Tetrahedron Letters No. 4, pp. 217-223, 1963. Pergamon Press Ltd.
Printed in Great Britain.

AROMATIC OXYGENATION PATTERNS OF SOME TRIOXYL-ARYL AMARYLLIDACEAE ALKALOIDS BELONGING TO THE HEMI-ACETAL AND LACTONE GROUP

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(Received 26 October 1962)

ALTHOUGH structures have been proposed[1] for the alkaloids which are the subject of this paper, with the exception of krigenamine (I; R = OH, R' = H),[2] no direct evidence has been presented for the aromatic oxygenation pattern

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1a C. K. Briggs, P. F. Highet, R. J. Highet and W. C. Wildman, J. Amer. Chem. Soc. 78, 2899, (1956).

b H. G. Boit and H. Emke, Chem. Ber.. 90, 57, (1957).

c P. W. Jeffs and F. L. Warren, Chem.and Ind. 468, (1961).

2 Krigenamine has been converted to falcatine methiodide which in view of the recent unambiguous synthesis of a falcatine degradation product,[3] identifies it as having a 9,10,11-aryl oxygenation pattern. D. F. C. Garbutt, P. W. Jeffs and F. L. Warren, J. Chem. Soc. (in press 1962).

3 K. Torsell, Acta Chem. Scand. 15, 94F(1961).

in these bases. A previous argument,[4] based on ultraviolet spectral data, favouring a 9,10,11-substitution was later shown[5] to be fallacious in Amaryllidaceae alkaloids of the 5,10b-ethanophenanthridine series and therefore similar assignments[1c,4] made for alkaloids of the hemi-acetal—lactone group must be considered invalid.

Evidence now obtained from NMR and kinetic experiments is presented which defines unequivocally the aromatic oxygenation patterns in the known[6] trioxyaryl alkaloids of the hemi-acetal—lactone group. In conjunction with previous evidence[7] full structures may be assigned to krigeine (II; R = H, R' = OH) neronine (II; R = R' = O), nerinine (III; R = H, R' = OH) and albomaculine (III; R=R'=O).

Inspection of models in this series (cf, stereostructure V) reveal that one side of the nitrogen atom is sterically hindered by a C_{11}-substituent. In view of this the rate of formation of methiodides for these alkaloids would be expected to be faster in bases unsubstituted in this position than

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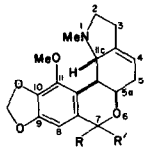
[4] E. Warnhoff and W. C. Wildman, J. Amer. Chem. Soc. 82, 1472, (1960).

[5a] H. A. Lloyd, E. A. Kielar, R. J. Highet, S. Uyeo, H. M. Fales and W. C. Wildman, Tetrahedron Letters 105, (1961).

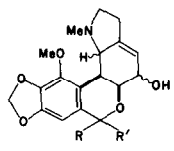
[b] H. A. Lloyd, E. A. Kielar, R. J. Highet, S. Uyeo, H. M. Fales and W. C. Wildman, J. Org. Chem. 27, 373, (1962).

[6] The alkaloids urceoline, urminine and nerine were not available to us but assignment of the aromatic oxygen functions was possible in the case of nerinine in view of its demonstrated relation to albomaculine.

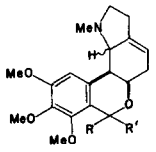
[7] For a summary of this work see W. C. Wildman, The Alkaloids, Vol. VI, R. H. F. Manske, ed., Academic Press, N.Y.



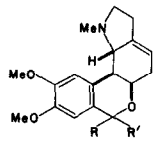
I



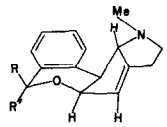
II



III



IV



for the corresponding C_{11}-methoxy compounds.

A comparison of the rate of methiodide formation[8] for the C_{11}-methoxy compounds derived from krigenamine, viz, (I; R = H, R' = OH), (I; R = R' = O) and (I; R = H, R' = H) was made with rates obtained from the analogous 9,10-dimethoxy alkaloids lycorenine (IV; R = H, R' = OH), homolycorine (IV; R = R' = O) and deoxylycorenine (IV; R = H, R' = H). The krigenamine series, as anticipated, showed significantly slower rates (see Table I). The magnetude of the difference

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[8] Rates were followed by means of conductance measurements, for experimental details see M. Shamma and J. B. Moss, J. Amer. Chem. Soc., 83, 5038, (1961).

for analogous compounds in the two series was sufficiently great to indicate that the method could be used to ascertain the presence of a C_{11}-methoxyl group in this type of Amaryllidaceae alkaloid.

The application of this method to alkaloids in the krigeine and nerinine series necessitated the preparation of two new compounds,[9] deoxykrigeine (II; R = H, R' = H), m. p. 171—172°, $[\alpha]_D$ +196°, $\lambda_{max.}^{EtOH}$ 280mμ (ε,990), $\lambda_{max.}^{KBr}$ 6.18μ and deoxynerinine (III; R = H, R' = H), oil, $[\alpha]_D$ +83°, $\lambda_{max.}^{EtOH}$ 280mμ (ε, 1230), $\lambda_{max.}^{KBr}$ 6.20μ and 6.26μ which were obtained in the usual way from their respective lactones.

Examination of the rate constants for the complete series showed that bases related to krigeine had almost identical rates to the analogous compounds derived from krigenamine whereas albomaculine and deoxynerinine showed rates corresponding well with those obtained for homolycorine and deoxylycorenine respectively. From this it must be concluded that krigeine and neronine have a C_{11}-methoxyl and this position in nerinine and albomaculine is occupied by hydrogen. Since the aryl oxygen functions in krigeine and neronine are assumed to be vicinal, on the bases of absorption at 6.18μ in certain compounds[7] in this series a 9,10,11-aryl oxygen pattern is indicated. However in the case of series (III) the aromatic band appears as a doublet, 6.20μ and 6.26μ, in tetrahydroalbomaculine and deoxynerinine. Since this could be a reflection of a

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Satisfactory analytical data were obtained for these compounds.

different substitution pattern other evidence was sought on this point.

TABLE I

	$K \times 10^4$
krigenamine(I; R=H, R'=OH)	3.5
oxokrigenamine(I; R=R'=O)	3.0
deoxykrigenamine(I; R=H, R'=H)	3.6
krigeine(II; R=H, R'=OH)	3.7
neronine(II; R=R'=O)	2.3
deoxykrigeine(II; R=H, R'=H)	2.8
albomaculine(III; R=R'=O)	7.5
deoxynerinine(III; R=H, R'=H)	10.4
lycorenine(IV; R=H, R'=OH)	11.4
homolycorine(IV; R=R'=O)	7.2
deoxylycorenine(IV; R=H, R'=H)	10.8

The application of nuclear magnetic resonance provided the answer to this problem. Examination of the NMR spectra[10] of (II; R = R' = O) and (II; R = H, R' = H) showed the signal due to the aromatic proton at τ =2.70 and τ =3.72 respectively. These values are almost identical with those found for (I; R = R' = O) and (I; R = H, R' = H) at τ =2.66 and τ =3.68 respectively. The position of the resonance signal for the aromatic hydrogen is that expected for an aryl hydrogen which is <u>peri</u> to a carbonyl group and furthermore is in good agreement with the reported values of the

[10] NMR spectra were obtained on a Varian A60 using $CDCl_3$ as a solvent with tetramethyl-silane as an internal standard.

corresponding signal in piperonal (τ =2.65)[11] and 3:5-dimethoxybenzaldehyde (τ=2.60).[12] The correspondence of the chemical shifts of the aromatic proton in these compounds indicate, in view of the kinetic data, vide supra, that (II; R = H, R' = OH), (II; R = R' = O) and (II; R = H, R' = H) are 9;10 methylenedioxy-11-methoxyl aryl alkaloids.

In contrast to this the aromatic proton in the lactone (III; R = R' = O) and the cyclic ether (III; R = H, R' = H) show almost identical chemical shifts, τ =3.13 and τ =3.17 respectively. This observation is only compatable with absence of a C_8-hydrogen in these bases and in conjunction with the results of the above kinetic data indicates that these bases, and hence (III; R = H, R' = OH), are 8,9,10 trimethoxyaryl alkaloids.

Other assignments in the NMR spectra are listed in Table II as tau values.

TABLE II

	4	5	5a	7	8	11
Oxokrigenamine(I;R=R'=O)	4.45	-	5.33	-	2.66	-
Deoxykrigenamine(I; R=H, R'=H)	4.52	-	6.24	4.86	3.68	-
Neronine(II; R=R'=O)	4.30	5.45	5.45	-	2.70	-
Deoxykrigeine(II; R=H, R'=H)	4.33	5.83	6.29	5.09	3.72	-
Albomaculine(III; R =R'=O)	4.48	-	5.30	-	-	3.13
Deoxynerinine(III; R=H, R'=H)	4.50	-	6.10	5.07	-	3.17
Homolycorine*(IV; R=R'=O)	4.44	-	5.15	-	2.36	2.99

[11] Varian Associates Spectra Catalogue, Spectra No.236

[12] Varian Associates Spectra Catalogue, Spectra No.187

* The NMR of this compound was obtained by Mr. J. M^{c}Chesney Indiana University.

The spectra provide evidence for the stereochemical identity of the C_{5a}-hydrogen in all compounds.[13] Chemical evidence has shown that in lycorenine, homolycorine[14] and krigenamine[2] this hydrogen is α-equatorial and hence it must have this assignment in the krigeine and nerinine series. This necessitates a cis B:C ring fusion in all alkaloids which are the subject of this paper. Unfortunately the signal from the C_{11c}-hydrogen is surrounded by a complex multiplet originating from other protons and no correlation of its stereochemistry is possible. However molecular rotational comparisons in these alkaloids and their derivatives suggest that like lycorenine and krigenamine the C_{11c}-hydrogen is β-axial and hence are elaborated from the stereostructures (V) having the absolute configuration shown.

The occurrence of the two possible types of vic-trioxyl aryl substitution patterns within the same skeletal type in Amaryllidaceae alkaloids is so far unique and is of importance when considering biosynthetic schemes for this group. This aspect will receive further comment in our full paper.

The authors would like to express their thanks to Mr. J. F. Grove of the Akers Research Labs., I.C.I., England, for providing the NMR facilities and to Mr. B. K. Tidd for assistance with the interpretation of the NMR spectra.

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[13] A change in stereochemistry of the hydrogen to 5β-axial in any of these compounds would be expected to be reflected in the chemical shift of this proton.

[14] T. Kitagawa, S. Uyeo and N. Yokoyama, J. Chem. Soc. 3741, (1959).