SYNTHESIS OF 2-[2-^{14}C]-(2-AMINOETHYL)-THIAZOLE DIHYDROCHLORIDE: THIAZOLYL ETHYLAMINE DIHYDROCHLORIDE

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SUMMARY

The histamine H_1 agonist, 2-[2-^{14}C]-(2-aminoethyl)-thiazole dihydrochloride has been labelled with carbon-14 in the 2 position of the thiazole starting from potassium [^{14}C] cyanide. The overall radiochemical yield for the synthesis was 17% at a specific activity of 36mCi/mmol.

Key words: Thiazolyl ethylamine, carbon-14 labelling, histamine H_1 agonist, tlc radiochromatogram scanning, thioamide, N-(2-bromoethyl)-phthalimide.

INTRODUCTION

2-Thiazolylethylamine is a relatively selective agonist at histamine H_1 receptors[1], having 26% of the potency of the natural agonist histamine at H_1 receptors (guinea-pig ileum) and 2.2% of the agonist potency of histamine at H_2 receptors (guinea-pig atrium).

Carbon-14 labelled 2-thiazolylethylamine was synthesised in order to study the distribution of the compound in vivo.

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DISCUSSION

2-(2-aminoethyl)-thiazole dihydrochloride (6) has been prepared previously[2] and a key intermediate in the synthesis was 3-phthalimidopropionic acid thioamide (4) from 3-phthalimidopropionitrile (3) using thioacetic acid in acetic acid. The three month reaction time was avoided by development of a new method which entailed treating the propionitrile (3) with hydrogen sulphide gas and triethylamine in dimethylformamide to give the thioamide (4). Another literature method[3] using ammonium sulphide was attempted but was abandoned owing to poor yields. Treatment of N-(2-bromoethyl)-phthalimide with 1.1 equivalents of potassium cyanide in dimethylsulphoxide gave 3-phthalimidopropionitrile (3) in 83% yield. Subsequent treatment of (3) with hydrogen sulphide and triethylamine in dimethylformamide gave 3-phthalimidopropionic acid thioamide (4) in 70% yield. The formation of thiazoles from thioamides is reported in the literature[3]. This procedure entailed the treatment of (4) with 1.15 equivalents of bromoacetaldehyde diethylacetal to obtain 2-(2-phthalimidoethyl)-thiazole (5) in 48% yield. Hydrolysis of the protected thiazolyl ethylamine (5) was achieved by refluxing in 5N hydrochloric acid to yield the title compound in 73% yield. Trial reactions indicated that rapid extraction into chloroform was necessary as some decomposition occurred under basic conditions with the carbon-14 labelled material.

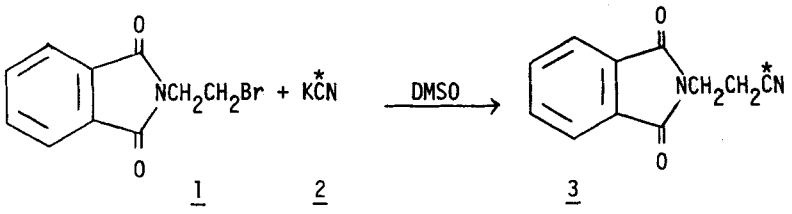
EXPERIMENTAL

[1-^{14}C]-3-Phthalimidopropionitrile (3)

To potassium [^{14}C] cyanide (2) (Benchmark Scientific Services, Lot 112982, 150mCi, 47mCi/mmol, 3.19mmole), potassium cyanide (62mg, 0.95mmole) and N-(2-bromoethyl)-phthalimide (1) (874mg,

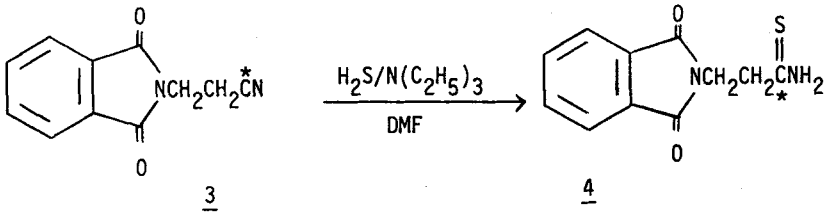
Scheme 1

STEP 1



1 2 3

STEP 2



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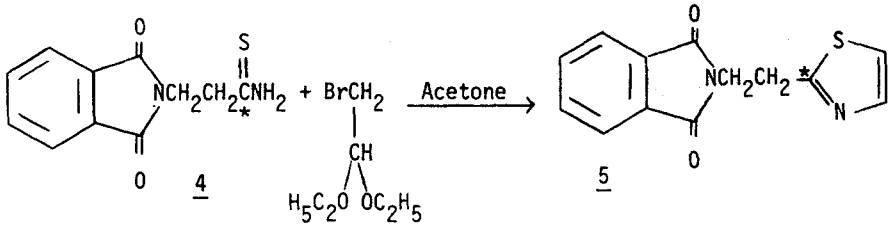
STEP 3



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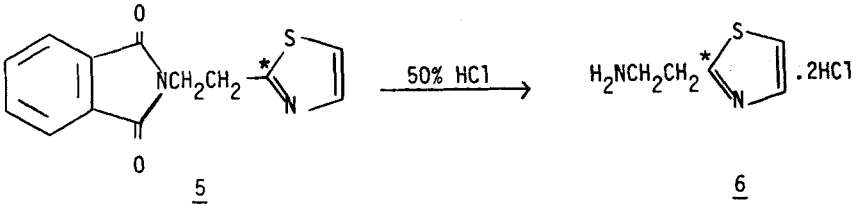
STEP 4



5 6

* denotes position of carbon-14

3.44mmole) was added dimethylsulphoxide (5ml) and the resulting slurry heated with stirring to 110°C for 2h. The yellow solution was cooled and water (50ml) added. An oil separated out and was extracted with chloroform (4 x 20ml). The combined extracts were dried ($MgSO_4$), before removal of the solvent under reduced pressure to yield the required product (3) (572mg, 83%). Tlc on silica gel GF developed in ethyl acetate: petroleum ether '40-60' (1:1, v/v) gave a radiochemical purity of 99.9% by radiochromatogram scanning.

[1-^{14}C]-3-Phthalimidopropionic acid thioamide (4)

Triethylamine (0.40ml) and dry dimethylformamide (5ml) were added to a flask containing (3) (572mg, 2.86mmole) and the resulting mixture was heated to 90°C. Hydrogen sulphide gas was bubbled through the solution at a slow rate for 4h. Further aliquots of triethylamine were added (3x400µl/h) to replace that lost by evaporation.

The resulting brown solution was added to water (50ml) and the precipitated solid extracted with chloroform (4x20ml). The extracts were combined and dried ($MgSO_4$) before removal of the solvent under reduced pressure to yield the required product (4) (470mg, 70%). Tlc on silica gel GF developed in ethyl acetate gave a radiochemical purity of 90% by radiochromatogram scanning.

[2-^{14}C]-2-(2-Phthalimidoethyl)-thiazole (5)

Bromoacetaldehyde diethylacetal (0.35ml, 2.33mmole) and acetone (10ml) were added to a flask containing (4) (470mg, 2.01mmole). The reaction mixture was refluxed for 2h during which time a white solid crystallised from solution. The reaction was cooled and the solid filtered off. The crude product (5) (510mg) was dissolved in

chloroform (20ml) and the solution washed with water (2x10ml). Tlc on silica gel GF developed in ethyl acetate: petroleum ether '40-60' (1:1, v/v), indicated the presence of the required product in the organic phase with a radiochemical purity of 99.3% by radiochromatogram scanning. The chloroform solution was dried ($MgSO_4$) before removal of the solvent under reduced pressure to give the required product (5) (250mg, 48%).

[2-^{14}C]-2-(2-Aminoethyl)-thiazole dihydrochloride (6)

5N Hydrochloric acid (20ml) was added to (5) (250mg, 0.965mmole) and the resulting solution was refluxed for 5h. The reaction mixture was cooled and the volume concentrated to 5ml under reduced pressure. The solution was basified with 40% sodium hydroxide solution (40% w/v) to pH11 and extracted with chloroform (8x5ml). The extracts were combined and washed with 0.2N hydrochloric acid (20ml). The acidic solution was separated and the solvent removed under reduced pressure. The solid residue was dissolved in methanol (1ml) and diethyl ether (20ml) added to precipitate a white solid. The product was filtered and dried under high vacuum to yield the title compound (6) (141.5mg, 73%). The specific activity was determined by liquid scintillation counting and found to be 180μCi/mg, 36mCi/mmol.

ANALYSIS

Two tlc systems were employed to determine the purity of the final product using Analtec 250 micron silica gel GF plates with subsequent scanning on the Berthold LB2832 tlc linear analyser. The Rf's of the final product in both systems were compared to a sample of authentic unlabelled thiazolyl ethylamine dihydrochloride and found to be identical.

Results of the analyses indicated radiochemical purities of 97.8% in ethyl acetate:methanol:ammonia (SG 0.880) (5:1:1, by vol) and 98.5% in chloroform:methanol:ammonia (SG 0.880) (20:2:1, by vol).

RESULTS

A total of 25.47mCi of 2-[2-^{14}C]-(2-aminoethyl)-thiazole dihydrochloride was prepared in four steps starting from potassium [^{14}C] cyanide. The chemical yield for the synthesis was 20% and the radiochemical yield 17%. The radiochemical purity of the product was 98.5% by tlc radiochromatogram scanning.
The specific activity of the product was found to be 180μCi/mg, 36mCi/mmol.

ACKNOWLEDGEMENTS

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REFERENCES

1. Ganellin C.R., Pharmacology of Histamine Receptors, eds C.R. Ganellin and M.E. Parsons pp10-102, Wright PSG, Bristol.
2. Behringer H., Hauser L., Kohl K., Chem. Ber. 92: 910-916 (1959).
3. Goldberg A.A., Kelly W., J. Chem. Soc. 1372 (1947).