SYNTHESIS OF ^{14}C and ^{3}H SPECIFICALLY LABELLED 1-BENZYL-4--PICOLINOYL-PIPERAZINE

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SUMMARY

Specifically labelled 1-benzyl-4-picolinoyl-piperazine (4) was synthetized for use in metabolism studies. Carbon-14 was introduced both in benzyl and picolinoyl groups, and tritium in the benzyl group. By using commercial n-butyllithium in n-hexane, the yield of picolinic acid was improved.

Key Words: Tritium, Carbon-14, Picolinic acid

INTRODUCTION

A number of N-substituted piperazides of pyridinecarboxylic acids have been synthetized by Körösi and coworkers (1). One of these, 1-benzyl-4-picolinoyl-piperazine (4), appeared to have a therapeutically useful antidepressant activity. We report the preparation of labelled analogues of this compound (4a, 4b and 4c) for pharmacokinetic and metabolism studies.

DISCUSSION

The labelled compounds were synthetized by applying the route described by Budai and coworkers (2,3) with some modifications, which made it suitable for microscale preparation.

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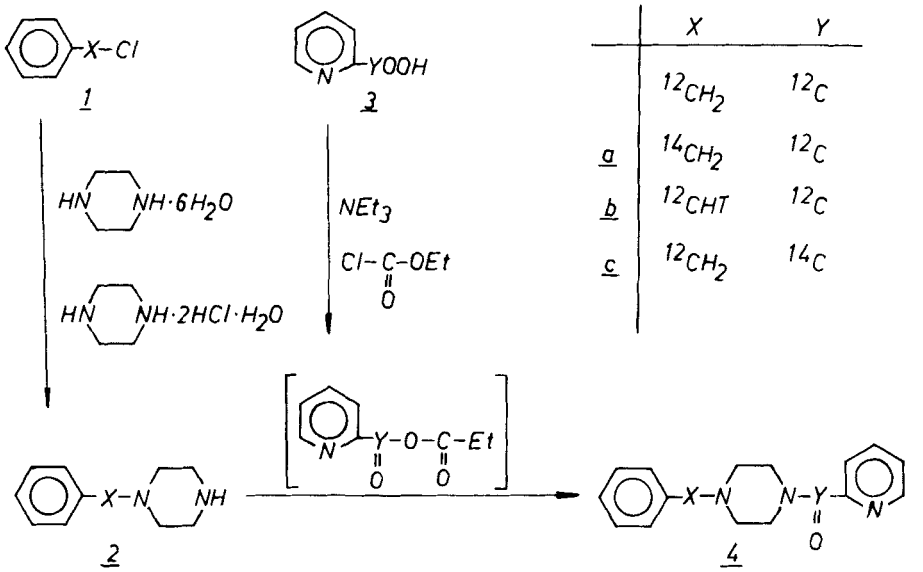

Starting from $BaCO_3$, benzyl-7-^{14}C chloride was prepared by a known method (4) and was used in the next step without purification. The tritium was introduced into the molecule by reduction of benzaldehyde with $NaBT_4$ resulting in benzyl alcohol, which was converted into 1b. Benzyl-piperazines (2a and 2b) were prepared from benzyl chloride by the method of Craig and Young (5) and the crude products thus obtained were purified by column chromatography using silica gel, eluting with an ethanol/chloroform/conc. NH_4OH mixture.

Schütte and Bachmann (6) described the synthesis of ^{14}C-labelled picolinic acid, but the relatively low yield compared to that of nicotinic (7) and isonicotinic (8) acids reported by Murray et al., prompted us to study this reaction. Paradies and Görbing (9) reported the preparation of 2-pyridylmagnesium bromide, characterizing this compound as a white odourless powder, which gives with benzaldehyde the corresponding secondary alcohol. Trying to reproduce this process we ran a series of experiments under different conditions without any success. Thereafter, considering that the ethereal

solution of n-butyllithium is not storable, we tried to carry out the metallation (and thereafter the carbonation) of 2-bromopyridine with commercial solution of n-butyllithium in n-hexane, in order to avoid the tedious preparation and analysis of this organometallic compound. Apart from a small amount of n-hexane, there was no change in the reaction conditions. Although we had been aware of the role of the solvent in the halogen-metal interconversions, it was surprising that no trace of picolinic acid could be detected. It was reasonable to assume that only by removing the n-hexane from the mixture could be the reaction carried out. Indeed, in the next experiment the hexane solution containing a known quantity of butyllithium was evaporated, then frozen with liquid nitrogen, and absolute ether was distilled into the residue: using this mixture for the metallation of 2-bromopyridine followed by carbonation, a 58 % yield of pure sublimed picolinic acid, based on $Ba^{14}CO_3$ was obtained.

EXPERIMENTAL

Melting points are determined on a Boëtius hot stage and are uncorrected. Radioactivities were measured with Packard TRI-CARB liquid scintillation spectrometer. TLC was carried out on silica gel HF_{254} (Merck) and a Berthold TLC scanner was used for evaluation. All evaporations were carried out under reduced pressure.

Benzyl-7-^{14}C-piperazine (2a).

$Ba^{14}CO_3$ (542 mg, 4.45 mmol, 54.5 mCi, 12.25 mCi/mmol) was converted into benzyl chloride, and the crude product obtained was added to a stirred solution of piperazine hexahydrate (864 mg, 4.45 mmol) and piperazine dihydrochloride monohydrate (770 mg, 4.45 mmol) in ethanol (7 ml) at 70°C. After being stirred for one hour the reaction mixture was cooled to -10°C, the precipitated piperazine dihydrochloride monohydrate was filtered off, and the solution was evaporated. To this 5 ml of 5 N NaOH was added and

extracted with chloroform. The combined organic extracts were washed with water, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel using chloroform/ethanol/conc. NH_4OH 10:10:1 eluent. Yield: 536 mg, (3.0 mmol, 67.5 %) of yellow oil.

1-Benzyl-7-^{14}C-4-picolinoyl-piperazine (4a).

To a stirred solution of picolinic acid (370 mg, 3.0 mmol) in ethyl acetate (20 ml), triethylamine (304 mg, 3.0 mmol, 0.42 ml) was added. After being stirred for one hour the reaction mixture was cooled, and ethyl chloroformate (330 mg, 3.0 mmol, 0.29 ml) was added dropwise at -5°C. After stirring for an additional hour, the solution of 2a in ethyl acetate (5 ml) was added. Then the reaction mixture was left at room temperature and filtered. The solid was washed with ethyl acetate and the filtrate was evaporated. The residue was chromatographed on silica gel using the same eluent as above. The obtained base was converted into the fumarate in ethanol to give 722 mg (1.82 mmol) white crystalline material, m.p. 162-163°C. The chemical and radiochemical purities were over 99 % (checked by TLC, using benzene/ethanol/conc. NH_4OH 86:30:4 solvent system). Total activity: 20.61 mCi at a specific activity of 11.78 mCi/mmol. Overall radiochemical yield based on $Ba^{14}CO_3$: 37.8 %.

Benzyl-7-^{3}H-piperazine (2b).

Benzaldehyde (530 mg, 5.0 mmol) and $NaBT_4$ (24.6 mg, 0.65 mmol, 1.07 Ci, 1.65 Ci/mmol) was stirred in 10 ml of ethanol at 0°C for 10 minutes. Then $NaBH_4$ (32.2 mg, 0.85 mmol) was added and the mixture was stirred for another 15 minutes. The complex was decomposed by adding 10 ml of 5 N HCl, and the ethanol was distilled off under reduced pressure. The residue was extracted continuously for 4 hours with ether, the etheral solution was dried over magnesium sulfate and evaporated. To the residue thionyl chloride (2 ml) was carefully added and refluxed for 3 hours. After removing the excess of thionyl chloride by distillation, the residue was dis-

solved in ether (20 ml), washed with a solution of $NaHCO_3$, and evaporated. The crude product obtained was converted into benzyl--piperazine (2b) as described above for the synthesis of 2a, resulting in 520 mg of yellow oil.

1-Benzyl-7-^{3}H-4-picolinoyl-piperazine (4b).

This compound was synthetized from 2b by the method described at the preparation of 4a. Yield: 649 mg (1.63 mmol) of 4b fumarate, 380 mCi (233 mCi/mmol), m.p. 160-162°C. By TLC only one radioactive spot could be detected.

Picolinic acid-^{14}C (3c).

Into a nitrogen-filled reaction flask attached to a vacuum manifold 4.6 ml of butyllithium (commercial solution in 15 % n-hexane, Merck) was pipetted and evaporated in vacuum at room temperature. The residue was frozen with liquid nitrogen and absolute ether (10 ml) was added by distillation. The system was filled with dry nitrogen to atmospheric pressure and 2-bromopyridine (2.37 g, 15 mmol) in absolute ether (5 ml) was carefully added at -60°C. The reaction mixture was stirred for one hour then frozen again, and after being evacuated it was carbonated at -78°C with carbon dioxide-^{14}C generated from $Ba^{14}CO_3$ (987 mg, 5 mmol, 40 mCi, 8.0 mCi/mmol). The cold reaction mixture, after hydrolysis with 5 N HCl (5 ml) was extracted continuously with ether for 4 hours, then 10 N NaOH (3 ml) was added and the solution was extracted further for 4 hours. The aqueous solution was adjusted to pH 2.7 and the extraction with fresh ether was prolonged for 45 hours. The ethereal extract was dried over magnesium sulfate, evaporated, and the residue was sublimed at 130-140°C to give 357 mg (2.9 mmol, 58 %) pure picolinic acid (3c), m.p. 135-137°C.

1-Benzyl-4-picolinoyl-^{14}C-piperazine (4c).

This material was prepared from 3c in a similar manner to the preparation of 4a. Yield: 708 mg (1.78 mmol), m.p. 165-166°C. The

material was shown to be homogeneous by radiochromatography. Total activity: 14.1 mCi at a specific activity of 7.88 mCi/mmol. Overall radiochemical yield based on $Ba^{14}CO_3$: 35.6 %.

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