SYNTHESIS OF ^{14}C-LABELLED 1-(4-CHLOROBENZYL)-3-METHYL--3-(2-HYDROXYETHYL)-THIOUREA[x/]

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SUMMARY

1-(4-Chlorobenzyl)-3-methyl-3-(2-hydroxyethyl)--thiourea labelled with ^{14}C at its urea group was synthesised starting from potassium cyanide-^{14}C, via potassium thiocyanate-^{14}C, 4-chlorobenzyl-thiocyanate-^{14}C and 4-chlorobenzyl-isothiocyanate-^{14}C. The conditions of the isomerisation of 4-chlorobenzyl-thiocyanate-^{14}C to 4-chlorobenzyl-isothiocyanate-^{14}C were studied in detail.

Key words: Potassium thiocyanate-^{14}C, 4-Chlorobenzyl--thiocyanate-^{14}C, 4-Chlorobenzyl-isothiocyanate-^{14}C, 1-(4-Chlorobenzyl)-3-methyl-3--(2-hydroxyethyl)-thiourea-^{14}C, Thiocyanate isomerisation

INTRODUCTION

1-(4-Chlorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiourea (4, GYKI 21 683) is a new, antihypertensive agent[1,2]. Its pharmacokinetical studies required an isotopic isomer of high specific activity, labelled with ^{14}C at its thiourea group.

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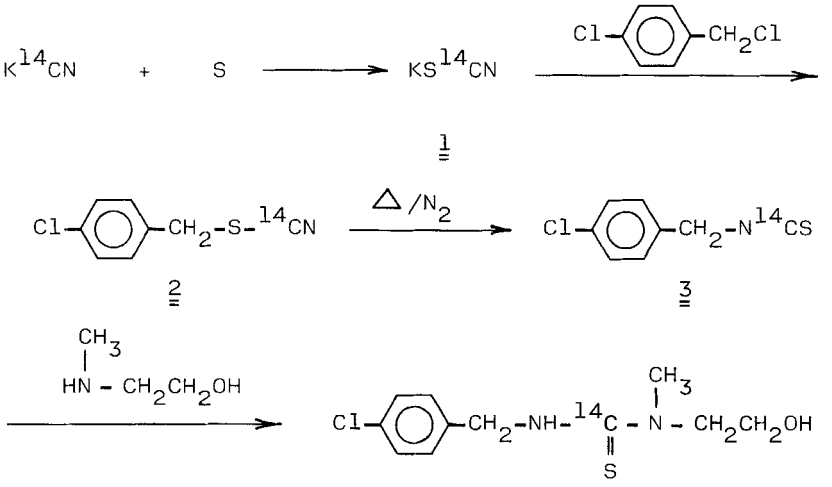
SYNTHESIS

The synthesis of 4 was performed starting from $K^{14}CN$ [3] by its reaction first with elemental sulphur (see scheme) to yield potassium thiocyanate-^{14}C (1). Careful study of the reaction conditions of the above reaction showed boiling acetonitrile to be the most suitable solvent instead of acetone as described previously[4]. Boiling acetonitrile proved to be a suitable solvent of the next reaction step too, i.e. the reaction of 1 with 4-chlorobenzyl-chloride (see scheme) to yield 4-chlorobenzyl-thiocyanate-^{14}C (2), improving the yields of both reaction steps. Compound 2 was purified by passage through a short column of silica-gel, and then rearranged thermally to 4-chlorobenzyl-isothiocyanate-^{14}C (3).

The reaction conditions of this rearrangement have not been studied previously. We showed that the isomerisation does not occur a/ under heating at 200°C and b/ in the presence of boiling n-octanol or ethylene glycol. Tars are produced a/ above 210°C, b/ in the absence of nitrogen atmosphere and c/ in the absence of

SCHEME



4, GYKI 21 683

vacuum during the isomerisation. Best results were obtained by the simple heating of neat 2 under nitrogen atmosphere in the presence of vacuum (about 200 Torr) at 205-210°C.

The 4-chlorobenzyl-isothiocyanate-^{14}C (3) obtained was then reacted without any purification with methylamino-ethanol in boiling acetonitrile[x/] to yield the required 1-(4-chlorobenzyl)--3-methyl-3-(2-hydroxyethyl)-thiourea-^{14}C (4, GYKI 21 683) (see scheme), which was passed through a short column of silica-gel and recrystallised from isopropanol to yield the required pure 4 (one radioactive spot by TLC) of high specific activity (162.75 mCi/g; 42.34 mCi/mmole).

EXPERIMENTAL

Melting points are not corrected. The one-dimensional thin layer chromatography was performed on 5x20 cm plates coated with an 0.2 mm layer of Kieselgel $PF_{254+366}$(Merck). The activity was measured by a Packard TRI-Carb liquid scintillation equipment.

Potassium thiocyanate-^{14}C (1)

349.7 mg (5.37 mmole 226.47 mCi; spec. activity 647.61 mCi/g) of potassium cyanide-^{14}C was refluxed under continuous stirring with 175 mg (5.45 mmole) of elemental sulphur in 50 ml of absolute acetonitrile for 2 hrs. The solution obtained was decanted and used directly to the synthesis of 2.

4-Chlorobenzyl-thiocyanate-^{14}C (2)

To the solution of 1 obtained above 840 mg (5.4 mmole) of 4--chlorobenzyl chloride was added and refluxed with stirring for additional 3 hrs. After cooling the solvent was removed in vacuo,

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x/ The reaction was described previously with chloroform as solvent giving a quantitative yield[2], but required 3 distilled before use.

the residue dissolved in 10 ml of benzene and purified by column chromatography (15x350 mm, filled with Kieselgel Merck, 75-135 mesh) using cyclohexane as eluent of impurities and an 1:2 mixture of benzene and ethyl acetate for the elution of the product. On removing the solvents, 871 mg (4.74 mmole· 88.3 %[x/]; 228.57 mCi) of 4-chlorobenzyl-thiocyanate-^{14}C (2) was obtained (R_f = 0.9 in benzene:ethyl acetate 1:2), which was used directly to the synthesis of 3.

4-Chlorobenzyl-isothiocyanate-^{14}C (3)

871 mg (4.74 mmole of 2 obtained above was isomerised under N_2 stream in vacuo (200 Torr) at 205-210°C for 3 hrs. After cooling, the product was taken in 10 ml of absolute acetonitrile and used directly to the synthesis of 4.

1-(4-Chlorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiourea-^{14}C (4)

To the solution of 3 obtained above 0.55 ml (6.84 mmole) of 2--methylamino-ethanol was added and the mixture was refluxed with stirring on a steam bath for 3 hrs. After cooling, the solvent was removed in vacuo and the crystalline residue obtained was chromatographed on a Kieselgel Merck (mesh 75-135) column (15x350 mm) using a 1:2 mixture of benzene and ethyl acetate as eluent. After evaporation of solvents 477 mg (1.84 mmole; 34.3 %) of 1-(4-chlorobenzyl)-3-methyl-3-(2-hydroxyethyl)-thiourea-^{14}C (4) was obtained, which was recrystallised from 7 ml of isopropanol to yield 359 mg (1.38 mmole; 25.8 %, 58.43 mCi; spec. activity 162.75 mCi/g, 42.34 mCi/mmole) of pure 4, m.p. 145-146°C (Lit.[1,2] m.p. 146-147°C), giving only one radioactive spot by TLC (benzene:ethyl acetate). Second crop (after dilution with inactive 4): 166 mg (0.63 mmole; 11.9 %; 2.87 mCi, spec. activity 17.27 mCi/g; 4.54 mCi/mmole). Total radiochemical yield: 27.1 %.

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x/ All yields calculated relatively to K^{14}CN.

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