SYNTHESIS OF ^{14}C-LABELLED 1-(2,6-DIMETHYLPHENYLAMINO)-2-DIMETHYLAMINO-PROPANE

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SUMMARY

The antiarrhytmic 1-(2,6-dimethylphenylamino)-2--dimethylamino-propane (6a) was labelled with ^{14}C for pharmacokinetic study. A convenient synthesis, using 2-bromopropionyl-1-^{14}C chloride as radioactive key intermediate, involving an improved method for the reduction of N-(2-dimethylaminopropionyl)-2,6--dimethylaniline (8) was elaborated.

Key Words: Carbon-14, antiarrhytmic, reduction of N-(1-^{14}C-2-dimethylaminopropionyl)-2,6-dimethylaniline

INTRODUCTION

The compounds of general formula 6 were found to have antiarrhytmic effect in animal experiments (1). One of them, 1-(2,6--dimethylphenylamino)-2-dimethylamino-propane, (6a), was selected for detailed pharmacokinetic investigation, and for this purpose radiolabelling was required.

DISCUSSION

The patented synthesis (1) of 6a outlined in Scheme 1 was not suitable for us, because ^{14}C-labelled propylene oxide with

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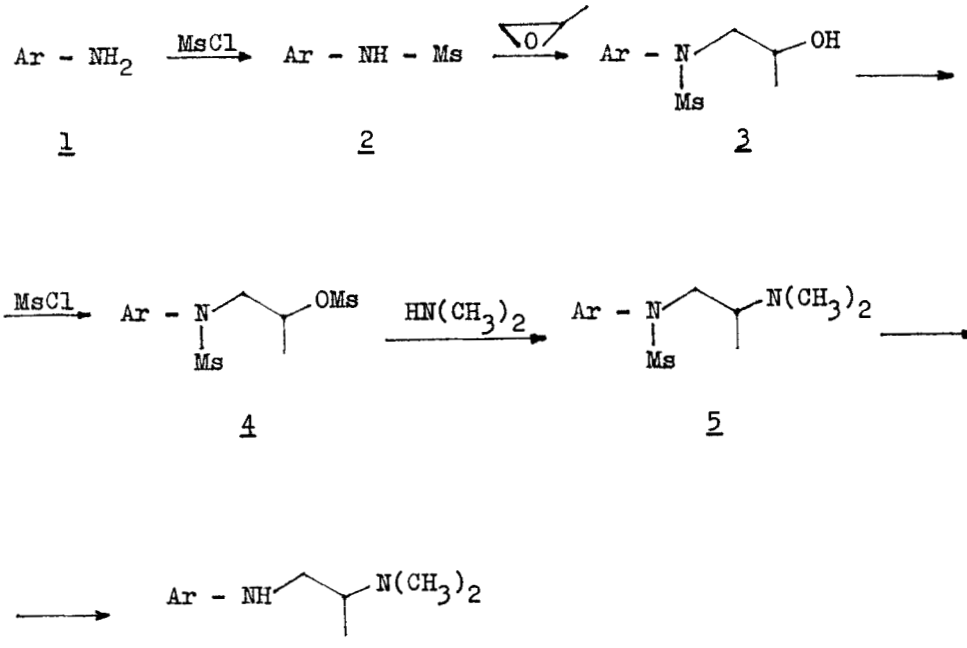
SCHEME 1

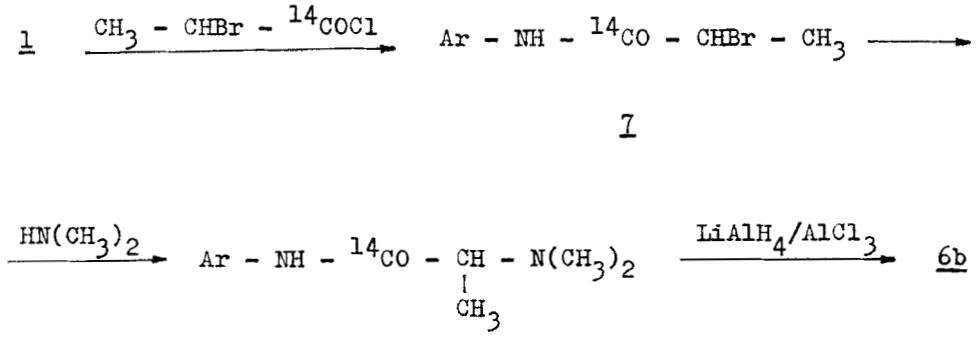


1 2 3 4 5 6

6a: Ar = 2,6-dimethylphenyl

6b: ^{14}C-labelled 6a

SCHEME 2



high specific activity is not readily available. Another route (Scheme 2) using 2-bromopropionyl chloride to incorporate the radiocarbon seemed to be more convenient. Some complications were encountered, however, upon endeavouring to reduce the intermediate N-(2-dimethylaminopropionyl)-2,6-dimethylaniline (8) with $LiAlH_4$. The conversion did not exceed 50% even if a large excess of reducing agent and a high boiling solvent (diglyme) was applied, and the product 6a could be isolated in a yield of only 30-35%. This result is in agreement with some published data, for example when N-[γ-(2,6-dimethylphenylamino)-butyryl]-2,6-dimethylaniline (2) or N-formyl-N-cyanomethyl-2,6-dimethylaniline (3) were reduced with $LiAlH_4$, about 50% of the starting materials remained unchanged.

By using the above method more than 60% of the radioactivity would have been lost in the last step, therefore we attempted the reduction of the carbonyl group with several other reducing agents. Finally a lithium aluminium hydride-aluminium chloride combination (4) in diethyl ether first applied for the reduction of this type of compounds by Zubovics and Toldy (5), proved to be significantly better than $LiAlH_4$ alone, giving nearly complete conversion and a reasonable yield, about 70%.

Propionyl-1-^{14}C chloride was prepared by a known method (6) and brominated similarly to acetyl chloride (7). The acylation of 2,6-dimethylaniline was performed with 2-bromopropionyl chloride in the presence of excess base, instead of the way described (8), simplifying the isolation of the material and at the same time improving the yield. The product obtained (7) was converted into 8 as reported (9), and the latter was reduced to give 6b which was isolated as dihydrochloride. The overall radiochemical yield based on sodium propionate-1-^{14}C was 37.8%.

EXPERIMENTAL

Radioactivities were measured with a Packard TRI-CARB 2660 liquid scintillation spectrometer. TLC was carried out on silica gel HF_{254} (MERCK), and a Berthold TLC scanner was used for evaluation. All evaporations were carried out under reduced pressure.

N-(2-Bromopropionyl-1-^{14}C)-2,6-dimethylaniline (7)

0.855 g (8.89 mmol) of anhydrous sodium propionate-1-^{14}C prepared from 10 mmol (5550 MBq; 555 MBq/mmol) of $Ba^{14}CO_3$ was converted into propionyl chloride, and the latter was brominated as described (6,7). The crude product was dissolved in ahydrous ethylene dichloride (20 ml) and under cooling, 2,6-dimethylaniline (2.014 g, 16.12 mmol) was added. After being stirred for 24 hours the reaction mixture was washed with 1 N HCl (15 ml), dried over anhydrous $MgSO_4$ and evaporated to give 2.016 g (7.87 mmol) of a white powder, which proved to be homogeneous by TLC (chloroform/ethyl acetate/formic acid = 60:10:2). Yield: 88.5%, based on sodium propionate.

N-(2-Dimethylaminopropionyl-1-^{14}C)-2,6-dimethylaniline (8)

To a solution of 7 (2.016 g, 7.87 mmol) in ethanol (6 ml) dimethylamine (7 ml of 18 wt-% in alcohol) was added, and stirred for 4 days. The reaction mixture was then poured into water (80 ml) and extracted with ethylene dichloride (3x30 ml). The organic phase was washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed on silica gel using chloroform/ethanol = 9:1 as eluent. 1.222 g (5.54 mmol, 70.4%) of oily product was obtained which crystallized on standing.

1-(2,6-Dimethylphenylamino)-1-^{14}C-2-dimethylamino-propane (6b)

1.222 g (5.54 mmol) of 8 was dissolved in dry diethyl ether (30 ml), and in a slow stream of nitrogen anhydrous $AlCl_3$

(0.739 g, 5.54 mmol) was added in small portions. After stirring for 15 min, 0.631 g (16.62 mmol) of $LiAlH_4$ was added to the reaction mixture in small portions, and stirring was continued for one hour. The complex was decomposed by dropwise addition of 5 N NaOH (10 ml) under cooling, and the organic layer was separated. The aqueous phase was extracted with diethyl ether (3x25 ml), the combined ethereal solutions were washed with water (3x20 ml), dried over anhydrous $MgSO_4$ and evaporated to give 1.022 g of an oil. The crude product was shown to contain two radioactive peaks in a ratio of 7:1 by TLC (acetone/water/conc. NH_4OH = 40:4:1), where the minor component was identical with the starting material. The major component proved to be the reduced product 6b which after purification by chromatography on silica gel using the same eluent as above, was converted into the dihydrochloride as follows. The radiochemically pure base was dissolved in methanol (10 ml), the solution was treated with charcoal, filtered and evaporated. The residue was redissolved in ethanol (2 ml), acidified by adding HCl (2 ml of 15 wt-% in ethanol) and the solution was mixed with anhydrous ethyl acetate (25 ml). Next day the precipitated crystals were filtered off and washed with ethyl acetate to give 1.063 g (3.81 mmol, 68.8%) of dihydrochloride of 6b. This material proved to be chemically and radiochemically homogeneous and identical with the authentic product by TLC. Total activity: 2099 MBq; specific activity: 551 MBq/mmol, practically the same as that of the starting material.

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