

SYNTHESIS OF *N*-OCTYL-2'-HYDROXY-5, 9-DIMETHYL-6, 7-BENZOMORPHAN

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N-Octyl-2'-hydroxy-5, 9-dimethyl-6, 7-benzomorphan (II) was synthesised from 3, 4-lutidine by a three step process. Only α -form could be isolated through acid cyclisation. Infrared and nmr spectra confirmed the structure II.

Non-availability of morphine in the last World War prompted the chemists in U.S.A. to find a substitute and it led to the discovery of 6, 7-benzomorphan. The potent analgesic with no or less addiction liability would be of paramount importance in the time of war. The addiction liability of the morphine is much lowered when used along with cyclopentazocine. The present study is an attempt to synthesise one of such compounds.

In the earlier communications^{1,2} it was observed that the analgesic potency of the 2-alkyl-2'-hydroxy-5, 9-dimethyl-6, 7-benzomorphans was appreciably reduced when methyl group at the nitrogen atom was replaced by ethyl, propyl or butyl groups and again restored when the group at nitrogen was amyl so much so that in *N*-hexyl compound it was comparable to morphine (ED_{50} , 1.5 mg/kg). *N*-Hexyl-compound seems to have optimum analgesic activity as *N*-heptyl compound was found to be inactive³. This is being further confirmed by synthesising *N*-Octyl-2'-hydroxy-5, 9-dimethyl-6, 7-benzomorphan (II) which is also found to be inactive.

II was prepared⁴ by reacting 1-octyl-3, 4-dimethyl-pyridinium iodide (I) with *p*-methoxybenzyl-magnesium chloride followed by subsequent reduction with sodiumborohydride to give tetrahydro compound, which was cyclised in 85% phosphoric acid⁵. The α -form, II, was obtained in 27.4% yield based on I (See Fig. 1).

In the infrared spectrum of II ($C_{22}H_{35}ON$) the absorption at 3400 cm^{-1} was ascribed for the presence of hydroxy group and characteristic absorption at 1625 cm^{-1} and 1600 cm^{-1} were comparable to other benzomorphans in the series⁵. From the complex nmr spectrum the presence of three aromatic protons (δ 6.7—7.2) and twenty four protons (δ 0.8—1.7), due to three methyl groups (nine protons) seven methylene groups (fourteen protons) and one proton at C-9, could be established. Seven protons; one at C-1, two at C-3, two at C-8 and two at C-10 were present in the range of δ 2.5—3.7.

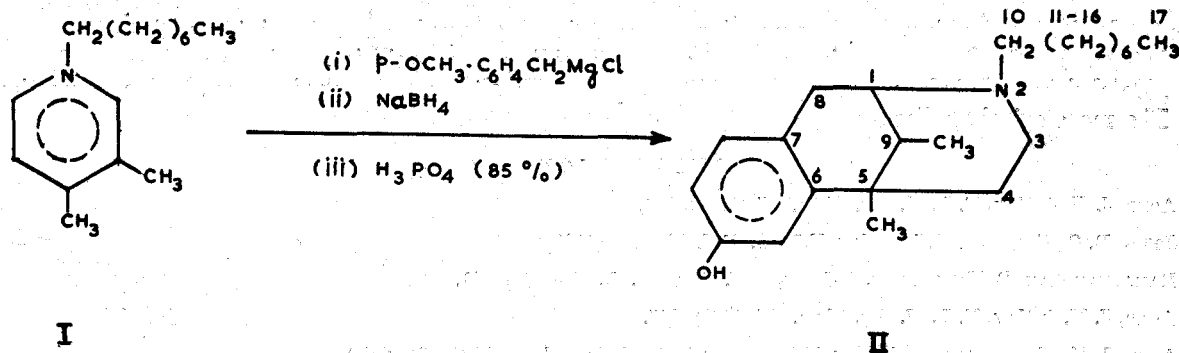


Fig. 1.—Synthesis of *N*-Octyl-2'-hydroxy-5, 9-dimethyl-6, 7-benzomorphan.

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Compound II was found to be inactive up to 40 mg/kg dose and the percentage of animals effected was zero. It shows that analgesic activity after reaching to a maximum value in *N*-hexyl compound has reached to minimum in *N*-octyl compound, II.

EXPERIMENTAL PROCEDURE

Melting points are uncorrected. Microanalyses are by Central Drug Research Institute, Lucknow (CDRI). Infrared spectrum was recorded in Perkin Elmer infracord and nmr spectrum on Varian A-60 D-model (using $CDCl_3$ as solvent and *TMS* as internal indicator) also at CDRI.

3, 4-Dimethyl-1-Octyl-Pyridinium Iodide (I) :

To 3, 4-dimethyl pyridine (5.35 g, 0.05 mole) in Me_2Co (5-7 ml), iodo-octane (18.0 g, 0.075 mole) was added dropwise. After refluxing for 30-35 hrs, the mixture was cooled at room temperature, the pasty mass was triturated with ethyl acetate. The crude product was crystallised from acetone-ethyl acetate at 0-5° (3 days) to give pure I, 9.0 g (51.3%), mp. 48.5°.

Analysis calcd. for $C_{15}H_{26}NI$: N, 4.03

Found : N, 3.94

N-Octyl-2'-Hydroxy-5, 9-Dimethyl-6, 7-Benzomorphan (II) :

Excess of freshly prepared ethereal solution of *p*-methoxybenzylmagnesium chloride⁶ (prepared from 2.4 g, 0.1 mole, Mg and 7.8 g, 0.05 mole *p*-methoxybenzylchloride) was added to a well stirred suspension of I (5.0 g, 0.0144 mole) in dry Et_2O in a course of 5-10 mins. The reaction mixture was further stirred for 1.5-2 hrs at 25° and then for 1 hr at 35-40°. After cooling and usual treatments⁴, the dihydro compound was extracted with Et_2O exhaustively. The combined ethereal extract was dried (anh. Na_2SO_4) and concentrated. $MeOH$ (ca. 20 ml) alongwith 10% $NaOH$ (ca. 20 ml) was added. To this well stirred mixture $NaBH_4$ (1.0 g) was added in portions during 1 hr. The mixture was stirred for another 2 hrs at 40-50°. After cooling to room temperature it was diluted with ice water and the tetrahydro compound was extracted with Et_2O exhaustively. The ethereal extract was dried (anh. Na_2SO_4) and solvent was removed. The product was distilled at reduced pressure (0.5 mm) when tetrahydro base (2 g., 40.4% based on I) was obtained as syrupy mass which was immediately kept in H_3PO_4 (85%) for cyclisation (60 hrs) at 150-60°. The reaction mixture was cooled, poured into ice-water, basified (NH_4OH) and extracted ($CHCl_3$). The $CHCl_3$ extract was dried (anhs. Na_2SO_4) and evaporation of solvent left 1.3 g of crude base (27.4%, based on I). It was repeatedly crystallised from Me_2Co -dry Et_2O to a pure form, m.p. 120°.

The hydrochloride, mp. 150-155° was crystallised from $MeOH$ - Me_2Co mixture.

Analysis calcd. for $C_{22}H_{35}ON$: C, 80.24; H, 10.61; N, 4.25

Found : C, 80.36; H, 10.72 ; N, 4.30.

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