NOTE

SYNTHESIS OF 5-ACETYLSPIRO[BENZOFURAN-2(3H),1'-CYCLOPROPAN]-3-[^{14}C]ONE (AG-629-^{14}C)

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During the course of studies of the relationship between structure and biological activity of spiro[benzofuran-2(3H),1'-cyclopropan]-3-one derivatives,[1] 5-acetylspiro[benzofuran-2(3H),1'-cyclopropan]-3-one (AG-629) was found to have both curative and prophylactic effects on the experimental chronic and acute gastric ulcers.[2] This paper deals with the synthesis of 5-acetylspiro-[benzofuran-2(3H),1'-cyclopropan]-3-[^{14}C]one (VI).

Esterification of [carboxyl-^{14}C]salicylic acid (I) by the reaction with dimethylsulfate in the presence of $NaHCO_3$, followed by acetylation with acetic anhydride in the presence of a small amount of $HClO_4$, led to methyl acetyl-[carboxyl-^{14}C]-salicylate (III) in almost quantitative yield based on I. The Fries rearrengement of III by treating with anhydrous $AlCl_3$ gave methyl 5-acetyl-[carboxyl-^{14}C]-salicylate (IV) in 73.5 % yield based on I. Condensation of IV with α-bromo-γ-butyrolactone in the presence of K_2CO_3 led to α-[(4-acetyl-2-methyloxy-[^{14}C]-carbonylphenyl)oxy]-γ-butyrolactone (V) in 48 % yield based on I.

VI having a specific activity of 1115 MBq/mmol was obtained via the decarboxylation of V in the presence of halide ions by an application of the method described for the preparation of cyclopropyl ketones.[3]

The overall radiochemical yield was 31 % and the radiochemical purity of VI was determined to be 99.8 % by the HPLC and 99.5 % by the radio-TLC methods.

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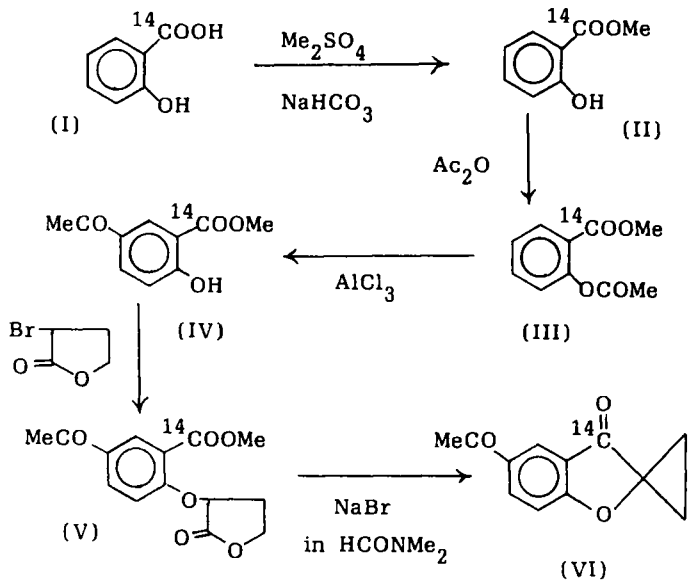

EXPERIMENTAL

Methyl [carboxyl-^{14}C]salicylate (II)

A mixture of 1688 MBq (1.5 mmol) of [carboxyl-^{14}C]salicylic acid (I), $NaHCO_3$ (153 mg) and dimethylsulfate (0.175 ml) in acetone (5 ml) was refluxed at 80° C for 3 h and then evaporated to dryness. To the residue was added water (20 ml) and the mixture was extracted with CH_2Cl_2 twice. The extract was washed with 10 % $NaHCO_3$, followed by water and dried over anhydrous Na_2SO_4. Evaporation of the extract left an oil which was used at next step without purification.

Methyl acetyl-[carboxyl-^{14}C]salicylate (III)

A mixture of II, acetic anhydride (1.2 ml) and a drop of 60 % $HClO_4$ was stirred at room temperature for 1 h. To the mixture was added water (6 ml). After allowing to stir at room temperature for an additional 1 h, the resulting mixture was extracted with CH_2Cl_2 twice. The extract was washed with 10 % $NaHCO_3$, then with water and dried over anhydrous Na_2SO_4. Evaporation of the extract left a residue which was chromatographed on silica gel using CH_2Cl_2 as eluent. Evaporation of the product fractions left a residue (285 mg) as III in almost quantitative yield.

Methyl 5-acetyl-[carboxyl-^{14}C]salicylate (IV)

To a solution of III (285 mg) in CH_2Cl_2 (5 ml) was added anhydrous $AlCl_3$ (480 mg, analytical grade: Wako Purechemicals) and stirring at room temperature overnight. To the mixture was added a small amount of ice, followed by water (20 ml) and conc HCl (2 ml) with stirring. The resulting mixture was extracted with CH_2Cl_2 twice. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated. The residue was passed through a silica gel column and eluted with CH_2Cl_2. Evaporation of the product fractions left white crystals (214 mg) as IV (yield: 73.5 % based on I).

α-[(4-Acetyl-2-methyloxy-[^{14}C]carbonylphenyl)oxy]-γ-butyrolactone (V)

After a mixture of IV (214 mg), K_2CO_3 (290 mg) and acetone solution (2 ml) containing α-bromo-γ-butyrolactone (175 mg) was heated at 70 ° C for 7 h, additionally, K_2CO_3 (145 mg) and α-bromo-γ-butyrolactone (175 mg) were added. The mixture was heated at 70° C for an additional 7 h with stirring and then concentrated in vacuo. To the residue was added water (20 ml) and the resulting mixture was extracted with AcOEt twice. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated to give a residue which was chromatographed on silica gel (50 ml) using CH_2Cl_2-AcOEt (100:15, v/v) as eluent.

Evaporation of the product fractions left colorless crystals (205 mg, yield: 49 % based on I).

5-Acetylspiro[benzofuran-2(3H),1'-cyclopropan]-3-[^{14}C]one (VI)

In anhydrous dimethylformamide (3 ml) containing 1,8-diazabicyclo[5,4,0]-7-undecene was dissolved NaBr (80 mg) by heating at 150° C under nitrogen stream. To the solution was added V (205 mg) in dimethylformamide (3 ml). The mixture was heated at 150° C for 2 h with stirring and then evaporated in vacuo. To the residue was added water (20 ml) and the resulting mixture was extracted with AcOEt. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated to afford a residue, which was chromatographed on

silica gel (50 ml) using CH_2Cl_2-AcOEt (100:8, v/v) as eluent. Evaporation of the product fractions left colorless crystals (108 mg). The product was purified by dissolving in AcOEt (0.5 ml) and addition of hexane (1.1 ml). After allowing to stand for 2 h in a refrigerator, colorless needles (96 mg) as VI were collected by filtration and dried. Identity of VI was confirmed by both its Rf-value on the TLC and its retention time of the HPLC with that of an authentic sample. The specific activity of VI was 1115 MBq/mmol and the overall radiochemical yield was 31 % (528 MBq). The radiochemical purity was found to be 99.8 % by the HPLC and 99.5 % by the radio-TLC methods.

Analytical procedure

The high performance liquid chromatography (HPLC) equipped with an UV-detector (254 nm) and a 4 x 250 mm column of Nucleosil 10C-18 was operated as follows: temperature 22° C, mobile phase MeOH-H_2O (7:4, v/v), flow rate 0.8 ml/min, pressure 90 Kg/cm^2. The radiochemical purity was determined by counting the radioactivity in each effluent of the HPLC (120 ul collection) using an Aloka liquid scintillation spectrometer and found to be 99.8 % in the peak which corresponded to the retention time (5.85 min) of VI. The radio-thin-layer chromatography analysis was carried out on a silica gel plate (F-254 precoated, 20 cm, Merck) in the two developing solvent systems as follows:
(a) benzene-ethyl acetate-acetic acid (4:1:0.1, v/v; Rf of VI, 0.56)
(b) ethyl acetate-dichloromethane (2:25, v/v; Rf of VI, 0.41).
The instrument for radioscanning was used an Aloka radiochromatogram TLC-101.

REFERENCES

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