SYNTHESIS OF ^{14}C LABELLED DROTAVERINUM HYDROCHLORIDE

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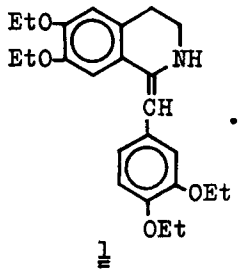
SUMMARY

Drotaverinum hydrochloride was labelled with ^{14}C isotope in position 1 of the isoquinoline ring. A rapid synthesis with high radiochemical yield was elaborated.

INTRODUCTION

Drotaverinum hydrochloride** (6,7,3',4'-tetraethoxy-1-benzylidene-1,2,3,4-tetrahydro-isoquinoline hydrochloride; 1)*** belonging to papaverine alkaloids has excellent spasmolytic effect.[1,2] As ^{14}C labelled 1 was needed for pharmaceutical investigations in the last years we have elaborated a simple route for its synthesis, in which the ^{14}C isotope was built into position 1 of the isoquinoline ring (1a).



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The synthesis started from 3,4-diethoxybenzyl chloride (2), which was reacted with $Na^{14}CN$ in DMSO to give 3,4-diethoxyphenyl-acetonitrile (3), and then it was hydrolyzed to 3,4-diethoxyphenyl-acetic acid-1-^{14}C (4); 4 was converted into

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** Other names: Dihydroperparine, NO-SPA.

*** This compound also exists in the tautomeric 6,7,3',4'-tetraethoxy-1-benzyl-3,4-dihydro-isoquinoline form.[3]

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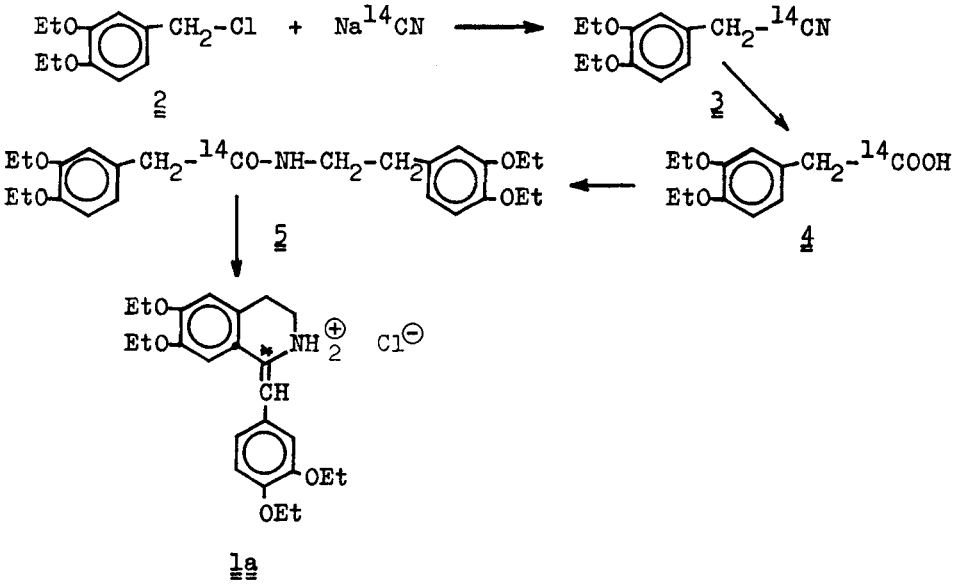
N-(3',4'-diethoxyphenyl-ethyl)-3,4-diethoxyphenyl-acetamide-1-^{14}C (5) by heating with 3,4-diethoxyphenyl-ethylamine in xylene; 5 was transformed into 1a using the method of Bischler and Napieralski.[4]

SCHEME 1.



EXPERIMENTAL

Melting points are uncorrected. Thin layer chromatography was carried out on 5 x 20 cm plates using Kieselgel $PF_{254+366}$ (MERCK). The radioactivity was measured by a Packard TRI-CARB liquid scintillation system.

3,4-Diethoxyphenyl-acetonitrile-1-^{14}C (3).

NaCN (350 mg, 7.0 mmoles) was dissolved in abs. dimethylsulphoxide (DMSO) (6 ml) and the solution was stirred at 80°C for one hour. $K^{14}CN$* (100 mg, 1.5 mmoles, 61.7 mCi) was added and the mixture was stirred at 80°C for one hour. The mixture was cooled to room temperature and 3,4-diethoxybenzyl chloride (2.14 g, 10 mmoles) dissolved in abs. DMSO (3 ml) was added. The stirring was continued at room temperature for 6 hours. Then

* $K^{14}CN$ was prepared by Bánfi's method[5]

the mixture was left overnight, NaCN (200 mg, 4 mmoles) was added and stirred at 60°C for one hour. Water (30 ml) was added to the cold mixture, which was extracted with 4 x 10 ml of ether. The ethereal extracts were washed with 10 ml of 25 % solution of NaCl and dried over $MgSO_4$. By evaporating the solvent, 2.01 g (98 %) of 3 were obtained as a pale orange oil. Calculated activity: 60.5 mCi. According to TLC (the solvent was benzene:ethyl acetate = 8:2) the material contained about 5 % impurity.

3,4-Diethoxyphenylacetic acid-1-^{14}C (4).

To the solution of 3 (2.01 g, 9.8 mmoles, 60.5 mCi) in ethanol (20 ml), 2 N NaOH (20 ml) was added, the solution heated to 90°C for 30 hours and kept at room temperature for two days. The solvent was evaporated, the oily residue was stirred with water (30 ml) at 60°C for 30 minutes and after cooling it was extracted with 2 x 10 ml of benzene. The aqueous layer was treated with charcoal, cooled with ice and the pH was adjusted to 3-4 by adding conc. HCl. A brown oil precipitated, which turned slowly into yellow-brown crystals. These were separated by filtration, washed with 2 x 5 ml of ice water, and dried in vacuo. Yield 1.66 g, 77%. Calculated activity 46.6 mCi. Mp: 74-76°C (lit.: 78-80°C).

N-(3',4'-Diethoxyphenyl-ethyl)-3,4-diethoxyphenyl-acetamide-1-^{14}C (5).

4 (1.66 g, 7.4 mmoles, 46.6 mCi) and 3,4-diethoxyphenyl-ethylamine (2.09 g, 10 mmoles) were dissolved in xylene (20 ml). The mixture was heated in a micro distillation apparatus on a 170-190 °C oil bath and the evaporated xylene was recycled. About 30 ml of xylene were evaporated during 3 hours. The mixture was kept at room temperature overnight and the procedure was repeated. Then the distillation was continued until the volume of the mixture was reduced to about 10 ml. The residue was cooled with ice and light petroleum (30 ml) was added. The precipitated crystals were separated by filtration and washed with 2 x 10 ml of light petro-

leum: 2.83 g (92 %) of 4 were obtained as white powder. Calculated activity: 42.9 mCi, m.p. 98-100°C (lit.: 106-108°C). The material showed one main spot (R_f 0.2) by TLC (the solvent was benzene:ethyl acetate = 7:3).

Drotaverinum-1-^{14}C hydrochloride (1a).

5 (2.83 g, 6.8 mmoles, 42.9 mCi) was dispersed in abs. benzene (13 ml), freshly distilled $POCl_3$ (1.3 ml) was added and the mixture was refluxed for 2 hours. The solvent was evaporated and the dark brown oily residue was crystallised by adding 20 % ethanolic HCl (9 ml). The mixture was kept overnight at 5°C, abs. ether (30 ml) was added and the crystals were separated by filtration, and washed with ether. After recrystallisation from ethanol (20 ml) 2.34 g (79 %) of 1a were obtained as pale yellow crystals. M.p. 197-200°C. Calculated activity: 36.8 mCi. Measured activity: 31.0 mCi (13.22 mCi/g). Radiochemical yield: 50.2 %. Upon TLC, using as solvent: ethyl acetate:ethanol:water = 70:30:1, 1a showed only one spot (R_f 0.4).

By adding inactive 1 to the mother liquor a further amount of 1a with lower specific activity was obtained.

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