The Stereochemistry at C-14 for the Rhoeadine-type Alkaloids

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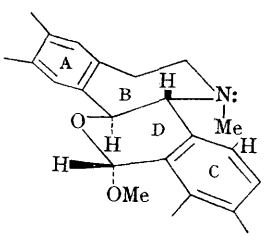
THE rhoeadine alkaloids can be separated into two broad classes possessing respectively a *trans*- and a *cis*-fused B/D ring juncture, and the nature of this fusion can be readily derived from n.m.r. spectroscopy.[1] For all of the 28 known bases (Table 1), however, the relative stereochemistry at the anomeric centre, namely C-14, had not been established. Glaudine, epiglaudine, and oreodine have identical substitution patterns (Table 1), the first two belonging to the B/D *trans*-series, while oreodine is *cis*-fused.[2]

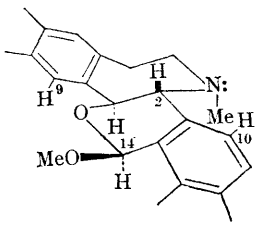
B/D trans-*Series*: The 'pseudo' first-order rates of methiodide formation were found to be 1·6 $\times$ 10^{-4} sec.$^{-1}$ for glaudine, and 2·1 $\times$ 10^{-4} sec.$^{-1}$ for epiglaudine.[3] These very slow rates point to the hindered nature of the molecules in the vicinity of the *N*-methyl group, due to the presence of the C-10 aromatic hydrogen, so that in the free base the *N*-methyl group prefers to occupy the less hindered axial position as indicated in expressions (I) and (II).

In Table 2 are listed the n.m.r. data for glaudine and epiglaudine. The chemical shifts for the *N*-methyl, the C-14 methoxy, and the C-1 proton are the most important, and will be discussed in some detail.

Isomerization at C-14 is known to occur for some members of the *trans*-series with 0·004N-HCl in methanol, so that glaudine can be transformed into epiglaudine. In the n.m.r. spectrum of epiglaudine, the C-1 proton at δ 5·55† is substantially shifted downfield in relation to the corresponding value for glaudine which is at 5·18 δ. This downfield shift for epiglaudine can be readily accommodated by assigning to epiglaudine the α-anomeric structure (II), in which the C-14 methoxy-oxygen is in the immediate vicinity of



(II)



(I)

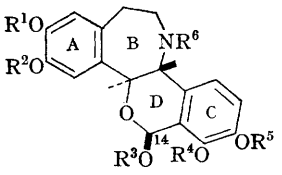
the C-1 proton. Consequently, stereo-expression (I) can be attached to glaudine. Molecular models of (I) and (II) indicate a dihedral angle of about 150° between the C-1 and C-2 hydrogens for a calculated coupling constant of about 9 c./sec. The experimentally found $J_{1,2}$ for glaudine and epiglaudine lie between 9 and 9·5 c./sec.

The *N*-methyl group in epiglaudine (II) also

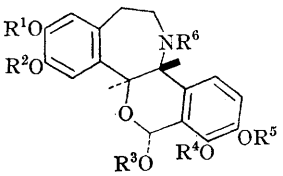
† δ $\times$ (p.p.m.) measured in $CDCl_3$ with Me_4Si as internal standard.

TABLE 1

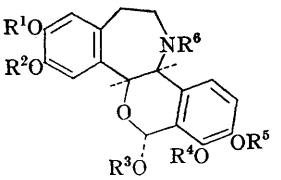
Known rhoeadine-type bases



(X)



(Y)



(Z)

	B/D *trans*, unstable at C-14 X	B/D *trans*, stable at C-14 Y	B/D *cis*, stable at C-14 Z
$R^1 = R^2 = R^3 = R^6 = Me$; $R^4 + R^5 = CH_2$ ..	Glaudine	Epiglaudine	Oreodine
$R^1 = R^2 = R^6 = Me$; $R^3 = H$; $R^4 + R^5 = CH_2$ ..	—	Glaucamine	Oreogenine
$R^1 = R^2 = R^3 = Me$; $R^4 + R^5 = CH_2$; $R^6 = H$	Papaverrubine B	Epipapaverrubine B	Papaverrubine F
$R^1 + R^2 = R^4 + R^5 = CH_2$; $R^3 = R^6 = Me$ ..	Isorhoeadine	Epiisorhoeadine	Rhoeadine
$R^1 + R^2 = R^4 + R^5 = CH_2$; $R^3 = H$; $R^6 = Me$ ..	—	Isorhoeagenine	Rhoeagenine
$R^1 + R^2 = R^4 + R^5 = CH_2$; $R^3 = Me$; $R^6 = H$ ..	Papaverrubine A	Epipapaverrubine A	Papaverrubine E
$R^1 = R^3 = Me$; $R^2 = R^6 = H$; $R^4 + R^5 = CH_2$ ..	Papaverrubine D (Porphyroxine)	Epipapaverrubine D (Papaverrubine C)	—
$R^1 = R^3 = R^6 = Me$; $R^2 = H$; $R^4 + R^5 = CH_2$ ..	*N*-Methylporphyroxine	*N*-Methylepiporphyroxine	*cis*-*N*-Methylepiporphyroxine
$R^1 = R^6 = Me$; $R^2 = R^3 = H$; $R^4 + R^5 = CH_2$ ..	—	*N*-Methyl-14-*O*-demethylepiporphyroxine	—
$R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = Me$	Alpinine	Epialpinine	*cis*-Alpinine
$R^1 = R^2 = R^4 = R^5 = R^6 = Me$; $R^3 = H$	—	Alpinigenine	*cis*-Alpinigenine
$R^1 = R^2 = R^3 = R^4 = R^5 = Me$; $R^6 = H$	Papaverrubine G	—	—

TABLE 2

N.m.r. data (δ *values*)

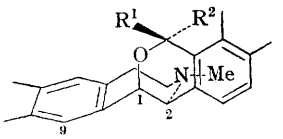
	N-CH_3	14-OMe	14-H	1-H	2-H	9-H	Stability in 0·004N-HCl in methanol
Glaudine (I)	2·23	3·68	5·76	5·18(d)	4·06(d)	7·33	Unstable
Epiglaudine (II)	2·30	3·55	5·73	5·55(d)	4·00(d)	7·30	Stable
Oreodine (III)	2·32	3·57	5·75	5·05(d)	3·66(d)	6·78	Stable

appears downfield at δ 2·30, whereas the corresponding absorption for glaudine (I) is at δ 2·23. This small downfield shift in epiglaudine may again be caused by the proximity of the *N*-methyl protons to the α-axial oxygen at C-14 as indicated in expression (II). The downfield shift is weaker in this case because of the larger distance involved from the C-14 oxygen.

It has been established that anomeric axial methoxy-hydrogens appear upfield from their equatorial counterparts,[4] and indeed the C-14 methoxy-protons for epiglaudine (II) fall at δ 3·55, while the corresponding value for glaudine (I) is at δ 3·68. No anomaly is involved with the equatorial methoxy-group in glaudine isomerizing in acid to the more stable axial position since the anomeric effect predicts such a change.[5] The stereochemistry at C-14 for the remaining known B/D *trans*-bases follow and is indicated in Table 1, n.m.r. and/or C-14 equilibration data for these compounds having already been published.[2]

B/D cis-*Series*: All the bases in the B/D *cis*-series are stable in acid.[2] Oreodine was found to have an *N*-methylation rate of moderate magnitude, $23{\cdot}1 \times 10^{-4}$ sec.$^{-1}$, indicating partial hindrance around the nitrogen atom. The favoured conformation (III) is in accord with such a rate, accessibility to the nitrogen atom being somewhat hindered by ring D. The alternate formulation (IV) can be discarded since it would result in

inordinate hindrance at the nitrogen by the C-14 methoxy-group with a subsequent very slow rate of methylation. Additional support for the assignment of stereo-structure (III) to all the B/D *cis*-fused rhoeadine type bases is forthcoming from n.m.r. data.



(III; R^1=OMe, R^2=H)
(IV; R^1=H, R^2=OMe)

The C-9 hydrogen in oreodine (Table 2) appears relatively upfield at δ 6·78, since the oxygen atom incorporated as part of ring D is distant from C-9.[6] Such is not the case for the *trans*-bases where the oxygen atom in question and the C-9 hydrogen are very close [*cf.* (I) and (II)], with a resultant downfield shift to δ 7·33 and δ 7·30 for glaudine and epiglaudine, respectively.

Furthermore, the C-14 methoxy-group in oreodine (III) is situated at 3·57 δ, and this value compares favourably with that for epiglaudine (II) which is 3·55 δ. If the C-14 methoxy-group in oreodine were to be as in (IV), a downfield shift would have been observed due to the proximity of the methoxy-group to the nitrogen atom, and such a shift is not detected. Finally, Stuart–Briegleb molecular models indicate that the dihedral angle between the C-1 and C-2 hydrogens in structure (III) is about 65°, for a calculated $J_{1,2}$ of about 1·5 c./sec. The corresponding experimentally found value for oreodine is 2 c./sec. The elucidation of the stereochemistry of oreodine at C-14 allows stereochemical assignments to the remaining known *cis*-fused bases (Table 1).

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[2] I. Mann, H. Döhnert, and S. Pfeifer, *Pharmazie*, 1966, **21**, 494; for additional information on the rhoeadine alkaloids, see Pfeifer, I. Mann, and L. Kuhn, *Pharm. Zentralhalle*, in the press.
[3] The rates of methiodide formation were measured on 3 mg. of sample in acetonitrile at 25° as described by M. Shamma and J. M. Richey, *J. Amer. Chem. Soc.*, 1963, **85**, 2507. For other studies using rates of methiodide formation, see M. Shamma, J. A. Weiss, and R. J. Shine, *Tetrahedron Letters*, 1967, 2489; and I. Ognyanov, B. Pyuskyulev, M. Shamma, J. A. Weiss, and R. J. Shine, *Chem. Comm.*, 1967, 579. The rates of glaucamine, rhoeadine, and rhoeagenine were also measured for the present study, and found to be $1·5 \times 10^{-4}$, $22·5 \times 10^{-4}$, and $24·9 \times 10^{-4}$ sec.$^{-1}$ respectively.
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[5] J. T. Edward and I. Puskas, *Canad. J. Chem.*, 1962, **40**, 711.
[6] A. D. Cross, I. Mann, and S. Pfeifer, *Pharmazie*, 1966, **21**, 181.