921. *Nuclear Magnetic Resonance Study of Aporphine Alkaloids.*

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The proton magnetic resonance spectra of a number of aporphine alkaloids have been recorded. Assignments have been made for the resonance frequencies of the aromatic protons. A qualitative explanation of various effects on the chemical shift data is presented.

Recently some structural correlations in the nuclear magnetic resonance (n.m.r.) spectra of aporphine alkaloids were reported by Bick *et al.*[1] concerning mainly the methoxyl and methylenedioxy resonances. No data were presented, however, on the aromatic proton resonances. Vernengo [2] reported τ-values for the aromatic protons of some aporphine alkaloids, but did not make definite assignments.

The investigation of the alkaloids present in *Phylica rogersii* Pillans [3] focused attention on the interesting possibilities of a more detailed study of the n.m.r. spectra of this family of alkaloids. Such a study was undertaken on a large number of substituted

[1] Bick, Harley-Mason, Sheppard, and Vernengo, *J.*, 1961, 1896.
[2] Vernengo, *Experientia*, 1963, **19**, 294.
[3] Arndt and Baarschers, *J.*, 1964, 2244.

aporphines of both natural and synthetic origin, available from a previous investigation [4] (Table 1).

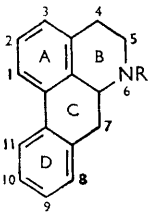

TABLE 1.

			Substituents on C-atom *				
No.	Alkaloid	R	1	2	9	10	11
I	9-Chloroaporphine	Me	—	—	Cl	—	—
II	9-Methoxyaporphine	Me	—	—	OMe	—	—
III	10-Methoxyaporphine	Me	—	—	—	OMe	—
IV	2-Methoxy-*N*-acetylnoraporphine †	Ac	—	OMe	—	—	—
V	Nuciferine	Me	OMe	OMe	—	—	—
VI	*N*-Acetylnornuciferine	Ac	OMe	OMe	—	—	—
VII	*N*-Ethylnornuciferine	Et	OMe	OMe	—	—	—
VIII	*N*-Benzylnornuciferine	ϕ-CH_2	OMe	OMe	—	—	—
IX	*N*-β-Phenethylnornuciferine	ϕ-C_2H_4	OMe	OMe	—	—	—
X	10-Trifluoromethylnuciferine	Me	OMe	OMe	—	CF_3	—
XI	Glaucine	Me	OMe	OMe	OMe	OMe	—
XII	*N*-Methyl-laurotetanine	Me	OMe	OMe	OH	OMe	—
XIII	*N*-Acetyl-laurotetanine	Ac	OMe	OMe	OH	OMe	—
XIV	Dicentrine	Me	OCH_2O		OMe	OMe	—
XV	Boldine diethyl ether	Me	OMe	OEt	OEt	OMe	—
XVI	Rogersine	Me	OMe	OMe	OMe	OH	—
XVII	Ocoteine	Me	OCH_2O		OMe	OMe	—
XVIII	Corydine	Me	OH	OMe	—	OMe	OMe
XIX	Isocorydine	Me	OMe	OMe	—	OMe	OH
XX	Bulbocapnine	Me	OCH_2O		—	OMe	OH
XXI	Bulbocapnine methyl ether	Me	OCH_2O		—	OMe	OMe

* All alkaloids carry protons at C-3 and C-8, except ocoteine, which has a 3-OMe group. † The origin of 2-methoxy-*N*-acetylnoraporphine will be reported elsewhere.

EXPERIMENTAL

The n.m.r. spectra were recorded on a Varian A-60 spectrometer operating at 60 Mc./sec. (probe temperature 38°). Dilute solutions ($\leqslant$5 mole %) in deuterochloroform were used. The chemical shifts were measured on the τ-scale relative to internal tetramethylsilane (τ 10·0) The τ-values are estimated to be accurate to $\pm$0·01 p.p.m. unless otherwise stated. Coupling constants reported are accurate to $\pm$0·2 c./sec. The experimental results are presented in Table 2.

ASSIGNMENTS

In the spectra of compounds with substituents at both positions 1 and 2, a one-proton peak at a characteristically low field (τ 1.26—2.32) was assigned to the proton at position 11, in accordance with the findings of Bernstein *et al.*[5]

Of the three aromatic proton resonances in the dicentrine (XIV) spectrum, the one at highest field was tentatively assigned to the proton in position 3 by Goodwin *et al.*,[6] on the basis of a comparison with bulbocapnine methyl ether (XXI). The present study places this assignment on a firm basis. A single one-proton peak at τ 3·25—3·46 was observed in the spectra of all those alkaloids in which no spin–spin coupling of the proton in position 3 could occur. In the spectrum of ocoteine (XVII), this proton resonance was absent, and instead a methoxyl peak at low τ-value was observed, in accordance with the

[4] Arndt, Baarschers, Douglas, Shoop, and Weisbach, *Chem. and Ind.*, 1963, 1163.
[5] Bernstein, Schneider, and Pople, *Proc. Roy. Soc.*, 1956, *A*, **236**, 515.
[6] Goodwin, Shoolery, and Johnson, *Proc. Chem. Soc.*, 1958, 306.

TABLE 2.

Compound No.	R	τ-Values 1	2	3	8	9	10	11
I	7·47	2·44 [a]	2·70 [b]	2·70 [b]	2·70 [b]	—	2·70 [b]	2·34 [a]
II	7·44	2·50 [a]	2·80 [b]	2·80 [b]	3·10 [b]	6·16	3·10 [b]	2·34 [a]
III	7·45	2·43 [a]	2·80 [b]	2·80 [b]	2·80 [b]	3·18 [a]	6·16	2·80 [b]
IV	7·80	2·75 [b]	6·16	3·38 [c]	2·75 [b]	2·75 [b]	2·75 [b]	2·30 [c]
V	7·44	6·30	6·09	3·30	2·65 [b]	2·65 [b]	2·65 [b]	1·33 [c]
VI	7·80	6·29	6·08	3·25	2·65 [b]	2·65 [b]	2·65 [b]	1·47 [c]
VII	—	6·30	6·11	3·30	2·65 [b]	2·65 [b]	2·65 [b]	1·53 [c]
VIII	—	6·32	6·13	3·37	2·60 [b]	2·60 [b]	2·60 [b]	1·56 [c]
IX	—	6·33	6·12	3·35	2·70 [b]	2·70 [b]	2·70 [b]	1·57 [c]
X	7·46	6·29	6·09	3·29	2·55 [b]	2·55 [b]	—	1·26 [c]
XI	7·41	6·28	6·07 [d]	3·32	3·11	6·03 [d]	6·03 [d]	1·79
XII	7·48	6·34	6·12	3·42	3·22	—	6·12	1·96
XIII	7·78	6·27	6·03	3·27	3·13	—	6·03	1·72
XIV	7·45	3·97 [e]		3·46	3·18	6·06	6·06	2·29
XV	7·32	6·28	—	3·32	3·12	—	6·60	1·80
XVI	7·47	6·31	6·11	3·39	3·18	6·11	—	1·91
XVII	7·48	4·03 [f]		6·01	3·22	6·09	6·09	2·39
XVIII	7·43	—	6·09	3·28	2·99 [g]		6·09	6·24
XIX	7·46	6·28	6·09 [d]	3·27	3·12	3·12	6·07 [d]	—
XX	7·48	4·00 [h]		3·39	3·18	3·18	6·11	—
XXI	6·98	3·95 [j]		3·31	2·99 [k]		6·08	6·13

[a] Identified by splitting pattern of high- or low-field lines, respectively; analysed by AB procedure, neglecting small *meta*-splittings, from intensity ratios; accuracy estimated to be ±0·02 p.p.m. [b] Complex pattern centred at τ-value indicated, accuracy ±0·1 p.p.m. [c] Multiplet centred at τ-value indicated. [d] These values may be interchanged. [e] AB-quartet, $\Delta\nu = 8{\cdot}7$ c./sec.; $J = 2$ c./sec. [f] AB-quartet, $\Delta\nu = 8{\cdot}5$ c./sec.; $J = 2$ c./sec. [g] AB-quartet, $\Delta\nu = 11{\cdot}9$ c./sec.; $J = 8{\cdot}5$ c./sec. [h] AB-quartet, $\Delta\nu = 8{\cdot}9$ c./sec.; $J = 1{\cdot}5$ c./sec. [i] Examined as the soluble hydrochloride. [j] AB-quartet, $\Delta\nu = 10{\cdot}9$ c./sec.; $J = 1{\cdot}3$ c./sec. [k] AB-quartet, $\Delta\nu = 6{\cdot}6$ c./sec.; $J = 8{\cdot}3$ c./sec.

recently established [2] structure of this alkaloid, which has a methoxyl group in position 3.

From the above it follows that signals at intermediate field must be attributed to protons in position 8 in the case of a 9,10-substitution, and to protons in positions 8 and 9 of a corydine-type substitution pattern. In the latter case, a normal AB-type quartet was found for these *o*-protons only if ring D contains 2 methoxyl groups, *e.g.*, corydine (XVIII) and bulbocapnine methyl ether (XXI). However, when the methoxyl group in position 11 is replaced by hydroxyl, as in isocorydine (XIX) and bulbocapnine (XX), no observable splitting was found. This constitutes another example of two aromatic ortho-protons in which an identical chemical shift leads to a collapse of the expected AB-quartet. This unusual phenomenon has also been observed in the spectra of otobain [7] and protopine.[8] In the latter two compounds the *o*-protons are adjacent to a methylenedioxy-group.

The aliphatic protons gave a complex pattern at τ 6·3—7·7. Resonances observed for methoxyl and methylenedioxy groups were in agreement with values reported in the literature.[1,2,6] Different *N*-substituents do not seem to have a significant effect on the methoxyl or aromatic proton resonances (V—IX).

DISCUSSION

Inspection of Table 2 reveals several general effects determining the magnitude of the chemical shift.

Factors Affecting Chemical-shift Data.—The τ-values of the protons in positions 2, 3, 8, 9, and 10 on unsubstituted aromatic rings (compounds I—IX) vary between 2·6 and 2·8. If one accepts the value 2·7 ± 0·1 (which is close to the τ-value of benzene) as a basis, then deviations larger than ±0·1 p.p.m. must be attributed to different substituent or ring-current effects.

[7] Bhacca and Stevenson, *J. Org. Chem.*, 1963, **28**, 1638.
[8] Bhacca, Johnson, and Shoolery, " N.M.R. Spectra Catalog," Varian Associates, 1962, No. 339.

Substituent effects on aromatic protons have been previously determined in detail.[9-11] It has been found that a proton *ortho* to a methoxyl group experiences a high-field shift of 0·4 to 0·7 p.p.m.

In the rigid ring-system of the aporphine molecule, protons in positions 1 and 11 are subject to the ring-current effect of the neighbouring aromatic ring. An estimate of this effect was made from the "isoshielding lines" for the benzene ring as calculated by Johnson and Bovey.[12] The co-ordinates of the hydrogen relative to the centre of the neighbouring aromatic ring were determined from Dreiding models. According to this estimate, a low-field shift of approximately 0·4 p.p.m. is expected.

Also, the ring-current effect on methoxyl groups has been estimated in the same manner. If the O–Me bond lies in the plane of the two aromatic rings, pointing away from the neighbouring ring, a negligible deshielding effect is expected. A position with the bond pointing towards the ring is improbable because of steric hindrance. If the O–Me bond sticks out of the plane of the benzene rings, the opposite ring will make a small positive shielding contribution. This is also the position where the deshielding effect of the ring, to which the methoxyl group is attached, is least.

Exceptionally low τ-values are found for protons in the 11 position if position 1 is substituted by a methoxyl group. The low-field shift (average 0·8 p.p.m.) must be attributed not only to the deshielding by the neighbouring ring, but also to anisotropy effects of the C–O single bond, or effects due to C–O electric dipoles, as the hydrogen is held very close to the opposite oxygen atom. This O · · · H distance has been estimated from models to be approximately 1·9 Å, which could allow for hydrogen-bonding. A similar shift caused by a methylenedioxy group in positions 1 and 2 is observed on the resonance of the proton in position 11. The O · · · H distance is 0·2—0·3 Å longer than for the methoxy compounds discussed above and the effect is correspondingly less pronounced.

Aromatic Proton Resonances.—Most of the chemical-shift values observed can be explained by one of the three effects discussed above or a combination of them.

Thus the proton in position 3 of 2-methoxyaporphines experiences a diamagnetic shift of 0·6—0·7 p.p.m., and the proton in position 9 of 10-methoxyaporphines (XIX and XX) shows a similar shift of 0·4—0·5 p.p.m. In 9-methoxyaporphine (II) both the protons in positions 8 and 10 are shifted to higher field by 0·45 p.p.m. These values are in agreement with those expected for protons *ortho* to a methoxyl group. An effect of similar magnitude has been found for protons *ortho* to a hydroxyl group (XII and XIII).

The τ-values measured for protons in positions 1 and 11, which experience the ring-current effect only vary from 2·3—2·5 (I—IV). This is 0·2—0·5 p.p.m. lower than the average τ-values of 2·7, and is in fair agreement with the estimate. They are, however, at τ 2·8 if they are also *ortho* to a methoxyl group (III and IV). Protons in position 11, in compounds with a methoxyl group in position 1, occur at τ 1·33—1·57 (V—IX), and they are shifted to τ 1·72—1·96 if they are also *ortho* to a methoxyl or hydroxyl group (XI, XII, XIII, XV, and XVI). Thus for this proton the average *ortho*-substituent effect of a methoxyl or hydroxyl group is +0·4 p.p.m.

The resonances of the protons in position 11 of the compounds XIV and XVII occur at τ 2·29 and 2·32, respectively. These protons are subject to the deshielding of the neighbouring ring (0·4 p.p.m.) and an *o*-methoxy-substituent effect of +0·4 p.p.m. Thus the low-field shift of the methylenedioxy group amounts to 0·4 p.p.m.

The exceptionally low value for the proton in position 11 in compound X (τ 1·26) may be attributed to an additional deshielding by the *o*-CF_3 group (approx. 0·3 p.p.m.).

Methoxyl Group Resonances.—The methoxyl groups have a resonance frequency in a very close range at τ 6·09±0·07, except those in the 1 or 11 positions, which occur at

[9] Diehl, *Helv. chim. Acta*, 1961, **44**, 829.
[10] Spiesecke and Schneider, *J. Chem. Phys.*, 1961, **35**, 731.
[11] Corio and Dailey, *J. Amer. Chem. Soc.*, 1956, **78**, 3043.
[12] Johnson and Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.

τ 6·30 $\pm$ 0·06. In the latter case the methoxyl groups experience a high-field shift, *i.e.*, a smaller deshielding effect.

As all the available compounds with **1** or **11** methoxyl groups also have another methoxyl group in the *ortho*-position, one would for steric reasons expect the conformation, with the O–Me bond out of the plane of the aromatic rings, to be favoured. In this position the influence of both aromatic rings probably accounts jointly for the high τ-value of methoxyl groups in these positions.

One cannot expect a perfect additivity of all the effects on the τ-values, as it has been shown previously that substituent effects on aromatic protons are only additive so long as steric hindrance of the substituents can be neglected.[9] Also the ring-current effect will be influenced by the magnitude of the twist of the biphenyl system, which apparently changes with substitution pattern.[13]

However, these results, together with the recently reported correlations of optical rotation with absolute configuration [14] and of ultraviolet spectra with substitution pattern, now constitute a powerful combination of physical methods for future structural work on members of this family of alkaloids.

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[13] Shamma, *Experientia*, 1960, **16**, 484.
[14] Djerassi, Mislow, and Shamma, *Experientia*, 1962, **18**, 53.