

Synthesis of 1-(3-Trideuteromethoxy-4-hydroxyphenyl)-[1,2,2-²H₃]-ethylene glycol
([²H₆]MHPG)

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SUMMARY

The four stage synthesis of a hexadeuterated analogue of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) is described. The overall yield from 3-trideuteromethoxy-4-hydroxyacetophenone is 29%.

Key words: methoxyhydroxyphenylglycol
 deuteration
 gas chromatography mass spectrometry

INTRODUCTION

3-Methoxy-4-hydroxyphenylethylene glycol (MHPG) is reported to be the major metabolite of noradrenaline produced in the central nervous system (1,2). Because of our interest in the role of central adrenergic mechanisms in the regulation of blood pressure, we have developed combined gas chromatographic mass spectrometric assays for the measurement of MHPG and its sulphate and glucuronide conjugates in plasma and urine (3,4). The internal standards for these assays are [²H₂]MHPG and [²H₃]MHPG sulphate. Since we wished to carry out infusion studies with labelled MHPG, so that it could be distinguished from the endogenous compound, we have synthesised a hexadeuterated analogue of MHPG. In this way endogenous MHPG, [²H₆]MHPG and their conjugates can be assayed simultaneously in plasma and urine using [²H₂]MHPG and [²H₃]MHPG sulphate as common internal standards (4).

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DISCUSSION

$[^2\text{H}_6]$ MHPG was synthesised in four stages from 3-trideuteromethoxy-4-hydroxyacetophenone (I) as outlined in figure 1.

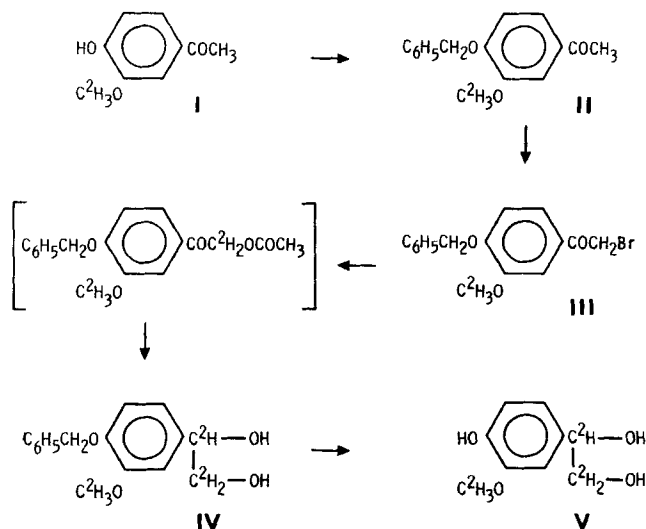


Figure 1: The synthesis of $[^2\text{H}_6]$ MHPG

The reactions leading to the glycol derivative IV were modifications of a previously published synthesis (3) in which 3-methoxy-4-hydroxyacetophenone (acetovanillone) had been used as a starting material.

3-Trideuteromethoxy-4-hydroxyacetophenone (I) was firstly benzylated, then converted to the monobromo derivative III. When the latter was heated under reflux with potassium acetate in monodeuteroethanol, the bromine atom was displaced by an acetate group and the two hydrogen atoms of the ketomethylene group were exchanged for deuterium. The resulting acetoxyketone was reduced in situ with sodium borodeuteride to give the hexadeuterated glycol derivative IV. This compound was crystallised from benzene-hexane and nuclear magnetic resonance spectroscopy showed the crystalline product contained benzene of crystallisation (3,5). Hydrogenolysis of the glycol derivative IV removed the benzyl protecting group and gave $[^2\text{H}_6]$ MHPG as a viscous oil which was purified by thin layer chromatography. The overall yield of the required product from 3-trideutero-

methoxy-4-hydroxyacetophenone (1) was 29%. The mass spectrum of the tris-trifluoroacetate derivative of $[^2\text{H}_6]\text{MHPG}$ is shown in figure 2.

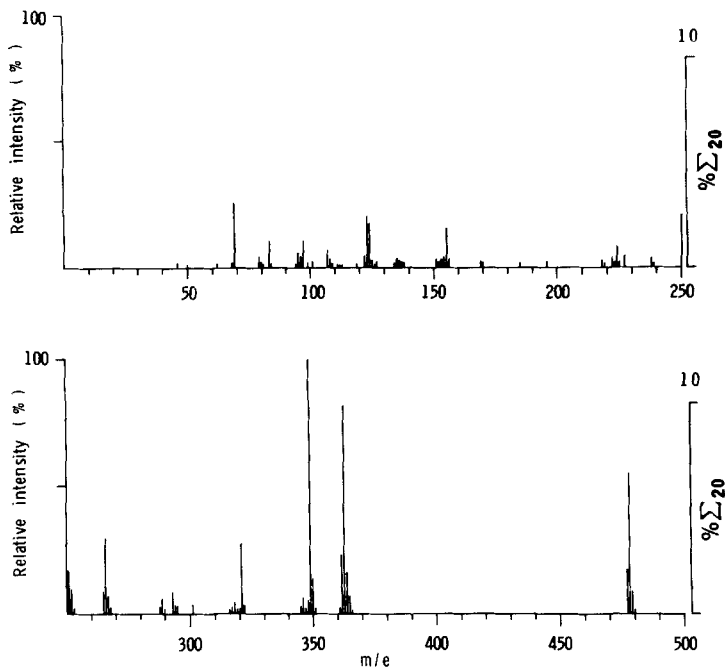


Figure 2: The mass spectrum of the tris-trifluoroacetate derivative of $[^2\text{H}_6]\text{MHPG}$

EXPERIMENTAL

Materials

3-Trideuteromethoxy-4-hydroxyacetophenone (deuterium content in atoms % excess, 0% $^2\text{H}_0$, 0% $^2\text{H}_1$, 1.69% $^2\text{H}_2$ and 98.31% $^2\text{H}_3$) was a gift from LKB (Stockholm, Sweden). Benzyl chloride, potassium acetate, $[0-^2\text{H}]$ ethanol and 5% palladium on charcoal were purchased from Koch-Light Laboratories Ltd (Colnbrook). Sodium borodeuteride and sodium deuterioxide in deuterium oxide (40%, w/w) were obtained from Merck Sharp & Dohme (Montreal, Canada) and bromine (analar grade) from BDH Chemicals Ltd (Poole). Thin layer chromatography (TLC) was carried out

using glass plates (5 x 20 cm) precoated with 0.25 mm layers of silica gel GF₂₅₄ manufactured by Merck (Darmstadt, FRG). Mass spectra were obtained from a Finnigan model 3200 quadrupole instrument operated in the electron impact mode with an electron energy of 25 eV.

3-Trideuteromethoxy-4-benzyloxyacetophenone (II)

To 2.5 ml absolute alcohol in which had been dissolved 37 mg sodium hydroxide was added 100 mg 3-trideuteromethoxy-4-hydroxyacetophenone (I; 0.59 mmole) and 0.15 ml benzyl chloride (1.30 mmole). The solution was refluxed for 90 min, allowed to cool and then poured into 20 ml water. The aqueous mixture was extracted with three 15 ml aliquots of ether and the combined ether extracts, after washing with water, dried over sodium sulphate. After filtration and removal of the solvent, the residue was recrystallised from benzene-hexane. Yield = 110 mg (72%) TLC (chloroform): single spot, $R_F = 0.42$, co-chromatographs with the non-deuterated reference compound (5).

3-Trideuteromethoxy-4-benzyloxy-*w*-bromoacetophenone (III)

To a stirred solution of 5 ml chloroform containing 110 mg (0.42 mmole) 3-trideuteromethoxy-4-benzyloxyacetophenone (II) was added over a fifteen minute period 10 ml chloroform containing 74 mg (0.46 mmole) bromine. The reaction mixture was left at room temperature for 45 min, then the chloroform solution was washed with saturated sodium bicarbonate solution (20 ml), distilled water (20 ml) and dried over sodium sulphate. After filtration and removal of the solvent, the residue was recrystallised from absolute alcohol. Yield = 106 mg (74%) TLC (chloroform): single spot, $R_F = 0.57$, co-chromatographs with the non-deuterated reference compound (5).

1-(3-Trideuteromethoxy-4-benzyloxyphenyl)-[1,2,2-²H₃]-ethylene glycol (IV)

To a solution of 3-trideuteromethoxy-4-benzyloxy-~~to~~-bromoacetophenone (III; 106 mg, 0.31 mmole) in [0-²H]ethanol (10 g) was added anhydrous potassium acetate (62 mg) and the mixture heated under reflux for 6.5 h. All glassware had been previously flame dried and the reflux condenser was fitted with a silica gel guard tube. When the reaction mixture had cooled to room temperature, sodium

borodeuteride (50 mg, 1.19 mmole) was added and the mixture left stirring for 5 h in a firmly stoppered flask. Then 1 ml of deuterium oxide and 0.5 ml sodium deuterioxide in deuterium oxide (40% w/w) were added and the mixture left a further 90 min. After this period the flask contents were poured into water (20 ml) and extracted with diethyl ether (three 15 ml aliquots). The combined ether extracts were washed with water (two 20 ml portions), dried over sodium sulphate, filtered and the solvent removed by rotary evaporation to leave a light yellow oil. Crystallisation from benzene-hexane gave the required product (77 mg) as white, very light crystals. TLC (ethyl acetate): single spot, $R_F = 0.29$, TLC (chloroform, 7 parts; dioxan, 3 parts; methanol, 2 parts): single spot, $R_F = 0.53$, co-chromatographs with the non-deuterated reference compound (5).

1-(3-Trideuteromethoxy-4-hydroxyphenyl)-[1,2,2- $^2\text{H}_3$]-ethylene glycol; [$^2\text{H}_6$]-MHPG (V)

The product from the above reaction (IV; 77 mg) was dissolved in methanol (25 ml) and 5% palladium on charcoal (60 mg) was added. The mixture was hydrogenated for 2 h on a Parr shaker at a hydrogen pressure of 30 p.s.i., then filtered and the solvent removed by rotary evaporation. The remaining light yellow oil was purified by chromatography on two, 0.25 mm thick, 20 cm by 20 cm silica gel plates to give a colourless, viscous oil (33 mg). TLC (chloroform, 7 parts; dioxan, 3 parts; methanol, 2 parts) single spot, $R_F = 0.43$.

Treatment of a portion of this oil with trifluoroacetic anhydride-ethyl acetate (1:1, v/v) at room temperature and subsequent gas chromatographic mass spectrometric analysis showed the formation of a single derivative. This derivative has gas chromatographic properties very similar to the tris-trifluoroacetate derivative of MHPG and a mass spectrum readily interpreted as that of the tris-trifluoroacetate derivative of [$^2\text{H}_6$]-MHPG (figure 2).

MS: m/e 478 (M^+ , 56), 363(82), 349(100), 321(28), 266(30), 69(26)

Deuterium content of this derivative, as measured from the molecular ion cluster, was as follows (atoms % excess): 0.04% $^2\text{H}_0$, 0% $^2\text{H}_1$, 0.06% $^2\text{H}_2$, 0.13% $^2\text{H}_3$, 2.38% $^2\text{H}_4$, 24.69% $^2\text{H}_5$ and 72.70% $^2\text{H}_6$.

REFERENCES

1. Schanberg S.M., Breese G.R., Schildkraut J.J., Gordon E.K. and Kopin I.J. - *Biochem. Pharmacol.* 17: 2006 (1968)
2. Karoum F., Moyer-Schwing J., Potkin S.G. and Wyatt R.J. - *Brain Res.* 125: 333 (1977)
3. Murray S., Baillie T.A. and Davies D.S. - *J. Chromatogr.* 143: 541 (1977)
4. Murray S., Boobis A.R., Frank H., Baillie T.A. and Davies D.S. - *Naunyn-Schmiedeberg's Arch. Pharmacol.* in press (1980)
5. Hegedüs B. - *Helv. Chim. Acta* 46: 2604 (1963)