1,2,3,5,6,10b-HEXAHYDROPYRROLO[2,1-*a*] ISOQUINOLINES. PREPARATION AND STEREOCHEMISTRY OF 3-BENZYL DERIVATIVES

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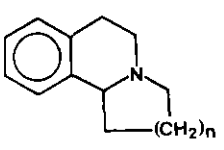
Abstract - The preparation of *cis*- and *trans*-3-benzyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*] isoquinolines **1** and **2** and the preferred conformation of the indolizidine ring system of these compounds are reported.

Although benzo[*a*]quinolizidines[1] (I, n=2) and related compounds[2-6] 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 **1** and **2**. These compounds were prepared by condensation between mescaline and γ-benzyl-γ-butyrolactone (**3**) followed by Bischler-Napieralski cyclization of the resulting *N*-arylethyl-γ-hydroxyamide **4**. 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 **3** 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]



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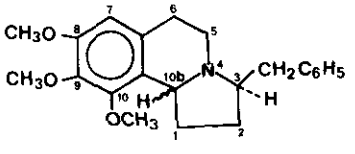
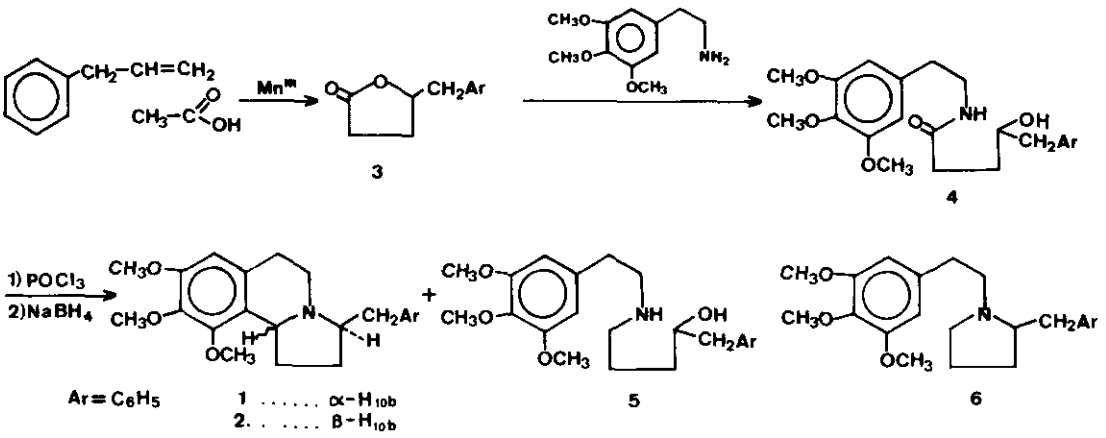


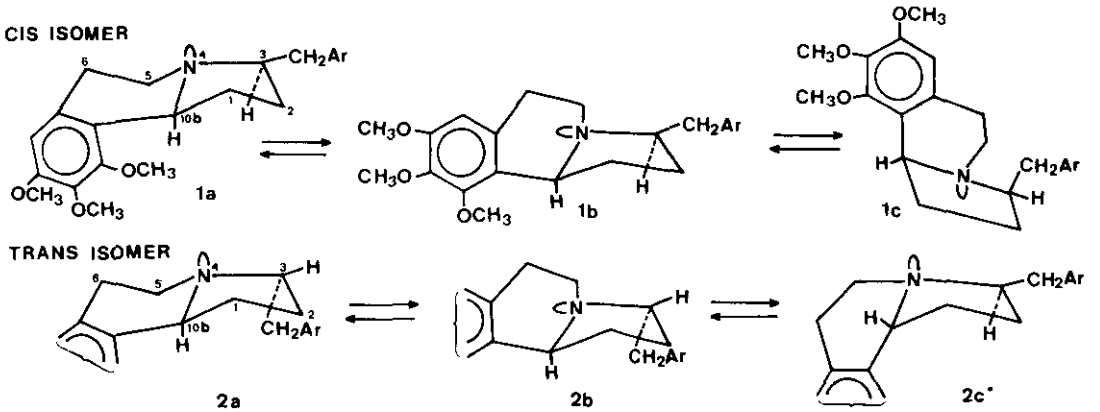
1 (cis), α-H_{10b}
2 (trans), β-H_{10b}



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 cyclodehydratation,[12] which is reduced during the final sodium borohydride treatment.

The stereochemical assignment of 1 and 2 was effected by their spectroscopic data (ir, ^{1}H- and ^{13}C-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→ b) and *cis*-indolizidine ring inversion (b→ c).

In the ir spectrum of isomer 1 Bohlmann bands[13] 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 ^{1}H-nmr spectrum the angular C_{10b}-H proton resonates at a field higher than δ3.8.[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 ^{1}H-nmr signal at δ4.35 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 C_1-



*For clarity, 2c as illustrated is the enantiomer resulting from the ring inversion of 2b.

methylene protons. This implies a *cis*-fused indolizidine conformation such as 2c. The different ring fusion of isomers 1 and 2 was also concluded from their ^{13}C-nmr spectra. Thus, the shielding of the C-6 benzylic methylene carbon in the *cis*-fused isomer 2 (δ25.56) relative to the *trans*-fused isomer 1 (δ~29) is analogous to that observed in other fused azacyclic systems having a *cis*-fusion of type c.[15] On the other hand, the chemical shift difference of C_{10b} between isomers 1 (δ62.85) and 2 (δ57.27) 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*]quinolizidine[18] systems.

^{13}C-Nmr Chemical Shifts[a,b] of Compounds 1, 2, and 6

Compound	C-1	C-2	C-3	C-5	C-6	C-6a	C-7	C-8	C-9	C-10
1	28.88	30.48	64.04	45.86	29.01	130.49	107.44	150.83	140.27	151.88
2	30.42	32.25	63.76	45.09	25.56	130.26	107.00	151.03	140.38	151.58
6[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_2Ar	C-1′	C-2′	C-3′	C-4′	C_8-OMe	C_9-OMe	C_{10}-OMe
1	124.85	62.85	39.55	139.72	129.12	128.27	125.99	55.92	60.52	60.69
2	125.61	57.27	41.63	140.07	129.22	128.22	125.93	55.92	60.37	60.68
6[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 $CDCl_3$ 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 system[19] in 2 could be accounted for by considering that this isomer has a *trans*-relationship between hydrogens at C_3 and C_{10b}, and that, consequently, in the *trans*-fused conformation 2a 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 $CDCl_3$ with TMS as internal standard (^{1}H-nmr: Perkin-Elmer R-24B; ^{13}C-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 SiO_2 (silica gel 60, Merck, 63-200 μm). Tlc was carried out on SiO_2 (silica gel HF_{254}, 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 (3). 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 $KMnO_4$ (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-H_2O, and extracted with ether. The organic extracts were washed with aqueous $NaHCO_3$, 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 3: 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 (CCl_4): 1.70-2.40 (m,4H,CH_2), 2.70 and 2.97 (2dd,1H each,J=14 and 6 Hz,CH_2Ar), 4.50 (q,1H,CH), 7.10 (s,5H,ArH). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.09; H, 6.99.

N-(3,4,5-Trimethoxyphenethyl)-5-phenyl-4-hydroxypentanamide (4). A mixture of lactone 3 (7.74 g, 44 mmol) and mescaline[20] (9.32 g, 44 mmol) was stirred at 110-120°C for 3 h under nitrogen. The resulting mixture was dissolved in $CHCl_3$ and the solution was successively washed with 1N HCl, aqueous $NaHCO_3$, and H_2O. Evaporation of the solvent followed by crystallization gave 11.8 g (69%) of hydroxyamide 4: mp 127-129°C ($CHCl_3$-petroleum ether); ir (KBr): 3500-3100 (OH), 3340 (NH), 1635 (C=O); nmr: 1.80 (m,3H,OH and 3-CH_2), 2.15-2.90 (m,8H,CH_2), 3.45 (m,1H,CHOH), 3.80 (s,9H, OCH_3), 5.75 (br,1H,NH), 6.35 (s,2H,ArH), 7.20 (s,5H,ArH). Anal. Calcd for $C_{22}H_{29}NO_5$: 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-hexahydropyrrolo[2,1-a]isoquinoline (1 and 2). To a solution of 2 g (5 mmol) of hydroxyamide 4 in 50 ml of anhydrous toluene was added 2.5 ml of freshly distilled $POCl_3$. After 2 h at reflux under nitrogen, the reaction mixture was evaporated, and CH_3OH (100 ml) and $NaBH_4$ (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/$CHCl_3$ gave 360 mg (30%) of amine 1 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,OCH_3), 6.40 (s, 1H,ArH), 7.20 (s,5H,ArH). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.79; H, 7.69; N, 3.96. Found: C, 75.04; H, 7.90; N, 3.69. Elution with $CHCl_3$ gave 340 mg (28%) of amine 2; nmr: 1.30-3.30 (m,11H), 3.75 (s,6H,OCH_3), 3.80 (s,3H,OCH_3), 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 $C_{24}H_{29}NO_7$: 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 $CHCl_3/CH_3OH$, 520 mg (28%) of 1-phenyl-5-(3,4,5-trimethoxyphenethylamino)-2-pentanol (5) 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,OCH_3), 6.40 (s,2H, ArH), 7.25 (s,5H,ArH). The oxalate melted at 154-156°C (EtOH). Anal. Calcd for $C_{24}H_{33}NO_8 \cdot 1/2C_2H_6O$: 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 (6). To a solution of alcohol 5 (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 $NaHCO_3$, and extracted with CH_2Cl_2. The extracts were dried and evaporated to a residue which was chromatographed using 9:1 $CHCl_3/CH_3OH$ as eluent to give 416 mg (53%) of pyrrolidine 6; nmr: 1.6-1.9 (m, 4H), 2.2-3.6 (m,9H), 3.8 (s,9H,OCH_3), 6.3 (s,2H,ArH), 7.1 (s,5H,ArH).

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