Molecular Rearrangements. XX. The Deamination of *erythro*- and *threo*-1-Amino-1-phenyl-2-*p*-methoxyphenyl-2-propanol and *erythro*- and *threo*-1-Amino-1-phenyl-2-*o*-tolyl-2-propanol[1]

CLAIR J. COLLINS, MUNI M. STAUM,[2] AND BEN M. BENJAMIN

Chemistry Division of Oak Ridge National Laboratory, Oak Ridge, Tennessee, and the College of Pharmacy of the University of Florida, Gainesville, Florida

Received April 11, 1962

The deaminations of optically active *erythro*- and *threo*-1-amino-1-phenyl-2-*p*-anisyl-2-propanol (III) and of *erythro*- and *threo*-1-amino-1-phenyl-2-*o*-tolyl-2-propanol (V) have been examined. The *erythro*- and *threo*-III gave ketonic products whose ratios of enantiomers were nearly identical with those previously obtained from analogous compounds.[3f,g] The ratio of inversion to retention in the ketonic products from the *erythro* series was about 75:25, and that from the *threo* series was about 43:57. The ratio of inverted to retained ketone from *erythro*-V was 96:4 and from *threo*-V was 55:45. These results are interpreted as a consequence of steric control of product formation and are additional support for the previously established open carbonium ion character of the intermediates.

In previous papers[3] we reported the results of our application of radiochemical and stereochemical techniques to the study of the deaminations of several aliphatic amines and amino alcohols. One of the purposes of the foregoing[3] work was to try to establish a relationship between the structures of the reacting amines and the type of ionic reaction intermediates. The general theory of the effects upon neighboring-group participation during solvolyses of alpha and beta substitution and of change in the leaving group were set down in 1948 by Winstein and Grunwald.[4a] Subsequent publications[4b,c] have proved the validity of these concepts.

We have demonstrated[3c-g] that certain systems which, upon solvolysis, produce bridged ions and exhibit marked neighboring-group participation, can deaminate through open ions even though the attending rearrangements are stereospecific. Some,[3b,e,h] but not all,[3a,c,d,f,g] of these results may seem by hindsight unsurprising when judged according to the theory of Winstein and Grunwald.[4a] Roberts and his co-workers[5] would seem, on the same grounds, to be relatively safe in favoring nonclassical ion intervention during the deamination of cyclopropylcarbinylamine and related compounds. The question still remains, however, whether participation is *ever* possible during aliphatic deaminations, for it is conceivable that the carbon–nitrogen bond fission *always* takes place so rapidly that participation by a neighboring group cannot occur. Phrased somewhat differently, the leaving group in the deamination reaction may be several orders of magnitude different in energy requirements than those groups, such as tosyl, hydroxyl, brosyl, and halogen, which are often employed during solvolytic cleavage studies. Our reasons for raising this question have been discussed previously.[3f,6] The difficulties in answering the question are considerable: (1) The rate-determining step for deamination appears to occur before the step in which participation[4] is possible, and (2) the stereochemical method for identifying bridged ions has been shown[3b-h] for several deamination reactions to be invalid. Thus, the criteria by which participation and bridging have been recognized previously cannot be applied to deaminations, and other means of identifying the ionic intermediates must be sought.

We have had considerable success[3] in identifying open carbonium ion intermediates in several stereospecific deaminations through the application of combined stereochemical and radiochemical methods to the reactions in question. Of particular significance were two facts[3f,g]: (1) D-*threo*-1-Amino-1-phenyl-2-*p*-tolyl-2-propanol (D-*threo*-I) underwent reaction with predominant *retention* (57:

(1) This paper is based upon work performed at Oak Ridge National Laboratory, which is operated by Union Carbide Corporation for the Atomic Energy Commission. Previous paper, Clair J. Collins, Joan B. Christie, and Vernon F. Raaen, *J. Am. Chem. Soc.*, **83**, 4267 (1961).

(2) Predoctoral Fellow of the Oak Ridge Institute of Nuclear Studies from the University of Florida, Gainesville. The portion of this paper concerned with *erythro*-1-amino-1-phenyl-2-*o*-tolyl-2-propanol was taken from the Ph.D. thesis of Muni M. Staum, whose advisor at the University of Florida was Professor W. M. Lauter.

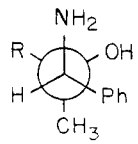
(3) (a) B. M. Benjamin and C. J. Collins, *J. Am. Chem. Soc.*, **78**, 4952 (1956); (b) W. A. Bonner and C. J. Collins, *ibid.*, **78**, 5587 (1956); (c) B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *ibid.*, **79**, 6160 (1957); (d) V. F. Raaen and C. J. Collins, *ibid.*, **80**, 1409 (1958); (e) C. J. Collins, W. A. Bonner, and C. T. Lester, *ibid.*, **81**, 466 (1959); (f) B. M. Benjamin, P. Wilder, Jr., and C. J. Collins, *ibid.*, **83**, 3654 (1961); (g) B. M. Benjamin and C. J. Collins, *ibid.*, **83**, 3662 (1961); (h) C. J. Collins, J. B. Christie, and V. F. Raaen, *ibid.*, **83**, 4267 (1961).

(4) (a) S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948); (b) for paper XXXIX on the subject "Neighboring Carbon and Hydrogen," see L. de Vries and S. Winstein, *ibid.*, **82**, 5363 (1960); (c) S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingraham, *ibid.*, **75**, 147 (1953); S. Winstein and R. Heck, *ibid.*, **78**, 4801 (1956); E. F. Jenney and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958).

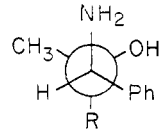
(5) M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 3671 (1961); E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *ibid.*, **83**, 2719 (1961); R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *ibid.*, **81**, 4390 (1959).

(6) See also pertinent discussions by R. Huisgen and H. Reimlinger, *Ann.*, **599**, 161, 183 (1956), and A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957), concerning the "compression of scale of energy differences for competing reactions."

43) of configuration at the migration terminus, and (2) *erythro*-I and *erythro*-II exhibited identical proportions (74:26) of predominant inversion in the formation of their ketonic products, contrary to what would be expected if aryl migration had



D-threo-series



D-erythro-series

I (R = p-C_7H_7)
II (R = C_6H_5)
III (R = p-$C_6H_4OCH_3$)
V (R = o-C_7H_7)

taken place with participation. The deaminations of two additional pairs of diastereomeric aminoalcohols are now reported. *erythro*- and *threo*-1-Amino-1-phenyl-2-*p*-methoxyphenyl-2-propanol (III) were studied in order to assess the effect of the *p*-anisyl group upon the proportion of inverted ketone produced. A marked increase of inversion with respect to the systems already studied (*erythro*- and *threo*-I, *erythro*-II) should be evidence for participation by the *p*-anisyl group,[4c] whereas a small or insignificant increase in inversion would be equated with an absence of such participation. The *erythro*- and *threo*-1-amino-1-phenyl-2-*o*-tolyl-2-propanol (V) were studied in order to find out how an aryl group (*o*-tolyl) with a large steric effect would influence the reaction.

If, as expected, the *p*-anisyl group is unable to participate during the deamination of *erythro*-III owing to (1) the energetic leaving group and (2) the ease with which the phenyl of *erythro*-III should stabilize the open carbonium ion, it was our hope that the present experiments would prove the value of the techniques here employed, so that we may apply them to systems which, according to Winstein and Grunwald,[4a] should be more nearly able to exhibit neighboring-group participation during scission of the carbon–nitrogen bond.

Methods and Results

The compounds needed for the research were obtained by synthetic routes similar to those described in our previous publications.[3] The hydrochloride of racemic *erythro*-1-amino-1-phenyl-2-*p*-methoxyphenyl-2-propanol (III) was synthesized by the addition of methylmagnesium iodide to racemic α-amino-α-phenyl-*p*-methoxyacetophenone hydrochloride.[7] The hydrochloride of racemic *erythro*-1-amino-1-phenyl-2-*o*-tolyl-2-propanol (V) was prepared by the addition of methylmagnesium iodide to α-amino-α-phenyl-*o*-methylacetophenone. The racemates were then resolved by fractional crystallization of their (+)-tartaric acid and (+)-10-camphorsulfonic acid salts. The (−)-*threo* isomer of III was prepared by the addition of *p*-anisylmagnesium bromide to (+)-α-amino-α-phenylacetone hydrochloride[3g] and (+)-*threo*-III was obtained in the same way from (−)-α-amino-α-phenylacetone hydrochloride. In an analogous manner, (+)- and (−)-*threo*-V were prepared by the addition of *o*-tolylmagnesium bromide to (−)- and (+)-α-amino-α-phenylacetone hydrochloride, respectively. The configurations of the four compounds, *erythro*- and *threo*-III and *erythro*- and *threo*-V, were related by dehydration of the hydrochloride salts of the resolved aminoalcohols, and these results are outlined in Fig. 1. Appropriate treatment of the compounds with strong acid results in dehydration to give terminal vinylic compounds, thus destroying the asymmetric center to which the hydroxyl group was originally attached and leaving unaltered the carbon bonded to nitrogen. The *threo* diastereoisomers were particularly sensitive to acid and decomposed when crystallized in the presence of small concentrations of hydrochloric acid. The *erythro*-V dehydrated after being boiled for several hours in 6 *N* hydrochloric acid, whereas *erythro*-III was quite stable and dehydrated only when heated with a solution of perchloric acid in acetic acid. Thus, we have shown (Fig. 1) that the four amine hydrochlorides,

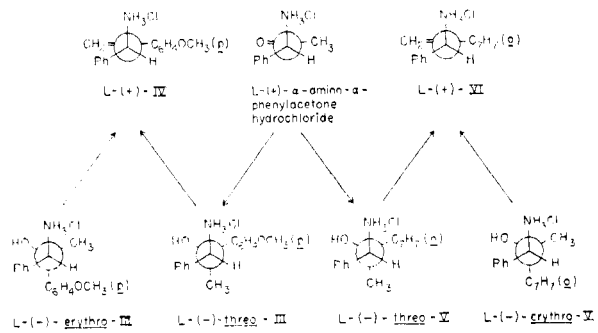


Figure 1

(−)-*erythro*-III, (−)-*threo*-III, (−)-*erythro*-V, and (−)-*threo*-V, all belong to the L-series and are configurationally related to L-(+)-α-amino-α-phenylacetone hydrochloride which has previously been related to L-(+)-phenylglycine.[3f]

The conditions for deamination reactions of the amino alcohols were the same as described in the preceding work.[3f] The hydrochloride salts were dissolved in 25% aqueous acetic acid and treated with sodium nitrite at room temperature. The distribution of enantiomeric ketones in the products was determined by the isotope-dilution technique as described by Berson[8] by adding radio-

(7) Such reactions are highly stereospecific. See, for example, J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Am. Chem. Soc.*, **82**, 3914 (1960).

active racemic diluents to unlabeled optically active products and reisolating a diluted racemic fraction for radioactivity assay.

1-Phenyl-1-*p*-methoxyphenylacetone-2-C^{14} (VII) for the isotope-dilution experiments was prepared by deamination–rearrangement of carbon-14-labeled, racemic *threo*-III. The purity of the triply distilled product was established by vapor phase chromatography. The synthesis of racemic, carbon-14-labeled 1-phenyl-1-*o*-tolyl acetone (VIII) was accomplished by the addition of dimethyl-C^{14} cadmium to phenyl-*o*-tolylacetyl chloride.

The proportions of inversion and retention in the ketones produced upon deamination of the two diastereomeric pairs of amino alcohols are given in Fig. 2. The yields of ketonic fractions

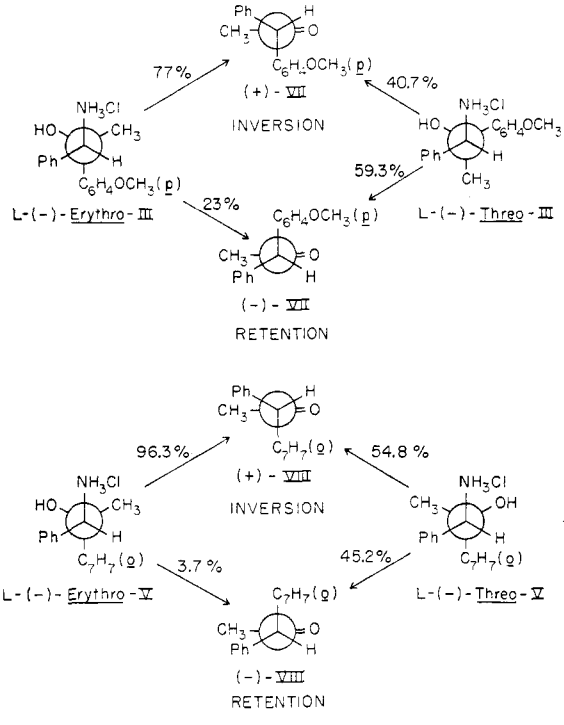


Figure 2

(VII) from *erythro*-III were 82–94% and from *threo*-III, 97–99%; both *threo*- and *erythro*-V yielded 70–75% of ketone VIII. Of the four amino alcohols studied, only *threo*-V exhibited methyl migration during deamination, yielding 2.8% of 2-methyl-α-phenylpropiophenone. Details of all experiments are given in the Experimental.

Discussion

The data of Fig. 2, together with those data[3f,g] previously reported in the ketone-forming deaminations of the *erythro* series of the amino alcohols, are summarized in Table I, from which it can be seen that the phenyl, *p*-tolyl, and *p*-methoxyphenyl groups exert nearly identical influences in determining the proportions of inversion and retention in their respective ketonic products, whereas the *o*-tolyl group is a special case. We interpret these results to mean that the electron-donating effects[4c] of the *p*-methyl and *p*-methoxyl groups are unimportant here, but that the steric properties of these molecules exert the major influence in determining the relative amounts of backside and topside attack by the migrating aryls. This interpretation is the same as that previously[3] given for similar deaminations, and is consistent with the observation[7] that the effective bulks of the phenyl, *p*-tolyl, and *p*-methoxyphenyl groups are identical.

In Table I we have also summarized the results for the deaminations of the *threo*-amino alcohols. Once again, the *p*-tolyl and *p*-methoxyphenyl groups exert identical influences on the product ratio. In the *threo* series, however, both prefer to attack the migration terminus from the topside to produce a product which is predominantly of *retained* configuration. The reasons for this have been adequately presented in a previous paper,[3g] and are concerned with the *trans* character of the transition states for topside migration and the *cis* character of the transition states for backside migration in the *threo*-amino alcohol systems studied.

TABLE I

SUMMARY OF STEREOCHEMICAL DATA FOR DEAMINATIONS OF THE *erythro*- AND *threo*-AMINO ALCOHOLS I, II, III, AND V

Amino alcohol	% Inversion in —$CH_3COCHPhR$[a]— From: *erythro*	*threo*	Reference
I. R = *p*-C_7H_7	74	43	3g
II. R = C_6H_5	73	...	3f
III. R = *p*-$C_6H_4OCH_3$	77	41	This paper
V. R = *o*-C_7H_7	96	55	This paper

[a] These percentages represent total inversion. Thus, for *erythro*-I the % retention = 100 − 74 = 26%.

Clearly the *o*-tolyl has special steric requirements which are different from those of *p*-anisyl, *p*-tolyl, or phenyl. It is apparent that the controlling factor for product formation during the deaminations reported here and previously[3] is steric in nature, that removal of nitrogen is not influenced by the neighboring group, and that the ionic intermediates are best represented as the classical open type. We, therefore, reassert our interpretation of the reaction mechanism.[3f,g] The three possible conformations. A, B, and C, of each of *erythro*-I, -II, -III, and IV (see Fig. 3) undergo loss of nitrogen to give the appropriate open carbonium ions. Maintenance of conformation of these three ions is sterically controlled by interference between the large groups so that the rate of rotation is not large compared with the rate of migration. Conformation A leads to inversion whereas B leads to retention during migration

(8) J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4083 (1959).

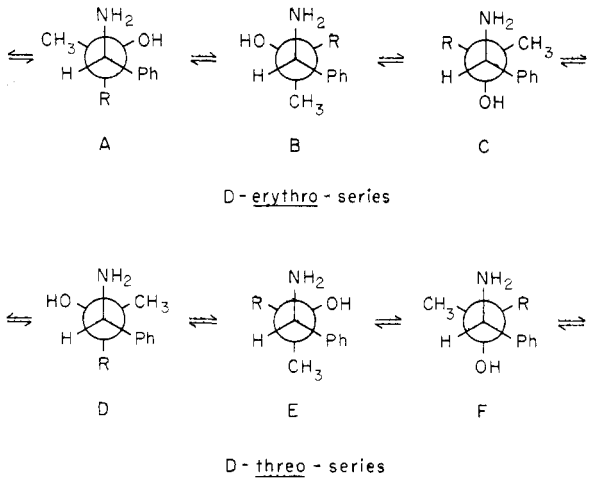


Figure 3

of R[3g]; all could conceivably produce glycol.[3g] The reasoning is synonymous for the compounds of the D-*threo* series, the equilibrium concentrations of D, E, and F being responsible for the product composition.

Experimental

All rotations were determined in alcohol (*c* 1) at 25°, using the sodium-D light unless otherwise stated. Melting points were taken on a Kofler Heizbank. When this method was not applicable, the melting points were taken in capillary tubes as noted in the appropriate places. Carbon–hydrogen analyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Colorado.

α-Amino-α-phenyl-*p*-methoxyacetophenone Hydrochloride.—4-Methoxyphenyl benzyl ketone[9] was converted to the isonitroso derivative.[10] The 4-methoxybenzil monoxime thus obtained (2.7 g.) was dissolved in 100 ml. of acetic acid containing 4 ml. of concentrated hydrochloric acid. To the mixture was added 0.5 g. of palladium-on-carbon catalyst and hydrogenation was allowed to proceed at atmospheric pressure until 550 ml. of hydrogen had been consumed. The catalyst was removed by filtration and the filtrate was evaporated on the steam bath in a current of air. The residue was dissolved in the minimum quantity of water. The solution was treated with Norit and concentrated hydrochloric acid was added to it. The solid amino ketone hydrochloride which crystallized was collected on a filter and dried, m.p. 256° (capillary).

Anal. Calcd. for $C_{15}H_{16}ClNO_2$: C, 64.86; H, 5.81. Found: C, 64.47; H, 5.84.

***erythro*-1-Amino-1-phenyl-2-*p*-methoxyphenyl-2-propanol Hydrochloride** (*erythro*-**III**).—To the Grignard reagent, prepared from 2 moles of magnesium and 2 moles of methyl iodide, was added 61 g. of α-amino-α-phenyl-*p*-methoxyacetophenone hydrochloride. The solution was heated under reflux for 1 hr. and then the reaction complex was hydrolyzed with ammonium chloride solution. Two fractions were isolated. The ether-soluble fraction containing the free amino alcohol was crystallized from benzene–hexane, m.p. 90°. The compound absorbed carbon dioxide from the atmosphere and, therefore, gave poor carbon–hydrogen analyses. The ether-insoluble fraction, the amine hydrochloride, was crystallized from water containing a little hydrochloric acid, m.p. 245° (capillary).

(9) E. Ney, *Ber.*, **21**, 2445 (1888).

(10) C. R. Kinney, *J. Am. Chem. Soc.*, **51**, 1592 (1929).

Anal. Calcd. for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86. Found: C, 65.56; H, 6.98.

Resolution of *erythro*-III.—A solution of 27.5 g. of racemic amino alcohol (III free base) in 50 ml. of ethanol was mixed with 25 g. of (+)-10-camphorsulfonic acid in 150 ml. of water. Fine needlelike crystals separated. The material was crystallized five times from water containing a little alcohol, [α] −0.012. The rotation did not change with further crystallization.

Anal. Calcd. for $C_{26}H_{35}NO_6S.H_2O$: C, 61.51; H, 7.35. Found: C, 61.54; H, 7.49.

The salt was dissolved in water and the solution was treated with sodium hydroxide. The solid amine which separated was crystallized from benzene–hexane mixture, m.p. 102°, [α] 22.5. The amine was converted to the hydrochloride salt, m.p. 249° (capillary), [α] −38.5.

The amino alcohol (33 g.) was recovered from the mother liquor from two batches of (+)-10-camphorsulfonic acid salt. It was dissolved in 100 ml. of ethanol and 20 g. of (+)-tartaric acid in 150 ml. of water was added. The crystals which separated, [α] 13.5 (water), were recrystallized and the rotation did not change, m.p. 210°. The free amino alcohol was recovered from the tartaric acid salt, m.p. 102°, [α] −22.1. It was converted to the hydrochloride salt and crystallized from water, m.p. 249°, (capillary), [α] 38.5.

***threo*-1-Amino-1-phenyl-2-*p*-methoxyphenyl-2-propanol-2-C^{14} Hydrochloride** (*threo*-**III**).—The Grignard reagent was prepared from 246 g. of *p*-bromoanisole and 32 g. of magnesium in tetrahydrofuran. To this was added 52 g. of α-amino-α-phenylacetone-*carbonyl*-C^{14} hydrochloride. The reaction mixture was heated under reflux for 1 hr. and then the tetrahydrofuran was removed by vacuum distillation. Ether was added and the reaction complex was hydrolyzed with ammonium chloride solution. The ether layer was separated and treated with cold 6 *N* hydrochloric acid. The crystals which separated were collected on a filter and dried. A small sample was crystallized from water containing a little hydrochloric acid, m.p. 233–235° (capillary). In a similar synthesis with nonradioactive material, the free amino alcohol was isolated and crystallized from ether–hexane mixture, m.p. 75°.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 75.13; H, 7.51.

The amino alcohol was converted to the hydrochloride salt by adding 4 *N* hydrochloric acid to its cold ether solution. It melted at 204° (capillary), resolidified, and melted again at 239–241°.

Anal. Calcd. for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86. Found: C, 65.22; H, 6.93.

(−)-*threo*-III.—Solid (+)-α-amino-α-phenylacetone hydrochloride, [α] +360 (19.4 g.), was added to the Grignard reagent prepared from 168 g. of *p*-bromoanisol and 24 g. of magnesium. The reaction mixture was worked up in the same way as described previously for the racemic compound. The ether solution of the free base was extracted three times with 50-ml. portions of cold, 1 *N* hydrochloric acid. The acid solution was neutralized with sodium hydroxide and the amino alcohol was recovered by ether extraction. The ether solution was concentrated to about 150 ml. and then cooled in an ice bath. The crystals which separated were collected on a filter and dried, yield 17 g., m.p. 101°, [α] −70.1. An additional 4.3 g. of amino alcohol was recovered from the filtrate, m.p. 101°; [α] −70.3.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.04; H, 7.30.

A solution of 9 g. of the free amine in ether was treated with 4 *N* hydrochloric acid. Crystals, 6.7 g., which separated were collected on a filter and dried, m.p. 250–251° (capillary), [α] −51.8. Rotation of the hydrochloric salt did not change when it was crystallized from acetone–ethanol–ether mixture.

Anal. Calcd. for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86. Found: C, 65.72; H, 6.99.

(+)- and (−)-1-Amino-1-phenyl-2-*p*-methoxyphenylpropene-2 Hydrochloride (IV).—A solution of 5.0 g. of commercial 71% perchloric acid in 50 ml. of acetic acid and 8.25 g. of acetic anhydride was prepared. To this was added 1 g. of (−)-*threo*-III. The mixture was heated on the steam bath for 2 hr. Five grams of sodium acetate was added and the acetic acid was evaporated in an air stream. The residue was taken up in water and the solution was treated with excess sodium hydroxide. The oily material which separated was taken up in ether. To the ether solution was added 6 *N* hydrochloric acid. The precipitate which separated was collected on a filter, washed well with ether, and dried, m.p. 264° (capillary), [α] 133.7. The compound was dissolved in 10 ml. of pyridine and treated with 0.5 g. of benzoyl chloride. Water was then added and the crystalline benzamide was crystallized from alcohol, m.p. 169 (capillary), [α] 119.3, *c* 0.5 (chloroform).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16. Found: C, 80.37; H, 6.14.

When (+)-*threo*-III, prepared from D-(−)-α-amino-α-phenylacetone, was repeatedly crystallized from ethanol–water mixtures containing hydrochloric acid, dehydration took place for the rotation gradually changed and reached a maximum value of [α] −123.3, m.p. 264° (capillary).

Anal. Calcd. for $C_{16}H_{18}ClN$: C, 69.68; H, 6.59. Found: C, 69.15; H, 6.65.

A sample of partially resolved *erythro*-III, [α] −8, was converted to the hydrochloride salt, [α] 9, which was subjected to treatment with perchloric acid in acetic acid as described above. A first crop of amine hydrochloride salt isolated had [α] −12.7 and second crop had [α] −64.5. This second crop of crystals was converted to the N-benzoyl derivative which was crystallized from ethanol, m.p. 166–184° (capillary), [α] −43.9, *c* 0.5 (chloroform).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.61. Found: C, 80.43; H, 6.10.

Samples of racemic *threo*-III and racemic *erythro*-III were converted to racemic IV in the same way as described for the optically active compounds. An amine was isolated and was crystallized from hexane–ether mixture, m.p. 45.5–46°. It was converted to the hydrochloride salt, m.p. 244° (capillary).

The N-benzoyl derivative of racemic IV was prepared, m.p. 186–188° (capillary).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16. Found: C, 80.85; H, 6.23.

The infrared spectra of the hydrochloride salts (+)-IV, (−)-IV, and racemic IV were identical and had a strong absorption in the region of 900 cm.$^{-1}$ characteristic of a terminal vinylic group.

1-Phenyl-2-*p*-methoxyphenylpropanone-2-C^{14} (VII).[11]—Carbon-14-labeled racemic *threo*-III, 58 g., was dissolved in 300 ml. of 25% acetic acid, and the solution was then treated with 20 g. of sodium nitrite. The oily product was recovered by ether extraction. The ether solution was washed with water, dried with Drierite, and concentrated. The concentrate was distilled three times, the center cut being saved each time, b.p. 150–152°, 0.2 mm. A vapor phase chromatogram[12] showed only one peak. A sample of the ketone, 1 g., was dissolved in 3 ml. of pyridine and 3 ml. of ethanol. The solution was treated with 1 g. of hydroxylamine hydrochloride and heated on the steam bath for 1 hr. Water was added and the oxime was recovered and crystallized twice from ethanol, m.p. 185°, 5.996 ± 0.026 mc./mole.

Deamination of *erythro*- and *threo*-III.—The deaminations were done in the same way as described for compound V. Thus treatment of 3.1168 g. of (−)-*erythro*-III gave 2.5193 g. of crude product, [α] 22. To the crude product was added 2.3379 g. of pure racemic radioactive ketone VII, 5.996 ± 0.026 mc./mole. The mixture was taken up in benzene and half of it was passed through a column of alumina. The recovered racemized ketone was converted to the oxime, crystallized three times, m.p. 185°, and assayed for carbon-14 content, 3.172 ± 0.007 mc./mole. The optically unaltered portion of diluted ketone was converted to the oxime, crystallized three times, m.p. 185°, and assayed for carbon-14 content, 3.413 ± 0.016 mc./mole. From these data it was calculated that the total yield of ketone was 2.081 g., 81.6%, and the ketone consisted of 78.2% of (+)- enantiomer and 21.8% (−)-enantiomer. In a second experiment, 3.6374 g. of (+)-*erythro*-III gave 2.1467 g. crude product, [α] −18.6. When treated with sodium hydroxide the product had no detectable rotation. The ketone was formed in 87.1% yield and consisted of 74.5% (−)-enantiomer and 25.5% (+)-enantiomer. In a third experiment, (−)-*erythro*-III gave product, [α] +19.7, which contained a 93.5% yield of ketone XI, 78.5% of which was (+)-enantiomer and 21.5% (−)-enantiomer.

(−)-*threo*-Amine-III, 2.5634 g., was deaminated and gave 1.1975 g. of product [α] −9.90. A portion of the product was treated with sodium hydroxide to racemize the ketone present. The rotation was then [α] −3.03. Therefore, the net rotation of the ketone was (−)-6.87. To 1.183 g. of this product was added 1.1223 g. of radioactive VII. Half of this was racemized as described above and converted to the oxime, m.p. 185°, 3.159 ± 0.013 mc./mole. Racemic oxime, m.p. 185° was also isolated from the optically unaltered fraction, 3.180 ± 0.005 mc./mole. Thus the yield of ketone was 96.9% and consisted of 59.6% (−)-enantiomer and 40.3% (+)-enantiomer. In a second run, 1.7848 g. of (−)-*threo*-III gave 1.5674 g. crude product, [α] −7.8. After treatment with sodium hydroxide [α] −2.3. The yield of ketone was 99.1% and consisted of 59% (−)-enantiomer and 41% (+)-enantiomer.

α-Amino-α-phenyl-*o*-methylacetophenone Hydrochloride.—Benzyl-*o*-tolyl ketone[13] was converted to the isonitroso derivative by an adaptation of the method of Taylor.[14] The monoxime, 5 g., was mixed with 1 g. of 30% palladium-on-carbon catalyst in 50 ml. ethanol containing 6 ml. of concentrated hydrochloric acid. The mixture was violently agitated in an atmosphere of hydrogen at ordinary pressure until the stoichiometric amount of hydrogen had been absorbed. The catalyst was removed from the hot solution by filtration. The solution was concentrated and cooled. The precipitated amino ketone hydrochloride was collected on a filter and dried, yield 85%, m.p. 246°.

Anal. Calcd. for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16. Found: C, 69.41; H, 6.22.

***erythro*-1-Amino-1-phenyl-2-*o*-tolyl-2-propanol Hydrochloride *erythro*-(V).**—The amino alcohol hydrochloride was prepared from 71.5 g. (0.27 mole) of α-amino-α-phenyl-*o*-methylacetophenone hydrochloride by adding the amino ketone to excess methylmagnesium iodide (2 moles) and heating the mixture to reflux for 3 hr. The Grignard addition product was hydrolyzed with saturated ammonium chloride solution, and the product was removed by two extractions with ether. The ether extracts were mixed with dilute hydrochloric acid and the acidic solution was treated with Norit and passed through a filter. The clear, chilled acidic solution was made slightly alkaline with 10% sodium hydroxide solution and the liberated amino alcohol was extracted with ether. The ether was evaporated in an air stream and the residue was dissolved in absolute ethanol. Concentrated hydrochloric acid was added and the precipitated amino alcohol hydrochloride was collected on a filter, washed with hexane, and dried under vacuum. The yield was 48%, m.p. 265°.

Anal. Calcd. for $C_{16}H_{20}ClNO$: C, 69.18; H, 7.26; Cl,

(11) J. Levy, P. Gallais, and D. Abragam, *Bull. Soc. Chim.*, (4), **43**, 868 (1928).

(12) A Burrell Kromo-Tog Model K-1, fitted with a 1/4-inch column packed with 5% silicon grease on Celite, was used.

(13) P. Hill and W. F. Short, *J. Chem. Soc.*, 1123 (1935).

(14) T. W. J. Taylor, *ibid.*, 2018 (1931).

12.8; N, 5.04. Found: C, 69.90; H, 7.20; Cl, 12.5; N, 5.25.

Resolution of *erythro*-(V).—A sample of the racemic *erythro* amino alcohol, 8.6 g., dissolved in a small amount of ethanol, was mixed with 5.4 g. of *d*-tartaric acid in 10 ml. of water. The solid salt which formed was collected on a filter and then fractionally crystallized from dilute ethanol. A portion was collected which did not change rotation when crystallized again, $[\alpha]$ −37.5, *c* 1 (water).

The tartaric acid salt was dissolved in water and the solution was treated with 10% sodium hydroxide. The free amino alcohol which separated was recovered by extracting it from the solution with ether. The ether was evaporated in a current of air and the residue was dissolved in a small amount of ethanol. Concentrated hydrochloric acid was added and the resolved amino alcohol hydrochloride precipitated, m.p. 266°, $[\alpha]$ −83.

The mother liquors from the tartaric acid salt were treated with dilute sodium hydroxide and the free amino alcohol was collected by extracting it with ether. The residue, after the ether was evaporated, was dissolved in ethanol and an equimolar amount of *d*-camphorsulfonic acid dissolved in alcohol was added to it. The salt which formed was fractionally crystallized from dilute ethanol until it reached constant rotation, m.p. 256°, $[\alpha]$ −28.4.

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

This amino alcohol *d*-camphorsulfonic acid salt was converted to the (−)-amino alcohol hydrochloride in the usual way, m.p. 266°, $[\alpha]$ −83.

The amine hydrochloride (1 g.) was dissolved in 10 ml. of pyridine and the solution was treated with 1 g. of benzoyl chloride. The solution was warmed for 0.5 hr. on the steam bath and then poured on crushed ice. The precipitated benzamide derivative of (−)-*erythro*-(III) was collected on a filter and crystallized from hexane, m.p. 157°, $[\alpha]$ −66.3.

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

Continued fractional crystallization of the *d*-camphorsulfonic acid salts resulted in the isolation of a second pure compound, m.p. 240°, $[\alpha]$ 72.

Anal. Calcd. for $C_{26}H_{35}NO_5S$: C, 65.97; H, 7.45. Found: C, 65.8; H, 7.40.

The amino alcohol hydrochloride was prepared in the usual way from this (+)-*d*-camphorsulfonic acid salt, m.p. 266°, $[\alpha]$ 83.

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

Phenyl-*o*-tolylacetyl Chloride.—Phenyl-*o*-tolylacetic acid,[15] 22.5 g. (0.1 mole), was dissolved in 28 g. (0.2 mole) of thionyl chloride, and the solution was heated to reflux temperature for 2 hr. on a steam bath with agitation. The excess thionyl chloride was removed with 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, m.p. 85°.

Anal. Calcd. for $C_{15}H_{13}ClO$: C, 73.62; H, 35.6; Cl, 14.49. Found: C, 73.93; H, 5.36; Cl, 14.14.

1-Phenyl-1-*o*-tolylpropanone (VIII).—The ketone was prepared by the addition of 44 g. (0.18 mole) of phenyl-*o*-tolyl acetyl chloride to dimethylcadmium, made from 28.8 g. (0.18 mole) of methyl iodide, in a manner similar to that used in the preparation of benzyl *o*-tolyl ketone. The product was recovered in the usual way. The benzene extract was washed with sodium thiosulfate solution to remove iodine and then was reduced in volume by evaporation of the benzene. The ketone precipitated with hexane was added. It was recrystallized from benzene–hexane mixture, m.p. 76–77°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.92; H, 7.16.

The 2,4-dinitrophenylhydrazone derivative was prepared and crystallized from chloroform–ethanol mixture, m.p. 150°.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99; N, 13.85. Found: C, 65.22; H, 4.96; N, 13.69.

1-Phenyl-1-*o*-tolylpropanone-3-C^{14} was prepared in the same way as the nonradioactive compound except that methyl-C^{14} iodide was used; m.p. 76–77°; 2.968 ± 0.0001 mc./mole.

(−)-*threo*-1-Amino-1-phenyl-2-*o*-tolyl-2-propanol Hydrochloride [(−)-*threo*-V].—Powdered (+)-α-amino-α-phenylacetone hydrochloride,[5] 19.3 g., $[\alpha]$ +360°, was added in small portions to the Grignard reagent prepared from 96 g. of *o*-bromotoluene and 14 g. of magnesium. The reaction complex was hydrolyzed by adding water dropwise until the magnesium salts became grainy. The ether was separated by decantation and the magnesium salts were washed several times with ether. The ether solutions were combined and concentrated. The dried, combined solution was saturated with dry hydrogen chloride and the crystals which formed were collected on a filter and dried in air, m.p. 210° dec., $[\alpha]$ 63.4. Crystallization of the amino alcohol hydrochloride was accomplished by dissolving it in warm water and carefully adding hydrochloric acid. By such treatment the rotation was raised only slightly, $[\alpha]$ −64.8; the compound crystallized with 1/2 molecule of water, and decomposed when heated only briefly in 6 *N* hydrochloric acid.

Anal. Calcd. for $C_{16}H_{20}ClNO\cdot 1/2H_2O$: C, 67.00; H, 7.38. Found: C, 67.03; H, 7.32.

The water of crystallization was removed by warming the compound in vacuum for 3 hr.

Anal. Calcd. for $C_{16}H_{20}ClNO$: C, 69.18; H, 7.26. Found: C, 69.30; H, 7.34.

(+)-*threo*-(V).—The *d*-10-camphorsulfonic acid salt of α-amino-α-phenylacetone, 54.8 g. $[\alpha]$ −150, was added to the Grignard reagent prepared from 1 mole of *o*-bromotoluene and 1 mole of magnesium. The product was worked up in the same way as the (−)-enantiomer, m.p. 210 dec., $[\alpha]$ 64.5; the yield was 26.3 g.

Anal. Calcd. for $C_{16}H_{20}ClNO\cdot 1/2H_2O$: C, 67.00; H, 7.38. Found: C, 67.37; H, 7.39.

(+)- and (−)-1-Amino-1-phenyl-2-*o*-tolylpropene-2 Hydrochloride (VII).—A sample of (−)-*threo*-(V), 2 g., was dissolved in 10 ml. of water and the solution was brought to the boiling temperature. An equal volume of concentrated hydrochloric acid was added and boiling was continued for a few minutes when a copious white precipitate formed. This was removed by filtration and crystallized from dilute hydrochloric acid, m.p. 279° (capillary), $[\alpha]$ 45.5. The infrared spectrum showed a strong absorption at 900 cm.$^{-1}$ and a weak absorption at 1800 cm.$^{-1}$, characteristic of a terminal vinyl group. The same olefinic amine hydrochloride was formed from (−)-*erythro*-(V), as shown by its infrared spectrum, rotation, melting point, and mixed melting point.

Anal. Calcd. for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98. Found: C, 73.68; H, 7.08.

The amine free base was a liquid. It reacted with permanganate in acetone as well as with bromine in carbon tetrachloride and had an infrared spectrum characteristic of a terminal vinylic compound. It was converted to the *p*-bromobenzenesulfonamide derivative which was crystallized from ethanol–ether mixture; m.p. 243–244° (capillary), $[\alpha]$ 27.2.

Anal. Calcd. for $C_{22}H_{20}BrNO_2W\cdot H_2O$: C, 57.40; H, 4.82. Found: C, 57.10; H, 4.80.

(+)-*threo*-(V) and (+)-*erythro*-(V) were treated in the same way as the corresponding (−)-enantiomers described above. The product in each case was (−)-1-amino-1-phenyl-2-*o*-tolylpropene-2 hydrochloride, m.p. 279° (capillary), $[\alpha]$ −45.3.

(15) B. M. Benjamin and C. J. Collins, *J. Am. Chem. Soc.*, **75**, 402 (1953).

Anal. Calcd. for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98. Found: C, 73.27; H, 6.99.

The *p*-bromobenzenesulfonamide derivative was prepared and crystallized from ethanol, m.p. 243–244° (capillary), [α] −26.5.

Anal. Calcd. for $C_{22}H_{20}BrNO_2S \cdot H_2O$: C, 57.40; H, 4.82. Found: C, 57.48; H, 4.80.

Deamination of *erythro*- and *threo*-(V).—In a typical experiment, 3.408 g. of the (−)-enantiomer of the *erythro* amino alcohol hydrochloride was dissolved in 140 cc. of 25% acetic acid. To this was added a solution of 1.8 g. of sodium nitrite in 14 ml. of water. The mixture was agitated for 2 hr. at room temperature, then diluted with water and extracted with three 100-ml. portions of ether. The ether extracts were successively washed with water, 5% sodium bicarbonate solution (300 ml.) and water. The ether solutions were combined and the ether was evaporated in an air stream and finally the residue was dried under vacuum. The remaining liquid weighed 2.754 g., [α] +79.

To this liquid was added exactly 2.7568 g. of racemic phenyl-1-*o*-tolylpropanone-3-C^{14}, 2.9679 mc./mole. The mixture was brought to a volume of approximately 100 ml. by dissolving it in 50 ml. of benzene and adding 50 ml. of hexane. A 50-ml. aliquot was removed and the solvent evaporated. Fractional crystallization of the ketone from hexane produced a racemic sample of ketone, m.p. 77.2°, with radioactivity of 2.0474 mc./mole.

A 25-ml. aliquot from the diluted ketone was completely racemized by passing it through a column of alumina. The ketone recovered from the alumina column was dissolved in a small amount of hot hexane and crystallized, m.p. 77.4°, 1.7504 mc./mole. From these results it can be calculated that the total yield of ketone was 70% and the yield of (+)-ketone was 96.4% of the total. The results of other deamination experiments are listed in Table I. In a second experiment the total yield of ketone was 72% and the yield of (+)-ketone was 96.1% of the total.

The deamination product of (+)-*erythro*-(V) in a third experiment had a rotation of [α] −84.4. A drop of 10% sodium hydroxide was added to the polarimeter tube to racemize the ketone. The solution was then [α] −14.7. Therefore, the ketone fraction should have a rotation of [α] −101–102° and the rotation of the pure enantiomeric ketone should be [α] −105.

Deamination of 3.1280 g. of *threo*-amino alcohol hydrochloride V, [α] −64.8, under the conditions described above gave a product with no optical rotation. A portion of the product when treated with a drop of sodium hydroxide in alcohol had a rotation of [α] −10. To 2.3832 g. of the product was added pure racemic VIII, 1.0467 g., 2.9498 mc./mole. Half of the material was passed through an alumina column and the racemic ketone was recovered and crystallized three times from hexane, m.p. 77°, 1.0787 ± 0.0002 mc./mole. From the other half of the material there was recovered a fraction of racemic ketone by three crystallizations from hexane, m.p. 77°, 1.0827 mc./mole. From the above data it can be calculated that the total yield of ketone was 1.8156 g., 75.1%, and the yield of (+)-enantiomer present was 54.8% of the total ketone fraction.

In another experiment (+)-*threo*-(V) was deaminated to give a product with [α] −3.5. A drop of 10% sodium hydroxide was added to the polarimeter tube to racemize the ketone. The material then had an [α] of +10. Therefore, the ketone fraction could have a rotation as high as [α] −18.8.

Deamination of 1.0085 g. of *threo*-V, [α] 63.5, gave 0.8027 g. of product [α] 0.9. The ketone was racemized as before and the remaining material had a gross [α] +10.0. The ketone, therefore, appeared to have [α] −12.7. The deamination product from 1.0203 g. of (+)-*threo*-V had [α] −6.5. A portion of it, 0.8258 g., was placed on a column of Fisher alumina. The ketone fraction, 0.7931 g., was recovered by eluting the column with benzene. The column was then eluted with 5% methanol in ether and 0.097 g. of hydroxylic material was recovered, [α] +32. The ketone derived from (+)-*threo*-V, therefore, had a net (−)-rotation.

***o*-Methyl-α-phenylpropiophenone (IX).**—Hydratropic acid, 33 g., was converted to hydroatropyl chloride by treating it with 30 g. of thionyl chloride. Excess thionyl chloride was removed on the water aspirator and the acid chloride was added to di-*o*-tolylcadmium prepared from 41 g. of *o*-bromotoluene. The product was isolated in the usual way and distilled at 0.2 mm., b.p. 110–116°. The distilled product was crystallized from hexane, m.p. 56°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.99; H, 7.30.

Mixtures of this ketone IX and 1-phenyl-1-*o*-tolylacetone VIII were analyzed by gas-liquid chromatography. The appearance time of IX was sufficiently shorter than that of VIII so that small percentages of it were easily detectable. It was then shown by gas-liquid chromatographic analysis that the deamination product of *erythro*-V contained less than 1% of X whereas the deamination product of *threo*-V contained as much as 2.8% of X.