The Proton Magnetic Resonance Spectra of Protoberberinium Salts †

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The ^{1}H n.m.r. spectra of a number of synthetic and naturally occurring protoberberinium salts have revealed several useful correlations between the chemical shifts of alkoxy and aromatic protons and the chemical structures of these molecules. The application of these correlations for the prediction of structures of new alkaloids of this group is discussed and the constitution of groenlandicine is revised.

STRUCTURAL correlations in the n.m.r. spectra of aporphine,[1-3] benzylisoquinoline,[3-7] and bisbenzylisoquinoline [3] alkaloids have been used extensively for structure elucidations of new members of these groups of alkaloids. MacLean and his co-workers [8,9] have recently examined the ^{1}H n.m.r. spectra of the tetrahydroprotoberberine alkaloids and found that the oxygenation pattern of ring D and the configuration of C(13)Me and H(14) can be deduced from an examination of the protons at C(8). Further, n.m.r. spectroscopy has been employed in the structure determination of the protoberberine alkaloids thalifendine (Ii) [10] and stepharanine (Ik),[11] but a detailed study of the chemical shifts of the protons of protoberberinium salts has not been undertaken. We now report our findings from a study of the n.m.r. spectra of 19 protoberberinium chlorides. The results show that n.m.r. can be used to define the substitution pattern of this class of compound.

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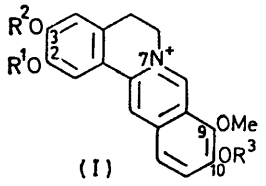
[1] S. Goodwin, J. N. Shoolery, and L. F. Johnson, *Proc. Chem. Soc.*, 1958, 306.
[2] W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *J. Chem. Soc.*, 1964, 4778.
[3] I. R. Bick, J. Harley-Mason, N. Sheppard, and M. Vernengo, *J. Chem. Soc.*, 1961, 1896.
[4] E. Brochmann-Hanssen and T. Furuya, *Planta Medica*, 1964, **12**, 328.
[5] M. Tomita, T. Shingu, K. Fujitani, and H. Furukawa, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 921.
[6] H. Furukawa, T. H. Yang, and T. J. Lin, *Yakugaku Zasshi*, 1965, **85**, 472 (*Chem. Abs.*, 1965, **63**, 5692).
[7] J. Comin and E. Sanchez, *Anales Asoc. quim. argentina*, 1966, **54**, 209.
[8] C.-Y. Chen and D. B. MacLean, *Canad. J. Chem.*, 1968, **46**, 2501.
[9] C. K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Canad. J. Chem.*, 1970, **48**, 3673.
[10] M. Shamma and B. S. Dudock, *J. Pharm. Sci.*, 1968, **57**, 262.
[11] R. W. Doskotch, M. Younas Malik, and J. L. Beal, *J. Org. Chem.*, 1967, **32**, 3253.

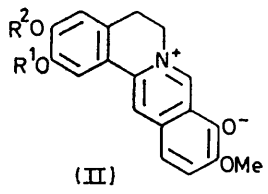
DISCUSSION

A number of synthetic protoberberinium chlorides required for the n.m.r. study were prepared as follows.



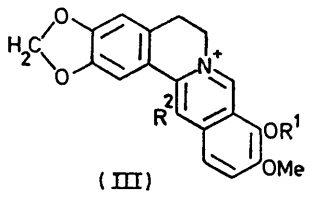
(I)

a; R^1R^2 = ·CH_2·, R^3 = Me
b; R^1R^2 = H, R^3 = Me
c; R^1 = H, R^2 = R^3 = Me
d; R^1 = R^3 = Me, R^2 = H
e; R^1 = R^2 = R^3 = Me
f; R^1 = H, R^2 = Et, R^3 = Me
g; R^1 = Et, R^2 = H, R^3 = Me
h; R^1 = R^2 = Et, R^3 = Me
i; R^1 = R^2 = Me, R^3 = Et
j; R^1R^2 = ·CH_2·, R^3 = H
k; R^1 = R^3 = H, R^2 = Me
m; R^1 = R^2 = Me, R^3 = H



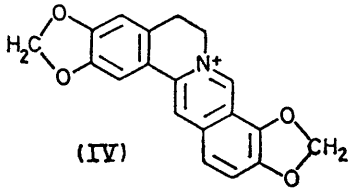
(II)

a; R^1R^2 = ·CH_2·
b; R^1 = R^2 = Me
c; R^1 = Me, R^2 = H



(III)

a; R^1 = R^2 = Me
b; R^1 = Me, R^2 = OH
c; R^1 = Me, R^2 = OMe
d; R^1 = Et, R^2 = H



(IV)

Methylation of demethyleneberberine (Ib) chloride gave a mixture of columbamine (Ic), jatrorrhizine (Id), and amine (If), 2-homojatrorrhizine (Ig), and 2,3-bishomopalmatine (Ih) chlorides. The constitutions of (If) and (Ig) were established by methylation of (If) to (Ii); this compound was identical with the ethylation product of jatrorrhizine chloride (Id).

Berberrubine (IIa), palmatrubine (IIb), and jatrorrhizrubine (IIc) were prepared from berberine (Ia), palmatine (Ie), and jatrorrhizine (Id) chlorides respectively by pyrolysis; their syntheses and properties will be discussed elsewhere.[14] Ethylation of berberrubine furnished 9-homoberberine (IIId) iodide.

Chemical Shifts of the Methylenedioxy-protons.—Seven of the compounds investigated had a methylenedioxy-group attached to C(2) and C(3) of the protoberberinium skeleton, and coptisine (19) had a second methylenedioxy group attached to C(9) and C(10). The protons of the methylenedioxy-group attached to C(2) and C(3) were observed in all the spectra as a singlet at τ 3·90 $\pm$ 0·05; its position was unaffected by changes in the substitution pattern at C(9), C(10), and C(13). However, the protons of the methylenedioxy-group attached to C(9) and C(10) in coptisine are deshielded and are observed downfield of the protons of the C(2),C(3)-methylenedioxy-group at τ 3·56. This difference in chemical shifts of the two sets of protons may prove useful to locate methylenedioxy-groups in protoberberinium salts.

Chemical Shifts of the Methoxy-protons.—Compounds (1)—(7) have two methoxy-groups attached to C(9) and C(10), and these are observed as three proton singlets at τ 5·70 $\pm$ 0·04 and 5·82 $\pm$ 0·04. The signal at τ 5·82 was assigned to the protons of the methoxy-group at C(10), as it was observed in the spectra of compounds (1)—(15) which have a methoxy-group at C(10) but not in (16)—(18) which have a hydroxy-group at this position. The lower-field resonance was attributed to the protons of the methoxy-group at C(9) as it was present in each compound except (8)—(11) which do not have a methoxy-group at this position.

Compounds (10)—(17) have additional methoxy-groups at C(2) and/or C(3), and the protons of these

TABLE 1

N.m.r. data (τ values) of protoberberinium salts in trifluoroacetic acid

			(OCH$_2$O)		(MeO-)					Aromatic protons					
No.	Compound	Structure	C(2,3)	C(9,10)	C(2)	C(3)	C(9)	C(10)	C(13)	H(1)	H(4)	H(8)	H(11)	H(12)	H(13)
(1)	Berberine	(Ia)	3·90				5·71	5·84		2·52	3·10	0·45	1·95(d);	2·06(d) *	1·56
(2)	Demethyleneberberine	(Ib)					5·68	5·81		2·26	2·96	0·44	1·92(d);	2·02(d) *	1·53
(3)	3-Homocolumbamine	(If)					5·69	5·83		2·31	3·00	0·47	1·94(d);	2·05(d) *	1·54
(4)	2-Homojatrorrhizine	(Ig)					5·70	5·83		2·35	2·96	0·45	1·95(d);	2·06(d) *	1·53
(5)	2,3-Bishomopalmatine	(Ih)					5·71	5·85		2·33	2·95	0·41	1·91(d);	2·01(d) *	1·51
(6)	13-Methylberberine	(IIIa)	3·91				5·71	5·84		2·74	3·04	0·38	1·88		
(7)	13-Methoxyberberine	(IIIc)	3·93				5·74	5·86	6·12	1·94	3·09	0·56	1·98(d)	1·76(d) *	
(8)	Berberrubine	(IIa)	3·94					5·82		2·55	3·06	0·36	1·99(d)	2·20(d) *	1·58
(9)	9-Homoberberine	(IIId)	3·92					5·82		2·51	3·10	0·37	1·99		1·53
(10)	Palmatrubine	(IIb)			5·88	5·93		5·83		2·39	2·95	0·37	2·02(d)	2·23(d) *	1·55
(11)	Jatrorrhizrubine	(IIc)			5·91			5·86		2·41	2·93	0·37	2·00(d)	2·22(d) *	1·55
(12)	Palmatine	(Ie)			5·88	5·94	5·69	5·82		2·37	2·94	0·42	1·92(d);	2·04(d) *	1·48
(13)	3-Homopalmatine	(If)			5·91		5·72	5·88		2·39	3·00	0·42	1·95(d);	2·05(d) *	1·51
(14)	Jatrorrhizine	(Id)			5·88		5·68	5·82		2·39	2·93	0·42	1·92(d);	2·03(d) *	1·48
(15)	Columbamine	(Ic)				5·93	5·70	5·82		2·30	2·97	0·44	1·93(d);	2·04(d) *	1·53
(16)	Stepharanine	(Ik)				5·92	5·77			2·27	2·95	0·48	2·05		1·48
(17)	Dehydrocorydalmine	(Il)			5·86	5·91	5·72			2·34	2·92	0·43	2·04		1·44
(18)	Thalifendine †	(Ij)	3·85				5·72			2·48	3·05	0·45	1·95		1·48
(19)	Coptisine	(IV)	3·90	3·56						2·54	3·09	0·59	2·19		1·54

* $J_{11,12}$ = 9·0 Hz. † Data from ref. 10.

palmatine (Ie) chlorides, which was separated by chromatography.[12,13] Similarly, ethylation of demethyleneberberine chloride afforded 3-homocolumb-

[12] M. P. Cava, T. A. Reed, and J. L. Beal, *Lloydia*, 1965, **28**, 73.

[13] M. P. Cava and T. A. Reed, *J. Org. Chem.*, 1967, **32**, 1640.

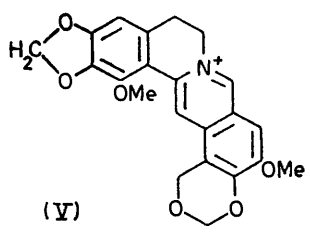
[14] K. Jewers, A. H. Manchanda, and H. M. Paisley, to be published.

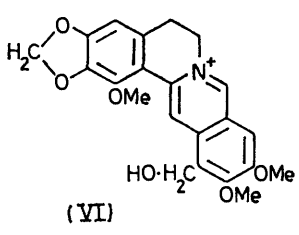
groups resonated at τ 5·88 $\pm$ 0·03 and τ 5·92 $\pm$ 0·02 respectively. The lower-field signal was assigned to the methoxy-protons at C(2), as it was absent in (15) and (16) which have a hydroxy-group at C(2), and the higher-field signal to the methoxy-protons at C(3), as it was missing from (11), (13), and (14) which lack a methoxy-group at this position. The protons of the methoxy-group attached to C(13) in (7) resonated at τ 6·12 and could readily be distinguished from the methoxy-groups at the other positions.

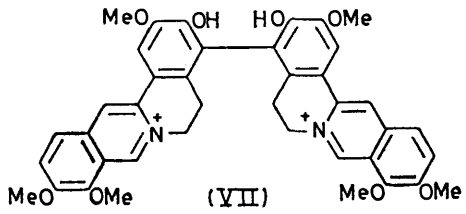
Chemical Shifts of Aromatic Protons.—Six aromatic protons, located at C(1), C(4), C(8), C(11), C(12), and C(13), are present in each compound except (6) and (7), which contain a methyl or methoxy-group at C(13). The lowest-field signal has been assigned to H(8), as it is adjacent to the quaternary nitrogen and would be expected to be considerably deshielded. Its position is affected by the substituents at C(9), C(10), and C(13); it is observed at τ 0·37 $\pm$ 0·01 in the protoberberrubines (15)—(17), at τ 0·59 in coptisine (19), and at intermediate positions between these extremes in the other compounds. The signal at τ 1·53 $\pm$ 0·05, which is observed in the spectra of the compounds containing a proton at C(13) [(1)—(5); (8)—(19)], but not in those with a methyl or methoxy-group at this position [(6), (7)], can be attributed to H(13). The chemical shift of H(1) should be affected by the substituent on C(13), and so it should be distinguishable from H(4). Thus, the signal at τ 2·52 in berberine (1), which is shifted downfield to τ 1·94 in 13-methoxyberberine (7) and upfield to τ 2·74 in 13-methylberberine (6), can be assigned to H(1), and the resonance at τ 3·10 in the spectrum of berberine, which is unaffected by substitution at C(13), can be attributed to H(4).

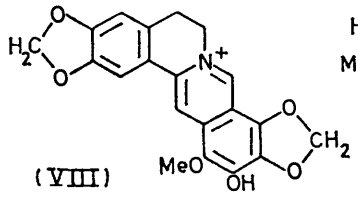
H(11) and H(12) have similar chemical shifts in most of the compounds examined and are observed as a 2-proton singlet or a poorly resolved AB quartet. The position of the signal is not constant and has been observed at τ 1·88 in 13-methylberberine (6), τ 2·19 in coptisine (19), and at *ca.* τ 2·00 in most of the other compounds examined. The chemical shifts of H(11) and H(12) are different, however, in 13-methoxyberberine (7) and the protoberberrubines (8), (10), and (11). Deshielding of H(12) by the 13-methoxy-group in (7) results in a downfield shift of this proton to τ 1·76 with the resulting effect that H(11) and H(12) are observed as a clearly resolved AB quartet. In the protoberberrubines (8), (10), and (11), H(12) is shielded by an inductive effect produced by C(9)–O^- and the greater electron density in ring D, and is observed as a doublet at τ 2·22 $\pm$ 0·02.

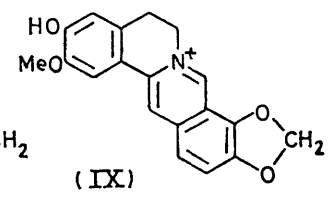
Conclusions.—The study has shown that useful correlations exist between the chemical shifts of alkoxy and aromatic protons and the structures of protoberberinium chlorides, and these have been used to assign structures to the new alkaloids (V),[15] (VI),[15] and (VII).[16] The results also suggest that the structure (VIII) given to alkaloid B isolated[17] from *Coptis groenlandica* is incorrect. The published chemical shifts











for the protons of this molecule, shown in Table 2, are inconsistent with (VIII); the presence of two sets of methylenedioxy-protons in the molecule cannot be inferred from the n.m.r. data. Undoubtedly the molecule

TABLE 2

Chemical shifts of groenlandicine (X) [16] (all resonances are singlets)

Proton	H(1)	H(4)	H(8)	H(11)(12)	H(13)	OMe	·OCH_2O·
τ-Value	2·31	2·84	0·00	2·08	1·34	5·84	3·48
Number of protons	1	1	1	2	1	3	2

contains one methoxy- and one methylenedioxy-group, and six aromatic protons, and the data in Table 1 suggest that (IX) is the most likely structure for the molecule. The reported chemical shifts of a number of the low-field protons of this molecule deviate from our results and we have been unable to obtain a sample to check these values. Structure (IX) is also consistent with the published u.v. data; the bathochromic shift produced by the addition of sodium hydrogen carbonate to a dilute solution of the alkaloid in ethanol is characteristic of a protoberberinium salt with a hydroxy-group at C(3).[12] We suggest that this new alkaloid be assigned the trivial name groenlandicine.

EXPERIMENTAL

N.m.r. spectra were taken for solutions in trifluoroacetic acid (*c*, 1—2%) with tetramethylsilane as internal standard

[15] V. Preininger, L. Hruban, V. Simanek, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1970, **35**, 124.

[16] Mrs M. Leal Carvalhas, *J.C.S. Perkin I*, 1972, 327.

[17] S. F. Cooper, J. A. Mockle, and J. Beliveau, *Planta Medica*, 1970, **19**, 23.

within 10 h of their preparation on a Varian HA100 n.m.r. spectrometer. M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Aluminium oxide refers to Woelm acid Alumina, Activity I. Protoberberinium iodides were converted into the corresponding chlorides by passage through a column of Amberlite resin 401 (Cl^- form).

Alkylation of Demethyleneberberine Chloride (Ib).[13]—Dialkyl sulphate (10 ml), saturated aqueous sodium hydrogen carbonate (50 ml), and demethyleneberberine chloride (2·4 g) in water (500 ml) were stirred for 16 h at 40—50 °C. Further quantities of alkyl sulphate and sodium hydrogen carbonate were added during this period to ensure that the pH of the solution remained greater than 7. The solution was concentrated to one-third of its original volume, acidified with concentrated hydrochloric acid to pH 2, heated to near its b.p., and a hot solution of potassium iodide (60 g) in water (100 ml) added. After being cooled, the precipitated quaternary iodides were filtered off, washed with water, dissolved in aqueous acetone (1 : 1) and converted into the corresponding chlorides. The resulting quaternary chlorides (1·8 g) were chromatographed on aluminium oxide (160 g) with chloroform and mixtures of chloroform and methanol as eluants. With dimethyl sulphate as alkylating agent, palmatine chloride (Ie; 17·3%), columbamine chloride (Ic; 29·6%), and jatrorrhizine chloride (Id; 11·1%) were obtained. Diethyl sulphate afforded 2,3-*bishomopalmatine chloride* (Ih; 22%), which crystallized from water as yellow needles, m.p. 210 °C (Found: C, 65·15; H, 5·3; N, 3·15. $C_{23}H_{26}ClNO_4,0{\cdot}5H_2O$ requires C, 65·0; H, 6·4; N, 3·3%); 3-*homocolumbamine chloride* (If; 35·7%), which crystallized from water as yellow needles, m.p. 154—155 °C (decomp.) (Found: C, 63·75; H, 6·0; N, 3·55. $C_{21}H_{22}ClNO_4,0{\cdot}5H_2O$ requires C, 63·55; H, 5·85; N, 3·55%); and 2-*homojatrorrhizine chloride* (Ig; 14·3%), which crystallized from water as yellow needles, m.p. 195—196 °C (Found: C, 63·85; H, 6·0; N, 3·6%).

Conversion of 3-Homocolumbamine Chloride (If) *into 3-Homopalmatine Iodide* (Ii).—3-Homocolumbamine chloride (If; 108 mg), methyl iodide (2 ml), acetone (10 ml), and fused potassium carbonate (2 g) were refluxed for 6 h. The solid was filtered off, the filtrate evaporated to dryness, and the residue crystallized from ethanol. This afforded 3-*homopalmatine iodide* (Ii; 96 mg) as yellow needles, m.p. 251 °C (Found: C, 53·6; H, 4·85; N, 2·9. $C_{22}H_{24}INO_4$ requires C, 53·55; H, 4·85; N, 2·85%).

Ethylation of Jatrorrhizine Chloride.—Jatrorrhizine chloride (50 mg), ethyl iodide (2 ml), acetone (10 ml), and fused potassium carbonate (2 g) were refluxed for 6 h. The solid was filtered off, the filtrate evaporated to dryness, and the 3-homopalmatine iodide (Ii) crystallized from ethanol to give yellow needles, m.p. 251 °C, identical (m.m.p., i.r., n.m.r.) with the product obtained from 3-homocolumbamine chloride.

Preparation of 9-Homoberberine Iodide (IIId).—Berberrubine (0·25 g), ethyl iodide (2 ml), and acetone (10 ml) were refluxed for 8 h. Removal of the solvent afforded 9-*homoberberine iodide* (IIId; 0·24 g), which crystallized from aqueous ethanol as yellow needles, m.p. 240—244 °C (decomp.) (Found: C, 51·2; H, 4·35; N, 2·9. $C_{21}H_{20}INO_4,1{\cdot}5H_2O$ requires C, 51·0; H, 4·7; N, 2·85%).

We thank Professors Doskotch and Slavik for samples of stepharanine, dehydrocorydalmine, and coptisine chlorides.

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