SYNTHESIS OF 3-MORPHOLINO-N-ETHOXYCARBONYL SYDNONIMINE-5-^{14}C (SIN-10-^{14}C)

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Since syndnonimines were synthesized in 1957[1,2], many derivatives of sydnonimines have been prepared[3,4] and it was found that 3-dialkylaminosydnonimines and their N-acyl derivatives have a remarkable hypotensive activity in animals[5,6]. The carbon-14 labelled compound of 3-morpholino-N-ethoxycarbonyl sydnonimine (I, SIN-10) was desired for the study of metabolic fate in animals, and the labelled position at 5 in I was chosen, because I is stable in acid and neutral solution but not so stable in alkaline solution due to the cleavage of ethoxycarbonyl group in I by the hydrolysis reaction[7]. N-Aminomorpholine (II) was reacted with formaldehyde-sodium bisulfite and K^{14}CN to give N-morpholinoaminoacetonitrile-1-^{14}C (III). Nitrosation of III led to intermediate, N-morpholino-N-nitrosoaminoacetonitrile-1-^{14}C (IV), and IV was cyclized to 3-morpholino sydnonimine-5-^{14}C hydrochloride (V) by the action of an excess of HCl. Finally, 3-morpholino-N-ethoxycarbonyl sydnonimine-5-^{14}C (VI) was obtained by the reaction of V with ethyl chlorocarbonate in the presence of $NaHCO_3$. The overall radiochemical yield of VI, at a specific activity of 2 mCi/mmole, was 22.5% based on K^{14}CN. The purity of VI was shown to be 99% based on radiochromatogram and isotope dilution method.

EXPERIMENTAL

3-Morpholino sydnonimine-5-^{14}C hydrochloride (V).

After a solution of 693 mg of N-aminomorpholino hydrochloride in 0.5 ml of water was neutralized with a solution of 0.875 ml of

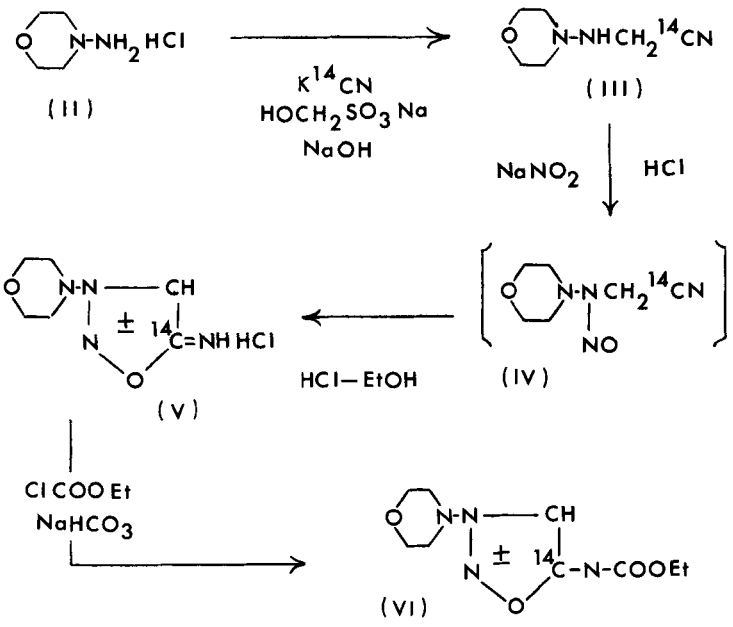

Chart 1

Synthesis of 3-morpholino-N-ethoxycarbonyl sydnonimine-5-^{14}C

20% NaOH, 762 mg of formaldehyde-sodium bisulfite was added to the solution. The mixture was heated at 55-60 for 3 h and then added to 326 mg of $K^{14}CN$ (10 mCi). The resulting mixture was further heated at 55-60 for 4 h with stirring and then extracted with ethyl acetate. The residue was obtained by evaporating the extract and dissolved into 1 ml of water. To this aqueous solution was subsequently added dropwise 0.41 ml of 35% HCl with stirring and cooling at 4-5, 0.81 ml of $NaNO_2$ solution and allowing to react for 1 h. The reaction mixture was extracted with chloroform, and the extract was dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was dissolved into a small amounts of ethanol and diluted with 2.52 ml of 20% ethanol-HCl. After the solution was kept in a refrigerator overnight, 3-morpholino sydnonimine-5-^{14}C hydrochloride was collected by filtration, washed with cooled ethanol and dried; yield 39% based on

$K^{14}CN$, mp 191 (dec), Rf 0.12 on silica gel-F TLC (Tokyokasei, Ltd., developing solvents: MeOH : EtOH=1 : 1, v/v) which were identical with that of authentic sample.

3-Morpholino-N-ethoxycarbonyl sydnonimine-5-^{14}C (VI).

To a solution of 358.3 mg of V in 0.9 ml of water was added 900 mg of $NaHCO_3$ and 970 mg of ethyl chlorocarbonate with stirring and cooling at 4-5. The rate of addition of $NaHCO_3$ and ethyl chlorocarbonate required reciprocally for 4 h. After the mixture was allowed to stand overnight in a refrigerator, the crystals were filtered off and dissolved into chloroform. The chloroform solution was dried over anhydrous Na_2SO_4 and then evaporated to dryness. The residue was recrystallized from toluene to give 2 mCi/mmole of VI, yield 22.5% based on $K^{14}CN$, mp 140, Rf 0.58 on TLC silica gel-F (Tokyokasei, Ltd., developing solvents: acetone : benzene = 1 : 1, v/v) and Rf 0.72 on TLC silica gel-F (Tokyokasei, Ltd., developing solvents: MeOH : EtOH = 1 : 1, v/v), which were identical with that of authentic sample.

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