

THE STRUCTURE OF ISOJERVINE

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THE veratrum alkaloid jervine (I),¹ when treated at room temperature with methanolic hydrogen chloride, is isomerized to isojervine,² which differs from I in the following respects: (1) in its U.V. spectrum the high maximum at 250 $m\mu$ (15,000) of I is replaced by strong end absorption showing only a shoulder with $\epsilon \sim 3000$ in that region, while the low intensity maximum at 360 $m\mu$ (60) is shifted to 330 $m\mu$ (~ 250);³ (2) instability to caustic alkali; (3) formation of a (di-O,N) triacetate instead of an O,N-diacetate.³ No other facts of relevance to the structure problem are on record.

On the basis of the findings reported below we have come to assign to isojervine structure (II).

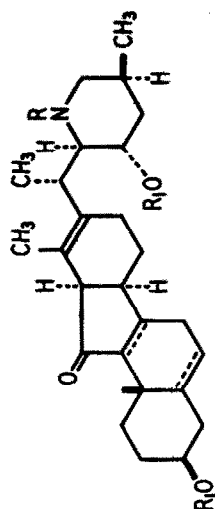
The 23-position of the new acetylatable hydroxyl group in II follows, inter alia, from the correlation (vide infra) of II with the veratramine derivative XII, and with 5,6-dihydrojervisine 17-monoacetate (Xa). The presence of the 5,6-double bond in II was established by Oppenauer oxidation of N-acetylisojervine³ to N-acetyl- Δ^4 -isojervone (III, m.p. 239-241^o,

¹ The stereochemistry specified in I derives from evidence adduced in the following papers: C-17, C-23, ref. 6 below; C-22:C-23, J. Sicher and M. Tichý, Tetrahedron Letters No. 12, 6 (1959); C-25, S. Okuda, K. Tsuda and H. Kataoka, Chem. & Ind. 512 (1961); C-22:C-25, R.L. Augustine, Ibid. 1448 (1961); C-8, C-9, C-14, H. Mutsuhashi and Y. Shimizu, Tetrahedron Letters No. 21, 777 (1961).

² W.A. Jacobs and L.C. Craig, J. Biol. Chem. 155, 565 (1944).

³ W.A. Jacobs and C.F. Huebner, J. Biol. Chem. 170, 635 (1947).

⁴ A similar change in the U.V. characteristic accompanies the saturation of the "opposed" double bond in 1,4-cyclohexadienyl-methyl ketone [λ_{max} 245 $m\mu$ (4000) \rightarrow 232 $m\mu$ (12,500)], E.A. Braude, E.R.H. Jones, F. Sordheimer and J.B. Toogood, J. Chem. Soc. 607 (1949).



II (WITH Δ^5, Δ^6 ; R = R₁ = H)

IV (NO Δ^5) a) R = R₁ = H

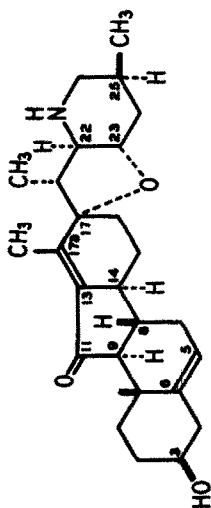
b) R = Ac, R₁ = H

c) R = R₁ = Ac

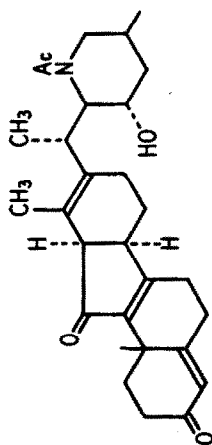
V (NO Δ^5, Δ^6) a) R = R₁ = H

b) R = Ac, R₁ = H

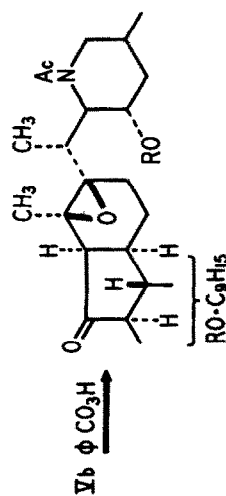
c) R = R₁ = Ac



I



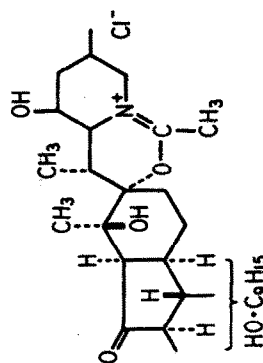
III



VIb $\xrightarrow{\phi \text{ CO}_3\text{H}}$

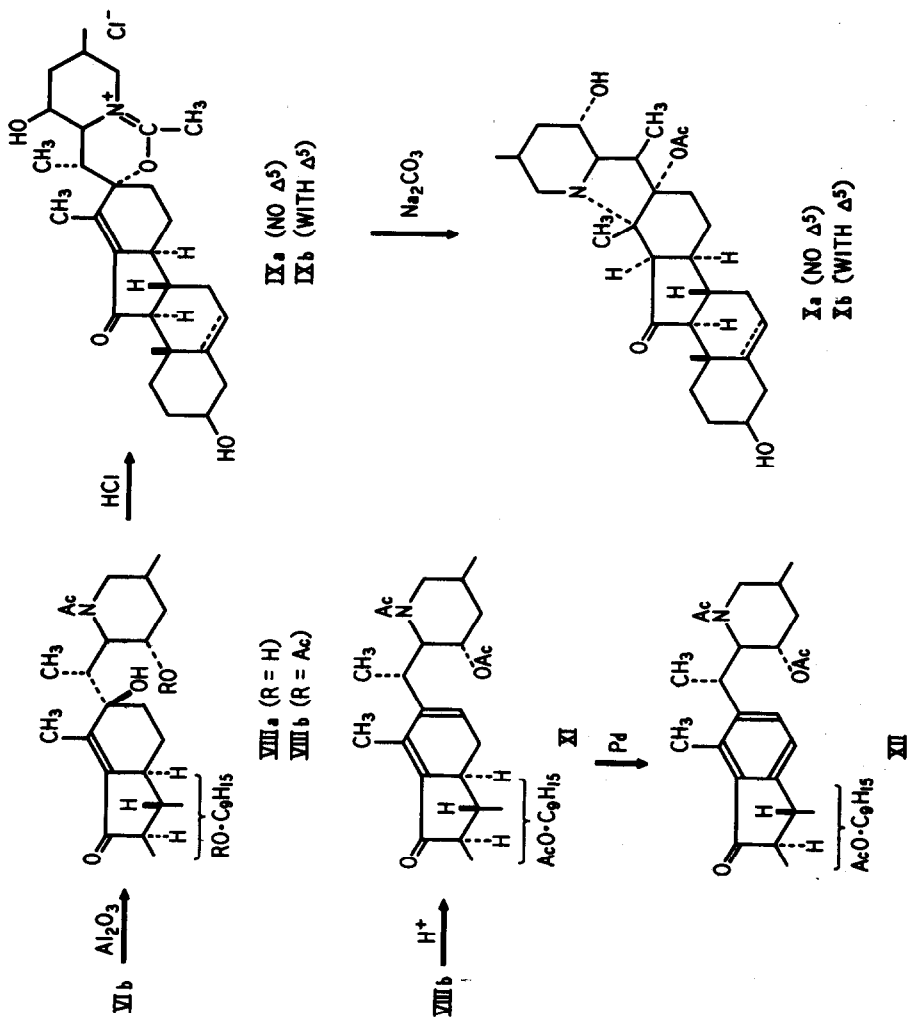
VIa (R = H)

VIb (R = Ac)



VII





$[\alpha]_D^{25} +199^\circ$) the U.V. spectrum of which $[\lambda_{\max}^{\text{alc}} 230 \text{ m}\mu (22,300), 331 \text{ m}\mu (200)]$ is a composite of that of N-acetyl-13,17a-dihydro- Δ^4 -jevriene and of isojevriene. Contrary to the finding of Jacobs and Huebner³ this double bond could be catalytically reduced (PtO_2 , acetic acid). The resulting dihydro base IVa (m.p. 155-157 $^\circ$; N-acetyl derivative IVb, m.p. 183-185 $^\circ$, $[\alpha]_D^{23} +31^\circ$; triacetate IVc, m.p. 209-211 $^\circ$, $[\alpha]_D^{23} +37.5^\circ$) exhibits typical α,β -unsaturated ketone absorption $[\lambda_{\max}^{\text{alc}} 238 \text{ m}\mu (9500), 330 \text{ m}\mu (210)]$ showing that the inhibition of resonance in the Δ^{8-9} -11-ketone system of II is released by the saturation of the 5,6-double bond;⁴ the same effect is produced by the reduction of the 4,5-double bond in N-acetyl- Δ^4 -isojevriene (III), the 4,5-dihydro-derivative [m.p. 216-218 $^\circ$, $[\alpha]_D^{21} +37^\circ$, showing $\lambda_{\max}^{\text{alc}} 237 \text{ m}\mu (9700)$].

Reduction of IVa and IVb with lithium in liquid ammonia gave, respectively, 5,6,8,9-tetrahydroisojevriene (Va) (m.p. 147-149 $^\circ$) and its N-acetyl derivative Vb (m.p. 225-228 $^\circ$, $[\alpha]_D^{20} +53^\circ$; triacetate (Vc), m.p. 173-175 $^\circ$, $[\alpha]_D^{22} +63^\circ$), all having U.V. spectra consonant with the assigned structure $[\lambda_{\max}^{\text{alc}} 310-320 \text{ m}\mu (150-200)]$. N-acetyl-5,6,8,9-tetrahydroisojevriene (Vb) could be converted with perbenzoic acid to the oxide (VIa) (m.p. 231-235 $^\circ$, $[\alpha]_D^{20} -21^\circ$), which on short treatment with 0.02 N-HCl in 90 per cent methanol rearranged to the quaternary base chloride VII (m.p. 198-201 $^\circ$, $[\alpha]_D^{21} +59^\circ$ in ethanol). This salt instantaneously reverted to the parent oxide on treatment with sodium carbonate in dilute methanol.

When the amorphous triacetate (VIb) derived from the oxide (VIa) was adsorbed from benzene solution on neutral alumina and then eluted with methanol, it was isomerized to the enone VIIIb [m.p. 222-223 $^\circ$, $[\alpha]_D^{20} +48^\circ$, $\lambda_{\max}^{\text{alc}} 261 \text{ m}\mu (10,300), 355 \text{ m}\mu (120)$], which for the reasons given farther below we formulate as the 5,6-dihydro-17-epimer of an acetolysis product $[\lambda_{\max}^{\text{alc}} 252 \text{ m}\mu (14,000), 355 \text{ m}\mu (85)]$ earlier obtained by us from diacetyljevriene.⁵ The amorphous N-acetyl derivative VIIIa, obtained from VIIIb by

⁵ O. Wintersteiner and M. Moore, J. Amer. Chem. Soc. **75**, 4938 (1953).

O-deacetylation with alkali, yielded with aqueous methanolic 0.025 N HCl the cyclic quaternary base chloride IXa [m.p. 221-224°, $[\alpha]_D^{20} +14^\circ$ in 95 per cent ethanol, $\lambda_{\max}^{\text{alc}}$ 243 m μ (14,830)], which must be the 5,6-dihydro derivative of a salt (IXb) showing similar U.V. characteristics which we had previously obtained as a by-product in the formation of N-acetyljervine.⁶ This follows from the fact that IXa on treatment with sodium carbonate gave 5,6-dihydrojervisine 17-monoacetate (Xa, m.p. 276-278°, $[\alpha]_D^{21} -61^\circ$), identical with the catalytic hydrogenation product (PtO₂, AcOH) of jervisine 17-monoacetate (Xb), the base obtained in the same manner from IXb.⁶

The enone triacetate VIIIb could be dehydrated by prolonged heating in dioxane containing maleic acid to the dienone XI [m.p. 189-191°, $\lambda_{\max}^{\text{alc}}$ 317 m μ (10,500), shoulders at 227 m μ (9000) and 260 m μ (5300)], which on dehydrogenation with palladium in boiling cymene⁷ afforded an indanone identical in every respect with the known⁸ triacetyl-5,6-dihydro-11-keto-veratramine (XII).

The sequences V \longrightarrow Xa and V \longrightarrow XI were also carried through with N-acetyl-5,6-dihydroisojervine (IVb) and N-acetyl- Δ^4 -isojervone (III) as the starting products. The spectral properties of the compounds thus obtained, for instance, of the cross-conjugated dienone of the dihydro series which corresponds to the enone VIIIa [$\lambda_{\max}^{\text{alc}}$ 273 m μ (11,300)], leave no doubt that the conjugated double bond in II occupies the 8,9-position. This phase of the work, as well as the mode of formation of II from I, will be the subject of a later communication.

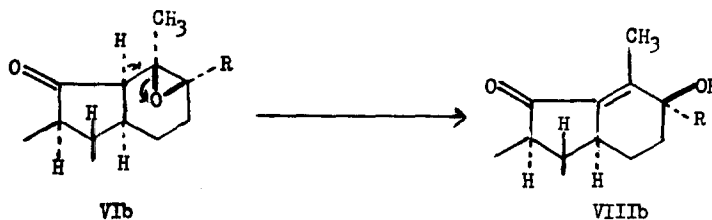
The fact that jervisine derivatives were obtained in all 3 series precludes a change in configuration at C-14 consequent to the reduction of

⁶ O. Wintersteiner and M. Moore, J. Amer. Chem. Soc. **78**, 6193 (1956).

⁷ D. Rosenthal, J. Fried, P. Grabowich and E.F. Sabo, J. Amer. Chem. Soc. **84**, 877 (1962).

⁸ O. Wintersteiner and N. Hosansky, J. Amer. Chem. Soc. **74**, 4474 (1952).

the 8,9-double bond in II, and since jervisine corresponds configurationally to jervine at C-14 (and at C-8 and C-9), the 14-hydrogen in II must be α -oriented. This must be true also of the 13-hydrogen atom, since the coplanarity of C-8, C-9 and C-11 in II demands that the ring C/D junction be cis. Now the facile formation of the enone VIIIb from the oxide VIb requires near coplanarity of the reacting centres involved, and this is the basis of the postulate that the oxiran ring in VIb is β -oriented.



This leads, as shown, to the enone stereoisomer with the 17-side chain in α -, and the 17-hydroxyl in β -configuration. In the subsequent conversion of the enone (as the N-acetyl derivative VIIa) with hydrochloric acid to the quaternary base chloride IXa inversion at C-17 must occur, since (1) IXa has been related to the base chloride IXb from N-acetyljervine through reactions (the jervisine rearrangement) in which inversion at C-17 is impossible, and (2) it is extremely likely that IXb, like all solvolysis products of jervine, has the latter's configuration at C-17,⁶ i.e. the "natural" configuration with the side chain β -oriented.

All melting points are corrected; $[\alpha]_D$ was measured in chloroform unless indicated otherwise; all crystalline compounds described gave correct analyses.