NOTE

SYNTHESIS OF N,N-DIMETHYL[2-^{14}C]MORPHOLINIUM CHLORIDE

Jan Adamus, Piotr Paneth and Władysław Reimschüssel
Institute of Applied Radiation Chemistry, Technical University, 90-924 Łódź, Poland.

SUMMARY

N,N-dimethyl[2-^{14}C]morpholinium chloride was obtained from [1-^{14}C]acetic acid in five-step synthesis with [2-^{14}C]morpholine as the intermediate.

Key Words: Morpholine, N,N-dimethylmorpholinium chloride, ^{14}C-ring labelling, Synthesis of growth retardant

INTRODUCTION

N,N-dimethylmorpholinium chloride (RW3) is a new growth retardant (1-3). Recently its synthesis has been described (4). In order to study the metabolic fate the compound labelled with ^{14}C in the morpholinium ring was required. The preparation of RW3-^{14}C appears not to have been reported. Accordingly, this paper describes the radiochemical synthesis of RW3-^{14}C. It was obtained with overall yield 11% based on [1-^{14}C]acetic acid (OPiDI, Poland).

DISCUSSION

Reaction sequences for the synthesis of RW3-^{14}C employ morpholine labelled with ^{14}C in the ring as the precursor.

There are two procedures available for the chemical synthesis of morpholine. The first one starts from ethylene, which is converted to bis-(2-iodoethyl) ether (5). The latter is then allowed to react with NH_3 to give morpholine. The overall yield based on ethylene is 10% (6). The main disadvantages of the above procedure are: hard accessibility of the ^{14}C labelled ethylene and low yield of the product.

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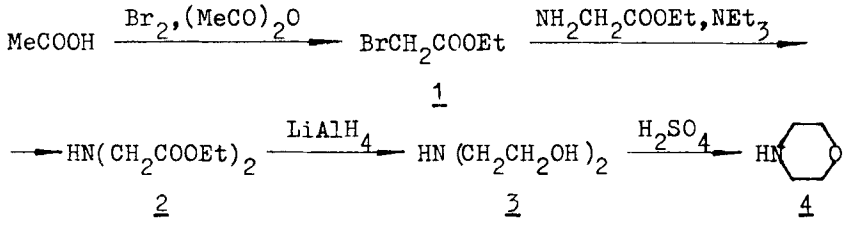
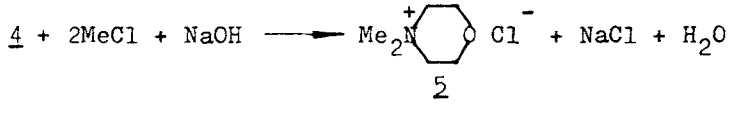
We utilized the alternative, four-step procedure with acetic acid as starting material (Scheme I). In the first step ethyl bromoacetate 1 is generated. We found Kögl reaction (7) to be better than Schweer's (8), who used red phosphorus as the catalyst. The contamination of 1 with forming phosphoric compounds (9) lowers the yield of morpholine. In the next step 1 reacts with glycine ethyl ester in the presence of NEt_3 to give bis-/(carboxyethyl)methyl/amine 2, which is then reduced to bis-(2-hydroxyethyl)amine 3 by $LiAlH_4$ (8). The last step, cyclization proceeds in the presence of H_2SO_4 at 180-200 °C (10). The use of HCl seems to be less convenient (11).
A yield of morpholine based on acetic acid is about 20%.



SCHEME I

The reaction, which leads to RW3 was a modification of the Witek et al. synthesis (4). This is the reaction of 4 with methyl chloride in the presence of alkalies (Scheme II).



SCHEME II

For labelling purposes we used MeCl in large excess. This allowed us to decrease the scale of RW3-^{14}C synthesis.

EXPERIMENTAL

The radiochemical purity was demonstrated by TLC analysis, which was carried out on Kieselgel G plates (Merck) using acetic acid/acetone/25% hydrochloric acid 85:10:5 (v:v) as developing solvent system. R_F-values are equal to 0.47 and 0.29 for com-

pounds 4 and 5, respectively. Chromatograms (developing path 10 cm) were cut into parts of 0.5 cm width and these parts were put into scintillation vials. Radioactivity of substances adsorbed on silica-gel (12) was determined in SL 30 (France) liquid scintillation counter using PPO-toluene (6 g/l) as the counting medium.

[2-^{14}C]morpholine, 4-^{14}C

H_2SO_4 (97%, 0.53 g) was added dropwise to (2-hydroxy[2-^{14}C]ethyl)(2-hydroxyethyl)amine, 3-^{14}C (2.75 mmol; 41.9 MBq/mmol; 95.0% radiochemical purity) at 0 °C. The solution was heated at 180 °C for 5 hrs. Saturated solution of NaOH (3 ml) at -10 °C and then solid NaOH (0.3 g) were added. The product was extracted with ether (4×1 ml). Extract was dried (NaOH) and the solvent was evaporated. Freshly-cut sodium metal (20 mg) was added to the residue which was then heated to 40 °C and freezed (liquid nitrogen). After reduction of pressure to 5 mmHg volatile product was distilled off. A 64% radiochemical yield of 4-^{14}C (1.77 mmol, 41.9 MBq/mmol) was recovered. The radiochemical purity was 96.0%.

N,N-dimethyl[2-^{14}C]morpholinium chloride, RW3-^{14}C, 5-^{14}C

The sealed glass ampul containing solution of [2-^{14}C]morpholine (1.76 mmol) in ethanol (1.5 ml), MeCl (3 g) and saturated aq. NaOH (80 μl) was kept at room temperature for 24 hrs. After that time the ampul was opened, the contents was filtered and the solvent was evaporated. The residue was cristallized from acetone/ethanol (1:1). A 60% radiochemical yield of product (1.07 mmol, 41.9 MBq/mmol) was recovered. The radiochemical purity was 99.5%.

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