SYNTHESIS OF 1,4-BIS(3'-BROMOPROPIONYL)-PIPERAZINE-2,3-^{14}C VIA PIPERAZINE-2,3-^{14}C

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SUMMARY

A simple procedure to synthesize 1,4-bis(3'-bromopropionyl) piperazine-2,3-^{14}C, pipobroman-^{14}C(I-^{14}C), via piperazine-2,3-^{14}C (V-^{14}C) was described.

The condensation of 1,2-bis(benzylamino)ethane(II) with ethylene dibromide-1,2-^{14}C gave 1,4-dibenzylpiperazine-2,3-^{14}C(III-^{14}C) in 34% yield. III-^{14}C was catalytically reduced in glacial acetic acid on Pd-C to afford piperazine-2,3-^{14}C diacetate(IV-^{14}C) in 90% yield, followed by the conversion in aqueous solution to free V-^{14}C which was in turn subjected to a Schotten-Baumann reaction with 3-bromopropionyl chloride to give I-^{14}C in 69% yield.

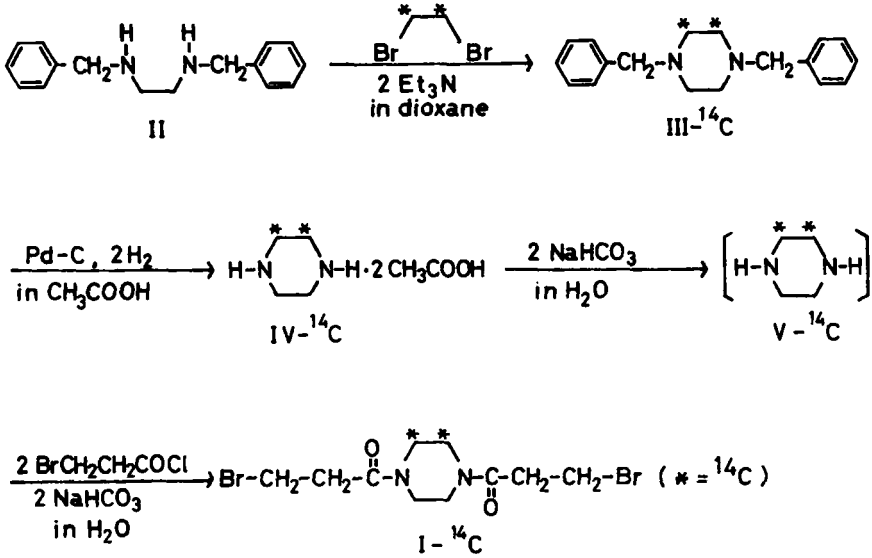
INTRODUCTION

Pipobroman, 1,4-bis(3'-bromopropionyl)piperazine(I), is known as an antineoplastic agent.

We investigated the synthesis of ^{14}C-labeled I for the drug metabolism studies. It was conceivable that a convenient method to prepare ^{14}C-labeled piperazine would be widely applicable for the syntheses of labeled drugs containing piperazine moiety in their molecules. At this point of view we studied the preparation of ^{14}C-labeled piperazine as well as ^{14}C-labeled I.

The established synthesis of ^{14}C-labeled I via ^{14}C-labeled piperazine is described in this paper as shown in Chart 1.

Chart 1



Herbert et al. [1] has reported the synthesis of piperazine-2,5-^{14}C by the reduction, with lithium aluminum hydride, of 2,5-diketopiperazine-2,5-^{14}C, which was obtained by the cyclization of glycine-1-^{14}C methyl ester.

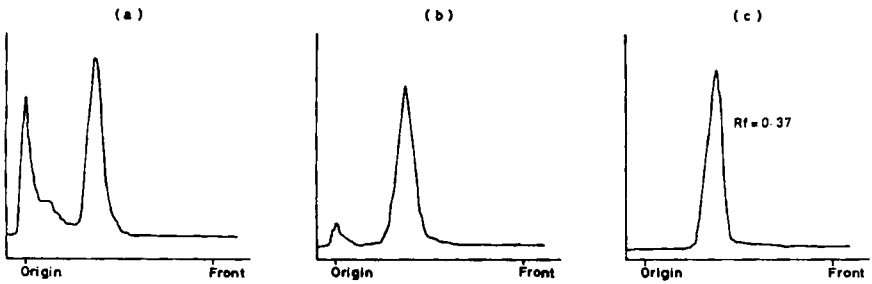
In the present study we adopted a synthetic route to ^{14}C-labeled piperazine that 1,2-bis(benzylamino)ethane(II) and ethylene dibromide(EDB) were condensed to form 1,4-dibenzylpiperazine (III) [2), 3)], which was in turn subjected to the catalytic reduction to give piperazine diacetate(IV) [4)], since the present method involves less reaction steps and more convenient procedure as compared with those described above.

The reaction of ethylene dibromide-1,2-^{14}C(EDB-^{14}C) and II is required to proceed in the small sealed tube, since minute quantity of volatile labeled compound is involved. The reaction was found to proceed smoothly in absolute dioxane in a sealed tube with an addition of a hydrogen bromide acceptor, triethylamine(TEA), instead of potassium carbonate [2), 3)] which might lead to the evolution of carbon dioxide.

A millimole-scale mixture of II, EDB-^{14}C(1 mCi), and TEA in absolute dioxane was sealed in the small ampule and heated. The thin layer chromatogram of the resultant crude product showed two radioactive peaks at origin and at Rf 0.37 as shown in Fig. 1a. The latter was identified as 1,4-dibenzylpiperazine-2,3-^{14}C(III-^{14}C), with 57 % of the total radioactivity. The crude product was purified successively on basic aluminum oxide and silica gel columns by using benzene as eluents, as shown in Fig. 1b and 1c. The yield of the purified specimen was 34 % calculated on EDB-^{14}C, and 51 % on II, respectively.

Fig. 1.

Radiochromatograms of 1,4-Dibenzylpiperazine-2,3-^{14}C(III-^{14}C).



a) Crude product.

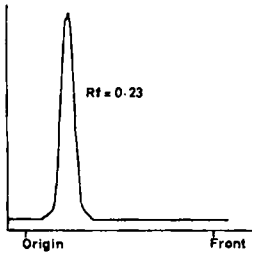
b) First purification by basic almina column.

c) Second purification by silica gel column.

Thin layer chromatography was all performed on silica gel G plate 0.25 mm thick. Solvent system : n-Hexane:EtOH = 10:1

Fig. 2.

Radiochromatogram of Piperazine-2,3-^{14}C diacetate(IV-^{14}C).

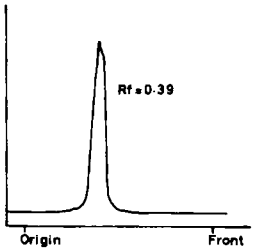


Solvent system :

EtOH : c-NH_4OH = 4 : 1

Fig. 3.

Radiochromatogram of Pipobroman-^{14}C(I-^{14}C).



Solvent system :

Benzene : Acetone = 7 : 3

III-^{14}C was subjected to the catalytic hydrogenation with Pd-C in glacial acetic acid to give piperazine-2,3-^{14}C diacetate (IV-^{14}C) with the yield of 90 %. The chemical and radiochemical purity of the product was found to be nearly 100 % by thin layer chromatography as shown in Fig. 2, indicating no further purification was necessary. The specific activity was 0.87 mCi/mmole.

Preparations of I have been reported that the condensation reactions of 3-bromopropionyl chloride(3-BPC) with free piperazine in anhydrous form [5] or in hexahydrate [6] were performed in organic solvents.

On the contrary, IV-^{14}C can be subjected to a successive condensation reaction in aqueous solution without isolation of free piperazine-2,3-^{14}C(V-^{14}C), when a Schotten-Baumann reaction is employed.

IV-^{14}C was dissolved in water and made free by the addition of sodium bicarbonate. Then, 3-BPC and the sodium bicarbonate solution were dropped alternately onto the free V-^{14}C solution. Recrystallization of the crude extracts with benzene gave colorless leaflets of 1,4-bis(3'-bromopropionyl)piperazine-2,3-^{14}C (I-^{14}C). The thin layer chromatogram of the specimen showed a Rf value identical with an authentic I, and its radiochemical purity was found to be nearly 100 % as revealed either by the radiochromatogram(Fig. 3) or by the inverse isotope dilution analysis. The specific activity was 0.87 mCi/mmole.

(EXPERIMENTAL)

All melting points are uncorrected.

Chromatogram was scanned on Actigraph III (Nuclear Chicago).

Radioactivity was determined on Tri-Carb liquid scintillation spectrometer (Packard).

IR spectrum was measured on Infrared spectrophotometer EPI-S2 (Hitachi).

1,4-Dibenzylpiperazine-2,3-^{14}C (III-^{14}C)

A mixture of 1 mCi of EDB-^{14}C(purchased from the Radiochemical Centre, Amersham, England, 9.7 mCi/mmole), 0.08 ml of non-labeled EDB, 0.35 ml of TEA and 160 mg of II [3] in 2 ml of abs. dioxane was heated at 137 °C for 4.5 hr. in a sealed tube. Then the excess TEA and dioxane were evaporated under reduced pressure. The residue was suspended in dil. NaOH and extracted with benzene. The benzene layer was washed with NaCl solution, dried over anhydrous sodium sulfate and evaporated. The residue was dissolved in the minimum volume of benzene and the solution was passed through the column of 3 g of basic aluminum oxide. Twenty five ml of benzene eluate contained 108 mg of III-^{14}C, whose radiochemical

purity was 93 % as revealed by thin layer chromatogram(Fig. 1b). The crude product was further purified on the column of 1 g of silica gel. One hundred ml of benzene completed the elution of III-^{14}C, 91.7 mg, whose final radiochemical purity was 100 % by thin layer chromatogram(Fig. 1c). The yield was 51 % from II and 34 % from EDB-^{14}C, respectively. The specific activity was 0.87 mCi/mmole.

Non-labeled III was similarly prepared from non-labeled EDB, recrystallized from dil. MeOH. m.p. 90-91 °C.

Analysis: $C_{18}H_{22}N_2$ = 266.4

	C	H	N
Calcd. (%)	81.16	8.32	10.52
Found (%)	80.78	8.50	10.29

Piperazine-2,3-^{14}C diacetate (IV-^{14}C)

A solution of 90 mg of III-^{14}C in 5 ml of glacial acetic acid was hydrogenated on 100 mg of Pd-C(13 %) at room temp. under atmospheric pressure. At the end of 3 hr. the theoretical amount of hydrogen had been consumed. After removal of catalyst and acetic acid, the residue was recrystallized from dil. EtOH. The product, IV-^{14}C, 62.8 mg(90 %), was obtained. The radiochemical purity was 100 % on thin layer chromatogram(Fig. 2).

Non-labeled IV was similarly prepared from non-labeled III, m.p. 202-205 °C.

Analysis : $C_4H_{10}N_2-C_4H_8O_4$ = 206.2

	C	H	N
Calcd. (%)	46.59	8.80	13.58
Found (%)	46.34	8.86	13.48

1,4-Bis(2'-bromopropionyl piperazine-2,3-^{14}C (V-^{14}C)

Sixty mg of IV-^{14}C in 1 ml of aqueous solution was mixed with 0.99 ml of 5.0 % $NaHCO_3$. The solution was cooled at 5 °C. And 149 mg of 3-BPC [7] in 3 ml of abs. benzene and 1.47 ml of 5.0 % $NaHCO_3$ was dropped alternately onto the solution with continuous stirring. The mixture was left stirring for 2 hr. at 5-10 °C, and extracted with benzene. The benzene layer was rinsed with NaCl solution, dried over anhydrous sodium sulfate and evaporated. The residue was recrystallized from iso-PrOH-n-Hexane. The colorless leaflets of I-^{14}C, 71.5 mg(69 %), were obtained with the specific activity of 0.87 mCi/mmole(2.45μCi/mg).

Non-labeled I was synthesized in the quite same way. m.p. 102-103 °C(iso-PrOH-n-Hexane).

Analysis : $C_{10}H_{16}N_2Br_2O_2$ = 356.1

	C	H	N	Br
Calcd. (%)	33.73	4.53	7.86	44.88
Found (%)	34.04	4.79	7.96	45.13

IR(KBr disk) : 1635 cm^{-1}(ν C=O.

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