Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXVI, No. 1

Convenient Synthesis of [2-^{14}C]-Methylglyoxal bis(guanylhydrazone), [^{14}C]-Mitoguazone

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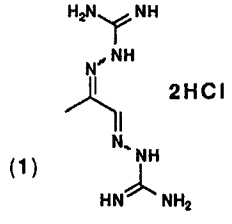
SUMMARY

[2-^{14}C]-Methylglyoxal bis(guanylhydrazone) dihydrochloride, [^{14}C]-mitoguazone, **3**, has been prepared in three steps from potassium [1-^{14}C]-acetate in an overall radiochemical yield of 16%. The key steps in this procedure are the formation of the sodium salt of[*acetone*-2-^{14}C]-methylsulfinylacetone, **5**, and Pummerer rearrangement to the [^{14}C] labelled hemithioacetal, **6**, which is trapped with two equivalents of aminoguanidine to afford the desired [^{14}C]-mitoguazone, **3**.

Key Words: [2-^{14}C]-Methylglyoxal bis(guanylhydrazone), [^{14}C]-Mitoguazone, Methylglyoxal bis(guanylhydrazone), Mitoguazone, Pummerer rearrangement

INTRODUCTION

Methylglyoxal bis(guanylhydrazone), mitoguazone, **1**, is a known anticancer agent which was first reported to show activity against acute myelocytic leukaemia in 1958.[1] After a decline in further investigation, due to apparent intolerable toxicity, modified dosing regimes have enabled reevaluation.[2]



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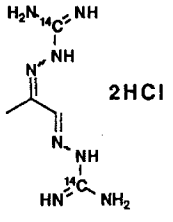
CCC 0362–4803/95/010093–04

Received 8 August, 1994
Revised 15 August, 1994

The mode of action of mitoguazone is not proven. However, the compound has been shown to inhibit both *S*-adenosylmethionine decarboxylase,[3] a rate limiting enzyme in spermidine biosynthesis, and diamine oxidase,[4] which is important in putrescine degradation. Additionally, mitoguazone activates both ornithine decarboxylase,[4] which is involved in the biosynthesis of putrescine from ornithine, and spermidine/spermine N^1-acetyltransferase,[5] which produces putrescine from spermidine. It is clear from this that mitoguazone should be expected to cause an imbalance between putrescine and spermine/spermidine. Mitoguazone has been shown to have a synergistic effect when used in conjunction with difluoromethyl-ornithine,[6] which is an inhibitor of polyamine biosynthesis. It has been suggested that difluoromethylornithine prevents accumulation of putrescine caused by mitoguazone, and thus allows higher doses of mitoguazone to be administered.[7]

Syntheses of mitoguazone labelled with [^{14}C] in the aminoguanidine portion of the molecule, i.e. **2**, have previously been reported,[8,9] but as part of a development programme and to assist with various biodegradation studies, mitoguazone was required labelled with [^{14}C] at either C-2 or C-3 of the methylglyoxal unit. The route chosen, using potassium [1-^{14}C]-acetate, afforded [2-^{14}C]-methylglyoxal bis(guanylhydrazone), **3**, and would have been equally applicable to labelling at C-3 had potassium [2-^{14}C]-acetate been used.



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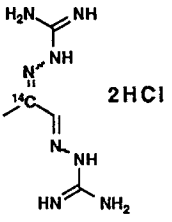

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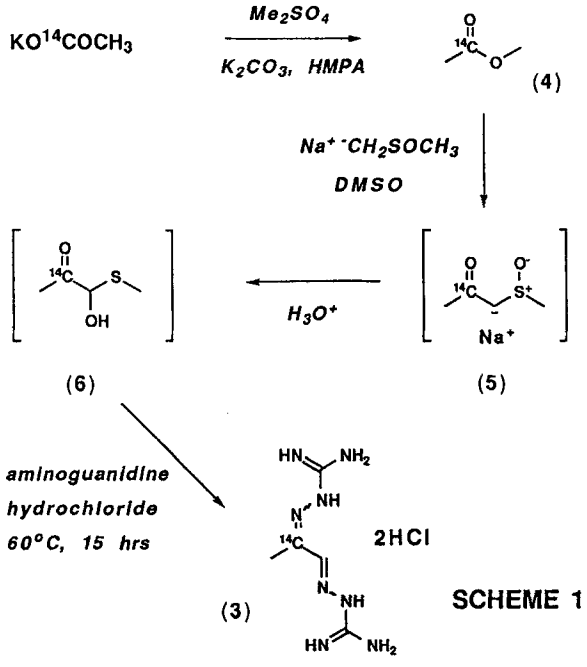
RESULTS AND DISCUSSION

[2-^{14}C]-Methylglyoxal bis(guanylhydrazone) dihydrochloride, [^{14}C]-mitoguazone, **3**, was prepared in three steps from potassium [1-^{14}C]-acetate by the route outlined in Scheme 1. Methylation of potassium [1-^{14}C]-acetate with dimethylsulfate in hexamethylphosphoramide afforded the desired [*acetic acid*-1-^{14}C]-methyl acetate, **4**, in virtually quantitative yield. The ester, **4**, was treated with sodium methylsulfinylmethylide (dimsyl sodium) in dimethylsulfoxide to afford crude sodium salt of [*acetone*-2-^{14}C]-methylsulfinylacetone, **5**, which was directly treated with dilute hydrochloric acid to cause Pummerer rearrangement[10,11] to the [2-^{14}C] labelled hemithioacetal, **6**. The intermediate, **6**, was trapped by addition of two equivalents of aminoguanidine and heating the reaction mixture to 60°C for ~15 hours, to form the desired [2-^{14}C]-methylglyoxal bis(guanylhydrazone) dihydrochloride, [^{14}C]-mitoguazone, **3**, in 16% isolated yield, following reverse phase chromatography and repeated trituration from water by addition of acetone, with both a chemical and radiochemical purity of >98.5%.



SCHEME 1

EXPERIMENTAL

[*acetic acid* 1-^{14}C]-Methyl acetate, 4: [1-^{14}C]-Potassium acetate (52.1 mCi, 8.27 mmole) was suspended in hexamethylphosphoramide (8 ml). Potassium carbonate (1.15g, 8.32 mmole) was added and the suspension stirred for 5 minutes before addition of dimethyl-sulfate (950 µl, 9.98 mmole). The reaction was warmed to 50°C and stirred for 15 hours. The reaction mixture was then frozen to liquid nitrogen temperature before being evacuated. The vacuum was adjusted to 8 x 10^{-2} mm Hg and the [*acetic acid*-1-^{14}C]-methyl acetate, **4**, transferred into a separate vessel by vacuum distillation. This product was used directly in the following step.

[*acetone*-2-^{14}C]-Methylsulfinylacetone, sodium salt, 5: Under an atmosphere of nitrogen, a dispersion of sodium hydride in mineral oil (60% suspension, 484 mg, 12.1 mmole) was suspended in dimethylsulphoxide (20 ml). The reaction was warmed to 80°C for 1 hour until no more gas evolved. The reaction mixture was then frozen to liquid nitrogen temperature and the [*acetic acid*-1-^{14}C]-methyl acetate, **4**, was vacuum transferred into this vessel. The reaction temperature was then allowed to rise to room temperature. In a separate vessel, a further dispersion of sodium hydride in mineral oil (60% suspension, 316 mg, 7.9 mmole) was suspended in dimethylsulphoxide (5 ml). This reaction was warmed to 80°C for 1 hour until no more gas evolved. The resulting solution was added to the previously described reaction mixture containing the [*acetic acid*-^{14}C]-methyl acetate. The resulting combined reaction mixture was stirred for 1 hour to form crude sodium salt of [*acetone*-2-^{14}C]-methylsulfinylacetone, **5**, which was used directly in Step 3.

[2-^{14}C]-Methylglyoxal bis(guanylhydrazone) dihydrochloride, 3: To the solution of crude sodium salt of [*acetone* -2-^{14}C]-methylsulfinylacetone, **5**, in dimethylsulfoxide (~25 ml), prepared in Step 2, was added dilute hydrochloric acid (10 ml, 2N) with the temperature maintained at 0^{o}C. Aminoguanidine bicarbonate (2.45g, 18 mmole) was dissolved in dilute hydrochloric acid (10 ml, 2N) and added at room temperature to the above reaction mixture. The pH was adjusted to pH1 by addition of concentrated hydrochloric acid. The reaction was stirred at room temperature for 15 hours before being warmed to 60^{o}C and stirred at this temperature for a further 15 hours. RadioHPLC showed that the mixture contained crude [2-^{14}C]-methylglyoxal bis(guanylhydrazone) dihydrochloride, **3**, which was purified by reverse phase column chromatography (C_{18} ; 100% H_2O/0.1% conc. HCl) and then precipitated from acetone. The precipitate was then dissolved in distilled water and triturated with acetone, and this trituration process repeated, to afford the desired [2-^{14}C]-methylglyoxal bis(guanylhydrazone) dihydrochloride, **3**, (8.3 mCi, overall radiochemical yield from Step 1 of 16%).

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