357. *The Alkaloids of the Amaryllidaceae. Part XII.*[1] *The Aromatic Oxygenation Patterns and Stereochemistry of Some Trioxyaryl Alkaloids of the Hemiacetal and Lactone Series*[2]

By W. A. Hawksworth, P. W. Jeffs, B. K. Tidd, and (in part) T. P. Toube

The structures and stereochemistry of krigeine (IV; R = OH, R′ = H, R″ = OH) and albomaculine (V; R = R′ = O) and their related alkaloids are elucidated from considerations of proton magnetic resonance (p.m.r.) spectra. Rates of quaternization support the aromatic oxygenation patterns assigned from p.m.r. spectra. Conformations of these alkaloids are discussed.

Amaryllidaceae alkaloids of the hemiacetal–lactone group, in common with other alkaloids of this family, have either two or three aryl-oxygen substituents. The chemistry of the dioxygenated members of this series—lycorenine (I; R = OH, R′ = H), homolycorine (I; R = R′ = O), and hippeastrine (II; R = OH)—has been extensively investigated and their complete stereostructures conclusively established by Uyeo and his coworkers.[3] Independent evidence[4] supporting the stereostructure of lycorenine has been provided.

The known trioxyaryl analogues are of rarer occurrence and as a consequence they have been, in general, the subject of only cursory chemical examination. However, these preliminary investigations, though obviously lacking rigour, have led to assignments of gross structures to a number of alkaloids.[5]

Our initial interest in these trioxyaryl alkaloids was to define, unambiguously, the orientation of the aromatic oxygen functions. A consideration of ultraviolet spectral data of alkaloids of the 5,10b-ethanophenanthridine series (III) led Warnhoff and Wildman[6] to assign the *ar*-methoxyl in the methoxymethylenedioxyphenyl group to the C_{10}-position. A logical extension was made on similar evidence to the hemi-acetal-lactone group in reassigning the position of the aromatic methoxyl to the C_{11}-position * in krigeine (IV; R = OH, R′ = H, R″ = OH) and its related lactone, neronine (IV; R = R′ = O, R″ = OH). The recent location[8] of the *ar*-methoxy at C_7 in powelline and related alkaloids of series (III) indicated the ultraviolet spectral arguments to be fallacious, and therefore assignments in the hemi-acetal-lactone set must be considered invalid.

In the present Paper[9] we discuss the elucidation of the aromatic oxygenation patterns

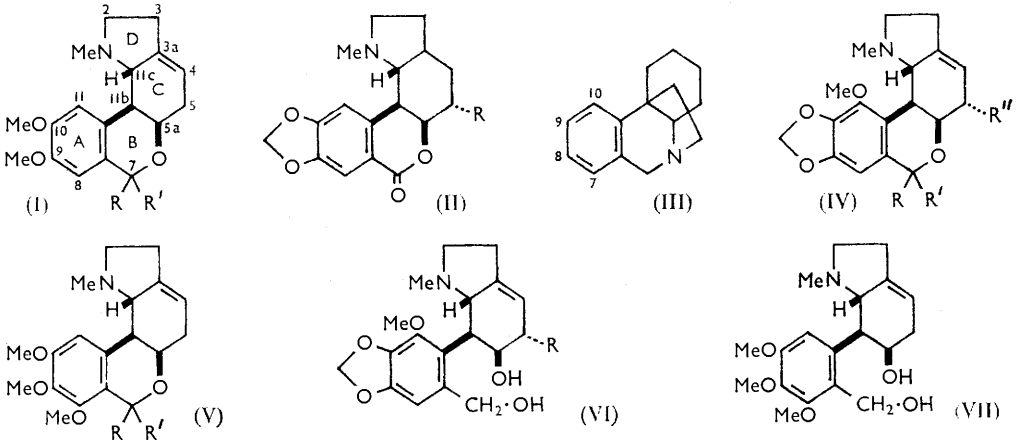
* Similar arguments were later used by Jeffs and Warren in a preliminary publication[7] in placing a C_{11}-methoxyl in krigenamine.

[1] Part XI, Garbutt, Jeffs, and Warren, *J.*, 1962, 5010.
[2] Contribution No. 1175, Department of Chemistry, Indiana University.
[3] Kitagawa, Uyeo, and Yokoyama, *J.*, 1954, 3741.
[4] Mizukami, *Tetrahedron*, 1960, **11**, 89.
[5] Briggs, Highet, Highet, and Wildman, *J. Amer. Chem. Soc.*, 1956, **78**, 2899.
[6] Warnhoff and Wildman, *J. Amer. Chem. Soc.*, 1960, **82**, 1472.
[7] Jeffs and Warren, *Chem. and Ind.*, 1961, 468.
[8] Lloyd, Kielar, Highet, Uyeo, Fales, and Wildman, *J. Org. Chem.*, 1962, **27**, 142.
[9] Some of the results were presented in a preliminary Note, Hawksworth and Jeffs, *Tetrahedron Letters*, 1963, **4**, 217.

and stereochemistry of the alkaloids[10] krigeine (IV; R = OH, R′ = H, R″ = OH), neronine (IV; R = R′ = O, R″ = OH), nerinine (V; R = OH, R′ = H), and albomaculine (V; R = R′ = O).

Kinetic Data.—The stereochemical modification of the benzopyrrolo[3,4-*g*]indole skeleton (cf. I), on which the dioxygenated members (I; R = OH, R′ = H) and (I; R = R′ = O) and the trioxyaryl alkaloid krigenamine (IV; R = OH, R′ = H, R″ = H) are elaborated, places a C_{11}-substituent close to the nitrogen atom. Thus, it was expected that the rates of methylation of the nitrogen atom in this system would be dependent on the size of the group occupying the C_{11}-position, the replacement of hydrogen by methoxyl being reflected in a decrease in rate of reaction.

An intercomparison of rates of methylation of the set, hemiacetal, lactone, and cyclic ether, was made for the C_{11}-methoxy-compounds from krigenamine, viz., (IV; R = OH, R′ = R″ = H), (IV; R = R′ = O, R″ = H), (IV; R = R′ = R″ = H), with the analogous 9,10-dimethoxy-alkaloids, lycorenine (I; R = OH, R′ = H), homolycorine (I; R = R′ = O), and deoxylycorenine (I; R = R′ = H). The krigenamine series showed significantly slower rates than those of the analogous compounds derived from lycorenine. This suggested that this method could be used as a diagnostic test for the presence of a C_{11}-methoxyl in this class of Amaryllidaceae alkaloid.



This study was extended to parallel compounds derived from krigeine, namely (IV; R = OH, R′ = H, R″ = OH), (IV; R = R′ = O, R″ = OH), and (IV; R = R′ = H, R″ = OH), and from albomaculine, viz. (V; R = R′ = O) and (V; R = R′ = H); the results are presented in Table 1.

TABLE 1

Rates of methiodide formation ($10^4 \times k$ sec.$^{-1}$)

Hemiacetals		**Lactones**	
(I; R = OH, R′ = H)	11·4	(I; R = R′ = O)	7·2
(IV; R = OH, R′ = H, R″ = H)	3·5	(IV; R = R′ = O, R″ = H)	3·0
(IV; R = OH, R′ = H, R″ = OH)	3·7	(IV; R = R′ = O, R″ = OH)	2·3
		(V; R = R′ = O)	7·5
Cyclic ethers			
(I; R = R′ = H)	10·8	**B-Seco-compounds**	
(IV; R = R′ = R″ = H)	3·6	(VI; R = H)	11·4
(IV; R = R′ = H, R″ = OH)	2·8	(VI; R = OH)	9·7
(V; R = R′ = H)	10·4	(VII)	10·2

[10] For a summary of the chemistry of these alkaloids see Wildman, " The Alkaloids," ed. Manske, Academic Press, Inc., New York, 1960, Vol. VI.

These results show that bases related to krigeine have rates of methylation which compare closely with those of the krigenamine analogues. In contrast, albomaculine (V; R = R′ = O) and its related cyclic ether (V; R = R′ = H) show faster rates of methylation which correspond well with homolycorine (I; R = R′ = O) and deoxylycorenine (I; R = R′ = H), respectively.

Somewhat unexpectedly the lactones showed slower rates of methylation than their related hemiacetals and cyclic ethers. Since the reason for the slower rates cannot be steric in origin we suggest it is due to a decrease of nucleophilic character in the nitrogen atom caused by the inductive effect on the lactone carbonyl which is transmitted through the aromatic ring.

The rate of methiodide formation in the ring B-*seco*-compounds (VI; R = H), (VI; R = OH), and (VII), obtained by lithium aluminium hydride reduction of the corresponding lactones, showed rates for the C_{11}-methoxy systems significantly greater than those for the parent hemiacetals or lactones (see Table 1). This is in accord with the view that these compounds will exist in a conformation such as to make the nitrogen more accessible.*

The above rates constitute reasonable evidence for placing the aromatic methoxy-group at the C_{11}-position in krigeine and neronine, which, in conjunction with the previous infrared spectral evidence for the presence of three vicinal aryl oxygen substituents in these alkaloids, identifies them with krigenamine as having a 9,10,11-trioxyaryl oxygenation pattern. Furthermore, the kinetic data indicate that albomaculine, and hence also the related hemiacetal, nerinine (V; R′ = OH, R′ = H), possess the alternative 8,9,10-aromatic oxygenation pattern. These assignments, however, may only be valid if all alkaloids studied are elaborated from the same stereochemical modification of the basic ring system.

We now describe evidence obtained from p.m.r. spectra which fully substantiates the above assignments of aromatic oxygenation patterns and also leads to an elucidation of the stereochemistry of the title alkaloids.

Proton Magnetic Resonance Studies.—(a) *Aromatic oxygenation patterns.* Aryl hydrogens situated *peri* to a carbonyl group are abnormally magnetically deshielded in comparison to other aromatic hydrogens. Consistent with this is the observation that the signals attributed to the aromatic hydrogens at positions C_8 and C_{11} in the p.m.r. spectrum of homolycorine (II; R = R′ = O) occur at quite different frequencies (τ 2·38 and 2·99). The low-field signal is therefore assigned the C_8-hydrogen resonance in view of the relationship of this hydrogen to the lactone carbonyl. The difference in frequency of these two signals illustrates well the effective deshielding of the C_8-hydrogen in comparison to that of the more remote C_{11}-hydrogen. The signal of the lone aromatic proton on C_8 in the p.m.r. spectrum of dehydrokrigenamine (IV; R = R′ = O, R″ = H) occurred at τ 2·66. The diamagnetic shift of this proton in comparison with the C_8-proton in the lactone (I; R = R′ = O) results from the presence of an additional aromatic oxygen function.[11]

Examination of the p.m.r. spectra of the lactones neronine (IV; R = R′ = O, R″ = OH) and albomaculine (V; R = R′ = O) revealed a considerable difference in chemical shift of the single aromatic proton in these compounds, which were located at τ 2·70 and 3·14, respectively. The low-field resonance of the aryl proton in (IV; R = R′ = O, R″ = OH) implies its location at C_8. This is supported by (i) its close correspondence in chemical shift to the C_8-hydrogen in the lactone (IV; R = R′ = O, R″ = H); (ii) the location of the signal of this hydrogen at much higher field (τ 3·72) in its derived cyclic ether (IV; R = R′ = H, R″ = OH).

* Examination of models reveals that unrestricted rotation around the Ar–C_{11b} bond is unlikely in these compounds. However, the absence of ring B results in greater flexibility about the Ar–C_{11b} bond and permits these bases to adopt the conformation(s) in which the non-bonded interactions of the *N*-methyl group, which are present in the parent alkaloids, to be relieved by appropriate changes in the ring A–ring C interplanar angle.

[11] Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, 1959, p. 63.

TABLE 2

	4	5	5a	7	8	11	11b	11c	*N*-Me	*O*-Me	O-CH_2-O	OAc
I; R = OH, R′ = H	4·56m		5·61m	4·00s	3·14s	2·99s	6·68—7·00m		7·91s	6·12s		
IV; R = OH, R′ = R″ = H	4·56m		5·84m	4·04s	3·40s				7·93s	5·97s	4·10s	
I; R = R′ = O	4·47m		5·16m		2·38s	2·99s	6·90d.d ($J_{11b,8a}$ = 2·5, $J_{11b,11c}$ = 10·0 c./sec.)	*ca.* 7·48o	7·99s	6·01s		
V; R = R′ = O	4·47m		5·30m			3·14s	6·88d.d ($J_{11b,8a}$ = 2·0, $J_{11b,11c}$ = 10·0 c./sec.)	*ca.* 7·48o	7·93s	6·08s 6·04s 5·97s		
IV; R = R′ = O, R″ = H	4·49m		5·33m		2·66s		6·88d.d ($J_{11b,8a}$ = 2·0, $J_{11b,11c}$ = 9·6 c./sec.)	7·48b, d ($J_{11c,11b}$ = 9·6 c./sec.)	7·95s	5·87s	3·90s	
IV; R = R′ = O, R″ = OH	4·29m	5·63m	5·45u, q		2·70s		6·65d.d ($J_{11b,8a}$ = 2·0, $J_{11b,11c}$ = 9·8 c./sec.)	7·47b, d ($J_{11c,11b}$ = 9·6 c./sec.)	7·95s	5·91s	3·90s	
IV; R = R′ = O R″ = OAc	4·42m	4·60m	5·57q ($J_{8a,5}$ = 3·3, $J_{8a,11b}$ = 1·8 c./sec.)		2·78s		6·72d.d ($J_{11b,8a}$ = 2·5, $J_{11b,11c}$ = 10·0 c./sec.)	7·48b, d ($J_{11c,11b}$ = 10·0 c./sec.)	7·97s	5·85s	3·94s	7·14
IV; R = R′ = O, R″ = O	4·53m		5·37m		2·78s		6·91d.d ($J_{11b,8a}$ = 2·0. $J_{11b,11c}$ = 9·6 c./sec.)	7·53d ($J_{11c,11b}$ = 9·6 c./sec.)	7·98s	5·91s	3·96s	
α-Dihydroneronine		*ca.* 5·90o	5·36u, q		2·76s				7·68s	5·94s	3·97s	
I; R = R′ = R″ = H	4·55m		6·10o	5·05d, 5·12d (J = 15·0 c./sec.)	3·47s	3·07s			7·90s	6·11s 6·13s		
V; R = R′ = R″ = H	4·50m		6·10o	5·00d, 5·13d (J = 17·5 c./sec.)		3·18s			7·97s	6·10s 6·08s		
IV; R = R′ = R″ = H	4·53m		6·18m	5·03d, 5·18d (J = 16·0 c./sec.)	3·70s				7·99s	5·92s	4·05s	
IV; R = R′ = H, R″ = OH	4·33m	5·83m	6·29u, q	5·08o, d, 5·10o, d (J = 15·5 c./sec.)	3·72s				7·90s	5·99s	4·09s	
IV; R = R′ = H, R″ = OAc	4·45m	4·72m	6·35u, q	5·10o, d, 5·12o, d (J = 15·5 c./sec.)	3·78s				7·97s	5·90s	4·09s	7·90s
α-Deoxydihydrolycorenine [3]			6·15c	5·22b, s	3·52s	2·90s	Remarks		7·79s	6·15s 6·12s		
β-Deoxydihydrolycorenine [3]			6·10o	5·14b, s	3·52s	3·05s	These spectra were measured in a microcell for 1—6 mg. which resulted in a loss in quality as compared to the standard spectra. This made the task of assigning multiplicities and coupling constants to one proton signals other than singlets impossible		8·00s	6·18s 6·12s		
α-Deoxydihydrokrigenamine *			6·25m	5·18o, d, 5·24o, d (J = 16·0 c./sec.)	3·79s				7·85s	6·02s		
β-Deoxydihydrokrigenamine *				5·20b, s	3·82s				8·00s	5·95s	4·13s	
α-Deoxydihydronerinine				5·18s, 5·25s		3·10s			7·80s	6·11s 6·16s		
β-Deoxydihydronerinine						3·26s			8·00s	6·15s 6·23s 6·28s		
α-Dihydrohomelycorine [3]			5·28m		2·43s	3·00s			7·84s	6·03s 6·06s		
β-Dihydrohomolycorine [3]			5·24m		2·46s	2·92s			8·08s	6·04s 6·06s		
Albomaculine methiodide	4·00m		5·08m			2·92s	Measured in D_2O. HDO signal 5·38		6·86s 7·08s	6·16s 6·10s		
Neronine methiodide	3·90o		5·25m			2·86s	Measured in D_2O. HDO signal 5·39		6·84s 7·08s	6·00s 5·83s	3·85d, 3·90d (J = 2·0 c./sec.)	
N-Methylpyrrolidine *N*-Methylpyrrolidine methiodide							Measured in D_2O. HDO signal 5·39		7·64s 6·82s			

Abbreviations: s, singlet; d, doublet; d.d, doublet of doublets; q, quartet; m, multiplet; b, broad; u, unresolved; o, overlapping.
Chemical shift values are reported on the τ-scale and are estimated to be within 0·02. Coupling constants are within 0·2 c./sec. and are reported from first-order considerations only.
* Formulæ (I) and (VI) in Part XI, *J.*, 1962, 5010 should be interchanged for these compounds.

In contradistinction, the assignment of the aromatic hydrogen in albomaculine to the alternative C_{11}-position is supported not only by its chemical shift (τ 3·14) but also by the close correspondence of this value with the chemical shift (τ 3·18) of the aromatic hydrogen in its derived cyclic ether (V; R = R′ = H).

The chemical shifts of the aromatic hydrogen(s) in these systems and some derivatives are collected in Table 2. These data, in conjunction with the foregoing kinetic results, constitute unequivocal evidence for a 11-methoxy-9,10-methylenedioxy substitution pattern in krigeine and neronine. Similarly, nerinine and albomaculine are now established as having the alternative vicinal 8,9,10-aryl-oxygenation pattern.

(*b*) *Stereochemistry.* The work of Mizukami,[4] and of Uyeo and his collaborators,[3] has provided firm evidence for the structures and stereochemistry of the dioxyaryl alkaloids, lycorenine, homolycorine, and hippeastrine. Using a similar approach, Garbutt, Jeffs, and Warren [1] have previously shown the trioxyaryl alkaloid, krigenamine, to be based on the same stereochemical modification of the benzopyrrolo[3,4-*g*]indole skeleton as the above-mentioned dioxyaromatic alkaloids. With these models available, a further study and analysis of the p.m.r. spectra was undertaken in an attempt to elucidate the stereochemistry of the remaining trioxyaryl alkaloids: krigeine, albomaculine, and their related bases.

Correlations of stereochemistry of hydrogen atoms at various positions of asymmetry in the model compounds [*e.g.*, I, IV (where R″ = H)], with that of those in the alkaloids under study, were made, where possible, on the basis of chemical shift values and multiplicity, and coupling constants of the various protons in the p.m.r. spectra; these results are now discussed.

The C_{5a}-hydrogen has been shown on chemical evidence to be in the α-position in lycorenine, krigenamine, and related alkaloids. These assignments are essentially corroborated by the chemical-shift values and multiplicity of the hydrogen resonance-signals in analogous compounds in each series (see Table 2 for these and all subsequent p.m.r. results). The small differences in chemical shift that exist between analogous compounds in each of these series, may, in view of the previous chemical evidence, be interpreted as being due to small changes in conformation of ring C which, therefore, affect the conformation of the C_{5a}-hydrogen. The C_{5a}-hydrogen signals in both the lactones (IV; R = R′ = O, R″ = OH) and (V; R = R′ = O) show a close correspondence with the chemical shifts of this hydrogen in the lactones (IV; R = R′ = O, R″ = H) and (I; R = R′ = O), respectively. Similar correlations of the chemical shifts of the C_{5a}-hydrogen signal are found in the cyclic ether (Table 2). Thus the results constitute strong evidence for the presence of a C_{5a}-α-hydrogen atom in all these alkaloids.

The *cis*-fusion of the B/C ring juncture and the *trans*-relationship of the hydrogens at positions C_{11b} and C_{11c} in lycorenine and krigenamine is established.[1,4] In order to investigate the stereochemistry at these centres in the krigeine and nerinine series it was necessary to identify the chemical shift of the hydrogens at these positions in both systems, and also in the lycorenine and krigenamine sets.

Without exception all compounds with 3a,4-unsaturation exhibit a two proton multiplet between τ 7·10 and 6·50 in their p.m.r. spectra which we originally assigned to the C_{11b}-hydrogen (benzylic) and the C_{11c}-hydrogen (adjacent to nitrogen and allylic).

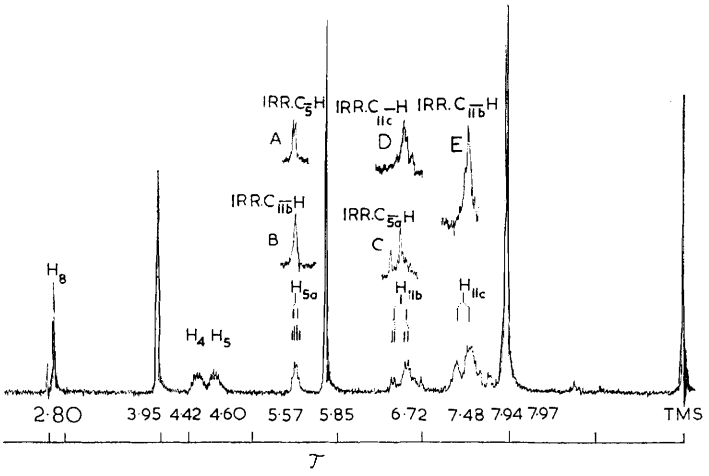
The multiplet occurring in the spectra at τ 6·50—7·10 could be divided into two groups on the basis of peak profiles: the 11-methoxy-systems (IV; R = R′ = O, R″ = H) (IV; R = R′ = O, R″ = OH, or OAc) and the 11-demethoxy-compounds (I; R = R′ = O) and (V; R = R′ = O). This multiplet is most clearly resolved in the lactones which were selected for further analysis.

From the *trans*-relation of the C_{11b}-H and the C_{11c}-H in the lactones (I; R = R′ = O), and (IV; R = R′ = O, R″ = H) a two-proton AB pattern with further coupling of A, and possibly small allylic coupling of B would have been predicted. Since analysis of the observed multiplets on this basis was not possible it became necessary to confirm the assignments. Nuclear double resonance studies were used and are now described.

The spectral region τ 6·50—710 in neronine 5-*O*-acetate was identical in appearance to that of the model lactone (IV; R = R′ = O, R″ = H). In view of this the acetate was chosen for further study since the functionality at the C_5-position provided a means of obtaining additional information.

Figure 1 shows the spectrum at 60 Mc./sec., including spin-decoupling data, of the lactone acetate (IV; R = R′ = O, R″ = OAc) and serves to illustrate the general features of the p.m.r. spectra of these alkaloids.

Assignments for hydrogens at positions C_5 and C_{5a} were confirmed by irradiating at the C_5-hydrogen resonance frequency while simultaneously observing the collapse of the signal from the C_{5a}-hydrogen to a doublet (J = 3·3 c./sec.), removing the small coupling (J = 1·8



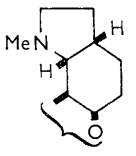
c./sec.) between these two adjacent protons (see insert A). The 3·3 c./sec. splitting of the signal from the C_{5a}-hydrogen was removed by irradiating with a side-band component of radio-frequency field 73 c./sec. to the high-field side of the C_{5a}-H signal (insert B). This result confirms the location (τ = 6·72) of the hydrogen at C_{11b}, which now becomes recognizable as a pair of doublets ($J_{5a,11b}$ = 3·3, $J_{11b,11c}$ = 10·0 c./sec.). Similarly the 3·3 c./sec. splitting in the C_{11b}-hydrogen signal is removed by irradiating at the C_{5a}-hydrogen resonance frequency (insert C). The location of the position of the resonance signal from the C_{11c}-hydrogen at the unexpectedly high field of 7·48 τ was established by observing the collapse of the large coupling in the C_{11b}-hydrogen signal while simultaneously irradiating (insert D) at a position 39 c./sec. up-field from the C_{11b}-hydrogen resonance. Likewise, irradiation of the C_{11b}-hydrogen while simultaneously observing the signal of the C_{11c}-hydrogen resulted in the removal of its 10·0 c./sec. coupling (insert E).

The large (10·0 c./sec.) coupling of the hydrogens at C_{11b}- and C_{11c}-positions is only consistent with their existing in a *trans*-diaxial relation. A similar large coupling of the C_{11b}- and C_{11c}-hydrogens is also found in the model lactone (IV; R = R′ = O, R″ = H).

Spin–spin decoupling experiments with homolycorine revealed that, despite the superficial differences in multiplicity of the two proton signals at τ 6·92—7·30, it contained a one-proton signal as a doublet of doublets ($J_{11b,5a}$ = 2·0, $J_{11b,11c}$ = 10·0 c./sec.) which is assigned unequivocally to the signal from the C_{11a}-hydrogen by appropriate decouplings. Inspection of the two-proton multiplet in albomaculine indicated that a similar assignment could be made (see Table 2) and demonstrated the *trans*-arrangement of the hydrogens at the C_{11b}- and C_{11c}-positions.

These results indicate that krigeine, neronine, nerinine, and albomaculine are elaborated on the same stereochemical modification of the benzopyrrolo[3,4-*g*]indole skeleton as that previously described [1,3,4] for lycorenine, hippeastrine, and krigenamine.

With the stereochemistry of its ring system established, the hydrogenation of neronine to a single dihydroneronine becomes relevant in assigning the stereochemistry of the C_5-hydroxyl group.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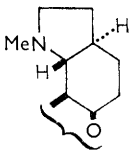
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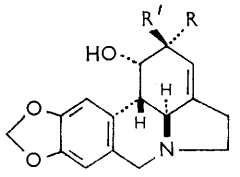
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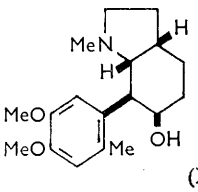
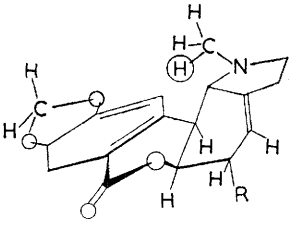

(XI)

Hydrogenation of the 3a,4 double bond in lycorenine, krigenamine, albomaculine [12] and their derivatives leads in each case to a pair of diastereomers which are epimeric at the C_{3a}-position, *e.g.*, partial structures (VIII) and (IX).

In contrast to these results, hydrogenation of the 3a,4 double bond in the 5-hydroxylactone, hippeastrine, affords a single dihydro-compound.[13] The stereochemistry of hippeastrine (II; R = OH) is conclusively established as shown and the formation of a single dihydro-derivative is most readily explicable on the grounds that the $C_5\alpha$-hydroxyl group influences the course of hydrogenation. This result is reminiscent of the hydrogenation of lycorine (X; R = H, R′ = OH), which in contrast to 2-epilycorine (X; R = OH, R′ = H),[14] also affords a single dihydrolycorine. Since a similar result has been reported recently for the lactone alkaloid, ungerine (II; R = OMe),[15] it indicates that the steric bulk of a C_5-α-hydroxyl or methoxyl in this ring system, cf. (II), is sufficient to prevent hydrogenation from the α-side. Thus, the results of hydrogenation then become a useful criterion in assigning the configuration of a C_5-oxygen function in the hemiacetal–lactone series and its extension to neronine indicates, therefore, an α-configuration of the C_5-hydroxyl in this alkaloid. Furthermore, since krigeine on lithium aluminium hydride reduction affords the same triol (VI; R = OH) as that obtained by a similar reduction of neronine, its C_5-hydroxyl group may be assigned the α-configuration.

The conformational assignments have been made for lycorenine [3] but since they involved arguments based on the extrapolation of results obtained from α-deoxodihydrolycorenine (XI), they must be considered tenuous.

Conformational analysis of the ring system present in these alkaloids is most simply considered from the conformation of ring C. Examination of models reveals that the energetically preferred system is that in which ring C adopts a "flattened" half-chair conformation as portrayed in structure (XII).

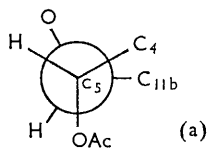


Evidence is presented from considerations of the magnitude of coupling of various vicinal hydrogen atoms, and chemical shift values of the hydrogens of the *N*-methyl group, in these alkaloids, and their derivatives, which support the contention that the predominant conformer of the benzopyrrolo[3,4-*g*]indole skeleton in these alkaloids is as represented by structure (XII).

Karplus [16] has shown that spin–spin coupling of hydrogen atoms bound to adjacent carbon atoms is a sensitive function of the dihedral angle between the carbon–hydrogen bonds. To apply the Karplus equation, or a later modification thereof, to evaluate dihedral angles is unreliable, since spin–spin coupling is also a function of the electronegativity of the substituents on carbon atoms bearing the hydrogen atoms under consideration.[17]

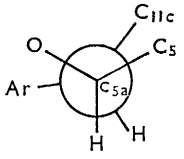
[12] Unpublished observations, Haugwitz, Jeffs, Toube, and Wenkert.
[13] Boit and Emke, *Ber.*, 1957, **90**, 57.
[14] Nakagawa and Uyeo, *J.*, 1959, 3736.
[15] Proskurnina, *Zhur. obshchei Khim.*, 1963, 35 (5), 1686.
[16] Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
[17] Williamson, *J. Amer. Chem. Soc.*, 1963, **85**, 516, and references cited therein.

Nevertheless, useful deductions from spin–spin coupling constants may still be made by intercomparisons within a series where the same substituent groups are present, *e.g.*, in the lactones described here.



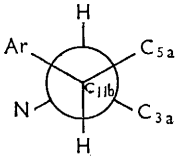
(a)

J = 1·8 c./sec.



(b)

J = 3·3 c./sec.



(c)

J = 10·0 c./sec.

(XIII)

Close correspondence of the magnitude of coupling constants of corresponding hydrogen atoms within each set support the contention that the same conformation is present in all systems, and also that this conformation is represented by structure (XII). Consideration of neronine 5-*O*-acetate (IV; R = R′ = O, R″ = OAc), is taken to illustrate this point. The small coupling ($J_{5,5a}$ = 1·8 c./sec.) is in accord with that expected for conformation (XII) in which the bond angle between the hydrogens on C_5–C_{5a} is *ca.* 100°. Two further coupling constants involving C-ring hydrogen atoms ($J_{5a,11b}$ = 3·3 c./sec. and $J_{11b,11c}$ = 10·0 c./sec.) are also in good agreement with that expected for this conformation (see Newman projections XIIIa—c).

The τ value of the *N*-methyl group in the title alkaloids is significantly greater (τ 0·27—0·35) than that of the *N*-methyl group in *N*-methylpyrrolidine. This observation is attributed to a long-range shielding of the *N*-methyl hydrogens by the aromatic ring. This is only readily accommodated in a conformation such as is represented in structure (XII), which places the hydrogens of the *N*-methyl group, when in its β-configuration (see below), over the plane of the aromatic ring.

The rate of configurational inversion of the *N*-methyl bond is undoubtedly extremely rapid in these systems,[18] and the signal observed results from an averaging of the two environments as reflected by the equilibrium ratio. The energy content of each isomer resulting from configurational inversion of the *N*-methyl group in these alkaloids will differ greatly since models reveal that with this group in the α-configuration (α is used in the usual sense) severe non-bonded interaction occurs with a C_{11}-methoxyl, and although this interaction is somewhat lessened in the 11-demethoxy-compounds it is still considerable.

The anisotropic effect of the aromatic ring at the sites of the two different space co-ordinates occupied by the *N*-methyl group during its configurational inversion was evaluated by an indirect method. On the assumption that both space co-ordinates corresponding to the α- and β-*N*-methyl positions in the tertiary bases are occupied by the two *N*-methyl groups in their methiodide salts,* a comparison of the chemical shifts of the hydrogens in these latter groups were made with those in a suitable model, *N*-methylpyrrolidine methiodide. This gave a direct measure of the magnitude of the anisotropic effect of the aromatic ring at both positions. The results obtained with the methiodides of the lactones (IV; R = R′ = O, R″ = OH) and (V; R = R′ = O), indicate that the hydrogens of a β-*N*-methyl group are subject to diamagnetic shielding (τ 0·26), while those in an *N*-methyl group in an α-configuration are essentially unperturbed from their normal resonant position in these salts.

Of the compounds containing a methylenedioxy-group that were examined, only the

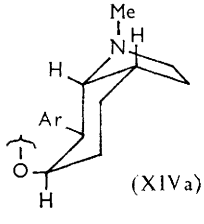
* The positive charge on the nitrogen would be expected to result in some shortening of the N–C bond length, and although this does not affect the qualitative aspect of the argument, a quantitative estimate is obviously not obtained from these data, as evidenced by the different shielding values of the *N*-methyl hydrogens in the alkaloids (τ 0·27—0·35) when compared with the β-*N*-methyl hydrogens in the two salts studied (τ 0·21).

[18] Bottini and Roberts, *J. Amer. Chem. Soc.*, 1958, **80**, 5203.

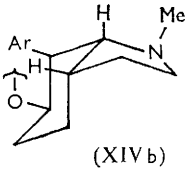
methiodide of the lactone (IV; R = R′ = O, R″ = OH) failed to show the signal assigned to the two protons of this group as a singlet. In this methiodide however, the signal from the hydrogens of the methylenedioxy-group appeared as a pair of doublets of very similar chemical shift. The magnetic non-equivalence of the hydrogens in the methiodide provides yet further evidence for structure (XII) as the predominant conformer since, on the basis of this structure, this non-equivalence can be readily rationalized as being a consequence of a field effect exerted by the positively charged nitroge atom, which would be predicted to deshield the β-hydrogen of the methylenedioxy-group, while the more remote α-proton of this group would remain unaffected.

Early in our work, we sought to eliminate the possibility that the 3a,4 double bond was the cause of the anomalous chemical shift of the *N*-methyl hydrogens, by examining the p.m.r. spectra of a number of 3a,4-dihydro-compounds (Table 2). In the α-dihydro-series, which contains a *cis*-perhydroindole system, these signals were located at positions considered to be normal, or unperturbed. In contrast, the signals from the *N*-methyl group hydrogens in the β-dihydro-series occurred at chemical shifts corresponding well with the anomalous values found for this group in the parent systems.

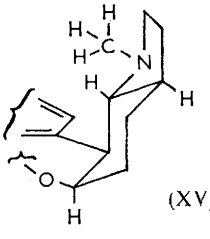
On the assumption that the α- and β-dihydro-systems are represented by conformations (XIVa) and (XV), respectively, then inspection of models reveals that the *N*-methyl group, irrespective of its configuration, in the α-isomer is not situated above the plane of the aromatic ring. Although the *cis*-perhydroindole system is very flexible, the conformational change associated with the alternative ring C chair-form in the α-dihydro-series (partial structure XIVb) would result in systems of higher energy content which might be expected to show profound changes in the p.m.r. spectra. Since such changes are not observed further consideration of this structure can be neglected.



(XIVa)



(XIVb)



(XV)

The situation in the β-dihydro-isomer, with regard to the geometrical relationship of a β-*N*-methyl group and the aromatic ring, is very similar to that in the parent systems.

Thus, the divergent chemical shifts of the signal from the *N*-methyl hydrogens in these structures can be rationalized on the basis of conformations (XIVa) and (XV), for the α- and β-dihydro-series, respectively, in which long-range shielding from the aromatic ring is only effective in structure (XV).

Assignments of stereochemistry at the C_{3a}-position in the α- and β-dihydro-series have previously been made on the basis of a comparison of molecular rational differences with models in the lycorenine series. For this method to be reliable both C_{3a}-epimers are required. Since in certain cases, however, only one dihydro-isomer is available, as in the 5α-oxygenated systems, or in the naturally occurring " dihydro "-alkaloid, clivonine (probably β-dihydro-II; R = OH), the p.m.r. method alone is reliable for establishing the stereochemistry in these systems. In this connection the suggestion made for the direction of hydrogenation in the 5α-oxygenated systems is corroborated by the chemical shift of the *N*-methyl group, in assigning dihydroneronine to the α-dihydro-series.

Absolute Configuration.—The absolute configurations of lycorenine and homolycorine has been deduced by Uyeo and his co-workers [2] from a consideration of Klyne's extension of Hudson's lactone rule, and are represented in structures (I; R = OH, R′ = H) and (I; R = R′ = O), respectively. These assignments are corroborated by the interconversions of lycorenine derivatives with alkaloids of the pyrrolo[*de*]phenanthridine ring

system (cf. X) which themselves have been correlated with lycorine (X; R = H, R′ = OH) whose absolute configuration rests on the application of Mills's rule.

The molecular-rotational differences (ΔM_D) of the various alkaloids presented in Table 3

TABLE 3

Molecular rotations of hemiacetal alkaloids and their related lactones

	M_D		M_D	ΔM_D
Lycorenine	+570°	Homolycorine	+368°	+202°
Krigenamine	+695°	Dehydrokrigenamine	+385°	+310°
Nerinine	+538°	Albomaculine	+245°	+293°
Krigeine	+813°	Neronine	+559°	+254°

indicate that krigeine, neronine, krigenamine, nerinine, and albomaculine are based on the same absolute configuration of the benzopyrrolo[3,4-*g*]indole skeleton as lycorenine and homolycorine. Thus structures in this Paper represent the absolute as well as relative configurations.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded on Varian A60 and DP60 spectrometers operating at 60 Mc./sec. for deuterochloroform solutions containing tetramethylsilane as an internal standard. Optical rotations were recorded for chloroform solutions. Compounds mentioned but not described below have been discussed previously in the literature and were purified until their physical constants agreed with those reported.

Kinetic Measurements.—The kinetics of methiodide formation were studied by following the conductivity of the solution as a measure of the amount of salt formed. The apparatus was the same as that described by Shamma and co-workers.[19]

A solution of the alkaloid (10 mg.) in acetonitrile (A. R. grade) (10 ml.) was introduced in the conductivity cell, which was maintained at 25° ± 0·03° in a constant-temperature bath. Nitrogen was bubbled through the solution. Methyl iodide (1 ml.) was added and resistance readings were taken at appropriate time intervals until the reaction had reached completion, as evidenced by hardly any change in resistance.

The large excess of methyl iodide used ensured that the second-order reaction would follow pseudo-first-order kinetics. Calculations from the rate expression,

$$-\ln (1/R_\infty - 1/R_t) = kt - \ln 1/R_\infty$$

where R_∞ is the resistance at the end of the reaction and R_t is the resistance at time t, afforded the pseudo-first-order rate constants, k.

Triol (VI; R = OH).—Krigeine (50 mg.) in tetrahydrofuran (50 ml.) was refluxed with lithium aluminium hydride (50 mg.) for 24 hr. The excess hydride was decomposed with water and, after filtering, the filtrate was extracted with chloroform containing 10% ethanol (3 × 20 ml.). Recovery of the product from the chloroform afforded a solid (43 mg.) which after several crystallizations from ethyl acetate gave the *triol* (VI; R = OH), m. p. 178—179°, identical (mixed m. p., infrared spectrum) with the triol obtained by the lithium aluminium hydride reduction of neronine.

Deoxykrigeine (IV; R = R′ = H, R″ = OH).—A solution of the triol (VI; R = OH) (287 mg.) in 5% sulphuric acid (15 ml.) was heated on a water-bath for 2 hr. After making the solution basic with 2N-ammonium hydroxide, extraction with chloroform followed by removal of the solvent afforded a gum (260 mg.) which crystallised from ethyl acetate to give the pure ether (IV; R = R′ = H, R″ = OH), as prisms, m. p. 171—172°, [α] +196°, $\lambda_{max.}$ (MeOH) 280—286 mμ (ε, 1320) (Found: C, 64·6; H, 6·4. $C_{18}H_{21}NO_5$ requires C, 64·2; H, 6·4%).

Deoxykrigeine 5-O-Acetate (IV; R = R′ = H, R″ = OAc).—Acetylation of deoxykrigeine (IV; R = R′ = H, R″ = OH) (85 mg.) in pyridine with acetic anhydride afforded a gum which after chromatography in benzene over alumina gave a solid (68 mg.). Two crystallizations of this solid from methanol gave the pure *acetate* (IV; R = R′ = H, R″ = OAc), m. p. 152—153° (Found: C, 64·2; H, 6·1. $C_{20}H_{23}NO_6$ requires C, 64·5; H, 6·0%).

[19] Moss and Shamma, *J. Amer. Chem. Soc.*, 1961, **83**, 5038.

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