# SYNTHESIS OF 3-[$^{14}$C]-(p-CHLOROPHENYLTHIO)-2-AMINOPROPANE HYDROCHLORIDE (C 2998-Go)†

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## SUMMARY

For pharmacokinetic and metabolism studies in animals and humans, C 2998-Go, an antidepressant was labelled with carbon-14 on the thiomethylene carbon. The radiolabelled compound having a specific activity of 1.82μCi/mg was obtained in an overall yield of 13.6% using [$^{14}$C]para-formaldehyde and with a radiochemical purity >98%.

Key words : C 2998-Go, antidepressant, Carbon-14, synthesis

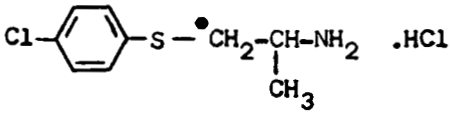
## INTRODUCTION

C 2998-Go, 3-(p-chlorophenylthio)-2-aminopropane hydrochloride (5) is an antidepressant[1,2] which has compared favourably with imipramine in clinical trials[3]. For pharmacokinetic and metabolism studies, it has been labelled with carbon-14 on the thiomethylene carbon in the side chain, the label being indicated by the asterisk (*) in the structure given below :

† Contribution No.738 from Hindustan Ciba-Geigy Ltd., Research Centre.

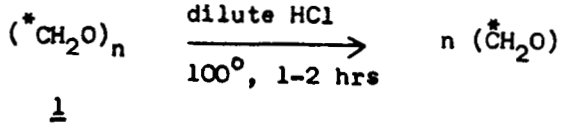
0362-4803/85/060577-05$01.00

Received August 2, 1984
Revised November 16, 1984



C 2998-Go

The labelling was carried out in two steps on a 5mM scale starting with [$^{14}$C]paraformaldehyde (1). Following acid-catalysed depolymerisation of paraformaldehyde, a Mannich-type condensation with 4-chlorothiophenol (2) and nitroethane (3) in the presence of piperidine afforded 3-[$^{14}$C]-(4-chlorophenyl-thio)-2-nitropropane (4). Reduction of 4 with stannous chloride, isolation of the basic product and conversion to the HCl salt gave [$^{14}$C] C 2998-Go (5). This had a specific activity of 1.82 μCi/mg and was obtained with a radiochemical purity of >98% and in an overall radiochemical yield of 13.6%. The synthetic scheme is outlined below :



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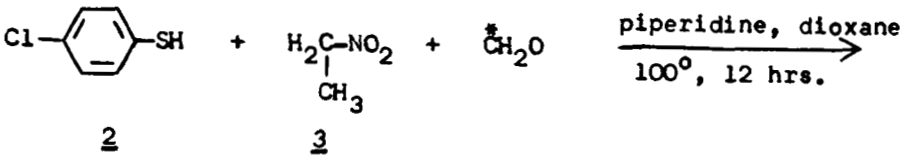

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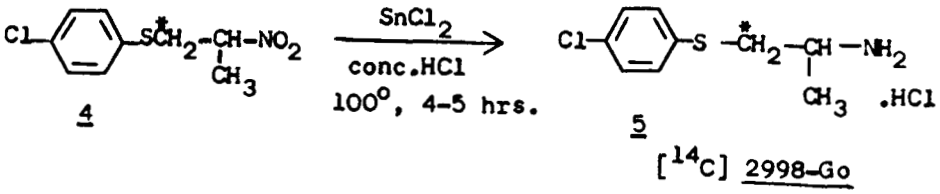

4 5

[$^{14}$C] 2998-Go

*position of $^{14}$C label

## EXPERIMENTAL

Melting and boiling points are uncorrected.

[$^{14}$C] Paraformaldehyde (16.4 mg; specific activity 183 μCi/mg; 3mCi) was procured from AMERSHAM INTERNATIONAL plc, Amersham, England.

Non-radioactive paraformaldehyde was of AnalaR grade, 4-chlorothiophenol (purum; m.p. 49-51°C) and nitroethane were purchased from Fluka A.G., Buchs, Switzerland. Nitroethane (bp 112-115°C) and 1,4-dioxane (bp 101°C) were distilled before use. Stannous chloride was from B.D.H.

Measurement of radioactivity was performed on a GM Counter, Nuclear Chicago Model 151A, with a $^{14}$C counting efficiency of 3.9 - 4.5%. Appropriate self-absorption corrections were done using external standardisation. Radiometric TLC was done on glass plates (20 x 10 cm) precoated with silica-gel (TLC grade, 150 μm thickness). The development distance in the solvent systems used was 10 cm.

The identity and chemical/radiochemical purity of the labelled preparation were established by comparison of mp, mmp, uv and TLC/PC with the analytically pure authenticated unlabelled C 2998-Go synthesised in our laboratories.

### 3-[$^{14}$C]-3-(p-Chlorophenylthio)-2-nitropropane (4)

A mixture of [$^{14}$C]paraformaldehyde (1) (16.4 mg; sp. acty. 183 μCi/mg; 3 mCi), inactive paraformaldehyde (135 mg) and dilute hydrochloric acid (0.04N; 0.5 ml) was heated in a stoppered flask at 80-90° over a water bath for 1½ hr to effect de-polymerisation of the paraformaldehyde. The flask was cooled, the stopper removed and p-chlorothiophenol (2)

(725 mg),nitroethane (3)(375 mg), piperidine (1 drop) and dioxane (2.5 ml) were added. The flask was re-stoppered and the mixture heated at 100° for 12 hrs. After cooling, the contents were evaporated to dryness on a rotary evaporator. The residue was extracted with ether; the ether extract was washed with a little water, dried over anhydrous sodium sulphate, and the solvent removed to yield a crude product as an oil (1 g) which was chromatographed on a column of silica gel (.05 - .2 mm mesh; 10 g). The column was eluted as follows, 20 ml fractions being collected and examined by TLC (Silica/ hexane : benzene; 1:1; Rf of 4 0.65).

Fr. Nos. 1, 2, 3 - hexane : benzene (4:1) eluates
Fr. Nos. 4 to 9 - hexane : benzene (1:1) eluates

Fr. Nos. 3 to 7 were combined and evaporated to dryness to obtain the nitro compound, 4 (0.6 g) as a viscous oil [$C_9H_{10}ClNO_2S$ (231.5); bp, 135-45°C/0.5 mm]. $^1H$ nmr ($CDCl_3$) δ 7.30 (4-aromatic H, s); 4.54 ($CHNO_2$, sextet, J 7.5 Hz); 3.50 (H-C-S, dxd, J 7.5, 14 Hz); 3.10 (H-C-S, dxd, J 7.5, 14 Hz); 1.59 ($CH_3$, d, J 7.5 Hz).

3-[$^{14}$C]-(p-Chlorophenylthio)-2-aminopropane hydrochloride (5)

A mixture of the nitro compound 4 (0.6 g), stannous chloride dihydrate (B.D.H. Grade; 4 g) and concentrated hydrochloric acid (3.0 ml) was heated in a stoppered flask at 100° over a water bath, with occasional shaking, for 4 hrs. The mixture was cooled, made strongly basic with 10% NaOH aq. and extracted with ether. The product was extracted by shaking the ether layer with 2 N HCl (3 x 10 ml). The combined acidic layers were re-extracted once with ether (10 ml) to remove all the non-basic material, cooled in an ice-bath,

basified with 10% NaOH aq. and then extracted with ether (3 x 35 ml). The combined ether extracts were dried (anhydrous $Na_2SO_4$), and the solvent removed to obtain the free base (0.3 g), which was converted into its hydrochloride by treatment with alcoholic HCl and the solution evaporated to dryness. Recrystallisation of the hydrochloride from chloroform-hexane yielded pure 5, 226 mg with a sp. acty. of of 1.82 μCi/mg. The labelled preparation was observed to be identical with an authentic inactive sample of C 2998-Go, $C_9H_{13}Cl_2NS$ (238.1), m.p. 151-153°C, uv $\lambda_{max}^{EtOH}$ 257 nm, on comparison of mp and mmp, uv spectra, TLC, Silica-n BuOH (75) : HOAc (10): $H_2O$ (15) - Rf 0.65 and PC, Whatman No. 1, same solvent system - Rf 0.8 and had radiochemical purity of >98%.

ACKNOWLEDGEMENT

The authors are grateful to Dr. B. Anjaneyulu for help in the preparation of the manuscript.

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