A NOVEL SYNTHESIS OF ETHANOLAMINE-2-^{14}C

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SUMMARY

Ethanolamine-2-^{14}C was prepared by the reduction of benzyloxycarbonyl-glycine-1-^{14}C methyl ester. The reduction was carried out with calcium borohydride and the protecting group was removed by hydrogenolysis.

Key Words: benzyloxycarbonyl-glycine-1-^{14}C, benzyloxycarbonyl--ethanolamine-2-^{14}C, L-benzyloxycarbonyl-ω-nitroargininol, L-ω-nitroargininol

INTRODUCTION

Ethanolamine labelled with ^{14}C is an important starting material in the synthesis of biologically active compounds and is often used for introducing radioactivity into the molecule. Some methods are mentioned for its preparation in the literature, but none is simple and the yield of neiter synthesis surpasses 50 %. The preparation of labelled ethanolamine by splitting the ethylene oxide ring[1,2,3]-including the preparation of ethylene oxide- requires very complicated equipment and skilful manipulation, while the methods using $LiAlH_4$ for the reduction of glycolonitrile benzoate,[4] ethyl cyanoformate,[5] glycine ethyl ester[6] and N-trityl--glycine ethyl ester,[7] respectively, are impracticable, because of the tedious separation of ethanolamine from alumina precipitates.

Our method has some advantages against the published ones,[1-7] avoids the difficulties referred above and consists of very simple

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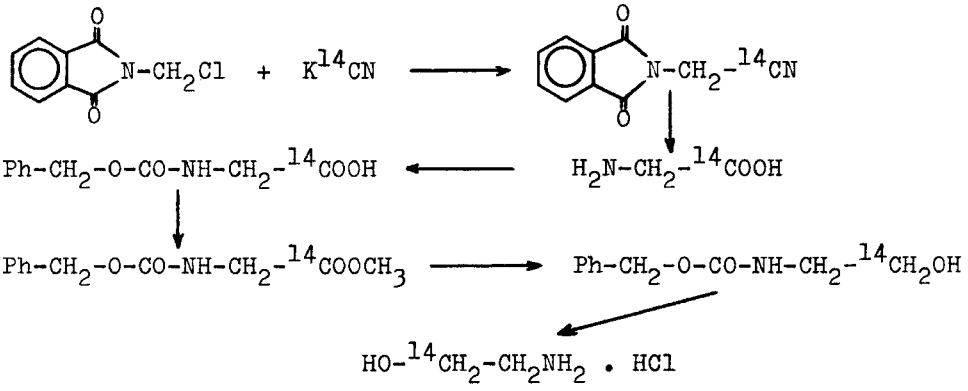
steps (see Reaction Scheme). Glycine-1-^{14}C was prepared by the known method[8] and it was isolated in the form of benzyloxycarbonyl-glycine-1-^{14}C. It was esterified with diazomethane and reduced with calcium borohydride to benzyloxycarbonyl-ethanolamine-2-^{14}C.* At last the protecting group was removed by hydrogenolysis. The yield calculated for K^{14}CN was 58 %.

This method is not only suitable for the preparation of ethanolamine, but for that of other amino-alcohols as well. A case in point is the preparation of L-ω-nitroargininol, which has not been prepared before. We report here its preparation as non-labelled product.

Reaction Scheme



EXPERIMENTAL

Melting points were determined with a BÜCHI-510 Melting Point Determinator. Thin layer chromatography was carried out on 5x20 cm plates coated with Silica gel 60 $PF_{254+366}$ (MERCK), the spots were detected by a Berthold LB 2723 scanner and chlorine-tolidine reagent. Activity was measured by a Packard Tri-Carb Liquid Scintillation Spectrometer.

Benzyloxycarbonyl-glycine-1-^{14}C

K^{14}CN (695.0 mg, 10.53 mmoles, 7.474 GBq) was dissolved in

* Benzyloxycarbonyl-ethanolamine-2-^{14}C was prepared by the reaction of ethanolamine-2-14C with benzyloxycarbonyl chloride.9 The reduction of glycine ethyl ester by calcium borohydride seems to be a very efficient method, but the isolation of ethanolamine is also very difficult, so we found more advantageous to use of the benzyloxycarbonyl protecting group.

methanol (20 ml) and a solution of chloromethyl-phthalimide (2.340 g, 12.0 mmoles) in warm dioxane (5 ml) was added. The mixture was stirred for one hour at room temperature and was refluxed for one hour more. After cooling the precipitate was filtered off, washed with methanol (2x5 ml) and the filtrate was evaporated in a rotary evaporator. The residue was dissolved in a mixture of acetic acid (16 ml), water (16 ml) and conc. HCl (16 ml) and refluxed for 18 hours. Then it was cooled to 0°C and phthalic acid was filtered off, washed with cold water (2x5 ml) and the filtrate was evaporated. The residue was dissolved in water (20 ml), treated with charcoal and 8 N NaOH (12 ml) was added. The solution was concentrated to about half volume (to expel ammonia) and benzyloxycarbonyl chloride (4 ml, about 25 mmoles) was added at 0°C. The mixture was stirred for one hour at 0°C, then for 18 hours at room temperature and during this time the pH of the mixture was maintained above 10 by adding 8 N NaOH. Then the mixture was extracted with ethyl ether (20 ml), saturated with NaCl, was cooled to 0°C and acidified to pH 1 with conc. HCl. The mixture was extracted with ethyl acetate (4x20 ml), the extracts were washed with 25 % NaCl (30 ml), dried over Na_2SO_4 and the solvent was evaporated. The residue was 1.564 g (7.48 mmoles) of benzyloxycarbonyl-glycine-1-^{14}C. M.p.: 113-5°C (Lit.[8]: 115-7°C). The material showed only one spot on a TLC plate (chloroform-metanol--acetic acid 95:5:3; R_f = 0.4). Total activity: 5.331 GBq (71.3 % calculated for $K^{14}CN$).

N-Benzyloxycarbonyl-ethanolamine-2-^{14}C

1.564 g of benzyloxycarbonyl-glycine-1-^{14}C (7.1 mmoles, 5.331 GBq) were dissolved in ethyl acetate (20 ml) and diazomethane in ethyl ether was added until gas evolution was finished and the solution remained yellow for 10 minutes. Then the solvent was evaporated, the residue (colourless oil) was dissolved in ethanol (40 ml) and $CaCl_2 \cdot 2H_2O$ (3.0 g) was added. When the solution became clear, 1.5 g of $NaBH_4$ (about 40 mmoles) were added in small por-

tions for 30 minutes at room temperature. The mixture was stirred for an additional hour, the solvent was evaporated, the residue was suspended with water (40 ml) and the mixture was acidfied to pH 1 with conc. HCl. It was extracted with chloroform (3x25 ml), the combined extracts were washed with water (20 ml), 5 % $NaHCO_3$ (2x20 ml) and 25 % NaCl (20 ml), successively, dried over Na_2SO_4 and the solvent was evaporated. 1.358 g of benzyloxycarbonyl--ethanolamine-2-^{14}C (6.96 mmoles) were obtained. The material proved to be pure by TLC (benzene-ethyl acetate 1:4; R_f = 0.3). Total activity: 4.762 GBq (89 %).

Ethanolamine-2-^{14}C hydrochloride

Benzyloxycarbonyl-ethanolamine-2-^{14}C (1.358 g, 6.96 mmoles, 4.762 GBq) was dissolved in ethanol, 0.5 ml of acetic acid and 0.2 g of palladium-charcoal catalyst were added and the mixture was stirred for 3 hours in hydrogen stream. The catalyst was filtered off, the filtrate was acidified with HCl in ethanol and the solvent was evaporated. The residue (a brownish solid) was dried in a vacuum desiccator over KOH and P_2O_5 and recrystallized from ethanol-ethyl ether. 563 mg of ethanolamine-2-^{14}C.HCl were obtained as white crystals. Total activity: 4.300 GBq. Yield: 90 %. M.p.: 77-81°C. The material showed one spot on TLC plate (butanol -acetic acid-water 4:1:1; R_f = 0.2).

Benzyloxycarbonyl-L-ω-nitroargininol

Benzyloxycarbonyl-L-ω-nitroarginine methyl ester (3.68 g, 10 mmoles) and $CaCl_2.2H_2O$ (6.0 g) were dissolved in ethanol (150 ml). After 10 minutes' stirring a clear solution was obtained, then $NaBH_4$ (2.2 g) was added in small portions for 30 minutes and the mixture was stirred for an additional hour at room temperature. Ethanol was evaporated, the residue was agitated with a mixture of water (30 ml) and acetic acid (3 ml), then the undissolved material was filtered off and washed with water (2x5 ml). After drying in a vacuum desiccator, 2.45-2.75 g of material (75-81 %)

were obtained. The material proved to be pure by TLC (ethyl acetate; R_f = 0.2), but contained some inorganics, from which it can be liberated by recrystallization from isopropanol. M.p.: 138-9°C. $[\alpha]_D$ = 13.94° (c = 1; methanol). Analysis: Found C 49.32 %, H 6.26 %, N 20.54 %. Calc. C 49.55 %, H 6.24 %, N 20.64%.

L-ω-nitroargininol hydrobromide

Benzyloxycarbonyl-L-ω-nitroargininol (850 mg) was dissolved in 4 N HBr in acetic acid (5 ml) and it was kept at room temperature for an hour. Then abs. ethyl ether was added (20 ml), the solvent was decanted and the precipitated gum was triturated with a further portion of ethyl ether (20 ml) and was dried in a vacuum desiccator. The gum slowly solidified. 630 mg of L-ω-nitroargininol.HBr were obtained (92 %). M.p.: 152-4°C. The material was very hygroscopic and seemed to be pure by TLC (ethyl acetate--ethanol 1:1; R_f = 0.3).

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