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Synthesis of 1-Methyl-4-(5-^{14}C-3-methyl-5-isoxazolyl) pyridinium Chloride

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1-Methyl-4-(3-methyl-5-isoxazolyl)pyridinium chloride (**1**) has been found to display interesting hypoglycemic activity in laboratory animals, and is currently undergoing extensive evaluation as a potential antidiabetic drug. To facilitate the study of the bodily distribution and metabolism of **1**, a radiolabelled sample was required.

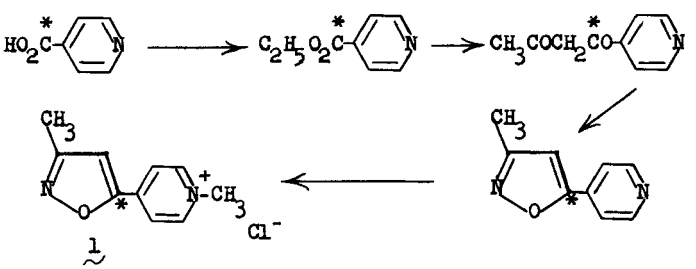

FIG. 1. Synthesis of 1-Methyl-4-(5-^{14}C-3-methyl-5-isoxazolyl)pyridinium Chloride (**1**).

The previously developed synthesis[2] of **1** was modified to permit efficient small-scale preparation. Commercially available labelled starting materials include ^{14}C-methyl chloride, 2-^{14}C-acetone, and α-^{14}C-isonicotinic acid, thus permitting a choice of three different sites of radioactivity in **1**. For metabolic studies, it is desirable to utilize compounds with the radio-label centrally located in the molecular skeleton to preclude loss of radioactivity at an early stage of the process. α-^{14}C-Isonicotinic acid, which leads to **1** labelled at the 5-isoxazolyl carbon (Fig. 1), was therefore chosen as the starting material. From 13.7 mCi of α-^{14}C-isonicotinic acid was obtained 4.0 mCi of labelled **1**.

Ethyl α-^{14}C-Isonicotinate.

The method of Gilman and Broadbent [3] was employed. A stream of dry hydrogen chloride was bubbled through a stirred refluxing suspension of

1.90 g (15.4 mmole, 13.7 mCi) of α-^{14}C-isonicotinic acid (Nuclear-Chicago, specific activity 0.89 mCi/mmole) in 18 ml of anhydrous ethanol for 1.5 hrs until complete solution was achieved. The solvent was distilled under reduced pressure, and the residual solid was treated with 30 ml of saturated aqueous sodium bicarbonate. The mixture was extracted with ether, and the ether phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a yellow liquid. Evaporative distillation at 125 °C (25 mm) gave 2.01 g (88 %) of colorless liquid.

4-(1-^{14}C-Acetoacetyl)pyridine.

A mixture of 2.01 g (13.3 mmole) of ethyl α-^{14}C-isonicotinate, 2.0 g (34 mmole) of acetone, 0.86 g (16 mmole) of sodium methoxide, and 20 ml of anhydrous benzene was heated under reflux with stirring for 19 hrs. The mixture was cooled and diluted with water, the layers were separated, and the benzene phase was extracted with water. The aqueous solution was acidified to pH 5 with 1.3 ml of concd. hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to an orange solid. Sublimation at 125 °C (25 mm) gave 1.13 g (52 %) of colorless solid, mp 58-59° C (unlabelled reference sample, mp 58-59° C).

4-(5-^{14}C-3-Methyl-5-isoxazolyl)pyridine.

A mixture of 1.13 g (6.9 mmole) of 4-(1-^{14}C-acetoacetyl)pyridine, 0.90 g (13 mmole) of hydroxylamine hydrochloride, 10 ml of water, and 7 ml of ethanol was stirred until solution was complete. Then, 0.90 g (9 mmole) of sodium carbonate was cautiously added. The solution was heated under reflux for 7 hrs, cooled, concentrated to a volume of 8 ml, diluted with 10 ml of water, and extracted with ether. The ether phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a colorless solid. Sublimation at 125° C (25 mm) gave 0.88 g (79 %) of colorless solid, mp 59-60° C (unlabelled reference sample, mp 60-61° C).

1-Methyl-4-(5-^{14}C-3-methyl-5-isoxazolyl)pyridinium Chloride.

A mixture of 0.88 g (5.5 mmole) of 4-(5-^{14}C-3-methyl-5-isoxazolyl)-pyridine and 5 ml of methyl chloride was heated at 82° C for 18 hrs in a glass-lined steel bomb. The excess methyl chloride was allowed to evaporate; a residue of 1.12 g of off-white solid, mp 235° C, was obtained. Recrystallization from 10 ml of 2-propanol gave 0.84 g of colorless solid, mp 238° C (monohydrate, unlabelled reference sample, mp 238° C). Addition of ether to the mother liquors provided 0.25 g of off-white solid, mp 231° C. The total yield of product was 87 % (4.0 mCi), specific activity 0.83 mCi/mmole.

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