SYNTHESIS OF ^{14}C-LABELLED 1-METHANESULPHONYL-3-(1-METHYL-5-NITRO-1H-IMIDAZOL-2-YL)-2-IMIDAZOLIDINONE, (Go 10213)†

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SUMMARY

For pharmacokinetic and metabolism studies in animals and humans, Go 10213 was labelled with carbon-14 at the 2-position of the 5-nitroimidazole ring system, in an overall yield of 22% starting with potassium $[^{14}C]$-thiocyanate. The labelled compound had a specific activity of 4.65 μCi/mg or 1.34 mCi/mmol.

Key words : Synthesis, Go 10213, 1-Methanesulphonyl-3-(1-methyl-5-nitro-1H-imidazol-2-yl)-2-imidazolidinone, carbon-14, antiamoebic-antitrichomonal agent

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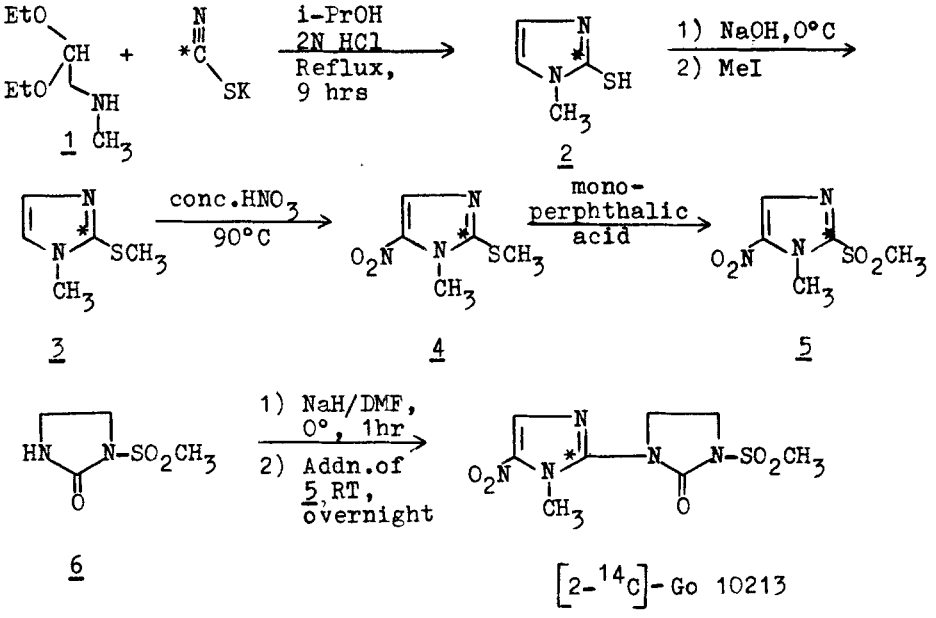
INTRODUCTION

Go 10213, 1-Methanesulphonyl-3-(1-methyl-5-nitro-1H-imidazol-2-yl)-2-imidazolidinone, is a novel compound[1-4] showing potent antiamoebic and antitrichomonal activity[5-7]. It belongs to the well recognised class of 5-nitroimidazoles, represented by metronidazole, tinidazole, ornidazole and secnidazole, but differs from them in having methyl and methanesulphonyl imidazolidinone groups in place of substituted ethyl and methyl respectively, most commonly located at positions 1 and 2 of the 5-nitroimidazole nucleus.

Go 10213 is now undergoing advanced clinical trials[8]. For pharmacokinetic and metabolism studies in laboratory animals and also in humans, it has been labelled with carbon-14 at the 2-position of the 5-nitroimidazole ring system, a position considered to be metabolically stable in vivo.

The labelling was performed on a 8 millimoles scale according to the scheme outlined starting with potassium [^{14}C] thiocyanate.

Synthetic Scheme is outlined below :



*position of ^{14}C label

The entire synthetic sequence was carried out, starting with nonradioactive potassium thiocyanate (8 millimoles) several times, before the final hot run, to optimise the yield and purity at each step.

Reaction of potassium [^{14}C] thiocyanate with N-methyl aminoacetaldehyde diethylacetal (1), under acidic conditions afforded 1-methyl-[2-^{14}C]-imidazole-2-thiol (2), which was converted to its S-methylether (3) by methylation with methyliodide under alkaline conditions at 0°C.

Extremely cautious nitration of (3) with fuming nitric acid at 90°C yielded the 5-nitroimidazole (4). Oxidation of (4) with ethereal monoperphthalic acid gave the corresponding sulphone (5). In the subsequent step, the methanesulphonyl group in (5) was displaced smoothly with the anion generated from reaction of 1-methanesulphonyl-2-imidazolidinone (6) with sodium hydride in dimethyl formamide to get [2-^{14}C]-Go 10213 (7), in an overall radiochemical yield of 22%.

EXPERIMENTAL

Relevant data from the final synthetic sequence using unlabelled intermediates is given below.

Compound No.	Molr. wt.	m.p.°C	Yield
2	114	142°	95%
3	128	pale brown oil	97%
4	173	88-90°	40.5%
5	205	92-93°	95%
6	164	190-192°	Ref.1
7	289	186-187°	55-60%

Melting and boiling points are uncorrected.

Potassium [^{14}C] thiocyanate (347 mg; specific activity 2.8 mCi/mmol, 10 mCi) was procured from Bhabha Atomic Research Centre, Trombay, Bombay 400 085, INDIA. Nonradioactive potassium thiocyanate was of AnalaR Grade.

N-Methylaminoacetaldehyde diethyl acetal was purchased from Fluka AG, Buchs, Switzerland and distilled before use (bp 165°C/760 mm).

Unlabelled Go 10213 was synthesized internally[1].

Go 10213 is a pale yellow crystalline compound sparingly soluble in water (< 1 mg/ml at RT), soluble in warm acetone and chloroform but less so in methanol. It exhibits a maximum at 315 nm (ε 9474) in methanol solution. It is stable thermally and to dilute acid and base.

Silica gel (100-200 mesh) for column chromatography and all other chemicals (reagent grade) were procured locally.

Radioactivity measurements were made with a Nuclear-Chicago, Mark I, Liquid Scintillation Counter, operating at a ^{14}C efficiency of 75% using external standardisation.

The Scintillator (cock-tail) contained 4 g PPO and 0.05 g POPOP per litre of toluene.

Reversed isotope dilution analysis was carried out by mixing the solutions of the ^{14}C labelled compound and the carrier (100-200 mg; analytically pure unlabelled Go 10213[1]) in acetone (5-6 ml). The combined solutions were concentrated to about 1 ml and diluted with methanol (3 ml). The crystalline material that separated was filtered, washed with a little methanol and dried <u>in vacuo</u>, 100°, 1 hr. The above procedure was repeated thrice and the specific activities of material from two successive crystallisations were determined. 5 mg of RIDA samples were dissolved in methanol (5 ml) and mixed with cocktail (15 ml) before counting.

Radiometric TLC: Glassplates (20x20 cm) precoated with silica gel F_{254} (tlc grade) (150 µm thickness) were used. The development distance in the solvent systems used was 15 cm. Measurement of radioactivity of (1x1 cm) sections of the radiochromatograms was carried out as suspensions in a mixture of methanol (5 ml) and cocktail (10 ml).

1-Methyl-[2-^{14}C]-imidazole-2-thiol (2) : A mixture of potassium [^{14}C] thiocyanate (347 mg; specific activity 2.8 mCi/m mol, 10 mCi) and inactive potassium thiocyanate (430 mg), isopropanol (8 ml), water (2 ml) and N-methyl aminoacetaldehyde diethylacetal, 1 (1.4 ml) was treated under vigorous stirring with 2N hydrochloric acid (5.4 ml) added dropwise, and the mixture was stirred under reflux for 9 hrs in a nitrogen atmosphere over an oil bath. The mixture was evaporated to dryness cautiously, the residue was extracted thoroughly with boiling benzene (3x40 ml). The extract was filtered and the solvent was removed by rotary evaporation. The residue was dried to afford (2). Yield 0.9 g.

1-Methyl-2-methylthio-[2-^{14}C]-imidazole (3) : A solution of (2) (0.9 g) in methanol (10 ml) was treated with sodium hydroxide (10N; 0.9 ml) at 0° with stirring, methyl iodide (0.6 ml) was added, the stirring at ice temperature was continued for 3 hrs and the mixture allowed to stand at 25°C in a nitrogen atmosphere overnight. A mercury-seal adapter was used to hold the nitrogen inside the flask. The mixture

was then evaporated to dryness, traces of methanol being eliminated using benzene. The residue was extracted with methylene chloride (50 ml), the extract washed once with water (5 ml), dried over anhydrous sodium sulphate, filtered and the solvent evaporated to yield (3) as a viscous oil. Yield 0.95 g.

1-Methyl-2-methylthio-5-nitro-[2-^{14}C]-imidazole (4) :
To concentrated nitric acid (d 1.4; 2.5 ml) heated and stirred over an oil bath in a nitrogen atmosphere, the foregoing S-methylether, (3) (0.9 g) was added with extreme caution very slowly at 85-90°. After the addition was completed temperature of the oil bath was gradually raised to 100-110°C and stirring in the nitrogen atmosphere was continued for 60 min. During this period all the nitrous fumes including the excess of nitric acid were swept off by the nitrogen stream leaving behind a bright yellow clear solution as a residue. After cooling to room temperature (25°C) crushed ice (5 g) was added, the pH adjusted to 6-6.5 at 0°C by careful addition of 10N NaOH. Any excess of alkali present was then neutralised by the addition of drops of glacial acetic acid to bring the pH to 6-6.5. The yellowish suspension was extracted with methylene chloride and the residue chromatographed on silica-gel (25 g). Evaporation of chloroform eluates (100 ml) afforded (4) as a crystalline solid (0.52 g).

1-Methyl-2-methanesulphonyl-5-nitro-[2-^{14}C]-imidazole (5) : A solution of (4) (0.52 g) in methylene chloride (15 ml) was added dropwise to ethereal monoperphthalic acid (concn. 1.05 m.moles/ml; 7 ml) under stirring, at 0°C. After the addition of (4) was over, the stirring at ice temperature was continued for 2-3 hrs, the ice-bath was removed, the mixture stirred at 25°C for 1 hr and then under reflux for 1 hr. After allowing it to stand overnight, the phthalic acid that had separated was filtered off and washed with methylene chloride. The combined filtrates and washings (totalling 50 ml) were stirred with saturated aqueous bicarbonate (15 ml) at 15°C for 1 hr. The organic layer was separated and the aqueous layer extracted once with methylene chloride (25 ml). The pooled methylene chloride extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to give (5) as a viscous gum. Yield 0.60 g.

1-Methanesulphonyl-3-(1-methyl-5-nitro-1H-[2-^{14}C]-imidazol-2-yl)-2-imidazolidinone (7); [2-^{14}C]- Go 10213 : To a suspension of 1-methanesulphonyl-2-imidazolidinone (6) (425 mg) in dimethylformamide (5 ml), stirred in a dry nitrogen atmosphere, at 0°C, was added sodium hydride (50% dispersion in oil, 140 mg) and the mixture stirred for 45 min. To the greyish white suspension of the sodium salt of (6) was added dropwise at 0°C, a solution of the sulphone (5) in dimethylformamide (3 ml). The resulting orange coloured suspension was stirred for 4 hrs. after removing the ice-bath. Then

the solvent was removed in vacuo, the residue was reextracted with chloroform (3x30 ml). The chloroform extract was concentrated to half its bulk and filtered through a column of silica-gel (40 g) equilibrated with the same solvent. Initial chloroform eluates (150-200 ml) containing mostly impurities (by TLC examination) were discarded. Later chloroform eluates (400 ml) containing mostly the product (by TLC) were evaporated to dryness to yield a glassy residue which on trituration with a mixture of acetone-methanol (1:3, v/v, 20 ml) followed by concentration to 5 ml gave (7) as a crystalline material. Yield 0.47 g; specific activity 4.65 μCi/mg; 2.18 mCi. (Radiochemical yield 22%). Radiochemical purity when determined by RIDA and radiometric TLC as described earlier was >99%. TLC comparisons with authentic Go 10213[1] in solvent systems (a, b) revealed single spots of ^{14}C activity corresponding to the reference sample having Rf 0.7 and 0.6 respectively.

a) $CHCl_3$ - Methanol (95:5, v/v)
b) Hexane - acetone (50:50, v/v)

M.p. 186-187°C, mmp with authentic Go 10213[1] 186-188°C and UV spectrum[1] (λ_{max} Methanol, 315 nm) established the identity of 7 with the unlabelled compound[1].

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