STRUCTURE RELATED TO MORPHINE

(Synthesis of α-2N-heptyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan from 3,4-lutidine : II)

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Synthesis of 2-N-heptyl-5,9-dimethyl-6,7-benzomorphan from 3,4-lutidine was effected in three step process and only α-form could be obtained through phosphoric acid cyclisation. This α-form of benzomorphan was converted in three steps to α-2N-heptyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan, which was also synthesised from alternative route. Infrared spectrum of the base confirmed the presence of α-form.

As has been remarked earlier[1] that when the sum of the carbon atoms (at C_5 and C_9) is 2-4 in 5,9-dialkyl-2′-hydroxy-2N-methyl-6,7-benzomorphan series there is optimum analgesic activity[2]. In this communication analgesic activity of the benzomorphan was studied by having 'heptyl' at nitrogen. As regards the role of alkyl group at nitrogen atom, it has been reported that the analgesic potency of the molecule was appreciably reduced when methyl group at nitrogen atom was replaced by ethyl, propyl or butyl groups and was again restored when it was replaced by amyl group, so much so that N-hexyl compound in this series was found to be more potent than N-amyl or N-methyl compound[3]. It is in view of these observations, the synthesis of the desired 6,7-benzomorphan has been carried out.

The N-heptyl analogue, without the 2′-hydroxy group was at first synthesised from 3,4-lutidineheptyl iodide by converting it through Freund's reaction[4,5] into 2-benzyl-1,2-dihydro-1-methyl-3,4-dimethyl pyridine followed with reduction with sodium borohydride to its tetrahydro derivative (2-benzyl-1-methyl-3,4-dimethyl-1,2,5,6-tetrahydropyridine) which was subsequently cyclised with 85% phosphoric acid when only α-form was obtained. The hydroxy group was introduced through nitration, reduction and subsequent diazolisation and hydrolysis. After separating the sparingly soluble α-form no β-form could be obtained from the mother liquor[1,2,6].

As α-form of the desired benzomorphan was obtained in a poor yield another method was followed by reacting *p*-methoxy benzyl magnesium chloride with N-heptyl iodide of 3,4-lutidine following in subsequent steps the same sequence of reactions as done in earlier method (8·5% based on 3,4-lutidine). The α-form of the benzomorphans obtained through the two methods were found to have same m.ps. and infrared spectra were superimposable (λ,6·12 (*m*) μ,6·35(s)μ) comparable to other benzomorphans in the series.

Pharmacological Studies

2N-heptyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan hydrochloride showed the analgesic activity comparable to codeine (ED_{50}-11·2 mg/kg mouse; hot plate method) while 2N-heptyl-5,9-dimethyl-6,7-benzomorphan hydrochloride with no hydroxyl group at 2′ position showed no analgesic activity.*

EXPERIMENTAL PROCEDURE

All the melting points are uncorrected and infrared spectra are recorded in Perkin Elmer infracord model 231.

3·4-Dimethyl 1-heptyl pyridinium iodide (I)

3·4-Lutidine (5·4 g, 0·05 mole), acetone (25 ml) and iodoheptane (13·5 g, 0·06 mole) were mixed. The mixture was refluxed for 2 hrs. and then cooled, diluted with ethyl acetate (15 ml) and left at 0-5° overnight to give 11·28 g. (67·8%) of pale yellow crystals m.p. 45-6° from acetone and ethyl acetate mixture.

ANALYSIS : Calcd for $C_{14}H_{24}IN$:

C, 50·04 ; H, 7·2 ;

Found : C, 50·01 ; H, 7·4.

2N-heptyl-5,9-dimethyl 6,7-benzomorphan (II)

To a well stirred suspension of I (9 g) in dry ether (15 ml.), freshly prepared benzyl magnesium chloride (prepared by taking Mg turning 1·5 g in 5 ml. of ether and benzyl chloride 6·5 g in ether (25 ml)) was added in 3-4 minutes. The reaction mixture was further stirred for 1·5 hr. with gentle refluxing. It was cooled and poured into ice water-ammonium chloride mixture, basified with ammonia and the liberated base was extracted several times with ether and combined ethereal extract was extracted with ether. Drying of the ethereal layer over anhydrous sodium sulphate and subsequent removal of the solvent afforded the dihydro product (5·8 g). It was dissolved in methanol (5·5 ml) and caustic soda (10%-25ml) was added. To a well stirred mixture of this, 1·5 g of sodium borohydride was added in small lots and the mixture refluxed for 2 hr. Cooled, poured in ice water and extracted several times with ether. Ether, from the combined ethereal ext. was distilled off and the crude product was distilled under reduced pressure 0·05 mm/150-55° to give 2·8 g (yield 35% based on starting methiodide) of tetrahydro pyridine base. 2·8 g of the tetrahydro base was refluxed with 25 ml. of 85% phosphoric acid for 48 hr. at 150-55°. The cooled dark coloured solution was poured into ice water, basified with ammonium hydroxide and the liberated base was extracted with ether. Drying of the ethereal layer over anhydrous sodium sulphate and subsequent removal of the solvent gave the crude product which was distilled off under reduced pressure (0·05 mm/180-5°). The hydrocholoride salt of the base was prepared by treating the base in acetone with saturated solution of the hydrochloric acid gas in dry ether. The product was crystallised from acetone-ether mixture m.p. 200-05°.

ANALYSIS: Calcd. for $C_{21}H_{33}N.HCl$; C, 75·3 ; H, 9·8 ;

Found: C, 75·6 ; H, 10·04 ;

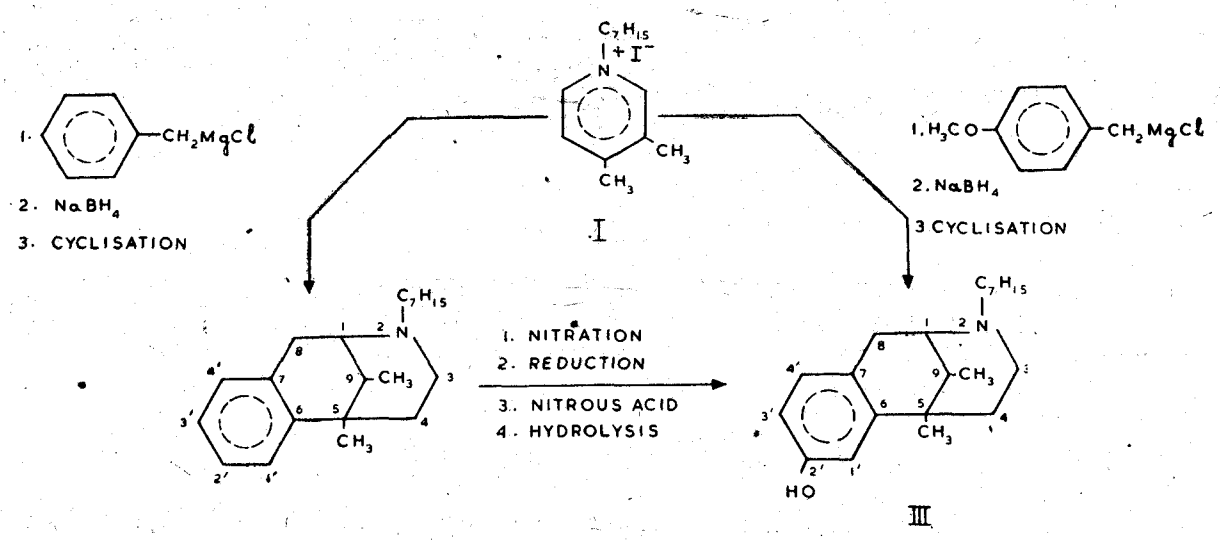

Fig. 1—Preparation of different morphines.

2-N-heptyl-2' hydroxy-5, 9-dimethyl-6, 7 benzomorphan (III)

Method I—The hydrochloride of the base (II) as described already[1] was nitrated, reduced, followed with subsequent nitrous acid oxidation, gave a crude base which was distilled under reduced pressure (0·05 mm) through short path distillation. The base was crystallised from acetone when a crop (m.p. 182-185° ; λ6·12 (m) μ ; 6·35(s) μ) was obtained. Nothing separated from the mother liquor.

The base was converted into its hydrochloride (m.p. 254-256°).

ANALYSIS : Calcd. for $C_{21}H_{33}NO.HCl.H_2O$; C, 68·24 ; H, 9·74 ; N, 3·78

Found : C, 68·12 ; H, 9·62 ; N, 3·45.

Method II—In the second method, p-methoxy benzyl magnesium chloride was reacted with 3,4 dimethyl 1-heptyl-pyridinium iodide on similar lines as described above.

In a cooled (10-15°) vigorously stirred suspension of I (10 g. 6·3 mole) in 50 ml. of dry ether was added during 4-5 minutes, a freshly prepared solution of p-methoxy benzyl magnesium chloride (prepared by taking 1·5 g of Mg turnings in 15 ml. of dry ether and 9 g of p-methoxy benzyl chloride in 50 ml. of dry ether). The mixture was stirred for 1·5 hr. without cooling and for 1 hr. with gentle refluxing. It was then cooled, poured cautiously into the ice-water containing ammonium chloride and basified with a little of ammonium hydroxide. Further separation and subsequent reaction with sodium borohydride and phosphoric acid (cyclisation) were carried out on similar lines as described above.

The crude base was distilled under reduced pressure (·05 mm) through short path distillation and crystallised from acetone (yield—1·35 g; m.p. 182-185° ; λ-6·12(m) μ ; 6·35(s) μ). Hydrochloride (m.p. 254-56°).

ANALYSIS : Calcd. for $C_{21}H_{33}NO.HCl.H_2O$; C, 68·24 ; H, 9·74 ; N, 3·78 ;

Found : C, 68·12 ; H, 9·62 ; N, 3·45.

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