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# SYNTHESIS OF 15-AZAYOHIMBAN, A NEW HETEROCYCLIC RING SYSTEM

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***Abstract.*** Two synthetic routes to the 15-azayohimban ring system have been studied. The first one, based on a Pictet-Spengler condensation between tryptamine and piperidine acetal **4**, gave very low yields of pentacycles **2a**. The second, more efficient route involves as the crucial step a cyclization of a *N*-acyliminium cation generated from imide **11**. The different course of the Pictet-Spengler reaction from amino acetals **4** and **8**, as compared with amido acetal **7**, is discussed.

Several derivatives of the tetracyclic octahydropyrazinopyridoindole system **1**[1,2] have shown to possess hypotensive activity of the same intensity as reserpine .[3] This result prompted us to synthesize the new heterocyclic system **2**, which incorporates an additional six-membered ring so that it can be considered as a 15-aza-analog of the pentacyclic skeleton of reserpine and yohimbine, two alkaloids whose effects upon the adrenergic system are well-known.

We report here two synthetic routes for the preparation of the 5-oxoderivatives **2a** (*cis* and *trans*) and their reduction to the fundamental ring system **2b** (*cis* and *trans*).[4]

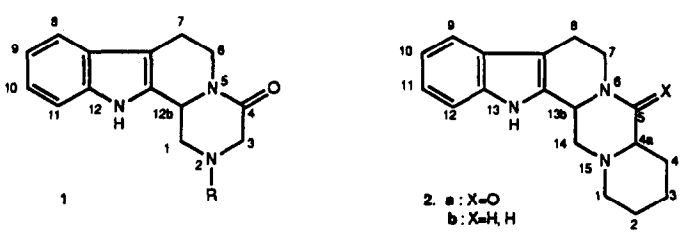
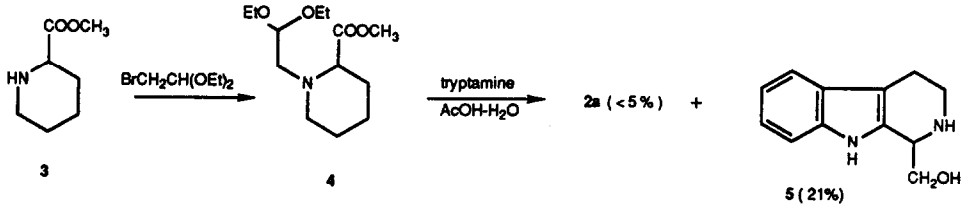



Figure 1

The first route investigated consists of only three steps, the key step being a Pictet-Spengler reaction between typtamine and the acetal **4** with simultaneous closure of the piperazine ring by lactamization (Scheme 1). Following a conceptually similar way we have recently reported the synthesis, in excellent yields, of several 2-acyl derivatives of **1**[1,2]. The required piperidine acetal intermediate **4** was prepared in 85% overall yield from piperidine-2-carboxylic acid by esterification followed by alkylation of the resulting ester **3** with bromoacetaldehyde diethyl acetal. However, unexpectedly, condensation of **4** with tryptamine under the reaction conditions we had successfully employed[1] for the synthesis of **1** (R=acyl) gave a *cis-trans* mixture of pentacycles **2a** in a yield lower than 5%. Hydroxymethyl-tetrahydro-β-carboline **5**[5] was obtained in 21% yield. The modification of the reaction conditions (time, temperature) did not result in a significant improvement of the yield of **2a**.

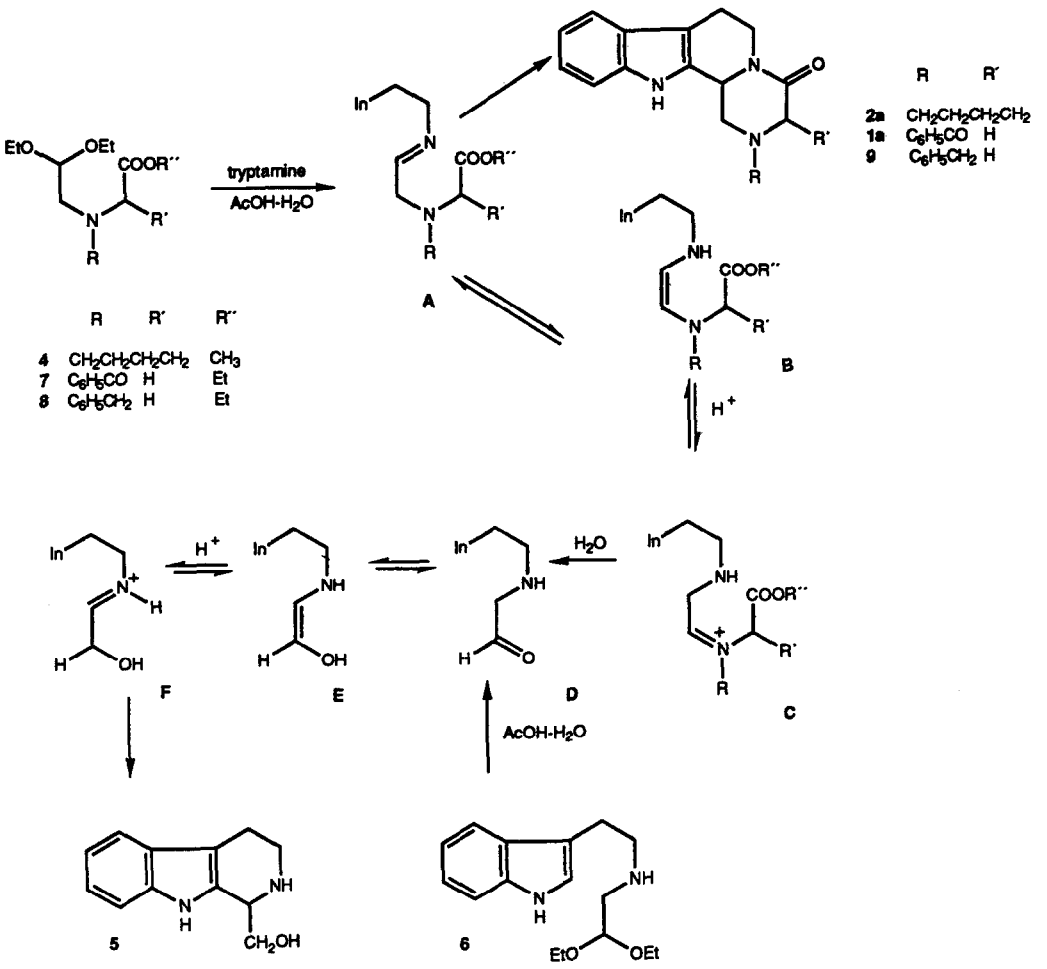



Scheme 1

The above result can be rationalized taking into account that the initially formed α-amino imine **A** [RR'= $(CH_2)_4$] can undergo a Pictet-Spengler cyclization followed by lactamization to give the expected pentacycles **2a** but can also undergo a competitive process as depicted in Scheme 2 [RR'=$(CH_2)_4$]. Thus, α-amino imine **A** would be in equilibrium, through the corresponding enamine, with the iminium cation **C**. Irreversible hydrolysis of **C** would give rise to the α-amino aldehyde **D**. This aldehyde would be in equilibrium through the enol-enamine **E**, with the iminium cation **F**, which would irreversibly cyclize to **5**. In support with the later stages of this mechanism, amino acetal **6** (prepared by alkylation of tryptamine) was converted in 24% yield into the same tetrahydrocarboline **5** by treatment with refluxing aqueous acetic acid (Scheme 2).[7]

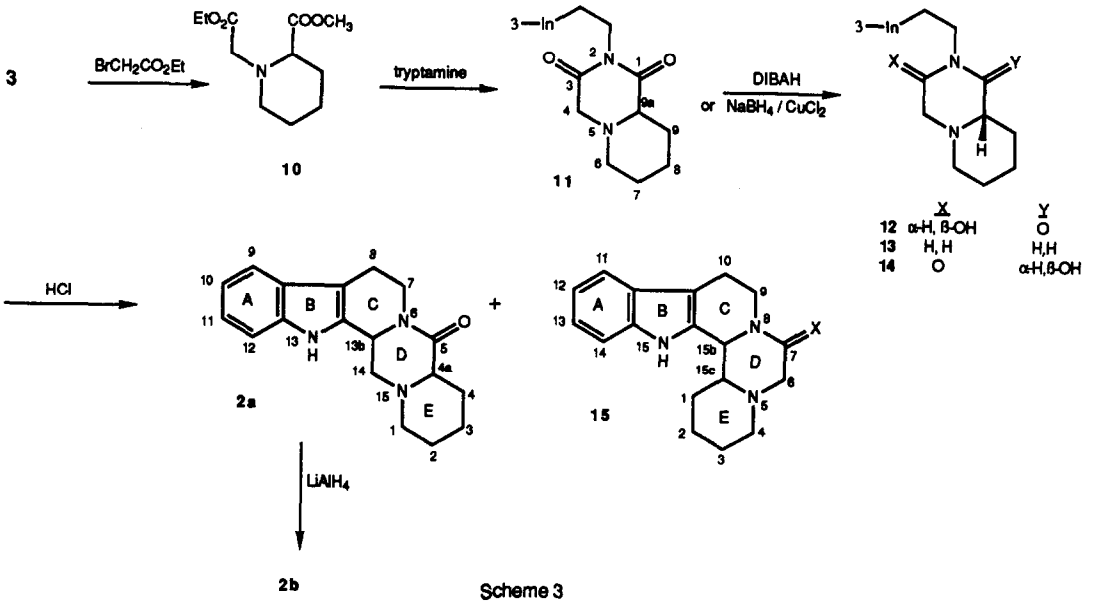
The different behavior between *amino* acetal **4** and *amido* acetal **7**, which is the precursor of **1a**,[1] in the condensation with tryptamine can be attributed to the availability of the electron pair of the trialkyl substituted nitrogen of **4** in the intermediate **B** [RR'=$(CH_2)_4$], which favors the formation of the iminium cation **C** and therefore, the operation of the reaction sequence depicted in Scheme 2. In accordance with this interpretation condensation of tryptamine with *amino* acetal **8** in refluxing aqueous acetic acid also gave tetrahydrocarboline **5** as the major product (12%), the tetracycle **9**[8] being formed in a yield lower than 5%.[9]

The second, more efficient route to the target pentacyclic ring system **2** is that outlined in Scheme 3. The crucial step involves the cyclization upon the indole ring of an *N*-acyliminium cation[11] generated by partial reduction of an imide and further dehydration. The required imide **11** was prepared in 55% overall yield from the piperidine ester **3** by alkylation with ethyl bromoacetate followed by heating of a mixture of the resulting diester **10** and tryptamine.




Scheme 2

Firstly, reduction of imide **11** was performed with DIBAH in order to obtain regioselectively the α-hydroxylactam resulting from the attack of the hydride ion to the less hindered imide carbonyl group.[12] However, under these conditions the expected hydroxylactam **12** was obtained in only 39% yield. The over-reduced amine **13** was also isolated in 9% yield.[13] The use of an ethanolic solution of sodium borohydride in the presence of copper(II) chloride[14] gave a clearly higher yield (67%) of the desired hydroxylactam **12**, although the regioselectivity was lower as the regioisomer **14** was also isolated in 17% yield.




Scheme 3

As expected, cyclization of **12** with concentrated hydrochloric acid gave a diastereomeric mixture of pentacycles ***trans*-2a** (41% yield) and ***cis*-2a** (33% yield).[4] When the above reduction-cyclization sequence was effected without separation of the intermediate hydroxylactams **12** and **14**, minor amounts of the regioisomeric pentacycles ***trans*-15**[15] (9%) and ***cis*-15**[16] (6%) were also obtained.[17]

Finally, lithium aluminum hydride reduction of lactams **2a** afforded in good yields the target pentacycles ***cis*-2b** and ***trans*-2b**.

The assignment of the relative *cis-trans* configuration of pentacycles **2a**, **2b**, and **15** was effected on the basis of the presence of Bohlmann's bands in the IR spectra as well as from the $^1$H NMR chemical shift and multiplicity of the signals corresponding to the methine protons at the ring junctions, assuming that both rings D and E adopt a chair conformation. Thus, both diastereomers of **2a** showed Bohlmann's bands indicative of a *trans* D/E ring junction and, therefore, at the fact, that 4a-H is axial. On the other hand, the magnitude of one of the coupling constants of 13b-H in the *trans* epimer is 11.4 Hz, thus indicating an axial disposition and, consequently, a *trans* relative stereochemistry. Accordingly, in the *cis* epimer 13b-H appears as a broad singlet. The same criteria were used for the stereochemical assignment of pentacyclic amides **15** and amine ***cis*-2b** (13b-H: $\delta$ 4.24, broad singlet). In the latter case, the chemical shift of 13b-H, downfield as compared with the *trans* isomer ($\delta$ 3.58, dd, $J$=11 and 3.2 Hz), confirms that this proton is equatorial. Finally, the chemical shift and multiplicity of 4a-H ($\delta$ 2.47, dd, $J$=10.8 and 3.3 Hz) in ***trans*-2b** confirms the axial disposition of this proton.

## EXPERIMENTAL

*General.* $^1$H-NMR spectra were recorded on a Varian XL-200 (200 MHz) or on a Perkin-Elmer R-24 (60 MHz) spectrometer. $^{13}$C-RMN were recorded on a Varian XL-200 (50.6 MHz) spectrometer. Chemical shifts are expressed in parts per million (δ) relative to internal TMS. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on $SiO_2$ (silica gel 60, 0.040-0.063 mm, Macherey-Nagel). TLC was performed on $SiO_2$ (silica gel 60 $F_{254}$, Macherey-Nagel), and the spots were located with UV light or iodoplatinate reagent. Melting points were determined in a capillary tube on a CTP-MP 300 hotplate apparatus. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by Departamento de Química Orgánica Biológica, Barcelona.

**Methyl 1-(2,2-Diethoxyethyl)piperidine-2-carboxylate (4).**

A mixture of methyl piperidine-2-carboxylate (4.5 g, 34.9 mmol), bromoacetaldehyde diethyl acetal (5.4 g, 34.9 mmol) and sodium hydrogen carbonate (10.5 g) in acetonitrile (34 ml) was refluxed for 24 h under nitrogen. The reaction mixture was poured into ice and extracted with ether. Evaporation of the extracts gave acetal **4** (7.43 g, 86%) as an oil. IR (NaCl) 1730 (C=O), 1120 and 1060 (C-O). $^1$H-NMR (60 MHz, $CDCl_3$) 1.2 (t, 6H, $OCH_2CH_3$), 1.3-1.9 (m, 6H, C-$CH_2$-C), 1.9-3.0 (m, 3H, CHN and $CH_2N$ piperidine), 2.6 (d, 2H, $NCH_2CH$), 3.0-3.6 (m, 4H, $OCH_2CH_3$), 3.6 (s, 3H,$OCH_3$), 4.4 (t, 1H, $NCH_2CH$).

***N*-(2,2-Diethoxyethyl)tryptamine (6).**

A mixture of tryptamine (10.0 g, 62 mmol) and bromoacetaldehyde diethyl acetal (1.9 ml, 12 mmol) in acetonitrile (80 ml) was refluxed for 24 h under nitrogen. Evaporation of the solvent gave an oily residue which was purified by flash chromatography. Elution with 15:3:10 ethyl acetate-absolute methanol-hexane gave **6** as an oil (2.1 g, 61%). IR (NaCl) 3400 and 3300 (NH), 1130 and 1050 (C-O). $^1$H-NMR (60 MHz, $CDCl_3$) 1.1 (t, 6H, $CH_3$), 1.9 (s, 1H, NH), 2.6 (d, *J*=6 Hz, 2H, $CH_2CH$), 2.8 (br s, 4H, $CH_2CH_2$), 3.0-3.6 (m, 4H, $CH_2CH_3$), 4.4 (t, *J*=6 Hz, 1H, CH), 6.6-7.4 (m, 5H, indole), 8.3 (br, 1H, NH).

**Ethyl *N*-Benzyl-*N*-(2,2-diethoxyethyl)glycinate (8).**

To a solution of *N*-(2-2-diethoxyethyl)glycine ethyl ester[18] (0.64 g, 2.92 mmol) in dichlorometane (30 ml) and 1N aqueous potassium carbonate (23 ml) was slowly added benzyl bromide (0.35 ml, 2.92 mmol). The mixture was stirred for 15 h at room temperature. Then water was added, the organic layer was separated, and the aqueos one was extracted with dichlorometane. The organic extracts were dried and evaporated affording 0.88 g (98%) of **8**. IR (NaCl) 1740 (C=O), 1200 (C-O ester), 1140 and 1060 (C-O). $^1$H-NMR (60 MHz, $CDCl_3$) 1.15 (t, *J*=7.0 Hz, 6H, $CH_3$), 1.23 (t, *J*=7.0 Hz, 3H, $CH_3$), 2.9 (d, *J*=5 Hz, 2H, $CH_2CH$), 3.43 (s, 2H, $NCH_2$), 3.3-3.8 (m, 4H, $CH_2O$), 3.9 (s, 2H, $NCH_2CO$), 4.1 (q, *J*=7.0 Hz, 2H, $CH_2O$), 4.6 (t, *J*=5 Hz, 1H, CH), 7.2 (s, 5H, Ar).

**Ethyl 2-Methoxycarbonyl-1-piperidineacetate (10).**

Operating as in the preparation of **4**, from methyl piperidine-2-carboxylate and ethyl bromoacetate, diester **10** was obtained in 70% yield as an oil. IR (NaCl) 1740-1725 (C=O). $^1$H-NMR (60 MHz, $CDCl_3$) 1.2 (t, 3H, C*H*$_3$CH$_2$), 1.4-1.9 (m, 6H, C-CH$_2$-C piperidine), 2.2-3.2 (m, 3H, CHN and CH$_2$N), 3.3 (s, 2H, NCH$_2$CO), 3.6 (s, 3H, CH$_3$O), 4.0 (q, 2H, CH$_2$O).

**2-[2-(3-Indolyl)ethyl]-1,3-dioxo-2,3,4,6,7,8,9,9a-octahydro-1*H*-pyrido[1,2-*a*]pyrazine (11).**

A mixture of diester **10** (10 g, 46.5 mmol) and tryptamine (4.96 g, 31.0 mmol) was heated in an oil bath at 175ºC for 5 h under nitrogen. After addition of absolute ethanol at room temperature imide **11** (7.61 g, 79%) precipitated. Mp 152-153ºC (ethanol). IR (KBr) 3370 (NH), 2800 and 2720 (Bohlmann's bands), 1680 and 1730 (C=O imida). $^1$H-NMR (200 MHz, DMSO-$d_6$) 1.2-2.1 (m, 6H, C-CH$_2$-C), 2.82 (t, *J*=8.8 Hz, 2H, CH$_2$-β), 2.82 (dd masked, 1H, 6-Hax), 2.94 (dd, *J*=11.2 and 3.7 Hz, 1H, 6-Heq), 3.21 (d, *J*=17,5 Hz, 1H, 4-Hax), 3.53 (d, *J*=17.5 Hz, 1H, 4-Heq), 3.88 (dd, *J*=11.2 and 6.0 Hz, 1H, 9a-H), 3.89 (t, *J*=8.8 Hz, 2H, CH$_2$-α), 6.6-7.7 (m, 5H, indole), 10.85 (s, 1H, NH). $^{13}$C-NMR (DMSO-$d_6$) 23.1* (β-C), 23.8* (8-C), 24.7 (7-C), 27.1 (9-C), 39.5 (α-C), 53.6 (6-C), 58.0 (4-C), 62.7 (9a-C), 111.2 (7'-C), 111.8 (3'-C), 118.6 (4'-C), 118.7 (5'-C), 121.4 (6'-C), 123.2 (2'-C), 127.5 (3a'-C), 136.6 (7a'-C), 170.0 (3-C), 172.1 (1-C). MS *m/e* (relative intensity) 312 (3), 311 (M+, 18), 168 (17), 152 (15), 144 (36), 143 (100), 130 (69), 125 (3), 115 (7), 103 (8), 97 (13), 96 (17), 77 (11), 69 (11), 41 (11). Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.45, H, 6.75, N, 13.50. Found C, 69.15, H, 6.73, N, 13.57.

**Reduction of imide 11.**

*A. With DIBAH.* To a suspension of imide **11** (1.94 g, 6.24 mmol) in dry tetrahydrofuran (20 ml) was added a solution of DIBAH (1.2M, 15ml, 18.0 mmol) in toluene at -72ºC. The mixture was stirred under nitrogen at this temperature for 3 h, treated with 5% aqueous sulfuric acid, basified with 2N aqueous potasium carbonate, and extracted with chloroform. Evaporation of the extracts gave a residue which was purified by flash chomatography. Elution with 15:1:1 ethyl acetate-methanol-hexane afforded 770 mg (39%) of **2-[2-(3-indolyl)ethyl]-3-hydroxy-1-oxo-2,3,4,6,7,8,9,9a-octahydro-1*H*-pyrido[1,2-*a*]pyrazine (12)**, and 180 mg (9%) of **2-[2-(3-indolyl)ethyl]-2,3,4,6,7,8,9,9a-octahydro-1*H*-pyrido[1,2-*a*]pyrazine (13)**.

**12**: mp 172-174ºC. IR (KBr) 3600-3200 (OH), 2820, 2770 and 2740 (Bohlmann's bands), 1625 (C=O). $^1$H-NMR (200 MHz, DMSO-$d_6$) 1.2-1.8 (m, 6H, C-CH$_2$-C), 2.2-2.5 (m, 2H, 4-Hax and 6-Hax), 2.7-3.1 (m, 4H, CH$_2$-β, 4-Heq and 6-Heq), 3.56 (m, 2H, CH$_2$-α), 4.93 (dd, *J*=11.2 and 7.2 Hz, 1H, 9a-H), 6.25 (br d, *J*=8.7 Hz, 1H, 3-H), 6.9-7.8 (m, 5H, indole), 10.80 (s, 1H, NH). $^{13}$C-NMR (DMSO-$d_6$) 23.8* (8-C), 24.2* (β-C), 25.0 (7-C), 28.0 (9-C), 42.3 (α-C), 55.0 (6-C), 59.5 (4-C), 65.0 (9a-C), 77.1 (3-C), 111.6 (7'-C), 112.3 (3'-C), 118.5 (4'-C), 118.9 (5'-C), 121.3 (6'-C), 122.8 (2'-C), 126.6 (3a'-C), 136.3 (7a'-C), 168.9 (C=O). MS *m/e* (relative intensity) 314 (4), 313 (M+, 18), 154 (9), 143 (48), 142 (72), 130 (19), 129 (100), 126 (22), 115 (16), 102 (17), 98 (37), 96 (23), 83 (17), 77(25), 69 (30), 55 (44), 41 (56). Calcd. for $C_{18}H_{23}N_3O_2.1/4H_2O$: C, 68.03; H, 7.24; N, 13.22. Found: C, 68.13; H, 7.42; N, 13.23.

**13**: mp 118-120ºC. IR (KBr) 3410 (NH), 2815 and 2770 (Bohlmann's bands). $^1$H-NMR (200 MHz, $CDCl_3$) 0.9-1.9 (m, 6H, C-CH$_2$-C), 1.9-3.3 (m, 12H, CH$_2$N), 3.4-3.8 (m, 1H, CHN), 7.0-7.7 (m, 4H, indole),

8.2 (s, 1H, NH). $^{13}$C-NMR ($CDCl_3$) 22.7 (β-C), 23.9 (8-C), 25.5 (7-C), 29.9 (9-C), 53.1 (6-C), 55.0 (4-C), 55.5 (3-C), 59.2 (α-C), 59.5 (1-C), 61.1 (9a-C), 111.1 (7'-C), 113.9 (3'-C), 118.7 (4'-C), 119.0 (5'-C), 121.6 (6'-C), 121.8 (2'-C), 127.4 (3a'-C), 136.2 (7a'-C). MS *m/e* (relative intensity) 283 (M+, 4), 153 (10), 152 (100), 143 (24), 142 (24), 139 (12), 129 (86), 128 (11), 110 (20), 103 (14), 102 (9), 96 (16), 83 (30), 82 (22), 77 (21). Calcd. for $C_{18}H_{25}N_3$: C, 76.32; H, 8.83; N, 14.84. Found: C, 76.55; H, 9.02; N, 15.13.

*B. With $NaBH_4/CuCl_2$.* Sodium borohydride (0.36 g, 9.5 mmol) was added to a mixture of imide **11** (0.6 g, 1.92 mmol) and copper (II) chloride dihydrate (0.36 g, 2.1 mmol) in absolute ethanol (45 ml) cooled at 0ºC. The mixture was stirred under nitrogen at 0ºC for 6 h, poured into water (200 ml), and extracted with chloroform (5x30 ml). The organic phase was washed with water, dried, and evaporated. The residue was separated by flash chromatrography (3:1 ethyl acetate-ether) to give 0.40 g (67%) of hydroxylactam **12** and 0.10 g (17%) of **2-[2-(3-indolyl)ethyl]-1-hydroxy-3-oxo-2,3,4,6,7,8,9,9a-octahydro-1*H*-pyrido[1,2-*a*]pyrazine (14)**. Mp 77-80ºC. IR (KBr) 3400 (NH), 3450-3260 (OH), 1635 (C=O), 2810-2760 (Bohlmann's bands). $^1$H-NMR (200 MHz, DMSO-$d_6$) 1.2-2.0 (m, 7H, C-$CH_2$-C and 6-Hax), 2.52 (m, 1H, 6-Heq), 2.66 (d, *J*=17.3 Hz, 1H, 4-Hax), 2.7-3.0 (m, 2H, $CH_2$-β), 3.21 (d, *J*=17.3 Hz, 1H, 4-Heq), 3.4-3.7 (m, 2H, $CH_2$-α), 4.46 (apparent t, *J*=10.8 Hz, 1H, 9a-Hax), 6.25 (d, *J*=10.6 Hz, 1H, 1-Hax), 6.9-7.7 (m, 5H, indole), 10.8 (s, 1H, NH). $^{13}$C-NMR (DMSO-$d_6$) 22.9 (8-C), 23.2 (β-C), 24.5 (7-C), 28.9 (9-C), 41.7 (α-C), 53.9 (6-C), 58.6 (4-C), 64.4 (9a-C), 82.8 (1-C), 111.8 (7'-C), 112.4 (3'-C), 118.1 (4'-C), 118.5 (5'-C), 122.3 (6'-C), 122.4 (2'-C), 127.1 (3a'-C), 136.2 (7a'-C), 166.2 (CO).

***Trans*- and *cis*-5-oxo-2,3,4,4a,5,7,8,13,13b,14-decahydro-1*H*-pyrido[1",2":4',5']pyrazino-[1',2':1,2]pyrido[3,4-*b*]indole (*trans*-2a and *cis*-2a).**

To the hydroxylactam **12** (780 mg, 2.5 mmol) was added 37.7% aqueous hydrochloric acid (5 ml) and the resulting solution was heated at 40ºC for 1 h. After cooling, the reaction mixture was neutralized with concentrated $NH_4OH$. The precipitated (770 mg) material was separated by flash chromatography. Elution with 25:1 ether-methanol gave 300 mg (41%) of pentacyclic compound ***trans*-2a** and 240 mg (33%) of ***cis*-2a**.

***Trans*-2a**: mp 245-246ºC. IR (KBr) 3200 (NH), 2810 and 2740 (Bohlmann's bands), 1620 (C=O). $^1$H-NMR (200 MHz, DMSO-$d_6$) 1.1-1.9 (m, 6H, C-$CH_2$-C), 2.12 (ddd, *J*=10.7, 10.7 and 3.0 Hz, 1H, 1-Hax), 2.21 (dd, *J*=11.4 and 11.4 Hz, 1H, 14-Hax), 2.42 (dd, *J*=10.0 and 4.0 Hz, 1H, 4a-H), 2.5-2.7 (m, 2H, 7-Hax and 8-Hax), 2,76 (dd, *J*=12.2 and 3.8 Hz, 1H, 8-Heq), 2.88 (dd, *J*=10.7 and 3.8 Hz, 1H, 1-Heq), 3.52 (dd, *J*=11.4 and 5.0 Hz, 1H, 14-Heq), 4.78 (dd, *J*=12.8 and 5.0 Hz, 1H, 7-Heq), 4.90 (ddd, *J*=11.4, 5.0 and 0.7 Hz, 1H, 13b-H), 6.9-7.5 (m, 4H, indole), 10.96 (s, 1H, NH). MS *m/e* (relative intensity) 296 (8), 295 (M+, 41), 266 (5), 225 (2), 212 (5), 183 (8), 170 (14), 169 (100), 168 (17), 156 (32), 153 (20), 142 (22), 128 (30), 115 (28), 97 (83), 96 (49), 83 (17), 69 (58), 56 (65), 55 (97). Calcd. for $C_{18}H_{21}N_3O$: C, 73.22; H, 7.11; N, 14.23. Found: C, 73.34; H, 7.15; N, 14.35.

***Cis*-2a**: mp 217-220ºC. IR (KBr) 3320 (NH), 2820, 2770 and 2730 (Bohlmann's bands), 1630 (C=O). $^1$H-NMR (200 MHz, DMSO-$d_6$) 1.0-1.7 (m, 5H, C-$CH_2$-C), 2.0-2.3 (m, 2H, 1-Hax and 4-Heq), 2.4-3.1 (m, 6H, 1-Heq, 4a-H, 7-Hax, 8-Heq, 8-Hax and 14-Hax), 3.52 (dd, *J*=11.9 and 2.1 Hz, 1H, 14-Heq), 4.72 (dd, *J*=12.5 and 5.0 Hz, 1H, 7-Heq), 4.84 (br d, *J*=2.1 Hz, 1H, 13b-H), 6.9-7.5 (m, 4H, indole), 10.95 (s, 1H, NH). MS *m/e* (relative intensity) 296 (14), 295 (M+, 63), 266 (7), 225 (5), 212 (7), 205 (5), 184 (39), 171 (33), 169 (43), 167 (13), 156 (27), 153 (20), 151 (10), 149 (28), 143 (29), 128 (12), 115 (13), 97 (100), 96 (29), 84 (16), 69 (25), 57 (15), 55 (25), 41 (27). Calcd. for $C_{18}H_{21}N_3O$: C, 73.22; H, 7.11; N, 14.23. Found: C, 73.36; H, 7.25; N, 14.53.

***Trans*-2,3,4,4a,5,7,8,13,13b,14-decahydro-1*H*-pyrido[1",2":4',5']pyrazino[1',2':1,2]pyrido[3,4-*b*]indole (*trans*-2b).**

To a suspension of lactam ***trans*-2a** (250 mg, 0.8 mmol) in dry tetrahydrofuran (20 ml) was added lithium aluminium hydride (240 mg, 6.4 mmol) under nitrogen. The mixture was refluxed for 24 h. After cooling, water and a saturated solution of sodium potasium tartrate (100 ml) were slowly added. The aqueous phase was separated and extracted with tetrahydrofuran (3 x 20 ml). Evaporation of the combined organic phases gave a solid which was purified by flash chromatography (20:1 ether- methanol) affording 0.19 g (79%) of *trans*-15-azayohimbane (***trans*-2b**), mp 160-162ºC. IR (KBr) 3200 (NH), 2840, 2790 and 2740 (Bohlmann's bands). $^1$H-NMR (200 MHz, $CDCl_3$) 1.2-2.1 (m, 6H, C-$CH_2$-C), 2.22 (ddd, *J*=10.1, 10.1 and 4.0 Hz, 1H, 1-Hax), 2.39 (dd, *J*=11.0 and 11.0 Hz, 1H, 14-Hax), 2.47 (dd, *J*=10.8 and 3.3 Hz, 1H, 4a-H), 2.40 (dd, *J*=10.4 and 10.2 Hz, 1H, 5-Hax), 2.5-2.8 (m, 3H, 6-Hax, 7-Hax and 7-Heq), 2.82 (dd, *J*=10.4 and 3.3 Hz, 1H, 5-Heq), 2.9-3.1 (m, 2H, 1-Heq and 6-Heq), 3.14 (dd, *J*=11.0 and 3.2 Hz, 1H, 14-Heq), 3.58 (dd, *J*=11.0 and 3.2 Hz, 1H, 13b-H), 7.0-7.5 (m, 4H, indole), 7.80 (s, 1H, NH). MS *m/e* (relative intensity) 282 (6), 281 (M+,26), 280 (6), 184 (9), 170 (20), 169 (32), 156 (16), 154 (10), 128 (9), 115 (13), 112 (11), 111 (14), 98 (100), 84 (10), 83 (15), 69 (11), 55 (14). Calcd. for $C_{18}H_{23}N_3$: C, 76.87; H, 8.18; N, 14.95. Found: C, 76.97; H, 8.28; N, 15.16.

***Cis*-2,3,4,4a,5,7,8,13,13b,14-decahydro-1*H*-pyrido[1",2":4',5']pyrazino[1',2':1,2]pyrido[3,4-*b*]indole (*cis*-2b).**

Operating as above, lactam ***cis*-2a** afforded *cis*-15-azayohimbane (***cis*-2b**) in 65% yield. Mp 170-171ºC. IR (KBr) 3160 (NH indole), 2850, 2800 and 2750 (Bohlmann's bands). $^1$H-NMR (200 MHz, $CDCl_3$) 1.1-1.8 (m, 6H, C-$CH_2$-C), 2.0-2.2 (m, 2H, 4-Hax and 14-Hax), 2.52 (ddd, *J*=12.1, 12.1 and 3.0 Hz, 1H, 1-Hax), 2.6-2.8 (m, 4H, 4a-H, 5-Hax, 7-Hax and 8-Hax), 2.81 (br d, *J*=11.1 Hz, 1H, 14-Heq), 2.9-3.3 (m, 3H, 1-Heq, 7-Heq and 8-Heq), 3.15 (dd, *J*=12.1 and 3.3 Hz, 5-Heq), 4.24 (br s, 1H, 13b-H), 7.0-7.5 (m, 4H, indole), 7.85 (s, 1H, NH). MS *m/e* (relative intensity) 282 (3), 281 (M+,18), 280 (6), 184 (8), 170 (9), 169 (39), 156 (22), 115 (12), 111 (22), 98 (100), 84 (29), 83 (35), 82 (24), 81 (29), 73 (29), 71 (32), 70 (33), 69 (79). Calcd. for $C_{18}H_{23}N_3$: C, 76.87; H, 8.18; N, 14.95. Found: C, 76.99; H, 8.30; N, 15.22.

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4. *Cis* and *trans* refer to the relative disposition of 4a and 13b hydrogens.

5. Compound **5** white solid, mp 137-138ºC (ethanol). IR (KBr) 3400 and 3770 (NH and OH). $^1$H-NMR (60 MHz, DMSO-$d_6$) 2.5-4.9 (m, 9H), 7.1-7.9 (m, 4H), 10.1 (s, 1H). Calcd. for $C_{12}H_{14}N_2O$: C, 71.28; H, 6.93; N, 13.86. Found: C, 71.16; H, 6.86; N, 13,70.

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7. For a similar *N*-dealkylation of a *N*-(2,2-diethoxyethyl) derivative, see: D. C. Lathbury, P. J. Parsons, and I. Pinto, *J. Chem. Soc, Chem. Commun.*, **1988**, 81.

8. This compound was also prepared in nearly quantitative yield by alkylation of **1**(R=H) with benzyl bromide in methanol-chloroform at r.t. for 18 h. Compound **9** was isolated by chromatography (silica 1:1 chloroform-ether). Mp 225-230ºC. IR (KBr) 3270 (NH indole), 1620 (C=O). $^1$H-NMR (200 MHz, $CDCl_3$) 2.37 (apparent t, J=12 Hz, 1H, 1-Hax), 2.6-2.9 (m, 3H, 7-H and 6-Hax), 2.95 (d, *J*=16.5 Hz, 1H, 3-Hax), 3.45 (br d, *J*=12 Hz, 1H, 1-Heq), 3.52 (d, *J*=16.5 Hz, 1H, 3-Heq), 3.52 and 3.61 (2d, *J*=13.1 Hz, 1H each, $NCH_2Ph$), 4.85 (br d, *J*=12 Hz, 1H, 6-Heq), 5.05 (br d, *J*=11 Hz, 1H, 11b-H), 7.0-7.5 (m, 4H, indole), 7.32 (s, 5H, Ph), 8.40 (s, 1H, NH). Calcd. for $C_{21}H_{21}N_3O$: C, 76.13; H, 6.34; N, 12.69. Found: C, 75.98; H, 6.49; N, 12.67.

9. A careful analysis of the reaction mixture allowed the identification of the $N_b$-acetylderivative of **5** [<5%;IR (KBr) 3400 and 3170 (OH and NH), 1600 (amide C=O); MS *m/e* 244 ($M^+$)] and of ethyl *N*-benzyl-glicynate[10] [<5%; IR (NaCl) 3300 (NH) and 1730 (C=O); $^1$H-NMR (60 MHz, $CDCl_3$) 1.2 (t, 3H, $CH_3$), 2.0 (br, 1H, NH), 3.3 (s, 2H, $NCH_2CO$), 3.7 (s, 2H, $PhCH_2N$), 4.1 (q, 2H, $OCH_2$), 7.1 (s, 5H, phenyl); MS *m/e* 193 ($M^+$)].

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15. Compound ***trans*-15**, mp 258-260ºC (ethanol). IR (KBr) 3330 (NH), 2800-2850 (Bohlmann's bands), 1630 (lactam C=O). $^1$H-NMR (200 MHz, DMSO-$d_6$) 1.2-2.9 (m, 12H, 1-H, 2-H, 3-H, 4-H, 9-Hax, 10-H, 15c-H), 2.65 (d, *J*=17.5 Hz, 1H, 6-Hax), 3.25 (d, *J*=17.5 Hz, 1H, 6-Heq), 4.62 (dd, *J*=12.8 and 1.2 Hz, 1H, 15b-H), 4.78 (dd, *J*=12.8 and 3.6 Hz, 1H, 9-Heq), 6.9-7.4 (m, 4H, indole), 10.5 (s, 1H, NH).

16. Compound ***cis*-15**, mp 138-140ºC (methanol). IR (KBr) 3230 (NH), 1650 (lactam C=O). $^1$H-NMR (200 MHz, DMSO-$d_6$) 1.2-3.6 (m, 11H, 1-H, 2-H,3-H, 4-H, 9-Hax, 10-H), 3.23 (d, *J*=18.0 Hz, 1H, 6-Hax), 3.65 (d, *J*=18.0 Hz, 1H, 6-Heq), 4.12 (m, 1H, 15c-H), 4.87 (dd, *J*=11.5 and 4.9 Hz, 1H, 9-Heq), 4.97 (d, *J*=4.9 Hz, 1H, H-15b), 6.9-7.4 (m, 4H, indole), 10.91 (s, 1H, NH).

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