LABELLING OF A NEW ANALGETIC AGENT, 5α , 9α-DIMETHYL-2-[4-(4-FLUOROPHENYL)-4-OXOBUTYL]-2'-HYDROXY-6,7-BENZOMORPHAN (ID-1229), WITH TRITIUM.

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SUMMARY

5α,9α-Dimethyl-2-[4-(4-fluorophenyl)-4-oxobutyl]-2'-hydroxy-6,7-benzomorphan (X) (ID-1229), a new analgetic agent, was labelled with tritium at C-3,4 or C-3 position of the benzomorphan nucleus for the use of metabolic studies. The procedures used are illustrated in Fig. 2. Catalytic reduction of the enamine (VI) with tritium gas afforded the benzomorphan-3,4-3H (VIIa) in 24% radiochemical yield while reduction of VI with sodium borotritide gave the benzomorphan-3-^3H (VIIb) in 40%. The tritiated benzomorphans (VIIa and VIIb) were easily converted to ID-1229-3,4-^3H (Xa) and ID-1229-3-^3H (Xb), respectively. The overall radiochemical yield of Xa was 7.5% based on tritium gas and that of Xb was 12.0% based on sodium borotritide.

INTRODUCTION

A new benzomorphan derivative, 5α,9α-Dimethyl-2-[4-(4-fluorophenyl)-4-oxobutyl]-2'-hydroxy-6,7-benzomorphan (ID-1229) has been found to have analgetic action in our laboratories[1]. In order to obtain a detailed knowledge of the metabolism of the agent in animals radioactive ID-1229 was required.

Ferrari, et al.[2] reported the metabolic studies of pentazocine and

cis-chloroallylnorpentazocine (CHDB), in which they employed pentazocine-3-^{3}H (IVa) and CHDB-3-^{3}H (IVb). These labelled compounds were synthesized from the 1,2-dihydropyridine (I) according to the well-known procedure[3,4] shown in Fig. 1. However, the procedure seems rather tedious and moreover has a disadvantage to produce diastereoisomers differing in configuration at C-9 position.

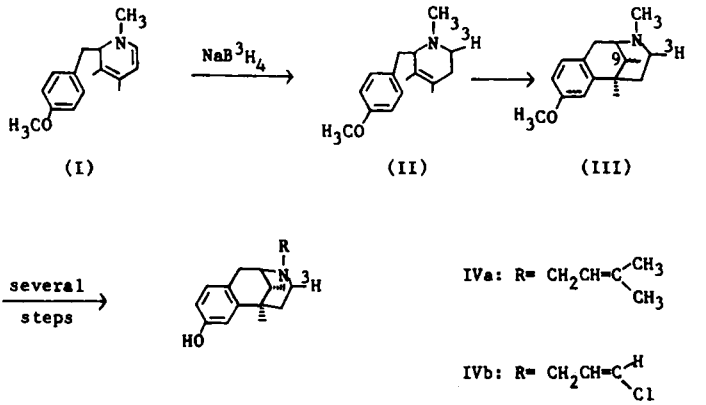

Fig. 1. Scheme for the syntheses of pentazocine-3-^{3}H and cis-chloroallylnorpentazocine-3-^{3}H

Recently, Pittman, et al.[5] reported the metabolism of pentazocine in rhesus monkey, in which they also employed tritiated pentazocine. In their report, however, no detail on the synthesis of the labelled compound was described.

We now report the syntheses of ID-1229-3,4-^{3}H (Xa) and ID-1229-3-^{3}H (Xb), which include a successful one-step tritium-labelling of the benzomorphan nucleus with the use of the enamine (VI) as a starting material.

DISCUSSION

The synthetic procedures used are demonstrated in Fig. 2.

By modifying Lewis' method[6], the N-benzylbenzomorphan (V) was allowed to react with mercuric acetate to give the N-benzylenamine (VI) in 80% yield. The structure of VI was confirmed on the basis of the spectroscopic data described in the experimental section.

Tritiation of VI with tritium gas in the presence of platinum oxide or 5% palladium on charcoal as a catalyst afforded the N-benzylbenzomorphan-3,4-^{3}H (VIIa) in 24% radiochemical yield. In this reaction hydrogenetic N-debenzylation was not observed.

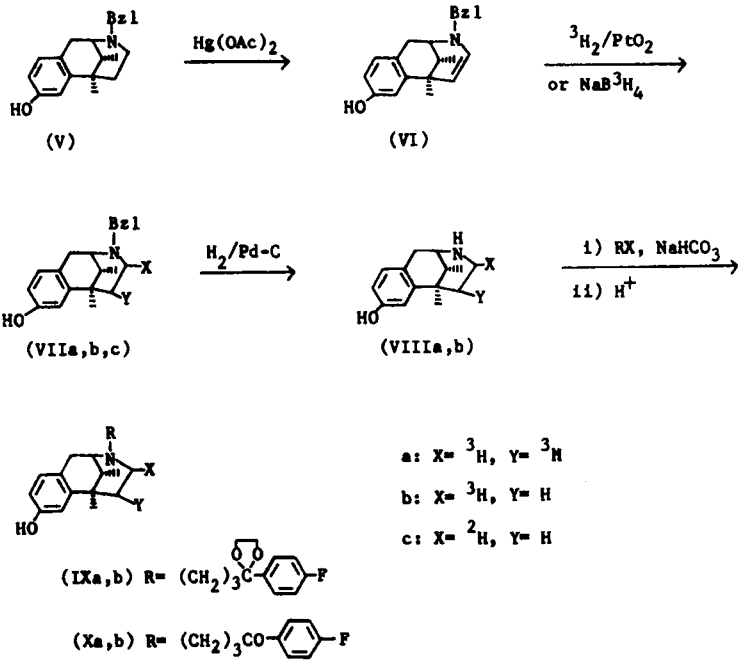

Fig. 2. Scheme for the syntheses of ID-1229-3,4-^{3}H (Xa) and ID-1229-3-^{3}H (Xb)

On the other hand reduction of VI with sodium borotritide gave the N-benzylbenzomorphan-3-^{3}H (VIIb) in 40% yield. The labelling position of this compound (VIIb) was confirmed as follows. Reduction of VI with sodium borodeuteride in the same reaction condition as tritiation gave the deuterated N-benzylbenzomorphan (VIIc). Its mass spectrum showed the molecular ion at m/e=308 ; demonstrating the incorporation of single deuterium in the molecule. In its NMR-spectrum one of C-3 methylene protons at δ 2.2 for the unlabelled N-benzylbenzomorphan (VII) was disappeared. The fact obviously indicates the deuterium-labelling at C-3 position.

N-Debenzylation of VIIa and VIIb was performed by catalytic hydrogenolysis with 10% palladium-charcoal to give VIIIa and VIIIb in approximately 70% yield, respectively. The N-norbenzomorphans (VIIIa,b) were treated with 4-(4-fluorophenyl)-4,4-ethylenedioxy-1-chlorobutane to afford IXa and IXb. Hydrolysis of the ketal group of IXa and IXb with hydrochloric acid gave ID-1229-3,4-^{3}H (Xa) (7.5% yield based on tritium gas) and ID-1229-3-^{3}H (Xb) (12.0% based on sodium borotritide). The specific activity of Xa and Xb was 118 and 112mCi/mmole, respectively.

EXPERIMENTAL

2-Benzyl-3,4-dehydro-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan (VI)

A mixture of 2-benzyl-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan (V) (3.0 g, 10 mmoles), mercuric acetate (13 g, 40 mmoles) and 5% acetic acid (45 ml) was heated at 120° for 2.5 hr. After cooling, the reaction mixture was filtered. The filtrate was saturated with hydrogen sulfide and allowed to stand at room temperature overnight. The inorganic precipitate formed was removed by filtration and washed with 2% acetic acid. The combined filtrate and washings were made basic with potassium carbonate to produce a

crystalline precipitate which was collected by filtration and washed with water. Reprecipitation of the crude product from 2.5% acetic acid afforded 2-benzyl-3,4-dehydro-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan (VI) (2.4 g, 80%); mp. 83 - 84°; ν max (nujol) 1640 cm^{-1} (C=C); NMR ($CDCl_3$, ppm) 0.80 (3H, doublet, J = 7.4 Hz, C_9-CH_3), 1.38 (3H, singlet, C_5-CH_3), 4.13 (2H, singlet, N-CH_2Ph), 5.9 (1H, multiplet, C_4-H), 6.7 (3H, multiplet, aromatic H), 7.3 (6H, multiplet, C_3-H and aromatic H); MS (m/e) 305 (molecular ion).

2-Benzyl-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3,4-^{3}H (VIIa)

2-Benzyl-3,4-dehydro-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan (VI) (305 mg, 1 mmole) in ethyl acetate (5 ml) was partially reduced with tritium gas (500 mCi) in the presence of platinum oxide (70 mg) and completely reduced with hydrogen gas in succession. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to leave an oily residue. In order to remove the labile tritium the residue was dissolved in methanol (5 ml) and the solvent was evaporated. This procedure was repeated 4 times to give 2-benzyl-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3,4-^{3}H (VIIa) (276 mg, 120 mCi, radiochemical yield 24%) with a specific activity of 133 mCi/mmole. This labelled compound showed the same R_f-value (0.56) as the unlabelled authentic sample on silica gel TLC developped with chloroform-ethyl acetate-methanol (6:3:1) and was used for the following reaction without any purification.

2-Benzyl-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3-^{3}H (VIIb)

To a stirred solution of 2-benzyl-3,4-dehydro-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan (VI) (305 mg, 1 mmole) in tetrahydrofuran (4 ml) was added a mixture of sodium borotritide (2 mg, 250 mCi), sodium borohydride (17 mg, 0.45 mmole) and sodium hydroxide (20 mg, 0.5 mmole) in water (1 ml). The mixture was heated under reflux for 3 hr. After cool-

ing, the reaction mixture was neutralized with 5% acetic acid and extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated to afford 2-benzyl-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3-^{3}H (VIIb) (278 mg, 99 mCi, specific activity 109 mCi/ mmole, radiochemical yield 40%) as colorless oil. The product showed the identical R_f-value (0.56) on silica gel TLC with the unlabelled authentic sample.

5α,9α-Dimethyl-2'-hydroxy-6,7-benzomorphan-3,4-^{3}H (VIIIa) and 5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3-^{3}H (VIIIb)

A mixture of 2-benzyl-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3,4-^{3}H (VIIa) (276 mg, 0.90 mmole, 120 mCi) and 10% palladium-charcoal (130 mg) in ethanol (10 ml) was stirred in an atmosphere of hydrogen until the cease of hydrogen uptake. The catalyst was removed by filtration and washed with ethanol. The combined filtrate and washings were evaporated to dryness to give a crystalline residue. Recrystallization of the residue from ethanol gave 5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3,4-^{3}H (VIIIa) (135 mg, 81.6 mCi, specific activity 131 mCi/mmole, radiochemical yield 68%), mp. 234 - 236°, identical in all respects with the authentic unlabelled sample.

Under the similar reaction condition 2-benzyl-5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3-^{3}H (VIIb) (278 mg, 0.9 mmole, 99 mCi) gave 5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3-^{3}H (VIIIb) (127 mg, 69.3 mCi, specific activity 118 mCi/mmole, radiochemical yield 70%),mp. 233 - 236°.

5α,9α-Dimethyl-2-[4-(4-fluorophenyl)-4-oxobutyl]-2'-hydroxy-6,7-benzomorphan-3,4-^{3}H (ID-1229-3,4-^{3}H) (Xa) and ID-1229-3-^{3}H (Xb)

A mixture of 5α,9α-dimethyl-2'-hydroxy-6,7-benzomorphan-3,4-^{3}H (VIIIa) (100 mg, 0.46 mmole, 60.3 mCi), 1-chloro-4,4-ethylenedioxy-4-(4-fluorophenyl)-butane (118 mg, 0.52 mmole), sodium bicarbonate (58 mg, 0.69 mmole) and dimethylformamide (1 ml) was heated at 125 - 130° for 3 hr. After removal of

the inorganic material by filtration, the filtrate was evaporated under reduced pressure to afford crude 5α,9α-dimethyl-2-[4-(4-fluorophenyl)-4,4-ethylenedioxybutyl]-2'-hydroxy-6,7-benzomorphan-3,4-^{3}H (IXa). The crude product was dissolved in methanol (1 ml), and to the solution were added water (0.5 ml) and 35% hydrochloric acid (0.1 ml). The mixture was heated to reflux for 1 hr. After removal of methanol, the mixture was made basic with 28% ammonium hydroxide and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to dryness to give a crystalline residue. The residue was chromatographed on silica gel and eluted with chloroform to give ID-1229-3,4-^{3}H (Xa) (89 mg, 27.7 mCi, specific activity 118 mCi/mmole, radiochemical yield 46% from VIIIa) as colorless needles, mp. 174 - 175°, identical in every respect with the unlabelled authentic sample.

By the same procedure ID-1229-3-^{3}H (Xb) (77 mg, 22.8 mCi) was obtained in 43% yield from VIIIb. The product had a specific activity of 112 mCi/mmole, mp. 174 - 175° and was identical in every respect with the authentic sample.

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