The Stereochemistry of Herbaceine and Herbaline

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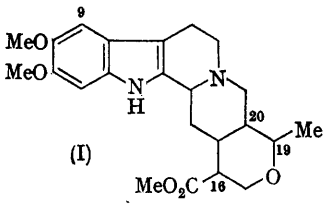
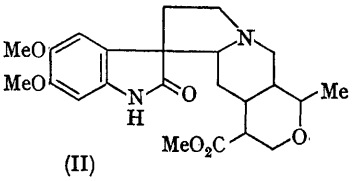
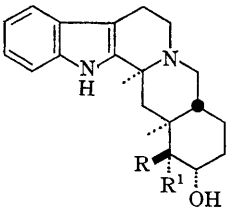
THE isolation and gross structural elucidation of herbaceine (I) and herbaline (II) from *Vinca herbacea* W.K. have recently been reported; these two bases being respectively the first dihydro-heteroyohimbine and the first dihydro(pentacyclic oxindole) alkaloids to be characterized.[1,2] The stereochemical problem connected with (I) and (II) is complicated by the fact that heteroyohimbine and oxindole alkaloids of known stereochemistry cannot be selectively hydrogenated to dihydro-structures of type (I) or (II). Nevertheless, it is the purpose of this Communication to show that herbaceine has the stereochemistry indicated in (Ia), and herbaline that in (IIa).



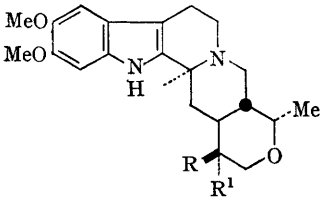
(I)



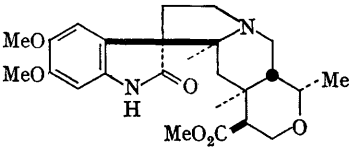
(II)



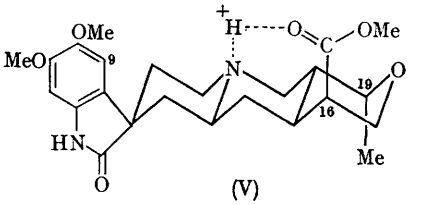
(III) R=CO_2Me, R^1=H
(IV) R=H, R^1=CO_2Me



(Ia) R=CO_2Me, R^1=H
(Ib) R=H, R^1=CO_2Me



(IIa)



(V)

The base-catalyzed isomerization of herbaceine (I) yields epiherbaceine.[1] This change can best be interpreted in terms of an axial to equatorial transformation for the methoxycarbonyl function, so that isomerization occurs at C-16.

The pseudo-first-order rates of methiodide formation for herbaceine and epiherbaceine are listed in the Table, together with those for corynanthine (III), yohimbine (IV), and other yohimbinoid bases, and these rates are primarily dependent upon the degree of steric hindrance around the basic nitrogen atom being quaternized.[3]

TABLE

Pseudo-first-order rates of methiodide formation in acetonitrile solution at 25°

Alkaloid	Stereochemistry	Rate of Methylation[a]
Herbaceine	(normal)	51 × 10^{-4} sec.$^{-1}$
Epiherbaceine ..	(normal)	33 ,,
Corynanthine (III) ..	normal	75 ,,
Yohimbine (IV) ..	normal	49 ,,
Pseudoyohimbine ..	pseudo	700 ,,
Alloyohimbine ..	allo	14 ,,
α-Yohimbine ..	allo	1 ,,
Reserpine	epiallo	10 ,,
Methyl reserpate ..	epiallo	17·5 ,,

[a] Determined on 3 mg. samples of each alkaloid. The experimental procedure is described in ref. 4.

The marked similarity of the rates for herbaceine and epiherbaceine on the one hand, and corynanthine and yohimbine on the other, indicate that the former two compounds must also possess the *normal* configuration; and this conclusion is reinforced by the presence of Bohlmann bands near 3·4 μ in herbaceine and epiherbaceine characteristic of *trans*-quinolizidine systems.[1] The methoxycarbonyl methyl group is at δ 3·60 in herbaceine and at δ 3·69 in epiherbaceine, and the same downfield trend prevails when going from corynanthine (III) (δ 3·56) to yohimbine (IV) (δ 3·78).

Spin-decoupling of the C-19 hydrogen in epiherbaceine by irradiation of the C-19 methyl group indicated a J_{19-20} value of 2·5 c./sec., for a dihedral angle of about 60°, consonant with an α-C-19 methyl.† Consequently, herbaceine must be (Ia), while epiherbaceine is (Ib). The chemical shifts of the α-C-19 methyl groups in herbaceine (δ 1·17) and in epiherbaceine (δ 1·16) are characteristically upfield, and compare very well with the value of δ 1·16 for the corresponding *C*-methyls in the *normal* heteroyohimbine alkaloids ajmalicine and tetraphylline.[3]

Turning now to the companion alkaloid herbaline (II), the stereochemistry of rings D and E of this dihydro-oxindole base must be as in herbaceine, as indicated by the high-field α-C-19 methyl chemical shift of δ 1·15, and a spin-decoupled J_{19-20} value of 5·7 c./sec. for a dihedral angle of about 30°, so that ring E must be twist-boat and

† The chemical shifts were such that the spin decoupling experiment on epiherbaceine was successful only in pyridine solution, using a 100 Mc./sec. Varian instrument. Deuteriochloroform was the solvent in the decoupling of herbaline.

the C-19 methyl is α. The oxindole carbonyl is in an *anti*-relationship to the pair of electrons on N_b because the C-9 aromatic hydrogen appears downfield at δ 6·97 due to its proximity to N_b. The corresponding C-9 proton chemical shifts for the *anti*-oxindoles isocarapanaubine, rauvoxine, and rauvanine-oxindole-A are respectively δ 6·90, 7·02, and 6·92. In the *syn*-series, on the other hand, where the C-9 proton is more distant from N_b, the chemical shifts are δ 6·76, 6·71, and 6·75 for carapanaubine, rauvoxinine, and rauvanine-oxindole-B respectively.[4] These data lead to expression (IIa) for herbaline.

Interestingly enough, herbaline is the only known *anti*-pentacyclic oxindole alkaloid that isomerizes only to a small extent in refluxing acetic acid.‡ This may be due to co-ordination of a proton with both N_b and the methoxycarbonyl oxygen in herbaline, as indicated in (V), so that the usual *anti* to *syn* acid-catalyzed transformation does not tend to occur. The mercuric acetate test[5] on herbaline is positive, in accord with its *anti*-stereochemistry,[6] but the precipitate appears only after 3½ to 4 min., whereas the other *anti*-oxindoles show a precipitate usually well within 3 min.

One of us (M.S.) acknowledges financial assistance from the National Institutes of Health.

(*Received, May 1st,* 1967; *Com.* 419.)

‡ Herbaline can also be recovered essentially unchanged after heating under reflux in pyridine for 24 hr.

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