A 400 MHz ^{1}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}H NMR study.

INTRODUCTION

To obtain useful ^{1}H NMR data for the structure determinations of ajmaline
alkaloids, we undertook a 400 MHz ^{1}H NMR study of ajmaline 1, isoajmaline 2,
diacetylsandwichine 3, isosandwichine 4, 17-O-acetylajmaline 5, diacetyl-
ajmaline 6 (ajmaline-subgroup), acetyldihydrovomilenine 7 (indolenine-subgroup),
quebrachidine 8, vincamajine 9, vincamedine 10 (quebrachidine-subgroup),
mauiensine 11 (tetraphyllicine-subgroup), and rauflorine 12 (17-keto alkaloid
possessing the tetraphyllicine ring skeleton).[1-3] For some earlier fragmentary
^{1}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
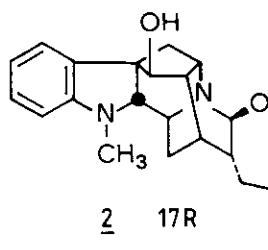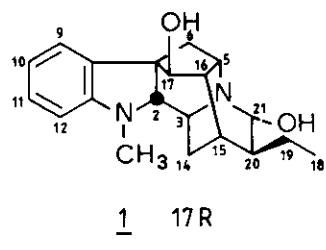
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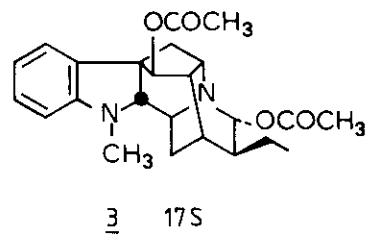
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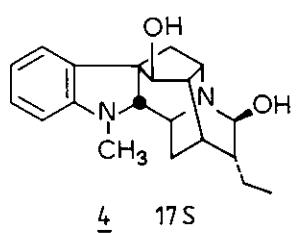
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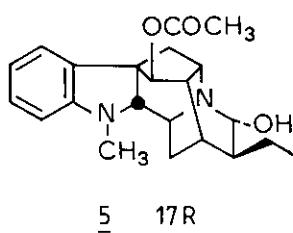
5　17R
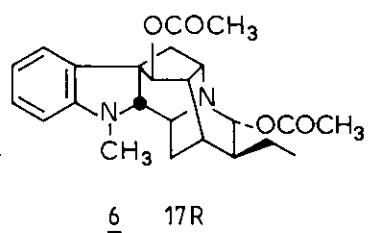
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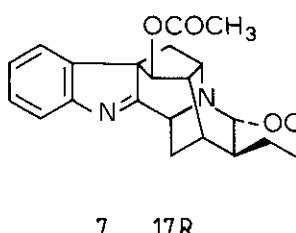
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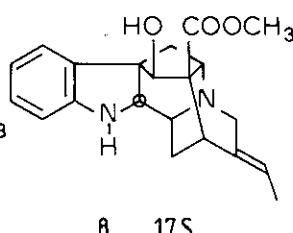
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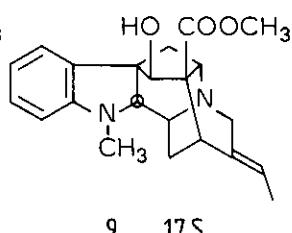
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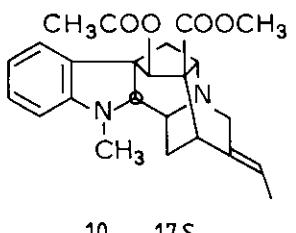
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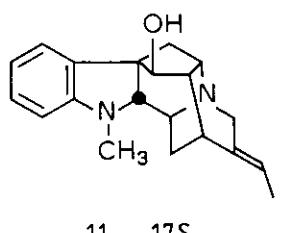
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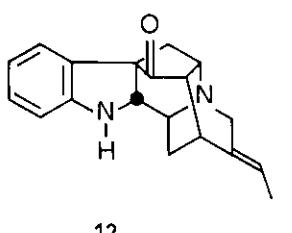
12

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

Chemical shifts

|	1	2	3	4	5	6	7
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-6α	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-6β	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-14α	1.84 dd(d)	1.76 dd(d)	1.68 def.	1.73 def.	1.85 m	1.77 m	1.82 def.
H-14β	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$_3$	2.77 s	2.78 s	2.78 s	2.82 s	2.78 s	2.78 s	-
-OCOCH$_3$		2.03 s			2.19 s	2.21 s	2.15 s
-OCOCH$_3$		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; $J_{5,6\alpha}$ ~ 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; $J_{14\beta,15}$ = 4 Hz; $J_{15,16}$ ~ 4 Hz; $J_{15,20}$ ~ 3 Hz; $J_{16,17}$ ~ 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; $J_{5,6\alpha}$ ~ 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; $J_{14\beta,15}$ = 4 Hz; $J_{15,16}$ ~ 4 Hz; $J_{15,20}$ ~ 1 Hz; $J_{16,17}$ ~ 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; $J_{5,6\alpha}$ ~ 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; $J_{14\beta,15}$ ~ 4 Hz; $J_{15,16}$ ~ 5 Hz; $J_{15,20}$ ~ 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; $J_{3,14\alpha}$ ~ 10 Hz; $J_{3,14\beta}$ < 1 Hz; $J_{5,6\alpha}$ ~ 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; $J_{14\beta,15}$ ~ 4 Hz; $J_{15,16}$ ~ 5 Hz; $J_{15,20}$ ~ 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

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

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

<u>7</u>: $J_{3,14\alpha}$ = 9 Hz; $J_{3,14\beta}$ = 2.5 Hz; $J_{5,6\alpha}$ ~ 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; $J_{14\beta,15}$ ~ 4 Hz; $J_{15,16}$ ~ 5 Hz; $J_{15,20}$ ~ 3 Hz; $J_{16,17}$ ~ 0.5 Hz; $J_{18,19}$ = 7 Hz; $J_{18,19'}$ = 7 Hz; $J_{20,21}$ < 0.5 Hz.

Spectra were run in $CDCl_3$ 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 for compounds <u>1</u>, <u>2</u>, <u>3</u>, <u>4</u>, <u>6</u>, and <u>7</u>, and 52°C for compound <u>5</u>. The correct assignment for the aromatic protons of compounds <u>1</u> - <u>6</u> was confirmed by NOE ($>$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}H NMR data of compounds <u>8</u> - <u>12</u>.

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-6α	1.65 d(d)	1.46 d(d)	1.81 d(d)	2.05 d(d)	2.47 d(d)
H-6β	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-14α	1.42 dd(d)	1.46 dd(d)	1.54 dd(d)	1.78 dd(d)	1.88 dd(d)
H-14β	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-21α	3.23 def.	3.34 def.	3.47 def.	3.34 d	3.50 def.
H-21β	3.25 def.	3.34 def.	3.49 def.	3.46 d	3.50 def.
$>$N-CH_3	-	2.58 s	2.64 s	2.78 s	-
-COOCH_3	3.63 s	3.65 s	3.64 s	-	-
-OCOCH_3	-	-	1.85 s	-	-

Table 2 continues

Coupling constants:

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

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

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

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

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

Spectra were run in $CDCl_3$ 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 <u>9</u>, <u>10</u> and <u>11</u> was confirmed by NOE ($>N-CH_3$ 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}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 <u>1</u> - <u>6</u> (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 <u>1</u>, <u>2</u>, <u>5</u> and <u>6</u>), C(5)-H (compounds <u>1</u>, <u>3</u>, <u>5</u> and <u>6</u>) and C(6)-Hβ (compounds <u>3</u> and <u>4</u>). This is in good agreement with what could be expected on structural basis.

The quebrachidine-subgroup alkaloids (quebrachidine <u>8</u>, vincamajine <u>9</u> and vincamedine <u>10</u>) 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 <u>11</u> and rauflorine <u>12</u>) the C(2)-H is presented by a singlet ($J_{2,3}$ is negligible) (Table 2). The 17S configuration of mauiensine <u>11</u> is supported by the δ 4.72 ppm doublet.

The strong shielding effect of the C(17) keto group in rauflorine 12 on the chemical shift of C(14)-Hβ 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[1], will prove useful in the determination of similar structures.

EXPERIMENTAL

The NMR spectra were recorded on a laboratory-built 400 MHz ^{1}H NMR high resolution spectrometer (I.E.F. 400)[10] and obtained by collecting 8 to 128 free-induction decay signals for a ~ 0.01 M solution of the samples in 450 μl of $CDCl_3$.

REFERENCES AND NOTES

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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)[6] which is much more soluble in $CDCl_3$ 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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