

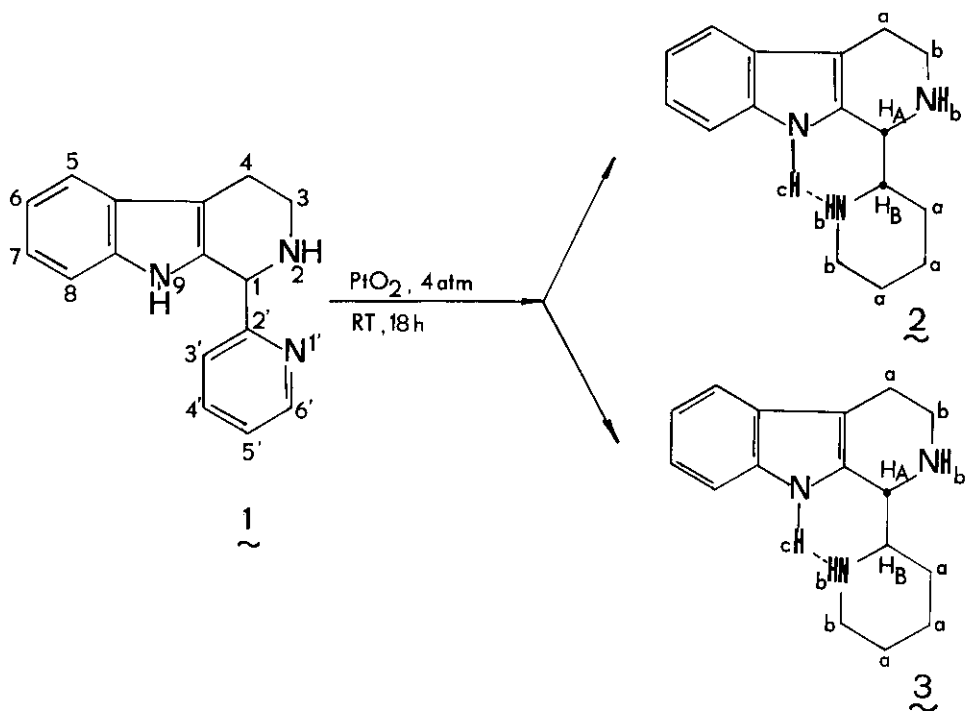
THE THREO AND ERYTHRO PRODUCTS OF THE CATALYTIC HYDROGENATION OF
1-(2-PYRIDYL)-1,2,3,4-TETRAHYDRO- β -CARBOLINE

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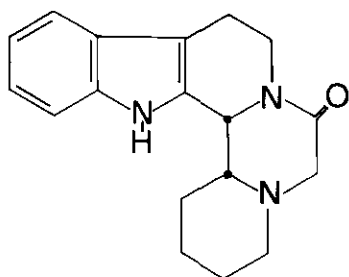
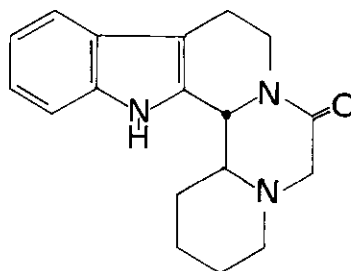
Abstract - The catalytic reduction of 1-(2-pyridyl)-1,2,3,4-tetrahydro- β -carboline to threo- and erythro- 1-(2-piperidyl)-1,2,3,4-tetrahydro- β -carbolines is described.

In our previous paper we described the synthesis of 9-methyl-1-(2-piperidyl)-1,2,3,4-tetrahydro- β -carboline via the selective reduction of 9-methyl-1-(2-pyridyl)-1,2,3,4-tetrahydro- β -carboline in diluted aqueous HCl in the presence of Pt.¹ Although we expected the formation of the diastereomers, we did not succeed in separating them. Now we wish to report the reduction of 1-(2-pyridyl)-1,2,3,4-tetrahydro- β -carboline ² (1) under different conditions and the successful separation and identification of the forming diastereomers due to chiral centers at C₁ and C₂, atoms. The reduction carried out in acetic acid with H₂ under 4 atm and with PtO₂ as catalyst led to the formation of two products which were spotted by TLC. We expected the compounds of R_f 0.79 and 0.76 to be the diastereomers of 1-(2-piperidyl)-1,2,3,4-tetrahydro- β -carboline (2 and 3). GLC of this mixture showed that the formation of 2 and 3 was as 1.5 : 1. We isolated these products chromatographically pure by the fractional crystallization. Elemental analysis and ms spectra indicated the same molecular formula for the compounds 2 and 3. In ir spectra of these products NH stretching vibration bands appear in the 3000-3500 cm⁻¹ region and their shape remains unchanged within the 10⁻² - 10⁻⁴ M concentration range. These data indicate the presence of the intramolecular hydrogen bond (Scheme).



This hydrogen bond can form either between the nitrogen atoms at the 2- and 1'-positions or between the nitrogen atoms of the indole ring and at the 1'-position. Since the hydrogen bond between indole nitrogen atom and that at the 1'-position forms easily³, it seems to be more preferable than that between nitrogen atoms at the 2- and 1'-positions. The presence of the hydrogen bond and some steric hindrance in the molecule (as it was observed on Dreiding models) restrict the rotation around the C₁ - C₂ bond. Thus the diastereomers 2 and 3 can adopt relatively stable - at room temperature - conformations with erythro and threo configurations, respectively, as shown in Scheme. ¹H nmr spectra of the compounds 2 and 3 are consistent with that described before for 9-methyl-1-(2-piperidinyl)-1,2,3,4-tetrahydro-β-carboline.¹ The analysis of the chemical shifts and vicinal coupling constant values for H_A atom indicates the existence of the threo and erythro forms. The observed ³J_{AB} values are typical^{4,6} and let us to assign the threo and erythro conformations to 3 and 2 structures, respectively. As described before, the NH proton signal of indole ring appears at δ 7.68 (in CCl₄), and it was found that its position strongly depends on the formation of the hydrogen bond to a solvent.³ In the triethylamine solution this signal shifts downfield to δ 11.21.³ For the investigated compounds the indole

NH signal appears at δ 9.28 and 9.98 for 2 and 3, respectively and is strongly broadened for the compound 3. The chemical shift as well as the shape of these signals led to the conclusion that there is the strong hydrogen bond between N₉ and N₁, atoms, particularly in the compound 3. The position of the hydrogen bond can be undoubtedly evidenced based on ¹H nmr spectra of the compounds 4 and 5, which were obtained by cyclization of 2 and 3, respectively.⁷ As one can expect the indole NH signals in 4 and 5, where there is no intramolecular hydrogen bond, are strongly shifted upfield to δ 7.98 and 8.04 and moreover these signals become sharp. Such significant changes in the chemical shifts and the shape of these signals in relation to those observed for 2 and 3 confirm our hypothesis.

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EXPERIMENTAL

Melting points were determined on a Boetius hot stage microscope and are uncorrected. Ir spectra were measured in CCl₄ solution (l=0.1 mm) and in KBr pellets on a Specord 71 IR spectrometer. ¹H nmr spectra were recorded on a Bruker apparatus at 200 MHz in CDCl₃ solution (with TMS as internal standard) and ms spectra were taken at 70 eV on an LKB 9000S spectrometer. Thin - layer chromatography was performed on Merck commercial chromatoplates (Kieselgel GF₂₅₄) with ethanol : NH₃ aq. (8 : 2) as a mobile phase. For GLC experiments a Pye Unicam GC system fitted with the flame ionization detector was used.

Reduction of 1-(2-pirydyl)-1,2,3,4-tetrahydro-*p*-carboline 1

The mixture of 1 (3.0 g, 0.01 mol) and PtO₂ (0.225 g) in acetic acid (45 ml)

was reduced in an autoclave with H_2 at 4 atm at room temp. for 18 h. Then the catalyst was filtered off and the solvent was evaporated in vacuo. The oily residue was dissolved in $CHCl_3$ (5 ml) and alkalized with NH_3 aq. to pH 11 and then extracted with $CHCl_3$ (3 x 20 ml). The combined extracts were dried over K_2CO_3 and evaporated, and the residue was fractionally crystallized.

The separation of the diastereomers of 1-(2-piperidyl)-1,2,3,4-tetrahydro- β -carboline by fractional crystallization.

(\pm)-erythro-1-(2-Piperidyl)-1,2,3,4-tetrahydro- β -carboline (2) : The oily residue (3.1 g) was dissolved in 20 ml of boiling ethanol, and the solution was cooled down to $0^\circ C$. The crystals were filtered off and recrystallized four times from ethanol giving chromatographically pure colourless crystals (1.35 g, 44 % yield), mp $137 - 140^\circ C$. Ir (KBr pellet) $\nu_{max}^{cm^{-1}}$: 3310, 2960, 2850, 1650. 1H nmr ($CDCl_3$) δ : 1.00 - 1.90 (8H, m, "a"), 2.50 - 3.50 (7H, m, "b" and H_B), 3.99 (1H, d, $^3J_{AB} = 1.8$ Hz, H_A), 7.00 - 7.50 (4H, m, arom.), 9.28 (1H, br-s, "c").

Ms m/z (relative abundance) : 255 (3), 172 (100), 171 (19.5), 84 (91.4);

Anal. Calcd. for $C_{16}H_{21}N_3$: C, 75.25; H, 8.29; N, 16.46. Found: C, 75.04; H, 8.35; N, 16.30.

(\pm)-threo-1-(2-Piperidyl)-1,2,3,4-tetrahydro- β -carboline (3) : The ethanol mother liquids were evaporated to dryness, and the residue (1.6 g) was dissolved in 5 ml of absolute ether and filtered off. The filtrate was cooled down to $+5^\circ C$ and the colourless crystals that resulted were recrystallized from methanol, giving 0.19 g (6 % yield) of 3, mp $130 - 133^\circ C$. Ir (KBr pellet) $\nu_{max}^{cm^{-1}}$: 3330, 2940, 1650. 1H nmr ($CDCl_3$) δ : 1.00 - 2.10 (8H, m, "a"), 2.50 - 3.50 (7H, m, "b" and H_B), 3.70 (1H, d, $^3J_{AB} = 9.8$ Hz, H_A), 7.00 - 7.50 (4H, m, arom.), 10.00 (1H, br-s, "c"). Ms m/z (rel. abund.) : 255 (1.9), 172 (100), 171 (18.4), 84 (97). Anal. Calcd. for $C_{16}H_{21}N_3$: C, 75.25; H, 8.29; N, 16.46. Found: C, 75.13; H, 8.44; N, 16.40.

The separation of 2 and 3 by GLC

The reaction mixture was separated by GLC using a glass column (1 m x 4 mm) packed with 3 % OV-17 on Gas Chrom Q (80 - 100 mesh). The temperature of injector and oven was $320^\circ C$ and at detector $230^\circ C$. Flow speed of N_2 60 ml/min. Retention time t_R 10 and 11 min for 2 and 3, respectively.

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REFERENCES

1. S. Misztal, Dissert. Pharm. Pharmacol., 1971, 23, 411.
2. S. Misztal, Dissert. Pharm. Pharmacol., 1970, 22, 127.
3. H. Saito and K. Nukada, J. Am. Chem. Soc., 1971, 93, 1072.
4. M. Karplus, J. Chem. Phys., 1959, 30, 11.
5. M. Karplus, J. Am. Chem. Soc., 1963, 85, 2870.
6. A.A. Bothuer-By and C. Naar-Colin, J. Am. Chem. Soc., 1961, 83, 231.
7. M. Dukat and S. Misztal, in preparation.

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