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NUCLEAR MAGNETIC RESONANCE STUDY OF APORPHINE ALKALOIDS—II[1]

THE STRUCTURE OF ROGERSINE

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Abstract—The influence of alkali on the nuclear magnetic resonance spectra of some phenolic aporphine alkaloids has been studied. It is shown that shifts of the aromatic proton resonances greatly facilitate the elucidation of unknown structures in this series. The identity of rogersine and N-methyllaurotetanine (II) has been established by this method.

INTRODUCTION

THE synthesis of 1,2,9-trimethoxy-10-hydroxy-aporphine (IV), reported in the preceding paper[2] has shown that the proposed structure[3] for rogersine, a minor alkaloid of *Phylica rogersii* Pillans must be incorrect. During a previous study[1] it was found that NMR is a powerful tool for structural work in aporphine chemistry. However, in comparing the NMR spectra of chloroform solutions of rogersine and other closely related aporphines, only small differences were found which did not permit assignment of the position of the hydroxyl groups.

Recently it came to our attention[4,5] that in the NMR spectra of phenoxide ions significant shifts of the aromatic proton resonances are observed with reference to the spectra of the undissociated phenols. Several available model substances were studied, and the structure of rogersine was established using this method.[6]

EXPERIMENTAL

The NMR spectra were recorded on a Varian A-60 spectrometer which was calibrated using a Hewlett–Packard electronic counter model 521C and a Hewlett–Packard oscillator model 200CD. Tetramethylsilane (TMS) and the sodium salt of 4,4-dimethyl-4-silapentanesulphonic acid (DSS) were used as internal references for dilute solutions (probe temp 38°) in $CDCl_3$ and dimethylsulphoxide, respectively. The chemical shifts are expressed in ppm on the τ-scale (with τ_{TMS} or $\tau_{DSS} = 10{\cdot}00$), and are estimated to be accurate to $\pm 0{\cdot}01$ ppm. The anion-shifts were studied by successively adding small amounts (3–5 λ) of alkali ($\approx 25\%$ NaOD solution in D_2O, prepared by dissolving Na in D_2O), and recording the low field portion of the spectrum after each addition until no further changes were observed. AB-spectra were analysed according to the usual procedure[7] and three-spin systems by

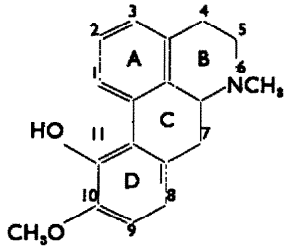
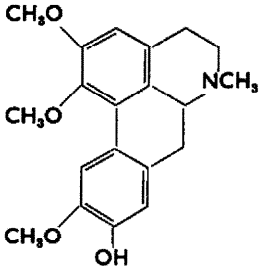
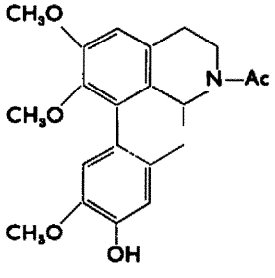
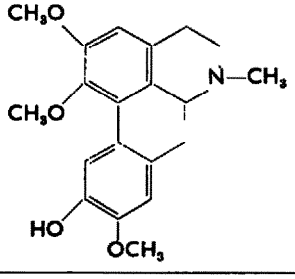
[1] Part I, W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *J. Chem. Soc.* 4778 (1964).
[2] W. H. Baarschers and R. R. Arndt, *Tetrahedron* **21**, 2155 (1965).
[3] R. R. Arndt and W. H. Baarschers, *J. Chem. Soc.* 2244 (1964).
[4] R. J. Highet and P. F. Highet, *J. Org. Chem.* **30**, 902 (1965). We are indebted to Dr. R. J. Highet for bringing this method to our attention, and for sending us a copy of his paper prior to publication.
[5] J. M. Brown, *Tetrahedron Letters* No. 32, 2215 (1964).
[6] The authors gratefully acknowledge a gift of samples of compounds I, III, V and VI from Dr. J. A. Weisbach, Smith, Kline and French Labs., Philadelphia.
[7] J. A. Pople, W. G. Schneider, and H. J. Bernstein *High Resolution Nuclear Magnetic Resonance*. McGraw-Hill, New York (1960).

using an IBM 704 programme[8] for the direct analysis of ABC-spectra, assuming all coupling constants to be positive. Coupling constants are reported in c/s with an estimated accuracy of ±0·2 c/s.

Spectral data

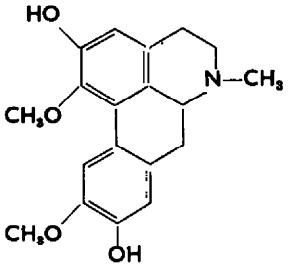
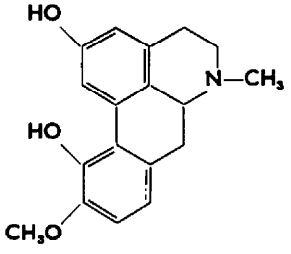
A. *Solutions in deuterated chloroform.* The NMR data obtained from $CDCl_3$ solutions are summarized in Table 1. Values for N-methyl-laurotetanine (II) and N-acetyl-laurotetanine (III) are taken from a previous publication.[1] The assignment is in agreement with the general features of aporphine spectra recorded there.

TABLE 1. τ-VALUES FOR $CDCl_3$ SOLUTIONS

No.		τ-values of groups at positions[a]							
		1	2	3	8	9	10	11	6(N)
I[b]		1·77	2·79	2·97	3·28	3·28	6·14	—	7·47
II		6·34	6·13	3·43	3·22	—	6·13	1·96	7·48
III		6·27	6·03	3·27	3·13	—	6·03	1·72	7·78
IV		6·31	6·10[c]	3·42	3·24	6·13[c]	—	2·00	7·43

[8] W. Brügel, Th. Ankel and F. Krückeberg, *Z. Elektrochem.* **64**, 1121 (1960).

TABLE 1. (*contd.*)

No.		τ-values of groups at positions[a] 1	2	3	8	9	10	11	6(N)
V		6·41	—	3·39	3·18	—	6·11	2·04	7·47
VI[d]		2·30	—	3·73	3·30	3·30	6·11	—	7·47
VII	rogersine	6·33	6·13	3·42	3·22		6·13	1·95	7·48

[a] Aliphatic protons attached to rings B and C gave complex patterns at τ 6·3–7·7.
[b] Coupling constants $J_{12} = 7·5$, $J_{13} = 1·2$, $J_{23} = 8·1$.
[c] These values may be interchanged.
[d] Coupling constant $J_{13} = 2·5$.

B. *Solutions in dimethylsulphoxide.* Due to the strong solvent peak at τ = 7·45 most of the high field part of the spectra was obscured. The measurable values are reported in Table 2. The numbering of compounds and substituents corresponds to Table 1.

TABLE 2. τ-VALUES FOR DMS SOLUTIONS

Compound no.	τ-values of groups at positions 1	2	3	8	9	10	11	Coupling constants
I	1·78	2·79	2·97	3·24	3·14	6·18	—	$J_{12} = 8·2$, $J_{13} = 1·1$, $J_{23} = 7·6$, $J_{89} = 7·9$
II	6·39	6·20	3·33	3·25	—	6·20	2·13	—
III	6·39	6·20	3·21	3·28	—	6·20	2·04	—
IV	6·41	6·20	3·33	3·13	6·20	—	2·26	—
V	6·41	—	3·48	3·26	—	6·21	2·13	—
VI	2·26	—	3·53	3·29	3·19	6·17	—	$J_{13} = 2·5$, $J_{89} = 8·1$
VII	6·38	6·20	3·32	3·25		6·20	2·13	

C. *Anion shifts in dimethylsulphoxide.* We have found that the anion shifts are best studied by successive addition of small amounts of a concentrated solution of alkali to the compound dissolved in dimethylsulphoxide. Plotting the chemical shift versus the relative amount of alkali added, greatly facilitates the interpretation of the data obtained, and gives the most comprehensive information.

These plots are given in Figs. 1–5, for five of the compounds studied. The values along the abscissa have been roughly normalized to express moles of alkali per mole of alkaloid. The measurements for rogersine are included in Fig. 2. The maximum shifts observed are presented in Table 3.

TABLE 3. MAXIMUM VALUES OF ANION SHIFTS

Compound No.	Proton[a]	Max. Shift (ppm)
I	1 *n*	−0·79
	2 *n*	0·19
	3 *n*	0·26
	8 *p*	0·86
	9 *m*	0·42
II	3 *n*	0·21
	8 *o*	0·51
	11 *m*	0·25
III	3 *n*	0·23
	8 *o*	0·54
	11 *m*	0·26
IV	3 *n*	0·11
	8 *m*	0·37
	11 *o*	0·47
V	3 *n,o*	0·54
	8 *n,o*	0·52
	11 *n,m*	0·16
VI	1 *n,o*	0·01
	3 *n,o*	0·42
	8 *n,p*	0·71
	9 *n,m*	0·37
VII	3 —	0·22
	8 —	0·53
	11 —	0·26

[a] The designations *o*, *m* and *p* indicate that there is a hydroxyl group resp. in the *ortho*, *meta* or *para* position relative to the proton concerned, while *n* indicates a hydroxyl group on the neighbouring aromatic ring.

DISCUSSION

A. *Solvent effect.* Comparison of the τ-values in Tables 1 and 2 indicates the occurrence of solvent effects in dimethylsulphoxide solution. However, no consistent pattern arises. The solvent shifts are usually less than $\pm$0·1 ppm. Only the proton in position 11 is consistently shifted to high field (0·09–0·32 ppm).

B. *Anion shifts.* It has been shown[5] that the NMR of aromatic protons of phenols in dimethylsulphoxide solutions experience a characteristic high field shift when dissociation to the phenoxide ion occurs. As this anion shift is a function of the relative positions of the phenolic hydroxyl group and the aromatic proton, being most pronounced in *ortho* and *para* positions, it has been suggested that the electron density at these positions is increased by contributions of mesomeric structures. In a detailed study of a series of polysubstituted phenols[4] the following ranges for anion shifts in alkyl and alkoxy substituted phenols in dimethylsulphoxide solution are given, *ortho:* 0·42–0·59 ppm, *meta:* 0·19–0·39 ppm, and *para:* 0·71–0·79 ppm. It was, however, found that the absolute values of these shifts are dependent on the entire substitution

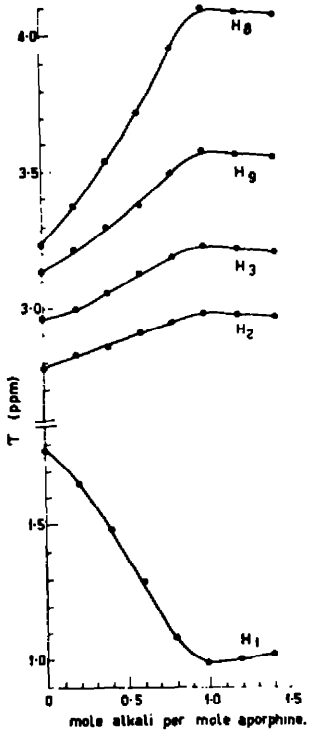


FIG. 1. 10-Methoxy-11-hydroxy-aporphine (I).

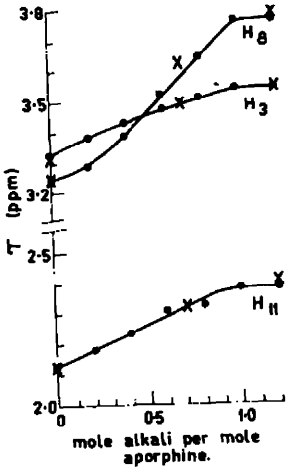


FIG. 2. – · – · – · N-Methyl-laurotetanine (II) – × – × – × – Rogersine (VII).

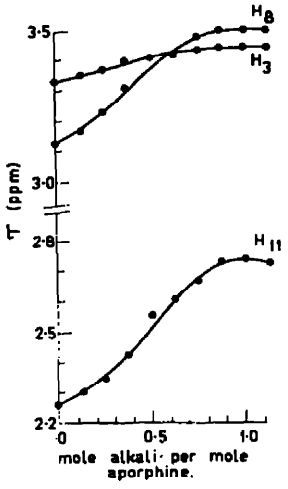


FIG. 3. 1,2,9-Trimethoxy-10-hydroxy-aporphine (IV).

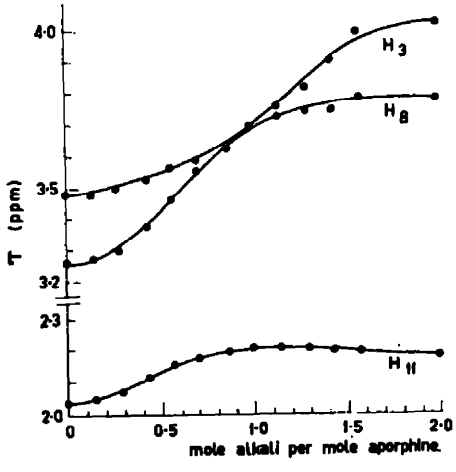


FIG. 4. 1,10-Dimethoxy-2,9-dihydroxy-aporphine (V).

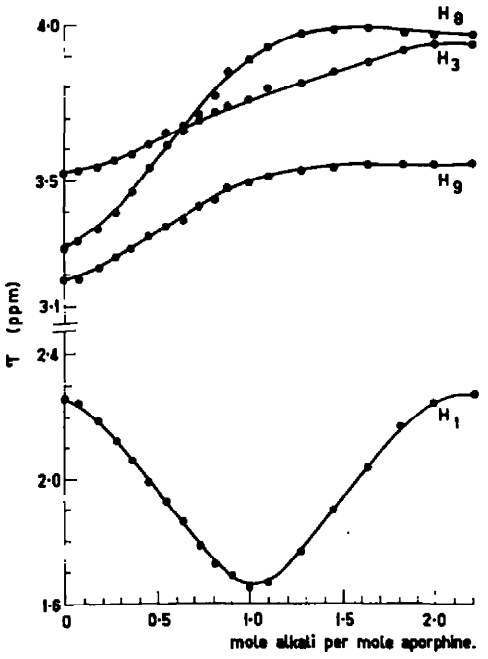


FIG. 5. 2,11-Dihydroxy-10-methoxy-aporphine (VI).

pattern of the compound concerned. Thus an investigation of closely related model substances was required for an application of this method to the present problem.

An inspection of the maximum shifts of the first four compounds (Table 3) indicates the limits of the anion shifts to be as follows, *ortho:* 0·47–0·54 ppm, *meta:* 0·25–0·42 ppm, and *para:* 0·86 ppm. Thus the relative magnitude of the shifts is the same as found by other authors,[4,5] and no overlap of the various ranges occurs for the examples measured.

We furthermore found a high field shift (0·11–0·26 ppm) for protons attached to the aromatic ring not bearing the hydroxyl group. The two aromatic rings of the aporphine skeleton are in conjugation, and the dissociation of a hydroxyl group is therefore expected to influence the chemical shifts of all aromatic protons. Mesomerism will affect both rings if the hydroxyl group is in positions 1, 3, 9, or 11, influencing the protons in alternate positions as shown by the example in Fig. 6. In the other positions mesomerism is confined to the ring bearing the hydroxyl group. In agreement with this we found larger shifts on protons subject to mesomeric effects (0·21–0·26 for the proton in position 3 in compounds I, II and III) than on others (0·19 ppm for the proton in position 2 in I, and 0·11 ppm for the proton in position 3 in IV).

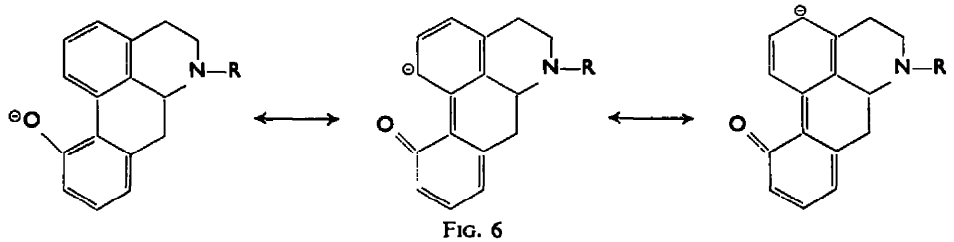


FIG. 6

Compounds V and VI have two phenolic hydroxyl groups. This complicates the interpretation of their spectra as a combination of various effects occurs (see below). Nevertheless the maximum shifts observed fall within the ranges derived for the other compounds as the anion shift of protons of a neighbouring ring is relatively small.

C. *Low field shifts and dissociation sequence.* Figures 1–5 have been most valuable in the unambiguous assignment of the proton resonances, especially in those cases where an overlap or crossing-over of resonance lines occurred (II, IV, V and VI). The graphs furthermore reveal some interesting details for compounds with two phenolic hydroxyl groups (V and VI).

The large low field shift of the proton in position 1 (−0·79 ppm) in compound I should be attributed to either hydrogen bonding effects, or to the electric field effect[9] of the phenol anion. Similarly the proton in position 1 of compound VI experiences the same low field shift, followed by an ortho anion shift (Fig. 5).

The shape of the curves for compounds V and VI (Figs. 4 and 5) gives information on the dissociation sequence of the two hydroxyl groups present. In compound V the hydroxyl group in position 9 dissociates first as the resonances of the protons in positions 8 and 11 start shifting immediately after the addition of alkali. The proton in position 3, subject to mesomeric effects, also shifts. The protons in positions 8 and 11 reach more or less constant τ-values after approximately one mole of alkali has been added. Then the dissociation of the second hydroxyl group (in position 2) begins, causing a further shift of the proton in position 3 to high field, but having hardly any effect on the protons in positions 8 and 11 (no mesomeric contributions).

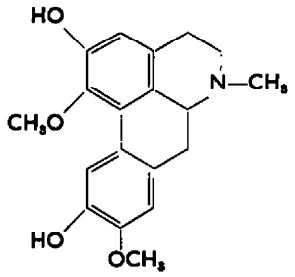
The plots for compound VI may be interpreted in a similar fashion. The dissociation of the hydroxyl group in position 11 occurs first, leading to a high field shift of the protons in positions 8 and 9, and to a large low field shift of the proton in position 1. Its τ-value reaches its minimum at about the same point where the protons in positions 8 and 9 stop shifting to high field. On further addition of alkali a reversal in the shift of the proton in position 1 occurs, caused by the *ortho*-anion effect of the 2-hydroxyl group. The proton in position 3 also shifts further to its final τ-value.

The difference in acidity between two hydroxyl groups in an aporphine molecule is also demonstrated by the selective methylation, resulting in the formation of only one of two possible monomethyl ethers, of N-methyl-laurelliptine[10] (X), and of boldine[11] (V). In both cases the hydroxyl group at ring D is methylated in preference to that at ring A. Our present results are in agreement with these findings, as it was found that in the two compounds of this type studied, compounds V and VI, the hydroxyl group on ring D dissociates first.

In many of the curves a slight backward shift is observed after reaching the maximum τ-value. This is probably a dilution effect as Brown has shown[5] that maximum shifts are obtained in pure dimethylsulphoxide solutions, while the anion shifts decrease steadily on addition of methanol.

D. *Coupling constants.* Coupling constants have been measured for compounds

[9] A. D. Buckingham, *Canad. J. Chem.* **38**, 300 (1960).
[10] P. S. Clezy, A. W. Nichol and E. Gellert, *Experientia* **19**, 1 (1963).
[11] R. Tschesche, P. Welzel, R. Moll and G. Legler, *Tetrahedron* **20**, 1435 (1964).



X

I and VI, and are included in Tables 1 and 2. The measurements in alkaline dimethylsulphoxide solutions were too inaccurate to give any quantitative results, but there is some indication that the magnitude of *ortho* coupling constants decreases with increasing dissociation of the phenolic hydroxyl groups, while *meta* coupling constants increase.

THE STRUCTURE OF ROGERSINE

It has been shown in the preceding paper[2] that the structure proposed for rogersine must be in error. In previous investigations[1,3] NMR spectra of $CDCl_3$ solutions of aporphine alkaloids were recorded and compared. The spectra of compounds II, IV and VII are identical within experimental error (Table 1), except for a slightly higher τ-value of the proton in position 11 of compound IV. However, comparison of the τ-values of the dimethylsulphoxide solutions reveals significant differences between compound VII (rogersine, $\tau_8 = 3{\cdot}25$; $\tau_{11} = 2{\cdot}13$) and the synthetic compound IV ($\tau_8 = 3{\cdot}13$; $\tau_{11} = 2{\cdot}26$), while the chemical shifts for compounds II and VII are the same. Unambiguous proof of the identity of rogersine (VII) and N-methyl-laurotetanine (II) is provided by the anion shifts observed for compounds II, IV and VII (Table 3 and Fig. 2). Further support is provided by the previous observation[3] that the UV spectra of rogersine and N-methyl-laurotetanine as well as their IR spectra were identical.

A sample of amorphous[12] N-methyl-laurotetanine, prepared from an authentic specimen of its hydrobromide, crystallized from methanol on seeding with rogersine giving no depression in m.p. on admixture with rogersine. An NMR spectrum of the crystalline N-methyl-laurotetanine gave the expected peak (intensity 1·5 H) at τ 6·55, indicating 0·5 mole methanol of crystallization that was also observed before in the spectrum of rogersine.[3]

As rogersine has thus been identified as a crystalline form of N-methyl-laurotetanine, the name rogersine should now be removed from the literature.

The false identification of rogersine by comparing its ethyl ether l-tartrate (mixed m.p., R_f-values, and IR spectra) with the same derivative of 1,2,9-trimethoxy-10-ethoxy-aporphine synthesized by Manske[13] was rectified by a comparison of X-ray powder photographs of these compounds,[14] which showed considerable differences.

[12] A. Rüegger, *Helv. Chim. Acta* **42**, 754 (1959). We gratefully acknowledge a generous gift of N-methyl-laurotetanine hydrobromide from Dr. Rüegger (Sandoz Ltd, Basel).

[13] R. H. F. Manske, E. H. Charlesworth and W. R. Ashford, *J. Amer. Chem. Soc.* **73**, 3751 (1951).

[14] We thank Dr. G. Gafner, National Physical Res. Lab., Pretoria for his assistance in making these photographs.

Relatively small differences in paper chromatographic behaviour between the two N-methyl-laurotetanine fractions of *Phylica rogersii* must be attributed to the influence of small amounts of impurities.

This investigation illustrates once more the extreme care which should be exercised in making comparisons in the aporphine series, and stresses the importance of the present method in this field.

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