SYNTHESIS OF 3-[2',4',5'-TRIETHOXYBENZOYL-(CARBONYL-^{14}C)] PROPIONIC ACID (AA-149-^{14}C)

Nobuyoshi Hayashi, Tadashi Toga and Tadakazu Murata
Central Research Division, Takeda Chemical Industries, Ltd., Juso, Higashiyodogawa-ku, Osaka, Japan
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SUMMARY

The synthesis of 3-[2',4',5'-triethoxybenzoyl-(carbonyl-^{14}C)]-propionic acid (VII) is described. Chloroacetonitrile-^{14}C (IV) was prepared from chloroacetic-1-^{14}C acid (I) according to the well-known procedure. IV was reacted with 1,2,4-triethoxybenzene in the presence of $ZnCl_2$ and HCl, and the resulting ketoimine hydrochloride was hydrolyzed to 2',4',5'-triethoxyphenacyl-(carbonyl-^{14}C) chloride (V) in 66.5% yield. VII was obtained in 66% from ethyl [2',4',5'-triethoxyphenacyl-(carbonyl-^{14}C)] malonate (VI) which had been prepared in 57% from V by an application of malonic ester synthesis. The overall radiochemical yield from I to VII was 11.2%.

3-(2',4',5'-Triethoxybenzoyl)propionic acid (AA-149)[1], a new spasmolytic agent for common bile duct, has been found in our research laboratories from among dozenes of polyoxybenzene derivatives. This compound has been shown to possess the potent smooth muscle relaxing activity on the Oddi's sphincter and gall bladder as well as choleretic action in dogs[1]. In order to further investigate the metabolic fate in animals, especially of the triethoxybenzoyl moiety, AA-149 labelled at the benzoyl-(carbonyl-^{14}C) position has been synthesized. The synthetic route used to prepare 3-[2',4',5'-triethoxybenzoyl-(carbonyl-^{14}C)] propionic acid (VII)

is shown in Chart 1. Chloroacetamide-1-^{14}C (III) was obtained by the reaction of aqueous ammonia with ethyl chloroacetate-1-^{14}C (II) which had been prepared from chloroacetic-1-^{14}C acid (I) according to the well-established procedure[2,3]. The dehydration of III was effected by heating the mixture with P_2O_5 to give chloroaceto-nitrile-1-^{14}C (IV)[4] in a quantitative yield. IV was allowed to react with 1,2,4-triethoxybenzene by bubbling HCl in the presence of $ZnCl_2$, and the resulting ketoimine hydrochloride was hydrolyzed to 2',4',5'-triethoxyphenacyl-(carbonyl-^{14}C) chloride (V) in a yield of 66.5%. Ethyl [2',4',5'-triethoxyphenacyl-(carbonyl-^{14}C)]-malonate (VI) was prepared in 57% yield by condensing V with ethyl malonate in the presence of NaH. Hydrolysis and decarboxylation of VI at refluxing temperature in a mixture of acetic acid, aqueous HCl and dioxane afforded the final product VII in 66% yield. The overall radiochemical yield from I to VII was 11.2%. The purity of VII was 99% on the basis of radiochromatography and isotope dilution method.

EXPERIMENTAL

Chloroacetic-1-^{14}C acid (I)

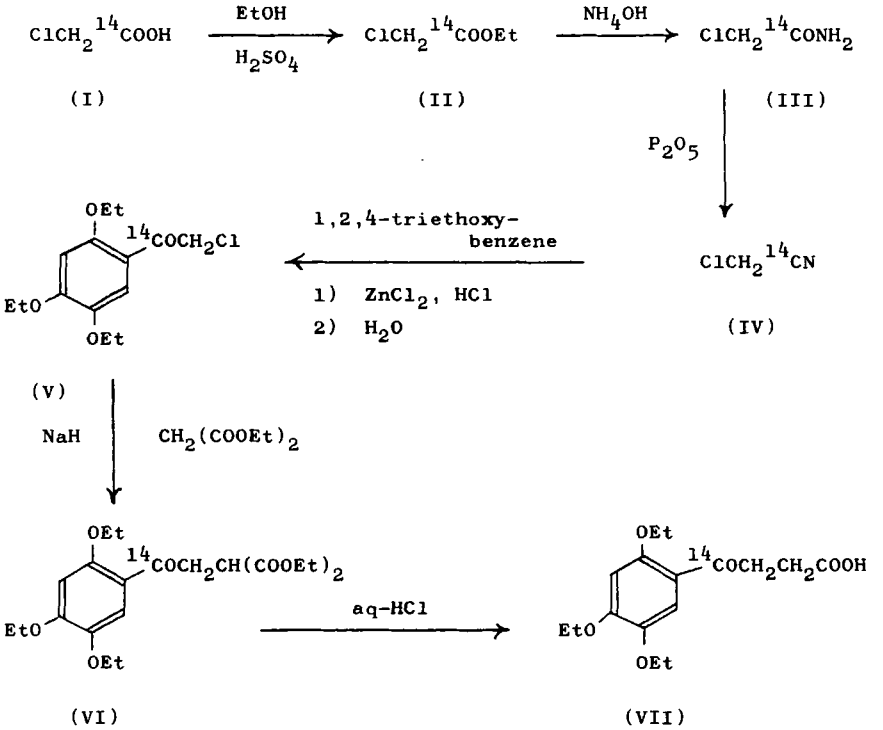
Chloroacetic-1-^{14}C acid (45 mCi, specific activity 49 mCi/mmol) purchased from The Radiochemical Centre, Amersham, England was diluted with unlabelled chloroacetic acid (total weight: 1134 mg).

Ethyl chloroacetate-1-^{14}C (II)

To a solution of 1134 mg (45 mCi) of I in 0.9 ml of anhydrous EtOH was added slowly 0.1 ml of H_2SO_4, and the mixture was refluxed for 6 h, cooled and diluted with ice water. The resulting solution was then extracted with several portions of ether, and the combined

Chart 1

Synthesis of 3-[2',4',5'-triethoxybenzoyl-(carbonyl-^{14}C)]-propionic acid



extract was washed with water, dried over Mg_2SO_4 and evaporated to give II (1192 mg, 81%).

Chloroacetamide-1-^{14}C (III)

A mixture of 1192 mg of II and 2.2 ml of 28% NH_4OH was stirred at -10 - 0° and stored for 1 h at 0°. The crystalline product was filtered off, washed with cold water and dried (453 mg, 50%).

Chloroacetonitrile-1-^{14}C (IV)

III (453 mg) was mixed with 692 mg of P_2O_5 in a microdistillation apparatus. The dehydration was effected by heating the mixture for 10 min at 140-150°. The cold finger was cooled to -50°, and the product was distilled under reduced pressure (30 mmHg) at a bath temperature of 180° (308.6 mg, 84%).

2',4',5'-Triethoxyphenacyl-(carbonyl-^{14}C) chloride (V)

Anhydrous HCl gas was bubbled for 3 h through a mixture of 308.6 mg of IV, 1.8 ml of 1,2,4-triethoxybenzene, 8 ml of anhydrous ether and 400 mg of anhydrous $ZnCl_2$ cooled in a dry ice-acetone bath at -20°. The resulting mixture was allowed to stand overnight in a freezer to precipitate a violet solid. After being collected and washed with ether, the solid was dissolved in 10 ml of water and the aqueous solution was heated for 1 h at 80-90°. The precipitated crystals were filtered off, washed with water and then recrystallized from 80% aqueous acetone (v/v) to afford 999 mg of V as fine crystals. The product was confirmed by the identity of its physico chemical properties: mp alone or mixed with 2',4',5'-triethoxyphenacyl chloride, 115-116° (Kofler block). Infrared spectrum (KBr, Hitachi Model-215), 1660 cm^{-1} (CO streching). T.l.c., Rf 0.7 (silicagel spot film f, Tokyokasei Ltd. Developing solvent, MeOH).

Ethyl [2',4',5'-triethoxyphenacyl-(carbonyl-^{14}C)] malonate (VI)

To a solution prepared by dissolving 200 mg of NaH (50% oil dispersion) in a mixture of 20 ml of anhydrous C_6H_6 and 0.6 ml of diethyl malonate was added 999 mg of V in 5 ml of C_6H_6, and then the solution was heated at 60-65° for 2 h with stirring. The solvent was evaporated in vacuo, and the residue was dissolved in 10 ml of EtOH. The resulting solution was diluted with water and

allowed to stand overnight in a refrigerator. The precipitated crystals were filtered off and washed with water. Recrystallization from 15 ml of EtOH provided 811 mg (57% yield) of fine crystals, mp alone or mixed 97-98° (Kofler block) and Rf 0.77 on t.l.c. [Silicagel spot film f, Tokyokasei Ltd., developing solvent, C_6H_6 : $CHCl_3$ (9 : 1, v/v)], identical with that of authentic unlabelled ethyl (2',4',5'-triethoxyphenacyl) malonate.

3-[2',4',5'-Triethoxybenzoyl-(carbonyl-^{14}C)] propionic acid (VII)

A solution of 811 mg of VI in a mixture of 14 ml of dioxane, 7 ml of AcOH and 7 ml of 4N-HCl was refluxed for 7.5 h on an oil bath (125-130°) and then allowed to stand overnight at room temperature. The mixture was diluted with 100 ml of water. The precipitated crystals were filtered off, washed with water and dissolved in 46 ml of 5% aqueous NaOH. The alkaline solution was washed with several portions of AcOEt, and the organic layer was extracted with 5% aqueous NaOH. The combined alkaline solution was acidified with HCl to give the product VII. Recrystallization from 50% aqueous EtOH provided 418.5 mg (66% yield) of fine needles, mp alone or mixed 145-146° (capillary tube), Rf 0.77 on t.l.c., [silicagel spot film f, Tokyokasei Ltd., developing solvent, MeOH : $CHCl_3$ (1:4, v/v)], identical with that of authentic unlabelled AA-149. Specific activity, 3.74 mCi/mmol. Total activity, 5.05 mCi. The overall radiochemical yield was 11.2% based on I.

Radioactivity

A liquid scintillator was prepared by dissolving 4 g of PPO (2,5-diphenyloxazole) and 100 mg of dimethyl-POPOP (1,4-bis [2-(4-methyl-5-phenyloxazolyl)] benzene) in 1 L of toluene. A sample solution was prepared by dissolving 0.1 mg of the counting sample

in 100 ml of toluene. A mixture of 15 ml of the liquid scintillator and 1 ml of the sample solution was counted in Aloka LSC-502 liquid scintillation spectrometer with five channel systems and automatic channel ratio computor. Absolute counting efficiency was determined in comparison with a standard calibration curve by the external standard method. The radiochromatograms were checked by means of Aloka thin-layer chromatogram scanner (Model TRM-1B). The purity of VII was measured by the isotope dilution method as follows: A sample of 0.680 mg of VII (specific activity, 26762295 dpm/mg) was mixed with 13.055 mg of authentic unlabelled AA-149, and the mixture was recrystallized triply from 50% aqueous EtOH. The activity of diluted VII was 1309798 dpm/mg and the purity of VII was shown to be 99%.

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