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SYNTHESIS OF 2,5-DIMETHYL-6,7-(2':3'-PYRIDO)-MORPHAN

BY

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ABSTRACT

2,5-Dimethyl-6,7-(2[1]-3[1]-pyrido)morphan was synthesised from 1,4-dimethyl pyridinium iodide based on Grewe's morphinan synthesis.

A large number of 2'-hydroxy-6,7-benzomorphans with various alkyl substituents at 2,5 and 9 positions (I) have been thoroughly studied for their analgesic activity [1]. Here attempts have been made to synthesise a molecule having pyridine ring in place of benzene ring in 6,7-benzomorphan molecule resulting in a new class of compounds, known as 6,7-pyrido-morphan with the analgesic activity comparable to codeine.

The synthesis of the above compound was achieved through 1,2-dihydro-1,4-dimethyl-2-(2'-picolyl)-pyridine (*1*), which was prepared by reacting 1,4-dimethyl pyridinium iodide with 2-picolyl magnesium bromide [2] under the Freund reaction conditions [3]. The unstable dihydro intermediate product *1*, was immediately reduced with $NaBH_4$ to the corresponding tetrahydro compound, *2* [4, 5]. *2* was immediately kept for cyclisation in 85% H_3PO_4 to give *3*. The crude *3* after purification was converted into its hydrochloride salt.

The NMR spectrum of the hydrochloride salt of *3* (in $CDCl_3$) indicated the presence of 3 protons of -C-CH_3 as singlet at δ 1.05, 3 protons of N-CH_3 at δ 2.85 and three aromatic protons in the range of δ 6.60-7.35. The presence of protons at δ 2.25 could be attributed to the presence of 4 protons of two -CH_2- groups. The presence of five protons at δ 3.05-3.55, could be due to five protons adjacent to N-CH_3 group. The above observations in the NMR spectrum of this compound confirmed its structure as 2,5-dimethyl-6,7-(2' : 3'-pyrido) morphan (*3*).

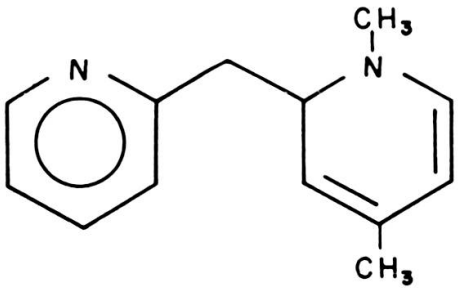
The iminoethano system being geometrically constrained to a cis-fusion, alkyl groups at 5, 9 positions may be in the either cis (3*a*- -isomer) or trans (3*b*- -isomer) juxtaposition for ring B. However, in the present case, only one form is possible as there is no alkyl group at position 9. N-CH_3 and C_5-CH_3 groups are trans to each other.

EXPERIMENTAL

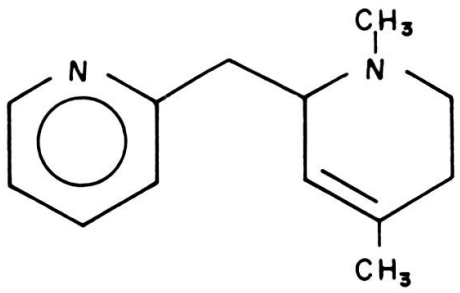
The melting point is uncorrected. Microanalysis was done at Central Drug Research Institute (CDRI), Lucknow (India). NMR spectrum was recorded on Varian A-60D model using TMS internal reference and $CDCl_3$ as solvent.

2,5-Dimethyl-6,7-(2' : 3'-pyrido)-morphan hydrochloride

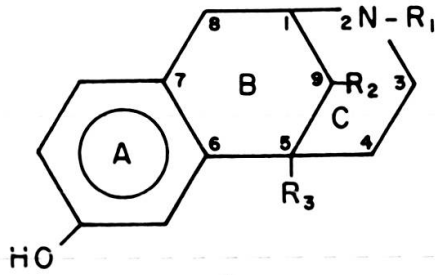
To a suspension of 2-picolyl magnesium bromide from ethyl magnesium bromide (0.06M) in anisole (50 ml) and 2-picoline (0.062M) in dry ether (100 ml) was added with stirring, 11.7 g. (0.05M) 1,4-dimethyl pyridinium iodide in one lot. The mixture



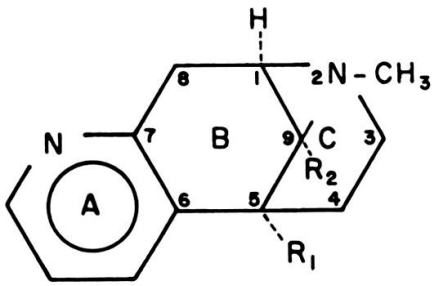
1



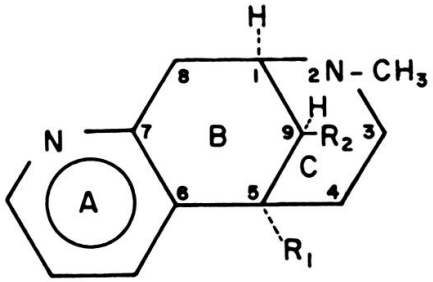
2



I



3 (a)



3 (b)

R_1 - CH_3
R_2 - H

was stirred at 26° for 1 hr and then for another 1 hr at elevated temperature (120° C). The cold reaction mixture was poured into ice-ammonium chloride mixture. Treatment of this mixture in the usual manner yielded 4.02 g of the crude dihydro base [4, 5] (*1*). To a well stirred mixture of *1*, in methanol (ca. 100 ml) and N.NaOH (ca. 500 ml), sodium borohydride (2.8 g) was added in small portions, during 15-20 min. The temperature of the reaction mixture was maintained at 35-40° for 6.5 hr. The cold reaction mixture was poured into ice cold water and extracted with ether. Washing of the ethereal layer with water, drying over anhydrous sodium sulphate and subsequent removal of the solvent under reduced pressure gave 3.2 g (ca. 31.8%) of *2*, as reddish brown oil. *2*, (3.2 g) was dissolved in 85% phosphoric acid (20 ml) and was kept at 120-130° for 72 hr. The cold mixture was poured in ice water, basified with ammonia, and was extracted with chloroform. The solvent layer was washed with water and was dried over anhydrous sodium sulphate. The removal of the solvent under reduced pressure yielded the crude base *3*, which was dissolved in acetone and was treated with ethereal hydrogen chloride. The hydrochloride salt so obtained was dissolved in methanol and passed through the charcoal column. The product so obtained was crystallised from methanol. Yield 1.8 g (ca. 13%) m.p. 157°.

Analysis: calcd. for $C_{13}H_{18}N_2 2HCl$

C, 56.72; H, 7.27; N, 10.18; Cl, 25.81%

Found: C, 56.32; H, 7.42; N, 10.42; Cl, 25.08%.

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