Studies on the Syntheses of Heterocyclic Compounds. Part DCLV. (1). Two Stereoisomers of 1-Benzyl-5-hydroxy-6-(4-methoxybenzyl)-4,5-dimethylpiperidin-2-one

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The stereochemistry of two diastereoisomers of 1-benzyl-5-hydroxy-6-(4-methoxybenzyl)-4,5-dimethylpiperidin-2-one (IV), which is an intermediate for synthesis of pentazocine (I), was elucidated.

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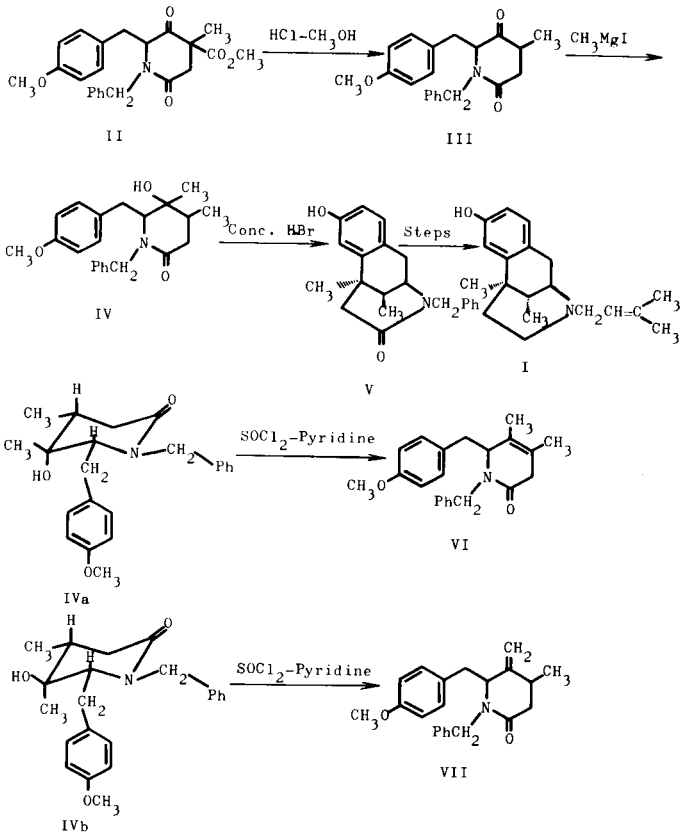
Recently we have reported a synthetic method of pentazocine (I) from L-tyrosine, which involved a decarbomethoxylation of the keto ester (II), followed by a reaction of the ketone (III) with methylmagnesium iodide and a cyclization of the alcohol (IV) with hydrobromic acid as shown in Scheme 1 (3). In the present paper we wish to describe the stereochemistry of the alcohols (IV).

Previously, an alcohol (IVa), m.p. 119.5°, had been isolated in 71.2% yield by the Grignard reaction of the ketone (III) after purification by column chromatography on silica gel followed by recrystallization from benzene (3). The crude product from the faster eluate in the above chromatography was further purified by a preparative tlc, followed by recrystallization from benzene, to give a product, m.p. 153.5°, in 3.3% yield, which was assumed to be a stereoisomer (IVb) of the above alcohol on the basis of the spectral data. Refluxing both alcohols with concentrated hydrobromic acid in acetic acid, respectively, for 38 hours gave the same amide (V), in about 77% yield. Treatment of the compound (IVa) with thionyl chloride and pyridine at room temperature for 4.5 hours, yielded 1-benzyl-3,6-dihydro-6-(4-methoxybenzyl)-4,5-dimethyl-2-pyridone (VI) as a main product. The nmr spectrum of VI (δ deuteriochloroform) showed two olefinic methyl groups at 1.52 and 1.66 ppm. On the other hand, the same treatment of IVb gave 1-benzyl-3,4,5,6-tetrahydro-6-(4-methoxybenzyl)-4-methyl-5-methylene-2-pyridone (VII) as a main product. The olefinic protons were observed at 4.42 and 4.75 ppm as each broad singlet while one methyl group appeared at 1.10 ppm in the nmr spectrum (δ deuteriochloroform). In the consideration that the ketone (III) should be the most thermodynamically stable form in which the methyl and anisyl group were *cis* to each other and equatorially oriented, the former alcohol (IVa) was expected to have an axial hydroxyl group and to be (±)-1-benzyl-5α-hydroxy-6α-(4-methoxybenzyl)-4α,5β-dimethylpiperidin-2-one, whereas the latter alcohol (IVb) to be (±)-1-benzyl-5β-hydroxy-6α-(4-methoxybenzyl)-4α,5α-dimethylpiperidin-2-one.

Scheme



EXPERIMENTAL

Melting points are uncorrected. Ir spectra were measured with a Hitachi H-60 spectrometer, nmr spectra with a JEOL PMX-60 spectrometer using TMS as an internal standard and mass spectra with a Hitachi RMU-7 spectrometer.

(±)-1-Benzyl-5α-hydroxy-6α-(4-methoxybenzyl)-4α,5β-dimethylpiperidin-2-one (IVa) and (±)-1-Benzyl-5β-hydroxy-6α-(4-methoxybenzyl)-4α,5α-dimethylpiperidin-2-one (IVb).

The Grignard reaction of 9.9 g. of the ketone (III) (3) with methylmagnesium iodide followed by silica gel column chromatography using chloroform gave 2.5 g. of the starting material (III) and the following two products. The crude product from the first eluate was purified by a preparative tlc on silica gel with ether, followed by recrystallization from benzene, to give 340 mg. of 1-benzyl-5β-hydroxy-6α-(4-methoxybenzyl)-4α,5α-dimethylpiperidin-2-one (IVb) as crystals, m.p. 153.5°, ir (chloroform): 3610, 3410 (OH), and 1620 cm^{-1} (C=O); δ (deuteriochloroform): 0.77 (4H, s, C_5-Me), 0.93 (3H, d, J = 6 Hz, C_4-Me), 1.90 - 3.70 (7H, m), 3.79 (3H, s, OMe), 5.36 (1H, d, J = 15 Hz, NCH_2Ph), 6.75 - 7.25 (9H, m, Ar-H); mass spectrum m/e: 353 (M^+).

Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.51; H, 7.61; N, 3.94.

The product as a powder from the second eluate was recrystallized from benzene to afford 7.38 g. of 1-benzyl-5α-hydroxy-6α-(4-methoxybenzyl)-4α,5β-dimethylpiperidin-2-one (IVa) as crystals, m.p. 119.5°, ir (chloroform): 3610, 3410 (OH), and 1630 cm^{-1} (C=O); δ (deuteriochloroform): 0.95 (3H, s, C_5-Me), 1.04 (3H, d, J = 6 Hz, C_4-Me), 1.60 - 3.66 (7H, m), 3.78 (3H, s, OMe), 5.30 (1H, d, J = 15 Hz, NCH_2Ph), 6.71 - 7.29 (9H, m, ArH); mass spectrum m/e: 353 (M^+).

Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.58; H, 7.73; N, 3.96.

1-Benzyl-3,6-dihydro-6-(4-methoxybenzyl)-4,5-dimethyl-2-pyridone (VI).

To a solution of 250 mg. of IVa in 7.5 ml. of pyridine was added 0.6 ml. of thionyl chloride under ice-cooling. After stirring for 4.5 hours at room temperature, the reaction mixture was diluted with ice-water and extracted with benzene. The benzene layer was washed with 10% hydrochloric acid, 10% sodium carbonate, water, and saturated aqueous sodium chloride solution, dried over sodium sulfate and evaporated to give a green gum-like material, which was purified on silica gel chromatography using benzene-methanol (99.5:0.5 v/v) to afford a pale yellow solid. Recrystallization from benzene-*n*-hexane gave 152 mg. of VI as colorless crystals, m.p. 129.5-130.5°, ir (chloroform): 1620 cm^{-1} (C=O); δ (deuteriochloroform): 1.52 (3H, broad s, C_4-Me), 1.66 (3H, broad s, C_5-Me), 3.75 (3H, s, OMe), 5.57 (1H, d, J = 15 Hz, NCH_2Ph), 6.79 (4H, broad s, 4 x ArH), 7.20 (5H, borad s, Ph); mass spectrum m/e: 335 (M^+), 333.

Anal. Calcd. for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.85; H, 7.60; N, 4.23.

1-Benzyl-3,4,5,6-tetrahydro-6-(4-methoxybenzyl)-4-methyl-5-methylene-2-pyridone (VII).

To a solution of 59 mg. of IVb in 1.5 ml. of pyridine was added 0.6 ml. of thionyl chloride under ice-cooling. After stirring for 4.5 hours at room temperature, the reaction mixture was worked up as above to give a green gum, which was purified by a preparative tlc on silica gel with ether to give 20 mg. of VII as a colorless caramel, ir (chloroform): 1620 cm^{-1} (C=O); δ (deuteriochloroform): 1.10 (3H, d, J = 6 Hz, C_4-Me), 3.76 (3H, s, OMe), 4.42 and 4.75 (each 1H, each broad s, >C=CH_2), 5.44 (1H, d, J = 15 Hz, NCH_2Ph), 6.71 and 6.92 (each 2H, each d, J = 8 Hz), 7.22 (5H, s, Ph); mass spectrum m/e: 335 (M^+).

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REFERENCES AND NOTES

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