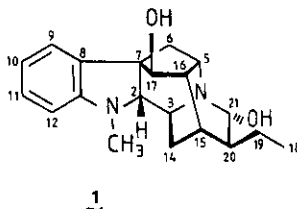


2D NMR STUDY OF AJMALINE

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Abstract - A high field 2D NMR study of ajmaline 1 is presented, settling the discrepancy existing in the interpretation of the earlier results.

Common to the ajmaline type indole alkaloids¹ is the rigid hexacyclic molecular framework, as represented in the parent structure of ajmaline 1 itself. The group consists of some 50 naturally occurring plant bases most abundant in the genus *Rauvolfia* (Apocynaceae). Complete structure 1 for ajmaline, first isolated in the early 1930's,² was worked out by Woodward in 1956.³



Ajmaline itself is in current use for treatment of cardiac arrhythmia, and several of its analogues and modifications have shown promising pharmacological properties. New plant bases of related structure are constantly being isolated, and their structures are deduced from chemical and spectroscopic correlations to the already known structures.

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Nuclear magnetic resonance techniques provide an especially powerful means of obtaining structural information on molecules in solution. This is especially the case with modern two-dimensional (2D) methods,⁴ which allow for direct independent elucidation of atom connectivities without having to rely on correlations to similar structures. Combined with the development of high-field magnets and computer instrumentation, selective pulse sequences provide structural and conformational information in reasonable time.

Recently, a 400 MHz ^1H NMR study of several ajmaline type indole alkaloids was reported by one of us.⁵ As pointed out in that report, a discrepancy exists between that and an older work.⁶ We have now undertaken a more comprehensive study on ajmaline 1 using 2D NMR methods on 500 MHz level, and have been able to confirm the spectral assignment given in Ref. 5.

The NMR work was performed on a Bruker WM 500 spectrometer, and the pulse sequences are described in the literature.⁴ Normal one-dimensional ^1H NMR spectrum showed severe broadening of lines at r.t., probably due to conformational equilibration.

However, at slightly elevated temperatures (40°C), the line shapes were much improved. Therefore, all subsequent spectra were acquired at 40°C.

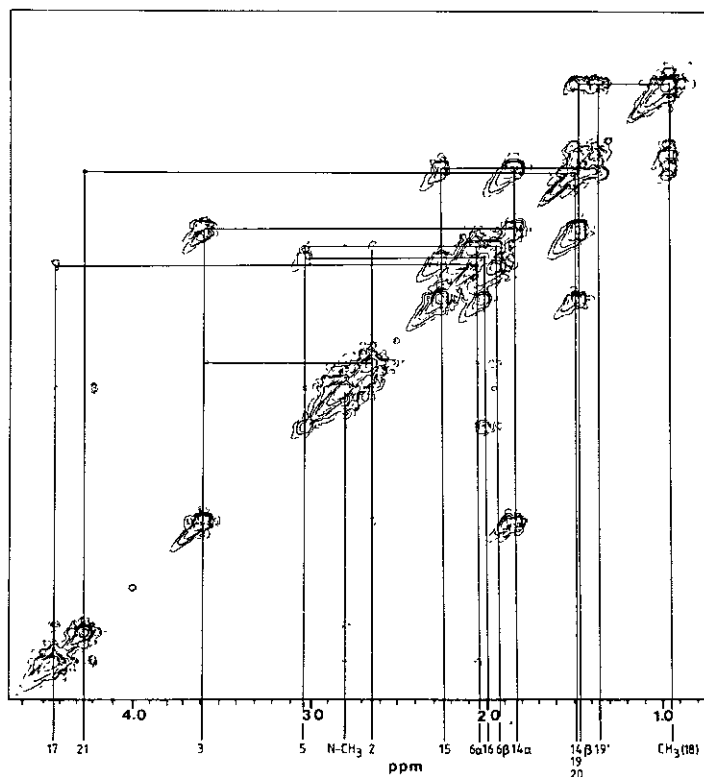


Fig. 1. COSY spectrum of ajmaline 1.

Homomuclear J-resolved experiment⁷ allowed us to locate individual protons and their respective multiplicities and coupling constants. The proton - proton connectivities were deduced from a COSY spectrum (Figure 1).⁸ The spectral data are collected in the Table 1. The following points deserve special comments. H-2 is shifted upfield due to the shielding effects exerted by the cage-like structure present in the molecule. The couplings between H-3 and H-14 β , and between H-14 α and H-15 are close to zero, implying a geometry where the C-14 is tilted down, away from the C-16 - H-17 bridge. Strong long-range (W) couplings are observed between the pairs H-6 α and H-17, and H-2 and H-6 β , a consequence of proper orientation of the respective protons for nearly planar alignment. Concerning the assignments for protons H-17 and H-21, based on the connectivities, we must conclude that the one absorbing at lower field (δ 4.43) is H-17 and the one at slightly higher field (δ 4.26) is H-21.

Table 1. ¹H NMR Data of Ajmaline 1 (CDCl₃, TMS=0).

	δ ppm	multiplicity
H-2	2.63	s (dd)
H-3	3.58	d
H-5	3.04	m (dd)
H-6 α	2.05	d (dd)
H-6 β	1.93	dd
H-9	7.46	d
H-10	6.80	dd
H-11	7.17	dd
H-12	6.68	d
H-14 α	1.82	dd
H-14 β	1.48	m
H-15	2.24	ddd
H-16	2.00	dd
H-17	4.43	s (d)
H-18 (CH ₃)	0.95	t
H-19	1.48	m
H-19'	1.36	m
H-20	1.48	m
H-21	4.26	br s
N-CH ₃	2.79	s

Coupling constants:

$J_{2,3} < 0.5$ Hz; $J_{2,6\beta} \approx 0.5$ Hz; $J_{3,14\alpha} = 10$ Hz; $J_{5,6\alpha} \approx 1$ Hz; $J_{5,6\beta} = 6$ Hz; $J_{5,16} \approx 6$ Hz; $J_{6\alpha,6\beta} = 12.5$ Hz; $J_{6\alpha,17} \approx 1$ Hz; $J_{14\alpha,14\beta} = 14$ Hz; $J_{14\beta,15} = 4.4$ Hz; $J_{15,16} = 4.4$ Hz; $J_{15,20} = 3.2$ Hz; $J_{16,17} < 0.5$ Hz; $J_{18,19} = 7$ Hz; $J_{18,19'} = 7$ Hz; $J_{19',20} = 4.5$ Hz; $J_{20,21} \approx 0.5$ Hz.

In summary, 2D NMR spectroscopy has enabled us to assign the rather complicated NMR spectrum of ajmaline 1 unambiguously. The power of 2D NMR methods is reflected in the fact the total time required for acquiring and transforming the spectra was less than three hours.

ACKNOWLEDGEMENTS

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8. The protons H-14 β , H-19 and H-20 co-occur at δ 1.48, thus prohibiting separation of individual assignment of these three protons.

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