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The Synthesis of Two New Metabolites of Catecholamines: 3,4-Dihydroxyphenylethyleneglycol and 4-Hydroxy-3-methoxyphenylethyleneglycol[1]

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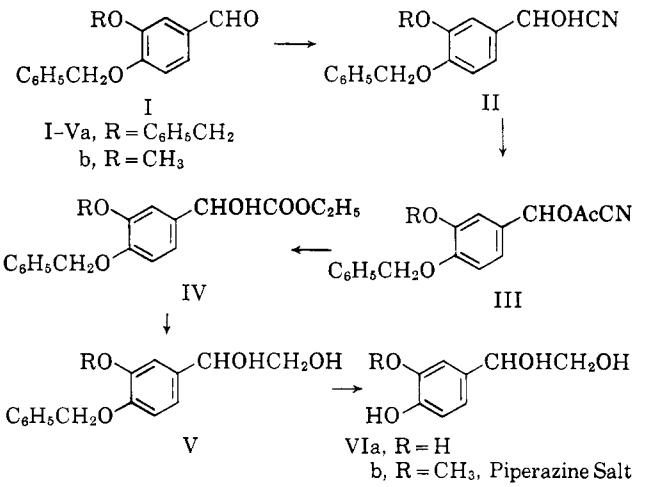
Recently two metabolites of epinephrine and norepinephrine have been identified as 4-hydroxy-3-methoxyphenylethyleneglycol[3-5] and 3,4-dihydroxyphenylethyleneglycol.[6,7] The preparation of these two metabolites was undertaken in order to complete their identification by chemical syntheses.

In the reaction sequence the benzylated aldehydes I were treated with a large excess of hydrogen cyanide to maximize their conversion to the mandelonitriles II. The mandelonitriles were unstable and difficult to separate from the starting aldehydes. Furthermore, when the crude mandelonitriles were converted to their corresponding ethyl mandelates (IV), the starting aldehydes and the esters proved to have nearly identical solubility and absorbance properties on alumina or silica gel and could not be separated. It was found that acetylation of the intermediate mandelonitriles afforded a mixture from which the acetylated mandelonitriles (III) could be fractionally crystallized. Ethanolysis of the acetylated mandelonitriles with ethanolic hydrogen chloride gave the easily purified ethyl mandelates (IV), which were reduced to the corresponding glycols (V) with lithium aluminum hydride. Hydrogenolysis of the protecting benzyl groups gave the glycols in good yield. An attempt to prepare these glycols by lithium aluminum hydride reduction of the unprotected ethyl mandelates[8] was unsuccessful.

3,4-Dihydroxyphenylethyleneglycol (VIa) is a crystalline solid which is stable on standing. However, in one attempt at purification a polymeric substance resulted. It is known that phenolic benzyl alcohols can be quite sensitive to acids, bases, and heat, giving phenol–formaldehyde type condensation products.[9]

4-Hydroxy-3-methoxyphenylethyleneglycol (VIb) has been reported[3] to be an oil, and numerous attempts on our part to obtain a solid product failed. However, a crystalline piperazine salt[10] complex formed which had several notable physical characteristics. It was easier to handle and more stable than the free phenolic-glycol. Furthermore, paper and thin layer chromatograms of the free glycol, the salt, and an acidified sample of the salt showed identical R_f values, a char acteristic of significance to biochemical investigations.



Experimental

Melting points were taken on a Hoover Uni-Melt capillary apparatus and are corrected. Ultraviolet spectra were determined in 95% ethanol using a Perkin–Elmer spectrophotometer Model 202. Infrared spectra were determined in chloroform using a Perkin–Elmer Infracord Model 137. Elemental analyses were performed by Midwest Microlab, Indianapolis, Indiana.

3,4-Dibenzyloxymandelonitrile Acetate (IIIa).—To a mixture of 31.8 g. (0.1 mole) of 3,4-dibenzyloxybenzaldehyde,[11] 40 g. (0.6 mole) of potassium cyanide, 225 ml. of dioxane, and 55 ml. of water was added with stirring 33 ml. (0.4 mole) of hydrochloric acid. The mixture was stirred and refluxed for 1 hr., after which time it was cooled to room temperature. Benzene was added to the dark mixture, and the aqueous layer discarded. The organic layer was diluted with 200 ml. of benzene and dried over sodium sulfate. To the dark filtered solution was added 125 ml. (1.2 moles) of acetic anhydride and 50 ml. of pyridine, and the solution allowed to stand at room temperature overnight. The mother liquor was removed under reduced pressure, fresh benzene was added to the oil, and it again was evaporated to dryness. The oil was dissolved in 200 ml. of ethanol whereupon 24.4 g. (42%) of IIIa crystallized. A white crystalline product, m.p. 67–68°, was obtained on recrystallization from ethyl acetate and hexane.

Anal. Calcd. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.47; N, 3.62. Found: C, 74.59; H, 5.58; N, 3.52. Infrared: 5.72 μ (C=O). The nitrile absorptions in this series were not detected in our study.

Ethyl 3,4-Dibenzyloxymandelate (IVa).—A solution of 28.0 g. (0.72 mole) of 3,4-dibenzyloxymandelonitrile acetate (IIIa), 300 ml. of ethanol, and 200 ml. of ethanolic hydrogen chloride was allowed to stand under nitrogen at room temperature for 16 hr. The mixture was evaporated under reduced pressure to an oil, which was covered with water and extracted with ether and twice with benzene. The extracts were combined, dried over sodium sulfate, and evaporated. The resulting oil was covered with hexane and allowed to crystallize. There resulted 24 g. (84%) of product, m.p. 58–61°. Two recrystallizations from ethyl acetate and hexane gave a white crystalline solid, m.p. 68–70°.

Anal. Calcd. for $C_{24}H_{24}O_5$: C, 73.46; H, 6.16. Found: C, 73.72; H, 6.05. Infrared: 2.80 μ (OH), 5.80 μ (C=O).

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3,4-Dibenzyloxyphenylethyleneglycol (Va).—A solution of 18.0 g. (0.046 mole) of ethyl 3,4-dibenzyloxymandelate (IVa) and 200 ml. of tetrahydrofuran was added over 15 min. with stirring to a solution of 10.0 g. (0.26 mole) of lithium aluminum hydride and 400 ml. of tetrahydrofuran. The resulting mixture was stirred and refluxed for 2.5 hr., cooled, and decomposed with 14.2 ml. of water and 15 ml. of hydrochloric acid in 50 ml. of tetrahydrofuran. The suspension was refluxed for 15 min., filtered, and the cake extracted by refluxing with 100 ml. of tetrahydrofuran. The tetrahydrofuran was evaporated to give a solid, which was found to contain inorganic salts. Therefore, the material was taken up in a small amount of ethanol, acidified with a few drops of hydrochloric acid, diluted with water, and extracted with benzene. The benzene was dried over sodium sulfate and evaporated to an oil, which was covered with hexane and allowed to crystallize. There resulted 13.7 g. (85%) of Va, m.p. 63–69°. Recrystallization from benzene and hexane gave white needles, m.p. 77–79°.

Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.27; H, 6.34. Infrared: 2.74 μ and 2.9 μ (OH).

3,4-Dihydroxyphenylethyleneglycol (VIa).—A mixture of 2.0 g. (0.0057 mole) of 3,4-dibenzyloxyphenylethyleneglycol (Va), 100 ml. of ethanol, 1.0 g. of 5% palladium on charcoal, and 2.8 kg./cm.^{2} of hydrogen was shaken for 3 hr. at room temperature. The catalyst was filtered, and the ethanol removed under reduced pressure. To the resulting oil was added 50 ml. of benzene and the mixture evaporated to dryness *in vacuo*. The oil was taken up in boiling ethyl acetate, charcoal treated, hexane added to the cloud point, and the mixture allowed to crystallize in the refrigerator. The pink crystalline solid was filtered, yielding 0.7 g. (72%) of VIa, m.p. 127–129°. Recrystallization from ethyl acetate and hexane with a charcoal treatment gave white needles, m.p. 128–129°.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.62; H, 6.08. Ultraviolet: 204 mμ (28,900), 223 mμ (6330), and 282 mμ (3060).

Chromatography.—Thin layer [Merck silica gel G.; ethyl acetate–ethanol, 95:5; detected with 50% H_2SO_4 and heat] showed a single spot, R_f 0.78. Paper [descending; Whatman No. 1, 1-propanol–water, 70:30; detected with a dilute aqueous solution of $FeCl_3$ and $K_3Fe(CN)_6$] showed one spot, R_f 0.71.

4-Benzyloxy-3-methoxymandelonitrile Acetate (IIIb).—Following our procedure as previously described, from 24 g. (0.099 mole) of 4-benzyloxy-3-methoxybenzaldehyde[12] there was obtained 14.6 g. (47%) of 4-benzyloxy-3-methoxymandelonitrile acetate m.p. 70–71°. Recrystallization from ethanol gave a white crystalline product, m.p. 72–73°.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51; N, 4.50. Found: C, 69.51; H, 5.40; N, 4.43. Infrared: 5.72 μ (C=O).

Ethyl 4-Benzyloxy-3-methoxymandelate (IVb).—The alcoholysis of 25 g. (0.08 mole) of IIIb, as reported above, yielded 17.2 g. (68%) of IVb, m.p. 120–123° (recrystallized from ethanol).

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.51; H, 6.56. Infrared: 2.80 μ (OH) and 5.80 μ (C=O).

4-Benzyloxy-3-methoxyphenylethyleneglycol (Vb).—Treatment of 14.0 g. (0.044 mole) of ethyl 4-benzyloxy-3-methoxymandelate (IVb) with lithium aluminum hydride as described previously gave 5.5 g. (47%) of Vb, m.p. 66–67° (from benzene then from a mixture of ethyl acetate and hexane).

Anal. Calcd. for $C_{16}H_{18}O_4$: C 70.05; H, 6.61; O, 23.33. Found: C, 69.73; H, 6.87; O, 23.22. Infrared: 2.74 μ and 2.89 μ (OH).

Bis-(4-hydroxy-3-methoxyphenylethyleneglycol) Piperazine Salt (VIb).—A mixture of 0.90 g. (0.0033 mole) of Vb, 0.4 g. of 5% palladium on charcoal, 200 ml. of ethanol, and 2.8 kg./cm.^{2} of hydrogen was shaken for 3 hr. at room temperature. The catalyst was removed and the ethanol evaporated *in vacuo*. To the resulting oil was added benzene and the mixture evaporated to dryness. All attempts to crystallize the oil met with failure. Therefore, the oil was dissolved in 3 ml. of ethanol, diluted with 100 ml. of benzene, and the gray solution filtered. To the clear filtrate was added 3 ml. (0.0016 mole) of a dry solution of piperazine in benzene (5 g./100 ml.), and the product crystallized by addition of 150 ml. of hexane. The white crystalline solid was filtered giving 0.7 g. (84%) of VIb, m.p. 115–116°. The product was recrystallized from benzene, m.p. 116–118°.

Anal. Calcd. for $C_{22}H_{34}N_2O_8$: C, 58.13; H, 7.54; N, 6.17. Found: C, 58.04; H, 7.30; N, 6.03. Ultraviolet: 204 mμ (34,800), 229 mμ (10,000), and 281 mμ (3850).

Chromatography.—Thin layer [Merck silica gel G.; ethyl acetate–ethanol, 95:5; detected with 50% H_2SO_4 and heat] had a single spot R_f 0.64. On the same plate were run a sample of sublimed free glycol oil, a sample of the complex which had been acidified with acetic acid, and piperazine. Each of the glycol samples indicated single spots R_f 0.64, while piperazine itself was not detected. Paper [descending; Whatman No.1, 1-propanol–water, 70:30; detected with dilute aqueous $FeCl_3$ and $K_3Fe(CN)_6$] showed one spot, R_f 0.80. Attempts to detect piperazine from the complex failed. Also run on paper were the sublimed material and the acidified complex both showing spots, R_f 0.80. A concentrated spot of piperazine on paper detected with phenolphthalein had R_f 0.48.

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The Synthesis of 15β-Fluoro Corticoids

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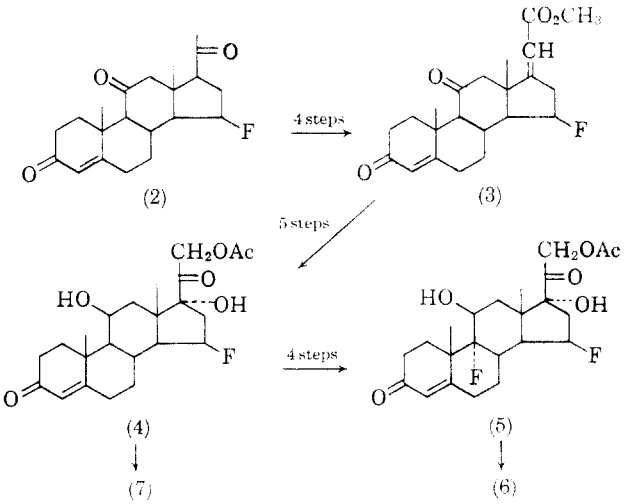
The availability of 15β-fluoropregn-4-ene-3,11,20-trione[1] (2) from the reaction of 15α-hydroxypregn-4-ene-3,11,20-trione (1) with N-(2-chloro-1,1,2-trifluoroethyl)diethylamine has made possible the synthesis of a series of 15β-fluorocortical steroids. The conversion of (2) to 15β-fluorohydrocortisone acetate (4) was achieved utilizing procedures described previously.[2] The intermediate methyl 3,11-dioxo-15β-fluoropregna-4,17(20)-[*cis*]-dien-21-oate (3) obtained from (2) by bisethoxa-



lylation, tribromination, Favorskii rearrangement, and zinc reduction was converted to the 3-cycloethylene ketal, reduced with lithium aluminum hydride, acetylated, subjected to mild acid hydrolysis, and allowed to react with N-methylmorpholine oxide–hydrogen peroxide complex in the presence of catalytic amounts of osmium tetroxide[3] to yield (4). The intermediate compounds were not rigorously purified. By

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