

1,2,3,5,6,10b-HEXAHYDROPYRROLO[2,1-a] ISOQUINOLINES.

PREPARATION AND STEREOCHEMISTRY OF 3-BENZYL DERIVATIVES

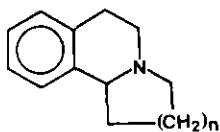
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Abstract - The preparation of *cis*- and *trans*-3-benzyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolines λ and λ' and the preferred conformation of the indolizidine ring system of these compounds are reported.

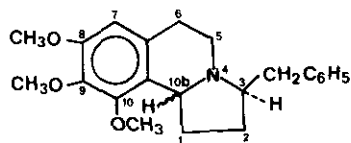
Although benzo[*a*]quinolizidines¹ (I, n=2) and related compounds²⁻⁶ have been extensively investigated as regards their stereochemistry, comparatively few studies have been made on the indolizidine nucleus of hexahydropyrrolo[2,1-a]isoquinolines (I, n=1).⁷

On the basis of their spectroscopic data, we discuss the preferred conformation of the indolizidine ring system in the epimeric 3-benzyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolines λ and λ' . These compounds were prepared by condensation between mescaline and γ -benzyl- γ -butyrolactone (λ) followed by Bischler-Napieralski cyclization of the resulting *N*-arylethyl- γ -hydroxyamide λ' . This approach constitutes the most common synthetic entry to the 1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]-isoquinoline ring system.^{8,9}

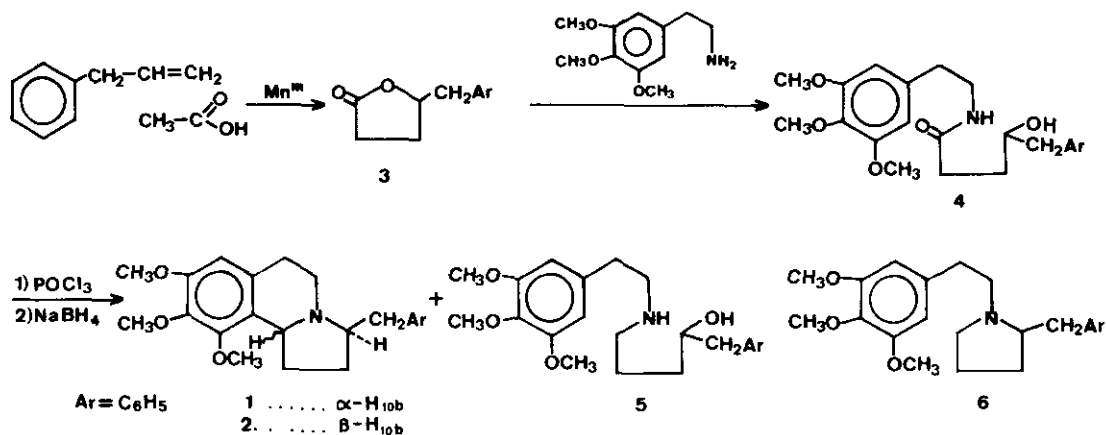
The required lactone λ was prepared from allylbenzene, acetic acid, and manganese (III) acetate, according to the method described for the one-step synthesis of γ -lactones from olefines, carboxylic acids and higher valent metal carboxylates.^{10,11}



I



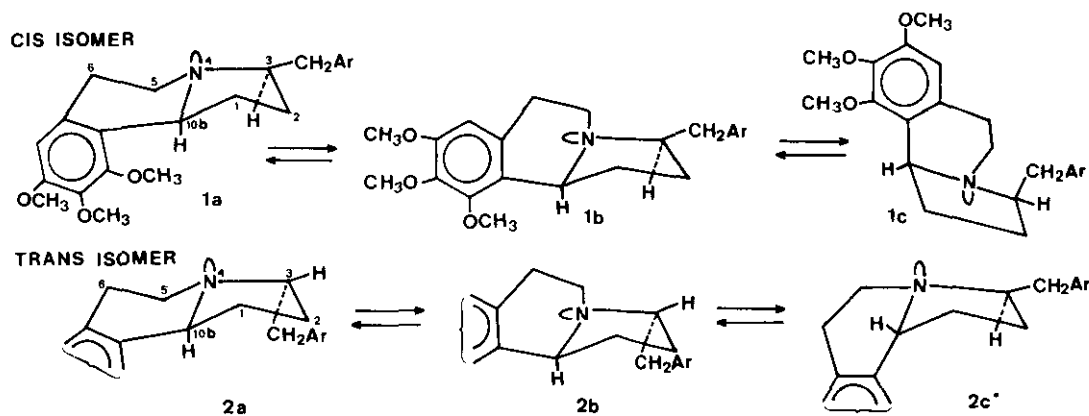
1 (*cis*), α -H_{10b}
 2 (*trans*), β -H_{10b}



The aminolysis of lactone **3** with mescaline produced γ -hydroxyamide **4**, which was characterized by its ir absorptions at 1635 and 3100-3500 cm^{-1} due to the amide carbonyl group and the OH and NH bonds, respectively. Treatment of **4** with phosphoryl chloride followed by sodium borohydride reduction furnished a diastereomeric mixture of tricyclic amines **1** and **2**, which were separated by column chromatography. Alcohol **5**, whose structure was confirmed by its conversion into pyrrolidine **6** with thionyl chloride, was isolated as a by-product. Its formation can be attributed to an incomplete cyclization of the nitrilium salt formed as intermediate in the Bischler-Napieralski cyclodehydration,¹² which is reduced during the final sodium borohydride treatment.

The stereochemical assignment of **1** and **2** was effected by their spectroscopic data (ir, ¹H- and ¹³C-nmr), taking into account that 3-substituted hexahydropyrrolo-[2,1-a]isoquinolines have two chiral centers and therefore can exist in two possible relative configurations. Each epimer can adopt, respectively, three conformations, readily interconvertible through nitrogen inversion (a \rightarrow b) and *cis*-indolizidine ring inversion (b \rightarrow c).

In the ir spectrum of isomer **1** Bohlmann bands¹³ at 2740 and 2800 cm^{-1} , characteristic of at least two α C-H bonds *trans* diaxial to the nitrogen lone pair, were observed. Moreover, in the ¹H-nmr spectrum the angular C_{10b}-H proton resonates at a field higher than δ 3.8.¹⁴ These data allow to establish the *trans* conformation **1a** for the indolizidine ring system. On the contrary, the isomer **2** shows no Bohlmann bands and exhibits a ¹H-nmr signal at δ 4.35 as a multiplet with $W_{1/2}$ =12 Hz, due to the C_{10b}-H methine proton. These observations indicate that this proton is *cis* to the nitrogen lone pair as well as in a *gauche* orientation with respect to the C₁₋



*For clarity, λ_c as illustrated is the enantiomer resulting from the ring inversion of λ_b .

methylene protons. This implies a *cis*-fused indolizidine conformation such as λ_c . The different ring fusion of isomers λ and λ was also concluded from their ^{13}C -nmr spectra. Thus, the shielding of the C-6 benzylic methylene carbon in the *cis*-fused isomer λ ($\delta 25.56$) relative to the *trans*-fused isomer λ ($\delta \sim 29$) is analogous to that observed in other fused azacyclic systems having a *cis*-fusion of type λ .¹⁵ On the other hand, the chemical shift difference of C_{10b} between isomers λ ($\delta 62.85$) and λ ($\delta 57.27$) is similar to that reported for the angular methine carbon between *trans*- and *cis*-fused indolizidine,¹⁶ benzo[*a*]quinolizidine,¹⁷ and indolo[2,3-*a*]quinolizidine¹⁸ systems.

^{13}C -Nmr Chemical Shifts^{a,b} of Compounds λ , λ , and λ^c

Compound	C-1	C-2	C-3	C-5	C-6	C-6a	C-7	C-8	C-9	C-10
λ	28.88	30.48	64.04	45.86	29.01	130.49	107.44	150.83	140.27	151.88
λ	30.42	32.25	63.76	45.09	25.56	130.26	107.00	151.03	140.38	151.58
λ^c	21.81	30.05	66.34	53.69	34.60	135.23	105.72	152.91	136.40	152.91
	C-10a	C-10b	CH ₂ Ar	C-1'	C-2'	C-3'	C-4'	C ₈ -OMe	C ₉ -OMe	C ₁₀ -OMe
λ	124.85	62.85	39.55	139.72	129.12	128.27	125.99	55.92	60.52	60.69
λ	125.61	57.27	41.63	140.07	129.22	128.22	125.93	55.92	60.37	60.68
λ^c	105.72	55.80	39.80	138.99	128.87	127.96	125.78	55.80	60.34	55.80

a. In ppm relative to TMS. Measured in CDCl₃ solution at 50.3 MHz.

b. The assignments are in agreement with off-resonance spectra.

c. For an easier comparison, the numbering of the pyrrolo[2,1-*a*]isoquinoline system has been maintained.

The modification of the conformational preference of the indolizidine system¹⁹ in λ could be accounted for by considering that this isomer has a *trans*-relationship between hydrogens at C₃ and C_{10b}, and that, consequently, in the *trans*-fused conformation λ_a the benzyl group adopts an axial orientation.

EXPERIMENTAL

Ir spectra were taken on a Perkin-Elmer 577 spectrophotometer, and only noteworthy absorptions (cm⁻¹) are listed. Nmr spectra were recorded in CDCl₃ with TMS as internal standard (¹H-nmr: Perkin-Elmer R-24B; ¹³C-nmr: Varian XL-200). Chemical shifts are reported in ppm downfield (δ) from TMS. Melting points were determined on a Büchi apparatus and are uncorrected. Column chromatography was carried out on SiO₂ (silica gel 60, Merck, 63-200 μ m). Tlc was carried out on SiO₂ (silica gel HF₂₅₄, Merck) and the spots were located with uv light or iodoplatinate reagent. The developing solvent was ether/acetone/diethylamine (35:15:2). Microanalyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

γ -Benzyl- γ -butyrolactone (λ). To a stirred solution of manganous (II) acetate tetrahydrate (67 g, 0.27 mol) in glacial AcOH (380 ml) maintained at 90°C was successively added KMnO₄ (10.1 g, 0.06 mol), acetic anhydride (100 ml), sodium acetate (158 g), and allylbenzene (22.5 g, 0.19 mol). The resulting mixture was refluxed for 6 h, after which it was cooled, diluted with ice-H₂O, and extracted with ether. The organic extracts were washed with aqueous NaHCO₃, dried, and evaporated. The residue was distilled to give 5.3 g of unreacted allylbenzene and 11.3 g (44% based on the unrecovered allylbenzene) of γ -lactone λ : bp 165-170°C (0.3 mm Hg). An analytical sample was obtained by column chromatography using 1:1 benzene-chloroform as eluent; ir (NaCl): 1770 (lactone); nmr (CCl₄): 1.70-2.40 (m, 4H, CH₂), 2.70 and 2.97 (2dd, 1H each, J=14 and 6 Hz, CH₂Ar), 4.50 (q, 1H, CH), 7.10 (s, 5H, ArH). Anal. Calcd for C₁₁H₁₂O₂: C, 74.97; H, 6.86. Found: C, 75.09; H, 6.99.

N-(3,4,5-Trimethoxyphenethyl)-5-phenyl-4-hydroxypentanamide (λ). A mixture of lactone λ (7.74 g, 44 mmol) and mescaline²⁰ (9.32 g, 44 mmol) was stirred at 110-120°C for 3 h under nitrogen. The resulting mixture was dissolved in CHCl₃ and the solution was successively washed with 1N HCl, aqueous NaHCO₃, and H₂O. Evaporation of the solvent followed by crystallization gave 11.8 g (69%) of hydroxyamide λ : mp 127-129°C (CHCl₃-petroleum ether); ir (KBr): 3500-3100 (OH), 3340 (NH), 1635 (C=O); nmr: 1.80 (m, 3H, OH and 3-CH₂), 2.15-2.90 (m, 8H, CH₂), 3.45 (m, 1H, CHOH), 3.80 (s, 9H, OCH₃), 5.75 (br, 1H, NH), 6.35 (s, 2H, ArH), 7.20 (s, 5H, ArH). Anal. Calcd for C₂₂H₂₉NO₅: C, 68.19; H, 7.54; N, 3.61. Found: C, 68.17; H, 7.45; N, 3.34.

(3R*,10bS*)- and (3R*,10bR*)-3-Benzyl-8,9,10-trimethoxy-1,2,3,5,6,10b-hexahydro-*p*-rrolo[2,1-*a*]isoquinoline (λ and λ'). To a solution of 2 g (5 mmol) of hydroxyamide λ in 50 ml of anhydrous toluene was added 2.5 ml of freshly distilled POCl₃. After 2 h at reflux under nitrogen, the reaction mixture was evaporated, and CH₃OH (100 ml) and NaBH₄ (2 g) were added. After being stirred overnight at room temperature, the

solvent was removed and the residue distributed between ether and water. The ethereal solution was extracted with 1N HCl. The extracts were basified with 5% aqueous NaOH and extracted with ether. The ethereal solution was dried and evaporated to give an oil which was chromatographed. Elution with 1:4 benzene/CHCl₃ gave 360 mg (30%) of amine λ which solidified on standing: mp 97-98°C (acetone); ir (KBr): 2740 and 2800 (Bohlmann bands); nmr: 1.40-3.45 (m, 12H), 3.80 (s, 9H, OCH₃), 6.40 (s, 1H, ArH), 7.20 (s, 5H, ArH). Anal. Calcd for C₂₂H₂₇NO₃: C, 74.79; H, 7.69; N, 3.96. Found: C, 75.04; H, 7.90; N, 3.69. Elution with CHCl₃ gave 340 mg (28%) of amine ζ ; nmr: 1.30-3.30 (m, 11H), 3.75 (s, 6H, OCH₃), 3.80 (s, 3H, OCH₃), 4.15-4.55 (m, 1H, C_{10b}-H), 6.25 (s, 1H, ArH), 7.10 (s, 5H, ArH). The oxalate melted at 126-128°C (EtOH). Anal. Calcd for C₂₄H₂₉NO₇: C, 64.99; H, 6.59; N, 3.15. Found: C, 64.68; H, 6.64; N, 2.87. Finally, on elution with 99:1 CHCl₃/CH₃OH, 520 mg (28%) of 1-phenyl-5-(3,4,5-trimethoxyphenethylamino)-2-pentanol (ξ) were obtained; ir (NaCl): 3100-3600 (OH); nmr: 1.20-2.10 (m, 5H), 2.40-3.00 (m, 7H), 3.10-3.40 (m, 3H), 3.80 (s, 9H, OCH₃), 6.40 (s, 2H, ArH), 7.25 (s, 5H, ArH). The oxalate melted at 154-156°C (EtOH). Anal. Calcd for C₂₄H₃₃NO₈·1/2C₂H₆O: C, 61.71; H, 7.46; N, 2.88. Found: C, 61.65; H, 7.22; N, 2.72.

2-Benzyl-1-(3,4,5-trimethoxyphenethyl)pyrrolidine (η). To a solution of alcohol ξ (797 mg, 2.1 mmol) in anhydrous benzene (12 ml) and pyridine (0.36 ml) was added thionyl chloride (0.2 ml). The mixture was stirred at room temperature for 1 h, poured into water, made alkaline with aqueous NaHCO₃, and extracted with CH₂Cl₂. The extracts were dried and evaporated to a residue which was chromatographed using 9:1 CHCl₃/CH₃OH as eluent to give 416 mg (53%) of pyrrolidine η ; nmr: 1.6-1.9 (m, 4H), 2.2-3.6 (m, 9H), 3.8 (s, 9H, OCH₃), 6.3 (s, 2H, ArH), 7.1 (s, 5H, ArH).

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Received, 15th November, 1983