

boiling between 35–65°. Fractional distillations were performed with a vacuum jacketed Vigreux column.

Method A

Pyrrolidine-2-¹⁴C picrate was prepared starting with potassium cyanide-¹⁴C and I. The latter compound was prepared from the corresponding chloride (VII) in 62.7% yield (8). The chloride in turn was synthesized from 3-methoxy-1-propanol in 83.9% yield (9), and the alcohol was prepared from 1,3-propanediol in 64.8% yield (10).

4 - Methoxybutyronitrile - 1 - ¹⁴C (II)—A solution containing 16.2 mg. (0.25 mmole, 0.123 mCi./mg.) of potassium cyanide-¹⁴C (New England Nuclear Corp., Boston, Mass.), 1.61 Gm. (24.8 mmoles) of unlabeled potassium cyanide, and 4.75 Gm. (23.8 mmoles) of freshly distilled I in 50 ml. of methyl alcohol was refluxed for 30 hr. and cooled. The solvent was removed under reduced pressure, and the residue was washed portionwise with 100 ml. of ether. The washings were filtered by suction, combined, allowed to stand over anhydrous sodium thiosulfate for 12 hr., and decanted. The solvent was removed under reduced pressure, and the residue was distilled yielding 1.42 Gm. (57.4% based on potassium cyanide) of a colorless liquid boiling at 63–64° (10 mm.), n_D^{20} 1.4083; reported (11) b.p. 172–175° (Atm.).

Pyrrolidine-2-¹⁴C Picrate (VI)—To 1.36 Gm. (35.9 mmoles) of lithium aluminum hydride in 50 ml. of anhydrous ether at 0–10° was added with stirring a solution containing 1.42 Gm. (14.3 mmoles) of II in 5 ml. of anhydrous ether. When the addition was complete (about 30 min.), two 2-ml. portions of anhydrous ether were added and stirring was continued for 2 hr. at 0–10°. To the mixture at 0–10° were added slowly with rapid stirring 30 drops of water, 23 drops of 20% sodium hydroxide, 5.0 ml. of water, and 20 ml. of ether. Stirring was continued for 30 min., the granular precipitate was filtered by suction, and washed portionwise with 100 ml. of ether, and the washings were combined with the filtrate.

The combined ethereal solution was saturated with hydrogen bromide and extracted with five 10-ml. portions of 10% hydrobromic acid. The extractions were combined and placed in a flask fitted with a fractionating column and adapter set for distillation. The solution was distilled under reduced pressure until about 30 ml. of liquid was removed. To the remaining volume was added 30 ml. of hydrobromic acid (d. 1.49), and the solution was distilled at atmospheric pressure until about 20 ml. of liquid was removed. This procedure was repeated using four 10-ml. portions of hydrobromic acid. The residual solution was then refluxed gently for 15 hr., and 20 ml. of liquid was removed by distillation under reduced pressure. The remaining volume was cooled to 0–10° and 15 ml. of 50% sodium hydroxide was added dropwise with stirring. When the addition was complete, the solution was heated slowly, and the fraction distilling below 95° was collected in a 25-ml. flask immersed in an acetone-dry ice bath and containing 1 Gm. of anhydrous sodium carbonate and 10 ml. of an ether-petroleum ether solution (4:1).

This solution was filtered by suction into a 500-ml. flask. The drying agent was washed portionwise

with 100 ml. of an ether-petroleum ether solution (4:1), and the washings were combined with the filtrate. To the combined solution was added, through a filter and with stirring, a solution containing 3.29 Gm. (14.4 mmoles) of picric acid (N.F. grade) in 250 ml. of anhydrous ether. When the addition was complete, the mixture was stirred for 15 min., and the precipitate was filtered by suction. Recrystallization of the pale yellow colored, light solid two times with ethyl propionate (b.p. 98–100°) and *n*-heptane (b.p. 97–98°) yielded 1.41 Gm. (18.8% based on potassium cyanide) of fine, yellow colored needles melting at 113–114°. [Reported (6) m.p. 113°.] The melting point did not change upon further recrystallization of a small sample.

Method B

Pyrrolidine-2-¹⁴C picrate was prepared starting with barium carbonate-¹⁴C and the Grignard reagent of VII.

4 - Methoxy - 1 - butanol - 1 - ¹⁴C (IX)—The procedure of Dauben *et al.* (4) for preparing carboxylic acids was followed for preparing 4-methoxybutanoic-1-¹⁴C acid (VIII).

Carbonation of 25.8 mmoles of the Grignard reagent of VII, prepared from 4.13 Gm. (0.17 mole) of magnesium and 16.3 Gm. (0.15 mole) of VII, was effected using 123.0 mg. (0.62 mmole, 0.129 mCi./mg.) of barium carbonate-¹⁴C (Oak Ridge National Laboratories, Oak Ridge, Tenn.) and 4.50 Gm. (22.8 mmoles) of unlabeled barium carbonate. The reaction mixture was worked up in the usual way; however, the product was not purified.

The crude material was dissolved in 20 ml. of anhydrous ether and added with stirring to 1.03 Gm. (27.1 mmoles) of pulverized lithium aluminum hydride in 40 ml. of anhydrous ether. When the addition was complete (about 15 min.), two 5-ml. portions of anhydrous ether were added, and stirring was continued for 4 hr. at room temperature. The mixture was cooled to 0–10° and decomposed by adding, slowly with stirring, 23 drops of water, 18 drops of 20% sodium hydroxide, and 3.8 ml. of water. Stirring was continued for 15 min., and the granular precipitate was filtered and washed portionwise with 100 ml. of ether. The washings and filtrate were combined, dried over anhydrous potassium carbonate, and decanted. The solvent was removed under reduced pressure, and the residue was fractionated giving 2.04 Gm. (83.7% based on barium carbonate) of a colorless liquid boiling at 77–79° (10 mm.). [Reported (12) b.p. 63–64° (7 mm.).]

1,4-Dibromobutane-1-¹⁴C (X)—Hydrogen bromide was bubbled through a solution consisting of 2.04 Gm. (19.6 mmoles) of IX, 7.5 ml. of glacial acetic acid, and 7.5 ml. of water while the temperature was increased slowly to 95°. When the solution was saturated (about 1–1.5 hr.), it was heated for 15 hr. between 90–100°, cooled, and poured into 20 ml. of water. The organic layer was separated and the aqueous layer was extracted exhaustively with petroleum ether. The extractions and organic layer were combined and washed with 5 ml. of 20% sodium hydroxide followed by 10 ml. of water. The aqueous washings were extracted with two 10-ml. portions of petroleum ether. The extractions and organic solutions were combined, dried over anhydrous sodium sulfate, and

decanted. The solvent was removed under reduced pressure, and the residue was distilled. There was obtained 3.47 Gm. (68.6% based on barium carbonate) of a colorless liquid boiling at 83–85° (14 mm.). [Reported (5) b.p. 85° (15 mm.).]

N-p-Toluenesulfonylpyrrolidine-2-¹⁴C (XI)—A mixture consisting of 3.47 Gm. (16.1 mmoles) of X, 2.75 Gm. (16.1 mmoles) of *p*-toluenesulfonamide, and 9 ml. of ethyl alcohol was heated with stirring until a clear solution resulted. A solution containing 3.3 ml. of 58% potassium hydroxide in 6.8 ml. of ethyl alcohol (95%) was then added portionwise with stirring over a 9–10-hr. period. When the addition was complete, the mixture was refluxed for 20 hr. and cooled. The alcohol was removed by distillation at atmospheric pressure, and 10 ml. of water was added to the residue. The mixture was poured while still hot into a 250-ml. flask, cooled, and extracted exhaustively with ether. The extractions were combined, and the solvent was allowed to evaporate. The residue was warmed for 20 min. with 15 ml. of 15% sodium hydroxide, filtered by suction, and washed with water. This process was repeated using 10 ml. of 15% sodium hydroxide. The residue was then allowed to dry, washed with 25 ml. of ice-cold ligroin (b.p. 100–115°), allowed to dry, and sublimed under reduced pressure (0.4 mm.). There was obtained 2.78 Gm. (52.7% based on barium carbonate) of a white crystalline powder melting at 120–121°. [Reported (6) m.p. 123°.]

Pyrrolidine-2-¹⁴C Picrate (VI)—A mixture consisting of 2.78 Gm. (12.4 mmoles) of XI and 15 ml. of hydrochloric acid (d. 1.19) was heated in a Pyrex bomb tube (19 × 25 × 400 mm.) for 15 hr. between 170–180°. The mixture was then cooled slowly and frozen in an acetone-dry ice bath. The tube was opened, the contents were allowed to liquefy, and 10 ml. of water was added. The organic layer was separated, and the aqueous layer was extracted with three 10-ml. portions of petroleum ether. The extractions and organic layer were combined and washed with two 5-ml. portions of water, and the washings were added to the aqueous layer. Approximately 15–20 ml. of the combined aqueous solution was removed by distillation at atmospheric pressure. The remaining volume was cooled to 0–10°, and 10 ml. of 40% sodium hydroxide was added with stirring. The mixture was distilled at atmospheric pressure until crystals began to form in the distilling flask. The distillate was then collected in a 100-ml. flask immersed in an acetone-dry ice bath and containing 5 Gm. of potassium hydroxide and 5 Gm. of sodium chloride. The distillate was allowed to liquefy and was extracted exhaustively with an ether-petroleum ether solution (4:1). The extractions were combined, dried over anhydrous potassium carbonate, and

filtered by suction into a 500-ml. flask containing a magnetic stirring bar. The drying agent was washed portionwise with 100 ml. of an ether-petroleum ether solution (4:1). The washings were combined with the filtrate.

To the ether-petroleum ether extractions was added, through a filter and with stirring, a solution containing 3.27 Gm. (14.3 mmoles) of picric acid in 230 ml. of an ether-petroleum ether solution (9:1). When the addition was complete the mixture was stirred for 15 min., and the precipitate was filtered by suction. Recrystallization of the pale yellow-colored, light solid once with ethyl propionate and *n*-heptane yielded 2.69 Gm. (38.3% based on barium carbonate) of fine, yellow colored needles melting at 113–114°. [Reported (6) m.p. 113°.] The melting point did not change upon further recrystallization of a small sample.

Cleavage of Pyrrolidine Picrate—Pyrrolidine picrate, 1.50 Gm. (5.0 mmoles), was cleaved by the method of Burger (7). The free base was recovered in 68.7% yield as the picrate salt by the procedure described above for preparing the picrate salt.

Radioactivity Determinations—The specific activity of pyrrolidine-2-¹⁴C picrate obtained by methods *A* and *B* was determined using a Tri-Carb liquid scintillation spectrometer. The XDC liquid scintillator (13) was used. Counting efficiency was determined using a benzoic-¹⁴C acid standard. The specific activities of the products from methods *A* and *B* were 0.203 μCi./mg. and 1.75 μCi./mg., respectively. These specific activities did not change upon further recrystallization.

SUMMARY

Pyrrolidine-2-¹⁴C was prepared by two different methods for the purpose of evaluating a suitable isotopic synthesis. Both methods were satisfactory. Method *B* is better than method *A* with respect to chemical yield (38.3% versus 18.8%). In addition, method *B* is more economical. Method *A*, however, is less time consuming.

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