SYNTHESIS OF SOME ^{14}C-LABELLED AZIRIDINE COMPOUNDS, PSYCHOTROPIC AGENTS

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SUMMARY

1-Methyl-2-(2-naphthyl)aziridine (I) and 1-methyl-2-(1,2,3,4-tetrahydro-2-naphthyl)aziridine (II), psychotropic agents, were labelled by incorporating carbon-14 into the carbon of the aziridine ring. Labelled products I and II were obtained in 32.4% and 14.4% radiochemical yield based on 2-acetyl-carbonyl-^{14}C-naphthalene (III), respectively.

Key Words: 1-Methyl-2-(2-naphthyl)aziridine, 1-Methyl-2-(1,2,3,4-tetrahydro-2-naphthyl)aziridine, Carbon-14.

DISCUSSION

A number of 1-methylaziridine compounds have been synthesized in our laboratory by Kotera and Kitahonoki. Among such compounds, 1-methyl-2-(2-naphthyl)aziridine[1] (I) and 1-methyl-2-(1,2,3,4-tetrahydro-2-naphthyl)aziridine[2] (II), exhibit excellent tranquilizing activity with few unfavorable effects and are useful as phychotropic agents.[3]

For absorption and metabolism studies with I and II, the isotope-labelled drugs were required. As it appeared desirable to label the naphthalene or aziridine ring of these drugs with ^{14}C, we chose the carbon of the aziridine ring, based on stability relative to

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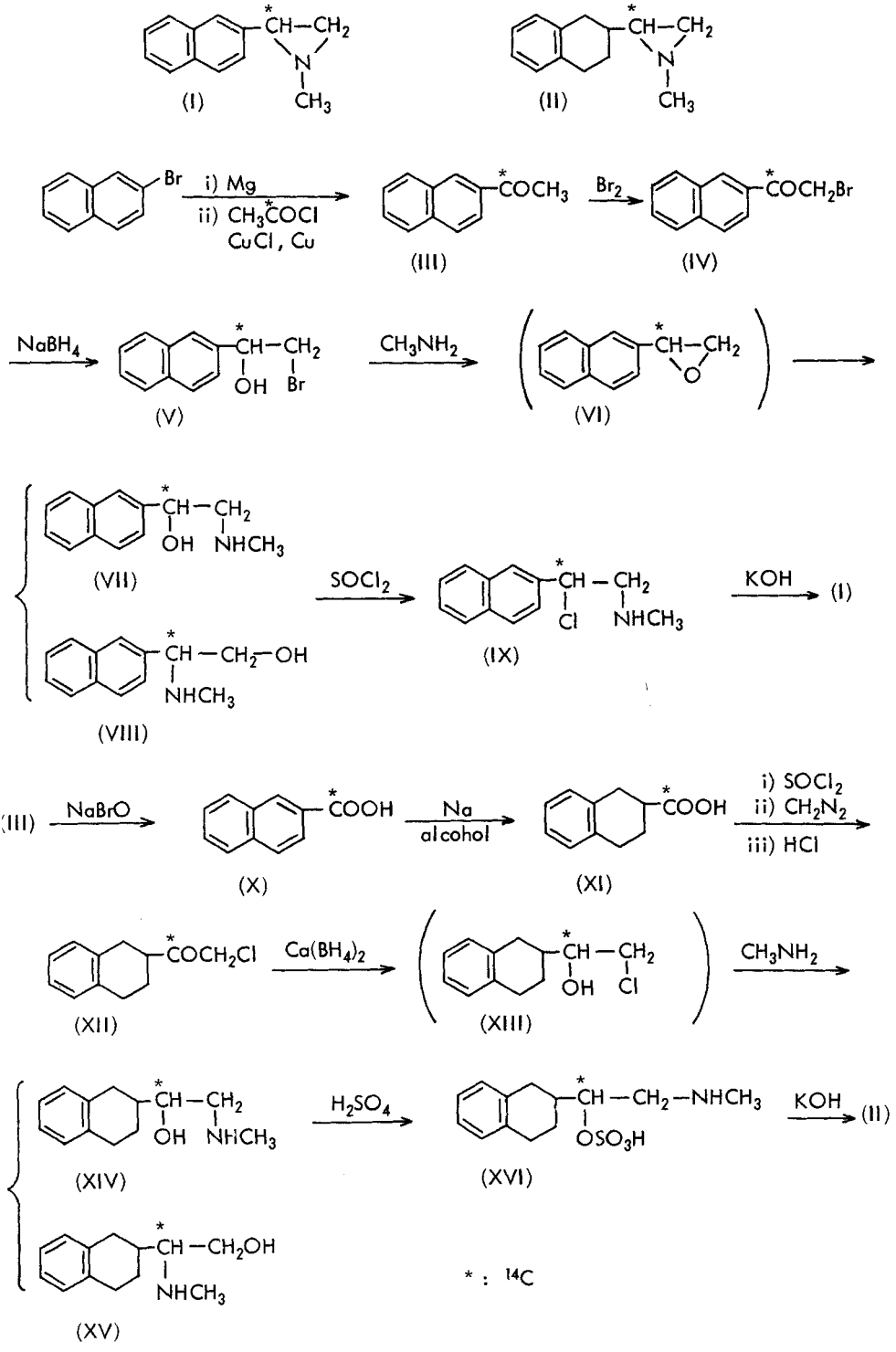
metabolic loss and facility of obtaining the ^{14}C-labelled starting material. The ^{14}C-labelled compounds were synthesized by the route shown in the synthetic scheme.



Acetyl-1-^{14}C chloride was prepared from sodium acetate-1-^{14}C by the procedure reported by Cox and Turner[4] in 83.3% radiochemical yield. 2-Acetyl-carbonyl-^{14}C-naphthalene (III) was obtained from a Grignard reagent prepared from 2-bromonaphthalene and magnesium, and acetyl-1-^{14}C chloride using cuprous chloride and copper powder in 50.8% radiochemical yield.

On bromination with trimethylanilinium perbromide, 2-acetyl-carbonyl-^{14}C-naphthalene (III) gave 2-bromo-1-(2-naphthyl)-1-ethanone-^{14}C (IV), which was used without purification. The bromoketone (IV) was reduced with sodium borohydride to give a bromohydrin (V), which was converted in situ into a crystalline mixture of 1-(2-naphthyl)-2-methylaminoethanol-1-^{14}C (VII) and 2-(2-naphthyl)-2-methylaminoethanol-2-^{14}C (VIII) via an epoxide (VI) by treatment with 30% methylamine in methanol. When the product was treated with thionyl chloride, it gave N-methyl-2-chloro-2-(2-naphthyl)ethylamine-2-^{14}C hydrochloride (IX) in 36.7% overall radiochemical yield based on III. On heating IX in 10% potassium hydroxide in methanol under reflux, 1-methyl-2-(2-naphthyl)-aziridine-2-^{14}C (I) was obtained as crystals in 88.4% radiochemical yield and in 32.4% overall radiochemical yield based on 2-acetyl-carbonyl-^{14}C-naphthalene (III).

To synthesize 1-methyl-2-(1,2,3,4-tetrahydro-2-naphthyl)aziridine-2-^{14}C (II), a variety of compounds can be used as the starting material. Although 2-acetyl-carbonyl-^{14}C-naphthalene (III) is not suitable for the synthesis of II, it is useful as a common starting material for I and II. When III was oxidized with sodium hypobromite, 2-naphthoic carboxyl-^{14}C acid (X) was obtained in quantitative yield. Reduction of X into a tetraline derivative was performed using sodium metal in isoamyl alcohol to give 1,2,3,4-tetrahydro-2-naphthoic carboxyl-^{14}C acid (XI) in 98% radiochemical yield. 2-Chloro-1-(1,2,3,4-tetrahydro-2-naphthyl)-1-ethanone-1-^{14}C (XII) was obtained by treatment[5] of the acid chloride of XI with diazomethane and hydrochloric acid in 75.5% radiochemical yield. On reduction of the chloroketone-^{14}C (XII) with calcium borohydride at -60 to -70°, it gave a chlorohydrin (XIII), which was treated in situ with methylamine to give a crystalline product. The product was crystallized from ether to

give 1-(1,2,3,4-tetrahydro-2-naphthyl)-2-methylaminoethanol-1-^{14}C (XIV) and a mixture of 2-(1,2,3,4-tetrahydro-2-naphthyl)-2-methylaminoethanol-2-^{14}C (XV) and XIV. The radiochemical yield of XIV was 44.2%. 1-Methyl-2-(1,2,3,4-tetrahydro-2-naphthyl)aziridine-2-^{14}C (II) was obtained as a colorless oil by treatment of the hydrogen sulfate ester (XVI) with potassium hydroxide in 44% radiochemical yield and in 14.4% overall radiochemical yield based on 2-acetyl-carbonyl-^{14}C-naphthalene (III).

EXPERIMENTAL

Radioactivity determination was carried out with an Aloka Model LSC-653 liquid scintillation spectrometer with an automatic quenching monitor. Unless otherwise stated, silica gel plates (Merck 5724/0100) were used for radio-t.l.c. and scanned with an Aloka Model JTC-201 TLC scanner.

Acetyl-1-^{14}C Chloride--Acetyl-1-^{14}C chloride was obtained from sodium acetate-1-^{14}C (300 mCi, 490 mg, 6.0 mmol) by the method of Cox and Turner.[4] The product (250 mCi) was diluted with carrier acetyl chloride to bring the total weight up to 950 mg (12.1 mmol). Radiochemical yield was 83.3%.

2-Acetyl-carbonyl-^{14}C-naphthalene (III)--The Grignard reagent was prepared from 5.02 g (24.2 mmol) of 2-bromonaphthalene and 690 mg (28.4 mmol) of magnesium in 30 ml of anhydrous tetrahydrofuran. Twenty ml (14.3 mmol) of the reagent was added dropwise to a mixture of 250 mCi (950 mg, 12.1 mmol) of freshly distilled acetyl-1-^{14}C chloride, 370 mg of cuprous chloride, and 50 mg of copper powder in 5 ml of anhydrous tetrahydrofuran with stirring at 2-3° for 30 min and stirred for an additional 2 hr at the same temperature. The mixture was decomposed by addition of 5 ml of 3% hydrochloric acid and evaporated in vacuo to remove tetrahydrofuran. An oily residue was dissolved in 20 ml of water and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated leaving a residue (173 mCi), the purity of which was shown to be 90% by radio-t.l.c. (solvent system: benzene-chloroform = 1 : 1). The residue was dissolved in benzene (600 ml) and chromatographed on silica gel (60 g). Elution with benzene gave 2-acetyl-

carbonyl-^{14}C-naphthalene (III) as colorless needles (from ether-hexane), m.p. 52-53° (1.02 g, 127 mCi, specific activity: 21.1 mCi/mmol), in 50.8% radiochemical yield. The radiochemical purity was confirmed to be 98% by radio-t.l.c.

2-Bromo-1-(2-naphthyl)-1-ethanone-1-^{14}C[§] (IV)--2-Acetyl-carbonyl-^{14}C-naphthalene (III) (12.0 mCi, 96.3 mg) was diluted with 154 mg of carrier acetylnaphthalene to bring the specific activity down to 8.18 mCi/mmol. To a solution of the acetylnaphthalene-^{14}C in 5 ml of anhydrous tetrahydrofuran, 580 mg of trimethylanilinium perbromide was added with stirring during 25 min at room temperature, and the mixture was stirred for 1 hr at the same temperature. Ether (10 ml) was added to the reaction mixture to separate the precipitates, which were filtered and washed with ether (2 ml). The filtrate and the washing were combined and evaporated *in vacuo* at below 30°, leaving a bromoketone-^{14}C (IV) as a light yellow crystalline residue (252 mg), which was used for the next reaction without purification.

1-(2-Naphthyl)-2-methylaminoethanol-1-^{14}C[§] (VII)--The bromoketone-^{14}C (IV) (250 mg) was dissolved in 3 ml of methanol and reduced with 74 mg of sodium borohydride with stirring in an ice bath for 40 min. To this mixture, 12 ml of 30% methylamine in methanol was added dropwise with stirring for 10 min in an ice bath, and the mixture was left for 20 hr at room temperature. The reaction mixture was evaporated *in vacuo* at below 30° to leave a residue, which was dissolved in 10 ml of 5% hydrochloric acid and extracted with dichloromethane (10 ml x 2). The aqueous layer was neutralized with sodium carbonate powder in an ice bath, salted out with sodium carbonate, extracted with dichloromethane (10 ml x 2), dried (Na_2SO_4), and evaporated at below 40°, leaving a crystalline residue. The residue was dried at 35-45° for 1.5 hr under 1 mmHg to give a crystalline product (210 mg), which was shown to be a mixture of 1-(2-naphthyl)-2-methylaminoethanol-1-^{14}C (VII), RF 0.36, and 2-(2-naphthyl)-2-methylaminoethanol-2-^{14}C (VIII), RF 0.27, by radio-t.l.c. (solvent: benzene).

N-Methyl-2-chloro-2-(2-naphthyl)ethylamine-2-^{14}C[§] (IX)--The above-mentioned crystalline mixture (205 mg) was dissolved in 2.5 ml of chloroform. Thionyl chloride (0.5 ml) was

added dropwise to the solution with stirring in an ice bath. The mixture was heated under reflux for 2 hr and then evaporated in vacuo to leave a crystalline residue, which was dissolved in 1.5 ml of acetone and crystallized with cooling to give N-methyl-2-chloro-2-(2-naphthyl)ethylamine-2-^{14}C hydrochloride (IX) (4.41 mCi, 138 mg), m.p. 180-181° (dec.), in 36.7% overall radiochemical yield based on 2-acetyl-carbonyl-^{14}C-naphthalene (III).

1-Methyl-2-(2-naphthyl)aziridine-2-^{14}C[§] (I)--N-Methyl-2-chloro-2-(2-naphthyl)ethylamine-2-^{14}C hydrochloride (IX) (2.32 mCi, 72.7 mg) was dissolved in 1 ml of 10% potassium hydroxide in methanol and heated under reflux for 1 hr under nitrogen atmosphere. The mixture was evaporated to leave a residue. The residue was extracted with ether (2.5 ml x 2). The extract was distilled at 100-110° (bath temperature) under 0.1 mmHg to give a crystalline product, which was recrystallized from hexane to give 1-methyl-2-(2-naphthyl)aziridine-2-^{14}C (I), m.p. 50-51° (46 mg, 2.05 mCi, specific activity: 44.5 μCi/mg, 8.18 mCi/mmol), in 88.4% radiochemical yield. The overall radiochemical yield was 32.4% based on III. This compound was confirmed to be pure by t.l.c.-autoradiogram and t.l.c.-radioactinogram [X-ray film, silica gel plate KGF-Merck (treated with 10% KOH and dried), solvent: benzene].

2-Naphthoic Carboxyl-^{14}C Acid[§] (X)--2-Acetyl-carbonyl-^{14}C-naphthalene (III) (10 mCi, 80.6 mg) and carrier 2-acetylnaphthalene (919.4 mg) were mixed and ground down into a fine powder in a mortar. The powder was added in small portions to sodium hypobromite solution (prepared from 2 ml of bromine and 16 ml of 25% sodium hydroxide) with stirring in an ice bath, and the mixture was stirred for 3 hr at room temperature and left for 24 hr. This mixture was diluted with water (80 ml) and extracted with ether (50 ml). The aqueous layer was adjusted to pH 1.0 by addition of 6.5 ml of concentrated hydrochloric acid and extracted with ether (50 ml x 2). The extract was washed with 30% sodium sulfite and water, dried (Na_2SO_4), and evaporated, leaving 2-naphthoic carboxyl-^{14}C acid (X) as colorless needles, m.p. 181-182° (1 g, 10 mCi, specific activity: 1.72 mCi/mmol), in quantitative yield.

1,2,3,4-Tetrahydro-2-naphthoic Carboxyl-^{14}C Acid[5] (XI)--Sodium (2 g) was added to a solution of 10 mCi (1 g) of 2-naphthoic carboxyl-^{14}C acid (X) in 50 ml of isoamyl alcohol, and the mixture was heated at 150° (bath temperature) with stirring under nitrogen atmosphere for 10-15 min, during which time sodium completely disappeared. An additional 2 g of sodium was added to the solution which was heated at the same temperature with stirring for 40 min. Isoamyl alcohol was evaporated in vacuo. A residue was dissolved in ether (50 ml) and extracted with water (30 ml x 3). The aqueous layer was acidified with concentrated hydrochloric acid, salted out with sodium chloride, and extracted with ether (30 ml x 3). The extract was dried over Na_2SO_4 and evaporated to leave 1,2,3,4-tetrahydro-2-naphthoic carboxyl-^{14}C acid (XI) as crystals, m.p. 95-96° (1 g, 9.8 mCi), in 98% radiochemical yield.

2-Chloro-1-(1,2,3,4-tetrahydro-2-naphthyl)-1-ethanone-1-^{14}C[5] (XII)--A mixture of 9.8 mCi (1 g) of 1,2,3,4-tetrahydro-2-naphthoic carboxyl-^{14}C acid (XI) in 4 ml of thionyl chloride was stirred for 20 min at room temperature and heated at 50° for 1 hr. This was evaporated in vacuo to remove hydrochloric acid, sulfur dioxide, and an excess of thionyl chloride. Diazomethane-ether solution (60 ml) [prepared from nitrosomethylurea (8 g), ether (80 ml), and 40% sodium hydroxide] was added dropwise to an oily residue in an ice bath and left for 2 hr with ice-cooling. The ether solution was slowly evaporated leaving about 20 ml, through which hydrogen chloride gas [prepared from NaCl (10 g) and conc. H_2SO_4] was passed with ice-cooling. The reaction mixture was evaporated in vacuo to leave a residue, which was dissolved in 10 ml of benzene and chromatographed on silica gel (Merck: KG 60). Elution with benzene (30 ml x 3) gave 2-chloro-1-(1,2,3,4-tetrahydro-2-naphthyl)-1-ethanone-1-^{14}C (XII) as a crystalline product (0.9 g, 7.4 mCi) in 75.5% radiochemical yield.

2-Methylamino-1-(1,2,3,4-tetrahydro-2-naphthyl)ethanol-1-^{14}C[5] (XIV)--Calcium borohydride (300 mg) was added to a solution of 7.4 mCi (0.9 g) of 2-chloro-1-(1,2,3,4-tetrahydro-2-naphthyl)-1-ethanone-1-^{14}C (XII) in 6 ml of absolute methanol with stirring at -60 to -70° and stirred for 1 hr during which time the mixture turned into an emulsion.

This was stirred for an additional 20 min at 0°, and then a clear reaction solution was obtained. Without isolation of a chlorohydrin-^{14}C (XIII) from this solution, 55 ml of 30% methylamine in methanol was added to the solution with stirring, and the mixture was stirred for 2 hr at room temperature and left for 2 days. The reaction mixture was filtered and the filtrate was evaporated in vacuo to remove an excess of methylamine and methanol. The residue was dissolved in 20 ml of 15% hydrochloric acid and extracted with ether (30 ml). The aqueous layer was adjusted to ca. pH 9.5 by addition of sodium carbonate and extracted with ether (10 ml x 3). The extract was washed with water, dried (Na_2SO_4), and evaporated, leaving an oily residue (1 g). The residue was dissolved in 4 ml of ether and allowed to stand for 2.5 hr at room temperature to separate 1-(1,2,3,4-tetrahydro-2-naphthyl)-2-methylaminoethanol-1-^{14}C (XIV) as colorless prisms, m.p. 107-109° (390 mg, 3.27 mCi, specific activity: 8.38 μCi/mg), in 44.2% radiochemical yield. Concentration of the mother liquor gave a mixture (108 mg) of colorless prisms and colorless needles, which consisted of XIV and 2-(1,2,3,4-tetrahydro-2-naphthyl)-2-methylaminoethanol-2-^{14}C (XV).

1-Methyl-2-(1,2,3,4-tetrahydro-2-naphthyl)aziridine-2-^{14}C[§] (II)--2-Methylamino-1-(1,2,3,4-tetrahydro-2-naphthyl)ethanol-1-^{14}C (XIV) (3.27 mCi, 385 mg) was dissolved in a solution of 195 mg of sulfuric acid in 4 ml of water and evaporated in vacuo at 30-40° to remove water. The mixture was further evaporated in vacuo at 150° (bath temperature) for 30 min to give a hydrogen sulfate ester (XVI) as a solid residue, which was used for the next reaction without purification. The hydrogen sulfate ester (XVI) was added to 15 ml of 10% potassium hydroxide, and the mixture was heated under reflux for 2 hr under nitrogen atmosphere. The reaction mixture was extracted with hexane (10 ml x 3) and the extract was washed with water, dried (Na_2SO_4), and evaporated, leaving an oily residue. The residue was dissolved in hexane and chromatographed on alumina (Woelm, neutral, 1.5 g). Elution with hexane (30 ml x 2) gave 1-methyl-2-(1,2,3,4-tetrahydro-2-naphthyl)-aziridine-2-^{14}C (II) as a colorless oil, b.p. 100-115° (bath temp.)/0.1 mmHg (157 mg, 1.44 mCi, specific activity: 9.2 μCi/mg, 1.72 mCi/mmol), in 44% radiochemical yield.

The overall radiochemical yield was 14.4% based on III. This compound was confirmed to be pure by t.l.c.-autoradiogram and t.l.c.-radioactinogram [X-ray film, silica gel plate (KGF-Merck), solvent: benzene].

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