PREPARATION OF CARBON-14, TRITIUM AND DEUTERIUM LABELLED TERODILINE, AND CARBON-14 AND DEUTERIUM LABELLED EMEPRONIUM BROMIDE

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SUMMARY

Selectively ring-labelled terodilines (N-tert-butyl-1-methyl-3,3-diphenylpropylamine; 1) were prepared by homogeneous catalytic exchange of aromatic hydrogens for ^{3}H and ^{2}H. In addition, terodilines specifically labelled with ^{14}C, ^{3}H or ^{2}H were prepared from the appropriate 1-methyl labelled 4,4-diphenylbutan-2-ol, by treating the corresponding tosylates with tert-butylamine.

Emepronium bromide (N-ethyl-N,N,1-trimethyl-3,3-diphenylpropylammonium bromide; 2) specifically labelled with ^{14}C or ^{2}H were similarly prepared by treating the labelled tosylates with N-ethylmethylamine or dimethylamine, followed by quaternization with methyl bromide or ethyl bromide, respectively.

Keywords: N-tert-Butyl-1-methyl-3,3-diphenylpropylamine, N-Ethyl-N,N,1-trimethyl-3,3-diphenylpropylammonium bromide, Terodiline, Emepronium bromide, Resolution

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INTRODUCTION

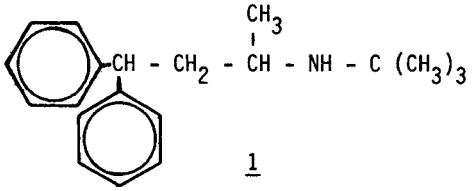
Terodiline hydrochloride (1) is a drug with both antimuscarinic and calcium blocking effects. It was originally introduced as a coronary dilator and is presently undergoing extensive studies as a remedy for motor urge urinary incontinence (1). Kinetic and metabolic studies have therefore become important and in this paper we describe the syntheses of ^{14}C, ^{3}H and ^{2}H labelled terodiline. The method used for preparing ^{14}C labelled terodiline was also applied to the labelling of emepronium bromide (2), another anticholinergic drug in clinical use for the treatment of urinary incontinence (2).

RESULTS AND DISCUSSION

Exchange labelling of terodiline

Selectively tritiated terodiline (1d) was obtained using the tritiated phosphoric acid-boron trifluoride reagent developed by Yavorsky and Gorin (3). This reagent causes equilibrium exchange labelling mainly of aromatic hydrogens and hydrogens adjacent to a tertiary carbon atom. Systematic investigations on the effect of reaction conditions have been carried out (4,5). In the case of terodiline, we consider the number of exchangeable "stable" hydrogens to be identical with the aromatic hydrogens, and calculations based on the specific activity of the product show 100% theoretical labelling of the aromatic positions.

Generally deuterated terodiline (1e) was similarly prepared using a deuterated Yavorsky reagent. The amine has a mean isotopic content of 8.3 deuterium atoms per molecule, which is in accordance with a statistical distribution of deuterium atoms between the reagent and the ten exchangeable aromatic positions. The mass spectrum also shows that all deuterium atoms are located in the aromatic rings.



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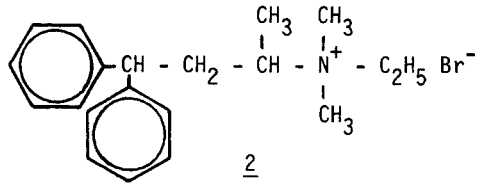

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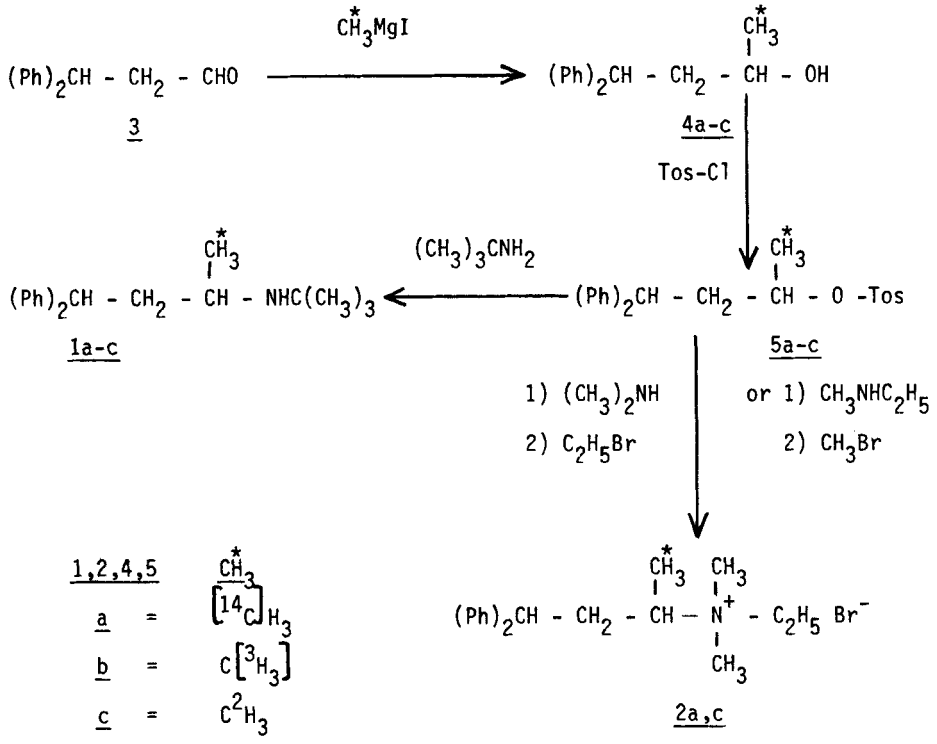
Specific labelling of terodiline

Specifically ^{14}C labelled terodiline has previously been prepared from [carbonyl - ^{14}C]benzaldehyde, via condensation with acetone to give 4-phenyl-[4-^{14}C]but-3-en-2-one. Addition of benzene under Friedel-Crafts conditions gave 4,4-diphenyl-[4-^{14}C]butan-2-one, and subsequent Leuckart-Wallach amination with N-tert-butylformamide gave N-tert-butyl-1-methyl-3,3-diphenyl-[3-^{14}C]propylamine (Sven Carlsson, KabiVitrum, unpublished). The overall yield was, however, moderate and [^{14}C]benzaldehyde is not routinely available commercially. An alternative route was therefore chosen in the present study, which permitted carbon-14 (1a), tritium (1b) and deuterium (1c) labelling of terodiline, using easily available starting materials and almost identical reaction conditions (Reaction Scheme). Labelled methylmagnesium iodide was added to 3,3-diphenylpropanal (3) and the 1-methyl labelled 4,4-diphenylbutan-2-ols (4a-c) thus obtained were converted to their tosylates (5a-c), which were then treated with an excess of tert-butylamine in acetonitrile. Due to steric hindrance, the substitution proceeded only slowly and was accompanied by considerable elimination. The other reaction steps proceeded smoothly and with good yields. However, some of the 3,3-diphenylpropanal was reduced to 3,3-diphenylpropan-1-ol by the Grignard reagent, and substitution of the corresponding tosylate gave N-tert-butyl-3,3-diphenylpropylamine as an impurity.

Reaction Scheme



Optical resolution of deuterated terodiline

Studies with the individual enantiomers of terodiline have shown that these are metabolized with a high degree of stereoselectivity (6). For further biological studies deuterated terodiline (1c) was resolved *via* salts with L(+)- and D(-)-tartaric acid, principally using the procedure published for the unlabelled material (6).

Preparation of labelled emepronium bromide

In preliminary experiments, 4,4-diphenyl-[1-^{14}C]butan-2-yl *p*-toluenesulfonate (5a) was treated with dimethylamine and the tertiary amine obtained was quaternized with ethyl bromide to give 2a. The latter reaction was, however, slow and accompanied by extensive radiolysis. The amine obtained from the

tosylate and N-ethylmethylamine was however quaternized rapidly and in good yield using methyl bromide. It may be noted that contrary to the reaction of the tosylate with tert-butylamine the reactions with N-ethylmethylamine or dimethylamine were rapid and gave high yields.

EXPERIMENTAL

General

Radioactivity measurements were carried out using a Packard TriCarb liquid scintillation spectrometer (3371) with Packard's Instagel scintillation cocktail. Radiochemical analysis of TLC plates was done with a Berthold Radio-Chromatogram Scanner II.

Infrared spectra were obtained with a Perkin Elmer 599 B spectrometer. Mass spectra were recorded with a Varian Mat 311 A spectrometer operating at 70 eV, and are presented as m/z (% relative intensity). These spectra were routinely recorded for non-radioactive compounds and are in agreement with the proposed structures.

Optical rotations were measured on a Perkin-Elmer 141 spectropolarimeter.

Melting points were determined with a Reichert hot stage microscope.

TLC were generally run on Merck pre-coated silica gel F_{254} (0.25 mm) plates, using the following solvent systems (given by volume):

A) Cyclohexane/ethyl acetate/ammonia (20:35:1)

B) Diethyl ether/light petroleum/ammonia (75:25:2)

C) Diethyl ether/light petroleum (1:1)

D) Cyclohexane/ethyl acetate/ammonia (20:90:2)

Chromatograms were also run on:

E) Merck pre-coated aluminium oxide F_{254} (0.25 mm) plates, developed in cyclohexane/chloroform/ethanol/acetic acid (60:45:30:5)

TLC of all labelled compounds were identical to their unlabelled reference counterparts.

HPLC analyses were performed on a C-18 column (Spherisorb S5 ODS 2) with 70% methanol in phosphate buffer (pH 4.0) as the eluent. The detector was a

Schimadzu SPD-2A operating at 220 nm.

GLC analyses were carried out with a Varian 1400 gas chromatograph equipped with a fused silica capillary column (DB-1).

Materials

C^2H_3I was purchased from CEA (France) and Fluka AG (West Germany), tritiated water, $[^3H]CH_3I$, and $[^{14}C]CH_3I$ from Amersham International plc (England).

Syntheses

N-tert-Butyl-1-methyl-3,3-[^{3}H-G]diphenylpropylamine hydrochloride (1d)

A boron trifluoride complex of tritiated phosphoric acid (Yavorsky reagent) with a nominal specific activity of 811 mCi/g was prepared (4) from phosphorous pentoxide (1.58 g; 11.1 mmol) and tritiated water (0.6 ml; 33.3 mmol; 3.0 Ci). Terodiline hydrochloride (0.64 g; 2.0 mmol) was dissolved in the reagent (3.69 g; 22.2 mmol) and the mixture was stirred at room temperature for 4 days. The complex was decomposed by carefully adding water (5 ml) and the solution was made alkaline with 12M sodium hydroxide and extracted with ether (3x20 ml). The combined ether extracts were dried (K_2CO_3) and the solvent was removed in vacuo. The residue was purified by preparative thin layer chromatography on Merck pre-coated silica gel F_{254} (2 mm) plates developed in system A. The amine was obtained as a colourless oil, which was at least 96% radiochemically pure (TLC systems A and B). The amine was precipitated with hydrogen chloride in diethyl ether and labile tritium was removed by dissolving the salt in methanol (20 ml) and evaporating the solvent in vacuo. This procedure was repeated six times and gave colourless crystals. Yield 0.20 g (31%), m.p. 171-173^0. The specific activity was 347 mCi/mmol (100% theoretical labelling). The radiochemical yield based on tritiated water was 7%.

N-tert-Butyl-1-methyl-3,3-[^{2}H-G]diphenylpropylamine hydrochloride (1e)

In a manner similar to the tritiation above, terodiline hydrochloride (0.25 g; 0.79 mmol) was deuterated with a Yavorsky reagent (2.53 g; 15 mmol) prepared from phosphorous pentoxide (1.06 g; 7.5 mmol) and deuterium oxide (0.45 g; 22.5 mmol).

The deuterated amine hydrochloride, 95 mg (38%), m.p. 170-172°C, had a mean isotopic content of 8.3 deuterium atoms per molecule. MS: 291 (46, M^+) 275 (60), 217 (8), 176 (40), 100 (100), 44 (40).

3,3-Diphenylpropanal (3), was prepared according to a published method (7).

4,4-Diphenyl-[1-^{14}C]butan-2-ol (4a)

A solution of methyl iodide (235 mg; 2.29 mmol) in diethyl ether (8 ml) was introduced into a chilled (-70°) break-seal ampoule containing [^{14}C] methyl iodide (110 mg; 0.76 mmol; 45 mCi). A Grignard reagent was prepared from the resulting solution and magnesium (80.5 mg; 3.4 mg atom) under reflux for 60 min. A solution of 3 (640 mg; 3.05 mmol) in ether (5 ml) was then added and the mixture was refluxed for 1 h. The magnesium salt was hydrolyzed with saturated aqueous ammonium chloride solution (2 ml) and water (5 ml). Extraction with ether, drying (K_2CO_3) and concentration afforded a colourless oil (690 mg; 100%), which was used directly in the next step.

4,4-Diphenyl-[1-^{14}C]butan-2-yl p-toluenesulfonate (5a)

To a cold solution of 4a (690 mg; 3,05 mmol) in pyridine (6 ml) was added p-toluenesulfonyl chloride (1.16 g; 6.1 mmol) in portions during 20 min at 0-2°. The reaction mixture was left at 4° over night. Ice-water (12 ml) was added, whereupon a crystalline product precipitated, which after washing with water and drying in vacuo at room temperature weighed 894 mg. TLC in system C showed a radiochemical purity of 92%.

N-tert-Butyl-1-[^{14}C]methyl-3,3-diphenylpropylamine hydrochloride (1a)

A solution of 5a (0.89 g; 2.34 mmol) and tert-butylamine (1.7 g; 23 mmol) in acetonitrile (6 ml) was kept in a sealed vial at 65° for 12 days. Precipitated tert-butylammonium p-toluenesulfonate was filtered off and the filtrate was taken to dryness in vacuo. The residue was taken up in 2M NaOH, the organic material was extracted into ether, washed with water and dried (K_2CO_3). The

hydrochloride was precipitated with hydrogen chloride in ether, filtered off and washed with ether. It was dissolved in 2-propanol (4 ml) and precipitated with a 1:1 mixture of diethyl ether-light petroleum (10 ml). Yield 278 mg (38%) of colourless crystals (m.p. 175-178°). Radiochemical yield 29% (calculated on the alcohol 4).

TLC in systems A and B showed that the material had a radiochemical purity higher than 97%. The specific radioactivity was 15.9 mCi/mmol. HPLC showed that the product contained about 5% of (non-radioactive) N-tert-butyl-3,3-diphenylpropylamine, formed as pointed out above.

4,4-Diphenyl -[1-^{3}H]butan-2-ol (4b)

The preparation was done in conformity with the one described for 4a. A Grignard reagent was prepared in ether from magnesium (50 mg; 2.05 mg atom) and a mixture of methyl iodide (283 mg; 2.0 mmol) and [^{3}H]methyl iodide (1.42 mg; 10 μmol; 100 mCi). A solution of 3 (420 mg; 2.0 mmol) in ether was added. The product was obtained as a colourless oil (370 mg; 82%) with a specific activity of 17 mCi/mmol.

4,4-Diphenyl -(1-$^2H_3$)butan -2-ol (4c)

The alcohol was synthesized in analogy with 4a from a Grignard reagent prepared from deuterated methyl iodide (100 g; 0.69 mol) and magnesium (18.4 g; 0.77 g atom) in ether (860 ml). The aldehyde 3 (145 g; 0.69 mol) dissolved in ether (440 ml) was added. Usual work-up afforded a colourless oil (153 g; 97%). MS: 229 (8, M^+), 211 (74), 193 (35), 107 (100), 152 (22), 133 (25), 48 (10).

N-tert-Butyl-1-[^{3}H] methyl-3,3-diphenylpropylamine hydrochloride (1b) and N-tert-Butyl-1-($^2H_3$)methyl-3,3-diphenylpropyamine hydrochloride (1c)

These amines were prepared from the alcohols 4b and 4c, respectively, using analogous procedures as have been described from the synthesis of 1a via 5a.

The tritium labelled product had a chemical as well as radiochemical purity of 99% as determined by TLC (systems A and B). The overall yield was 50% and the product (m.p. 181-183°) had a specific activity of 13 mCi/mmol.

The deuterium labelled product (m.p. 174°) had a chemical purity of 99% as determined by TLC in systems A and B, and non-aqueous titration. The overall yield was 50% and the deuterium content in the 1-methyl group was over 99%. MS: 284 (25, M^+) 269 (25), 211 (5), 167 (30), 103 (75), 47 (100).

Optical resolution of N-tert-butyl-3,3-diphenyl-1-($^{2}H_3$)methylpropylamine (1c)

The deuterium labelled terodiline base (9.0 g; 32 mmol) was resolved into optical isomers using L(+)-and D(-)-tartaric acid. The resolved hydrogen tartrates thus obtained were converted to the hydrochloric acid salts following the procedure described for unlabelled terodiline (6).

The optical rotation of (-)-N-tert-butyl-1-($^{2}H_3$)methyl-3,3-diphenylpropylamine hydrogen L(+)-tartrate was $[\alpha]_D^{25}$ -31.0° (c=5.23 in water) and of the hydrochloride (c=2.68 in 50% ethanol-water) $[\alpha]_D^{25}$ -66.9°. Yield 1.0 g of the hydrochloride.

The optical rotation of the (+)-N-tert-1- ($^{2}H_3$) methyl-3,3-diphenylpropylamine hydrogen D(-)-tartrate was $[\alpha]_D^{25}$ +29.8° (c=5.40 in water) and of the hydrochloride (c=2.72 in 50% ethanol-water) $[\alpha]_D^{25}$ +66.9°. Yield 0.9 g of the hydrochloride.

N-Ethyl-N,N-dimethyl-1-[^{14}C]methyl-3,3-diphenylpropylammonium bromide (2a)

To a solution of 5a (510 mg; 1.34 mmol) in acetonitrile (4.5 ml) was added N-ethylmethylamine (634 mg; 10.7 mmol). The mixture was kept in a sealed vial at 55° for 3 days. The solution was taken to dryness in vacuo and the residue was taken up in 2M HCl and washed with n-hexane. The aqueous phase was basified with 2M NaOH. Extraction with ether, washing with water and brine, drying (K_2CO_3) and evaporation in vacuo gave 290 mg (80%) of N-ethyl-N,N-dimethyl-1-[^{14}C]methyl--3,3-diphenylpropylamine. An ethereal solution of the amine (290 mg; 1.1 mmol) was cooled to -10°, an excess of methyl bromide was added and the reaction mixture was kept in a sealed vial at room temperature for 2 days. The crystalline precipitate was filtered off and washed with ether. After drying in vacuo the product was recrystallized from 2-propanol (0.7 ml) giving 130 mg

(33%) of colourless crystals, m.p. 198-201°. The radiochemical yield was 21% calculated on the alcohol 4a. TLC run in system E showed a chemical as well as radiochemical purity higher than 98%. Specific activity 12 mCi/mmol.

N-Ethyl-N,N-dimethyl-1-($^2H_3$)methyl-3,3-diphenylpropylammonium bromide (2c)

4,4-Diphenyl-(1-$^2H_3$)butan -2-ol was prepared from 3,3-diphenylpropanal and ($^2H_3$)methylmagnesium iodide and converted to the tosylate by conventional procedures. The deuterated tosylate (250 g; 0.52 mol) was treated with dimethylamine (270 g; 6 mol) in acetonitrile at 50° for 2 days. The reaction mixture was taken to dryness in vacuo and the residue was taken up in 2M HCl and washed with ether. The aqueous phase was basified with 2M NaOH. Extraction with ether, washing with water and brine, drying (K_2CO_3) and evaporation in vacuo gave 111 g (83%) of N,N-dimethyl-1-($^2H_3$)methyl-3,3-diphenylpropylamine. An ethereal solution of the amine (80 g; 0.31 mol) was treated with ethyl bromide (169 g; 1.5 mol) at room temperature. After 14 days the product was filtered off and washed with ether. Two recrystallizations from 2-propanol gave 94 g (84%) of colourless crystals, m.p. 207-208°. The product had a chemical purity of 99% by TLC run in system E and non-aqueous titration. The isotopic purity was determined by GLC-MS MID-technique on the molecular ion of N-mono-demethylated product (8) and showed 99.6% deuteration of the 1-methyl group. MS: 270 (7), 256 (2), 211 (2), 167 (20), 89 (100), 75 (50), 61 (15).

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