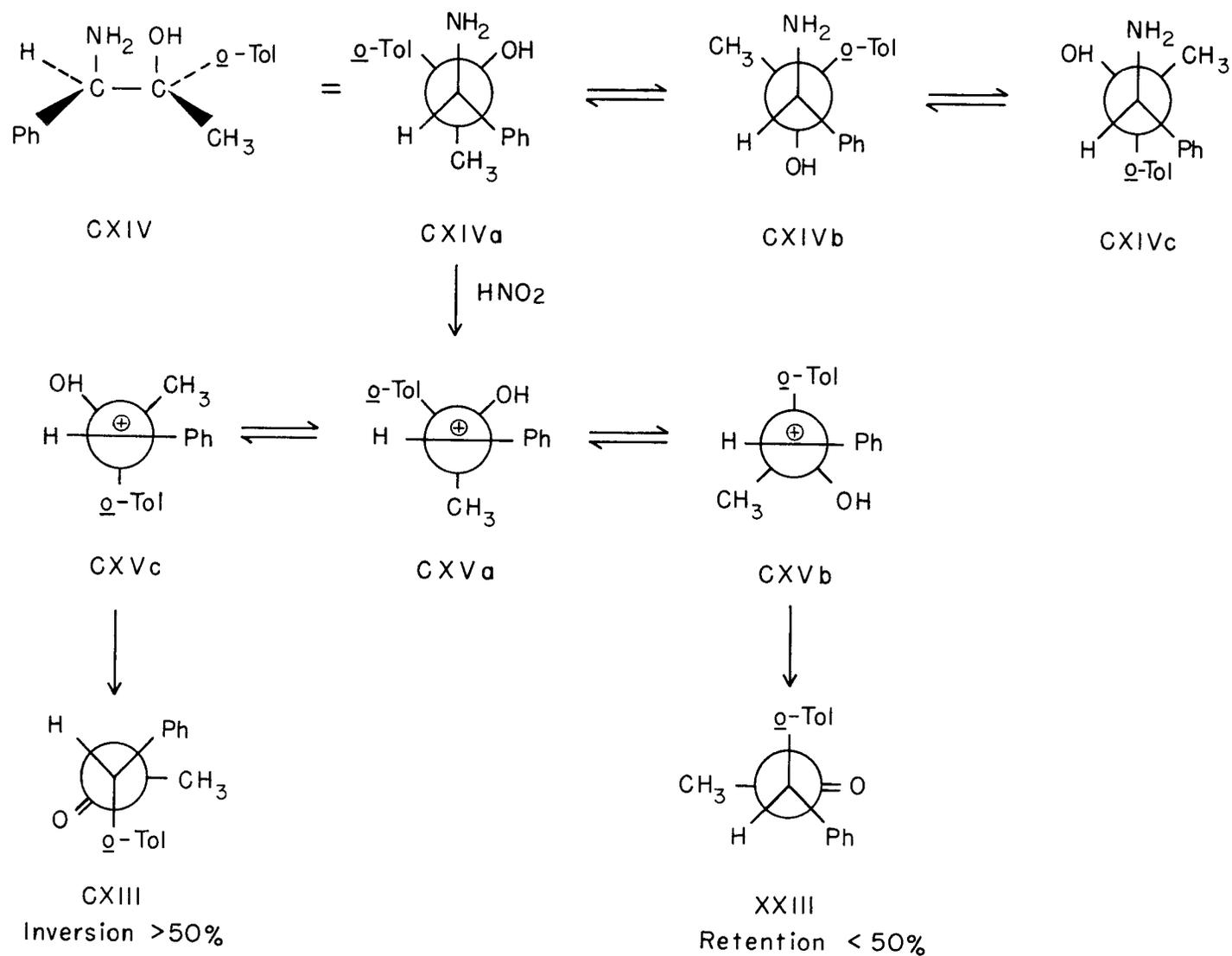
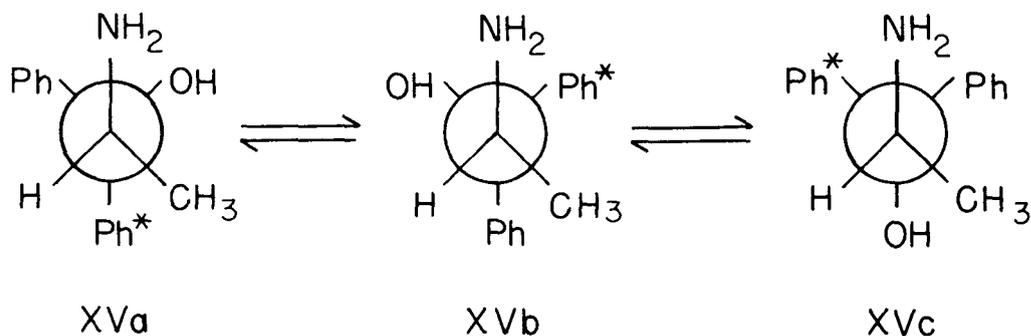


Chart 18.—Proposed pathways for the deamination and rearrangement of D-(+)-threo-1-amino-1-phenyl-2-o-tolyl-2-propanol.

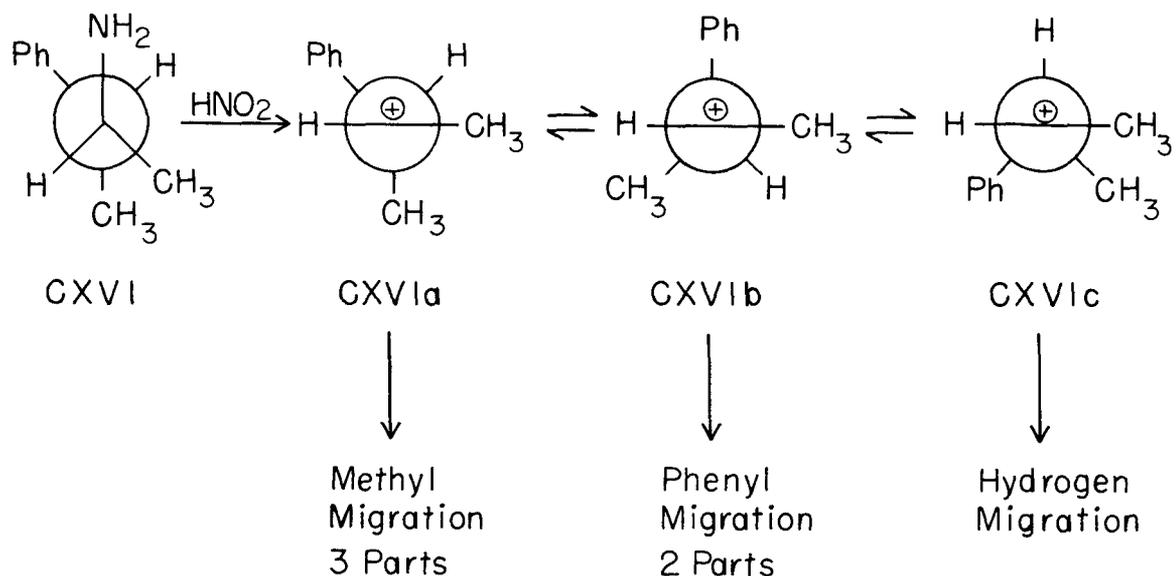
In the Semipinacolinic Deamination, the identity and direction of the migrating group seem to be very largely dependent on the conformation of the molecule. Despite the fact that one can write formulas for three ground state conformations in equilibrium—for example, for 1,1-diphenyl-2-amino-1-propanol, stereospecifically labeled with carbon-14 in one of the phenyl groups, XVa, XVb and XVc



can be written—not more than 1 per cent of the product was identified which could have originated from conformation XVb. All of the product resulting from nonlabeled-phenyl migration had retained configuration (Charts 3 and 4).

However, where the migratory aptitudes of the substituents on the migration origin differ greatly, there are noticeable differences in the distribution of rearrangement products from the erythro and threo aminoalcohols. Belonging to this series are the phenyl- and p-tolyl-substituted aminoalcohols referred to previously⁵⁷ on

Charts 6, 9 and 10 and the o-tolyl-substituted aminoalcohol XXI, which is the subject of this dissertation. In the threo compound CXVI, the methyl migration is reported⁶⁴ to compete with phenyl migration in the ratio 3:2. In erythro-3-phenyl-2-butylamine, with phenyl in the favored



position to migrate with inversion, phenyl migration is reported to predominate over methyl migration in the ratio of 8:1. Evidence here seems to indicate that the presence of a hydroxyl group in the aminoalcohol has a stabilizing effect on one conformation of the ground state, possible through hydrogen bonding.

EXPERIMENTAL

erythro-1-Amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride

(a) Benzyl o-tolyl ketone. Approximately 1 mole of the Grignard reagent, o-tolyl magnesium bromide, was prepared from 171 gms. (1 mole) of o-bromotoluene and 24.3 gms. (1 mole) of magnesium in dry ether. The ether was then cooled in an ice bath and 98 gms. (0.535 moles) of anhydrous cadmium chloride added with agitation. The mixture was allowed to warm up to room temperature, then heated under reflux for one hour. Ether was rapidly distilled from the reaction mixture, which then became very dark and viscous. Benzene was added and distillation continued to insure removal of all the ether. More benzene was added to permit easy dispersal of the solids in the reaction mixture.

To the di-o-tolyl cadmium thus prepared and cooled in an ice bath, there was added as rapidly as possible a solution of 123.7 gms. (0.8 moles) of phenylacetyl chloride in benzene. The ensuing vigorous reaction was controlled by cooling and slow agitation. When the reaction subsided, vigorous agitation was started and the contents refluxed on a steam bath for one hour.

The reaction mixture was hydrolyzed with 4 N hydrochloric acid, extracted twice with benzene, and the

individual benzene extracts were washed successively with water, 5 per cent sodium carbonate solution, water and saturated sodium chloride solution. The benzene extracts were dried with anhydrous sodium sulfate and filtered through Celite. The benzene was evaporated in an air stream, leaving a dark-brown liquid.⁶⁵

Vacuum distillation of this brown liquid yielded a light-yellow liquid ketone, boiling point 150-155^o, at 0.5 mm. Its refractive index at 24^o was 1.5780 \pm .0015. Yield (based on o-bromotoluene) was 46 per cent.

A 2,4-dinitrophenylhydrazone derivative⁶⁶ had a melting point of 146-147^o when crude but reached a melting point of 190^o after recrystallization from chloroform and ethanol. This derivative is listed in the literature^{67,68} as having a melting point of 146-147^o and 191-192^o. A mixed melting point with known 2,4-dinitrophenylhydrazone of benzyl o-tolyl ketone obtained from Raaen⁶⁸ showed no depression.

(b) 2-Methyl benzil monoxime. To a two-liter flask, fitted with a mechanical stirrer and addition funnel, there were added 52.5 gms. (0.25 moles) of benzyl o-tolyl ketone, 1 liter of anhydrous methanol and 13.5 gms. (0.25 moles) of sodium methoxide. After cooling the mixture to 0^o in an ice bath, 29.25 gms. (0.25 moles) of freshly prepared⁶⁹ or distilled (43-46^o at 110 mm.) isoamyl nitrite was added slowly with agitation and the mixture was left standing 12 hours.

Most of the methanol was removed under reduced pressure with slight warming (40°). The residue solidified on cooling. One liter of water and 40 cc. of 2 N sodium hydroxide solution were added to extract the sodium salt of the oxime. The aqueous layer was extracted twice with ether to remove unreacted isoamyl nitrite, amyl alcohol and unreacted ketone.

The separated aqueous layer was cooled in an ice bath and acidified slowly with concentrated hydrochloric acid. The solids which formed, as well as the mother liquors, were extracted with ether, and the combined ether solutions reduced in volume. The residue was dissolved in hot carbon disulfide, decolorized with charcoal and allowed to crystallize by cooling. Ether, carbon disulfide, benzene and ethanol are excellent solvents for the oxime, and the latter may be crystallized effectively from a concentrated solution with any of these hot solvents. The addition of hexane causes more complete precipitation.^{70,71}

The crystals were collected on a filter, washed with hexane and dried under vacuum, m.p. 121° .⁷² A 2,4-dinitrophenylhydrazone derivative⁶⁶ had a melting point of 233° .

(c) 2-Amino-2-phenyl-2'-methylacetophenone hydrochloride. This compound was prepared by catalytic reduction with hydrogen, using 3 per cent palladium on carbon as catalyst. The palladium on carbon was prepared

following the method for 5 per cent palladium on carbon described in Organic Syntheses, Coll. Vol. III, p. 686, Procedure B, scaled up to 30 per cent. Five gms. (0.021 moles) of 2-methyl benzil monoxime, 50 cc. absolute ethanol, 6 cc. concentrated hydrochloric acid and 1 gm. of 30 per cent palladium on carbon catalyst were agitated very rapidly while admitting hydrogen from a suitable atmospheric pressure apparatus. After three hours, a stoichiometric amount of hydrogen had been absorbed.

The filtered alcoholic solution was evaporated in an air stream and the precipitated white solid, collected on a filter, was washed with hexane and dried under vacuum. Yield of the aminoketone hydrochloride was 85 per cent, m.p. 246^o.

Anal. Calcd. for C₁₅H₁₆NOCl: C, 68.83; H, 6.16.
Found: C, 69.41; H, 6.22.

(d) 1-Amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride. This aminoalcohol hydrochloride was prepared from 71.5 gms. (0.27 moles) of 2-amino-2-phenyl-2'-methylacetophenone hydrochloride by adding the aminoketone to excess methyl magnesium iodide (2 moles) and refluxing for three hours. The Grignard addition product was hydrolyzed with saturated ammonium chloride solution and extracted twice with ether. The ether extracts were mixed with dilute hydrochloric acid and the acidic solution decolorized with charcoal. The clear, chilled acidic solution was

made slightly alkaline with 10 per cent sodium hydroxide solution and the liberated aminoalcohol was extracted with ether. The ether was evaporated in an air stream and the residue dissolved in absolute ethanol. Concentrated hydrochloric acid was added and the precipitated aminoalcohol hydrochloride was collected on a filter, washed with hexane and dried under vacuum. The yield was 48 per cent.

Anal. Calcd. for $C_{16}H_{20}ClNO$: C, 69.18; H, 7.26; Cl, 12.8; N, 5.04. Found: C, 69.90; H, 7.20; Cl, 12.5; N, 5.25.

Resolution of erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol

(a) Monobasic tartrate of erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol. A sample of 10.0 gms. of erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride was dissolved in hot water, cooled in an ice bath and made alkaline with 10 per cent sodium hydroxide solution. The liberated aminoalcohol was extracted in ether and the ether removed in an air stream. The residue was dissolved in a minimum amount of ethanol, filtered and added to a clear solution of 5.4 gms. of d-tartaric acid in 10 cc. of water.

Fractional crystallization of the precipitate was effected in 50-75 per cent ethanol and the specific rotation reached a constant value of -37.5° .

Anal. Calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44. Found: C, 59.67; H, 6.56.

Hydrolysis of this salt was accomplished by dissolving a sample of it in water and making the solution alkaline with 10 per cent sodium hydroxide. The liberated aminoalcohol was extracted with ether, and the ether was evaporated in an air stream. The residue was dissolved in a small amount of absolute ethanol with enough concentrated hydrochloric acid to cause precipitation of the aminoalcohol hydrochloride, $[\alpha]_D^{25} = -83^\circ$ (ethanol).

(b) d-10-Camphorsulfonate of erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol. A sample of the aminoalcohol hydrochloride, and an equimolar quantity of d-10-camphorsulfonic acid, each dissolved in a minimum amount of hot ethanol, were mixed and the resulting solution allowed to cool. Fractional crystallization was effected with 80-90 per cent ethanol. There was first obtained the less soluble diastereomer of $[\alpha]_D^{25} = -28.4^\circ$ (ethanol), m.p. 256° .

Anal. Calcd. for $C_{26}H_{35}NO_5S$; C, 65.93; H, 7.45.
Found: C, 65.98; H, 7.50.

When this salt was substantially depleted from the mother liquors, there precipitated the other diastereomer of $[\alpha]_D^{25} = +72^\circ$ (ethanol), m.p. 240° .

Anal. Calcd. for $C_{26}H_{35}NO_5S$: C, 65.93; H, 7.45; N, 2.96. Found: C, 65.89; H, 7.40; N, 2.78.

(c) Enantiomers of erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol. Hydrolysis of these diastereomeric salts was effected in the identical manner described for the tartrate, p. 66.

The diastereomer of $[\alpha]_D^{25} = +72^\circ$ yielded erythro-(+)-1-amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride, $[\alpha]_D^{25} = +83^\circ$ (ethanol).

Anal. Calcd. for $C_{16}H_{20}ClNO$: C, 69.18; H, 7.26; Cl, 12.76, N, 5.04. Found: C, 69.10; H, 7.19; Cl, 12.76; N, 5.30.

The diastereomer of $[\alpha]_D^{25} = -28.4^\circ$ produced the aminoalcohol hydrochloride of $[\alpha]_D^{25} = -83^\circ$ (ethanol). The N-benzamide derivative of the (-)-aminoalcohol hydrochloride was prepared,⁶⁶ m.p. 157° , $[\alpha]_D^{25} = -66.3^\circ$ (ethanol).

Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 79.80; H, 6.96; N, 3.80.

1-Phenyl-1-o-tolylpropanone

(a) Phenyl o-tolyl carbinol. The Grignard reagent o-tolyl magnesium bromide was prepared from 171 gms. (1 mole) of o-bromotoluene and 24.3 gms. (1 mole) of magnesium in ether. To this was added with agitation 106 gms. (1 mole) of benzaldehyde in ether. The Grignard complex was decomposed with 4 N hydrochloric acid and the ether extract washed successively with water, 5 per cent sodium bicarbonate solution and water. The carbinol precipitated

from the ether solution after it was reduced in volume. The crystals were collected on a filter, washed with a small amount of cold hexane and dried under vacuum. The melting point was 92° . The yield was 67 per cent.

(b) Phenyl-*o*-tolylchloromethane. Thionyl chloride, 80 gms. (0.67 moles), was added dropwise to a suspension of phenyl *o*-tolyl carbinol in hexane while it was being vigorously agitated. When the reaction subsided, the volatile residue was removed on a water pump. The chloride was then distilled under vacuum, b.p. $143-144^{\circ}$, at 0.5 mm. The condenser was warmed with a heat lamp because the chloride solidifies at about $40-45^{\circ}$. The yield was 91.6 per cent.

(c) Phenyl-*o*-tolylacetonitrile. In a 500-cc. flask, 133.5 gms. (0.61 moles) of phenyl-*o*-tolylchloromethane and 60 gms. (0.67 moles) of cuprous cyanide were heated together at $180-185^{\circ}$ in an oil bath for three hours with agitation. At the end of this time the contents of the flask became dark and viscous. This material was extracted with 500 cc. of hot ether and the ether extract kept aside. The remaining residue was then extracted with acetone. The acetone was evaporated on a stream of air and ether was added. Resinous matter precipitated, and the filtered ether solution was combined with the first ether extract. The ether was evaporated in an air stream. It was not necessary to purify the nitrile for the next step.

(d) Phenyl-o-tolylacetic acid. The ether-soluble residue, containing phenyl-o-tolylacetoneitrile was refluxed for four hours with 500 cc. of 50 per cent sulfuric acid and 5 cc. of toluene in a three-necked, one-liter flask fitted with a mechanical stirrer and a water-jacketed condenser. The cooled reaction mixture containing the hydrolyzed nitrile was neutralized with concentrated sodium carbonate solution. The alkaline solution was then extracted with ether to remove neutral impurities. The alkaline solution was chilled and cautiously (to control frothing) acidified and the liberated acid extracted with ether. The ether solution was reduced in volume and the acid permitted to crystallize from ether-hexane after decolorizing with charcoal. The acid had a melting point of 97° .⁷³

(e) Phenyl-o-tolylacetyl chloride. Phenyl-o-tolylacetic acid, 22.5 gm. (0.1 moles), was dissolved in 28 gms. (0.2 moles) of thionyl chloride, and the solution refluxed for two hours on a steam bath with agitation. The excess thionyl chloride was removed on a water pump. Benzene (50 cc.) was added and distilled under vacuum to remove the remaining traces of thionyl chloride.

The acid chloride crystallized from the benzene solution after it was reduced in volume. The acid had a melting point of 85° .

Anal. Calcd. for $C_{15}H_{13}ClO$: C, 73.62; H, 5.36; Cl, 14.49. Found: C, 73.93; H, 5.36; Cl, 14.14.

(f) 1-Phenyl-1-o-tolylpropanone. The ketone was prepared by the addition of 44 gms. (0.18 moles) of phenylacetyl chloride to dimethyl cadmium, made from 28.8 gms. (0.18 moles) of methyl iodide, in a manner similar to that used in the preparation of benzyl o-tolyl ketone, p. 61. An equimolar quantity of the reagent was used in this case to avoid double addition. The product was recovered the same way but, in addition, was washed with sodium thiosulfate solution to remove iodine. The benzene extract was reduced in volume, and the ketone precipitated when hexane was added. The ketone was recrystallized with benzene-hexane and had a melting point of 76-77° and boiling point of 157-158° at 0.5 mm.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19.

Found: C, 85.92; H, 7.16.

A 2,4-dinitrophenylhydrazone derivative,⁶⁶ had a melting point of 150°.

Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C, 65.33; H, 4.99; N, 13.85. Found: C, 65.22; H, 4.96; N, 13.69.

A thiosemicarbazone derivative⁷⁴ had a melting point of 207-208°.

Anal. Calcd. for $C_{17}H_{19}N_3S$: C, 68.64; H, 6.44; N, 14.12. Found: C, 68.57; H, 6.57; N, 13.91.

1-Phenyl-1-o-tolylpropanone-3-C¹⁴

(a) Methyl-C¹⁴ iodide. Methyl-C¹⁴ iodide was prepared from 20 cc. (0.5 moles) of methanol-C¹⁴ (2 milligrams), 20 gms. (0.1575 gm.-atoms) of iodine, 1 gm. of white and 1 gm. of red (0.064 gm.-atoms total) phosphorus, following the method described in Organic Syntheses, Coll. Vol. II, p. 399.

Excess iodine was removed from the methyl-C¹⁴ iodide with sodium thiosulfate solution. The methyl-C¹⁴ iodide was stored over anhydrous calcium chloride and used in the preparation of the next compound.

(b) 1-Phenyl-1-o-tolylpropanone-3-C¹⁴. The methyl-C¹⁴ iodide was used to make 1-phenyl-1-o-tolylpropanone-3-C¹⁴ in the same manner described for the nonradioactive ketone on page 70.

Resolution of phenyl-o-tolylacetic acid

(a) Phenyl-o-tolylacetate of cinchonidine. One-fourth mole of each of phenyl-o-tolylacetic acid (56 gms.) and cinchonidine (73.6 gms.) were dissolved in hot methanol. Cinchonidine did not dissolve well, but the salt that formed went into solution rapidly.

Fractional crystallization yielded a salt of $[\alpha]_D^{25} = -46.5^{\circ}$ (methanol), m.p. 185^o.

Anal. Calcd. for C₃₄H₃₆N₂O₃: C, 78.43; H, 6.97; N, 5.38. Found: C, 77.87; H, 6.77; N, 4.94.

(b) (+)-Phenyl-o-tolylacetic acid. A sample of 33.9 gms. of the phenyl-o-tolylacetate of cinchonidine, $[\alpha]_D^{25} = -46.5^\circ$ (methanol), was suspended in 150 cc. of water containing 25 cc. of concentrated hydrochloric acid. After some agitation, the liberated acid was extracted in ether. The ether was removed in an air stream and the residue dissolved in a minimum amount of hot hexane. The acid crystallized on cooling, m.p. 97° , $[\alpha]_D^{25} = +53.5^\circ$ (ethanol).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24.
Found: C, 79.92; H, 6.17.

(c) (-)-Phenyl-o-tolylacetic acid. Similar treatment as in (b) above using the mother liquors from the resolution of the diastereomers of the phenyl-o-tolyl acetate of cinchonidine yielded (-)-phenyl-o-tolylacetic acid, $[\alpha]_D^{25} = -53.5^\circ$ (ethanol).

threo-(-)-1-Benzamido-1-phenyl-2-o-tolyl-2-propanol

This derivative of the threo-(-)-aminoalcohol was prepared in connection with the configurational relationship to the corresponding erythro-(-)-aminoalcohol. It was made in the same manner⁶⁶ (see page 67). In order to obtain a solid derivative, it was necessary to evaporate the last traces of solvent under vacuum. The solid that was isolated had a melting point of 70° and $[\alpha]_D^{25} = +37^\circ$ (ethanol).

Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 79.06; H, 6.62; N, 3.76.

(+)-1-Amino-1-phenyl-2-o-tolylpropene-2 hydrochloride

(a) Method 1: A sample of 2 gms. of erythro-(-)-1-amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride was dissolved in 10 cc. of water, heated to the boiling point, and 10 cc. of concentrated hydrochloric acid was added. The mixture was refluxed for 24 hours and the precipitated solid was collected on a filter and dried under vacuum. The product was fractionally crystallized from aqueous hydrochloric acid to a constant specific rotation of $+45^{\circ}$ (ethanol).

(b) Method 2. A sample of 5 gms. of threo-(-)-1-amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride was dissolved in 10 cc. of water and the solution heated to the boiling temperature. Ten cc. of concentrated hydrochloric acid was added and the contents boiled for a few minutes. The crystals which precipitated were collected on a filter, m.p. 279° dec., $[\alpha]_D^{25} = +45^{\circ}$ (ethanol). A mixture with the product of Method 1 did not exhibit a melting point depression. The infrared absorption curve for this compound showed a maximum at 900 cm^{-1} , a characteristic of a terminal vinyl group.

A sample of the amine base was oxidized by a solution of potassium permanganate in acetone. Under the same conditions, ethyleneimine is not oxidized.⁷⁵ The amine base decolorizes bromine in carbon tetrachloride; its hydrochloride decolorizes bromine water.⁶⁶

Anal. Calcd. for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98.

Found: C, 73.68; H, 7.08.

The p-bromobenzenesulfonamide derivative of products from each method had an individual and mixed melting point of 248° (no depression) and $[\alpha]_D^{25} = +27.2^{\circ}$ (ethanol).

Anal. Calcd. for $C_{22}H_{20}BrNO_2S$: C, 59.80; H, 4.55.

Found: C, 56.95, 57.08, 57.28; H, 4.88, 4.77, 4.75. This is correct for one molecule of water of crystallization.

Radioactivity determinations and the radioactivity dilution method of yield determination

(a) Apparatus. The radioactivity assays reported in this dissertation were determined on a vibrating reed electrometer. The dry-combustion apparatus, the ionization chamber for the collection of carbon dioxide and the experimental procedure used in preparing the sample for measurement have been described by Tolbert.⁷⁶ The calculation of the yields of the reaction products was performed by the following equations adapted from the work of Berson and Ben-Efraim⁵⁹ and Mayor and Collins.⁶⁰

(b) Determination of total ketone yield.

$$D_0 A_0 = (D_0 + K_T) A_1$$

K_T = total weight of nonradioactive ketone produced in the deamination reaction

D_0 = weight of radioactive racemic ketone added

A_0 = molar radioactivity of D_0

A_1 = molar radioactivity of the ketone after racemization.

(c) Determination of yield of racemic ketone and yield of excess enantiomer.

$$E = \left[(D_0 + K_T)^2 - \frac{A_0}{A_2} (D_0^2 + D_0 K_T) \right]^{1/2}$$

K_T = total weight of nonradioactive ketone produced in the deamination reaction

R = weight of racemic ketone

E = weight of excess of one enantiomer

$$\therefore K_T = R + E$$

D_0 = weight of radioactive racemic ketone added

A_0 = molar radioactivity of D_0

A_2 = molar radioactivity of diluted, reisolated and purified racemic ketone.

The deaminations and the radioactivity dilutions are discussed in the next sections.

Deamination of erythro-1-amino-1-phenyl-2-o-tolyl-2-propanol hydrochloride

In a typical experiment, 3.408 gms. of one enantiomer of the erythro aminoalcohol hydrochloride was dissolved in 140 cc. of 25 per cent acetic acid. To this was added a solution of 1.8 gms. of sodium nitrite in 14 cc. of water.

The mixture was agitated for two hours at room temperature and then extracted with three 100 cc. portions of ether. The ether solutions were successively washed with water, 5 per cent sodium carbonate solution (300 cc.) and water. The ether solutions were combined, the ether

evaporated in an air stream and was finally dried under vacuum. The remaining liquid weighed 2.754 gms., $[\alpha]_D^{25} = +79^\circ$. A 2,4-dinitrophenylhydrazone derivatived showed no melting-point depression when mixed with the same derivative prepared from 1-phenyl-1-o-tolylpropanone, p. 70.

To this liquid was added exactly 2.7568 gms. (D_0)* of dl-1-phenyl-1-o-tolylpropanone-3- C^{14} , radioactivity of 2.9679 millicuries/mole (A_0). The mixture was brought to a volume of approximately 100 cc. by dissolving it in 50 cc. of benzene and adding 50 cc. of hexane.

A 50-cc. aliquot was removed and the solvent was evaporated. Fractional crystallization of the ketone from hexane produced racemic ketone, m.p. 77.2° , radioactivity of 2.0474 millicuries/mole (A_2).

A 25-cc. aliquot from the diluted ketone was completely racemized by passage through a column of alumina eluted with 50 per cent benzene-hexane. The solvent was evaporated from the eluate and the residue was dissolved in a small amount of hot hexane. The ketone that crystallized from this solution was racemic, m.p. 77.4° , radioactivity of 1.7504 millicuries/mole (A_1).

Solution of the algebraic equations of the previous section for the values of R, the amount of racemic ketone,

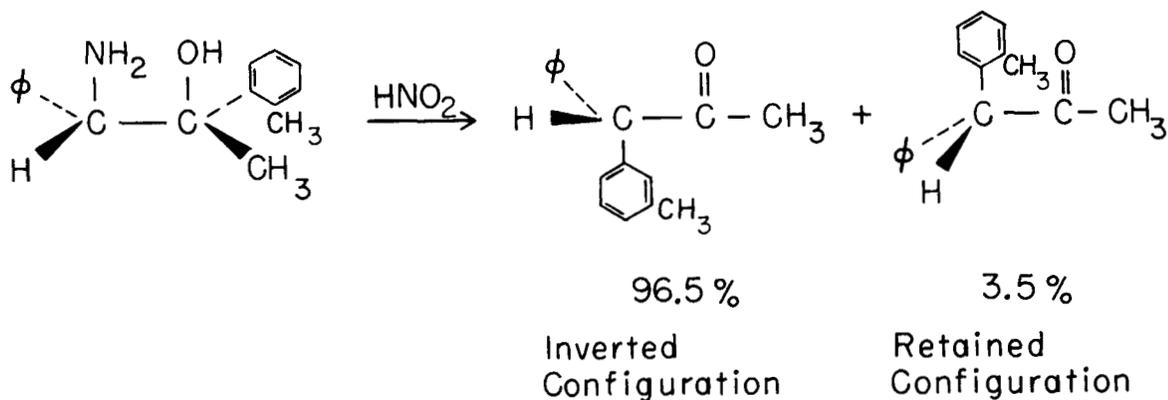
* These letters refer to the quantities to be inserted in the algebraic equations of the previous section, pp. 74-75, for the determination of yield.

and E, the amount of excess enantiomer, formed in the deamination, is possible with the data given in this section. The results form the basis for the final calculation of the amounts of inverted and retained configuration given under Methods and Results of this dissertation, p. 42.

SUMMARY

This investigation was undertaken to determine the identity and ratio of products in the deamination of an aminoalcohol containing an *o*-tolyl group in a migrating position. erythro-1-Amino-1-phenyl-2-*o*-tolyl-2-propanol was prepared for this purpose. The (-)-enantiomer is related to L-(+)-phenylglycine with respect to the amino-carbon atom.

Nitrous acid deamination of one enantiomer of the aminoalcohol produced the expected ketone, 1-phenyl-1-*o*-tolylpropanone. A radioactivity dilution analysis showed that the product consisted of 96.5 per cent of one enantiomer. The results indicated that the reaction proceeded almost completely with inversion about the migration terminus.



The results of this reaction are compared with those for the corresponding threo aminoalcohol, for the corresponding erythro and threo p-tolyl aminoalcohols and for the 1,1-diphenyl and 1,2-diphenyl aminoalcohols. A reaction mechanism satisfying the identities and configurations of the products of deamination of the aminoalcohols is postulated on the basis of an open carbonium ion, with a minimum of rotation about the C-C + bond. In this mechanism, the controlling factor in determining the identity and direction of the migrating group is the ground state conformation of the molecule.

This mechanism implies that there are negligible contributions from other conformations which could be produced by rotation about the C-C bond in the ground state. Bonding between amino and hydroxyl groups is proposed as a cause of this ground state control.

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