SYNTHESIS OF THE RING—AND SIDE—CHAIN—^{14}C—LABELED 1,2—BIS—(4—MORPHOLINOMETHYL—3,5—DIOXOPIPERAZIN—1—YL) PROPANE

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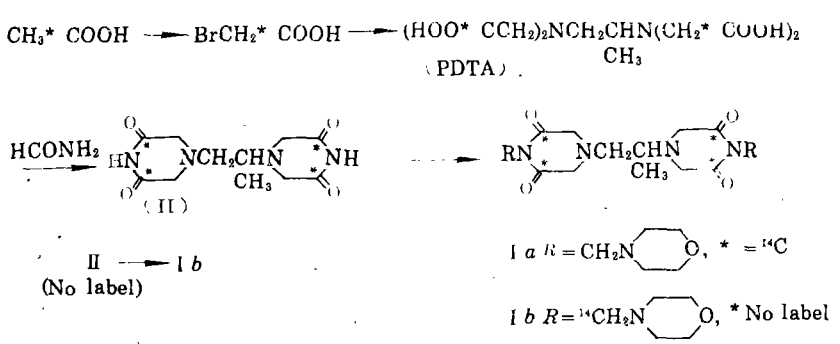
ABSTRACT

The ring-and side-chain-^{14}C-labeled probimane, 1,2-bis (4-morpholino-methyl-3,5-dioxopiperazin-1-yl) propane were synthesized from acetic acid-1-^{14}C in 4 steps and from ^{14}C-formaldehyde in 1 step respectively. The radiochemical yeild for the ring labeling was 28.1%; for the side-chain labeling was 18.5%.

Keywords: Probimane 1,2-bis (4-morpholinomethyl-3,5-dioxopiperazin-1-yl) propane ^{14}C-labeled

I. INTRODUCTION

Probimane [1,2-bis(4-morpholinomethyl-3,5-dioxopiperazin-1-yl) propane] exhibited antitumor activites against sarcomas 37 and 180, heptoma 22, P388 and L615



Scheme 1 Synthesis of Probimane

leukemias in mice[1]. The labeled drugs were required for metabolic and other pharmacological studies. This report describes the synthesis of ^{14}C-probimane labeled at piperazine ring (I*a*) and at the methylene side-chain (I*b*). The method of synthesis was outlined in scheme 1. The synthesis of the key intermediate, bis-

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(3,5-dioxopiperazinyl) propane (Ⅱ) was based on the Lin's method[2]. According to his method propylenediamine tetraacetic acid (PDTA) was prepared by condensation of propylenediamine with chloroacetic acid, when bromoacetic acid was used the condensation reaction failed. However in this laboratory PDTA was successfully synthesized in good yield by using bromoacetic acid-1-^{14}C. ^{14}C-labled (Ⅱ) was prepared by heating ^{14}C-PDTA with formamide in 57% yield. Ⅱ was converted to the ring-labeled compound (I*a*) by Mannich condensation of Ⅱ with formaldehyde and morpholine. The total radiochemical yield of Ia was 28.1% on the basis of the excess of bromoacetic acid and the chemical yield was 35.2% on the basis of propylene diamine. The side-chain-labeled probimane was prepared in a similar mannar in 18.5% radiochemical yield, using ^{14}C-formaldehyde.

Ⅱ. EXPERIMENTAL

All the melting points reported were not corrected. HNMR were determined on a JEOL-PS100 spectrometer. Radioactivity was measured on a YSJ-78 liquid scintillation system. Acetic acid-1-^{14}C was purchased from Shanghai Institute of Chemical Reagents.

Bromoacetic acid-1-^{14}C: Prepared as described by G.A.Ropp[3] yield from acetic acid-1-^{14}C was 100%.

Propylenediamine (tetraacetic acid-1-^{14}C): A mixture of propylenediamine (185 mg in 3ml H_2O) and NaOH (520 mg in 3ml H_2O) solution was added to a cold stirred solution of bromoacetic acid-^{14}C (1.8g) in H_2O (3ml) neutrized with equivalent Na_2CO_3. The reaction mixture was stirred at 50-60°C for 4h. and then 100-110°C for 3h. After cooling and filtration the reaction mixture was acidified with concentrated HCl (pH 1) and kept at room temperature for 48h. The insoluble tetraacetic acid was collected by filtration and washed with water and dried. The crude product (680 mg, yield 89%) was used directly in the next step. The purified product melt at 238-240°C (Ref.[4] m.p. 236°C). Anal (cold run).: $C_{11}H_{18}N_2O_8$, Calc. for C,43.14; H,5.92; N,9.15; Found: C,43.16; H,5.97; N,9.10.

Bis-(3,5-dioxopiperazin-1-yl-3,5-^{14}C) propane (II): A mixture of ^{14}C-labeled PDTA (637 mg) and formamide (4ml) was heated at 150°C for 5h. The reaction mixture was kept at 4°C for 48h. The solid collected was washed well with alcohol and dried, yield 320 mg (57%), m.p. 229-230°(dec.) (literature[2] m.p. 230-232°C). Anal. (cold run): $C_{11}H_{16}N_4O_2$, calc. for C,49.24; H,6.01; N,20.88; found: C,48.96; H,5.99; N,20.74.

^{14}C-ring-labeled probimane (I*a*): A mixture of compound II (320 mg in 8ml alcohol) and morpholine (0.6 ml) was heated at 85°C, from the top of the reflux condenser formaldehyde solution (37%, 1.5ml) was added dropwise. The heating was continued for 10 min. The insoluble material was removed from the warm reaction mixture. The

filtrate standed over night. The white crystal was collected by filtration and washed with alcohol and dried, yield 410 mg (73.7%), m.p. 165°C, specific activity 65.2 MBq/mmol, total radiochemical yield 28.1% (from acetic acid-1-^{14}C), radiochemical purity 96% (by TLC), cold run HNMR ($CDCl_3$) δ 1.1 (3H,d,methyl), 2.7 (8H, A_2B_2, morpholine), 3.68 (8H, A_2B_2, morpholine), 2.2-3.0 (3H, m, propylene), 2.55 (8H, d, $COCH_2N$), 4.7 (4H, s, m, ethylene), Anal: $C_{21}H_{34}N_6O_6$ calc. for C, 54.07; H, 7.35; N,18.01; found C, 54.21; H,7.51; N,18.26.

^{14}C-formaldehyde: Prepared by reduction[5] of CO_2 generated from $Ba^{14}CO_3$.

Side-chain-^{14}C-labeled probimane [*Ib*]: Essentially, the procedure for preparing I*b* followed that of I*a* except ^{14}C-formaldehyde was used, radiochemical yield 18.5% from $H^{14}CHO$, specific activity 34.4 MBq/mmol.

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