NOTES

A HIGH YIELD SYNTHESIS OF 2-^{14}C-METHIMAZOLE

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SUMMARY

2-^{14}C-Methimazole was prepared in a condensation reaction between methylaminoacetaldehyde dimethyl acetal and potassium ^{14}C-thiocyanate in acidic medium. The yield of final product was 86.3% of theoretical with a radio purity of greater than 99.5%.

Key Words: Methimazole, 1-Methyl-2-Mercaptoimidazole, Antithyroid Agent, Radiosynthesis

INTRODUCTION

Methimazole (1-methyl-2-mercaptoimidazole) (I) is a drug commonly used in the treatment of thyrotoxicosis. This drug has a number of toxic side-effects including fever, skin rashes, jaundice, gastrointestinal disturbance, neuropathy and bone marrow depression. Experiments studying the mechanisms of these methimazole-induced toxic effects are currently underway in this laboratory.

Although the use of ^{14}C-methimazole in metabolic studies had been reported previously (1,2,3), a procedure for the radiosynthesis of methimazole has not been described in detail. Jones et al (4) have reported the synthesis of substituted imidazoles by reaction of α-aminoacetals (II) with potassium thiocyanate. This procedure is best suited for the preparation of imidazole derivatives with substituents such as carboxylates in the 4 (or 5)-position. This reaction leading to

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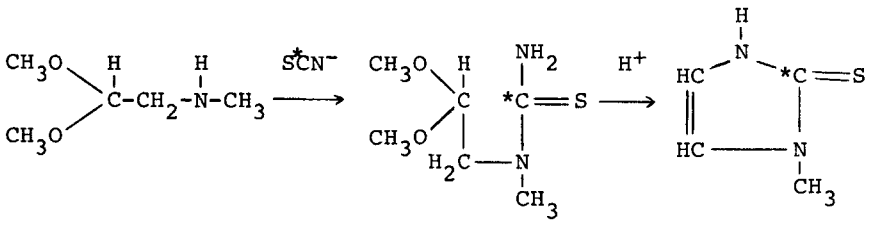
the synthesis of methimazole proceeds in two distinct steps. The initial phase involves the formation of the α-ureidoacetal (III) which is converted to methimazole upon exposure to dilute acid.



(II) (III) (I)

A preliminary small scale synthesis using this procedure (4) gave a poor yield of methimazole. Further investigation revealed that the α-ureidoacetal was formed in high yield (85-92%) but the cyclization of this intermediate in diluted sulfuric acid (0.08 N) to methimazole was less than 10% after 72 hours at room temperature. This communication presents a modified procedure for the microsynthesis and purification of 2-^{14}C-methimazole.

EXPERIMENTAL

All glass-distilled solvents were used. Radioactivity was measured using a Packard Tricarb Model 3320 liquid scintillation spectrophotometer. Radiochemical purity was determined by thin layer chromatography (tlc) with liquid scintillation counting as the detection method. Flexible silica gel tlc plates (Baker) were used to monitor the progress of the reaction. Analytical and preparative isolation of the products was performed on silica gel GF_{254} tlc plates (0.25 mm and 1 mm thickness, Analtech) using two solvent systems: isopropanol-benzene 1:1 and tetrahydrofuran-formic acid 10:1. The R_f values for methimazole in these solvent systems were 0.57 and 0.89, respectively.

The location of radioactivity on tlc plates was monitored by either zone scraping and scintillation counting or by autoradiography using Kodak No-Screen x-ray film. NMR spectra were determined on a EM-360 Mz NMR spectrometer (Varian) and mass spectra were obtained using a direct sample introduction probe in a LKB Model 9000 mass spectrometer.

Diluted hydrochloric acid (5 ml, 0.28 mmole) was added with swirling to a 5 ml mixture of potassium ^{14}C-thiocyanate (Amersham, specific activity 60 mCi/mmole, 1.62 mg, 0.0167 mmole) and unlabeled potassium thiocyanate (23.4 mg, 0.24 mmole) in a 50 ml round bottom flask. Methylaminoacetaldehyde dimethyl acetal (Aldrich, 30 mg, 0.25 mmole) in 5 ml methanol was added dropwise while the temperature of the reaction was maintained at 5°. The reaction was refluxed for 24 hours. Tlc indicated the quantitative formation of α-ureidoacetal. Sulfuric acid in a final concentration of 1.6 N (10 ml, 20 mmole) was next added and the reaction mixture refluxed for an additional 3 hours. The progress of the reaction was monitored by examining for the formation of methimazole using tlc.

The reaction mixture was cooled to room temperature, saturated with sodium chloride (4 g) and extracted five times with 15 ml portions of chloroform. These extractions removed approximately 92% of the radioactivity originally present in the reaction mixture. The chloroform extracts were combined, dried over anhydrous sodium sulfate, concentrated under vacuum and the product purified by preparative tlc. Analytical tlc indicated the presence of two areas of radioactivity (R_f = 0.65 and 0.33 in the isopropanol-benzene solvent system) which correspond to methimazole (98.2%) and α-ureidoacetal (1.8%), respectively. The ^{14}C-methimazole was extracted from the silica gel of the preparative tlc plate using ethyl acetate. After evaporation of the solvent, the residue yielded 24.6 mg

^{14}C-methimazole (m.p. 144°-146° uncorrected); 86.3% of theoretical. The specific activity of the ^{14}C-methimazole was calculated to be 4.85 mCi/mmole with greater than 99.5% radiopurity.

The NMR spectrum of ^{14}C-methimazole in methanol consisted of δ 3.6 (S, 3H, N-CH_3) and 6.8 (S, 2H, CH = CH). The mass spectrum was interpreted as: m/e 114 [M^+] (100%), 81 (63.6%), 72 (75.0%), 69 (47.7%), 54 (29.5%), 42 (59.0%).

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