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INDOLE ALKALOIDS OF RAUWOLFIA REFLEXA. THE STRUCTURES OF RAUFLEXINE AND REFLEXINE[1,2]

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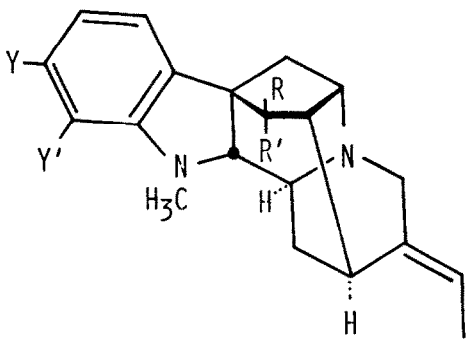
Recently the structure of two indole alkaloids isolated from the leaves of Rauwolfia reflexa was reported[3]. One of these compounds, $C_{21}H_{24}N_2O_2$ (M^+ 336) m.p. 154-155°, was identified as the known alkaloid purpeline[4] (1a), mostly based on its chemical conversion into mitoridine[4], as indicated by superimposable IR spectra. The second base, $C_{21}H_{26}N_2O_2$ (M^+ 338) m.p. 260° (dec.), a new alkaloid designated reflexine, was assigned structure 1b. The relationship between 1b and 1a was established by $NaBH_4$ reduction of the latter to yield a product identical (m.p. m.m.p., superimposable I.R.) to 1b[3].

In connection with continued structure analysis of the alkaloidal components of Rauwolfia species the ^{13}C-NMR spectra of several ajmaline-type bases were examined. This study reveals that the aromatic substitution pattern assigned to the indolic bases from R. reflexa[3] require revision. The following analysis establishes that the structure of reflexine is represented by formula 1c and that the substance originally identified as purpeline is, in fact, a new alkaloid, now designated rauflexine (1d).

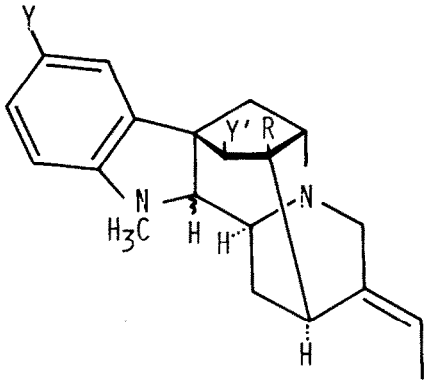
The chemical shift assignment of vincamajoreine (2a), majoridine (2b), vincamajine (2c), rauflexine (1d) and ajmaline (3), based on chemical shift theory[5,6] and carbon-hydrogen coupling correlation[7], is given in Table I. Comparison of the tetrahedral carbon resonances of 2a and 2b indicate the rationale for the assignments. The methylene carbons C(6), C(14), and C(21) in these substances are unaffected by the structural difference at C(17). The low-field resonance of the aminomethylene C(21) makes its identification straightforward. The differentiation of the C(6) and C(14) signals is based on their correlation with the methylene signals of ajmaline, (3). The alteration of ring D of 3 with respect to 2a perturbs the C(14) resonance but not that of C(6). The excellent correlation of C(2) and C(17) assures that the further removed C(6) site will remain unaffected by the changes in the D-ring.

One of the C,C,C-methines[8], C(15), is constant between 2a and 2b and mildly deshielded in 2c by the ester function. The low field C(16) methine signal is uniquely identified by the effect of acetylation between 2a and 2b. The same conversion also distinguishes the C(2) and C(17) signals. The aminomethine pair C(3) and C(5) remains undifferentiated.

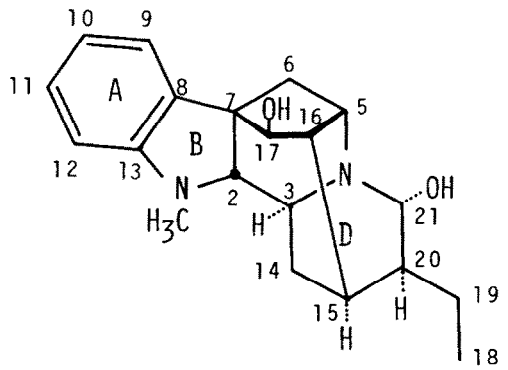
Comparison of the tetrahedral carbon resonances of 2a and 1d reveals the close relationship of these compounds. Only C(14) and the sites comprising the cyclopentanone ring of 1d are shifted strongly.



1A, Y=H , Y'=OCH_3, R,R'=O
B, Y=H , Y'=OCH_3, R=H,R'=OH
C, Y=OCH_3, Y'=H , R=H,R'=OH
D, Y=OCH_3, Y'=H , R,R'=O



2A, Y=OCH_3, Y'=OH , R=H , 2βH
B, Y=OCH_3, Y'=OAc, R=H , 2βH
C, Y=H , Y'=OH , R=CO_2CH_3, 2αH



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The indoline nucleus of the ajmalinoid substances is a structural moiety common to many Aspidosperma alkaloids whose ^{13}C NMR spectra have been interpreted fully[9,10]. Examples of the Na-alkylindoline moiety containing a single methoxy substituent in the C(10), C(11)[9], or C(12)[10] position are recorded. Each presents a distinctive pattern of aromatic methine shifts which is only minimally dependent on the nature of the C(2), C(7), and Na alkyl substituents. A methoxy group in position 10, 11, or 12 of the indoline ring results in three, two, and one methines, respectively, situated ortho to either the methoxy group or the indoline nitrogen. Methines in such an environment are subject to strong shielding (ca. 12-16 ppm) and consequently resonate above 112 ppm. Thus, inspection of the number of aromatic methines which fulfills this criterion unambiguously identifies the location of the methoxy group.

The aromatic resonances of rauflexine (1d) (two methines above 112 ppm) indicate an 11-methoxyindoline moiety. The chemical shifts of 1d duplicate (± 1 ppm) those of the aromatic ring of vindoline[9], an Aspidosperma alkaloid containing an 11-methoxy indoline unit. This array, in contrast to the C(10) or C(12) substitution pattern, places a single methine C(12), ortho to

Table I. ^{13}C Chemical Shifts of Ajmalinoid Substances[a]

	1d[b]	2a[c]	2b[b]	2c[c]	3[d]
C(2)	78.4	79.6	79.6	74.4	79.4
(3)	50.1[e]	49.0[e]	49.3[e]	52.7	44.6[e]
(5)	53.1[e]	55.8[e]	55.9[e]	61.1	52.5[e]
(6)	35.3	34.9	36.1	35.0	35.3
(7)	57.8	54.9	53.6	56.5	55.5
(8)	121.6	134.4	133.3	129.7	134.5
(9)	122.5	110.2	110.0	124.2	123.1
(10)	103.8	153.0	153.0	118.5	118.5
(11)	160.1	111.4	111.1	127.6	126.7
(12)	97.5	109.2	109.6	108.4	109.1
(13)	155.1	147.7	147.8	153.8	154.0
(14)	31.5	29.2	29.4	21.4	31.6
(15)	28.5	27.9	27.8	29.6	28.4
(16)	50.3[e]	51.9	50.1	59.6	48.7[e]
(17)	214.0	76.0	79.1	73.9	76.3
(18)	12.9	12.5	12.8	12.3	12.3
(19)	115.7	114.2	114.3	116.1	25.5
(20)	137.3	138.6	139.3	135.6	42.2
(21)	55.7	54.6	55.2	54.7	87.6
NCH_3	34.2	34.8	35.1	33.8	34.3
$ArOCH_3$	55.3	55.6	55.5		
ester					
C=O			169.9	172.8	
ester CH_3			21.1	51.1	

[a]Values are in ppm downfield from TMS: $\delta^{TMS} = \delta^{CDCl_3} + 76.9$ ppm $= \delta^{DMSO\text{-}d_6} + 39.5$ ppm. [b]Deuteriochloroform solution. [c]5:1 Deuteriochloroform:methanol-d_4 solution. [d]Dimethylsulphoxide-d_6 solution. [e]Signals in any vertical column may be reversed.

both the methoxy group and Na. The combined resonance effects of these groups shift C(12) to exceptionally high field (ca. 96-98 ppm) providing a single resonance which is highly characteristic of the C(11)-oxygen substitution pattern.

The aromatic region of the ^1H NMR spectrum of 1d is also diagnostic for the position of the methoxy substituent: δ 7.08 [1H, d, J_o = 8 Hz, H(9)], δ 6.35 [1H, dd, J_o = 8 Hz, J_m = 2 Hz, H(10)], δ 6.25 [1H, d, J_m = 2 Hz, H(12)].

In view of the chemical correlation of reflexine with rauflexine (1d)[4], the methoxy group of the former must also be attached to C(11). This conclusion is supported fully by the ^1H NMR

spectrum of reflexine in the aromatic region: δ 7.08 [1H, d, J_o = 8 Hz, H(9)], δ 6.30 [2H, dd, J_o = 8 Hz, J_m = 2 Hz, H(10) + H(12)]. Thus, formula 1c depicts the structure of reflexine.

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