# *SYNTHESIS OF [$^{14}C$]ZOLPIDEM*

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***SUMMARY***

*The synthesis of [$^{14}C$]Zolpidem, a new hypnotic agent having a non-benzodiazepine structure, is described. This compound was synthesised in a 64% overall radiochemical yield from potassium [$^{14}C$]cyanide and with a specific radioactivity of 56 mCi/mmol. It was used for pharmacokinetic and drug metabolism studies.*

*Keys words : Carbon-14, Imidazo[1,2-a]pyridine, Hypnotic.*

## INTRODUCTION

Zolpidem (1), N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide (R,R)-hemitartrate, is a novel non-benzodiazepine hypnotic agent possessing an imidazopyridine structure, which after oral or i.p. administration to rats, mice and cats produces a rapid onset short acting sedative effect. In man, Zolpidem is a hypnotic agent which increases the duration of slow wave sleep and is free of accumulation effects on daily ingestion as well as adverse effects on sleep and shows no signs of residual effects the day after[1].

Zolpidem represents a novel chemical class of benzodiazepine agonists, with pharmacological advantages over classical benzodiazepines. Its biochemical and pharmacological profile has been fully reported[2,3,4].

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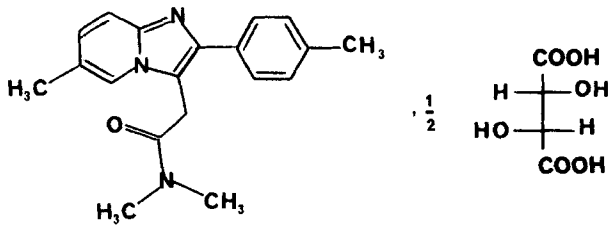

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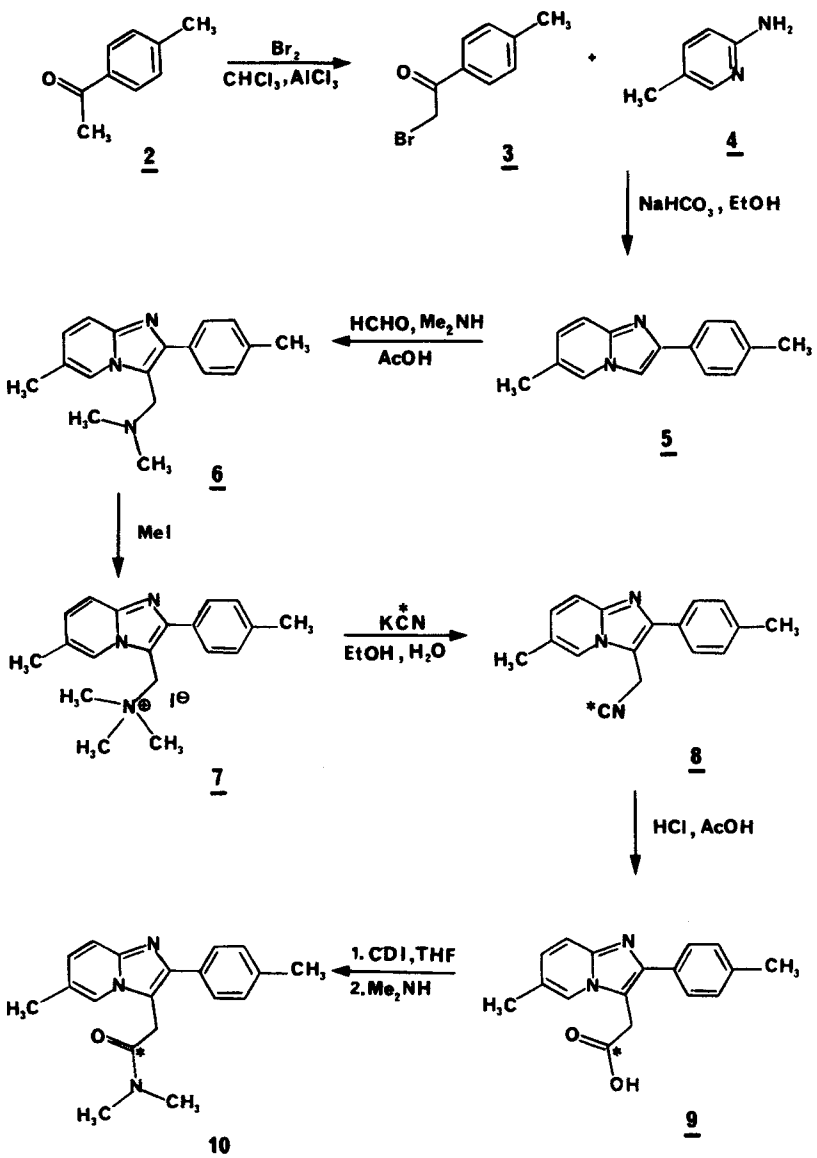
## DISCUSSION

At an early stage in the development of this drug carbon-14 labelled Zolpidem was required for pharmacokinetic and drug metabolism studies. Our initial thoughts were to ensure labelling this compound in a metabolically stable position. This could be achieved by synthesising the [2-$^{14}$C]imidazo-[1,2-a]pyridine analogue. This synthesis could be undertaken via the 4-methyl-[carbonyl-$^{14}$C]acetophenone which can be synthesised relatively cheaply via 4-[carboxyl-$^{14}$C]toluic acid. Bromination of 4-methyl[carbonyl-$^{14}$C]-aceto-phenone would yield the bromoketone which on condensation with 2-amino-5-picoline would afford the labelled imidazo[1,2-a]pyridine nucleus and then by a scheme which has already been described [7] to give ring labelled Zolpidem.
Before attempting this multistep synthetic approach we decided to carry out a small pilot synthesis to introduce the label at a later stage and into a position which can be considered to be not necessarily metabolically stable. With this pilot radiolabelled compound one could undertake a balance study in the rat in a metabolism cage to see if there was any loss of the radiolabel metabolically.

In this case there was no significant loss of the label and we had the advantage of introducing the label at a later stage in the synthesis, the overall radiochemical yield was therefore greater and the synthesis was a lot quicker and cheaper.

**SCHEME 1**




The synthesis of [$^{14}$C]Zolpidem was achieved as outlined in Scheme 1. 4-Methylacetophenone (2) was readily brominated with bromine in chloroform to afford the bromoketone (3) which was condensed with 2-amino-5-picoline (4) to afford the imidazo[1,2-a]pyridine heterocycle (5). This was the only isomer

formed and there was no evidence that the other possible positional isomer was formed during this condensation. This result was in agreement with the literature since it is considered that the reaction of 2-aminopyridines with 2-haloketones proceeds via the initial alkylation of the pyridine nitrogen atom followed by ring closure leading in our case to (5). The formation of an intermediate pyridinium salt, which is stabilised by resonance, has been supported by molecular orbital calculations and time dependent nmr studies[5,6]. Treatment of (5) with dimethylamine and formaldehyde under Mannich conditions yielded (6) which on alkylation with methyl iodide gave the quaternary salt (7)[7].

Nucleophilic displacement of the quaternary salt (7) with potassium [$^{14}$C]cyanide in aqueous ethanol yielded the desired [$^{14}$C]nitrile (8) which by acid hydrolysis gave the corresponding [$^{14}$C]acid (9). This compound was extremely insoluble in organic solvents and had to be isolated from the reaction mixture by careful filtration using a sintered filter flask and thorough washing and drying of the product before proceeding to the next stage. The [$^{14}$C]acid (9) was found to be chromatographically pure following this procedure.

A suspension of the [$^{14}$C]acid (9) in dry THF was treated with 1,1'-dicarbonylimidazole to form the corresponding imidazolide "in situ". Once formed this was treated with dimethylamine to yield [$^{14}$C]Zolpidem base which was isolated by extraction and was used directly to prepare the (R,R)-hemitartrate salt without purification. The [$^{14}$C]Zolpidem (R,R)-hemitartrate was obtained in a 64% radiochemical yield from potassium[$^{14}$C]cyanide and with a radiochemical purity greater than 99% as shown by radiochromatography.

## EXPERIMENTAL

Potassium [$^{14}$C]cyanide was supplied by Amersham France (Amersham International, UK).Radiochemical purity was determined by thin layer chromatography (TLC). An appropriate amount of the labelled compound was chromatographed

on glass plates (20 x 5 cm) precoated with 0.2 mm of silica gel 60F 254 (Merck AG, Darmstadt, Germany). After elution in the appropriate solvent system the radioactivity on the plates was scanned using a Chromelec radiochromatogram scanner linked to a Interzoom computer and the spots were also visualized by viewing under U.V.-light at 254 nm. Radioactive samples were counted using a Searle Mark III counter using Instagel (Packard) as counting medium.

The photographic film used for autoradiography was Kodak "Kodirex" X-ray film. Mass spectra were run in a direct inlet mode with an ionization energy of 70 eV using a VG 7070 mass spectrometer. Development of a suitable synthesis was carried out using unlabelled material. The unequivocal structure of each intermediate was confirmed by m.p., i.r. and n.m.r. The radiolabelled synthesis was then carried out under identical reaction conditions to that of the cold synthesis using a sample of each of the cold intermediates as TLC markers.

6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-[cyano-$^{14}$C]acetonitrile (8)

The quaternary salt (7)[7] (420.4 mg, 1.0 mmol), potassium[$^{14}$C]cyanide (50 mCi, 57.2 mCi/mmol) and a mixture of ethanol and water (5 ml, 1:1) were heated under reflux for 4 hours. The solvents were evaporated under a gentle stream of argon and the residue purified by chromatography using a silica column (Merck silicagel 60, 70-230 mesh) using a mixture of dichloromethane : ethanol (95:5, v/v) as eluting solvent. The[$^{14}$C]nitrile (8) (200.8 mg, 0.76 mmol, 87%) was recovered and was pure by tlc (dichloromethane : ethanol (9:1, v/v), Rf 0.75) analysis and was used directly for the next stage.

6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-[carboxyl-$^{14}$C]acetic acid (9)

A mixture of concentrated hydrochloric acid and glacial acetic acid (2.6 ml, 1:1, v/v) was added to the [$^{14}$C]nitrile (8) (200.8 mg, 0.76 mmol) and the solution heated at 100°C for 4 hours. The solvents were evaporated under

argon and the residue obtained was basified with aqueous sodium hydroxide and the resulting solution filtered through a 5 $\mu$millipore filter. The filtrate was acidified with glacial acetic acid and the product filtered, washed with water and then with a minimum quantity of acetone. The product was dried under vacuum to yield the [$^{14}$C]acid (9) (182 mg, 0.64 mmol) as a white solid and in a 84% radiochemical yield from the [$^{14}$C]nitrile (8). Tlc (dichloromethane : ethanol (8:2, v/v), Rf 0.28) indicated that the product was chromatographically pure.

N,N,6-Trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-[carbonyl-$^{14}$C] acetamide (10)

1,1'-Carbonyl diimidazole (120 mg, 0.74 mmol) was added to a suspension of the [$^{14}$C]acid (9) (182 mg, 0.64 mmol) in dry tetrahydrofuran (15 ml) and the resulting mixture stirred for 1 hour at room temperature and for 1 hour at 50°C. The reaction mixture was allowed to cool to room temperature and was then saturated by dimethylamine gas and stirred at room temperature for 1 hour. The solvent was evaporated under a stream of argon and the residue treated with a 10% solution of sodium bicarbonate (10 ml). The product was extracted with dichloromethane (4 x 30 ml), washed with water, dried ($MgSO_4$) and evaporated to yield [$^{14}$C]Zolpidem base (10) (35.0 mCi, 193.2 mg, 56 mCi/mmol) in an overall radiochemical yield of 71% from potassium[$^{14}$C]cyanide.

[$^{14}$C]Zolpidem (R,R)-hemitartrate

A solution of (R,R)-tartaric acid (46.5 mg, 0.31 mmol) in methanol (1.5 ml) was added to [$^{14}$C]Zolpidem base (10) (191.8 mg, 0.62 mmol) in dichloromethane (3.2 ml). Diethyl ether (15 ml) was added until the tartrate started to crystallise. The product was filtered and dried to yield [$^{14}$C]Zolpidem (R,R)-hemitartrate (32.2 mCi, 221 mg, 0.58 mmol) in a 64% radiochemical yield from potassium[$^{14}$C]cyanide.

The radiochemical purity was found to be greater than 99% by thin layer

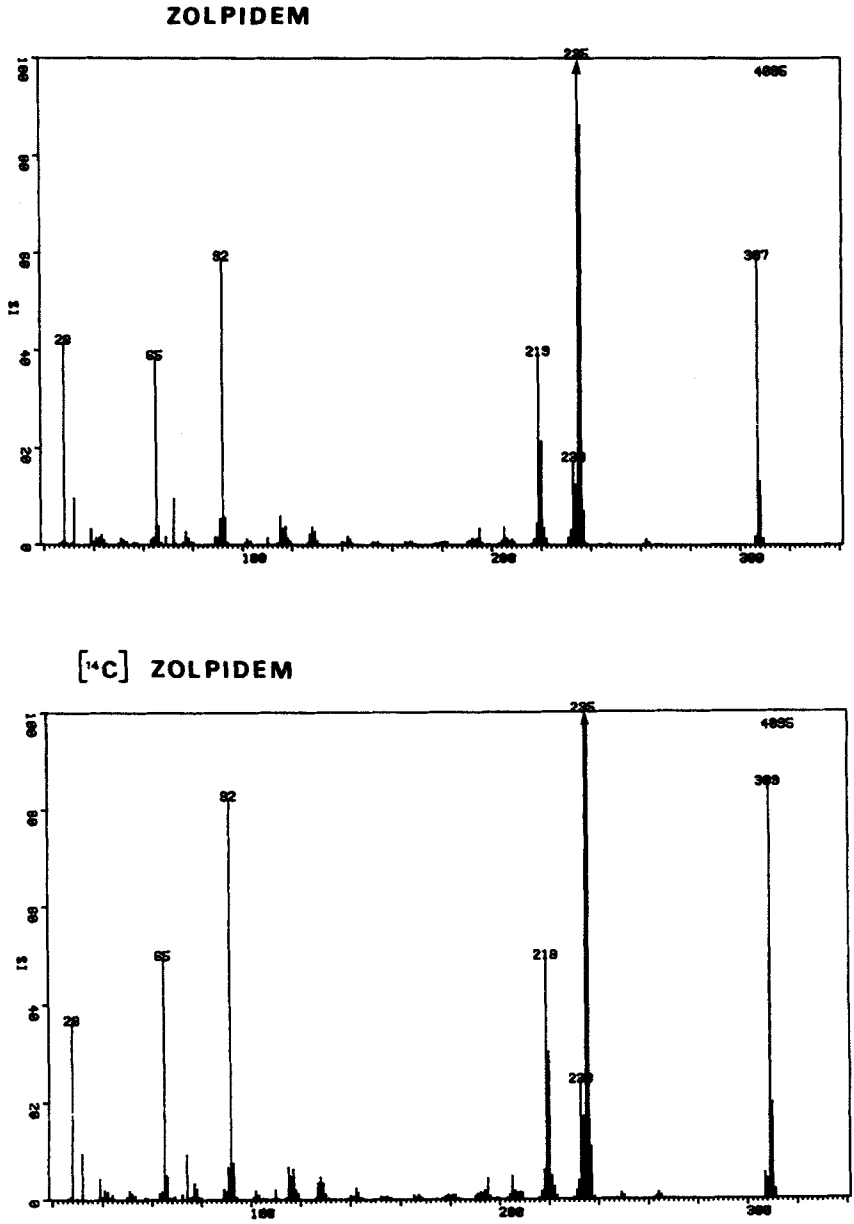



Figure 1. Mass spectrum of Zolpidem and [$^{14}$C]Zolpidem

radiochromatography in the following systems :

1) Dichloromethane : methanol (9:1, v/v) Rf 0.83 .

2) Ethyl acetate : methanol (2:1, v/v) Rf 0.58 .

3) Dichloromethane : acetone (1:1, v/v) Rf 0.30 .

Each sample spotted was co-chromatographed with an authentic sample of unlabelled Zolpidem.

The mass spectrum, $^{m}/z$ = 309 ($M^{+}$, $^{14}C$) was identical with that of unlabelled Zolpidem taking into account the mass difference for the presence of $^{14}C$ in the molecule (Figure 1).

**REFERENCES**

1. Nicholson A.N. and Pascoe P.A. - Br. J. Pharmacol., 1985 (in press).
2. Arbilla S., Depoortere H., George P. and Langer S.Z. - Naunyn-Schmiedeberg's Archives of Pharmacology, 330 : 248 (1985).
3. Langer S.Z., Depoortere H., Sanger D., George P., Zivkovic B., Arbilla S., Lloyd K. and Bartholini G. - J. Neurochem. 44 (1985), Suppl. S179.
4. Arbilla S., Depoortere H., George P. and Langer S.Z. - Proceedings of the British Pharmacological Society Meeting, Southampton, England, 17-19th July, 1985.
5. Elliott A.J., Guzik H. and Soler J.R. - J. Heterocyclic Chem., 19 : 1437 (1982).
6. Hand E.S. and Paudler W.W. - Tetrahedron, 38 (1) : 49 (1982).
7. a) Kaplan J-P. and George P. - Synthelabo, European Patent n° 0050563 (1982).
   b) Kaplan J-P. and George P. - Synthelabo, US Patent, n° 4,382,938 (1983), and references cited therein.