SYNTHESIS OF PETHIDINE DERIVATIVES : ^{14}C LABELLED DL-PHENOPERIDINE

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SUMMARY

The phenoperidine hydrochloride was labelled with ^{14}C at the carboethoxy group, in six steps from diethanolamine. The carbon-14 labelled benzyl cyanide precursor was prepared from $Na^{14}CN$ and benzyl chloride

Key Words : Carbon-14, Phenoperidine, Pethidine derivatives, Morphine-like

INTRODUCTION

In order to investigate its biological role and its stereospecific binding to morphine-like receptors (μ-receptors), ^{14}C labelled phenoperidine **1** has been prepared. The choice of the labelling site (the carbon bearing the ester group) was based on the convenience of the synthetic method and the biological stability of the phenoperidine molecule (scheme 1).

Direct condensation between bis(2-chloroethyl)amine chloride and p-toluene sulfonic acid did not give a satisfactory result. The preparation of compound **2** in two steps as shown in the scheme 1 was the best method. Cyclization in the presence of sodamide from benzyl [^{14}C]cyanide **4** gave the labelled compound **5**. The use of sodamide in toluene suspension was better than its use in small pieces. Increasing the reaction time or the amount of sodamide did not give a higher yield of **5**. When the reduction of compound **7** to compound **1** is carried out with sodium borohydride the reaction is very rapid and the yield obtained is better than with any other classical hydrogenation reagent (3).

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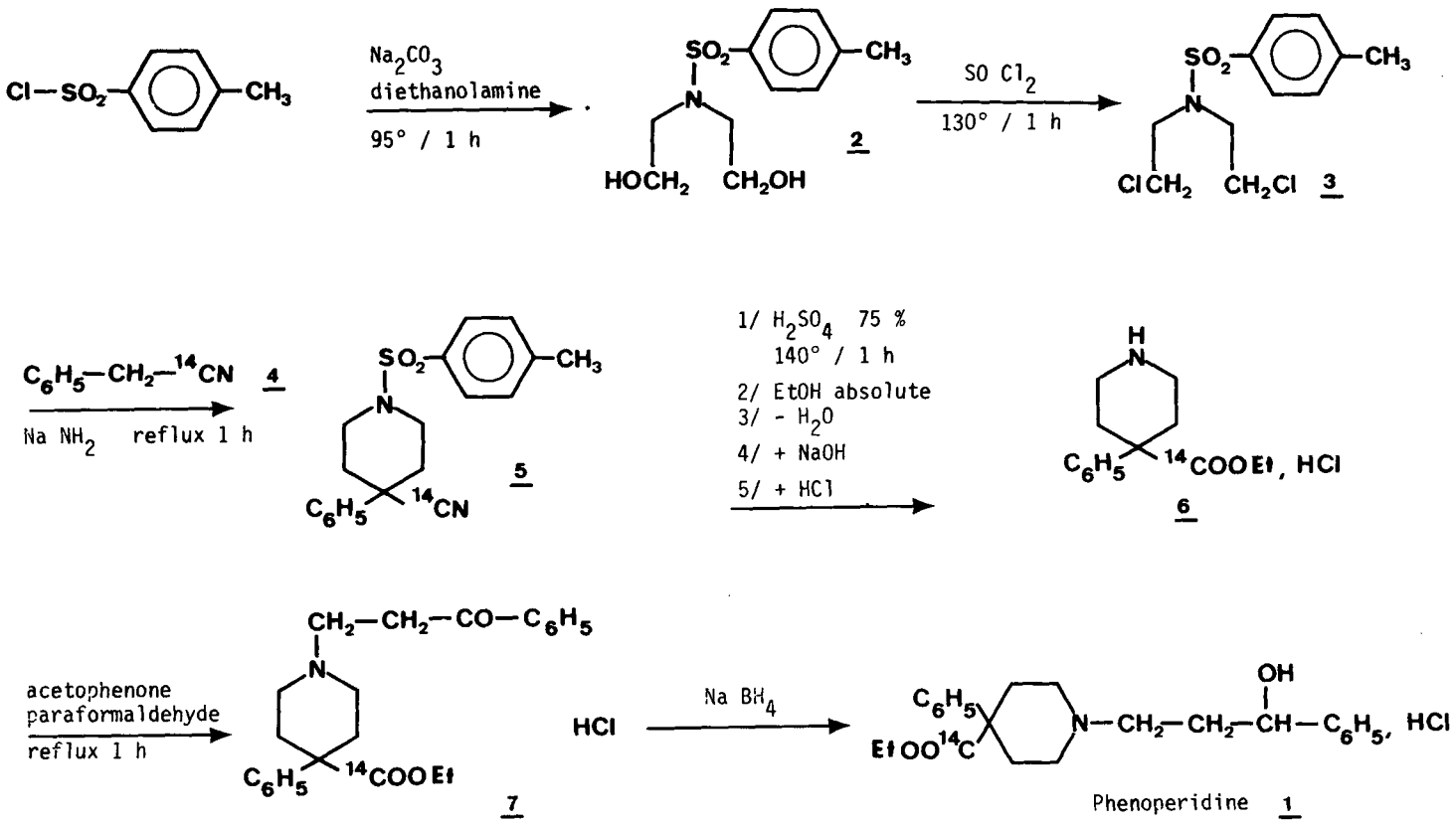
Cl—SO2—CH3
Na2CO3
diethanolamine
95° / 1 h
SO2—CH3
N
HOCH2 CH2OH
2
SO Cl2
130° / 1 h
ClCH2 CH2Cl 3
C6H5—CH2—14CN 4
Na NH2 reflux 1 h
14CN
C6H5
5
1/ H2SO4 75 %
140° / 1 h
2/ EtOH absolute
3/ - H2O
4/ + NaOH
5/ + HCl
H
14COOEt, HCl
6
acetophenone
paraformaldehyde
reflux 1 h
CH2—CH2—CO—C6H5
14COOEt
7
HCl
Na BH4
OH
EtOO14C
N—CH2—CH2—CH—C6H5, HCl
Phenoperidine 1

scheme 1

EXPERIMENTAL

(with the technical contribution of Ch.Beney)

All solvents used were dried and distilled. Radioactivity was measured using the Inter Technique ABAC SL.40 liquid beta scintillation spectrometer. For proof of structure NMR spectra were recorded using a Hitachi Perkin Elmer R-24 A 60 MHz spectrometer. IR spectra were recorded using a Beckman Acculab IV spectrometer.

N,N-bis(β-Hydroxyethyl)-p-toluene sulfonamide **2** and N,N-bis(β-chlorethyl) p-toluene sulfonamide **3** were obtained by the method described by Eisleb (2).

Benzyl[^{14}C]cyanide **4**

The preparation of **4** was based on the method described in Org. Syn.(1) from 3.21 g of benzyl chloride, 0.08 g of sodium[^{14}C]cyanide (100 mCi) and 1.37 g of carrier sodium cyanide.

The yield is 2.9 g (97.3% of the theoretical amount).

1-p-Toluene sulfonyl 4-[^{14}C]cyano-4-phenylpiperidine **5**

To a stirred solution of 2.9 g of **4**, 8.2 g of **3** in 40 ml of toluene, a suspension of sodamide (2.5 g) in toluene (5 ml) was added in five portions. The mixture was heated under reflux for one hour. After cooling, water (5 ml) was added. The organic layer was dried over anhydrous sodium sulfate and then evaporated to give a red solid crystalline product which was washed with methanol (5 ml). 4.79 g of **5** were obtained (56.8% yield). This material was used in the subsequent reaction without further purification.

[^{14}C]Norpethidine hydrochloride **6**

A mixture containing 4.79 g of **5** and 6.5 g of 75% sulphuric acid was heated under reflux at 140° in a oil bath for two hours. The reaction mixture was then cooled to 110°, 15 ml of ethanol were added and stirred for two more hours. The ethanol was evaporated and the residue was treated with sodium hydroxide. The cyclized product was extracted with ether. Gaseous hydrogen chloride was bubbled through the ether solution for one hour. The residue was 1.56 g of **6** (41.2% yield).

β-(4-[^{14}C]Carboethoxy-4-phenylpiperidino)propiophenone **7**

A reaction mixture containing 1.56 g of **6**, paraformaldehyde (2.10 g), acetophenone (0.51 g), and anhydrous ethanol (10 ml), was heated to refluxing temperature for one hour.

An additional amount of paraformaldehyde (2.1 g) was then added and the reaction mixture heated under reflux for further 18 hours.

Ethanol was evapored in vacuo, and the residue was dissolved in water. Ether (10 ml) was added. After cooling 1.47 g of 7 was isolated as a crystalline solid. (63.1 % yield) m.p. 175-176°

DL-β-(4-[^{14}C]Carboethoxy-4-phenylpiperidino)-1-phenyl-1-propanol 1

To a mixture containing 1.47 g of 7, methanol (20 ml), 0.1 g of sodium borohydride in 5 ml of water was added dropwise. The reaction mixture was stirred at room temperature for 18 hours.

The solution was treated with acetic acid and then with ammonium carbonate. Methanol was removed in vacuo and the residue was extracted with ether (3x10 ml). Gaseous hydrogenchloride was bubbled through the solution for 1 hour. The precipitated solid was treated with ethyl acetate to give 420 mg of 1 (28.6% yield).

The radiochemical purity was determinated by autoradiography of a thin-layer chromatogram over silicagel (Merck F_{254}) in methanol solvent. The total radioactivity, measured by liquid betascintillation was 4.74 mCi, and the molar specific activity was 4.56 mCi/m.mol. m.p. 191° (corrected).

^{1}H NMR, (DMSO-d_6, TMS) : 1.15 (t,3 H), 4.1 (q,2 H), 7.3 (s,10 H)
2.38 (m,12 H), 4.6 ppm (m,1 H).

IR (KBr) : ν_{CO}= 1745 cm^{-1}, ν_{OH}= 3500 cm^{-1}

REFERENCES

1. Org.synth., coll.vol. 1, 107
2. Eisleb O., Ber. 74 1433 (1941) and Médicaments Organiques de Synthèse, Masson et Cie, Paris, vol.V, 66, (1972)
3. US. Patent: 2,951,080 (1960) and 2,962,501 (1960)