

A 400 MHz  $^1\text{H}$  NMR STUDY OF TWELVE AJMALINE-TYPE ALKALOIDS

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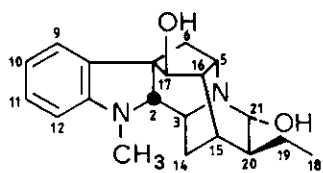
Abstract - The chemical shifts and most of the main coupling constants of twelve ajmaline alkaloids 1 - 12 have been determined in a 400 MHz  $^1\text{H}$  NMR study.

## INTRODUCTION

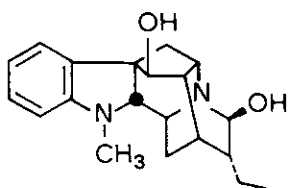
To obtain useful  $^1\text{H}$  NMR data for the structure determinations of ajmaline alkaloids, we undertook a 400 MHz  $^1\text{H}$  NMR study of ajmaline 1, isoajmaline 2, diacetylsandwichine 3, isosandwichine 4, 17-O-acetyljmaline 5, diacetylajmaline 6 (ajmaline-subgroup), acetyldihydrovomilenine 7 (indolenine-subgroup), quebrachidine 8, vincamajine 9, vincamedine 10 (quebrachidine-subgroup), maiensine 11 (tetraphyllicine-subgroup), and rauflorine 12 (17-keto alkaloid possessing the tetraphyllicine ring skeleton).<sup>1-3</sup> For some earlier fragmentary  $^1\text{H}$  NMR data concerning the alkaloids under investigation, see Refs. 4-9.

## RESULTS AND DISCUSSION

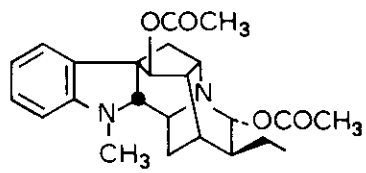
Application of the normal consecutive single- and multi-line decoupling techniques permitted all the protons in the twelve alkaloids 1 - 12 to be discovered and the coupling constants presented in Tables 1 and 2 to be determined.



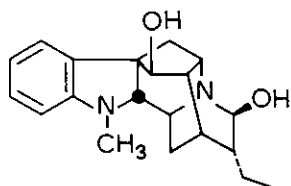
1 17R



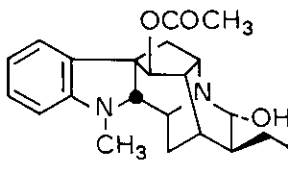
2 17R



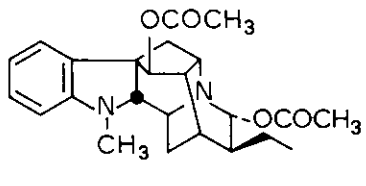
3 17S



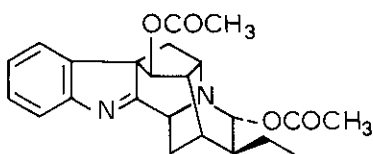
4 17S



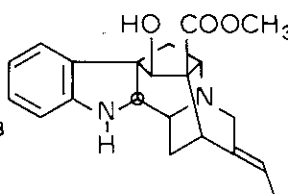
5 17R



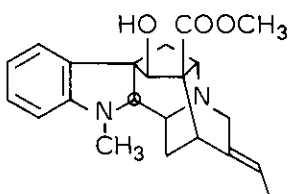
6 17R



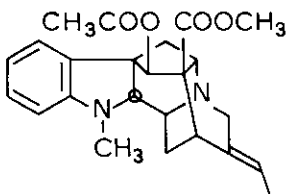
7 17R



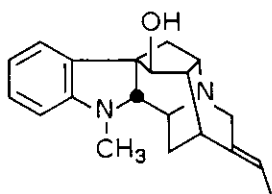
8 17S



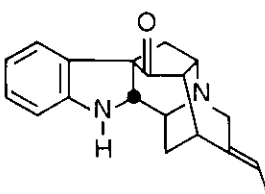
9 17S



10 17S



11 17S



12

Table 1.  $^1\text{H}$  NMR data of compounds 1 - 7.

Chemical shifts	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>
H-2	2.62 s(d)	2.62 s(d)	3.02 s(d)	3.04 s(d)	2.72 s(d)	2.72 s(d)	-
H-3	3.58 d(dd)	3.37 d(dd)	3.71 d(dd)	3.56 d(dd)	3.65 d(dd)	3.63 d(dd)	4.26 d(d)
H-5	3.00 m	3.68 dd(d)	2.98 dd(d)	3.57 m	3.06 m	3.05 dd(d)	3.40 dd(d)
H-6 $\alpha$	2.04 d(d)	2.13 d(d)	2.15 d(d)	2.04 d(d)	2.15 d(d)	2.15 d(d)	1.69 d(d)
H-6 $\beta$	1.95 dd	1.95 dd	1.36 dd	1.32 dd	1.89 dd	1.93 dd	2.78 dd
H-9	7.46	7.45	7.08	7.08	7.26	7.30	7.61
H-10	6.75	6.78	6.78	6.80	6.78	6.81	7.39
H-11	7.13	7.17	7.15	7.14	7.15	7.18	7.21
H-12	6.63	6.66	6.64	6.67	6.66	6.68	7.47
H-14 $\alpha$	1.84 dd(d)	1.76 dd(d)	1.68 def.	1.73 def.	1.85 m	1.77 m	1.82 def.
H-14 $\beta$	1.48 m	1.18 dd(d)	1.68 def.	1.73 def.	1.62 ddd	1.74 dd(d)	1.82 def.
H-15	2.25 m	2.12 m	1.96 m	2.00 m	2.44 m	2.50 m	2.49 m
H-16	2.02 m	1.98 br dd(d)	2.58 ddd	2.46 ddd	2.07 dd(d)	2.07 dd(d)	2.28 dd(d)
H-17	4.42 s(d)	4.38 s(d)	5.68 d	4.78 d	5.28 s(d)	5.28* s(d)	5.36* s(d)
H-18	0.95 t	1.00 t	0.90 t	1.00 t	0.95 t	0.95 t	0.96 t
H-19'	1.36 m	1.42 m	1.40 m	1.41 m	1.37 m	1.40 m	1.45 m
H-19	1.46 m	1.70 m	1.65 m	1.68 m	1.47 m	1.70 m	1.66 m
H-20	1.48 m	1.38 m	1.38 m	1.33 m	1.52 m	1.47 m	1.51 m
H-21	4.23 s(d)	4.00 d	5.25 s(d)	4.08 d	4.33 s(d)	5.25* s(d)	5.00* s(d)
>N-CH <sub>3</sub>	2.77 s	2.78 s	2.78 s	2.82 s	2.78 s	2.78 s	-
-OCOCH <sub>3</sub>			2.03 s		2.19 s	2.21 s	2.15 s
-OCOCH <sub>3</sub>			2.10 s		-	2.10 s	2.09 s

## Coupling constants:

1:  $J_{2,3} < 0.5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} < 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} \sim 6$  Hz;  
 $J_{6\alpha,6\beta} = 12$  Hz;  $J_{14\alpha,14\beta} = 14$  Hz;  $J_{14\alpha,15} < 1$  Hz;  $J_{14\beta,15} = 4$  Hz;  $J_{15,16} \sim 4$  Hz;  $J_{15,20} \sim 3$  Hz;  
 $J_{16,17} \sim 0.5$  Hz;  $J_{18,19} = 7$  Hz;  $J_{18,19'} = 7$  Hz;  $J_{20,21} < 0.5$  Hz.

2:  $J_{2,3} < 0.5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} < 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} \sim 6$  Hz;  
 $J_{6\alpha,6\beta} = 12$  Hz;  $J_{14\alpha,14\beta} = 14$  Hz;  $J_{14\alpha,15} < 1$  Hz;  $J_{14\beta,15} = 4$  Hz;  $J_{15,16} \sim 4$  Hz;  $J_{15,20} \sim 1$  Hz;  
 $J_{16,17} \sim 0.5$  Hz;  $J_{18,19} = 7$  Hz;  $J_{18,19'} = 7$  Hz;  $J_{20,21} = 7$  Hz.

3:  $J_{2,3} < 0.5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} < 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} \sim 6$  Hz;  
 $J_{6\alpha,6\beta} = 12$  Hz;  $J_{14\alpha,15} < 1$  Hz;  $J_{14\beta,15} \sim 4$  Hz;  $J_{15,16} \sim 5$  Hz;  $J_{15,20} \sim 3$  Hz;  $J_{16,17} = 9$  Hz;  
 $J_{18,19} = 7$  Hz;  $J_{18,19'} = 7$  Hz;  $J_{20,21} < 0.5$  Hz.

4:  $J_{2,3} < 0.5$  Hz;  $J_{3,14\alpha} \sim 10$  Hz;  $J_{3,14\beta} < 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} = 6$  Hz;  
 $J_{6\alpha,6\beta} = 12$  Hz;  $J_{14\alpha,15} < 1$  Hz;  $J_{14\beta,15} \sim 4$  Hz;  $J_{15,16} \sim 5$  Hz;  $J_{15,20} \sim 1$  Hz;  $J_{16,17} = 9$  Hz;  
 $J_{18,19} = 7$  Hz;  $J_{18,19'} = 7$  Hz;  $J_{20,21} = 7$  Hz.

Table 1 continues

- 5:  $J_{2,3} < 0.5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} < 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} = 6$  Hz;  
 $J_{6\alpha,6\beta} = 12$  Hz;  $J_{14\alpha,14\beta} = 14$  Hz;  $J_{14\alpha,15} < 1$  Hz;  $J_{14\beta,15} \sim 4$  Hz;  $J_{15,16} \sim 4$  Hz;  $J_{15,20} \sim 3$  Hz;  
 $J_{16,17} \sim 0.5$  Hz;  $J_{18,19} = 7$  Hz;  $J_{18,19'} = 7$  Hz;  $J_{20,21} < 1$  Hz.
- 6:  $J_{2,3} < 0.5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} < 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} = 6$  Hz;  
 $J_{6\alpha,6\beta} = 12$  Hz;  $J_{14\alpha,15} < 1$  Hz;  $J_{14\beta,15} \sim 4$  Hz;  $J_{15,16} \sim 4$  Hz;  $J_{15,20} \sim 3$  Hz;  $J_{16,17} \sim 0.5$  Hz;  
 $J_{18,19} = 7$  Hz;  $J_{18,19'} = 7$  Hz;  $J_{20,21} < 0.5$  Hz.
- 7:  $J_{3,14\alpha} = 9$  Hz;  $J_{3,14\beta} = 2.5$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} = 7$  Hz;  $J_{6\alpha,6\beta} = 12$  Hz;  
 $J_{14\alpha,15} < 1$  Hz;  $J_{14\beta,15} \sim 4$  Hz;  $J_{15,16} \sim 5$  Hz;  $J_{15,20} \sim 3$  Hz;  $J_{16,17} \sim 0.5$  Hz;  $J_{18,19} = 7$  Hz;  
 $J_{18,19'} = 7$  Hz;  $J_{20,21} < 0.5$  Hz.

Spectra were run in  $\text{CDCl}_3$  at 400 MHz. Values are in ppm (TMS = 0), s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad, def., deformed. The sample temperatures used were  $20^\circ\text{C}$  for compounds 1, 2, 3, 4, 6, and 7, and  $52^\circ\text{C}$  for compound 5. The correct assignment for the aromatic protons of compounds 1 - 6 was confirmed by NOE ( $>\text{N-CH}_3$  irradiated). The coupling constants between the aromatic protons are not included. The signals due to the OH-groups are omitted.

Table 2.  $^1\text{H}$  NMR data of compounds 8 - 12.

Chemical shifts	<u>8</u>	<u>9</u>	<u>10</u>	<u>11</u>	<u>12</u>
H-2	3.67 d	3.15 d	3.23 d	3.07 s(d)	3.37 s(d)
H-3	3.30 dd(d)	3.45 dd(d)	3.58 dd(d)	3.62 d(dd)	3.59 d(dd)
H-5	3.44 d(d)	3.49 d(d)	3.63 d(d)	2.89 dd(d)	3.22 dd(d)
H-6 $\alpha$	1.65 d(d)	1.46 d(d)	1.81 d(d)	2.05 d(d)	2.47 d(d)
H-6 $\beta$	2.55 dd	2.56 dd	2.54 dd	1.23 dd	1.69 dd
H-9	7.16	7.15	6.98	7.10	7.22
H-10	6.74	6.78	6.73	6.81	6.85
H-11	7.05	7.16	7.17	7.16	7.10
H-12	6.72	6.63	6.66	6.66	6.77
H-14 $\alpha$	1.42 dd(d)	1.46 dd(d)	1.54 dd(d)	1.78 dd(d)	1.88 dd(d)
H-14 $\beta$	2.49 dd(d)	2.41 dd(d)	2.63 dd(d)	2.08 dd(d)	1.42 dd(d)
H-15	3.43 d(d)	3.47 d(d)	3.50 d(d)	2.97 dd(d)	3.17 dd(d)
H-16	-	-	-	2.44 dd(d)	2.58 dd
H-17	4.18 s	4.21 s	5.67 s	4.72 d	-
H-18	1.58 br d	1.57 br d	1.55 br d	1.62 br d	1.64 br d
H-19	5.22 br q	5.24 br q	5.29 br q	5.22 br q	5.31 br q
H-21 $\alpha$	3.23 def.	3.34 def.	3.47 def.	3.34 d	3.50 def.
H-21 $\beta$	3.25 def.	3.34 def.	3.49 def.	3.46 d	3.50 def.
$>\text{N-CH}_3$	-	2.58 s	2.64 s	2.78 s	-
$-\text{COOCH}_3$	3.63 s	3.65 s	3.64 s	-	-
$-\text{OCOCH}_3$	-	-	1.85 s	-	-

Table 2 continues

Coupling constants:

8:  $J_{2,3} = 5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} \sim 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{6\alpha,6\beta} = 12$  Hz;  
 $J_{14\alpha,14\beta} = 14$  Hz;  $J_{14\alpha,15} \sim 2$  Hz;  $J_{14\beta,15} \sim 5$  Hz;  $J_{18,19} = 7$  Hz.

9:  $J_{2,3} = 5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} \sim 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{6\alpha,6\beta} = 12$  Hz;  
 $J_{14\alpha,14\beta} = 14$  Hz;  $J_{14\alpha,15} \sim 2$  Hz;  $J_{14\beta,15} = 5$  Hz;  $J_{18,19} = 7$  Hz.

10:  $J_{2,3} = 5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} \sim 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{6\alpha,6\beta} = 12$  Hz;  
 $J_{14\alpha,14\beta} = 14$  Hz;  $J_{14\alpha,15} \sim 2$  Hz;  $J_{14\beta,15} = 5$  Hz;  $J_{18,19} = 7$  Hz.

11:  $J_{2,3} < 0.5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} \sim 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} = 7$  Hz;  
 $J_{6\alpha,6\beta} = 12$  Hz;  $J_{14\alpha,14\beta} = 14$  Hz;  $J_{14\alpha,15} \sim 1$  Hz;  $J_{14\beta,15} \sim 4$  Hz;  $J_{15,16} \sim 4$  Hz;  $J_{16,17} = 9$  Hz;  
 $J_{18,19} = 7$  Hz;  $J_{21\alpha,21\beta} = 15$  Hz.

12:  $J_{2,3} < 0.5$  Hz;  $J_{3,14\alpha} = 10$  Hz;  $J_{3,14\beta} \sim 1$  Hz;  $J_{5,6\alpha} \sim 1$  Hz;  $J_{5,6\beta} = 5$  Hz;  $J_{5,16} = 7$  Hz;  
 $J_{6\alpha,6\beta} = 12$  Hz;  $J_{14\alpha,14\beta} = 14$  Hz;  $J_{14\alpha,15} \sim 1$  Hz;  $J_{14\beta,15} = 5$  Hz;  $J_{15,16} = 5$  Hz;  $J_{18,19} = 7$  Hz.

Spectra were run in  $\text{CDCl}_3$  at 400 MHz. Values are in ppm (TMS = 0), s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad, def., deformed. The sample temperatures used were 20°C. The correct assignment for the aromatic protons of compounds 9, 10 and 11 was confirmed by NOE ( $>\text{N-CH}_3$  irradiated). The coupling constants between the aromatic protons are not included. The signals due to the OH- and NH-groups are omitted.

The present results clearly indicate that in the ajmaline-subgroup the four basic skeletons, characterised by 17R,21R, 17R,21S, 17S,21R, and 17S,21S configurations (ajmaline-, isoajmaline-, sandwichine-, and isosandwichine-skeletons, respectively), are easily distinguished by their  $^1\text{H}$  NMR spectra. In R-configurations, C(17)-H and C(21)-H are represented by singlets ( $J_{16,17}$  and  $J_{20,21}$  are negligible), whereas in S-configurations they are represented by doublets (Table 1).

Scrutiny of the spectral data of compounds 1 - 6 (Table 1) reveals that the main shielding effects, due to the C(17) and/or C(21) OH-groups (or their acetylated counterparts), are seen in the chemical shifts of C(2)-H (compounds 1, 2, 5 and 6), C(5)-H (compounds 1, 3, 5 and 6) and C(6)-H $\beta$  (compounds 3 and 4). This is in good agreement with what could be expected on structural basis.

The quebrachidine-subgroup alkaloids (quebrachidine 8, vincamajine 9 and vincamedine 10) are easily distinguished from the other ajmaline alkaloids present by the C(2)-H doublets and C(17)-H singlets (Table 2). For the compounds possessing the tetraphyllicine ring skeleton (mauiensine 11 and rauflorine 12) the C(2)-H is presented by a singlet ( $J_{2,3}$  is negligible) (Table 2). The 17S configuration of mauiensine 11 is supported by the  $\delta$  4.72 ppm doublet.

The strong shielding effect of the C(17) keto group in rauflorine 12 on the chemical shift of C(14)-H<sub>B</sub> is noteworthy. These results are in full agreement with the generally accepted structures.

It is hoped that the present results, which cover most of the ring skeletons known for ajmaline alkaloids<sup>1</sup>, will prove useful in the determination of similar structures.

#### EXPERIMENTAL

The NMR spectra were recorded on a laboratory-built 400 MHz <sup>1</sup>H NMR high resolution spectrometer (I.E.F. 400)<sup>10</sup> and obtained by collecting 8 to 128 free-induction decay signals for a ~ 0.01 M solution of the samples in 450 µl of CDCl<sub>3</sub>.

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2. To be able to measure all the spectra in the same solvent we transformed sandwichine to its diacetate (compound 3)<sup>6</sup> which is much more soluble in CDCl<sub>3</sub> than sandwichine itself.
3. It is noteworthy that the priority sequence for the C(17) substituents in the Cahn-Ingold-Prelog system is different in the ajmaline and quebrachidine series. Thus the 17R configuration in the ajmaline series and the 17S configuration in the quebrachidine series correspond to the "same" three-dimensional arrangement of the substituents at C(17).
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8. G. Neukomm, E. Kletzhändler and M. Hesse, Helv. Chim. Acta, 64, 90 (1981).
9. A discrepancy exists between the present investigation and Ref. 8 concerning some <sup>1</sup>H NMR data of ajmaline 1 and isoajmaline 2.
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