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SYNTHESIS OF [IMIDAZOLIDINONE-2-^{14}C]Go 10213 (SATRANIDAZOLE, CIBEMID®)†

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SUMMARY

For additional pharmacokinetic and metabolism studies in laboratory animals and in humans, Go 10213 was labelled with carbon-14 located on the carbonyl carbon atom of the ethyleneurea ring (Ring B) of the molecule. [imidazolidinone-2-^{14}C]Go 10213 having a specific activity of 6.06 μCi/mg (1.75 mCi/mmol) was synthesised starting with [^{14}C]ethyleneurea in two steps.

Keywords : Synthesis, Go 10213, ethyleneurea, carbon-14

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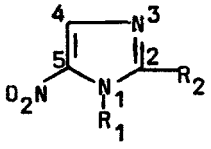
INTRODUCTION

Go 10213 (Satranidazole, Cibemid®) is a potent anti-amoebic/antitrichomonal agent exhibiting quite marked antianaerobic and antigiardial activities as well[1-5]. It belongs to the well known 5-nitroimidazole class of compounds represented by metronidazole, tinidazole, ornidazole, secnidazole, etc. but structurally differs from them in having a methanesulphonyl imidazolidinone moiety at position 2 of the 5-nitroimidazole ring system, as shown in Figure 1.



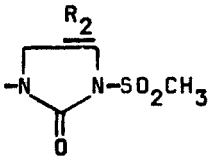
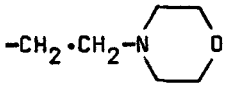
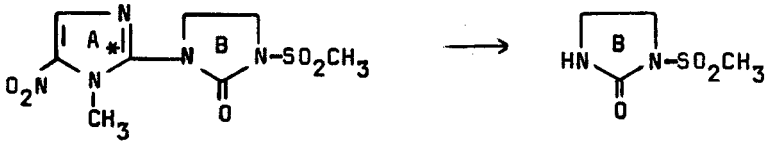
	R_1	R_2
Go 10213 (Satranidazole, Cibemid®)	$-CH_3$	
Metronidazole	$-CH_2 \cdot CH_2OH$	$-CH_3$
Tinidazole	$-CH_2 \cdot CH_2 \cdot SO_2C_2H_5$	$-CH_3$
Ornidazole	$-CH_2 \cdot CH(OH) \cdot CH_2Cl$	$-CH_3$
Secnidazole	$-CH_2 \cdot CH(OH) \cdot CH_3$	$-CH_3$
Nimorazole		$-H$
Ronidazole	$-CH_3$	$-CH_2OCONH_2$

Figure 1 : Structure of Go 10213 and some widely known 5-nitroimidazole class of compounds.

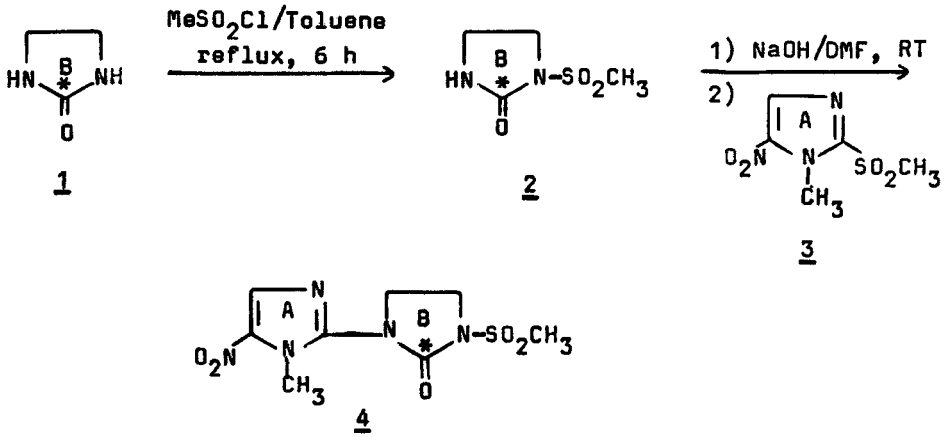
Extensive metabolism studies in various animal species and also in man[6] with Ring A (nitroimidazole)^{14}C-labelled Go 10213[7] had revealed the formation of the nonradioactive metabolite methanesulphonylethyleneurea (MSEU).



Ring A ^{14}C-Go 10213 MSEU

Unfortunately, MSEU, being nonradioactive, was not amenable for quantitation by isotope dilution analysis method in metabolism studies with Ring A ^{14}C-Go 10213. Hence Go 10213 was labelled with carbon-14 at the C_2 position of the imidazolidinone ring for additional metabolism studies. The synthetic scheme is outlined below.

Synthetic Scheme



[imidazolidinone-2^{14}C]Go 10213

* = position of ^{14}C label

DISCUSSION

The synthesis of [imidazolidinone-2-^{14}C]Go 10213 (4) was carried out in two steps starting with [^{14}C]ethyleneurea, (1).

Heating (1) (11·55 mCi, 6·1 mmol) with methanesulphonyl chloride in toluene yielded [^{14}C]methanesulphonylethyleneurea, [^{14}C]MSEU (2) having a specific activity of 10·84 μCi/mg, (60%). The sodium salt† of (2) (3·56 mCi, 2 mmol) prepared by reaction with powdered sodium hydroxide in dimethylformamide on condensation with 2-methanesulphonyl-1-methyl-5-nitro-imidazole (3)[8] afforded (4) having a specific activity of 6·06 μCi/mg, (80%).

EXPERIMENTAL

Materials and methods

Melting and boiling points are uncorrected.

[^{14}C]Ethyleneurea, (2-[^{14}C]imidazolidine-2-one, 328 mg, 11·55 mCi) was obtained from Isotope Division, Bhabha Atomic Research Centre, Trombay, Bombay 400 085, India. Analytically pure nonradioactive ethyleneurea (m·p. 132°C) and Go 10213 m·p. 186–187°C were synthesized internally[9].

Methanesulphonyl chloride, purchased from Fluka AG, Buchs, Switzerland was distilled, b·p. 160–162°C, and stored in sealed ampoules (1 ml).

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†Modification of salt preparation using powdered sodium hydroxide was more facile and convenient as compared to that with sodium hydride[7], and yields of 4 were also better and consistent.

Dimethylformamide (b.p. 152°C) and toluene (b.p. 110°C) were distilled and the latter was kept anhydrous by storing over strips of metallic sodium.

Sodium hydroxide, Puriss, E. Merck, was powdered and dried thoroughly in vacuo at room temperature prior to use in reaction.

Radioactivity measurements were made on a Packard TRICARB (Model 460 CD) Liquid Scintillation Counter, operating at a carbon-14 efficiency of 94%, by the channels ratio method. The scintillator (cocktail) contained 4 g PPO and 0.05 g POPOP per litre of toluene.

Radiometric TLC and reversed isotope dilution analysis of Go 10213 were carried out as described earlier[7].

Reversed isotope dilution analysis of MSEU was performed by mixing the solutions of ^{14}C-labelled and nonradioactive compounds in acetone and concentration to induce crystallization.

1-Methanesulphonyl-2-[^{14}C]-2-imidazolidinone, methanesulphonylethyleneurea, MSEU (2)

A mixture of [^{14}C]ethyleneurea (1), 2-[^{14}C]-2-imidazolidinone, 328 mg; specific activity 2.75 mCi/mmol; 11.55 mCi, and nonradioactive ethyleneurea (200 mg), in anhydrous toluene (7 ml) was treated with freshly distilled methanesulphonylchloride (0.8 g) and then stirred under reflux in an oil bath at 115-120°C for 6 hrs in an oxygen-free dry nitrogen atmosphere, and allowed to stand at room temperature overnight. The lumps of crystalline product were cautiously broken up with a glass rod, the solid filtered, washed with dry toluene and dried at 100°C in vacuo for 30 min. The crude product, 786 mg, upon recrystallization from water (3 ml) with cooling in ice afforded pure (2) (566 mg, specific activity 10.84 μCi/mg).

Radiochemical purity was observed to be > 99% as determined by RIDA and RTLC, Silica/$CHCl_3$ - MeOH (88:12 v/v), R_f 0·47. Dilution of the mother liquors (filtrate and washings) with nonradioactive MSEU[9] yielded a second sample of (2) 1·15 g, having a specific activity of 0·68 μCi/mg, the radiochemical yield being 60%.

1-Methanesulphonyl-3-[1-methyl-5-nitro-1H-imidazol-2-yl]-2-[^{14}C]-2-imidazolidinone, [imidazolidinone-2-^{14}C]Go 10213, (4)

To a solution of (2) (328 mg, 3·56 mCi) in dimethylformamide (8 ml) was added powdered sodium hydroxide (100 mg) and the mixture stirred for 2 hrs at room temperature (25°C). To the resulting greyish suspension of the sodium salt of (2) was added dropwise, under stirring, a solution of 2-methanesulphonyl-1-methyl-5-nitroimidazole (3) (425 mg) in dimethylformamide (10 ml). The resulting orange-red reaction mixture was stirred for another 20 hrs and evaporated to dryness *in vacuo* below 50°C. The residue was stirred with water (10 ml) for 30 min; the solid filtered, washed with water (10 ml) and dried *in vacuo* to give crude (4) 475 mg. This was dissolved in chloroform (35 ml) and the solution was adsorbed on a column of silica gel (100-200 mesh; 20 g; 1·8 cm i.d. x 20 cm.h) equilibrated with the same solvent. Initial chloroform eluates (150 ml) containing mostly the impurities were discarded. Evaporation of later chloroform-methanol (99:1 v/v; 300 ml) eluates containing mostly (4) by TLC, yielded a glassy residue which on trituration with methanol (3 ml) gave a solid. The suspension was redissolved by addition of acetone (12 ml) and warming. The solution was filtered, diluted with methanol (15 ml), concentrated to 5 ml and cooled. The pale yellow crystals were filtered, washed with methanol (3 x 1 ml) and dried to give (4), (435 mg, specific

activity, 6·06 μCi/mg)· Dilution of mother liquors (filtrates and washings) with nonradioactive Go 10213[9] afforded a second sample of (4) 312 mg, having a specific activity 0·73 μCi/mg, the radiochemical yield thus being 80%· Radiochemical purity determined as described earlier[7] was observed to be > 99%·

ACKNOWLEDGEMENT

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