

SYNTHESIS OF 1-[2-HYDROXY-4-(3-SULFO-1-PROPYLOXY)-PHENYL]-3-(3-HYDROXY-4-METHOXYPHENYL)-PROPAN-1-ONE-1-¹⁴C SODIUM SALT

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SUMMARY

1-[2-hydroxy-4-(3-sulfo-1-propyloxy)-phenyl]-3-(3-hydroxy-4-methoxyphenyl)-propan-1-one sodium salt labelled with ¹⁴C at its carbonyl group (1) was synthesized starting from sodium acetate-1-¹⁴C through acetyl chloride-1-¹⁴C, resacetophenone-carbonyl-¹⁴C (2), 2-hydroxy-4-(3-sulfo-1-propyloxy)-acetophenone-carbonyl-¹⁴C sodium salt (3) and 1-[2-hydroxy-4-(3-sulfo-1-propyloxy)-phenyl]-3-(3-hydroxy-4-methoxyphenyl)-2-propen-1-one-1-¹⁴C (4).

Key Words: acetyl-chloride-1-¹⁴C, Resacetophenone-carbonyl-¹⁴C

INTRODUCTION

1-[2-Hydroxy-4-(3-sulfo-1-propyloxy)-phenyl]-3-(3-hydroxy-4-methoxyphenyl)-propan-1-one (1) is an artificial sweetening agent possessing very high LD₅₀ value (50000 mg/kg).¹ For investigating its pharmacokinetical properties as well as its metabolism the ¹⁴C labelled compound was needed.

SYNTHESIS

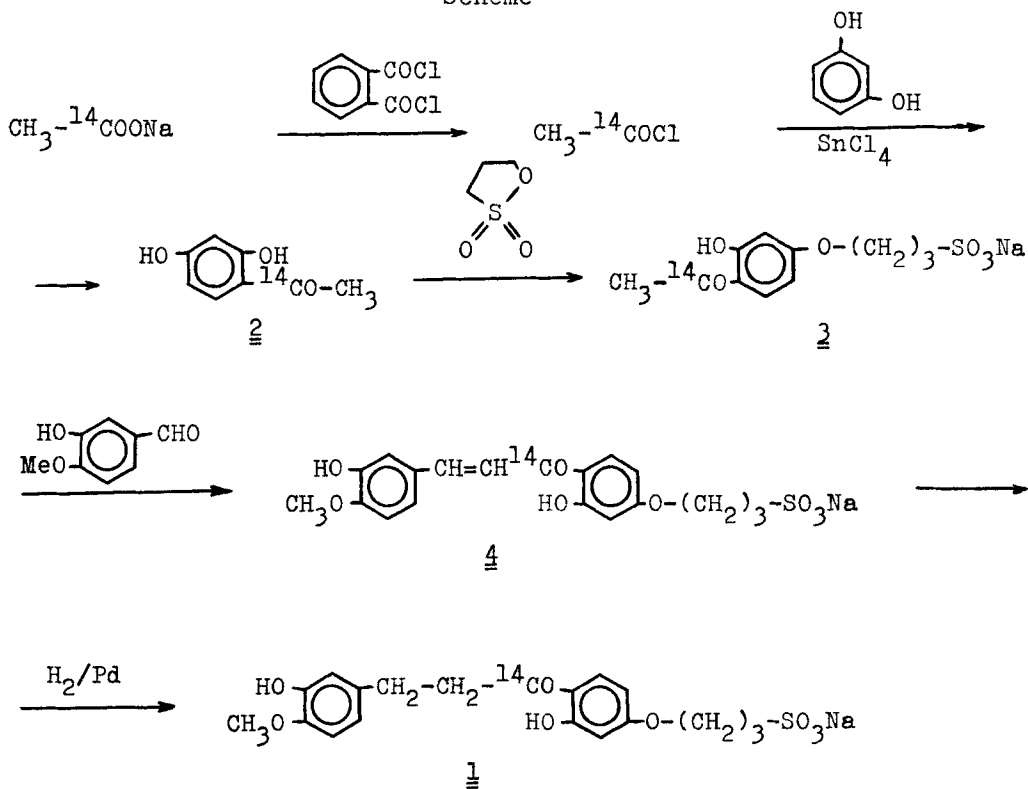
The synthesis of 1 labelled with ¹⁴C at its carbonyl group was performed starting from sodium acetate-1-¹⁴C which was converted into acetyl chloride-1-¹⁴C by the modified method of Cox² using phthaloyl dichloride instead of benzoyl chloride. The acetyl

chloride- $1-^{14}\text{C}$ obtained was then reacted with resorcine by a newly elaborated method using SnCl_4 in benzene to give resacetophenone-carbonyl- ^{14}C (2) in good yield.*

The further steps of the synthesis were performed following the described method.¹ Thus 2 was reacted with propane sultone to give 2-hydroxy-4-(3-sulfo-1-propyloxy)-acetophenone-carbonyl- ^{14}C sodium salt (3). This was then condensed with isovanilline to a chalcone (4) which was hydrogenated in the presence of palladium-charcoal catalyst to the required 1.

The overall radiochemical yield was 18 %.

Scheme



* The known synthesis of resacetophenone³ uses ZnCl_2 as catalyst in acetic acid. As acetic acid can not be used in our synthesis, the reaction was repeated in benzene as solvent, but under these reaction conditions the yields of resacetophenone decreased to about 30-40 %.

EXPERIMENTAL

Melting points are uncorrected. Thin layer chromatography was carried out on 5x20 cm plates coated with Kieselgel FF₂₅₄₊₃₆₆ (MERCK). The spots were detected in UV light and with a Berthold LB 2723 Scanner. Radioactivity was measured with a Packard Tri-Carb liquid scintillation instrument.

Acetyl chloride-1-¹⁴C

The apparatus consisted of a reaction flask equipped with a hydrogen inlet and a short cold-finger reflux condenser with a vent situated at the upper part of the condenser. The vent was attached to a trap. Sodium acetate-1-¹⁴C (820 mg, 10 mmoles, 90.4 mCi = 3.34 GBq) was placed into the flask and phthaloyl dichloride (5 ml) was added in one portion at ambient temperature. The trap was cooled with liquid nitrogen and a low stream of hydrogen was passed through the system. The flask was then heated to 170°C during a period of 30 minutes and maintained at this temperature for 2.5 hours. At the end of the reaction, the trap was detached from the reaction flask, attached to a vacuum line and its content was distilled into a small flask by vacuum transfer. Thus 735 mg (9.36 mmoles, 84.6 mCi = 3.13 GBq) of acetyl chloride-1-¹⁴C were obtained as colourless liquid. Yield: 93.6 %.

Resacetophenone-carbonyl-¹⁴C (2)

Resorcine (1.10 g, 10 mmoles) and benzene (10 ml) were placed in a 100 ml round-bottomed flask. The flask was cooled with liquid nitrogen, evacuated and acetyl chloride-1-¹⁴C (735 mg, 9.36 mmoles, 84.6 mCi = 3.13 GBq) was added by vacuum transfer. The pressure in the flask was then allowed to rise to normal pressure, a further portion of benzene (10 ml) was added and the mixture was warmed to room temperature. SnCl₄ (3.5 ml) was added and the stirred mixture was refluxed for 4 hours. After cooling, 1N HCl (20 ml) was added, the mixture was stirred for 45 minutes

at room temperature and then poured onto a mixture of chloroform and isopropanol (4:1) (50 ml). The separated aqueous layer was extracted with 3x20 ml of chloroform-isopropanol (4:1) mixture. The combined organic extracts were washed with 25 % NaCl solution (2x25 ml), dried over Na_2SO_4 and the solvent was evaporated. The dark-brown low-melting (about 120-130°C) residue obtained (1.546 g, more than 100 %) showed only one active spot (R_f 0.35) on TLC (hexane-benzene-acetone 4:2:1), but it contained resorcine (R_f 0.25) and some immobile coloured impurities. It was purified by vacuum sublimation at 1 mmHg pressure at 120°C.

The obtained white crystals (M.p.: 125-135°C) of 2 (1.336 g, 8.8 mmole, 94 %) still contained some resorcine.* This impurity did not lower significantly the yield of the next steps. Molar activity: 8.14 mCi/mmole (lower than the calculated one: 9.04 mCi/mmole = 334 MBq/mmole). Total activity: 71.5 mCi = 2.64 GBq. Radiochemical yield: 79 %.

2-Hydroxy-4-(3-sulfo-1-propyloxy)-acetophenone-carbonyl-¹⁴C sodium salt (3)

To a solution of 2 (1.336 g, 8.8 mmoles, 71.5 mCi = 2.64 GBq) in methanol (15 ml) sodium methoxide (prepared from 243 mg of sodium) in 15 ml of methanol was added. The mixture became dark. Then propane sultone (1.22 g, 10.0 mmoles) in methanol (10 ml) was added. The stirred mixture was refluxed for 3 hours. Then methanol was evaporated and the residue was suspended in acetone (5 ml), filtered off and washed with acetone (5 ml) and petroleum ether (3x5 ml). A light-brown powder (1.927 g, 6.51 mmoles) was obtained which showed only one active spot beside some inactive ones on TLC (chloroform-methanol-water 35:15:1.5). Molar activity: 4.88 mCi/mmole = 180 MBq/mmole,** total activity: 31.75 mCi = 1.17

* The material can be further purified by recrystallisation from water or by column chromatography. Pure 2 melts at 143-144°C.

** The very low molar activity was a consequence of inactive impurities.

GBq. Yield (calculated from radioactivity): 44 %.*

2',3-Dihydroxy-4-methoxy-4'-(sulfo-1-propyloxy)-chalcone-
-carbonyl-¹⁴C sodium salt (4)

A mixture of 3 (1.927 g, 31.75 mCi), isovanilline (1.0 g, 6.57 mmoles) and NaOH (2.08 g, 52 mmoles) in 9 ml of water was stirred for 3 days at room temperature. A yellow paste was obtained. This was cooled with ice, then it was acidified with conc. HCl (about 4.5 ml) to pH 3. The mixture became a clear red solution, then yellow crystals precipitated and at last a yellow paste was obtained again.

It was kept in a refrigerator overnight then the crystals were separated by centrifugation, washed with ice water (5 ml), acetone (3x10 ml) and petroleum ether, when 1.258 g of 6 were obtained with 6.87 mCi/mmole = 254 MBq/mmole molar activity (total activity: 20.1 mCi = 743 MBq). After recrystallization from 6 ml of water, 990 mg of 4 were obtained as a yellow powder (molar activity: 8.47 mCi/mmole = 313 MBq/mmole, total activity: 19.5 mCi = 721 MBq). Yield: 61.5 %. The material showed only one spot by TLC (chloroform-methanol-water 35:15:1.5, R_F 0.4).

1-[2-Hydroxy-4-(3-sulfo-1-propyloxy)-phenyl]-3-(3-hydroxy-4-
-methoxy-phenyl)-propan-1-one-1-¹⁴C sodium salt (1)

A solution of compound 4 (990 mg, 2.3 mmoles, 19.5 mCi = 721 MBq) in water (10 ml) was hydrogenated at 60°C in the presence of Pd/C catalyst (purchased from Engelhardt). After the calculated amount of hydrogen (55 ml) was consumed, the catalyst was filtered off from the hot solution and on cooling white crystals separated. The mixture was kept in a refrigerator overnight and after filtration 793 mg of 1 were obtained. The molar activity (8.86

* Our yields differ from the described one,¹ because the intermediates often contained inorganic salts and our yields are calculated not on the weight, but on the measurement of radioactivity. Using pure resacetophenone the yield is about 50-55 %.

mCi/mmole = 327 MBq/mmole) was in good agreement with the calculated one (9.04 mCi/mmole = 334 MBq/mmole). Specific activity: 20.51 mCi/g = 759 MBq/g, total activity: 16.26 mCi = 602 MBq. Yield: 81 %. The purity of 1 was checked by TLC (ethyl acetate-ethanol 1:1, R_f 0.4) and the R_f proved to be identical to the inactive material.

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