Facile Synthesis of Glycol Metabolites of Phenethylamine Drugs[1]

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Abstract □ High yields of potential glycol metabolites of *p*-synephrine, epinephrine, octopamine, and normacromerine can be obtained from the readily available monosubstituted and disubstituted acetophenones. The general procedure involves alpha-bromination followed by displacement with acetate ion and reduction with lithium aluminum hydride. Yields ranged from 46 to 91%. Furthermore, the procedure minimizes some problems inherent in aromatic glycol synthesis which include dimerization and pinacol–pinacolone rearrangement.

The last decade has witnessed the isolation and identification of a number of aromatic glycol metabolites of both exogenous and endogenous phenethylamines. Identification has been largely achieved by GC–MS,[2,3] fluorometric procedures,[4] and enzymatic isotopic methods.[5] However, the commercial unavailability of glycol standards has made cochromatographic analysis difficult. Currently, no viable synethic procedure for the production of these standards exists.

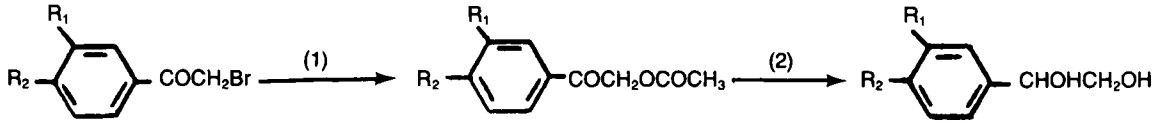
The two glycol metabolites of norepinephrine and epinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG) and 3,4-dihydroxyphenylglycol (DHPG), are well known. The analysis of each in the blood and urine has been utilized as a measure of certain central nervous system abnormalities such as endogenous depression and childhood schizophrenia.[6] Furthermore, glycol metabolites of octopamine and *p*-synephrine have been identified in both rat and human urine.[7] Preliminary data from our laboratory have indicated that a glycol metabolite 3,4-dimethoxyphenylglycol (DMPG) exists from administration of normacromerine [1-(3,4-dimethoxyphenyl)-2-methylaminoethanol] to Sprague–Dawley rats.[8]

Of these metabolites, only MHPG and DHPG have been synthesized from readily available starting materials.[9] This synthesis involves a five-step procedure utilizing the appropriately substituted benzaldehyde as the starting material.

Results and Discussion

The achievement of a general synthetic scheme for the preparation of aromatic glycols is dependent on decreasing the extensive parallel reactions that occur. Under both acidic and basic conditions, aromatic glycols are labile. In the presence of moderate or high alkalinity, the substances dimerize to form a high-melting dioxane dimer.[10] Moreover, it has also been demonstrated that under conditions of high acidity or in the presence of heat, phenolic glycols undergo pinacol–pinacolone rearrangements followed by phenol–aldehyde condensation.[11,12]

The syntheses described here make use of readily available inexpensive starting materials and afford high yields of the desired materials. Alpha-bromination of acetophenones is a well-known reaction with yields generally >80%.[13] Subsequent alpha-substitution utilizing potassium acetate and the mild catalyst, sodium iodide, was carried out directly on compounds **1**, **4**, **5**, and **6** (see Scheme I).[14] On the other hand, the phenolic hydroxyl groups of compounds **2** and **3** were protected before the reduction step to avoid significant disproportionation reactions as well as the formation of the lithium and aluminum phenolate salts,[11,12,15] using the method of Ferrari and Casagrandi for simultaneous alpha and phenolic acetylation.[16]



1, $R_1 = R_2 = OCH_3$ **7**, $R_1 = R_2 = OCH_3$ **13**, $R_1 = R_2 = OCH_3$

2, $R_1 = H, R_2 = OH$ **8**, $R_1 = H, R_2 = OAc$ **14**, $R_1 = H, R_2 = OH$

3, $R_1 = OCH_3, R_2 = OH$ **9**, $R_1 = OCH_3, R_2 = OAc$ **15**, $R_1 = OCH_3, R_2 = OH$

4, $R_1 = OCH_3, R_2 = H$ **10**, $R_1 = OCH_3, R_2 = H$ **16**, $R_1 = OCH_3, R_2 = H$

5, $R_1 = H, R_2 = OCH_3$ **11**, $R_1 = H, R_2 = OCH_3$ **17**, $R_1 = H, R_2 = OCH_3$

6, $R_1 = H, R_2 = H$ **12**, $R_1 = H, R_2 = H$ **18**, $R_1 = H, R_2 = H$

Scheme I—*Synthesis of possible metabolites of phenethylamine drugs. Compounds 1–6 were formed with bromine/chloroform. Key: (1) either KOAc/NaI or KOAc/Ac_2O, (2) $LiAlH_4$.*

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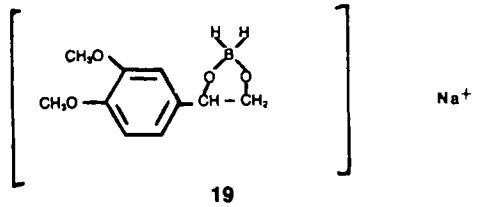
The use of lithium aluminum hydride to reduce ketones, phenolic esters, and alkanolic esters provided the key step to the synthetic procedure. Landor et al. used excess lithium aluminum hydride to reduce beta-keto esters to diols because of its ability to form hydrolyzable bidentate ligands.[17] In this work we were not able to isolate the bidentate ligand. However, when sodium borohydride was utilized as the reducing agent, the product obtained from the 3,4-dimethoxy derivative was the stable nonhydrolyzable ligand, **19**, the structure of which was confirmed by NMR and elemental analysis.



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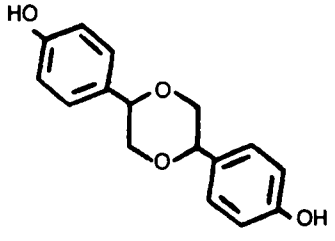
Phenolic hydroxyl groups have been protected using the benzyl protecting group which is routinely removed by catalytic hydrogenation.[9] A simpler procedure was used here in which all hydroxyl groups were protected by acetylation. The use of a slight molar excess of lithium aluminum hydroxide not only resulted in the formation of the glycol but also reduced the phenolic esters to phenols. This one-step reaction (*Scheme I*) occurs only if a 10–20% excess of lithium aluminum hydride is used. If a 10-fold excess is used, the tetrahydroaluminate anion appears to be a strong enough base to cause significant dioxane dimer formation. Hence, compound **20** was formed in an attempt to synthesize **14**.



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Attempts to prepare 3,4-dihydroxyphenylglycol (DHPG) were unsuccessful although the intermediate (α,3,4-triacetoxyacetophenone) was synthesized in excellent yield. Furthermore, the proposed method can be used successfully to prepare 3-methoxyphenylglycol, **17**; and 4-methoxyphenylglycol, **18**.

Experimental Section

Apparatus—Melting points were determined on a Thomas-Hoover melting point apparatus and were uncorrected. Combustion analyses were performed by Atlantic Microlab, Atlanta, GA, and agreed with theoretical values to within ±0.4%. Proton NMR spectra were taken on a JEOL Fx90Q spectrometer using tetramethylsilane as the internal standard. Infrared spectra were obtained using a Perkin-Elmer model 257 IR spectrometer. All IR and NMR spectra are consistent with assigned structures. Only spectra of the prototype compound for each reaction are provided. After purification and spectral identification, all compounds were immediately introduced into the next reaction. Unless otherwise indicated, all reagents were used as received from suppliers.

General Procedure for Bromination—The method of Mannich and Hahn was used.[13] The appropriately substituted acetophenone (0.166 mol) was either dissolved or suspended in 30–50 mL of chloroform and cooled to 0°C. Then, 0.167 mol of bromine was added in a dropwise manner over a 1-h period with stirring. The resulting mixture was then allowed to reach room temperature, and was stirred for an additional 4 h. During this time, significant quantities of hydrogen bromide evolved and all suspended material dissolved. The organic phase was evaporated under reduced pressure and the residue was recrystallized from the appropriate solvent. As is true with most alpha-bromoacetophenones, the compounds synthesized proved to be severe lacrimators and irritants.

α-Bromo-3,4-dimethoxyacetophenone (1)—Crystals from methanol, 80%, mp 80–81°C (lit.[13] 80–81°C); IR (KBr): 1581 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.32 ppm (s, 2, CH_2).

α-Bromo-4-hydroxyacetophenone (2)—Light brown powder from petroleum ether:benzene (8:2), mp 125–126°C (lit.[18] 126–128°C), 56%.

α-Bromoacetophenone (6)—White needles from chloroform, mp 165–166°C (lit.[13] 165°C), 80%.

α-Bromo-3-methoxy-4-hydroxyacetophenone (3)—White crystals from $CHCl_3$:petroleum ether (4:6), mp 74–75°C (lit.[19] 78–79°C), 63%.

α-Bromo-3-methoxyacetophenone (4)—Crystals from benzene:petroleum ether (1:1), mp 59–61°C (lit.[20] 63–64°C), 71%.

α-Bromo-4-methoxyacetophenone (5)—Crystals from benzene:petroleum ether (1:1), mp 64.5–66.0°C (lit.[21] 70–71°C), 91%.

General Procedure for alpha-Acetylation of Nonphenolic Compounds—The procedure of Kaufmann and Muller was used.[14]

α-Acetoxy-3,4-dimethoxyacetophenone (7)—Crystals from ether, mp 91–92°C (lit.[14] 91–92°C), 88%, IR (nujol): 1755 (ester carbonyl), and 1590 cm^{-1} (ketone); ^1H NMR ($CDCl_3$): δ 5.3 ppm (s, 2, CH_2).

α-Acetoxyacetophenone (12)—Crystals from absolute ethanol, mp 46–48°C (lit.[22] 49.5°C), 68%.

α-Acetoxy-3-methoxyacetophenone (10)—Nondistillable brown oil, 55%. This oil was ~90% one spot by TLC and was used directly in the subsequent reaction.

α-Acetoxy-4-methoxyacetophenone (11)—Crystals from chloroform:petroleum ether (1:8), mp 55–56°C (lit.[23] 58–59°C).

General Procedure for Acetylation of Phenolic Compounds The procedure of Ferrari and Casagrandi was used.[16]

α,4-Diacetoxyacetophenone (8)—White crystals from methanol, mp 86–87°C (lit.[16] 86–87°C), 88%, IR (nujol): 1755 (α-ester carbonyl), 1742 (phenolic ester carbonyl), and 1598 cm^{-1} (ketone): ^1H NMR ($CDCl_3$): δ 5.26 ppm (s, 2, CH_2).

α,4-Diacetoxy-3-methoxyacetophenone (9)—Brown powder from benzene:petroleum ether (1:9), mp 83–84°C (lit.[16] 77–78°C), 75%.

General Procedure for Lithium Aluminum Hydride Reduction—All reductions were performed utilizing anhydrous ether as the solvent. For the preparation of compounds **13**, **16**, **17**, and **18**, a 5-fold molar excess of lithium aluminum hydride was added to anhydrous ether in a dry reflux apparatus with appropriate moisture protection. The mixture was stirred at room temperature for 3 h, and then was brought to reflux. A solution of the acetoxy compound in anhydrous ether was added in a dropwise manner over a 2-h period. Refluxing was continued for 2 additional hours, and then the mixture allowed to stir at room temperature overnight. The excess lithium aluminum hydride was neutralized by the dropwise addition of ether saturated with water followed by the cautious addition of 5 mL of water and 50 mL of sulfuric acid:water (1:2). The organic layer was removed and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was recrystallized appropriately. Compounds **14** and **15** were prepared using 3.3 equivalents of lithium aluminum hydride. For all glycol compounds, the IR spectra showed OH bands at 3310–3190 cm^{-1} and no carbonyl bands.

1-(3,4-Dimethoxyphenyl)-1,2-ethanediol (13)—White needles from ether, 88%, mp 80.0–81.5°C (lit.[24] 83°C), ^1H NMR (acetone-d_6): δ 3.67 (d, 2, CH_2) and 4.62 ppm (t, 1, CH). Anal. ($C_{10}H_{14}O_4$) C, H.

1-(4-Hydroxyphenyl)-1,2-ethanediol (14)—White crystals from ether, 90%, mp 139–141°C (lit.[25] 143.5-145.0°C); ^1H NMR (acetone-d_6): δ 3.56 (d, 2, CH_2), and 4.60 ppm (t, 1, CH). Anal. ($C_8H_{10}O_3$) C, H.

1-Phenyl-1,2-ethanediol (18)—White needles from petroleum ether, 68%, mp 67–68°C (lit.[26] 67–68°C).

1-(3-Methoxy-4-hydroxyphenyl)-1,2-ethanediol (15)—A brown oil resulted which was isolated as the piperazine salt by the method of Benigni and Verbiscar,[9] 46%, mp 114–116°C (lit.[9] 116–118°C).

1-(3-Methoxyphenyl)-1,2-ethanediol (16)—White flakes from ether, 81%, mp 63–65°C, ^{1}H NMR ($CDCl_3$): δ 3.74 (d, 2, CH_2) and 4.78 ppm (t, 1, CH). Anal. ($C_9H_{12}O_3$) C, H.

1-(4-Hydroxyphenyl)-1,2-ethanediol (17)—White needles from $CHCl_3$:petroleum ether (1:3), 63% m.p. 76.0–77.5°C, ^{1}H NMR ($CDCl_3$): δ 3.72 (d, 2, CH_2) and 4.60 ppm (t, 1, CH). Anal. ($C_9H_{12}O_3$) C, H.

Sodium 3,4-Dimethoxyphenylborohydride (19)—Compound 7 (1.18 g) was refluxed for 4 h in a saturated solution of $BaCO_3$ in water. The solution was cooled, neutralized with conc. HCl, and extracted with ether. The organic layer was evaporated leaving an oil which was used directly in the next reaction. The oil (300 mg) was treated with 38 mg of $NaBH_4$ (1.1 Eq.) in 5 mL of EtOH at room temperature for 1 h. Evaporation then gave **19** as a white powder which was recrystallized from ether; mp 187–189°C, 85%; ^{1}H NMR (acetone-d_6): δ 3.81 (d, 2, CH_2), 4.75 (m, 1, CH), and 6.95 ppm (m, 3, ArH). Anal. ($C_{10}H_{14}BNaO_4$) C, H.

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