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THE C(2) STEREOCHEMISTRY OF IBOLUTEINE[1]

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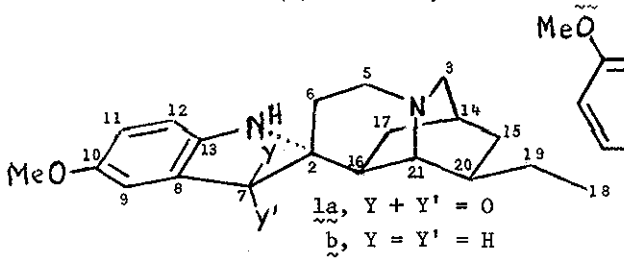
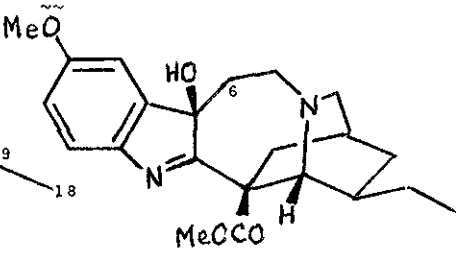
Dedicated to Professor Robert B. Woodward on the occasion of his sixtieth birthday

All carbon shifts of iboluteine and its hydroxyindoline and indoline reduction products have been assigned. A lanthanide shift study revealed a R configuration for the spiro carbon of these substances.

Despite early investigations of the gross structure[2] and stereochemistry[3] of iboluteine, a Tabernanthe iboga alkaloid and/or the air oxidation product of ibogaine, no direct determination of the configuration of its spiro carbon-2 ever has been performed. This center could be assumed to be as depicted in 1a by analogy with the C(2) stereochemistry of voaluteine (16-carbomethoxyiboluteine). Structure 16-carbomethoxy-1a had been assigned to this Iboga alkaloid and/or product of air oxidation of voacangine (16-carbomethoxyibogaine) on the basis of the expected retention of C(6) configuration during its production from voacangine β-hydroxyindolenine (2) by Wagner-Meerwein rearrangement[4] and the earlier establishment of a cis relationship between the hydroxy and carbomethoxy groups of 2 by infrared spectral means.[5] The following new data now confirm the C(2) chirality shown in 1a for iboluteine.



1a, Y + Y' = O
b, Y = Y' = H
c, Y = OH, Y' = H



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In connection with the ^{13}C NMR spectral study of a group of Iboga alkaloids[6] an investigation of iboluteine (1a) and two reduction products,[7] 1b and 1c, was undertaken. Assignment of the carbon signals of the three compounds was based on multiplicities in the single-frequency off-resonance decoupled (sford) spectra and by comparison with like carbons in ibogaine.[6] The aromatic methines were differentiated by the absence of second-order coupling of the C(9) signal in the sford spectra[8,9] and the absence of $^3J_{CH}$ (meta) coupling in the C(12) signal.[8] The carbon shifts for compounds 1 are presented in the Table.

^{13}C NMR Data of Iboluteine and its Derivatives[a]

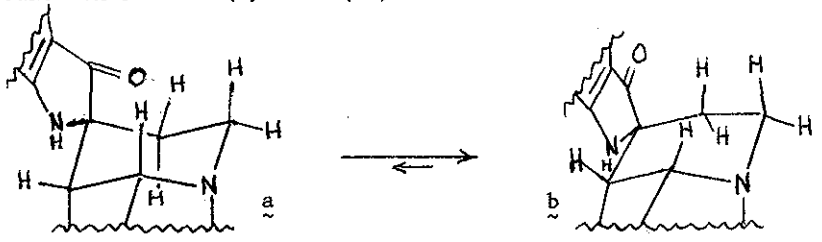
	1a[b]	1a[c]	1b[b]	1c[b]
C(2)	67.2	12.7	66.3	68.6
C(3)	52.0	4.7	52.5[d]	52.5[d]
C(5)	48.2	8.8	50.8[d]	52.2[d]
C(6)	22.6	8.8	27.7	21.6
C(7)	204.7	27.5	40.1	76.8
C(8)	120.3	11.3	129.4	131.2
C(9)	104.5	3.9	111.7	111.6
C(10)	153.1	0.9	153.0	153.3
C(11)	127.3	2.6	112.0	115.9
C(12)	113.8	3.1	109.6	111.1
C(13)	154.8	7.8	143.1	142.2
C(14)	25.7	3.2	25.9	25.8
C(15)	32.3	2.6	32.8	32.8
C(16)	36.6	8.8	42.8	38.3
C(17)	28.6	4.6	28.2	28.4
C(18)	11.9	0.6	12.0	12.0
C(19)	28.4	2.2	28.8	28.8
C(20)	38.9	4.3	39.8	39.8
C(21)	48.5	8.2	53.6	52.8
OMe	55.6	-1.3	55.8	55.9

[a] Spectra recorded on a Varian XL-100-15 NMR spectrometer operating at 25.2 MHz in the Fourier transform mode. [b] Chemical shifts in ppm downfield from TMS; δ(TMS) = $\delta(CDC\ell_3)$ + 76.9 ppm. [c] $\Delta\delta$ values extrapolated to a 1:1 molar ratio of alkaloid to Yb(dpm)$_3$. [d] Values within any vertical column may be interchanged.

A crucial experiment in the determination of the stereochemistry of 1a was a study of Yb(dpm)$_3$-induced shifts. The molar $\Delta\delta$ values are presented in the Table. The data agree well with the R configuration depicted in 1a and with a twist-boat conformation for the six-membered ring involved in the spiro linkage, but not at all with a chair form of the latter ring or with C(2)-S in any conformation. Expectedly the substrate-agent complex is

formed mostly through the carbonyl group, although the $\Delta\delta$ values for carbons 3, 5 and 21 are slightly larger than theoretically predicted, indicating a <10% degree of N_b complexation. In the twist-boat form C(21) is in a stem-to-stern γ-interaction with C(6). This relationship accounts for most of the 8.8 ppm shielding of the former carbon in iboluteine (1a) relative to the like site in ibogaine[6] as well as for the high-field C(6) resonance relative to the field position predicted by chemical shift theory[10] in the absence of the shielding inherent in the twist-boat form. Finally, the ca. 10 ppm deshielding of C(11) and C(13) in iboluteine (1a), as compared to its reduced derivatives 1b and 1c, is worthy of note. This is due probably to strong N_a-carbonyl resonance interaction, also responsible for the nearly exclusive complexation of $Yb(dpm)_3$ at the site of the carbonyl group.

Carbon-21 of deoxodihydroiboluteine (1b)[7] is deshielded by 5.1 ppm relative to iboluteine, indicating the six-membered ring to be now in the chair form. In iboluteine a chair conformation would force the carbonyl oxygen to be located in sterically unfavorable position between H(21) and axial H(5) (see 3). Reduction removes this interaction and the chair form becomes favored (4, R = H). Shielding effects are observed also at C(16) due to the removal of the γ effect from the oxygen and at C(6) because of the loss of two strong γ interactions with the oxygen and C(21) and a gain of two weaker ones with C(3) and C(17).



a ⇌ b

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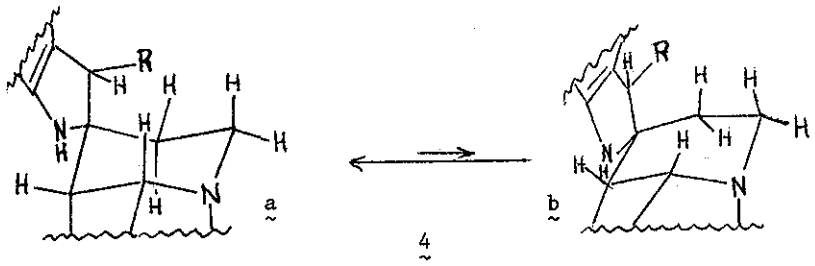

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Dihydroiboluteine B (1c),[7] the major product of the sodium borohydride reduction of iboluteine, has a C(21) shift practically identical to that of 1b. This fact indicates both a six-membered ring chair and a C(7)-S configuration (4a, R = OH). A boat form and/or an alcohol oxygen pointing towards C(21) should cause shielding of the latter. The heretofore undefined C(7) stereochemistry[7] is confirmed by the larger (6.1 ppm) shielding of C(6) than of C(16) (4.5 ppm) on the introduction of a hydroxy group (1b → 1c), a consequence of the anti-periplanar, equatorial γ effect.[11]

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