SYNTHESIS OF CARBON-14 AND DEUTERIUM LABELED 3-NITRO-6-PROPOXYIMIDAZO [1,2-B]PYRIDAZINE - AN ANTIPARASITIC AGENT

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SUMMARY

A potent antiparasitic agent 3-nitro-6-propoxyimidazo[1,2-b]-pyridazine (3) was synthesized, labeled with carbon-14 in the propoxy side chain, from n-propanol-1-^{14}C and 6-chloro-3-nitroimidazo-[1,2-b]pyridazine (2). The final product was obtained in 58% radiochemical yield with specific activity of 1.13 mCi/mmole and radiochemical purity of greater than 99%. The deuterium labeled compound (4) was also synthesized for absorption and metabolism studies.

Key Words: 3-Nitro-6-propoxyimidazo[1,2-b]pyridazine, Carbon-14, Deuterium, Antiparasitic Agent.

INTRODUCTION

3-Nitro-6-propoxyimidazo[1,2-b]pyridazine (1) is a new potent agent which is active against cecal Entamoeba histolytica infections in rats, hepatic Entamoeba histolytica infections in hamsters and Trichomonas vaginalis infections in mice. Proper preclinical analysis of metabolic pathways required the synthesis of a radiolabeled drug. This was prepared by introduction of an n-propoxy-1-^{14}C group into the molecule.

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RESULTS AND DISCUSSION

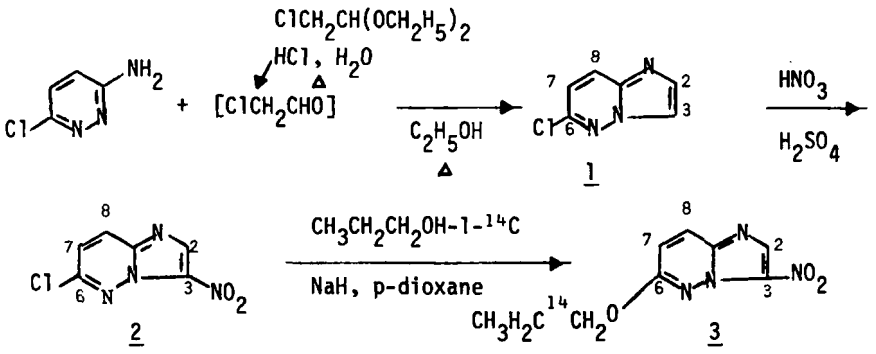
Introduction of a carbon-14 label into the molecule was conveniently achieved by reaction of 6-chloro-3-nitroimidazo[1,2-b]pyridazine (2) with n-propanol-1-^{14}C.

The synthetic scheme is a convenient three step process starting with the readily available 3-amino-6-chloropyridazine. The 6-chloroimidazo [1,2-b]pyridazine (1) was obtained in a yield of 78% by the reaction of 3-amino-6-chloropyridazine with chloroacetaldehyde, prepared *in situ* by hydrolysis of the diethylacetal.

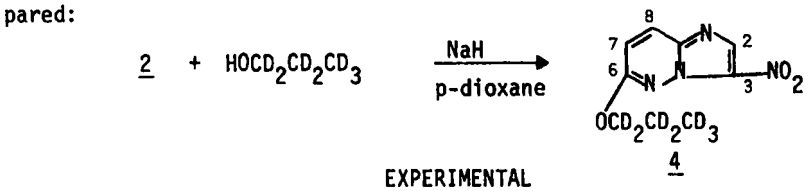
The nitro derivative (2) was obtained in a yield of 63% with fuming red nitric acid in concentrated sulfuric acid. Whereas Kobe *et al* (3) reported a 210° m.p. for (2), we found m.p. 142-143°.

The carbon-14 label was conveniently introduced in the final step by reaction of 6-chloro-3-nitroimidazo[1,2-b]pyridazine (2) with n-propanol-1-^{14}C in a radiochemical yield of 58%. The specific activity was 5.09 μCi/mg (1.13 mCi/mmole) and the radiochemical purity was greater than 99% as determined by thin layer chromatography.

SYNTHETIC SCHEME



To help in the identification of metabolites of (3) the deuterium labeled compound, 3-nitro-6-(propoxy-d_7)imidazo[1,2-b]pyridizine (4) was also prepared:



EXPERIMENTAL

Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. The NMR spectrum was obtained with a Varian Model HA-100 spectrometer. The mass spectrum was obtained with an AEI MS902. TLC's were performed on silica gel F-254 precoated plates (Brinkman). The plates were developed in the ascending mode in the following solvent system:

System (A). Upper phase of benzene - acetone - water (10:9:10, v/v).

System (B). Upper phase of benzene - acetone - water (10:5;10, v/v).

After radioautography the ^{14}C areas were scraped and counted in 1 cm segments using a Beckman LS-250 Liquid Scintillation Spectrometer.

6-Chloroimidazo[1,2-b]pyridazine (1)

This compound was prepared by a modification of the procedure employed by Stanovnik and Tisler (2). A mixture of 80 ml (80 g, 0.524 mole) of chloroacetaldehyde diethylacetal, 10 ml of concentrated hydrochloric acid and 20 ml of water was refluxed for 1 hour. To this was added 52 g (0.4 mole) of 3-amino-6-chloropyridazine and 150 ml of alcohol and the mixture was refluxed for 30 minutes. After the cautious addition of 10.5 g of sodium bicarbonate the mixture was heated for 1 hour. An additional 17 g of sodium bicarbonate was added in portions and heating was continued for 30 minutes. To the mixture was added 25 ml of concentrated hydrochloric acid and Darco-G-60 activated carbon. The hot mixture was filtered and the filtrate was concentrated to a small volume with a water pump. The concentrate was filtered and the solid was washed with alcohol. The insoluble white solid

was dissolved in hot water. The solution was treated with excess solid sodium bicarbonate, in portions, to precipitate 47.9 g (78%) of product, m.p. 115.5-117.5° (lit. (2), m.p. = 115°).

6-Chloro-3-nitroimidazo[1,2-b]pyridazine (2)

To a mixture of 10 g (0.065 mole) of 6-chloroimidazo[1,2-b]pyridazine (1) in 10 ml of concentrated sulfuric acid was added 6 ml of fuming red nitric acid (d, 1.59-1.60). The mixture was heated with stirring, on the steam bath, for 4 hours. The reaction mixture was poured onto cracked ice and was allowed to stand for 1 hour. A yellow solid was collected by filtration and washed with water. Recrystallization from 3A alcohol gave 8.2 g (63%) of yellow product, m.p. 142-143°. An analytically pure sample, m.p. 142-143°, was obtained by recrystallization from aqueous alcohol (lit. (3), m.p. 210°).

Anal. Calcd. for ($C_6H_3ClN_4O_2$, 198.6): C, 36.29; H, 1.52; N, 28.21. Found: C, 36.43; H, 1.49; N, 28.68.

NMR spectrum (d_6-DMSO): δ 7.85 (d, 7-CH), δ 8.53 (d, 8-CH), δ 8.84 (2-CH).

Mass spectrum: molecular ion at 198 m/e.

3-Nitro-6-(propoxy-1-^{14}C)imidazo[1,2-b]pyridazine (3)

To a suspension of 1.26 g (29.9 mmole) of sodium hydride (57% in oil dispersion) in 50 ml of p-dioxane was added 1.8031 g (30.0 mmole) (1.1 mCi/mmole) of n-propanol-1-^{14}C in 20 ml of p-dioxane. The mixture was stirred for 40 minutes. To the reaction mixture was added 5.40 g (27.2 mmole) of 6-chloro-3-nitroimidazo[1,2-b]pyridazine (2). The mixture was stirred for 18 hours and poured into 250 ml of distilled water. The solid was collected by filtration and washed with two 20 ml portions of water, 2B alcohol and ether. The air dried solid was dissolved in 40 ml of boiling 2-methoxyethanol. To the hot solution was added Darco G-60 activated carbon and the hot mixture was filtered through a diatomaceous earth padded

filter. The filtrate was cooled at -4° for 3 days and was filtered. The solid was washed with two 8 ml portions of cold 2-methoxyethanol and dried at 50° for 4 hr in a vacuum oven to give 3 as beige crystals, m.p. 162-163.5° (3.83 g, 19.5 mCi, specific activity: 5.09 mCi/mg, 1.13 mCi/mmole) in 58% radiochemical yield. The radiochemical purity was found to be greater than 99% by thin layer chromatography on silica gel in the upper phase of two solvent systems, benzene:acetone:water (10:9:10, v/v) and 10:5:10, v/v). Countercurrent distribution, using n-butanol-acetic acid-water (4:1:5) solvent system gave a single peak.

3-Nitro-6-(propoxy-d_7)imidazo[1,2-b]pyridazine (4)

To suspension of 1.4 g (33.3 mmol) of sodium hydride (57% oil dispersion) in 100 ml of p-dioxane was added 2.0 g (29.8 mmol) of n-propyl alcohol-d_7 (Merck). The mixture was stirred for 40 min. To the mixture 5.96 g (30.0 mmol) of 6-chloro-3-nitroimidazo[1,2-b]pyridazine was added and the mixture was stirred at room temperature for 18 hours.

The reaction mixture was poured into 300 ml of cold water. The solid collected by filtration was washed with two 50 ml portions of water, followed by two 50 ml washes with 2B alcohol and ether. The dried solid, 2.2 g (32%), was dissolved in 50 ml of boiling 2-methoxyethanol, treated with Darco G-60 activated carbon and gave, on cooling, 1.5 g (22%) of analytically pure product, m. p. 160.5-161.5°.

Anal. Calcd. For ($C_9D_7H_3N_4O_3$, 229.3): C, 47.15; H, (D measured as H) 4.36; N, 24.44. Found: C, 47.00; H, 4.51; N, 24.44.

Mass spectrum: molecular ion at 229 m/e.

NMR spectrum (d_6-DMSO): δ 7.29 (d, 7-CH), δ 8.27 (d, 8-CH), δ 8.59 (2-CH).

REFERENCES

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