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NMR Spectroscopy of Hexa- and Octahydropyrazino[1′,2′:1,2]pyrido[3,4-*b*]indoles and 15-Azayohimbanes

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The ^1H (200 MHz) and ^{13}C (50.3 MHz) NMR spectra of some hexa- and octahydropyrazino[1′,2′:1,2]pyrido-[3,4-*b*]indoles (1–13), 15-azayohimbanes (15–18), and related compounds (14, 19, 20) are reported. The data have been analyzed in terms of the preferred conformation (9–13, 15–20) and configuration (15–20).

KEY WORDS ^1H NMR ^{13}C NMR Octahydropyrazino[1′,2′:1,2]pyridol[3,4-*b*]indoles Praziquantel analogues 15-Azayohimbanes

INTRODUCTION

We have recently reported the synthesis of several hexahydro- and octahydropyrazino [1′,2′:1,2]pyrido [3,4-*b*]- (**I**, X = NR)[1,2] and [4,3-*b*]indoles,[2] as well as of 15-azayohimbanes (**II**, X = N),[3] all of them containing a partially reduced pyrido[1,2-*a*]pyrazine system (Scheme 1). This heterocyclic two-ring system appears in a fully saturated, non-fused form as a compound with hypotensive activity,[4] whereas in a benzo-fused form it constitutes the framework of praziquantel, a powerful anthelmintic agent.[5] The synthesis of several analogues of the latter structure, such as thieno analogues,[6] B-homo derivatives,[7] and octahydropyrazino [2′,3′:3,4] pyrido[1,2-*a*]indoles,[8] has recently been reported.

Although octahydroindolo[2,3-*a*]quinolizines (**I**, X = CH_2) and yohimbanes (**II**, X = CH) have been extensively investigated with regard to their stereochemistry and conformational aspects,[9] few studies have been made on the hetero analogues mentioned above.

In this paper we report a study of the ^1H and ^{13}C NMR spectra of compounds **1–20** by two-dimensional NMR homo- (^1H-^1H) and heteronuclear (^{13}C-^1H) correlation spectroscopy, as well as by selective decoupling experiments, which allows the establishment of a pattern type for compounds of types **I** and **II**. Details of the antihypertensive and anthelmintic activities of these compounds or have been reported elsewhere.[10]

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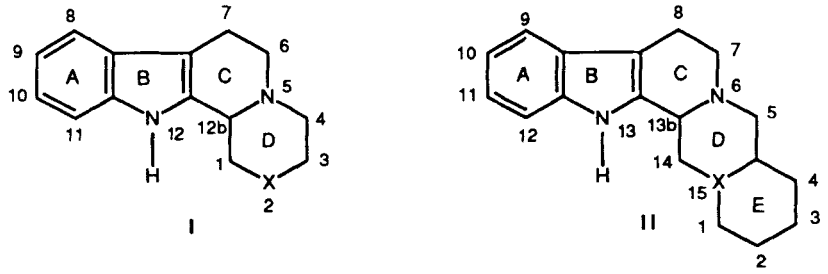
RESULTS AND DISCUSSION

Hexa- and Octahydropyrazino[1′,2′:1,2]-pyrido[3,4-*b*]indoles

The NMR analysis of the hexa- and octahydropyrazino [1′,2′:1,2]pyrido[3,4-*b*]indoles includes that of amido lactams **1–6**, lactams **7** and **8**, amides **12** and **13**, and amines **9–11** (Scheme 2). While lactam derivatives **1–8** have rigid ring systems, the corresponding amines **9–13** may exist in the three conformations (T, C_1, C_2) occurring in compounds embodying the quinolizidine ring system.[11]

The amido lactams can be expected to exist as a mixture of two rotamers due to the restricted rotation of the amide group. In fact, the two rotamers were observed by NMR spectroscopy for compounds **2–5** whereas, at room temperature, the benzoyl derivative **1** showed an unique broad signal for each proton or carbon as a consequence of its lower rotational barrier. In contrast, the greater rotational barrier in compound **6**, due to the steric interactions between the cyclohexyl



Scheme 1. Stereoparents of octahydropyrazino[1′,2′:1,2]pyrido[3,4-*b*]indoles and 15-azayohimbanes.

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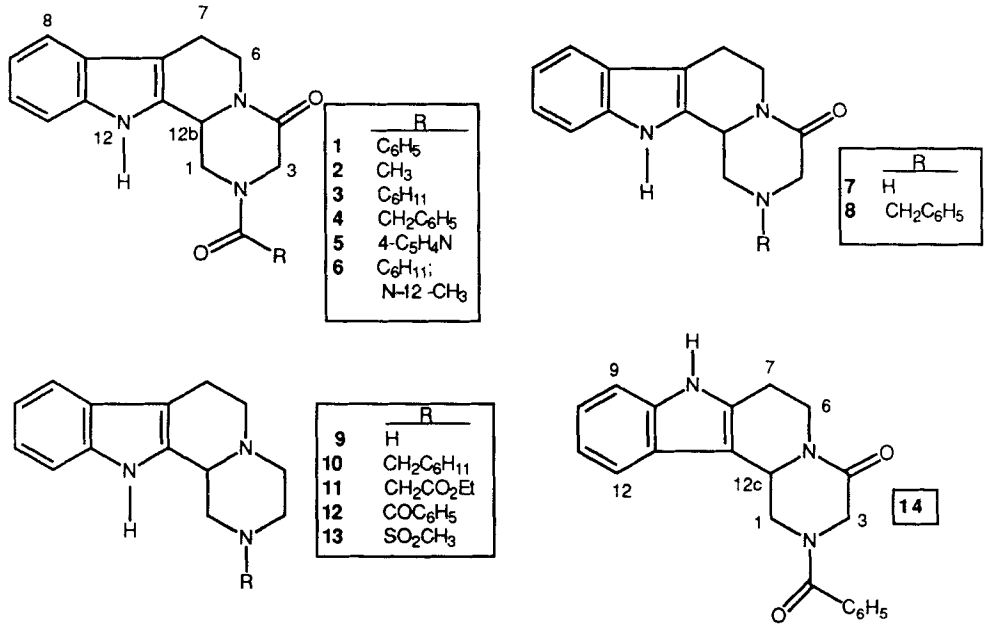


Scheme 2

substituent and the N-12-CH_3, precludes the (Z)-conformation and, consequently, the NMR spectra are the simplest of this series and were analysed first.

In the 200 MHz ^1H NMR spectrum of **6** (Table 1) the C-3 methylene protons resonate as an AB quartet with $J(gem)$ = 17.8 Hz, a value reconcilable only with a conformation possessing a nearly bisecting geometry between the plane of the lactam carbonyl group and the C-3 methylene protons.[4] The remaining signals of **6** were assigned from the ^1H-^1H homocorrelated 2D NMR spectrum, which shows the following significant correlations: (i) between H-3eq and the signal at δ 5.25, which therefore corresponds to H-1eq (J_W = 3.2 Hz); (ii) between the signals centred at δ 5.25 (H-1eq) and δ 2.70 (H-1ax) and the signal at δ 4.91 (H-12b). The magnitudes (10.9 and 1.9 Hz) of the vicinal coupling between the C-1 methylene protons and H-12b are consistent with ax-ax and ax-eq couplings arising from dihedral angles of *ca.* 180° and 60°, respectively, as required by a half-chair perhydropyrazine ring; (iii) coupling of the homobenzylic-type[12] (J = 1.3 Hz) between H-12b and H-7ax. Finally, the absorption at δ 5.08 can be assigned to a H-6eq, which in turn correlates with H-6ax and the methylene protons at C-7.

Both rotamers of compound **2** were easily assignable on the basis of the chemical shift of the protons at positions 1 and 3 of the pyrazine ring, from the 2D homonuclear (^1H-^1H) shift correlation spectrum. As expected, the equatorial H-1 and H-3 are more strongly deshielded when they are located *syn* with respect to the carbonyl group. Again, the coupling constant J(12b,1ax) (9.7 Hz) establishes the axial disposition of H-12b. The signals corresponding to the other amido lactams **3–5** have been assigned by taking into account the spectral features of this compound. The relative integration of the signal due to H-3ax of compounds **2–5** indicated an approximately 55% population of the *Z* rotamer, in which the bulkier substituent on the amide nitrogen is located *anti* with respect to the lactam carbonyl group.

As expected because the energy barrier to rotation around the C—N amide bond in benzamides is lower than in alkylamides,[13] the NMR spectrum of the benzamido lactam **1** (as well as of **12** and **14**) showed broad signals for the protons adjacent to the nitrogen atom, thus indicating that the spectrum was recorded at a temperature near the coalescence temperature. In fact, when the spectrum was recorded at 85 °C the signals coalesced, and the chemical shifts for all protons showed average values with respect to those of the individual rotamers.

As with lactams **1–6**, lactams **7** and **8** also show H-12b and H-6eq as the more deshielded aliphatic protons. The upfield absorption of H-6eq is analogous to that observed in 4-oxoquinolizidines[14] as well as in octahydropyrido [1,2-*a*]pyrazin-4-ones.[4]

The ^{13}C NMR spectra of amido lactams **1–5** (Table 2) showed the presence of two rotamers, *Z* (major) and *E* (minor), as observed in the ^1H NMR spectra. Again, benzamido lactam **1** showed averaged signals, whereas only the *E* rotamer was detected for *N*-methyl derivative **6**.

Rotamer assignments were made from the 2D heteronuclear (^{13}C-^1H) shift correlation spectra of compounds **2** and **6**, (Figs 2 and 1, respectively), which allowed the unambiguous identification of signals corresponding to C-1 and C-3. These assignments are in agreement with the known shielding for the carbon *syn* to the amide carbonyl oxygen as compared with the corresponding *anti* carbon.[15]

The ^{13}C NMR data of **3** suggest that the assignments for both the benzo (praziquantel) (C = O[16] and C-1–C-3 for the minor *E* rotamer[17]) and the thieno analogues (C-1–C-6)[6a] should be reversed.

The presence of Bohlmann bands in the IR spectrum[18] and the significant chemical shift of H-12b (δ 3.35–3.65),[19] C-7 (δ 21.3–21.6), and C-12b (δ 58.1–60.1)[20] in the NMR spectra indicated that the amino derivatives **9–13** possess a *trans* C/D ring juncture,

Table 1. Aliphatic ^{1}H NMR spectral parameters for 2,3,6,7,12,12b-hexahydropyrazino[1', 2':1,2]pyrido[3,4-*b*]indol-4(1*H*)-ones[a,b]

Compound	H-1eq	H-1ax	H-12b	H-3eq	H-3ax	H-6eq[c]	H-6,7[c]
1[d]	4.90 br d	3.25 dd	5.09 ddd	4.36 brd	4.02 d	4.87 ddd	2.5–2.8
	13.2	13.2, 10.8	10.8, 4.2, 2.4	18.0	18.0	12.5, 4.5, 2.0	unres
2(*E*)	5.16 ddd	2.4–3.2	4.84	4.34 dd	4.06 d	4.84 dd	2.4–3.2
	13.7, 3.6, 3.2	unres	masked	17.7, 3.2	17.7	129, 4.8	unres
2(*Z*)	4.63 ddd	3.27 dd	5.04 ddd	4.52 dd	3.65 d		
	13.7, 3.6, 3.2	13.7, 9.7	9.7, 3.2, 1.6	17.7, 3.2	17.7		
3(*E*)	5.18 dd	2.5–3.0	4.84	4.44 d	4.10 d	4.84 dd	2.5–3.0
	14.0, 3.5	unres	masked	18.0	18.0	12.1, 4.0	unres
3(*Z*)	4.72 dd	3.0–3.3	5.02 br d	4.54 d	3.65 d		
	14.0, 3.5	unres	9.5	18.0	18.0		
4(*E*)	5.16 dd	2.5–3.0	4.7–4.9	4.46 d	4.03 d	4.7–4.9	2.5–3.0
	14.0, 3.5	unres	unres	18.3	18.3	unres	unres
4(*Z*)	4.7–4.9	3.7–3.9	4.98 brd	4.56 d	3.65 d		
	unres	masked	10.5	18.3	18.3		
5(*E*)	5.29 br d	2.5–3.0	4.88 br d	4.32 d	4.15 d	4.90 br d	2.5–3.0
	13.0	masked	10.5	17.7	17.7	12.0	unres
5(*Z*)	4.33 br d	3.0–3.3	5.08 br d	4.67 d	3.89 d		
	13.0	unres	10.5	17.7	17.7		
6(*E*)	5.25 ddd	2.70 dd	4.91 ddd	4.52 dd	4.16 d	5.08 dd	2.8–2.9
	13.8, 3.2, 1.9	13.8, 10.9	10.9, 1.9, 1.3	17.8, 3.2	17.8	9.5, 2.5	unres
7	3.4–3.8	2.4–2.9	4.88 ddd	3.70 dd	3.33 d	4.84 dd	2.4–2.9
	masked	unres	12.4, 4.2, 2.8	14.0, 4.0	14.0	11.0, 4.0	unres
8	3.45 br d	2.37 dd	5.05 br d	3.53 d	2.95 d	4.85 br d	2.6–2.9
	12.0	12.0, 11.0	11.0	16.5	16.5	12.0	unres
14[d]	4.85	3.07 dd	5.08 ddd[e]	4.48 brd	4.02 d	4.90 dd	2.7–3.0
	masked	11.9, 10.7	10.7, 4.0, 1.1	17.8	17.8	13.0, 2.5	unres

[a] Chemical shifts, δ (ppm); Multiplicity; Coupling constants, J(Hz). Recorded in DMSO-d_6, except for **6** which was measured in $CDCl_3$. Substituent signals: **2**, $COCH_3$ 2.06 (*Z* isomer), 2.17 (*E* isomer); **4**, $COCH_2C_6H_5$ 3.16; **6**, NCH_3 3.81; **8**, NCH_2Ar 3.52 and 3.61 (2d, J = 13 Hz, 1H each).
[b] For amino derivatives **9–13** the chemical shifts of H-12b are: **9**, 3.35 (dd, J = 12.0 and 2.8 Hz); **10**, 3.51 (dd, J = 11.4 and 2.3 Hz); **11**, 3.61 (br d, J = 10.0 Hz), **12**, 3.6–3.7 (br), **13**, 3.51 (br d, J = 12 Hz); solutions in DMSO-d_6, except for **9** and **11** which were measured in $CDCl_3$.
[c] An unique signal for the two rotamers.
[d] Spectrum recorded at 85 °C.
[e] H-12c.

which is present in octahydroindolo[2,3-*a*]quinolizine compounds with only one or no equatorial substituent at C-2.[20,21] The changes of the shift values for the D ring carbons of **10–13**, as compared with the unsubstituted compound **9**, are consistent with those expected taking into account the different degree of substitution on N-2.

In spite of the fact that the ^{1}H NMR data of compound **14**[2] are very similar to those of the regioisomeric derivative **1**, the ^{13}C NMR data clearly allow the assignment of both compounds on taking into account the different connectivity of the β-indole carbon, which has the highest electron density (see Table 2). Thus, in compound **1** C-7 resonates at δ 20.4, and is more shielded that C-7 in compound **14** (δ 22.9), where it is bonded to the indole α-position. Moreover, the structural assignment is unambiguous from the synthetic standpoint.[2]

15-Azayohimbanes

Wenkert *et al.*[22] have shown that some ^{13}C NMR chemical shift values are of diagnostic interest for configurational and conformational purposes in yohimboid compounds: C-5, C-8, and C-13b can be used for this aim. 15-Azayohimban derivatives can belong to only two configurational series, depending on the relative configuration of the C-4a and C-13b stereocentres.

Compound **15** (Scheme 3) is the stereoparent of the *trans* series and shows a good correlation in its ^{13}C NMR chemical shifts (Table 3) compared with the normal series (yohimbane). The differences can be accounted for by considering the deshielding α-effect of the nitrogen atom and that the β-carbons are slightly shielded. Therefore, a *trans* relative configuration as well as a *trans* (C/D), *trans* (D/E) conformation is assigned.

The ^{13}C NMR spectrum of the *cis* isomer **16** shows a large shielding for C-5, C-8, and C-13b, which is a characteristic feature for yohimboid compounds of the pseudo series. This implies both a *cis* configuration and a *cis* (C/D), *trans* (D/E) conformation.

The ^{1}H NMR data corroborate these assignments. Although the ^{1}H NMR spectra of the saturated fragment of 15-azayohimbanes are fairly complex,[3] the H-13b signal does not overlap with other signals and can be easily analysed. Thus, the chemical shift and multiplicity (δ 3.58, dd J = 11.0 and 3.2 Hz) of H-13b in pentacycle **15** determine the *trans* C/D conformation as well as the axial disposition of H-13b. The *trans* fusion of the D/E rings was established from the multiplicity of

Table 2. ^{13}C NMR chemical shifts (ppm) of hexa- and octahydropyrazino[1′,2′:1,2]pyrido[3,4-*b*]- and [4,3-*b*]indoles[a]

Compound	C-1	C-3	C-4	C-6	C-7	C-7a	C-7b	C-8	C-9	C-10	C-11	C-11a	C-12a	C-12b
1[b]	42–48[c]	42–48[c]	163.5	38.7	20.4	108.1	126.0	117.7	118.6	121.1	111.1	136.3	130.3	52.5
2(*E*)	42.6	49.2	163.9	38.7	20.5	108.8	126.1	117.8	118.6	121.3	111.2	136.4	130.6	51.9
2(*Z*)	47.2	45.6	164.4	38.6	20.5	108.2	126.1	117.9	118.8	121.4	111.3	136.2	130.3	52.4
3(*E*)	43.4	48.6	164.1	38.5	20.4	108.2	126.1	117.2	118.6	121.2	110.1	136.2	130.2	51.9
3(*Z*)	46.2	45.8	164.1	38.5	20.4	108.2	126.1	117.2	118.6	121.2	110.1	136.2	130.2	52.8
4(*E*)	42.9	48.9	163.9	38.6	20.5	108.1	126.1	117.8	118.7	121.3	111.2	136.4	130.6	51.9
4(*Z*)	46.9	46.0	164.3	38.6	20.5	108.3	126.1	118.0	118.8	121.5	111.2	136.2	130.2	52.6
5(*E*)	43.2	50.3	163.1	38.8	20.5	108.3	126.1	117.9	118.8	121.1	111.1	136.3	130.1	51.7
5(*Z*)	47.7	45.9	163.9	38.8	20.5	108.3	126.1	117.9	118.8	121.1	111.1	136.2	130.0	52.4
6(*E*)	44.6	49.3	164.6	39.9	21.3	109.7	126.0	118.5	119.7	122.4	110.6	138.2	130.2	52.9
7	47.7	49.9	166.9	38.6	20.7	107.4	126.3	117.7	118.6	121.0	111.1	136.2	132.2	53.8
8.HBr	50.4	52.4	160.7	38.8	20.4	108.5	126.1	118.1	119.0	121.8	111.4	136.4	129.3	49.7
9	48.6	45.4	54.8	52.5	21.3	106.7	127.4	117.3	118.2	120.3	110.9	135.9	133.6	60.1
10	54.1	52.2	56.9	53.4	21.6	108.8	127.3	118.1	119.4	121.4	110.8	136.0	132.8	58.8
11	59.2	55.8	53.1	53.1	21.3	108.6	127.3	118.1	119.3	121.4	111.0	136.2	132.4	58.3
12	47.3[c]	44.7[c]	53.6	51.8	21.4	107.6	126.5	117.6	118.5	120.8	111.3	136.2	132.1	58.7
13	48.3	45.5	52.9	51.4	21.4	107.6	126.5	117.7	118.5	120.8	111.1	136.1	131.8	58.1
	C-1	C-3	C-4	C-6	C-7	C-7a	C-8a	C-9	C-10	C-11	C-12	C-12a	C-12b	C-12c
14(*Z*)[d]	49.5	46.4	164.0	37.7	22.9	133.8	136.0	111.8	120.7	118.8	116.8	124.1	105.0	52.6

[a] Solutions in DMSO-d_6, except for **6** and **10** which were measured in $CDCl_3$; δ in ppm. Substituent signals: **1**, COC_6H_5 168.9 (CO), 134.7 (*ipso*-C), 130.0 (*p*-C), 128.3 (*o*-C), 127.1 (*m*-C); **2**, $COCH_3$ (*Z*) 168.2 (CO), 20.9 (CH_3); (*E*), 168.5 (CO), 21.1 (CH_3); **3**, COC_6H_{11}, 173.6 (CO), 39.2 (C-1′, E), 38.7 (C-1′, Z), 29.0 (C-2′, 6′), 25.4 (C-3′, 5′), 24.5 (C-4′); **4**, $COCH_2C_6H_5$ 169.1 (CO, *E*), 168.9 (CO, *Z*), 135.4 (*ipso*-C, *Z*), 135.2 (*ipso*-C, *E*), 129.3 (*p*-C, *Z*), 129.1 (*p*-C, E), 128.3 (*o*-C), 126.4 (*m*-C), 48.5 (CH_2); **5**, $CO(4\text{-}C_5H_4N)$ 166.9 (CO, *Z*), 166.8 (CO, *E*), 150.2 (α-pyr), 142.8 (γ-pyr), 121.4 (β-pyr); **6**, COC_6H_{11} 174.9 (CO), 40.8 (C-1′), 31.0 (NCH_3), 29.2 (C-6′), 29.1 (C-2′), 25.7 (C-3′, 4′, 5′); **8**.HBr, $CH_2C_6H_5$ 131.2 (*ipso*-C), 129.0 (*o*-C), 128.8 (*m*-C), 128.5 (*p*-C), 59.0 (CH_2); **10**, $CH_2C_6H_{11}$, 52.2 (CH_2), 35.0 (C-1′), 32.0 (C-2′, 6′), 26.8 (C-4′), 26.1 (C-3′, 5′); **11**, CH_2CO_2Et 170.5 (CO), 60.8 (OCH_2), 51.9 (NCH_2), 14.2 (CH_3); **12**, COC_6H_5 169.5 (CO), 135.9 (*ipso*-C), 129.7 (*p*-C), 128.5 (*m*-C), 127.1 (*o*-C); **13**, SO_2CH_3 33.9.
[b] Recorded at 80 °C.
[c] Broad signal.
[d] Minor signals for isomer (*E*) 51.0 (C-3), 44.4 (C-1).

H-4a in the 5,5-dideuterated derivative. Thus, the signal at δ 2.47, attributable to this proton on the basis of decoupling experiments, was a doublet of doublets (J = 10.8 and 3.0 Hz), which implies that this proton is axial with respect to the E ring. The *cis* C/D fusion in pentacycle **16** has been corroborated by the H-13b signal, which appears at δ 4.24 as a broad singlet.

The possible conformations in the 5-oxo derivatives **17** and **18** are restricted to the three resulting from the fusion mode of rings D/E. The IR (presence of Bohl-

Table 3. ^{13}C NMR chemical shifts (ppm) of 15-azayohimbines 15–18 and inside compounds 19–20

yohimbane[a]	carbon	15[b]	16[b]	17[c]	18[c]	carbon	19[c]	20[c]
32.5	1	55.5	55.6	55.1	55.0	4	54.2	49.1
26.2	2	25.6	24.7	24.9	23.7	3	24.3	16.7
25.8	3	23.8	23.9	24.1	23.7	2	23.2	20.5
30.1	4	29.5	28.8	27.8	26.4	1	30.6	24.3
41.6	4a	61.3	60.7	65.3	64.2	6	57.9	51.6
61.7	5	58.1	52.1	167.0	168.1	7	165.6	166.0
52.8	7	51.9	51.0	38.5	41.3	9	39.5	38.1
21.4	8	21.6	17.3	20.7	20.4	10	20.7	16.5
107.1	8a	108.7	107.9	107.5	108.0	10a	109.1	108.8
127.0	8b	127.3	127.8	126.2	126.9	10b	126.1	126.2
117.6	9	118.0	117.9	117.7	117.4	11	117.6	117.7
118.7	10	119.3	119.3	118.6	118.5	12	118.8	118.6
120.6	11	121.3	121.3	121.1	120.8	13	121.3	121.1
110.6	12	110.8	111.0	111.1	111.1	14	111.6	111.1
135.8	12a	136.1	135.9	136.2	135.6	14a	136.4	136.4
134.7	13a	132.4	132.9	131.9	134.4	15a	132.3	130.8
60.1	13b	58.9	54.5	52.2	52.8	15b	61.9	57.3
36.3	14	60.5	55.8	56.2	52.6	15c	58.8	56.0

[a] Ref. 21, in $CDCl_3$.
[b] In $CDCl_3$.
[c] In DMSO-d_6.

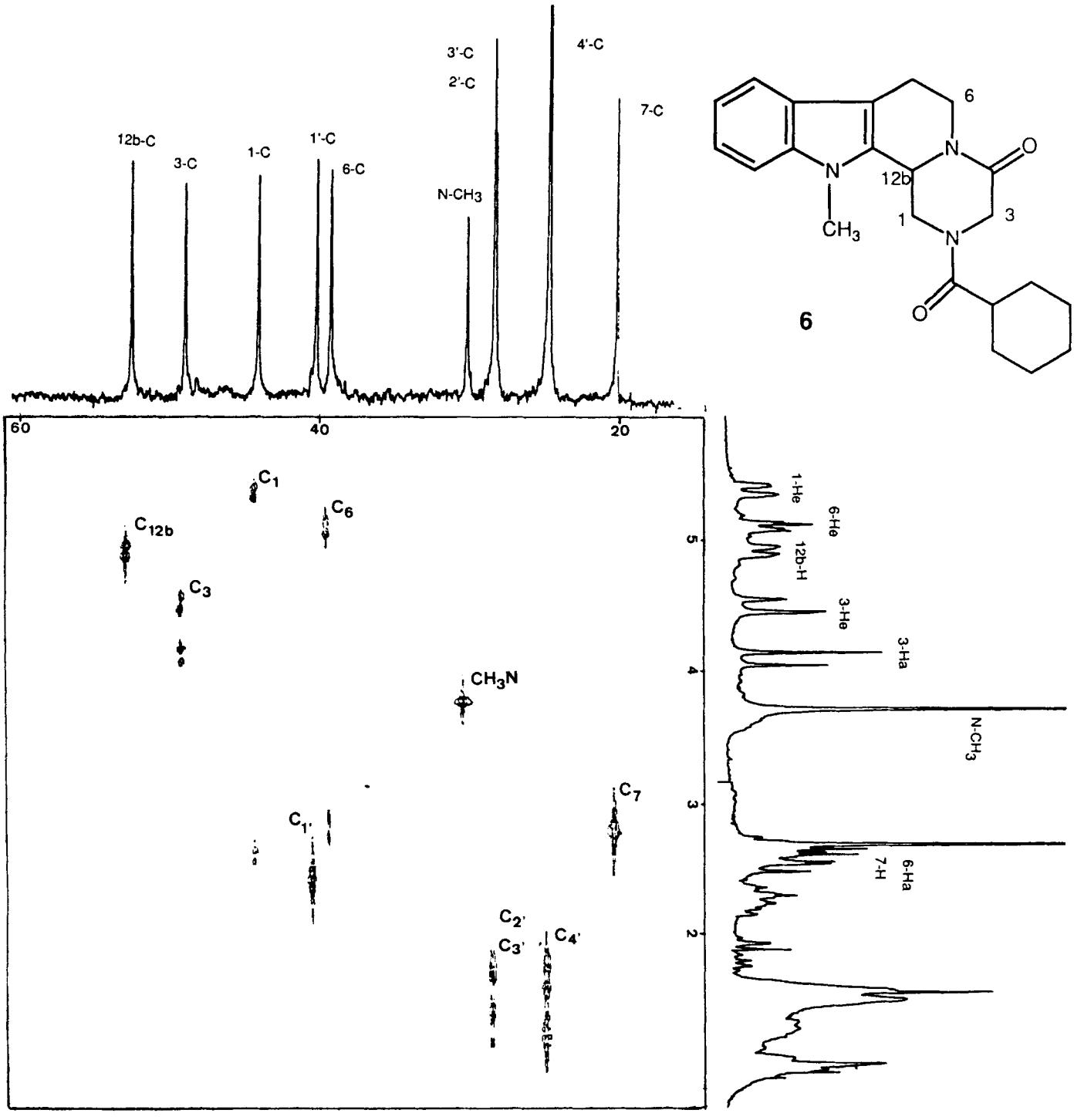


Figure 1. Contour plot of the ^{13}C-^{1}H shift correlated 2D NMR spectrum of **6**. Only the aliphatic region is shown.

mann bands), ^{1}H NMR, and ^{13}C NMR data indicate that both compounds exist in the *trans* conformation. In the *trans* isomer **17**, H-13b resonates a δ 4.90 (J = 10.6, 4.3, and 0.7 Hz), thus proving an axial disposition. The chemical shift (δ 2.4) of H-4a was established from decoupling experiments and indicates that this proton is also located axially. The absence of further shielding for the carbons of the E ring in the ^{13}C NMR spectra, compared with the parent compounds **15** and **16**, also allows us to conclude that the preferred conformation of the D/E rings is *trans*. In the ^{1}H NMR spectrum of **18** the signal attributable to H-13b appears at δ 4.84 as a broad singlet and, consequently, indicates that this proton is equatorial. Using the 2D COSY method it was possible to establish the chemical shift (δ 2.52) of the overlapped H-4a proton and, consequently, its axial disposition.

During our synthesis of 15-azayohimbanes, the inside products **19** and **20** were isolated as minor by-products.[3] These compounds have also been recently reported in the context of the synthesis of the new heterocyclic system pyrido[1'',2'':1',2']pyrazino[4',3':1,2] pyrido[3,4-*b*]indole.[23] Our spectroscopic measurements were made in DMSO-d_6, whereas those reported

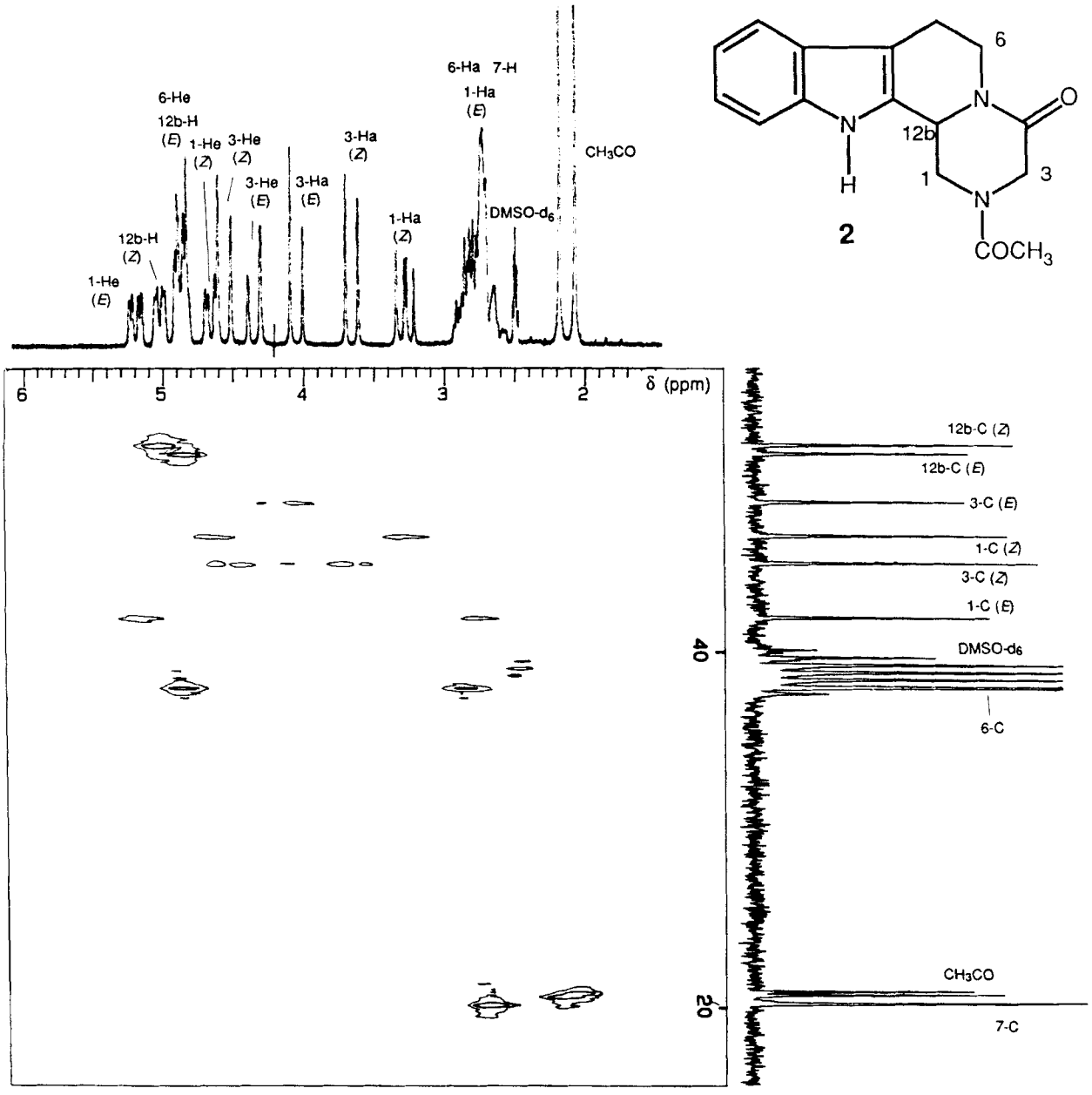
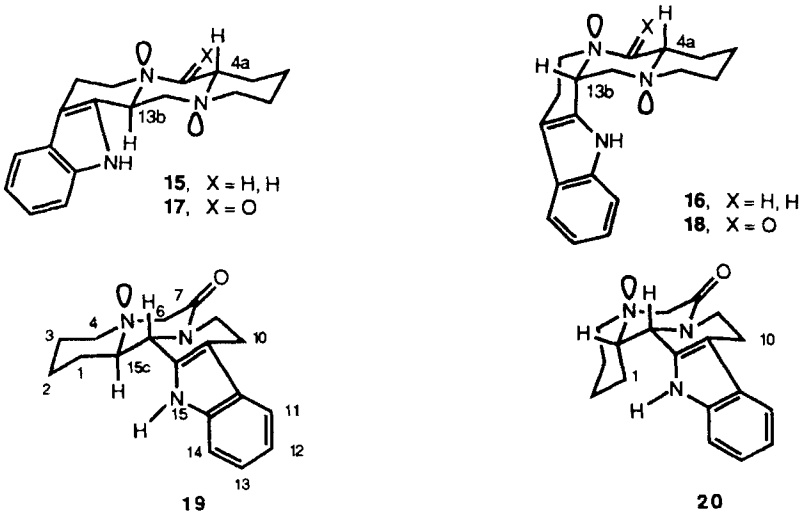


Figure 2. Contour plot of the ^{13}C-^{1}H shift correlated 2D NMR spectrum of **2**. Only the aliphatic region is shown.



Scheme 3. Stereostructures of 15-azayohimbanes and inside compounds.

by Mokrosz *et al.*[23] in $CDCl_3$, and the small differences in the ^1H NMR values are probably due to the solvent effect. On the contrary, the ^{13}C NMR data of our lactams **19** and **20** are very similar to those reported by Mokrosz.[23] However, in the light of the results presented here, the assignment of the signals for C-6 and C-9[23] should be reversed. The preferred conformations for **19**, a configurational *trans* derivative (H-15b, δ 4.62, dd, J = 12.8 and 1.2 Hz), and **20**, a configurational *cis* derivative (H-15b, δ 4.97, d, J = 1.9 Hz), are depicted in Scheme 3. The ^{13}C NMR spectrum of **20** (see Table 3) shows the usual upfield signals[20a] associated with a *cis* D/E conformation.

EXPERIMENTAL

NMR spectra were recorded on a Varian XL-200 spectrometer operating at 200 MHz and 50.3 MHz, for protons and carbons, respectively. Chemical shifts are given in ppm relative to tetramethylsilene. The ^1H-^1H homonuclear correlation experiments (COSY) were performed using the standard sequence,[24] and 32 transients were accumulated for 256 values of evolution period, with a spectral width of 1283 Hz in both dimensions. The time between transients was 2.5 sec, and the acquisition time was 0.399 sec. A 1024 × 1024 points data matrix was measured with pseudoecho[25] data for improved peak definition and triangular folding for improved sensitivity. The ^{13}C NMR and ^1H-^{13}C heteronuclear shift correlation experiments were recorded using a high sensitivity ZENS probe. For the ^1H-^{13}C correlation experiment 288 transients were used for each of the 128 values of the evolution period. The ^{13}C NMR spectral width was 2063 Hz, with an acquisition time of 0.248 sec and a delay of 1 sec. The ^1H NMR spectral width was 2000 Hz and 1024 × 1024 data points were used.

Synthesis of compounds

The synthesis of the tetracyclic compounds **1**–**5** and **7**, as well as that of the pentacyclic derivatives **15**–**20**, has been previously reported.[1,3] For an alternative synthesis of **1** and the synthesis of compound **14**, see reference 2. Amines **9** and **10** were obtained by lithium aluminium hydride reduction of lactams **7** and **3**, respectively. Compounds **11** and **13** were prepared from amine **9** by alkylation and sulphonylation, respectively. Experimental details will be reported elsewhere.

2-Cyclohexylcarbonyl-12-methyl-2,3,6,7,12,12b-hexahydropyrazino[1',2':1,2]pyrido[3,4-*b*]indol-4(1*H*)-one (6)

To a stirred suspension of indole **1** (900 mg, 2.56 mmol) in 90 ml of acetone, triturated potassium hydroxide (850 mg, 15.2 mmol) was added. After 10 min, methyl iodide (0.32 ml, 5.1 mmol) was added, the reaction mixture was stirred at room temperature for 2 h, and the solvent was evaporated. The resulting solid was recrystallized from absolute ethanol, yielding 690 mg (82%) of **6** as white needles, m.p. 203-205 °C. IR (KBr): 1645 cm^{-1} (C = O). Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.32; H. 7.39; N, 11.50. Found; C, 72.32; H, 7.36; N, 11.49.

2-Benzyl-2,3,6,7,12,12b-hexahydropyrazino-[1',2':1,2]pyrido[3,4-*b*]indol-4(1*H*)-one (8)

To a solution of **7** (650 mg, 2.69 mmol) in 40 ml of methanol and 18 ml of chloroform, benzyl bromide (0.38 ml, 3.23 mmol) was slowly added. The reaction was stirred at room temperature for 18 h, and was then concentrated to $\frac{1}{3}$ of its volume. The resulting precipitate was recrystallized from absolute ethanol, yielding 640 mg (72%) of **8**.HBr, m.p. 225–230 °C. IR (KBr) 3270 (NH), 1620 cm^{-1} (CO). ^1H NMR (DMSO-d_6) 2.5–3.8 (m, 4H), 3.86 and 3.97 (2d, J = 15.8 Hz, 1H each, NCH_2Ar), 4.23 (br d, J = 10.4 Hz, 1H, H-1eq), 4.36 (d, J = 13.1 Hz, 1H, H-3ax), 4.52 (d, J = 13.8 Hz, 1H, H-3eq), 4.85 (dd, J = 13.1 and 4.1 Hz, 1H, H-6eq), 5.37 (br d, J = 9.7 Hz, 1H, H-12b), 7.0-7.7 (m, 4H, indole), 7.61 (s, 5H, ArH), 10.97 (s, 1H, NH). An analytical sample was obtained by treatment of the hydrobromide with concentrated sodium hydroxide, followed by extraction with methylene chloride and further flash chromatograph (1:1 diethyl ether-chloroform). Anal. 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.

2-Benzoyl-1,2,3,4,6,7,12,12b-octahydropyrazino-[1',2':1,2]pyrido[3,4-*b*]indole (12)

To a suspension of amine **9** (210 mg, 0.9 mmol), methylene chloride (14 ml), and aqueous 1N potassium carbonate solution (7 ml), benzoyl chloride (0.15 ml, 1.3 mmol) was slowly added. The reaction mixture was stirred at room temperature for 18 h. The organic phase was separated, dried, and evaporated. The residue was crystallized from methanol to yield 220 mg (73%) of amine **12**, m.p. 245–248 °C. IR (KBr) 3230 (NH), 2840, 2800, 2740 (Bohlmann bands), 1610 cm^{-1} (CO). Anal. Calcd. for $C_{21}H_{31}N_3O$: C, 76.13; H, 6.34; N, 12.69. Found: C, 76.07; H, 6.39; N, 12.66.

trans-[5,5-$^2H_2$]-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 ([5,5-$^2H_2$]-15)

To a suspension of lactam **17** (250 mg, 0.8 mmol) in dry THF (20 ml) was added tetradeuterated lithium aluminium hydride (240 mg, 6.4 mmol) under nitrogen. The mixture was refluxed for 24 h. After cooling, water and a saturated aqueous sodium potassium tartrate solution (100 ml) were slowly added. The aqueous phase was separated and extracted with THF (3 × 20 ml). Evaporation of the combined organic phases gave a solid which was purified by flash chromatography (20:1 diethyl ether-methanol) to afford 190 mg (79%) of dideuterated compound as a white solid, m.p. 155–

158 °C. ^{1}H NMR ($CDCl_3$) 1.2–1.9 (m, 6H), 2.22 (ddd, J = 10.1 and 4 Hz, 1H, H-1ax), 2.39 (dd, J = 11.0 and 11.0 Hz, 1H, H-14ax), 2.47 (dd, J = 10.8 and 3.3 Hz, 1H, H-4a), 2.5–2.8 (m, 3H, H-4ax and 7-CH_2), 2.9–3.2 (m, 2H, H-1eq and H-6eq), 3.51 (dd, J = 11.0 and 3.7 Hz, 1H, H-14eq), 3.71 (dd, J = 11.0 and 3.7 Hz, H-13b), 7.0–7.5 (m, 4H, indole), 8.01 (s, 1H, NH). EM (m/z, %); 284 (6), 283 (M^+, 38), 186 (10), 170 (33), 169 (59), 156 (27), 154 (12), 153 (10), 115 (17), 114 (20), 113 (16), 99 (14), 98 (100), 96 (14), 85 (12), 84 (12), 83 (22), 69 (14), 57 (11), 56 (12), 55 (22).

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