SYNTHESIS OF
(4-HYDROXY-3-METHOXYPHENYL)-$\alpha,\alpha,\beta,\beta$-TETRADEUTERO ETHYLAMINE

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A five step synthesis of $\alpha,\alpha,\beta,\beta$-$d_4$-3 methoxytyramine is described with an overall yield of 45% starting from methyl 4-benzyloxy-3-methoxy benzoate.

Key words : 3-methoxy-tyramine - Deuterium labelling

In the last few years, mass fragmentography has become a very useful analytical method. For quantitative studies, internal standards are required, the most interesting being deuterated analogs of the compounds to be measured; of course, the deuterium atom(s) must be kept in the fragment used for measurement, since the retention times of the deuterated and non-deuterated compounds are too close to allow working with the same ion.

We wished to use a deuterated analog of 3-methoxy-tyramine (3-MT); two possibilities were open to us : deuteration of either the aromatic nucleus, or of the side-chain. But we knew that, in an acidic medium, the deuterium atoms of nucleus-

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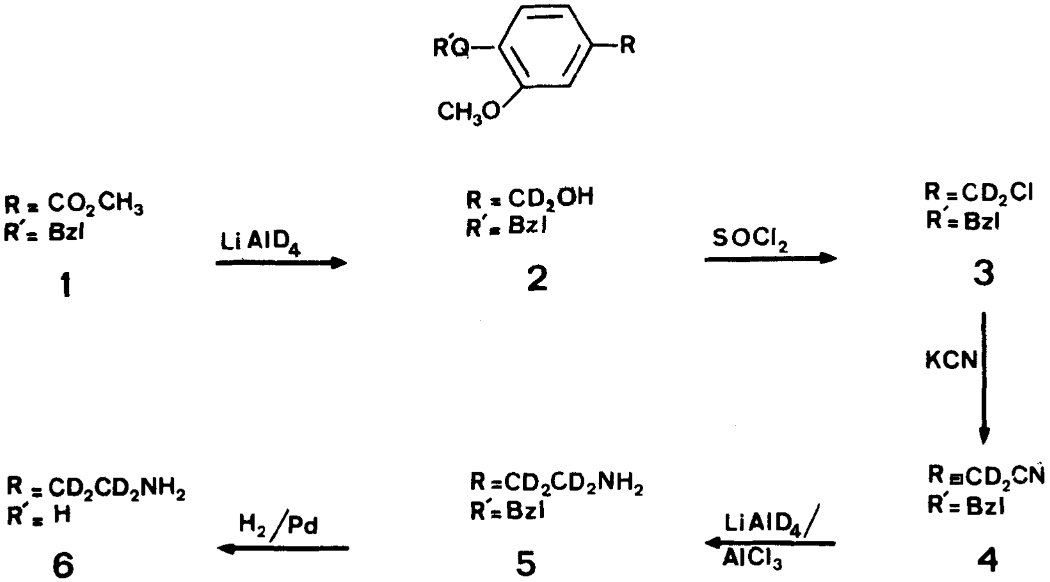
labelled dopamine (1) were exchanged even at room temperature when working with 1 or 2 ng (2); so this product could not be used .

We therefore synthesized side-chain deuterium-labelled 3-MT, modifying the method used by Liebman (3) to synthesize ^{14}C homovanillic acid.

The methyl ester of 4-benzyloxy-3-methoxy-benzoic acid (Aldrich) was reduced with LiAlD$_4$ to the corresponding dideuterated benzyl alcohol, which after treatment with SOCl$_2$ and then with KCN, gave (4-benzyloxy-3-methoxyphenyl)-acetonitrile. Reduction of this nitrile with LiAlD$_4$ and hydrogenolysis of the benzyloxy group gave α,α,β,β -d4-3-MT with a good yield and high isotopic purity (Schema).

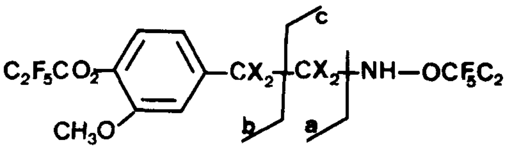


SYNTHESIS OF α, α, β, β -d$_4$-3-MT

It is noteworthy that in the nitrile synthesis, the use of acetonitrile as solvent is followed by the exchange of the two D atoms already introduced; on the other hand, the use of $LiAlH_4$ instead of $LiAlD_4$ in the first or second reduction gives of course rise to the formation of 3-MT selectively labelled with deuterium on side-chain carbon β or α.

The chemical and isotopic purity of the compounds was checked with gas-chromatography-mass spectrometry, and table 1 gives the most important peaks of the bis(pentafluoropropronyl) derivatives of 3-MT and α,α,β,β-d_4 3-MT.

The intensity of the M-1 ion (m/e 462) of the labelled 3-MT derivative was about 7% of that of ion 463; so our compound contained less than 6% d_3.



	3-MT	3-MT-d_4
M^+	459 (4%)	463 (6%)
a	296 (100%)	299 (100%)
b	283 (26%)	285 (27%)
c	176 (14%)	178 (18%)
a-C_2F_5CO	149 (65%)	152 (76%)
C_2F_5	119 (48%)	119 (48%)

Table 1. Fragmentation of 3-MT and 3-MT-d_4

EXPERIMENTAL

4-benzyloxy-3-methoxy-α,α-dideutero benzyl alcohol 2

30 mM (8.16g) of 1 were dissolved in 80 ml dimethoxyethane freshly distilled over $LiAlH_4$. This solution was added under argon to 45 mM (1.89g) $LiAlD_4$ in 80 ml dimethoxyethane. After half an hour, the reaction was completed (thin-layer chromatography); after the cautious addition of 15 ml AcOEt, 300 ml Et_2O, 15 ml H_2O and 150 ml H_2SO_4N, the ether layer was decanted, washed, dried and evaporated to give 7.3g of pure 2 (yield 100%).

4-benzyloxy-3 methoxy-α,α-dideutero benzyl chloride 3

30 mM (7.3g) of 2 were suspended in 80 ml dry toluene; after the addition of 40 mM (4.76g) $SOCl_2$ at 0°C, the mixture was stirred for 3 hours under argon. After evaporation, 7.50g ($\sim$ 95%) of crude 3 were obtained.

(4-benzyloxy-3-methoxyphenyl-α,α-dideutero-acetonitrile 4

The chloride was dissolved without purification in dry dimethoxyethane under argon and refluxed for 18 hours with 40 mM (2.60g) KCN and 2 ml D_2O; after cooling, the solution was filtered, dried and the solvent evaporated.

(4-benzyloxy-3-methoxyphenyl)-$\alpha,\alpha,\beta,\beta$-tetradeutero ethylamine 5

To 30 mM (1.26g) $LiAlD_4$ in 30 ml Et_2O distilled over $LiAlH_4$ were added, at 0°C, 40 mM (5.3g) $AlCl_3$ in 50 ml dry Et_2O;

after 10 min of stirring, nitrile 4 dissolved in dry Et_2O was added dropwise; after 1 h, 10 ml D_2O, 50 ml AcOEt and 100 ml H_2SO_4 N were added and the organic phase was discarded. After alcalization, the aqueous phase and the $Al(OH)_3$ precipitate were extracted with AcOEt. After drying and evaporation of AcOEt, 4g (50% from 3) of 5 were obtained.

(4-hydroxy-3 methoxyphenyl)-α,α,β,β-tetradeutero ethylamine

5 was dissolved in MeOH and hydrogenolysed over Pd/C at atmospheric pressure and room temperature. After completion of the reaction (T.L.C.), the solution was filtered; the addition of HCl/MeOH, followed by evaporation gave the chlorhydrate of 6, which was crystallised from EtOH-Et_2O (3g; 96%).

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