# STRUCTURES RELATED TO MORPHINE—SYNTHESIS OF ∝-2′-OH-2-METHYL-5-PROPYL-9 ETHYL-6, 7-BENZOMORPHAN—PART I

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A three step synthesis of 2-methyl-5-propyl-9-ethyl-6, 7-benzomorphan from 3-ethyl-4-propyl pyridine was effected and only the α-form could be obtained through phosphoric acid cyclisation. This α-form of benzomorphan was converted to α-2-methyl-2′-hydroxy-5-propyl-9-ethyl-6, 7-benzomorphan in three steps again. Infrared spectra of the base confirmed the presence of α-form.

It has been reported that when the sum of the carbon atoms (at $C_5$ and $C_9$) is 2-4 in 5, 9-dialkyl-2′-hydroxy-2-methyl-6, 7-benzomorphan series there is optimum analgesic activity[1]. Analgesic activities of β- and α-2, 9-dimethyl-5-propyl-6, 7-benzomorphan are comparable to morphine and codeine respectively[2], while the activities increased with 2′-OH group to 2·9 ($ED_{50}$) in α-form[1]. The analgesic activity of the benzomorphan was studied by having ethyl at $C_9$ and propyl at $C_5$, where the sum of carbon atoms is five. Analgesic activity of α-form was found to be almost as half as that of codeine[3] ($ED_{50}$19·8). In general it is observed that the benzomorphans with substituents R at $C_5$ and H at $C_9$ are more active than the benzomorphans with different alkyl groups (at $C_5$ and $C_9$) whose sum of carbon atoms are equal to carbon atoms of R at $C_5$ (Table 1).

This was observed in the present case when the analgesic activity was found less than the activity of 5-amyl benzomorphan[4].

The methiodide of 3-ethyl-4-propyl pyridine* (I) was converted to 2-benzyl-1, 2-dihydro-1-methyl-3-ethyl-4-propyl pyridine (III) by the Freunds reaction[5] and was reduced with sodium borohydride to its tetrahydro derivative (IV) (2-benzyl-1-methyl-3-

Table 1

Comparison of the activities of benzomorphans with substituents R, H and alkyl groups at $C_5$ and $C_9$ position

| R at $C_5$ and H at $C_9$ | $ED_{50}$ | $R_1+R_2=R$ | | $ED_{50}$ |
|---|---|---|---|---|
| | | $R_1$ at $C_5$ | $R_2$ at $C_9$ | |
| $C_2H_5$ | 2·3 | $CH_3$ | $CH_3$ | 3·0 |
| $C_3H_7$ | 2·1 | $C_2H_5$ | $CH_3$ | 4·9 |
| $C_4H_9$ | 2·0 | $C_3H_7$ | $CH_3$ | 2·9 |
| | | $CH_3$ | $C_2H_5$ | 4·2 |
| $C_5H_{11}$ | 3·4 | $C_3H_7$ | $C_2H_5$ | 19·8 |
| $C_6H_{13}$ | 10·8 | $C_3H_7$ | $C_3H_7$ | 71·2 |

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ethyl-4-propyl-1, 2, 5, 6-tetrahydropyridine). The cyclisation of tetrahydro compound with 85 per cent phosphoric acid gave only the α-form and no β-form was isolated. Nitration of α-form (V) followed by reduction[6] and nitrous acid oxidation of the resultant 2′-amino derivative gave 2′-hydroxy compound (Fig. 1).

After separating the first crop (α-form) nothing could be obtained from the mother liquor. α-forms are less soluble and crystallise out first[1, 2].

## EXPERIMENTAL PROCEDURE

Melting points are uncorrected and infrared spectra were recorded in Perkin Elmer Model 231.

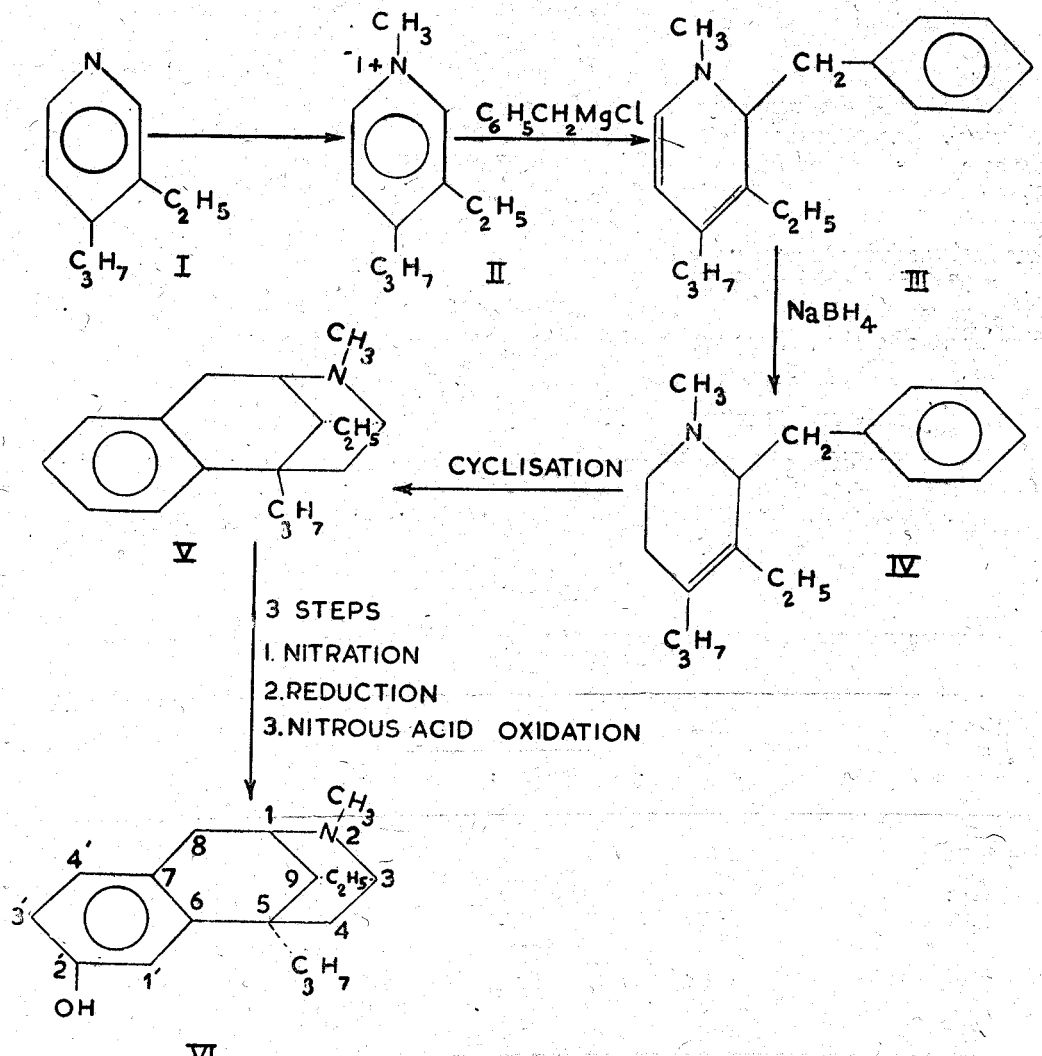


Fig. 1—Different stages involved in the synthesis of α-2-methyl-2′-hydroxy-5-propyl-9-ethyl-6, 7-benzomorphan.

*1-Methyl-3-ethyl-4-propylpyridinium Iodide (II)*

3-Ethyl-4-propylpyridine (6·0 gm.) was dissolved in acetone (5·0 ml.) and methyliodide (9·0 gm.) dissolved in acetone (12·0 ml.) was added in half an hour with continuous stirring. The solution was refluxed for one hour and then cooled in the refrigerator overnight. The pale yellow crystals formed were filtered and crystallised from acetone-ethylacetate, yield 10·0 gm. (83 per cent); m.p. 59·8°C (C, 45·1; H, 6·0; cal. val. for $C_{11}H_{18}NI$: C, 45·3; H, 6·1).

*2-Benzyl-1-methyl-1-3-ethyl-5-propyl-1, 2-dihydropyridine (III)*

To the well-stirred cold suspension of II (10·0 gm.) in dry ether (sodium dried) was added freshly prepared benzylmagnesium chloride (6·8 gm. of benzyl chloride freshly distilled, 1·6 gm. of magnesium turnings (G.R. grade) and 30·0 ml. of dry ether) in 3 to 4 min. when vigorous exothermic reaction took place. The solution was kept stirred for 2 to 2·5 hr. without cooling. The reaction mixture was kept under reflux by warming with hot water and after cooling, it was poured into ice water/ammonium chloride solution basified with ammonia and the liberated base was extracted thoroughly with ether. The ethereal layer was extracted several times with dilute hydrochloric acid (8-10 per cent). The combined extracts were basified with ammonia and then extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and then the solvent was distilled off (crude product, 5·0 gm., yield, 57·3 per cent).

*2-Benzyl-1-methyl-3-ethyl-4-propyl-1, 2, 5, 6-tetrahydropyridine (IV)*

The crude dihydroproduct (III) was dissolved in methanol (5·0 ml.) and caustic soda (10 per cent, 25 ml.), and to the well-stirred solution, sodium borohydride (1·6 gm.) was added gradually. After the addition was complete, the solution was stirred for half an hour and then refluxed for 2·5 hr. The solution was cooled and poured into ice water and extracted several times with ether. The ethereal layers were combined and dried over anhydrous sodium sulphate. Ether was distilled and the crude product (4·3 gm.) was distilled under reduced pressure (0·05 mm. at 150-55°C, yield 2·6 gm. (29·3 per cent) based on starting methiodide).

*2-N-methyl-5-propyl-9-ethyl-6, 7-benzomorphan (V)*

Cyclisation of IV with 85 per cent phosphoric acid was carried out by refluxing 2·8 gm. of IV with 25 ml. of 85 per cent phosphoric acid for 52 hr. at 160-65°C. The reaction mixture was then poured in ice water, basified with ammonia and then the liberated base was extracted with ether. The combined ethereal extract was dried over anhydrous sodium sulphate and the solvent distilled off when a crude product was obtained which was distilled under reduced pressure (0·05 mm. bath temp. 190-95°C). The distillate was crystallised as hydrochloride (m.p. 195-9°C). (C, 73·9; H, 9·5; cal. val. for $C_{18}H_{27}N.HCl$; C, 73·59; H, 9·54).

*Conversion of V to-2-methyl-2'-hydroxy-5-propyl-9-ethyl-6, 7-benzomorphan*

V (500 mg.) was converted to 2'-hydroxy derivative through nitration with fuming nitric acid (6·0 ml.) in glacial acetic acid (6·0 ml.). The solution was left overnight at room temperature and then at 0°C for two days. After distilling the acetic acid under reduced pressure and making the resulting mixture alkaline with 9 per cent $NH_4OH$, the crude product was obtained by extracting with $CHCl_3$ which was evaporated under reduced pressure. The crude nitro product was reduced on similar lines as 2'-nitro group in codeine is reduced[6]. The crude product thus obtained (2'-amino) was treated with nitrous acid[4]

($NaNO_2$ and dilute $H_2SO_4$). The crude 2′-hydroxy compound was crystallised from acetone (85.0 mg.) (m.p. 213-16°C; C, 69·92; H, 8·98; N, 4·68; cal. val. for $C_{18}H_{27}NO$ : C, 69·7; H, 8·7; N, 4·52. $\lambda_{max}^{najol}$, 6·15 (*m*)$\mu$, 6·30 (*s*)$\mu$.

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