SYNTHESIS OF [CARBONYL-^{14}C]-LABELLED REMOXIPRIDE AND RACLOPRIDE. TWO POTENTIAL NEUROLEPTIC AGENTS.

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SUMMARY

The synthesis of two benzamide derivatives labelled with carbon-14 at the carboxamide position is described. The radioactive label was introduced by the reaction of 1,3-dimethoxy-2-lithiobenzene with [^{14}C]carbon dioxide to furnish 2,6-dimethoxy[carboxy-^{14}C]benzoic acid (2). Halogenation of 2 with dioxane dibromide or sulphuryl chloride followed by reaction with thionyl chloride led to the corresponding labelled acid chlorides. These were reacted with (S)-2-(aminomethyl)-1-ethylpyrrolidine (5) and converted into [^{14}C]remoxipride (6) and [^{14}C]raclopride (8), respectively.

Key words: Remoxipride, raclopride, benzamides, carbon-14

INTRODUCTION

A number of substituted N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamides has been demonstrated as potential neuroleptic agents (1, 2). Preliminary metabolic studies of one of these, remoxipride, in animals had shown that the N-ethyl and O-methyl groups were eliminated from the

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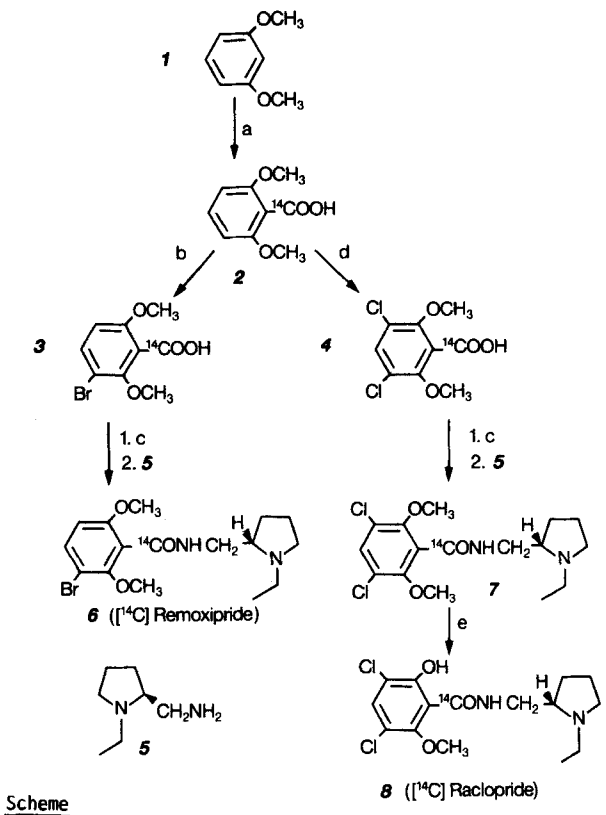
molecule. Furthermore, when compounds labelled with tritium, in the 3- and 4-positions of the pyrrolidine ring (3) or in the 5-position of the phenyl ring, were employed, part of the radioactivity was recovered as tritiated water (4). These findings suggested that a carbon-14 label in the structural backbone of the compounds was needed for further elucidation of the metabolism of these compounds in man and animals. With the methods for the preparation of remoxipride (1) and raclopride (2) at hand, the following procedure led to the title compounds.

SYNTHESIS

A solution of 1,3-dimethoxybenzene (1) (Scheme) in THF was subjected to lithium-hydrogen exchange with n-butyllithium to produce 2-lithio-1,3-dimethoxybenzene. *In situ* exposure to [^{14}C]carbon dioxide gave the carboxyl-^{14}C labelled acid 2. Monobromination of 2 was then accomplished with one equivalent of dioxane dibromide affording bromo-acid 3. Treatment with thionyl chloride and subsequent reaction of the acid chloride with the optically active pyrrolidine 5 (5) furnished after recrystallization carbon-14 labelled remoxipride (6) with a radiochemical purity greater than 98%.

By treating the acid 2 with 2 equivalents of sulphuryl chloride, aromatic chlorination produced dichloroacid 4 as identified by TLC with unlabelled acid. Without isolation, the product was reacted with thionyl chloride in the presence of a catalytical amount of DMF. Subsequent *in situ* reaction between the acid chloride formed and amine 5 furnished after work-up benzamide 7 (39% yield from 2). Monodemethylation of compound 7 was accomplished with 1.5 equivalents of BBr_3 at room temperature. To the crude product unlabelled raclopride was added, but all attempts to isolate the product by crystallization after work-up were unsuccessful. Instead, isolation by low pressure LC furnished a hexane/i-PrOH solution of [^{14}C] raclopride (8) with a specific activity of 19.5 mCi/mmol.



Scheme

Reagents; a: BuLi, $^{14}CO_2$ b: Dioxane-Br_2 c: $SOCl_2$
d: SO_2Cl_2 e: BBr_3

EXPERIMENTAL

Barium [^{14}C]carbonate was purchased from Amersham International plc, Amersham, England. The radiochemical purity was determined from TLC plates using a Berthold LB 283 TLC Linear Analyzer. Radioactivity was determined in a Packard Tri-Carb 460 C liquid scintillation spectrometer using Bioflour (New England Nuclear) as the counting medium. TLC analyses were done on silica gel 60 F_{254} (Merck) glass plates.

2,6-Dimethoxy[carboxy-^{14}C]benzoic acid (2).

A solution of 1,3-dimethoxybenzene (1) (275 mg, 2 mmol) in THF (5 ml) was cooled to -40°C and treated with 1.2-M n-butyllithium in hexane (1.68 mmol). After being stirred at -30°C for 4.5 hours, the mixture was cooled to -70°C and evacuated in a vacuum manifold. $^{14}CO_2$, from $Ba^{14}CO_3$ (25 mCi, 22.2 mCi/mmol) and concentrated H_2SO_4, was introduced and the reaction mixture was stirred at -70°C for 90 min. Evaporation of the solvent left a residue which was partitioned between water (3 ml) and ether (1.5 ml). The organic layer was discarded and the aqueous solution was washed with ether (2 x 1.5 ml) and acidified to pH 3 with conc. HCl. A precipitate was formed and collected by filtration. Recrystallization from ethanol-water furnished 114 mg(56%) of 2 which was identified by TLC with unlabelled material (SiO_2; petroleum ether 40°-60°/diethyl ether/HOAc, 20:10:1.5, Rf ≈ 0.16).

(S)-2-[(3-Bromo-2,6-dimethoxy[carbonyl-^{14}C]benzamido)methyl]-1-ethyl-pyrrolidine ([^{14}C]Remoxipride) (6).

To a suspension of 2 (114 mg, 0.63 mmol) in $CHCl_3$ (1.5 ml), dioxane dibromide (162 mg, 0.65 mmol) dissolved in $CHCl_3$ (500 µl) was added. After stirring for 4 hours at room temperature TLC (SiO_2; petroleum ether 40°-60°/diethyl ether/HOAc, 20:10:1.5) showed complete conversion of 2. The solvent was evaporated under vacuum and the residue crystallized from ethanol-water to furnish bromo acid 3 identified by TLC with unlabelled material. To the vacuum dried crystals of 3, thionyl chloride (150 µl) was added and the mixture heated at 50°C for 30 minutes. Excess thionyl chloride was removed under reduced pressure leaving a dark coloured oil. (S)-1-Ethyl-2-(methylamino)pyrrolidine (5) (75 mg, 0.58 mmol) in $CHCl_3$ (3 ml) was added with stirring. After 4 hours, 1 M NaOH (2 ml) was added and the aqueous phase discarded. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to 1 ml. Ether-HCl was added and the solution evaporated to

dryness. Recrystallization twice of the residue from ethanol-diisopropyl ether gave 95 mg of (6)-HCl as white crystals with a specific activity of 21.6 mCi/mmol and a radiochemical purity greater than 98% as measured by TLC (SiO_2; $CHCl_3$/EtOH/conc. NH_3, 15:1:0.05).

(S)-2-[(3,5-Dichloro-2,6-dimethoxy[carbonyl-^{14}C]benzamido)methyl]-1-ethylpyrrolidine (7)

To a slurry of acid 2 (68 mg, 0.49 mmol), prepared as described above from $Ba^{14}CO_3$ (25 mCi, 39.2 mCi/mmol), in $CHCl_3$ (500 µl), a solution of SO_2Cl_2 (134 mg, 1 mmol) in $CHCl_3$ (200 µl) was added. The crystals dissolved accompanied by gas evolution and the reaction mixture was stirred at room temperature until TLC (SiO_2; petroleum ether 40°-60°C/diethyl ether/HOAc, 20:15:1.5) showed complete conversion of 2 (~2.5h). The solvent was evaporated leaving acid 4 as an oil, identified by TLC with unlabelled material. Thionyl chloride (100 µl) and one drop of DMF were added and the mixture stirred for 3 hours at room temperature and finally heated to 50°C. Excess thionyl chloride was removed under vacuum and to the residue, dissolved in $CHCl_3$ (1 ml), (S)-1-ethyl-2-(methylamino)pyrrolidine (5) (100 mg, 0.78 mmol) in $CHCl_3$ (500 µl) was added and the mixture left overnight. The reaction mixture was successively washed with 1 M NaOH (1 ml), H_2O (2 x 1 ml) and dried (Na_2SO_4). Evaporation of the chloroform solution and recrystallization of the residue from diisopropyl ether furnished 69 mg of 7 (43.9 mCi/mmol, 39% from 2) identified by TLC with unlabelled material. (SiO_2; $CHCl_3$/CH_3OH/conc. NH_3, 45:5:0.05).

(S)-2-[(3,5-Dichloro-2-hydroxy-6-methoxy[carbonyl-^{14}C]benzamido)methyl]-1-ethylpyrrolidine ([^{14}C]Raclopride) (8)

Compound 7 (68 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (1 ml) and BBr_3 (75 mg, 0.30 mmol) in 1.5 ml of the same solvent was added. After stirring at room temperature for 6 hours the reaction mixture was successively treated with 2 M NH_3 (2 x 2 ml), H_2O (2 ml) and dried (Na_2SO_4). 40 mg of

unlabelled raclopride was added to the solution and the product isolated by low pressure LC (SiO_2; n-hexane/ethanol/conc. NH_3, 9:1:0.2) affording 0.98 mCi of 8. The specific activity was 19.5 mCi/mmol as determined by quantitative HPLC analysis; Spherisorb ODS-2 (C_{18}, 3 µ) column eluted with 35% CH_3CN in 0.05 M NaH_2PO_4 (pH 3) buffer containing $1 \cdot 10^{-3}$M dimethylnonylamine. The radiochemical purity was greater than 98% as determined by TLC (SiO_2; $CHCl_3/CH_3OH$/conc. NH_3, 95:5:0.05).

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