SYNTHESIS OF 4-|2-(DIMETHYLAMINO)ETHYL-2-^{14}C| PHENOL (HORDENINE-α-^{14}C)

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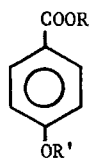
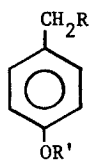
SUMMARY

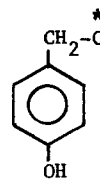
4-|2-(Dimethylamino)ethyl-2-^{14}C| phenol (hordenine-α-^{14}C) has been synthesised in three steps from |^{14}C|potassium cyanide and p-benzyloxybenzyl chloride which in turn was obtained in four steps from p-hydroxybenzoic acid.

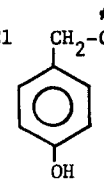
Key Words: Hordenine-α-^{14}C, Tyramine-α-^{14}C, Synthesis.

In an attempt to clarify the details of the metabolic degradation of the alkaloid hordenine in plants[1,2] we needed hordenine labelled at the carbon α to the dimethylamino group. The required compound was synthesised as follows: methylation of p-hydroxybenzoic acid (1) produced the methyl ester (2) that was treated with benzyl chloride to protect the phenolic hydroxyl group[3,4] as its benzyl ether (3). Lithium aluminum hydride reduction of 3 gave the p-benzyloxybenzyl alcohol (4) that was in turn transformed[5,6] into the corresponding chloride (5). Treatment of compound 5 with |^{14}C|potassium cyanide in dimethyl sulphoxide at room temperature[7,8] afforded the nitrile (6)[9] in excellent yield. Catalytic hydrogenation of compound 6 in acidic conditions[10-12] gave labelled tyramine hydrochloride (7) which upon reductive methylation in the presence of formaldehyde[13] afforded the title product (8) with an overall radioactive yield of 80%.









1: R=R'=H
2: R=Me; R'=H
3: R=Me; R'=CH_2Ph
4: R=OH; R'=CH_2Ph
5: R=Cl; R'=CH_2Ph
6: R=*CN; R'=CH_2Ph
7
8

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Marion et al.[14] have reported the synthesis of tyramine-α-^{14}C hydrochloride (7) but following a more difficult procedure and with much lower chemical and radiochemical yields. Besides, the synthesis of 4-|2-(dimethylamino)ethyl-1-^{14}C| phenol (hordenine-β-^{14}C) has been reported in the literature[15].

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded at 60 MHz, and mass spectra at 70 eV. IR spectra were registered as KBr dispersions. Radioactivity was measured by liquid scintillation counting.

2-(p-Benzyloxyphenyl) acetonitrile-1-^{14}C (6). Compound 5 (314 mg) was dissolved in dry dimethyl sulphoxide (20 ml) and to this solution |^{14}C|potassium cyanide (80.9 mg; 1 mCi) was added, and the mixture was kept at room temperature for 90 min. It was then poured into water (100 ml) and extracted with methylene chloride (4 x 50 ml). The organic extract was washed with water (5 x 50 ml) and dried. Evaporation of the solvent gave a solid (315 mg) identical (m.p., TLC, IR) to unlabelled 2-(p-benzyloxyphenyl) acetonitrile of m.p. 68-69°C. IR: 2250, 1620, 1580, 1510, 1250, 815, 745 and 700 cm^{-1}. NMR ($CDCl_3$-TMS): δ 3.61 (s, 2H, -CH_2-CN), 5.03 (s, 2H, -CH_2-O), 6.93 and 7.23 (dd_{AB}, 4H, J=9 Hz, disubstituted phenyl), 7.35 (s, 5H, CH_2-C_6H_5). MS (m/e, %): 223 (M^+, 6), 91 (100). Specific activity: 0.63 mCi/mmol.

Tyramine-α-^{14}C Hydrochloride (7). Compound 6 (313 mg) was dissolved in absolute ethanol (30 ml), concentrated hydrochloric acid (0.36 ml) was added, and the mixture was hydrogenated over 10% palladium on charcoal at room temperature and atmospheric pressure for 24 h. The reaction mixture was filtered the solid was washed with ethanol (2 x 1 ml), and the filtrate was concentrated to about 3 ml; addition of methylene chloride and petroleum ether gave a crystalline product (173 mg) that was identified as tyramine hydrochloride by comparison with an authentic standard (TLC, IR, MS). IR: 3100, 1620, 1500, 1230 and 840 cm^{-1}. NMR (D_2O-DSS): δ 2.7-3.4 (m, A_2B_2 system, 4H, -CH_2-CH_2-), 6.92 and 7.23 (dd_{AB}, 4H, J=9 Hz, -C_6H_4-). MS[16,17] (m/e, %): 137 (41), 108 (100), 107 (83), 91 (13), 77 (58). Specific activity: 0.62 mCi/mmol.

Hordenine-α-^{14}C (8). Compound 7 (172 mg) was dissolved in ethanol (20 ml) containing 40% formaldehyde (0.3 ml) and the solution was hydrogenated over 10% palladium on charcoal at room temperature and atmospheric pressure for 16 h. The catalyst was filtered off and washed with ethanol. Evaporation of the solvent afforded a residue that was dissolved in methanol (25 ml) and evaporated again; this procedure was repeated 4 times in order to eliminate the paraformaldehyde. The residue (176 mg) was taken in concentrated ammonia (2 ml) and evaporated. The final residue was purified by sublimation (5 x 10^{-4} torr, 100-105°C) yielding compound 8 (145 mg, 89%) of constant specific activity of 0.63 mCi/mmol. Its physical properties (TLC, IR, MS) were identical to those of an authentic standard. IR: 3100, 2700, 1620, 1520, 1240 and 840 cm^{-1}.

NMR (CD_3OD-TMS): δ 2.92 (s, 6H, N-$\underline{CH}_3$), 2.7-3.5 (m, A_2B_2 system, 4H, -$\underline{CH}_2$-$\underline{CH}_2$-) 6.80 and 7.15 (dd_{AB}, 4H, J=9 Hz, -$C_6\underline{H}_4$-); (TFA acid-TMS): δ 3.08 (s, 6H, $\underline{CH}_3$-N) 3.0-3.8 (m, A_2B_2 system, 4H, -$\underline{CH}_2$-$\underline{CH}_2$-), 7.11 (dd_{AB}, 4H, J=9 Hz, -$C_6\underline{H}_4$-).
$MS^{(16,17)}$ (m/e, %): 165 (6), 121 (9), 107 (14), 91 (9), 77 (18), 65 (7), 58(100).

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