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Smiles Rearrangement on Borohydride Reduction of a Nitrophenoxy Ester[1]

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An attempted preparation of the acetophenetidin metabolite 2-methyl-2-(4-acetamidophenoxy)propanol (**2**), which started with the reduction of the ester function of ethyl 2-methyl-2-(4-nitrophenoxy)propionate (**3a**) by $LiBH_4$ in diglyme, led to an isomer of **2**. Initial platinum/hydrogen reduction of the nitro function of **3a**, to give amino ester **4**, followed by $LiAlH_4$ reduction of the ester moiety, then acetylation, gave correct **2**. That a rearrangement had occurred at the borohydride reduction step was shown by reduction of the nitro acid **3b** by diborane to 2-methyl-2-(4-nitrophenoxy)propanol (**5**), different from the $LiBH_4$ product **8**, and rearranged to **8** by strong bases. Reduction of **3a**, labeled with ^{18}O at the aromatically bound O, and mass spectral analysis of the fragments showed that a Smiles rearrangement (intramolecular attack on a aromatic carbon) was the mechanism operating. Considerably less rearrangement during $LiBH_4$ reduction of the analogous monomethyl nitro ester, ethyl 2-(4-nitrophenoxy)propionate (**9a**), was shown by isolation of 2-(4-acetamidophenoxy)propanol starting with this step, as well as by using either diborane reduction of the corresponding acid **9b** to 2-(4-nitrophenoxy)propanol (**10**), or platinum and hydrogen reduction of ester **9a** as the initial step. The Smiles arrangement product, 1-(4-nitrophenoxy)-2-propanol (**11**), however, was present and could also be produced from **10** by strong bases. Under the reduction conditions used, the ratio of alcohols found after $LiBH_4$ reduction of **3a** or **9a** was identical with that produced by equilibration of either nitro alcohol with base.

The metabolic degradation of the commonly used mild analgesic *p*-acetophenetidin (Phenacetin) was shown some time ago[2] to occur largely by dealkylation to give *p*-acetamidophenol. Such dealkylations appear to be oxidative,[3] as if a hydrogen on the ethereal carbon of the aliphatic moiety is replaced by hydroxyl in the step leading to cleavage. Pursuing this, 4-acetamidophenyl *tert*-butyl ether (**1**), which has no such hydrogen, was made and found to be essentially unattacked by the drug-hydroxylating liver microsomal enzymes.[4] Preliminary testing in mice revealed that **1** appeared to have substantial analgesic activity, more prolonged in duration than that of phenacetin.[5] A metabolite was isolated as its glucuronide from the urine of dogs fed **1** and was postulated[6] to have the structure **2**. Since production of **2** would represent an unusual hydroxylation at an unactivated methyl group,[7] it seemed desirable to prove the structure of **2** by synthesis.

The route chosen involved preparation of ester **3a** (Scheme I) from the *p*-nitrophenol anion and ethyl 2-bromo-2-methylpropionate, to be followed by reduction of the ester function and of the nitro group. A single nitro ester was isolated. The alternatives to **3a**, either the product of ring alkylation rather than O-alkylation or the product of dehydrohalogenation of the bromo ester and subsequent Michael addition of *p*-nitrophenolate anion to the resulting ethyl 2-methylmethacrylate, could be ruled out by the hydrogen nmr (pmr)[8] of the nitro ester.

To avoid the necessity of doing a lithium aluminum hydride reduction of the amino ester **4**, with its two active hydrogens, use was made of the low activity toward the nitro group and the ability to reduce the ester function reported for complex borohydrides.[9] Although magnesium borohydride in hot diglyme showed no reaction, the more active lithium borohydride in hot diglyme reacted vigorously with **3a**. In addition to dark materials, presumably azo and/or azoxy compounds, which were not investigated further, a yield of about 70% of a seemingly pure (boiling point, tlc, and glpc) liquid was obtained which had the expected elemental analysis and pmr for the desired nitro alcohol **5**. This was then reduced with Adams' catalyst and hydrogen, and acetylated to an acetamino alcohol *isomeric*

(1) A portion of the material in this paper was presented in *Chem. Commun.*, 730 (1969).

(2) B. B. Brodie and J. Axelrod, *J. Pharmacol. Exp. Ther.*, **97**, 58 (1949).

(3) See R. T. Williams, "Detoxication Mechanisms," 2nd ed, Wiley, New York, N. Y., 1959, p 331.

(4) A. H. Conney, M. Sansur, and M. Harfenist, *Pharmacologist*, **7**, 160 (1965).

(5) A. H. Conney, M. Sansur, F. Soroko, R. Koster, and J. J. Burns, *J. Pharmacol. Exp. Ther.*, **151**, 133 (1966).

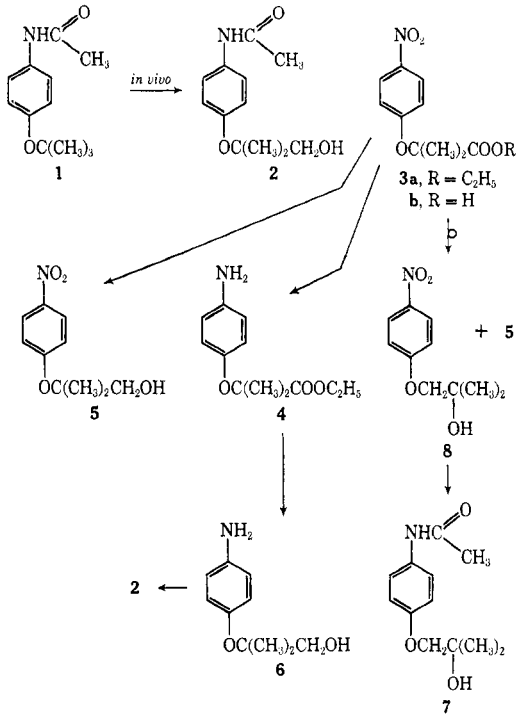
(6) A. Klutch and M. Bordun, *J. Pharm. Sci.*, **56**, 1654 (1967).

(7) Earlier reports of *in vivo* hydroxylations which occurred at nonethereal aliphatic carbons showed attack at *tertiary* carbons sufficiently activated that in some cases the same alcohols could be produced by chromic acid oxidations. *E.g.*, see E. W. Maynert, *J. Biol. Chem.*, **196**, 397 (1952). More recently attacks at *secondary* carbons not activated by α-ether bonding have been reported: R. W. Balsiger, Th. Leuenberger, W. Michaelis, and O. Schindler, *Helv. Chim. Acta*, **52**, 1323 (1969).

(8) Only the ethyl triplet and quadruplet, an isolated singlet for two CH_3 groups, and the A:B:B′:A′ quartet with meta splitting characteristic of a para-disubstituted benzene were found.

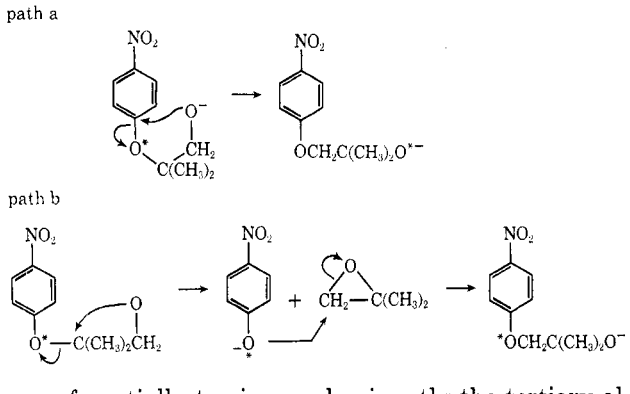
(9) R. F. Nystrom, S. W. Chaikin, and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 3245 (1949).

SCHEME I



with 2, and with an almost identical pmr. This isomer of 2 gave *p*-acetamidophenol with acid, but only after more prolonged treatment than was required by the metabolite 2. The structure best fitting these facts was 7. (Evidence that the nitro alcohol antecedent to 7 was indeed 8 was obtained subsequently by mass spectral study of 8, as described below.)

Two mechanistic routes could be postulated which would lead from **3a** eventually to 7. The first of these, which we regarded as more likely, would involve the attack of a nucleophilic reduced species, here shown as the alkoxide of 5, at the aromatic ethereal carbon para to the nitro group, to form a real or quasi five-membered ring in the transition state (path a). This would open



up preferentially to give predominantly the tertiary alcohol 8 convertible to 7, because the rate of attack at the electrophilic aromatic carbon by the primary alkoxide of 5 would be more rapid than that of the tertiary alkoxide corresponding to 8. The equilibrium constant would then represent the ratio of the two rate constants in the usual way, very much in favor of 8 upon equilibration.

The alternative route (path b) would involve attack of the same nucleophilic alkoxide oxygen or equivalent, but here at the *aliphatic* ethereal carbon to form the three-membered epoxide ring, with loss of *p*-nitrophenolate anion. Since base-catalyzed attack on such an epoxide would go at the least substituted carbon, isolation of 8 rather than 5 by this mechanism is explicable.

Either of these alternatives shows that such an arrangement would require an electron-withdrawing (here the para nitro) group, and would require a sufficiently strong base to form the alkoxide. The first of these requirements allowed a straightforward synthesis of the metabolite 2, by the reduction of the nitro ester **3a** to the amino ester **4** with Adams' catalyst and hydrogen as the first step. Despite the active hydrogens, the reduction of 4 with lithium aluminum hydride in ether went in excellent yield to give 6, unrearranged because the nitro group was not present during the hydride treatment. Compound 6 was acetylated with acetic anhydride in ethanol to give the desired metabolite 2.

The second requirement for the rearrangement of nitro alcohol 5, strong base, could be avoided completely by the use of a nonbasic reducing agent. Diborane, which has been reported[10] to reduce acids at a rapid rate but to be inert toward aromatic nitro groups, would be expected to be a Lewis acid rather than a base. Indeed, careful saponification of the nitro ester **3a** to give the nitro acid **3b**, followed by treatment of this acid with diborane in tetrahydrofuran, gave the unrearranged nitro alcohol 5, different from that isolated from the borohydride reduction of the ester. Having samples of both nitro alcohols, it was now possible to show by column chromatography that the borohydride product, in accord with expectations, did contain a small proportion ($\leqslant 10\%$) of unrearranged 5, while the borane product contained no detectible rearranged nitro alcohol 8. This diborane reduction also made pure 5 available. Further, it was now possible to demonstrate the rearrangement of the nitro alcohol 5 in the presence of its alkoxide salt with any of several metals but without borohydride present. Rearrangement of 5 to the anticipated mixture, predominantly 8, in hot diglyme was shown with 5 lithium alkoxide (from lithium butyl or from less than the theoretical amount of lithium borohydride) or 5 sodium alkoxide (from sodium hydride) or 5 potassium alkoxide (by addition of potassium *tert*-butoxide).[11]

Having pure 5 and 8 available also allowed us to find one absorption maximum each in the ir spectrum of 5 and 8 not present in the other, although the spectra were remarkably similar. These, as well as the slightly different positions of the pmr absorptions of the CH_2 hydrogens of 5 and of 8, allowed crudely quantitative measurement of the proportion of 5 and 8 at base-catalyzed equilibrium approached from pure 5 and pure 8. This was found to be essentially the same as that obtained from the borohydride reduction of nitro ester **3a**, almost wholly 8.

It should be possible to distinguish a mechanism of rearrangement involving path a from the alternative path b by labeling one of the oxygens. For example, if the ether oxygen of the unrearranged nitro alcohol 5 were labeled, rearrangement by path a would lead to 8 with the terminal oxygen labeled. Conversely, the

(10) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962, p 29.

(11) Substantial amounts of *p*-nitrophenol (as anion) were also produced, as well as what appeared to be products of partial reduction of the nitro group.

epoxide of path b is produced without aryl-to-oxygen bond cleavage, and the attack on the epoxide by the aryloxy anion also proceeds with retention of the aryl-to-oxygen bond, so a labeled ether oxygen in **5** would remain as such in **8** produced by way of path b. An orienting experiment with unlabeled **8** showed that its mass spectrum[12] showed intense peaks attributable to $[O_2NC_6H_4OCH_3]^+$ and to $[(CH_3)_2COH]^+$, so that it would be possible to determine unequivocally the position of a labeled oxygen in **8**. Reduction with rearrangement of ether-oxygen labeled nitro ester **3a** seemed the approach most economical of synthetic effort.

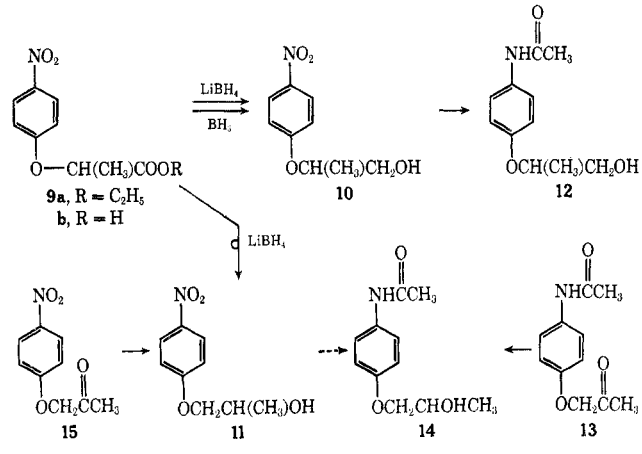
Labeled **3a** was made from *p*-fluoronitrobenzene; potassium hydroxide (40% ^{18}O) was made *in situ* from water (40% ^{18}O) and potassium *tert*-butoxide in *tert*-butyl alcohol.[13] The *p*-nitrophenol produced by reaction of this $K^{18}OH$ with *p*-fluoronitrobenzene in the same solvent was isolated. The ^{18}O-containing *p*-nitrophenol had mass spectral peaks at 139 and 141 mass units (parent) and at 93 and 95 mass units (parent less NO_2) in a ratio indicating approximately 38% ^{18}O at one of the three oxygens in the parent, and at the only oxygen in the fragments with *m/e* 93 and 95. This shows that exchange of oxygen had occurred neither with the alcoholic solvent nor between the $K^{18}OH$ and the nitro group.[14]

The product of the lithium borohydride reduction with rearrangement of the aryl ^{18}O-labeled **3a** made from this was found to show significant peaks: (a) at 211 and 213 (the product, *i.e.*, largely **8**) with the ratio showing 41% of ^{18}O at one oxygen; (b) at 153 and 155 (*i.e.*, $[O_2NC_6H_4OCH_3]^+$) showing not over 2% ^{18}O; (c) at 59 and 61 (*i.e.*, $[(CH_3)_2COH]^+$) showing 37% of ^{18}O.

The rearrangement, therefore, goes by path a and represents an example of the Smiles rearrangement.[15] This rearrangement can be described as an intramolecular attack at an aromatic carbon by a nucleophilic portion of the molecule, leading to displacement of a group previously attached at that carbon by the more nucleophilic portion. Although an example was found in the literature of attack by an alkoxide with displacement of a sulfurous acid amide,[16] and there are examples reported of internal displacement of alkoxide by an amino group leading to (*o*- and *p*-nitro-substituted) ω-hydroxypropylanilines[17] rather than the desired ω-aminopropyl aryl ethers, we do not know of any previously recognized examples of Smiles rearrangement by displacement of one alkoxide by another.

It was of interest to see whether this Smiles rearrangement would occur at a detectible rate with the *secondary* alkyl ether, 2-(4-nitrophenoxy)propanol (**10**). We therefore prepared ethyl 2-(4-nitrophenoxy)propionate (**9a**) and from it the corresponding nitro acid **9b**. Both lithium borohydride reduction in diglyme of the ester and reduction of the acid with diborane in THF gave what appeared to be the *same* nitro alcohol. Each of these nitro alcohol reduction products was reduced with hydrogen and Adams' catalyst to an amino alcohol, which was acetylated with acetic anhydride in ethanol to give, after purification (with substantial loss for the lithium borohydride product), the same acetanilide (shown by melting point and mixture melting point). This was assumed to be *unrearranged*, *i.e.*, **12**. Proof of this was obtained by an unequivocal synthesis of the isomeric *rearranged* acetamido alcohol **14** by the route shown in Scheme II, sodium borohydride reduction of **13**.[18]

SCHEME II



Isolation of **12**, suggesting that unrearranged nitro alcohol **10** was the major product of lithium borohydride reduction of ester **9a**, seemed in contradiction to the reasoning given as to the cause of preponderance of **8** over **5** in the corresponding reduction products of **3a** by borohydride. Rearrangement of **10** alkoxide should be comparable in speed to rearrangement of **5** alkoxide. This means that equilibrium would be reached here under our reaction conditions, as it was in the dimethyl case. Since the rate of attack of the primary alkoxide of **10** should be faster than the reverse attack of the secondary alkoxide of **11** (though the ratio should not be as overwhelming as in the **5** → **8** case), the equilibrium should favor **11**. We therefore made **11** from **15**, the chloroacetone plus *p*-nitrophenol product,[19] by reduction with sodium borohydride in aqueous ethanol. The product differed in pmr of the CH_2 and CH groups from that found for the diborane reduction product of **9b**, and neither **11** made from **15** nor the **10** made by BH_3 reduction had detectible quantities of the other, indicating the important point that rearrangement of **11** did not occur under conditions of the sodium borohydride reduction. The "pure" borohydride reduction product of ester **9a**, however, was found by pmr to be about 70%[20] rearranged, *i.e.*, **11**, and 30% **10**. Thus isolation of the unrearranged acetamido alcohol **12** was fortuitous and the rearrangement had occurred as predicted although not to the extent expected. It is of interest that neither of two tlc systems tried, nor two analytical glpc systems, could distinguish between **10** and **11**, nor could more than one substantial absorption

(12) Mass spectra were determined in most cases by the Morgan-Schaffer Co., Montreal, Canada. In the critical ^{18}O case (see below), they were independently corroborated through the courtesy of Dr. Keith Palmer of the Research Triangle Institute, Research Triangle Park, N. C.

(13) In one orienting run with unlabeled water, use of tetramethylene sulfone instead of the tertiary alcohol gave no detectible increase in yield.

(14) The lack of exchange in the nitro group was also indicated by a peak at *m/e* 46 with essentially nothing visible at *m/e* 48.

(15) A summary of the elegant work of S. Smiles, *et al.*, can be found in W. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935), and also J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(16) K. G. Kleb, *Angew. Chem., Int. Ed. Engl.*, **7**, 291 (1968).

(17) W. T. Caldwell and G. C. Schweiker, *J. Amer. Chem. Soc.*, **74**, 5187 (1952).

(18) C. D. Hurd and P. Perletz, *ibid.*, **68**, 38 (1946).

(19) D. S. Tarbell, *J. Org. Chem.*, **7**, 251 (1942).

(20) An adequate separation required use of the Varian 220-MHz nmr instrument at Rockefeller University. We thank Dr. Earl Whipple for these data.

peak be found in which the ir curves of **10** and **11** differed in the 3–16-μ region.

Using the pmr, it was next shown that the same proportion of **11** and **10** was found starting with either pure isomer and heating with NaH in diglyme, a finding in keeping with the scheme presented.

Experimental Section[21]

Caution! Salts of *p*-nitrophenol can deflagrate if allowed to become dry, especially if heated.

Ethyl 2-Methyl-2-(4-nitrophenoxy)propionate (3a).—A solution of sodium ethoxide from 48.5 g of sodium (2.1 g-atoms) and 1800 ml of commercial absolute ethanol had 295 g (2.12 mol) of *p*-nitrophenol added with stirring and was stirred an additional 15 min. Much orange sodium salt precipitated. There was no obvious reaction when 476 g (2.45 mol) of ethyl 2-bromo-2-methylpropionate was added, so the reaction was stirred and heated on a steam bath under reflux (NaOH tube) for 48 hr. It was then concentrated on steam to approximately 1/4 of its volume (see Caution above) and partitioned between water and ether. The ethereal solutions were extracted with 0.5 *N* aqueous NaOH until acidification of an aliquot gave no oil (three portions, 1 l. each), washed with water, and dried ($MgSO_4$). The crude product was distilled at 132–166° (0.4 mm). This distillate was redistilled at a temperature varying markedly with the rate of distillation, nominally bp 125–138° (0.03 mm), yielding 297 g (56%) of a yellow liquid 97–100% pure by glpc.

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.92. Found: C, 57.23; H, 6.20.

From the alkaline washes 84.5 g of *p*-nitrophenol was readily recovered.

2-Methyl-2-(4-nitrophenoxy)propionic Acid (3b).—Nitro ester **3a** (25.2 g, 0.1 mol) dissolved in 55 ml of 95% ethanol and 15 ml of water was treated with 12.4 g (0.11 mol) of potassium *tert*-butoxide. The reaction spontaneously heated to about 80°. It was stoppered and allowed to stand with occasional shaking for 3 hr and diluted with water to 500 ml. The clear solution was brought to pH 2 (test paper) cautiously, shaking to avoid local excess of strong acid, and extracted with ether, and the ether was washed with water and dried ($MgSO_4$). Removal of ether left 21 g of crude solid which sintered at 80° but with mp 124°. This, twice recrystallized from acetone–benzene–hexane, yielded 6.6 g of **3b** (mp 123.4–124.4°).

Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.65; H, 4.99; N, 6.06.

Ethyl 2-Methyl-2-(4-aminophenoxy)propionate (4).—Reduction of 50 g of nitro ester **3a** in 150 ml of 95% ethanol in a Parr hydrogenator at an initial H_2 pressure of 3 atm required 2 days and a change of the Adams' catalyst used to reach the calculated H_2 uptake. Filtration and solvent removal on steam at 15 mm pressure left 40.5 g of a liquid which darkened rapidly in air. Most was therefore immediately used to prepare **6**, and the by then dark remainder subsequently distilled, bp 100–103° (0.08 mm), and converted to the HCl salt. This was recrystallized from absolute ethanol–ether, mp 161–162°.

Anal. Calcd for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.94; N, 5.39. Found: C, 55.30; H, 7.02; N, 4.99.

2-Methyl-2-(4-nitrophenoxy)propanol (5).—A solution of 155 ml of 1 *M* borane in tetrahydrofuran solution (Alfa Inorganics, Inc.) was added dropwise with stirring under nitrogen to a solution of 35 g (0.156 mol) of the acid **3a** in 70 ml of peroxide-free tetrahydrofuran. Gas was evolved. The solution was allowed to remain overnight, and water was added, slowly at first, to a total of 1200 ml. Extraction with three 300-ml portions of ether, drying ($MgSO_4$), and removal of the ether by distillation on steam left 33 g of yellow oil. Two distillations, each at 115–121° (0.01 mm), gave 24 g of product (73%): nmr ($CDCl_3$) δ 1.4 (s, 6, CH_3), 3.68 (s, 2, CH_2OH), 7.12 (d, 2, J = 9 Hz of d, J = 2 Hz, ArH ortho to OR), 8.20 (d, 2, J = 9 Hz of d, J = 2 Hz, ArH ortho to NO_2). A broad OH peak about δ 2.37 was observed when *p*-nitrophenol was absent.

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.80; H, 6.15; N, 6.63. Found: C, 56.33; H, 6.21; N, 6.57.

2-(4-Aminophenoxy)-2-methylpropanol (6). A. From Amino Ester 4.—A solution of 10.2 g (45.6 mmol) of crude **4** in 100 ml of anhydrous ether was added dropwise to 11 g (290 mmol) of $LiAlH_4$ in 350 ml of ether and then heated under reflux for 4 hr. Cautious addition of 22 ml of water, filtration, washing the solids with anhydrous ether, and removal of the ether on a water bath finally at reduced pressure left 7.2 g of a liquid **6** which was acetylated without further purification.

B. From Nitro Alcohol 5.—Use of Adams' catalyst, 95% ethanol as solvent, and 3 atm of initial hydrogen pressure in a Parr hydrogenator gave rapid uptake of the theoretical amount of hydrogen. The catalyst was removed by filtration, and the ethanolic solution of **6** was acetylated directly with 2 equiv of acetic anhydride.

2-(4-Acetamidophenoxy)-2-methylpropanol (2). A. From 6 Made from 4.—The 7.2 g of amino alcohol **6** from **4** was dissolved in 30 ml of ether, and 6 ml of acetic anhydride was added with swirling. After 5 min the resulting crystals were filtered off and washed with ether to remove the yellow color. Recrystallization from benzene–hexane gave 3.6 g, mp 119–119.5°. This was identical in ir (KBr pellet) and in tlc in the test system (silica gel, lower layer of the mixture of $CHCl_3$–H_2O–MeOH–HOAc = 1:1:0.5:0.025, all by volume) to the metabolite of **1** isolated from dog urine[6] and gave no mixture melting point depression with that metabolite. The R_f found for **2** was 0.185; that for the rearrangement product **7** was 0.235.

B. From 6 Made from 5.—The ethanolic solution was treated with a 200% excess of acetic anhydride, mixed, and heated on steam after 10 min, for 15 min. Crystallization followed addition of water. The product was **2**, identical in all tests with that isolated from natural sources or made from **4**.

1-(4-Acetamidophenoxy)-2-methyl-2-propanol (7).—The amino alcohol corresponding to **7** was made from rearranged nitro alcohol **8** (see below) by reduction in a Parr hydrogenator as in the conversion of **5** to **6**. It was not isolated but instead acetylated in ethanol following the same procedure used to make **2** from **6** and recrystallized to constant mp 142° from benzene, then from much water, final mp 144°.

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.47; H, 7.70; N, 6.27.

1-(4-Nitrophenoxy)-2-methyl-2-propanol (8). A. By $LiBH_4$ Reduction of 3a.—A mixture of 0.82 g (21.7 mmol) of $NaBH_4$ and 0.93 g (22 mmol) of oven-dried LiCl in 15 ml of dried (CaH_2) diglyme was heated (N_2) for 1 hr at 110° with stirring. A solution of 5.5 g (21.7 mmol) of nitro ester **3** in 10 ml of dried diglyme was added dropwise (15 min), and the reaction was stirred at 110° bath temperature for 2 hr more. The now dark orange solution was cooled under N_2 and 10 ml of H_2O added slowly. The reaction was then poured into 100 ml of water and extracted three time with Et_2O. The Et_2O layers were extracted in turn with 0.1 *N* HCl and 0.1 *N* NaOH (two 50-ml portions of each), dried ($MgSO_4$), concentrated, and distilled giving 3.3 g, bp 107–111° (0.007 mm).

The product was a yellow oil which appeared homogeneous when run on tlc[21] either in a mixture of hexane–ether–acetone–acetic acid, 30:4:2:0.75, or in benzene–ethanol, 22:3 (all solvents by volume), apart from a colored impurity which remained near the origin. This last was retained on an alumina column[21] developed with hexane containing increasing amounts of anhydrous ether. Combined column eluents were distilled to remove solvent and analyzed.

The pure product eventually crystallized and could be recrystallized from hexane: mp 60–61.5°; nmr ($CDCl_3$) δ 1.4 (s, 6, CH_3), 3.96 (s, $ArOCH_2$), 7.0 (d, 2, J = 9.5 Hz of d, J = *ca.* 1.5 Hz, ArH ortho to O), 8.22 (d, 2, J = 9.5 Hz of d, J = *ca.* 1.5 Hz, ArH ortho to NO_2). Unless *p*-nitrophenol was present, the OH absorption was at δ *ca.* 2.4.

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.15; N, 6.63; mol wt, 211.2. Found: C, 56.54; H, 6.14; N, 6.44; mol wt (mass spectrum), 211.

B. By Rearrangement of Nitro Alcohol 5.—A solution of 5 g (25 mmol) of **5** in 10 ml of dried (CaH_2) diglyme was heated at 115° for 1 hr after addition of 20 mmol each (separate experiments) of the bases, NaH (50% in mineral oil emulsion), and KH in mineral oil). In each case, after quenching in water, washing the ethereal solution with dilute HCl (amino compound was removed), dilute NaOH to remove *p*-nitrophenol, and water, the ethereal solution was dried ($MgSO_4$) and distilled All of the

(21) All melting points were taken on thermometers calibrated with standard compounds and are corrected. Nmr measurements were made using a Varian A-60 instrument by Mr. A. Ragouzeos. Column chromatography used Woelm neutral alumina, activity grade I. Tlc were run on Eastman K301R2 prepared silica gel.

fraction boiling within 10° of the boiling point was taken for pmr in $CDCl_3$.

Ethyl 2-(4-Nitrophenoxy)propionate (9a).—This was made from 155 g of *p*-nitrophenol similarly to **3** but using potassium *tert*-butoxide as base. Distillation was not required as the product solidified on removal of ether, mp 50–52° raised to 55–56° after two recrystallizations from hexane.

Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.44; N, 5.86. Found: C, 55.61; H, 5.54; N, 5.75.

Acidification of the basic aqueous extracts gave 34 g of *p*-nitrophenol.

2-(4-Nitrophenoxy)propionic Acid (9b).—A solution of 101 g (0.421 mol) of nitro ester **9a** in 800 ml of warm 95% ethanol was cooled to *ca.* 35° and treated, with stirring, with 50 ml of 50% w/v aqueous NaOH followed by 20 ml of water washes.

After 24 hr the mixture was concentrated *in vacuo* to a small volume, dissolved in *ca.* 200 ml of water, and filtered from a little water-insoluble material, and acidified with concentrated HCl. After overnight storage at 4°, the solid was filtered from the solution and recrystallized twice from benzene (*ca.* 2 l.), yielding 80 g of yellow crystals, mp 140–140.5°.

Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 50.94; H, 4.17; N, 6.37.

Reduction of Ester 9a by Lithium Borohydride.—The procedure used to reduce **3a** to **8** gave from 50 g of **9a**, 20.5 g of a liquid with bp 126–131° (0.03 mm).

2-(4-Nitrophenoxy)propanol (10). By Borane Reduction of the Acid 9b.—A solution of 60.2 g (0.283 mol) of acid **9b** in 250 ml of tetrahydrofuran (peroxide-free, dried over molecular sieves) was added dropwise to 250 ml of a molar solution of BH_3 in tetrahydrofuran, stirred under N_2. After remaining at 26° overnight, the reaction was treated with 1 l. of water added slowly with stirring, extracted with three 50-ml portions of 1 *M* $NaHCO_3$, dried ($MgSO_4$), and distilled, retaining fractions of bp 118–122° (0.06 mm): nmr ($CDCl_3$) δ 1.33 (d, 3, J = 6 Hz, CH_3), 2.37 (s, 1, OH), 3.80 (d, 2, J = 5 Hz, CH_2OH), 4.66 (q, 1, J = 7 Hz, CHOAr of d or m, J = *ca.* 1 Hz), 7.00 (d, 2, J = 9 Hz, *o*-ORArH, of d, J = *ca.* 2 Hz), 8.20 (d, J = 9 Hz, *o*-NO_2ArH, of d, J = *ca.* 2 Hz).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.11. Found: C, 55.11; H, 5.75; N, 7.16.

Ethyl 2-(4-Aminophenoxy)propionate.—A solution of 62 g (0.26 mol) of nitro ester **9a** in 250 ml of 95% ethanol had to be heated to 45° in a Parr hydrogenator to allow reduction with Adams' catalyst and hydrogen. The solvent was removed after filtration, using steam bath and water pump, to leave 56.3 g of residual oil. Most of this was used to make **10** but 6 g was converted to ethyl 2-(4-acetamidophenoxy)propionate by acetic anhydride in ethanol solution for analysis. Two recrystallizations from ethanol–water gave 3.2 g, mp 81–82°.

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.87; N, 5.65. Found: C, 61.84; H, 6.87; N, 5.65.

2-(4-Acetoamidophenoxy)propanol (12). A. By Reduction of Ethyl 2-(4-Aminophenoxy)propionate and Subsequent Acetylation.—A solution of 35.9 g (0.172 mol) of the named amino ester in 500 ml of commercial anhydrous ether was added to 25.8 g (0.68 mol) of $LiAlH_4$ in 1 l. of ether in the usual way and heated under reflux for 2 days. After cautious addition of 52 ml of H_2O and 0.5 hr of stirring, the solid was removed by filtration and washed with anhydrous ether, and then suspended in 100 ml of 95% ethanol and refiltered. The combined ether and ethanol solutions were treated with 50 ml of acetic anhydride with swirling over 10 min and then concentrated on steam at the water pump to a small volume. The residue was boiled with 1 l. of 95% ethanol for 1 hr and water was added at the boiling point to faint turbidity.

On cooling, 1.5 g of orange solid crystallized. This was recrystallized from benzene–hexane, mp 147–150°, and was shown to be 4,4′-bis(1-methyl-2-hydroxyethoxy)azobenzene (or an isomer) by elemental analysis, indicating that the starting amino ester had been contaminated with unreduced nitro ester.

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.40; H, 6.71; N, 8.48. Found: C, 65.22; H, 6.67; N, 8.45.

Concentration of the mother liquors and recrystallization of the residual 12.8 g of material from ethanol–water and from benzene–hexane gave 8 g of solid, mp 120–121°. An additional 10 g was obtained by further washings of the reduction "inorganic" solids with 95% ethanol, acetic anhydride treatment, and recrystallization.

B. By Adams' Catalyst and H_2 Reduction of 10 with Subsequent Acetic Anhydride Treatment.—Following the usual reduction procedure **10** yielded **12** of melting point undepressed on admixture with **12** prepared from the amino ester as outlined in A above, and with identical ir absorption in thin film. This was true for **12** made from **10** which had been prepared either by the $LiBH_4$ reduction of ester **9a** or BH_3 reduction of acid **9b**, but the $LiBH_4$ product initially was an oil requiring five recrystallizations to give an acceptable melting point, while that from **10** from the BH_3 reduction gave 93% of nearly pure material directly.

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 63.16; H, 7.18; N, 6.70. Found: C, 63.18; H, 7.43; N, 6.67.

1-(4-Acetamidophenoxy)-2-propanol (14).—A suspension of 10 g (50 mmol) of 1-(4-acetamidophenoxy)acetone[18] in 100 ml of 50% by volume of methanol–water was stirred, while 2.0 g of $NaBH_4$ dissolved in 20 ml of water was added dropwise, while cooling with flowing tap water. After addition was complete and an additional 45 min had elapsed, 2 ml of HOAc was added, and the solvents were removed on steam at water pump pressure. The resulting oil was extracted repeatedly with acetone, and the filtered acetone extracts were concentrated. The 5.8 g of oil crystallized after addition of water and was recrystallized from water, mp 122–123.5°. The ir absorption had lost the C=O peak present in the starting material and a peak attributed to OH was now present at 3300–3450 cm^{-1}. Elemental analysis showed that this product was isomeric with **12**, when taken with the mixture melting point depression found.

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 63.16; H, 7.18; N, 6.70. Found: C, 62.69; H, 7.34; N, 6.73.

1-(4-Nitrophenoxy)-2-propanol (11).—Reduction of a solution of 10 g of *p*-nitrophenoxyacetone by $NaBH_4$ was carried out by the procedure used to prepare **14**, but work-up consisted of diluting the mixture after the addition of the acetic acid, extraction with ether, drying the ether over $MgSO_4$, and removal of solvent. The resulting orange oil crystallized and was recrystallized from ethanol–hexane and then from hexane: mp 90–92°; nmr ($CDCl_3$) δ 1.33 (d, 3, J = 6 Hz, CH_3), 2.56 (s, 1, OH), *ca.* 4.05 (m, 3, $ArOCH_2$ + CHOH), 7.00 (d, 2, J = 9 Hz, *o*-ORArH of d, J = *ca.* 2 Hz), 8.21 (d, 2, J = 9 Hz, *o*-NO_2ArH of d, J = *ca.* 2 Hz); ir showed no C=O absorption.

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.11. Found: C, 54.92; H, 5.63; N, 7.09.

Preparation of ^{18}O-Enriched *p*-Nitrophenol.—Dry potassium *tert*-butoxide (21 g) (MSA Research Corp.) was added to 100 ml of *tert*-butyl alcohol which had been dried previously over calcium hydride. ^{18}O-Enriched water (3 ml, 3.061 g) [labeled 41.90% ^{18}O, containing 0.145% ^{17}O (Miles Laboratories)] was added, and the stoppered flask's contents were stirred for 1 hr. A 29.5-g portion of *p*-fluoronitrobenzene was then added, and the now red-brown solution was stirred for 22 hr at approximately 40°. It was then added to 500 ml of water and extracted with ether twice. The ethereal extracts were washed with 1 *N* aqueous sodium carbonate solution, and that combined with the initial aqueous solution brought to pH less than 2 (test paper) with concentrated HCl and extracted with ether (300 ml) and with benzene (100 ml). The combined organic layers were dried ($MgSO_4$) and solvent was removed on the steam bath at 15 mm pressure. The residue was 12.5 g, mp 112.6–113.5°.

Registry No.—**2**, 15971-28-5; **3a**, 23501-39-5; **3b**, 17431-97-9; **4**, 28048-87-5; **5**, 28048-88-6; **7**, 28048-89-7; **8**, 23501-60-2; **9a**, 28059-69-0; **9b**, 13794-10-0; **10**, 28059-71-4; **11**, 10572-15-3; **12**, 28059-73-6; **14**, 28059-74-7; ethyl 2-(4-aminophenoxy)propionate, 28059-75-8.