Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXVII, No. 8

SYNTHESIS OF 7-BENZYL-7-AZA-3-THIABICYCLO[3.3.1]NONANE HYDROPERCHLORATE-*6,8,10*-$^{14}C_3$

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SUMMARY

A synthesis of 7-benzyl-7-aza-3-thiabicyclo[3.3.1]nonane hydroperchlorate-*6,8,10*-$^{14}C_3$ (**2**) is described via a Mannich type of condensation. 4-Thianone (**3**) was treated with ^{14}C-labelled benzylamine ($^{14}CH_2$) and paraformaldehyde [$(H_2{}^{14}C{=}O)_n$] in a solution of acetic acid with a small amount of concentrated HCl added for a period of six hours at reflux under nitrogen. Workup with aqueous sodium hydroxide followed by treatment with a high vacuum technique provided 7-benzyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one-*6,8,10*-$^{14}C_3$ (**4**). Reduction of **4** under Wolff-Kishner conditions with hydrazine/KOH in triethylene glycol at the boiling point of *o*-xylene provided the corresponding crude amine after workup. Treatment with 60% perchloric acid (below 5°C) resulted in the formation of the title compound **2** which could be recrystallized (95% ethanol). The melting point and spectral data confirmed the structure which had a specific activity of 0.64 μCi/mg.

Key Words: 7-Benzyl-7-aza-3-thiabicyclo[3.3.1]nonane Hydroperchlorate-*6,8,10*-$^{14}C_3$, Mannich condensation, antiarrhythmic agent.

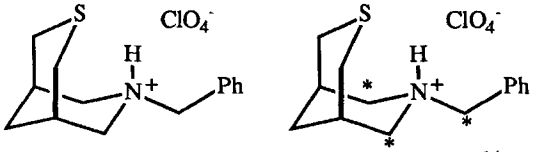
INTRODUCTION

Antiarrhythmic activity of certain members of the family of 3, 7-dihetera-bicyclo[3.3.1]nonanes and derivatives is well established (1). Indeed, 7-benzyl-7-aza-3-thiabicyclo[3.3.1]nonane hydroperchlorate (**1**) exhibited marked ability to reduce or prevent reoccurence of sustained ventricular tachycardia (VT) induced in dog models (1) as

0362–4803/89/080885–04$05.00

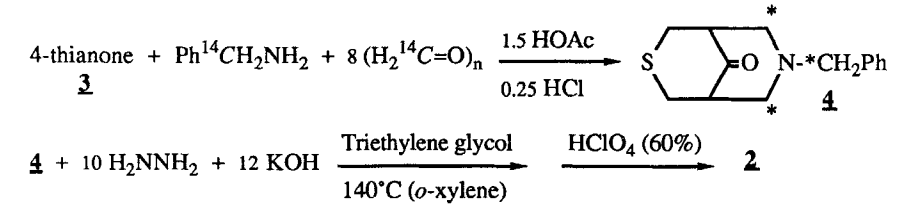
Received October 13, 1988
Revised February 7, 1989

have several related systems (2). Both NMR and X-ray diffraction studies on several members of the above family of heterocycles have revealed (1-3) that the solid compounds may exist in the chair-chair form or chair-boat form and that the same conformation likely persists in solution. With the objective to determine the pharmacokinetics and metabolites generated in test animals, it was decided to develop a synthesis for a labelled compound. In view of the strong activity of **1**, the labelled system **2** was selected as the target. Consideration of potential sites of metabolic degradation for **1** led us to introduce the ^{14}C



1 **2** * = ^{14}C

label at the benzyl carbon and at the carbon alpha to the nitrogen atom as shown in **2**. The scheme for the synthesis is shown below. 4-Thianone (**3**) is commercially available from



Aldrich as were the two as other labelled materials shown in the scheme. The general method paralleled to some degree the procedure described for unlabelled **1** (1).

EXPERIMENTAL

7-Benzyl-7-aza-3-thiabicyclo[3.3.1]nonan-9-one-*6,8,10*-$^{14}C_3$ (**4**). A mixture containing benzylamine [0.428 g, 4 mmol], benzylamine-7-^{14}C ·HCl [0.001 g, 7 x 10^{-3} mmol, 0.5 mCi (minimum activity for $^{14}CH_2$, ICN)] in H_2O (2.5 mL), and deoxygenated CH_3OH (15 mL) was made acidic with the addition of HCl [37%, 0.099 g, 1 mmol] followed by glaciel acetic acid [0.36 g, 6 mmol]. Addition in one portion of paraformaldehyde [0.960 g, 32 mmol] and paraformaldehyde-$^{14}CH_2$ [0.001 g, 3.3 x 10^{-2} mmol, 0.5 mCi (minimum activity for $^{14}CH_2$, ICN)] to the mixture was followed by subsequent addition of 4-thianone [**3**, 0.465 g, 4 mmol] all at once with stirring. After the mixture was heated at reflux under N_2 for 6 h, the solution was concentrated to 2-3 mL and then diluted with H_2O (30 mL). The aqueous solution was extracted with ether (2 x 30 mL), and the latter

was discarded. Chilling the aqueous solution to below 5°C was followed by basification with NaOH pellets [97%, 0.29 g, 7 mmol] which resulted in formation of a cloudy suspension. Combined extracts (ether, 4 x 30 mL) were dried (Na_2SO_4), filtered, and concentrated to give a viscous oil, which was then digested in 200 mL of Skelly B (bp 60-68°C) for 0.5 h. Concentration of the supernatant afforded a yellow oil which was subjected to heating under high vacuum (110°C, 0.1 mm) in a sublimation apparatus to give 126 mg of ketone **4**; mp 91-93°C [lit (1) 91-93°C]. The residue remaining was again dissolved in ether, and the latter solution was dried (Na_2SO_4), filtered, and concentrated to an oil. Digestion of the oil was effected in 50 mL of Skelly B for 0.5 h, and the supernatant was concentrated to a viscous oil. This material was heated under vacuum (110°C, 0.1 mm) in a sublimation apparatus and gave 50 mg of slightly crude ketone **4**; mp 78-80°C. A mixture melting point determination with the first crop was 86-88°C. All other properties of **4** were identical to those of the known unlabelled ketone (1). This gave a total yield of 176 mg (17.7%) of ketone **4** which was used without further purification in the next step.

7-Benzyl-7-aza-3-thiabicyclo[3.3.1]nonane Hydroperchlorate-*6,8,10*-$^{14}C_3$ (**2**). To a mixture of KOH pellets [85%, 0.48 g, 8.5 mmol] and the ketone [**4**, 0.176 g, 0.71 mmol] in triethylene glycol (5 mL) was added hydrazine [95%, 0.23 g, 7.1 mmol] in one portion in a 50 mL, jacketed flask equipped with a lower take-off condenser and magnetic stirrer. A temperature of 140°C for 4 h was produced by boiling *o*-xylene in the jacket. After cooling to RT, the solution was diluted with chilled water (30 mL) and extracted with ether (4 x 20 mL). Combined extracts were dried (Na_2SO_4), and filtered. Cooling of the ethereal solution to below 5°C was followed by the dropwise addition of $HClO_4$ [60%, 1 mL] over 10 min with stirring, which resulted in the formation of a white precipitate. Crude product was filtered, recrystallized (95% EtOH), and dried over P_2O_5 (78°C, 0.1 mm) to give 139 mg (58.6%) of white crystals of salt **2**; mp 154.5-155.0°C [lit (1) 155-156°C for **1**]. A stock solution (3.49 mg/mL) of salt **2** was prepared using DMSO, H_2O, and 0.1 N HCl (40 : 53.5 : 6.5 by volume). Samples were made by diluting 4 μL of the stock solution with 10 mL of Aquasol 2 scintillation cocktail (New England Nuclear Research Products). Measurements of activity were obtained at room temperature using a TRI-CARB liquid scintillation analyzer, model 1900 CA (Packard Instrument Company). An average count of 19,800 DPM was observed for each sample and the specific activity

was determined to be 0.64 μCi/mg. In similar fashion, samples were prepared from stock solution of the salt **2** in methanol and the specific activity was determined to be 0.63 μCi/mg.

RESULTS AND DISCUSSION

The direct introduction of the ^{14}C label at the three carbons alpha to the ring nitrogen atom occurs in the initial Mannich reaction. Although the yield is somewhat variable in the experiment with unlabelled materials (1), all physical data for labelled ketone **4** supported the structure when compared with similar properties of the unlabelled compound. Removal of the carbonyl oxygen atom by Wolff-Kishner reduction gave the crude amine (not isolated) which was converted immediately to the hydroperchlorate. Since no reactions occurred at the nitrogen atom or adjacent carbons, the ^{14}C isotope should remain intact. A mixture melting point determination of labelled **2** with **1** did *not* show a depression. All physical data for labelled **2** were identical to those of unlabelled **1**, thus establishing the structure of **2**.

The modest activity found for **2** suggests that the initial radioactivity was either less than stated by the manufacture or the label was lost to some degree during the reactions. The material is currently undergoing use in metabolic studies in animals.

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