

distilled, collecting 2-ml. fractions. The last two fractions had infrared absorption at 2250, 2285, and 2400 cm^{-1} characteristic of acetonitrile. V.p.c. analysis of these fractions showed a peak with the same retention time as acetonitrile.

C. In Concentrated Sulfuric Acid. The powdered oxime (1.5 g.) was stirred into 15 g. of concentrated sulfuric acid and allowed to stand overnight. The reaction mixture was diluted with 150 ml. of ice-water and extracted with ether. Concentration of the dried extracts left a residue which was chromatographed on alumina. Elution with carbon tetrachloride gave 0.36 g. of a hydrocarbon, identified by its infrared and n.m.r. spectra as *cis*-decalin. Further elution with ether gave 0.70 g. of solid, m.p. 181.5–182.5° after recrystallization from ether. It was identified by mixture melting point determination and comparison of infrared spectra with an authentic sample²⁰ as *N*-(*trans*-9-decalyl)-acetamide (XI), m.p. 182–183°.

Treating 0.50 g. of the oxime IX with 10 g. of 85% sulfuric acid under the same conditions yielded 0.15 g. of the *trans* amide (XI) and 0.22 g. of recovered starting material.

D. In Polyphosphoric Acid. A mixture of the oxime (1.5 g.) and polyphosphoric acid (30 g.) was stirred for 10 hr. at 25°. The reaction mixture was stirred into 250 ml. of ice-water and extracted with ether. After drying and treatment with charcoal, concentration of the ether extracts left 0.92 g. of *N*-(*trans*-9-decalyl)-acetamide (XI), m.p. 181.5–182.5°.

Another run was carried out at a higher temperature; the oxime (2.0 g.) was heated with stirring in 80 g. of PPA at 125–130° for 10 min. and worked up as before. Chromatography of the products over alumina gave first *cis*-decalin (0.78 g.), eluted with carbon tetrachloride and identified by its infrared and n.m.r. spectra, followed by *N*-(*trans*-9-decalyl)acetamide (0.24 g.), m.p. 181–182°, eluted with ether.

Stability of Amide X in Acid. *A.* *N*-(*cis*-9-decalyl)-acetamide (0.14 g.) was dissolved in 1.4 g. of 85% sulfuric acid and allowed to stand overnight. On working up as described above, 0.12 g. of starting material, m.p. 125–126°, was recovered.

B. The *cis* amide (0.11 g.) was stirred with 3 g. of PPA at room temperature for 9 hr. Working up as described above led to 0.10 g. of recovered starting amide.

Preparation of XI by Ritter Reaction. To a solution of 3.4 g. of acetonitrile and 5 g. of *cis*- β -decalol (m.p. 105°) in 25 ml. of di-*n*-butyl ether was added 10 ml. of concentrated sulfuric acid dropwise, with stirring. The mixture was stirred for 1 hr., kept overnight, poured onto ice, and made alkaline with ammonium hydroxide. After cooling, the precipitate was collected, washed with water, and dried. Recrystallization from carbon tetrachloride gave colorless crystals, m.p. 179–181°, with an infrared spectrum indistinguishable from that of authentic XI. No amide product could be isolated from runs in which acetic acid was used as solvent.

Intermediates in the Nitrous Acid Deamination of 2-[*p*-(2'-Hydroxyethoxy)phenyl]ethylamine¹

Marjorie C. Caserio, Robert D. Levin,² and John D. Roberts

Contribution No. 3274 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California. Received July 6, 1965

Nitrous acid deamination in water and in acetic acid of the para-substituted 2-phenylethylamine, p-HOCH₂-CH₂OC₆H₄CH₂CH₂NH₂, and the corresponding deuterated amine p-HOCD₂CH₂OC₆H₄CH₂CD₂NH₂, resulted in 39–40% isotope-position migration in the ethyl group as determined from the nuclear magnetic resonance spectra of the products obtained from the deuterated amine. Aryl migration between the oxygens of the hydroxyethoxy group was considered possible but was not observed.

Introduction

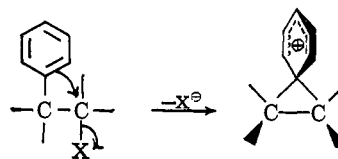
The role of phenyl-bridged (phenonium) ions in the ionization reactions of 2-phenylethyl and 3-phenyl-2-butyl derivatives is a topic that has provoked considerable discussion. On the one hand,^{3a} it is argued that

(1) Supported in part by the National Science Foundation.

(2) Participant in the Undergraduate Research Program of the National Science Foundation.

(3) For leading references see (a) D. J. Cram, *J. Am. Chem. Soc.*, **86**, 3767 (1964); (b) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *ibid.*, **87**, 2137 (1965).

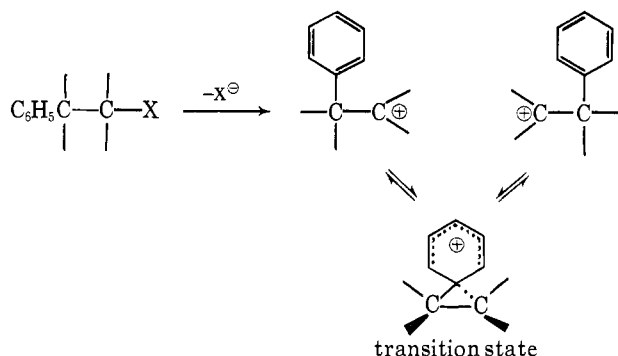
phenonium ions are discrete intermediates which may be formed by participation of a neighboring phenyl group in ionization reactions of compounds of the type $\text{C}_6\text{H}_5-\text{C}-\text{C}-\text{X}$. The other view is that phenonium



ions are at most merely the transition states for the migration of phenyl groups in between isomeric "open" carbonium ions.

In ionization reactions of 2-phenylethyl derivatives, kinetic and isotopic labeling experiments⁴ have revealed that the extent of phenyl migration depends on the mode of carbonium ion formation (solvolysis or

(4) S. Winstein, C. R. Lindgren, H. Marshall, and L. L. Ingraham, *ibid.*, **75**, 147 (1953).

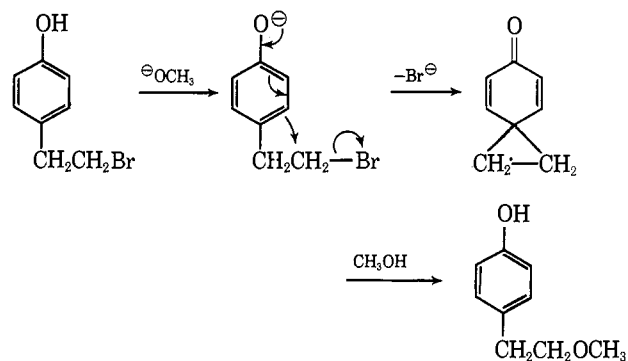


deamination), the nature of the solvent, and the nature and position of substituents in the aryl group. Thus, solvolysis of 2-phenylethyl-1-¹⁴C tosylate results in increasing phenyl migration with increasing ionizing power and decreasing nucleophilicity of the solvent^{3a,5-9} and increasing electron release by substituents in the aromatic ring.^{5,6}

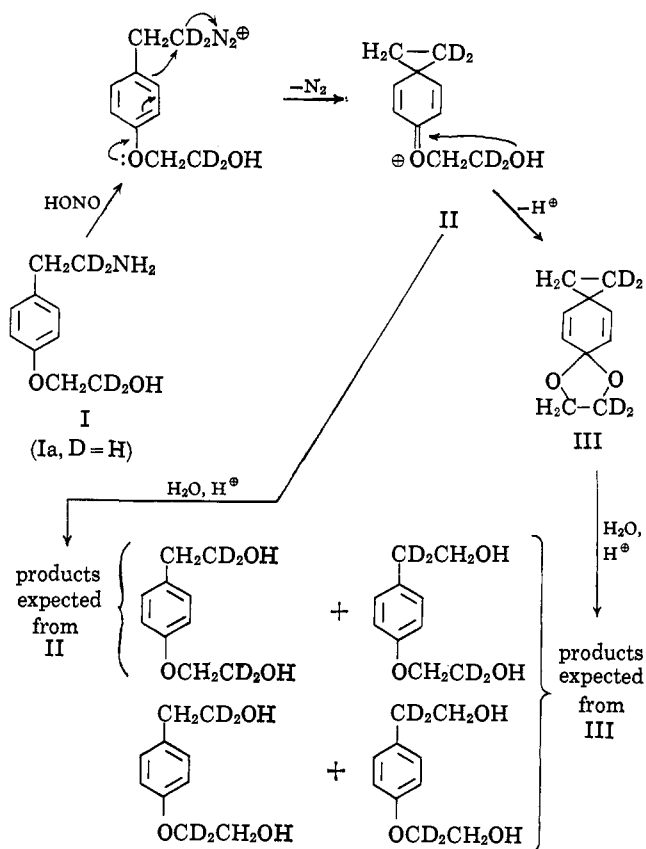
There is a difference of opinion³ regarding the interpretation of the rate data for the solvolysis of substituted 2-phenylethyl tosylates, but it cannot be denied that the rates are consistent with isotopic labeling experiments in that the rate enhancement increases as the extent of rearrangement increases. The greatest rate enhancement was found in acetolysis and formolysis of 2-anisylethyl tosylate which led to rearrangement corresponding to 100% aryl participation.⁵ However, participation of a phenyl group is less important since the amount of rearrangement in both 2-phenylethyl tosylate acetolysis (5%) and formolysis (45%) is short of the maximum of 50%. This means that solvent participation competes favorably with phenyl participation in this system. The same argument cannot apply, however, to deamination reactions. Labeling experiments in the deamination of 2-phenylethyl-1-¹⁴C amine and some *para*-substituted analogs^{7d,8} indicate that rearrangement is significant but in all cases falls short of the 50% predicted for exclusive formation of symmetrical phenonium ion intermediates. Phenonium ions cannot therefore be the sole intermediates in these deamination reactions, but the real question is whether the products are derived solely from open carbonium ions which are interconverted by way of phenonium ions as transition states or whether they are derived from both open and bridged carbonium ion intermediates.

Winstein and Baird¹⁰ have produced strong evidence for the formation of a bridged intermediate in the base-induced methanolysis of 2-(*p*-hydroxy)phenylethyl bromide. The enhanced solvolysis rate indicates phenyl participation, and, by working under carefully controlled conditions, they succeeded in isolating a spirodienone intermediate, and showed that it reacted rapidly under solvolysis conditions to give the solvolysis products.

- (5) S. Winstein and E. Jenny, *Helv. Chim. Acta*, **41**, 807 (1958).
 (6) D. J. Cram and L. A. Singer, *J. Am. Chem. Soc.*, **85**, 1075 (1963).
 (7) (a) C. C. Lee, R. Tkachuk, and G. P. Slater, *Tetrahedron*, **7**, 206 (1959); (b) C. C. Lee, G. P. Slater, and J. W. T. Spinks, *Can. J. Chem.*, **35**, 1417 (1957); (c) J. W. Clayton and C. C. Lee, *ibid.*, **39**, 1510 (1961); (d) C. C. Lee and J. W. T. Spinks, *ibid.*, **31**, 761 (1953).
 (8) J. D. Roberts and C. M. Regan, *J. Am. Chem. Soc.*, **75**, 2069 (1953).
 (9) W. M. Saunders, S. Asperger, and D. M. Edison, *ibid.*, **80**, 2421 (1958).
 (10) S. Winstein and R. Baird, *ibid.*, **85**, 567 (1963).



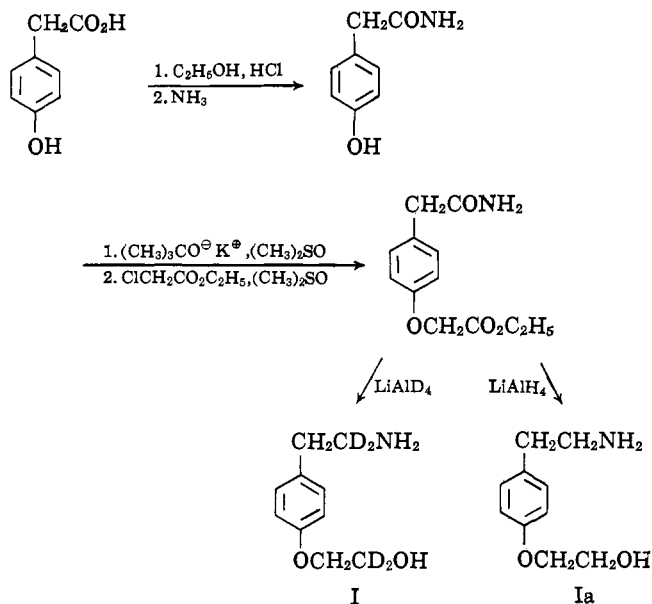
The present work is related to the work of Winstein and Baird in that we sought to distinguish between aryl-bridged carbonium ions as intermediates or transition states in the nitrous acid deamination of the deuterium-labeled *para*-substituted 2-phenylethylamine I. Here, participation of the aryl system by way of the cation II could lead to the formation of the tricyclic intermediate (III) by the transformations shown as follows.



Formation of III would constitute strong evidence in favor of bridged intermediates in this case and could be inferred from the isolation of III or from the extent of rearrangement of the labeled methylene groups at both ends of the aromatic ring in the products derived from III. Obviously, if III were not formed, this would hardly constitute evidence *against* bridged intermediates because reaction by way of II might well give final products much faster than it could cyclize to give III.

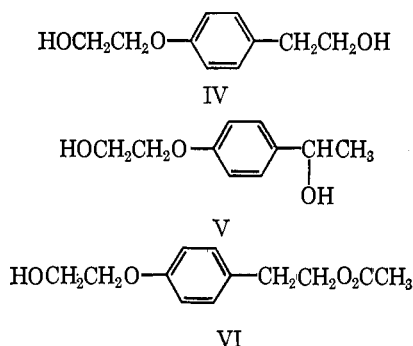
Results and Discussion

Synthesis of the amino alcohols Ia and I was carried out as shown below starting with *p*-hydroxyphenylacetic acid. The nuclear magnetic resonance spectra



of Ia and I are shown in Figure 1, and reveal that the chemical-shift difference between the methylene protons of the $\text{OCH}_2\text{CH}_2\text{OH}$ group is about 8 c.p.s. This may be ascertained from the fact that the $\text{OCH}_2\text{CD}_2\text{OH}$ resonance of I at 4.05 p.p.m. is shifted about 4 c.p.s. *downfield* from the band center of the A_2B_2 spectrum of the $\text{OCH}_2\text{CH}_2\text{OH}$ group of Ia. The chemical shift of the $\alpha\text{-CH}_2$ must then be 4 c.p.s. *upfield* from the band center and, therefore, any rearrangement of the $\text{OCH}_2\text{CD}_2\text{OH}$ group on deamination of I should be discernible in the spectrum of the products as two well-resolved peaks, about 8 c.p.s. apart.

Deamination of Ia was carried out in dilute aqueous fluoboric acid solution and in glacial acetic acid. The major products of aqueous deamination were identified from their infrared and n.m.r. spectra as the diol IV and the corresponding nitro compound, $p\text{-HOCH}_2\text{-CH}_2\text{OC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{NO}_2$. Only trace amounts of the hydride-shift product V could be detected, and no evidence was obtained for the formation of elimination products or the tricyclic intermediate III.



In acetic acid, deamination of Ia gave the monoacetate VI, identified from its infrared and n.m.r. spectra. On reduction with lithium aluminum hydride, VI gave the diol IV.

Deamination of the deuterium-labeled amine I was carried out exactly as for the unlabeled amine Ia. The n.m.r. spectra of the diols obtained on aqueous deamination of Ia and I are compared in Figure 2. The appearance of a peak at 3.88 p.p.m. in the spec-

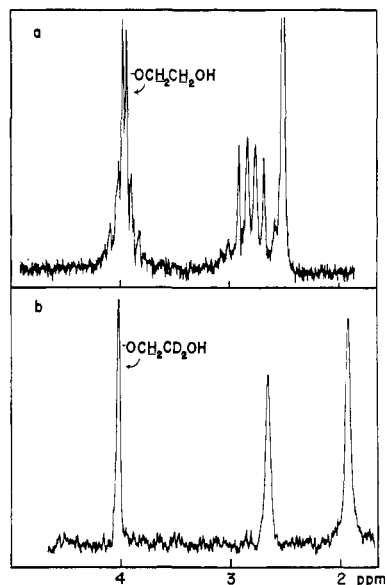


Figure 1. Nuclear magnetic resonance spectra of (a) $p\text{-HOCH}_2\text{-CH}_2\text{O-C}_6\text{H}_4\text{-CH}_2\text{CH}_2\text{NH}_2$ (Ia) and (b) $p\text{-HOCD}_2\text{-CH}_2\text{O-C}_6\text{H}_4\text{-CH}_2\text{CH}_2\text{NH}_2$ (I), in CDCl_3 at 60 Mc.p.s., with tetramethylsilane as internal reference. Resonances due to aromatic protons are not shown.

trum of the product from I corresponds to the α -methylene protons of $\text{ArCD}_2\text{CH}_2\text{OH}$ and indicates occurrence of phenylethyl rearrangement. From the areas of the $\alpha\text{-CH}_2$ and $\beta\text{-CH}_2$ peaks at 3.88 and 2.95 p.p.m., the per cent rearrangement was estimated as 40%. The *absence* of a peak at 4.0 p.p.m., 8 c.p.s. upfield from the singlet at 4.11 p.p.m. denotes that rearrangement of the $\text{OCH}_2\text{CD}_2\text{OH}$ group has not occurred. This is further confirmed by the observation that the sum of the areas of the $\alpha\text{-CH}_2$ and $\beta\text{-CH}_2$ peaks at 3.88 and 2.95 p.p.m. is equal to the area of the CH_2 peak at 4.11 p.p.m.

The nitro compound obtained from I is indicated by its n.m.r. spectrum to have the same deuterium distribution as in the diol, which implies that both compounds are derived from the same intermediate(s).

In Figure 3, the n.m.r. spectra of the monoacetates obtained from the deamination of Ia and I in acetic acid are compared. The peak at 4.31 p.p.m. in the spectrum from the labeled compound corresponds to the $\alpha\text{-CH}_2$ of $\text{ArCD}_2\text{CH}_2\text{OAc}$ and indicates that rearrangement has occurred. The extent of rearrangement was estimated as 39% from the relative areas of the α - and β -proton resonances at 4.31 and 2.90 p.p.m., and is essentially the same as that found in aqueous deamination. The absence of any signal at 4.0 p.p.m. due to the α -methylene protons of the $\text{OCD}_2\text{CH}_2\text{OH}$ group shows again that no rearrangement of the $\text{OCH}_2\text{CD}_2\text{OH}$ group occurred during deamination. Accordingly, the area of the $\text{OCH}_2\text{CD}_2\text{OH}$ resonance at 4.10 p.p.m. is equal to the sum of the areas of the peaks at 4.31 and 2.90 p.p.m. Reduction of the labeled monoacetate with lithium aluminum hydride gave the labeled diol VI. The n.m.r. spectrum of this product is compared with that of the unlabeled diol IV in Figure 2. The areas of the α - and $\beta\text{-CH}_2$ protons at 3.88 and 2.95 p.p.m. correspond to 40% rearrangement—in good agreement with the value obtained from analysis of the spectrum of the monoacetate.

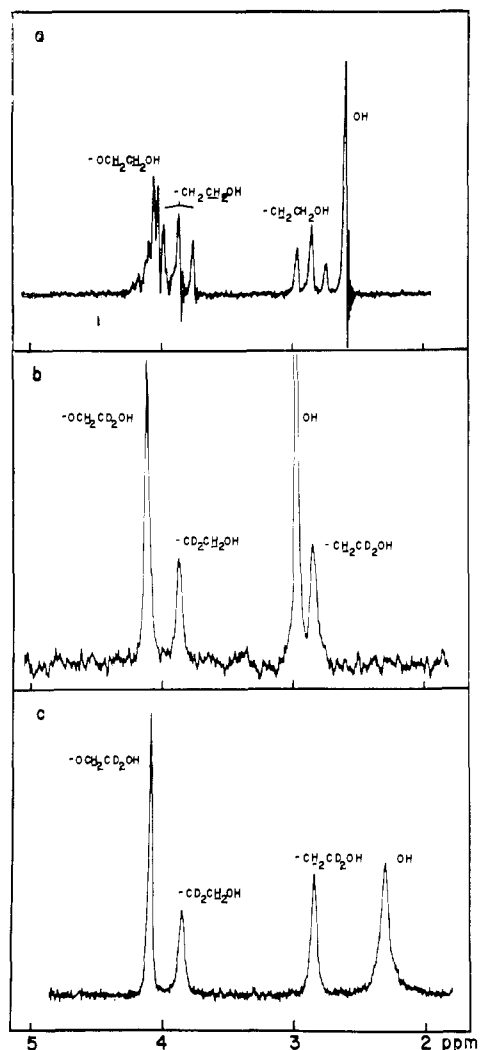


Figure 2. Nuclear magnetic resonance spectra of (a) *p*-HOCH₂-CH₂O-C₆H₄-CH₂CH₂OH (IV), (b) diol IVa obtained from deamination of I in water, and (c) diol IVb obtained from deamination of I in acetic acid followed by reduction with LiAlH₄. Spectra were taken at 60 Mc.p.s., in CDCl₃, with tetramethylsilane as internal reference. Resonances due to aromatic protons are not shown.

Again, there is no evidence of rearrangement of the OCH₂CD₂OH group. The extent of phenylethyl rearrangement observed (39–40%) is, as expected, reasonably consistent with that found previously⁸ in the deamination of the related 2-(*p*-methoxyphenyl)ethylamine-1-¹⁴C.

The foregoing results definitely eliminate intervention of spiro intermediate (III) in the deamination of the amino alcohol I, and indicate that if the symmetrical phenonium ion II is an intermediate in the reaction it must be converted to solvolysis products before cyclization to III occurs; or else, that formation of III from II is thermodynamically unfavorable.

Experimental Section

Ethyl *p*-Hydroxyphenylacetate. A solution of 100 g. (0.735 mole) of *p*-hydroxyphenylacetic acid in 500 ml. of absolute ethyl alcohol was saturated with dry hydrogen chloride and then heated under reflux for 20 hr. The solution was cooled and poured into 1 l. of ice water, neutralized with sodium carbonate, and

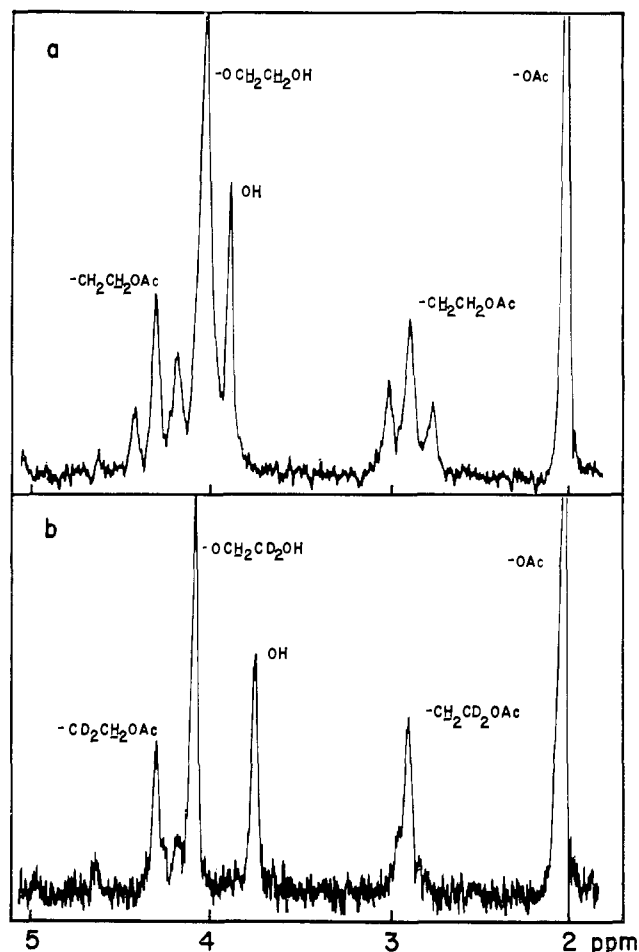


Figure 3. Nuclear magnetic resonance spectra of (a) *p*-HOCH₂-CH₂O-C₆H₄-CH₂CH₂OCOCH₃ (VI) and (b) the corresponding acetate VIA obtained from nitrous acid deamination of I in acetic acid. Spectra taken at 60 Mc.p.s., in CDCl₃, with tetramethylsilane as internal reference. Resonances due to aromatic protons are not shown.

extracted with ether. The ether extract was dried over sodium sulfate, filtered, and distilled. The yield was 77.0 g. (65%), b.p. 122° (0.6 mm.); lit.¹¹ b.p. 314° (760 mm.).

***p*-Hydroxyphenylacetamide.** A mixture of 60 g. (0.33 mole) of ethyl *p*-hydroxyphenylacetate and 90 ml. of 15 *M* ammonia solution was left to stand at room temperature for 7 days. Thereafter, the volatile materials were removed at aspirator pressure on a steam bath leaving 37.5 g. (82%) of almost colorless crystals, m.p. 174° (lit.¹¹ m.p. 175°).

Ethyl *p*-Acetamidophenoxyacetate. To a solution of 22 g. (0.146 mole) of *p*-hydroxyphenylacetamide in 100 ml. of dimethyl sulfoxide was added 17.0 g. (0.15 mole) of potassium *t*-butoxide in 100 ml. of dimethyl sulfoxide. To the stirred mixture was slowly added 17.9 g. (0.146 mole) of ethyl chloroacetate. The whole was further stirred for 1 hr. at room temperature, then left to stand overnight and finally poured into 700 ml. of ice water. The white crystals which separated were collected and recrystallized from hot water and yielded 25.0 g. (72%) of product, m.p. 139–140°. The infrared spectrum (C=O, 1750 and 1640 cm.⁻¹; N-H, 3350 and 3180 cm.⁻¹) and n.m.r. spectrum

(11) H. Salkowski, *Ber.*, 22, 2137 (1899).

(four-proton quartet centered at 7.05, two-proton singlet at 4.62, two-proton singlet at 3.50, two-proton quartet at 4.30, three-proton triplet at 1.30, and a broad NH resonance near 5.7 p.p.m.) are consistent with the assigned structure.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.91; H, 6.20; N, 6.05.

2-[p-(2'-Hydroxyethoxy)phenyl]ethylamine (Ia). To 4.50 g. (0.118 mole) of crushed lithium aluminum hydride suspended in 500 ml. of anhydrous ether was added an ether solution of ethyl *p*-acetamidophenoxyacetate over a period of 48 hr. The addition was carried out in a Soxhlet apparatus with 8.0 g. of the ester-amide in the thimble. At the end of the 48-hr. period, 3.1 g. of starting material was recovered from the thimble. The excess hydride was destroyed by the addition in order of 4.5 ml. of water, 4.5 ml. of 15% sodium hydroxide, and 13.5 ml. of water. The mixture was filtered and the filtrate was discarded. The solid residue was extracted with 100 ml. of refluxing chloroform and filtered, and the solvent was evaporated. There remained 2.0 g. of pale yellow crystals, m.p. 100–102°, which was further purified by sublimation at 120° (1 mm.) giving 1.60 g. (43%) of colorless crystals, m.p. 102–105°. Other preparations gave yields of pure Ia varying from 40–55%. The infrared spectrum (NH_2 and OH bands at 3325, 3250, and 3100 cm^{-1} (broad), KBr) and the n.m.r. spectrum (Figure 1) are consistent with the assigned structure.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.41; H, 8.36; N, 7.33, 7.40.

The tetradeuterated amino alcohol (I) was prepared similarly using lithium aluminum deuteride in 41% yield, m.p. 101–103.5°.

Deamination of Ia in Aqueous Solution. To an ice-cooled, magnetically stirred solution of 0.591 g. (3.17 mmoles) of Ia in 3.7 ml. of water containing 3.4 mmoles of fluoboric acid was added 0.291 g. (3.30 mmoles) of 98.7% sodium nitrite in 0.4 ml. of water. The mixture was stirred for 2 hr. then warmed at 50° for 1 hr., cooled, saturated with sodium chloride, and extracted with 10 ml. of chloroform. The organic extract was dried over potassium carbonate and sodium sulfate, decanted, and evaporated. A yellow oil remained (0.531 g.) which slowly crystallized. The crude product gave a thin layer chromatogram of one major and two minor spots. The n.m.r. and infrared spectra of the crude product showed it to be mainly the diol IV. When the impure product was washed with a little ether and chloroform, there was left 0.178 g. of crystals, m.p. 63–71°, which on recrystallization from chloroform gave 0.138 g. (23%) of colorless crystals, m.p. 72.5–74.0°. The n.m.r. spectrum of the diol IV is shown in Figure 2.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.96; H, 7.73.

The ether–chloroform washings were evaporated and the residue was distilled at 110° (0.3 mm.). A very pale yellow oil was obtained which partially crystallized. The dominant features in the n.m.r. spectrum of this distillate are those of the diol IV. In addition, very weak signals at 1.45 (doublet) and 4.8 p.p.m. (quartet) indicate the presence of trace amounts of *p*- $HOCH_2CH_2OC_6H_4CH(OH)CH_3$, presumably formed in the deamination of I by hydrogen migration. Stronger signals at 3.20 (triplet) and 4.55 p.p.m. (triplet) indicate that the principal impurity is the nitro compound, *p*- $HOCH_2CH_2OC_6H_4CH_2CH_2NO_2$. Consistent with this is the appearance of a band at 1570 cm^{-1} in the infrared spectrum of the distillate characteristic of the nitro group.

Deamination of Ia in Acetic Acid. To 0.547 g. (3.02 mmoles) of Ia in 4 ml. of glacial acetic acid was added 0.617 g. (8.8 mmoles) of 98.7% sodium nitrite over a period of 2 hr. The mixture was heated to 80° for 15 min., cooled, and added to 20 ml. of ice water. The product was extracted with 20- and 10-ml. portions of ether, and the combined extracts were neutralized with saturated sodium bicarbonate solution. The ether extract was dried over sodium sulfate, decanted, and evaporated. There remained 0.631 g. (93%) of a yellow oil which, by thin layer chromatography, was found to consist of one major component with traces of three other components. The infrared spectrum (OH, 3600, 3450 cm^{-1} ; C=O, 1740 cm^{-1}) and n.m.r. spectrum (Figure 2) of the crude product establish it as the monoacetate VI. Molecular distillation of VI gave a pale yellow oil with essentially the same spectra properties as the crude material.

Deamination of 0.534 g. of the deuterated amino alcohol I gave 0.591 g. (89%) of a yellow oil corresponding to the deuterated monoacetate VI. Molecular distillation gave 0.386 g. of product whose n.m.r. spectrum is shown in Figure 2. This material was dissolved in 4 ml. of ether and added slowly to a suspension of 0.11 g. of lithium aluminum hydride in 6 ml. of ether. The mixture was refluxed for 105 min. and cooled, and the excess hydride was destroyed with 0.11 ml. of water followed by 0.15 ml. of 15% sodium hydroxide solution and 0.33 ml. of water. The mixture was filtered and the solid residue was extracted with 15 ml. of hot chloroform. The chloroform extract was evaporated leaving 0.207 g. of the deuterated diol IV, m.p. 64–71°, which on recrystallization from chloroform had m.p. 74.5–74.5°. The n.m.r. spectrum of this product is shown in Figure 2.

N.m.r. spectra were taken on a Varian A-60 spectrometer. Samples were prepared in deuteriochloroform solution, and chemical shifts were measured relative to tetramethylsilane as an internal standard.