SYNTHESIS OF ^{14}C-LABELLED DIBENZO[d,g] [1,3,6]DIOXAZOCINE DERIVATIVES (EGYT-2474 and EGYT-2509)

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SUMMARY

Synthesis of 2-chloro-12-(3-dimethylaminopropyl)-dibenzo[d,g] [1,3,6]dioxazocine maleate (EGYT-2474) and 2-chloro-12-(3-dimethylamino-2-methylpropyl)-dibenzo[d,g] [1,3,6]dioxazocine hydrochloride (EGYT-2509) labelled with ^{14}C-isotope is reported. The synthesis of above compounds was based on [^{14}C] methylene diiodide which was prepared by the reduction of [^{14}C]iodoform. [^{14}C]Iodoform was synthesised by an improved method in a radiochemical overall yield of 44% calculated on barium [^{14}C]carbonate.

Key words: [^{14}C]iodoform, [^{14}C]methylene diiodide

INTRODUCTION

For studying the metabolism of 2-chloro-12-(3-dimethylaminopropyl)-dibenzo[d,g] [1,3,6]dioxazocine maleate and 2-chloro-12-(3-dimethylamino-2-methylpropyl)-dibenzo[d,g] [1,3,6]dioxazocine hydrochloride the preparation of these compounds labelled with carbon-14 isotope was required. The radioactive compounds were synthesised by employing the synthesis route (1) demonstrated in the scheme.

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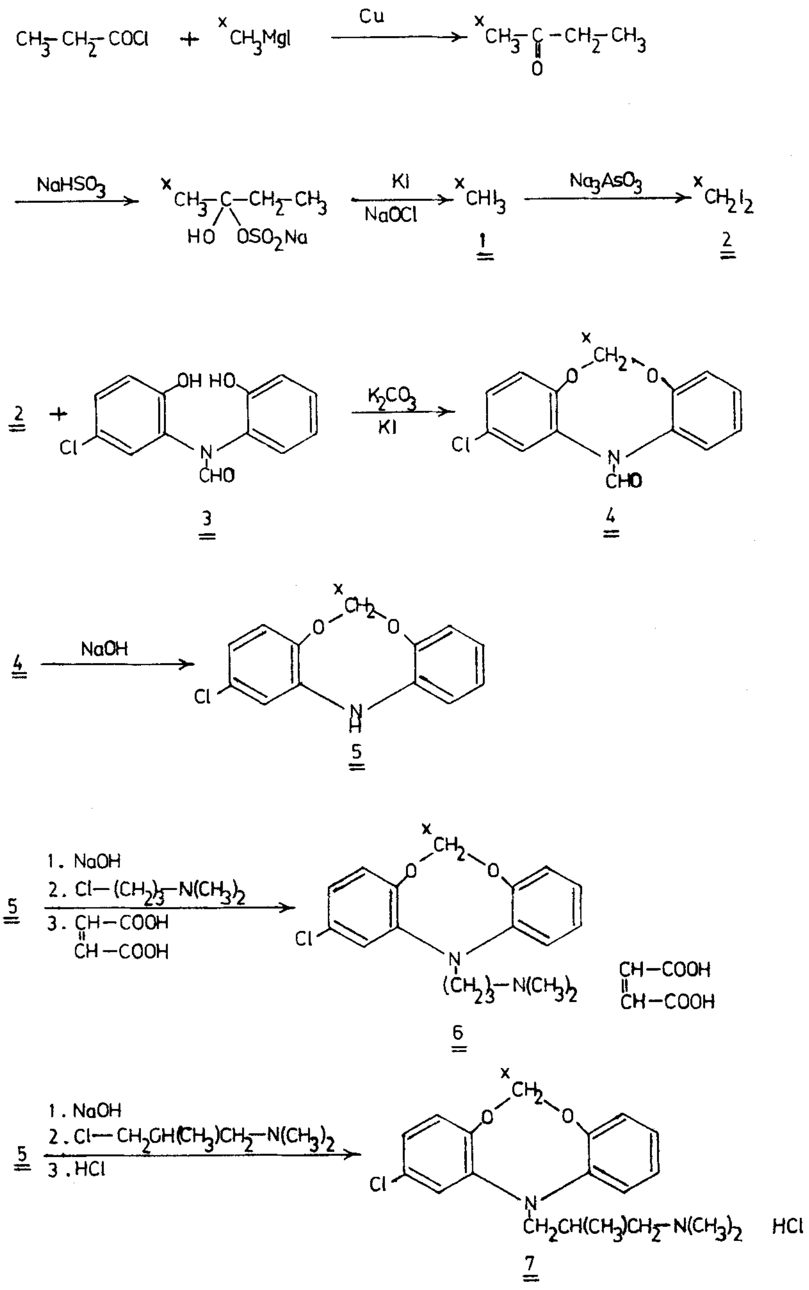
Cu
NaHSO3
KI
NaOCl
Na3AsO3
K2CO3
KI
NaOH
1. NaOH
2. Cl–(CH2)3–N(CH3)2
3. CH–COOH ‖ CH–COOH
1. NaOH
2. Cl–CH2CH(CH3)CH2–N(CH3)2
3. HCl
1
2
3
4
5
6
7

The easily available labelling of C-6 position of the dibenzodioxazocine ring system seemed to be suitable for metabolism and pharmacokinetic studies. Carbon-14 nuclide was built in by reacting (2,2'-dihydroxy-5-chloro)-diphenyl-N-formylamine (**3**) with [^{14}C]methylene diiodide. The radioactive CH_2I_2 was prepared by reducing [^{14}C]iodoform with sodium arsenite (2). The most favourable method for the preparation of [^{14}C]iodoform has been published by Jones (3). Although $^{14}CHI_3$ was prepared in a yield of 96% based on [1,3-$^{14}C_2$]2-propanone, because of the symmetry of the precursor only 48% of the radioactive carbon was utilized, and so the overall radiochemical yield based on $Ba^{14}CO_3$ was below 25%.

In the present synthesis [1-^{14}C]2-butanone was used as radioactive precursor. [1-^{14}C]2-Butanone prepared by a copper catalysed reaction of [^{14}C]methylmagnesiumiodide with propionyl chloride (4) was isolated as water soluble sodium bisulphite addition product which was oxidized with sodium hypochlorite in the presence of KI to give $^{14}CHI_3$ in 44% radiochemical yield based on $Ba^{14}CO_3$.

EXPERIMENTAL

The melting points were determined on a Boëtius hot stage and are uncorrected. TLC was carried out on Silica Gel 60 F_{254} (Merck), and a Berthold TLC scanner Model LB-2723 was used for evaluation. Radioactivity was measured by liquid scintillation technique using a Packard TRI-CARB Model 2660 spectrometer. All evaporations were carried out under reduced pressure.

[^{14}C]Iodoform (**1**)

Propionyl chloride (0.87 ml, 10 mmol) dissolved in dry ether (2 ml) was added to a suspension of copper powder (1.271 g, 0.02 atom-gram) in 3 ml of dry ether during a period of 15 minutes, and the mixture was stirred at 20°C for 60 minutes. The reaction mixture was then cooled and 1N ethereal solution of $^{14}CH_3MgI$ prepared by the known method (5) starting from $Ba^{14}CO_3$ (1.974 g, 10 mmol, 11.87 GBq) was added at 0°C during a period of 30 minutes. Having been stirred at 20°C for 60 minutes, the mixture was cooled, 4.16 g (40 mmol) of $NaHSO_3$ dissolved in 25 ml of water was added dropwise at 0°C, and stirring was continued at 20°C for an additional 30 minutes. The catalyst was filtered off, the organic layer was separated and extracted with aqueous $NaHSO_3$ (2x10 ml) containing altogether 1.04 g of $NaHSO_3$. KI (30 g, 180 mmol) was dissolved in the combined aqueous extracts, and a commercial aqueous sodium hypochlorite solution (about 10%, 350 ml) was added dropwise to the stirred mixture at 0°C during 30 minutes. The reaction mixture was kept in a refrigerator overnight, then it was centrifuged, and the solid containing $Mg(OH)_2$ was suspended in 20 ml of 2N HCl, filtered off, washed with water (3x5 ml) and dried to give 1.717 g (4.36 mmol, 5.176 GBq) of yellow crystals. M.p. 121°C. Radiochemical yield: 44% based on $Ba^{14}CO_3$.

[^{14}C]Methylene diiodide (2)

2.57 ml of a solution prepared from arsenious oxide (0.788 g) and sodium hydroxide (1.57 g) in water (8 ml) was added to 1 (1.717 g, 4.36 mmol, 5.176 GBq). The suspension was stirred under nitrogen and slowly heated to 60°C during 30 minutes. A further 2.57 ml of the reducing solution was added at 60°C during one hour and afterwards the mixture was stirred at this temperature for an additional hour. After cooling the upper layer was separated and extracted with ether (3x10 ml). The separated $^{14}CH_2I_2$ was dissolved in the ethereal extracts, dried over anhydrous $CaCl_2$, and the solvent was evaporated to give 0.94 g (3.49 mmol, 4.14 GBq) of a brown liquid. This product was used without purification in the next reaction step.

2-Chloro-12-formyl-[6-^{14}C]dibenzo[d,g] [1,3,6]dioxazocine (4)

$^{14}CH_2I_2$ (2) (0.94 g, 3.49 mmol, 4.14 GBq) in dry dimethylacetamide (2.5 ml), KI (0.06 g, 0.35 mmol) and anhydrous K_2CO_3 (1.94 g, 14.0 mmol) were added to the solution of 3 (1.118 g, 4.20 mmol) in dry dimethylacetamide (8 ml). The reaction mixture protected from light was stirred at 120°C under nitrogen for three hours, then the inorganic salts were filtered off. The filtrate was evaporated, and ethanol (4.1 ml, 96%) was added to the residue. The separated crystals were filtered off, washed with ethanol (3x2 ml) and dried in vacuo to give 0.493 g (1.78 mmol, 2.113 GBq) of 4. M.p. 134-138°C. The filtrate was evaporated and a second crop of **4** was obtained which was purified by chromatography on silica gel using benzene-methanol-2-butanone (94:5:1) as eluent. The amount of the second crop of **4** was 0.042 g (0.15 mmol, 0.178 GBq). M.p. 136-140°C.

2-Chloro-[6-^{14}C]dibenzo[d,g] [1,3,6]dioxazocine (5)

A mixture of the aqueous NaOH (1.16 ml, 20%) and ethanol (5.8 ml) was added to the stirred solution of **4** (1.932 g, 7.00 mmol, 2.291 GBq) in ethanol (9.2 ml) at 90°C during a period of 20 minutes. Having been stirred at 90°C for 30 minutes, the reaction mixture was cooled and the liquid was decanted from the precipitated brown resin. The solution was acidified to pH 5 with 2N HCl at 0°C. The precipitated crystals were filtered off, washed with water (3x10 ml), and dried in vacuo to give 2.3 g of a light brown material. This crude product was chromatographed using the same solvent system as above. 1.432 g (5.78 mmol, 1.892 GBq) of **5** was yielded, m.p. 180-182°C.

2-Chloro-12-(3-dimethylaminopropyl)-[6-^{14}C]dibenzo[d,g] [1,3,6]-dioxazocine maleate (6)

To the suspension of **5** (1.401 g, 5.66 mmol, 1.065 GBq) in dry xylene (17 ml) powdered NaOH (1.132 g, 28.3 mmol) and $K_2S_2O_5$ (0.19 g, 0.8 mmol) were added. The mixture was stirred at 160°C under nitrogen allowing to distil slowly, while its volume was kept above 17 ml by adding fresh solvent. Finally it was evaporated up to 10 ml, and KI (0.13 g, 0.78 mmol) was added. A solution of 1-chloro-3-dimethylamino-propane (8.5 mmol) in dry xylene (14 ml) was added dropwise to the stirred reaction mixture at 160°C during one hour and it was refluxed for ten hours, while the water formed in the reaction was retained by "ERSORB" molecular sieve in a "Dean-Stark" tube. The mixture was allowed to cool, then transferred into a separatory funnel, washed with water (15 ml) and extracted with D-tartaric acid (1.313 g, 12.4 mmol) dissolved in water (35 ml). Finally 4.2 ml of conc. NH_4OH was added to the aqueous layer and the separated base was extracted with ligroin (3x20 ml, b.p. 80-90°C). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated to give 1.5 g of a light oil. This oil dissolved in isopropanol (22 ml) was decolourized with charcoal, then maleic acid (0.540 g, 4.65 mmol) was added to the solution. The mixture was evaporated up to 3 ml and after cooling the precipitated white crystals were filtered off, washed with cold isopropanol and dried in vacuo to give 1.468 g (3.24 mmol, 0.615 GBq) of **6**. M.p. 132-134°C. The material showed only one spot by TLC (n-propanol-conc. NH_4OH = 70:30; R_f 0.8).

2-Chloro-12-(3-dimethylamino-2-methylpropyl)-[6-^{14}C]dibenzo-[d,g] [1,3,6]dioxazocine hydrochloride (**7**)

7 was prepared from 1.088 g (4.39 mmol, 0.827 GBq) of **5** as described above, reacting the sodium salt of **5** with 1-chloro-2-methyl-3-dimethylamino-propane. The crude base was dissolved in isopropanol (6 ml), the solution was decolourized with charcoal, and acidified with 16% HCl in isopropanol (3.5 ml). The mixture was evaporated up to a volume of 3 ml. After cooling the separated white crystals were filtered off washed with cold isopropanol, and dried in vacuo to give 1.166 g (3.04 mmol, 0.572 GBq) of **7**. M.p. 177-179°C. The material showed only one spot by TLC (n-butanol-acetic acid-water = 60:25:15; R_f 0.41).

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