THE SYNTHESIS OF TWO ^{14}C-LABELLED HYPOGLYCEMIC BENZENESULPHONYLUREA DERIVATIVES

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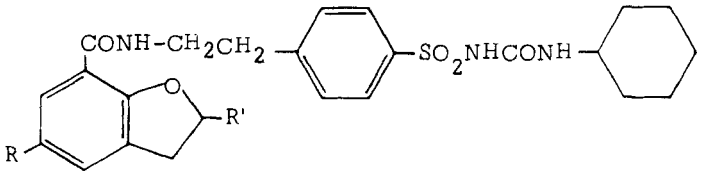
SUMMARY

The synthesis of two carbon-14 labelled oral hypoglycemic benzo(b)furansulphonylureas is described. The starting materials 2,3-dihydrobenzo(b)furan-7-carboxylic acid and 5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-^{14}C-carboxylic acid were prepared in high yield by carbonation of appropriate Grignard reagents. The final products were obtained with specific activities of 49 and 44 mCi/mmole and radiochemical purities of greater than 99%.

Key Words: Carbon-14, Grignard reagents, Carbonation, Benzo(b)furan-7-carboxylic acids.

INTRODUCTION

N-[4-(2-(2,3-dihydrobenzo(b)furan-7-carboxamido)-ethyl)-benzene sulphonyl]-N'-cyclohexylurea (Ia, CS-476) and N-[4-(2-(5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-carboxamido)-ethyl)-benzene sulphonyl]-N'-cyclohexylurea (Ib, CS-261) are two of a series of benzofuran derived benzenesulphonylureas[1] which have been shown to exert a strong hypoglycemic activity after oral administration:

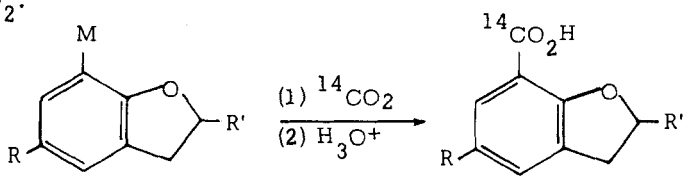


Ia: R = R' = H Ib: R = CH_3O, R' = CH_3

Studies on the metabolism of these compounds in animals and in man required carbon-14 labelled forms of both compounds. Due to the very low therapeutic doses of both compounds it was necessary to synthesise them with high specific activities in order to obtain sufficient sensitivity in the analysis of samples from the metabolism experiments. We were particularly interested in following the metabolic fate of the 2,3-dihydrobenzo(b)furan moiety since the metabolism of the sulphonyl cyclohexylurea group has been studied previously during investigations with other benzenesulphonylureas[2,3]. The carboxamido group attached to the 7-position of the 2,3-dihydrobenzo(b)furan ring system was chosen as a suitable site for labelling.

RESULTS AND DISCUSSION

Incorporation of a carbon-14 label into the desired position of the 2,3-dihydrobenzo(b)furan ring system can be most conveniently achieved by reaction of the corresponding organometallic intermediates (II) with $^{14}CO_2$.

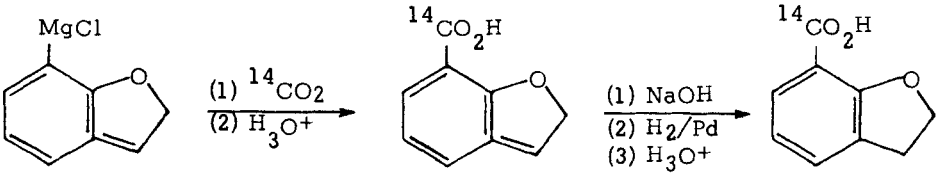


II III

(a) R = R' = H (b) R = CH_3O, R' = CH_3

The Grignard reagent corresponding to the 2,3-dihydrobenzo(b) furan-7-carboxylic acid (IIIa) was not available initially during this work but this acid had previously[1] been prepared in a 54% yield by carbonation of the 7-lithio derivative obtained by metalation of 2,3-dihydrobenzo(b) furan with a substantial excess of the 1:1 molar complex of n-butyllithium and N,N,N',N'-tetramethylethylenediamine (TMEDA). For the radiochemical synthesis it was necessary to use either equimolar amounts of generated $^{14}CO_2$ and organometallic substrate or an excess of the substrate in order to optimise the radiochemical yield. Various experiments were performed using different molar proportions of $^{14}CO_2$, generated in a manifold, and the 7-lithio substrate (IIa, M = Li). Using 4 mmoles of the n-BuLi-TMEDA complex, 3.5 mmoles of 2,3-dihydrobenzo(b)furan and 2 mmoles of $^{14}CO_2$, an average yield of 39%

of the acid (IIIa) was obtained. The yield was not increased when either 4 or 8 mmoles of the 2,3-dihydrobenzo(b)furan was used. Based upon these results an alternative process was investigated involving formation of the Grignard reagent (IV) in tetrahydrofuran with the aid of a small amount of ethylene dibromide and carbonation with carbon dioxide.

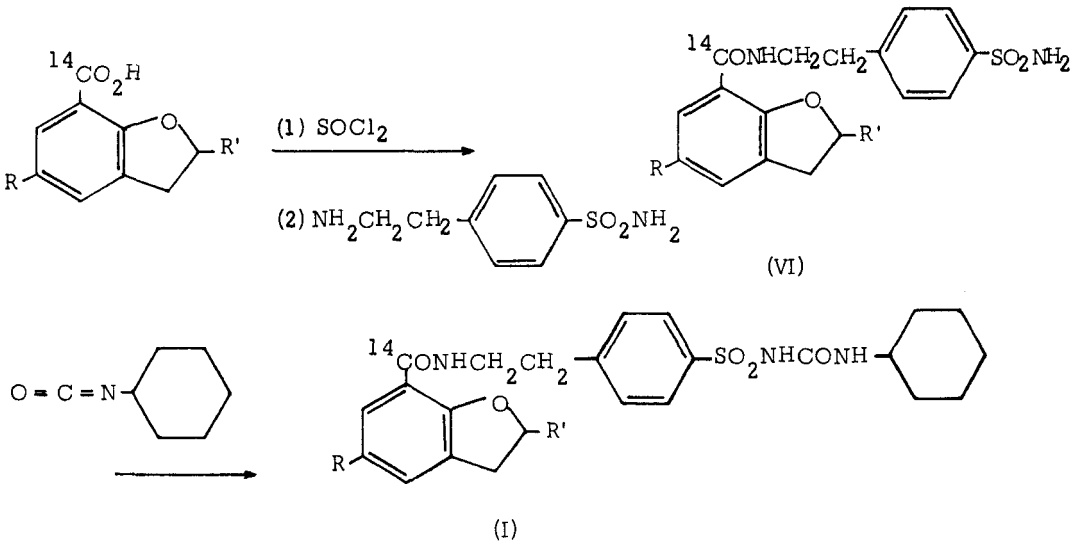


(IV) (V) (IIIa)

The carboxylic acid (V) was obtained in a yield of 74% and was reduced by low pressure hydrogenation (Pd/C catalyst) of a pH 6.5 aqueous solution of its sodium salt to give the 2,3-dihydrobenzo(b)furan-7-carboxylic acid (IIIa) in a yield of 90%. This route gave the highest overall yield and was then used for the radiochemical synthesis. The carbonation of approximately 4 mmoles of the Grignard reagent (IV) gave the ^{14}C-labelled carboxylic acid in a yield of about 89% based on barium ^{14}C-carbonate. The crude acid was reduced to give 2,3-dihydrobenzo(b)furan-7-^{14}C-carboxylic acid (IIIa) in a 97% yield and with a radiochemical purity greater than 96%.

For the preparation of 5-methoxy-2-methyl-2,3-dihydrobenzo(b)-furan-7-^{14}C-carboxylic acid by a similar carbonation procedure it was necessary to obtain a corresponding halogenated derivative. The 7-bromo derivative was prepared from the corresponding carboxylic acid via the isocyanate according to the method of Kricheldorf[6]. Hydrolysis of the isocyanate to the amine and treatment of the corresponding diazonium compound with cuprous bromide gave 7-bromo-5-methoxy-2-methyl-2,3,dihydrobenzo(b)furan. Carbonation of the Grignard reagent (IIb, M = MgBr) with $^{14}CO_2$ gave the carboxylic acid in a yield of about 93% and with a radiochemical purity greater than 95%. This method demonstrates a synthetic route for the preparation of a ^{14}C-carboxylic acid starting from the same unlabelled acid.

Having prepared the ^{14}C-labelled carboxylic acids (III), CS-476 (Ia) and CS-261 (Ib) were obtained using the synthetic route previously described[1] (Scheme). Treatment of the corresponding acid chlorides with 4-(2-aminoethyl)benzenesulphonamide yielded the sulphonamides (VI) and reaction with cyclohexylisocyanate gave ^{14}C-CS-476 (Ia) and ^{14}C-CS-261 (Ib).



(a) R,R' = H

(b) R = O Me, R' = CH_3

Scheme

This procedure furnished the ^{14}C-labelled drugs in overall radiochemical yields from barium ^{14}C-carbonate of 45% (Ia) and 34% (Ib). The specific activities were 104.3 μCi/mg Ia (49.1 mCi/mmole, CS-476) and 86.1 μCi/mg Ib (44.3 mCi/mmole, CS-261). The radiochemical purity of the isolated products, without further purification, was greater than 99% as determined by thin-layer chromatography on silica gel in the solvent system, ethyl acetate: propan-2-ol: ammonia (45:35:20, v/v), and liquid scintillation counting.

Mass Spectra

The partial chemical ionisation mass spectra of unlabelled and ^{14}C-CS-476 are shown in Figures 1 and 2 respectively. These spectra were obtained, using the direct insertion probe, on a VG-Micromass 16F mass spectrometer operating with an ionising voltage of 50 eV and an emission current of 500 or 1000 μA. The probe temperature was 150°C, the source temperature 200°C and isobutane was used as reagent gas. No molecular ion was observed for either CS-476 or CS-261 using either electron impact or chemical ionisation. The highest mass ion recorded corresponded to the fragment resulting from loss of cyclohexylisocyanate. The increase in the intensity of the ion at m/e 249 in the spectrum of the labelled CS-476 reflects the high incorporation (ca. 80%) of carbon-14 giving an increase of two mass units.

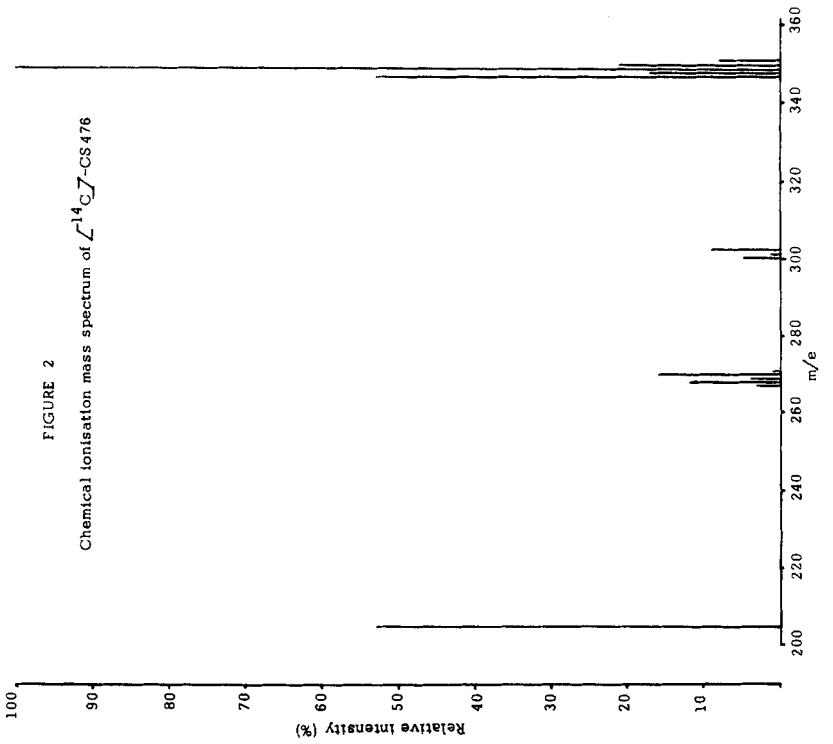


FIGURE 2

Chemical ionisation mass spectrum of ^{14}C-CS476

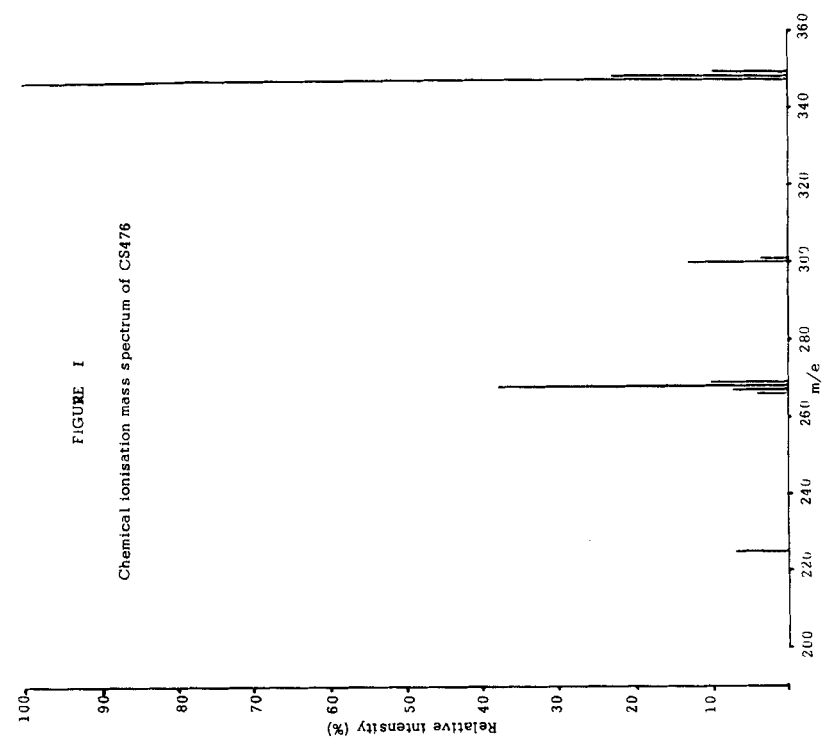


FIGURE 1

Chemical ionisation mass spectrum of CS476

EXPERIMENTAL

Synthesis of CS-476 (Ia)

Lithiation and carbonation of 2,3-dihydrobenzo(b)furan

N,N,N',N'-tetramethylethylenediamine (464.84 mg, 4 mmoles) was added during 10 minutes to a stirred mixture of n-butyllithium (4 mmoles in 1.7 ml hexane) and hexane (1.4 ml). 2,3-Dihydrobenzo(b)furan (402 mg, 3.35 mmoles) was added over 20 minutes at 20 - 25°C. The mixture was stirred at 25°C for 16 hours. The resulting organolithium compound was carbonated at 0°C with CO_2 prepared from barium carbonate (2 mmoles, 394.7 mg). The resulting solution was decomposed with 5% (w/v) sulphuric acid (10 ml) and extracted with ether (3 x 50 ml). The ether extract was extracted with 5% (w/v) sodium hydroxide solution (3 x 20 ml) and the ether layer discarded. The alkaline extract was acidified with 5% (w/v) sulphuric acid, extracted with ether to give 2,3-dihydrobenzo(b)furan-7-carboxylic acid (124.4 mg, 37.9%). The yields are all based on barium carbonate. Repeats of the above experiment gave 43.6% and 36.5% of the acid. Average yield: 39%.

7-Chlorocoumarilic acid

3-Chlorosalicyladehyde[4] (128.5 g), diethyl bromomalonate (195.9 g) and methyl isobutyl ketone (MIBK) were mixed and potassium carbonate (169.8g, dried at 150°C) was added cautiously. The slurry was then stirred under nitrogen at 105°C for 3 hours. The solvent was then distilled off until a heavy paste was formed. The slurry was cooled to 60°C and a solution of sodium hydroxide (131 g) in water (1130 g) was added after which the mixture was heated to refluxing while residual solvent was distilled off. After refluxing for 1 hour the slurry was cooled to room temperature and the sodium salt filtered off, washed with 10% sodium hydroxide solution (3 x 100 ml) and redissolved in water (3000 ml) by heating to reflux. Dilute hydrochloric acid (120 ml 37% hydrochloric acid and 500 g of ice) was added while hot after which the slurry was cooled to room temperature. The crystals were filtered off and washed with water (3 x 150 ml). After drying (at 60°C) the yield of 7-chlorocoumarilic acid was 149.7 g (92.9%), m.p. 245-247°C.

7-Chlorobenzo(b)furan

7-Chlorocoumarilic acid (190 g) was mixed with quinoline (700 ml) and copper powder (9.6 g) after which the mixture was heated under nitrogen to about 217°C (reflux). The evolution of CO_2 started at about 200°C and continued for 30 to 40 minutes. Refluxing was continued for 30 minutes after the gas evolution had ceased. The mixture was cooled to room temperature and benzene (700 ml) added. The copper was filtered off and the benzene solution added to a mixture of 37% hydrochloric acid (500 ml) and crushed ice (1000 ml) while the temperature was maintained below 15°C. The aqueous phase was separated and discarded. The benzene solution was washed once with 2N hydrochloric acid (400 ml), dried (Na_2SO_4), the benzene distilled off and the residue distilled in vacuo. Yield: 120 g (81%),

b.p. 91 - 93°C (12 mm Hg), $n_D^{20} = 1,582$, NMR (CCl_4) δ 6.7 (d,1,H at C-3), 6.9 - 7.8 ppm (m,4,H at C-2 + arom.) showing the complex pattern described earlier[5].

7-Benzo(b)furylmagnesium chloride (IV)

Ethylene dibromide (2 ml) was added to magnesium turnings (10.2 g) in dry tetrahydrofuran (200 ml). The mixture was heated to reflux and a solution of 7-chlorobenzo(b)furan (30.6 g) and ethylene dibromide (5 ml) in dry tetrahydrofuran (40 ml) added at reflux during two hours. Refluxing was maintained for an additional 4 hours after the addition and the reaction mixture was then cooled to room temperature. The Grignard solution was decanted from excess magnesium and assayed by acidimetric titration. Yield: 270 ml 0.64 M solution (86%).

Benzo(b)furan-7-[^{14}C]-carboxylic acid (V)

7-Benzo(b)furylmagnesium chloride (ca. 4 mmole) in tetrahydrofuran was carbonated at 0°C with $^{14}CO_2$, prepared from [^{14}C]-barium carbonate (103 mCi, 51.7 mCi/mmole, 396 mg, 2 mmoles, The Radiochemical Centre, Amersham). The resulting solution was diluted with 5% (w/v) sulphuric acid (20 ml) and extracted with ether (3 x 50 ml). The ether extract was extracted with 10% (w/v) sodium hydroxide solution (3 x 20 ml) and the ether layer discarded. The alkaline extract was acidified with sulphuric acid, extracted with ether, and the organic phase evaporated to give the crude acid (291 mg, 89%).

2,3-Dihydrobenzo(b)furan-[^{14}C]-carboxylic acid (IIIa)

The crude benzo(b)furan-7-[^{14}C]-carboxylic acid (291 mg) was slurried in distilled water (15 ml) and the acid brought into solution by dropwise addition of 50% (w/v) sodium hydroxide. The solution was adjusted to pH 6.5 by addition of 4 M hydrochloric acid. The acid was then hydrogenated at room temperature with 10% (w/w) palladium on charcoal. After 5 hours when uptake of hydrogen was complete, the solution was filtered to remove catalyst, acidified with 5% (v/v) hydrochloric acid, and the solution extracted with ether, and the organic phase evaporated to give 2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxylic acid (284 mg, 86% overall yield). T.l.c. of the product in the solvent system diisopropylether:ethanol:acetic acid (95:5:4, v/v) showed the acid to have a radiochemical purity greater than 96%. Specific activity was 314 μCi/mg.

2,3-Dihydrobenzo(b)furan-7-[^{14}C]-carbonyl chloride

2,3-Dihydrobenzo(b)furan-7-[^{14}C]-carboxylic acid (284 mg) was slurried with isooctane (1.42 ml) and dimethylformamide (5 μl), and to this stirred mixture was added thionyl chloride (190 μl). The mixture was heated slowly to 45°C, stirred for 30 minutes at 45° - 50°C, and then cooled to 0°C. The solvent was decanted from the crystals, which were washed with isooctane (1 ml) and finally dried in a vacuum desiccator.

4-(2-(2,3-Dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl)-benzenesulphonamide (VIa)

4-(2-Aminoethyl)-benzenesulphonamide (346 mg) was dissolved in a mixture of water (2.7 ml), and concentrated hydrochloric acid (165 µl). Dioxan (1.3 ml) was added, the mixture cooled to 5°C and the solution adjusted to pH 9.8. A solution of 2,3-dihydrobenzo(b)furan-7-[^{14}C]-carbonyl chloride (ca. 316 mg) in dioxan (1.3 ml) was added dropwise with stirring while the temperature was maintained at 5 - 10°C and at pH 9.8 by continuous addition of 2 M sodium hydroxide. The slurry was stirred at pH 9.8 and 5°C for another 2 hours and then adjusted to pH 3 by addition of 2 M hydrochloric acid. The slurry was left to stand overnight and the solid filtered off, washed with a mixture of water (0.5 ml), dioxan (0.5 ml) and finally with water (3 x 1 ml). The solid was dried in a vacuum desiccator to give 4-(2-(2,3-dihydrobenzo(b)-furan-7-[^{14}C]-carboxamido)-ethyl)-benzenesulphonamide (472 mg, 78.8%).

N-[4-(2-(2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl-benzenesulphonyl]-N'-cyclohexylurea (CS-476)

4-[2-(2,3-Dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl]-benzenesulphonamide (472 mg), potassium carbonate (415 mg), dry acetone (6.8 ml) and cyclohexyl isocyanate (209 µl), were heated together under reflux with stirring, for 16 hours. The mixture was then filtered and the solid washed with dry acetone (4 x 1 ml). The solid was dissolved in a mixture of water (26.2 ml) and acetone (8.9 ml) and adjusted to pH 9.2 by slow addition of 2 M hydrochloric acid. The solution was filtered and the filtrate poured into a stirred mixture of concentrated hydrochloric acid (394 µl) and water (71 ml). The crystalline precipitate was filtered off, washed with water and dried in a vacuum desiccator to give N-(4-(2-(2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl)-benzene-sulphonyl)-N'cyclohexylurea (443 mg, 69%). Specific activity was 104.3 µCi/mg, and total radioactivity was 46.2 mCi. Thin-layer chromatography in ethyl acetate:propan-2-ol:ammonia (45:35:20, v/v) and liquid scintillation counting showed the product to have a radiochemical purity greater than 99%.

Synthesis of CS-261 (Ib)

5-Methoxy-2-methyl-2,5-dihydrobenzo(b)furan-7-isocyanate (prepared by the method of Kricheldorf[6]

5-Methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-carbonyl chloride[1] (126 g, 0.55 mole) was added to a solution of trimethylsilylazide (73.5 g, 0.63 mole) in benzene (500 ml) at room temperature. The reaction mixture was heated and stirred at 70°C for 5 hours. The reaction mixture was heated and stirred at 70°C for 5 hours. The reaction mixture was evaporated *in vacuo* at 50°C and the residue of crude 5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-isocyanate (112 g) was used in the next step without further purification. IR-spectroscopy of the product showed a very strong band at 2250 cm^{-1} characteristic of the isocyanate group and only a very weak band at 2150 cm^{-1} characteristic of the azide group.

7-Amino-5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan

A stirred solution of 5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-isocyanate (100g, 0.49 mole) in THF (100 ml) was added slowly to conc. HCl (1000 ml). The temperature raised to 58°C and the reaction mixture was then cooled to 40°C and kept at this temperature for about 1 hour (until the nitrogen evolution ceased). The mixture was then stirred at 50°C for an additional hour followed by evaporation to dryness. The crystalline residue was recrystallised from isopropanol, m.p. 221°C, yield 67.4 g (64%). NMR ($(CD_3)_2SO$) δ 1.41 (d,3,CH_3), 2.7 - 3.5 (m,2,H at C-3), 3.7 (s,3, CH_3O), 4.6 - 5.2 (m,1,H at C-2), 6.8 - 7.0 (m,2,arom.), 9.7 - 10.2 ppm (broad s,3,NH_3^+).

7-Bromo-5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan

7-Amino-5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan hydrochloride (65 g, 0.30 mole) was dissolved in water (1000 ml). The aqueous solution was adjusted to pH 12 and extracted with chloroform (2 x 300 ml), the organic layers dried (Na_2SO_4) and evaporated to dryness. The free base, 7-amino-5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan, (52.3 g, 0.29 mole) was suspended in water (360 ml) and concentrated sulphuric acid (30.4 ml) was added and the resulting solution was cooled to 0 - 5°C. Sodium nitrite (20.0 g, 0.29 mole) dissolved in water (40 ml) was added slowly while the temperature was kept below 5°C.

In a flask arranged for steam distillation was placed a solution of cuprous bromide (41.6 g, 0.29 mole) in hydrobromic acid (196 ml, 48%). This solution was heated and steam distilled during the slow addition of the diazonium solution prepared above. The distillate was extracted twice with ether and the ether extract was washed once with 2 N sodium hydroxide solution, once with water, dried and evaporated. The liquid residue (38.9 g) was distilled and the fraction boiling at 103°C at 0.1 mm Hg was collected. Yield: 24.9 g (36%). Anal. calcd. for $C_{10}H_{11}O_2Br$: C, 49.40; H, 4.57; O, 13.16. Found: C, 49.39; H,4.53; O, 13.29.

5-Methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-magnesium bromide

The bromide (from above) was easily converted to the corresponding Grignard reagent in tetrahydrofuran. Yield 83%.

5-Methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxylic acid (IIIb)

5-Methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-magnesium bromide (ca. 4 mmole) in tetrahydrofuran (10 ml) was carbonated at 0°C with $^{14}CO_2$, prepared from [^{14}C]-barium carbonate (87 mCi, 51.7 mCi/mmole, 338 mg, 1.71 mmole, The Radiochemical Centre, Amersham). The resulting solution was diluted with 5% (w/v) sulphuric acid (20 ml) and extracted with ether (3 x 50 ml). The ether extract was extracted with 10% (w/v) sodium hydroxide (3 x 20 ml) and the ether layer discarded. The alkaline extract was acidified with sulphuric acid, extracted with ether and the

organic phase evaporated to give the acid (330.6 mg, 93%). T.l.c. of the product in the solvent system diisopropylether:ethanol:acetic acid (95:5:4, v/v) showed the acid to have a radiochemical purity greater than 95%.

5-Methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carbonyl chloride

5-Methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxylic acid (330.6 mg) was slurried with isooctane (2.4 ml) and dimethylformamide (5 µl), and to this stirred mixture, thionyl chloride (184 µl) was added. The mixture was heated slowly to 45°C, stirred for 30 minutes at 45 - 50°C and then cooled to 0°C. The solvent was decanted from the crystals, which were washed with isooctane (1 ml) and finally dried in a vacuum desiccator.

4-[2-(5-Methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl]-benzenesulphonamide (VIb)

4-(2-Aminoethyl)-benzenesulphonamide (311.7 mg) was dissolved in a mixture of water (2.4 ml), dioxan (432.7 mg) and concentrated hydrochloric acid (138.5 µl). The solution was cooled to 5°C and the pH adjusted to 9.8 by addition of 4 M sodium hydroxide. A solution of 5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carbonyl chloride (ca. 352.8 mg) in dioxan (1.9 g) was added dropwise with stirring while the temperature was maintained at 5 - 10°C and at pH 9.8 by continuous addition of 2 M sodium hydroxide. The slurry was stirred at 5°C and pH 9.8 for a further 2 hours and then the pH adjusted by addition of 2 M hydrochloric acid to pH 3. The solid was filtered, washed with water and dried in a vacuum desiccator to give 4-(2-(5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl)-benzenesulphonamide (510.51 mg, 84%).

N-[4-(2-(5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl)-benzenesulphonyl]-N'-cyclohexylurea (CS-261)

4-(2-(5-Methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl)-benzenesulphonamide (510.51 mg), potassium carbonate (402 mg), dry acetone (10.4 ml) and cyclohexylisocyanate (200.1 µl) were heated together under reflux with stirring, for 16 hours. The mixture was then filtered and the solid washed with dry acetone (4 x 1 ml). The solid was dissolved in a mixture of water (26.1 ml) and acetone (6.1 ml) and the pH of the solution adjusted to pH 9.2 by slow addition of 2 M hydrochloric acid. The solution was filtered and the filtrate poured into a stirred mixture of concentrated hydrochloric acid (370 µl) and water (43.6 ml). The crystalline precipitate was filtered off, washed with water and dried in a vacuum desiccator to give N-[4-(2-(5-methoxy-2-methyl-2,3-dihydrobenzo(b)furan-7-[^{14}C]-carboxamido)-ethyl)-benzenesulphonyl]-N'-cyclohexylurea (342.12 mg, 51%) of specific activity 86.12 µCi/mg, and total activity 29.46 mCi. Thin-layer chromatography in ethyl acetate:propan-2-ol:ammonia (45:35:20, v/v) and liquid scintillation counting showed the product to have a radiochemical purity greater than 99%.

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