

STRUCTURE OF IMPERIALINE

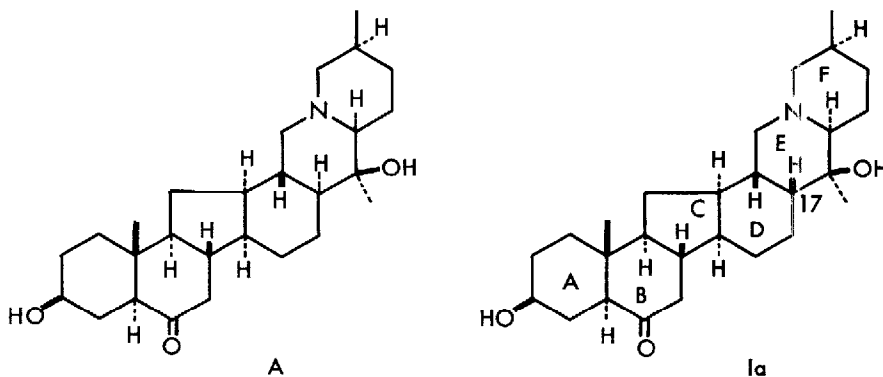
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Imperialine is the first *Fritillaria* alkaloid isolated in 1888 from *F. Imperialis* L. (Liliaceae) (1). It has since been isolated from several plants sources (2) and also named sipeimine (3a). Its structural studies were conducted by Boit (4), Chu and Loh (3) and Yunusov *et al.* (5), and culminated in the structure A. This



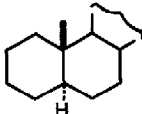
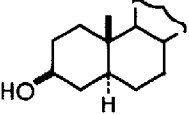
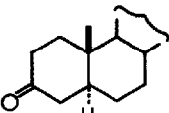
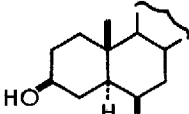
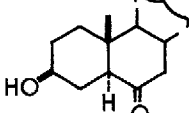
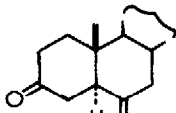
structure proposed by Yunusov (5b) is based on the PMR and mass spectral comparison of the imperialine derivatives with those of verticine (6). Since the structure (A with A/B cis) derived by them (5a) for verticinone is different from the one (A) established by us on the basis of spectral properties (6) and X-ray analysis (7), we have undertaken the structural study of imperialine with the specimen kindly provided us by Dr. O.E. Edward, National Research Council of Canada. We present herein the evidence which clearly reveals the structure 1a for this alkaloid.

Previous chemical studies (3,4) established beyond doubt the cevane skeleton for imperialine 1a. Its spectral data and physical properties (8), λ_{\max} 290 nm (ϵ 29); ν 3448 (OH), 2817, 2778 (trans-quinolizidine), 1701 cm^{-1} (6-membered carbonyl); MS (m/e) 429 (M^+), 112 (base peak), 111; NMR (Table); pK_a' 8.95, are very similar with those of verticinone 1b, λ_{\max} 288 nm (ϵ 38); ν 3450, 2816, 2778, 1705 cm^{-1} ;

MS (m/e) 429 (M^+), 112 (base peak), 111; NMR (Table), pK_a 8.92 (6) and are consistent with the planer structure proposed. If Ia and Ib are stereoisomeric only at C_5 position as Yunusov suggested, two series should easily be correlated. In reality, however, alkaline treatment of both compounds resulted in the complete recovery.

In order to determine the position and configuration of the functional groups in Ia, some known derivatives were prepared, *i.e.*, dihydroimperialine IIa (4), imperialone IIIa (3,4), deoxoimperialine IVa

TABLE Chemical Shift of Methyl Groups

partial structure	Imperialine (a) series			Verticine (b) series			5a, 14a-Steroids Δ 19-Me
	19-Me	21-Me	27-Me	19-Me	21-Me	27-Me	
VI 	0.75	1.05	1.08 ($J=7$)	0.80	0.99	1.06 ($J=8$)	
IV 	0.76 Δ 0.01	1.05	1.05 ($J=7$)	0.80 0.00	1.03	1.08 ($J=7$)	0.033
V 	0.96 Δ 0.21	1.06	1.06 ($J=6$)	1.00 0.20	1.00	1.07 ($J=6$)	0.242
II 	1.00 Δ 0.25	1.06	1.06 ($J=7$)	1.04 0.24	1.04	1.09 ($J=7$)	0.258
I 	0.73 Δ -0.02	1.04	1.06 ($J=6$)	0.76 -0.04	1.01	1.06 ($J=6$)	-0.017
III 	0.94 Δ 0.19	1.06	1.07 ($J=6.5$)	0.93 0.13	0.99	1.04 ($J=6$)	0.192
Average		1.05 ± 0.01	1.06 ± 0.02 ($J=6 \sim 7$)		1.01 ± 0.03	1.07 ± 0.03 ($J=6 \sim 8$)	

(Δ denotes the chemical shift difference of the 19-methyl group between partial structures in question and VI. Downfield shift is taken as positive.)

(3,4), dehydrodeoxoimperialine Va (3), and deoxodeoxyimperialine VIa (3). The presence of intramolecular hydrogen bonding between tert.OH and N in IIIa (concentration-independent IR band at 3448 cm^{-1}) and the similarity of methyl chemical shift and pKa' between Ia and Ib suggest the identical stereochemistry on E and F rings in Ia and Ib.

The chemical shift of methyl signals in these derivatives (a-series) was compared with those in the corresponding derivatives of verticinone derivatives (b-series), and is listed in Table (9). Within each series, two methyl signals (21-Me and 27-Me) remain almost constant, revealing the structure changes have occurred in the region far from these methyls. On the other hand, chemical shift of the 3rd methyl (19-Me) is affected by the change of functionality, and the change (Δ) is very similar between two series and almost equal to those of 19-methyl groups in 5 α ,14 α -steroids (10). This suggests that the Ia and its derivatives have the same relative stereochemistry (shown in Table) on A and B ring with verticinone derivatives and 5 α -steroids. Furthermore, the similarity of ORD curves of Va, ($[\phi]$: +2900 (306), -2100 (270), A: +50) and Vb ($[\phi]$: +2125 (315), -4150 (266), A: +63) suggests the same absolute configuration of the 19-methyl group as in steroids. The fact that none of the corresponding derivatives in these two series are identical suggests that structural difference between Ia and Ib is the stereochemistry of carbon skeleton. ORD curve of Ia exhibits a negative Cotton effect ($[\phi]$: -2600 (316), -2500 (311), -2700 (307), +2700 (270 nm)) amplitude of which (A: -54) is twice as much of verticinone (A: -26) (6a). This implies the difference originates from the configuration on C and/or D rings.

For the final structure proof, X-ray crystallographic analysis was undertaken. The derivative used for the analysis was imperialine methobromide monohydrate, colorless needles (crystallized out on evaporation of ethanol solution (11)), m.p. 268-270°C (dec.), which belongs to orthorhombic system, space group being $P2_12_12_1$ with four molecules in a unit cell of dimensions $a=10.44$, $b=35.47$ and $c=7.39\text{ \AA}$.

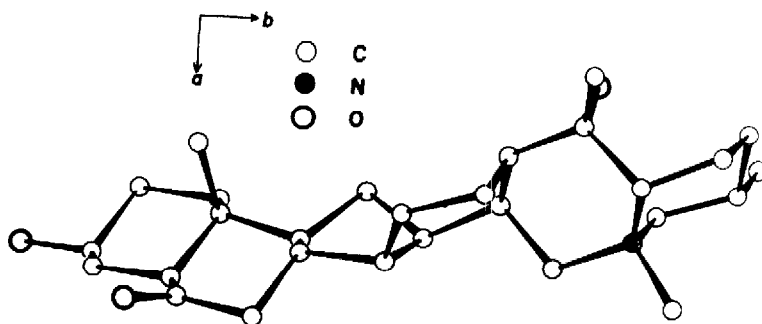
Three dimensional intensity data were collected by Rigaku's four circle automatic diffractometer using $\text{CuK}\alpha$ radiation with ω - 2θ scanning technique 2θ angle up to 105° . A total of 1391 independent structure factors were evaluated for this analysis. The structure was solved by several cycles of Fourier and difference Fourier syntheses and refined by the block-diagonal least squares calculation. At the final cycle of the refinement the R factor was 9.0%. The molecular structure viewed along c -axis is shown. All 6-membered rings are in chair conformation except D ring which assumes a twisted chair form. In any event, the

structure of imperialine methobromide was thus established as 17-*epi*-verticinone methobromide.

Since the presence of *trans*-quinolizidine ring system in Ia was indicated by IR and the configura-

tional change from *trans*-quinolizidine to *cis* upon quaternization is well known (7), the structure of imperialine was established to be 17-*epi*-verticinone.

We are deeply indebted to Dr. O.E. Edward, National Research Council of Canada and Dr. K.L. Handa, Regional Research Laboratory, Jammu, India, for their generous gift of Imperialine without which the present study would not have been completed.



References and Notes

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- 8) Spectra were measured under the following conditions: UV (λ) and ORD ($[\Phi]$) in methanol, IR (ν) in CHCl_3 , PMR (δ) in CDCl_3 , pKa' in ethanol.
- 9) The chemical shift values were also reported by Yunusov (5c).
- 10) R.F. Zürcher, Helv. Chim. Acta, 46, 2054 (1963).
- 11) The crystals obtained by normal crystallization from any organic solvent system were transparent in the solution but became turbid in air probably because of liberation of the solvent of crystallization.