NOTE

Synthesis of ^{14}C -Labelled Propranolol Hydrochloride, 1-Isopropylamino-3-(1-naphthoxy) propane-2-ol-1- ^{14}C Hydrochloride†

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Propranolol hydrochloride (I) is a well-known β -adrenergic blocking agent which is used clinically for the treatment of cardiac arrhythmias, angina pectoris and hypertension^{1,2)}. ^{14}C -Labelled propranolol hydrochloride was required for its metabolic studies. In this paper we describe the synthesis of the agent labelled at C-1 of the amino-propane chain.

1. Discussion

The large-scale preparation of propranolol hydrochloride (I) is carried out by condensation of 1-naphthol with 1-chloro-2, 3-epoxypropane followed by isopropylation

of the resulting epoxide (V)¹⁾ as shown in Fig. 1. The incorporation of ^{14}C into the desired position (C-1) by utilizing this procedure an effective synthesis of 1-halo-2, 3-epoxypropane- ^{14}C , and we devised a novel procedure to prepare 1-bromo-2, 3-epoxypropane-3- ^{14}C (IV) (Fig. 1).

The preparation of acrylic-1- ^{14}C acid (II) by carbonation of vinylmagnesium bromide with carbon- ^{14}C dioxide was already reported by Gensler³⁾ and Pichat⁴⁾. In the attempt to repeat their methods, it was found that purity of vinyl bromide and strict elimination of moisture were essential to lead high yields of II. By employing a new apparatus (Fig. 2), we obtained the acid (II) in 88 % yield. Bromination of II with bromine followed by diazomethane-esterification⁴⁾ gave methyl 2, 3-dibromopropionate-1- ^{14}C (III) in 82 %. Reduction of III to 2, 3-dibromopropanol-1- ^{14}C was efficiently achieved by a mixed hydride of lithium-aluminum hydride-aluminum chloride⁵⁾ and the yield was 87%. Treatment of the propanol with calcium hydroxide at room temperature afforded 1-bromo-2, 3-epoxypropane-3- ^{14}C (IV) in 91% yield.

The epoxypropane (IV) was condensed with 1-naphthol in the presence of sodium hydroxide to produce 1,2-epoxy-3-(1-naphthoxy)-propane-1- ^{14}C (V), which was then heated to reflux with a large excess of isopropylamine

Fig. 1 Scheme for the synthesis of propranolol- ^{14}C hydrochloride (I).

† ^{14}C 標識プロプラノロールハイドロクロライド,
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to give propranolol- ^{14}C . Purification of the crude product by column chromatography and subsequent salt-formation with hydrogen chloride gave propranolol- ^{14}C hydrochloride (1) of which the overall yield was 20% from barium carbonate- ^{14}C .

2. Experimental

2.1 Acrylic-1- ^{14}C Acid

Apparatus for the preparation of vinylmagnesium bromide was shown in Fig. 2. Into a reaction flask A equipped with a

Fig. 2 Apparatus for preparing vinylmagnesium bromide.

A: reaction flask, B: measuring flask,
C: distillation flask, D: reflux condenser,
E: calcium chloride tube

reflux condenser, thermometer and gas inlet tube connected to a measuring flask B, were placed magnesium turnings (580 mg), iodine (5 mg) and anhydrous tetrahydrofuran (40 ml). After the system had been flushed out with nitrogen, the flask A was cooled in a dry-ice bath. Vinyl bromide in a flask C was purified by distillation into a measuring flask B. The purified vinyl bromide (1.5 ml, 2.28 g) was passed into the flask A through the gas inlet tube and the mixture heated at 55° with stirring for 1.5 hr to give vinylmagnesium bromide. The solution (30 ml) of vinylmagnesium bromide was then placed in a flask, which was connected to a vacuum manifold⁶. After freezing with liquid nitrogen, to the frozen mixture was introduced carbon- ^{14}C dioxide liberated from barium carbonate- ^{14}C (29.6 mCi, 3.57 mmol). The mixture was then warmed to -20° and stirred for 1 hr. The mixture was hydrolyzed with 5% hydrochloric acid and hydroquinone (5 mg) added to the mixture. The mixture was

then extracted with ether, and the extract washed with water, dried and evaporated to give acrylic-2- ^{14}C acid (26.1 mCi); the radiochemical purity: 98% on TLC (silica gel, propanol/20% $\text{NH}_4\text{OH}=7/3$).

2.2 Methyl 2,3-Dibromopropionate-1- ^{14}C

To a solution of a acrylic-1- ^{14}C acid (26.1 mCi, 3.1 mmol) and acrylic acid (250 mg, 3.5 mmol) in ether (10 ml) was added bromine (1.3 g) in 3 portions at room temperature and stirred for 7 hr. To the solution was added an excess of the ethereal solution of diazomethane at room temperature and the mixture kept to stand for 2.5 hr. The mixture was washed with 5% sodium bicarbonate solution and then water, dried, and evaporated to give a residue. Chromatography of the residue on silica gel with ether gave methyl 2,3-dibromopropionate-1- ^{14}C (21.4 mCi); the radiochemical purity: nearly 100% on TLC (Silica gel, benzene).

2.3 2,3-Dibromopropanol-1- ^{14}C

A solution of anhydrous aluminum chloride (800 mg, 6.0 mmol) in anhydrous ether (6 ml) was added at room temperature to a stirred suspension of lithium aluminum hydride (330 mg, 8.3 mmol) in anhydrous ether (10 ml). To the suspension was added dropwise at -80° a solution of methyl 2,3-dibromopropionate-1- ^{14}C (21.4 mCi, 5.45 mmol) in anhydrous ether (10 ml). The mixture was stirred at -80° for 2 hr and then the excess of reagent decomposed at -15° with water. The mixture was extracted with ether and the extract dried over sodium sulfate. Evaporation of the solvent afforded 2,3-dibromopropanol-1- ^{14}C (18.6 mCi); the radiochemical purity: 90% on TLC (silica gel, benzene).

2.4 1-Bromo-2,3-epoxypropane-3- ^{14}C

To a suspension of 2,3-dibromopropanol-1- ^{14}C (18.6 mCi, 4.3 mmol) in water (3 ml) was added calcium hydroxide (370 mg, 5.0 mmol) and the mixture stirred vigorously at room temperature for 7 hr. The mixture was extracted with ether, and the extract washed with water, dried, and evaporated to give 1-

bromo-2,3-epoxypropane-3- ^{14}C (16.9 mCi); the radiochemical purity: 95% on radiogaschromatography (column: DC-550, column temperature: 150°, retention time: 1.3 min); the IR spectrum (liquid film) being identical with that of the authentic sample.

2.5 1,2-Epoxy-3-(1-naphthyloxy) propane-1- ^{14}C (V)

A mixture of 1-bromo-2,3-epoxypropane-3- ^{14}C (16.9 mCi, 3.7 mmol), 1-naphthol (680 mg, 4.7 mmol) and sodium hydroxide (190 mg, 4.7 mmol) in water (5 ml) was stirred at room temperature for 13 hr and extracted with chloroform. The extract was washed with 2N acetic acid and then water, dried, and evaporated to give 1,2-epoxy-3-(1-naphthyloxy) propane-1- ^{14}C (V) (13.1 mCi); the radiochemical purity: 85% on TLC (silica gel, benzene).

2.6 Propranolol- ^{14}C Hydrochloride (I)

A mixture of 1,2-epoxy-3-(1-naphthyloxy) propane-1- ^{14}C (13.1 mCi) and isopropylamine (20 ml) was refluxed for 8 hr. After removal of the excess reagent under reduced pressure, the residue was taken up in 10% hydrochloric acid and washed with ether. The aqueous solution was basified with 10% sodium hydroxide solution and extracted with ether. The extract was washed with water, dried and evaporated to give a residue. Chromatography

of the residue on silica gel with ethanol/cyclohexane=2/3 gave propranolol- ^{14}C (6.89 mCi). To a solution of propranolol- ^{14}C (6.89 mCi) in ether (15 ml) was added an ethereal solution (20 ml) saturated with hydrogen chloride and the mixture stirred in an ice bath for 10 min. The precipitate produced was collected by filtration and recrystallized from methanol-ethyl acetate to give propranolol- ^{14}C hydrochloride (I) (5.93 mCi, 3.93 mCi/mmol); the radiochemical and chemical purities: 99% on TLC (silica gel, butanol/acetic acid/water=8/2/1, ethanol/28% NH_4OH /water=80/4/5); the IR spectrum (nujol) being identical in every respect with that of the unlabelled authentic sample.

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