solution as the stationary phase.[33] The presence of XII in the detosylation product was confirmed by blending with a sample of the pure compound, obtained by the decomposition of XI. The blending technique was employed for identification purposes also in the case of the *cis*- and *trans*-1,3-pentadiene. The identity of the latter was further established by partial subtraction chromatography on a column containing chloromaleic anhydride.[34]

Geometric isomers of disubstituted cyclobutanes were separated on a capillary column, 150 ft. long and 0.01 in. wide, coated with squalane. 2-Methylcyclobutanol, as well as the dibromo derivatives of XII, was analyzed on a capillary column of the same dimensions, coated with polypropylene glycol.

A Varian A-60 spectrometer was employed for the measurement of the n.m.r. spectrum of XII, using carbon tetrachloride as a solvent and tetramethylsilane as the reference compound.

Acknowledgment.—Special thanks are due to Dr. B. Altman and Mr. H. Greener for their excellent assistance in the synthetic work. We also are indebted to Mrs. G. Fischer for her participation in the analytical work and to Dr. Y. Shvo for the measurement and interpretation of the n.m.r. spectrum.

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[33] J. Shabtai, J. Herling, and E. Gil-Av, *J. Chromatog.*, **11**, 32 (1963).

[34] Y. Herzberg-Minzly and E. Gil-Av, *Bull. Res. Council Israel*, **10A**, 86 (1961); E. Gil-Av and Y. Herzberg-Minzly, *J. Chromatog.*, in press.

Jervine. XI. The Structure and Stereochemistry of Isojervine

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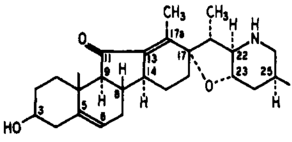
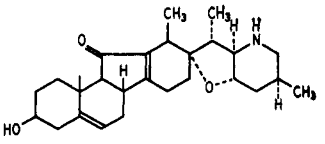
The structure of isojervine has been established as IVa by transformations which lead through its N-acetyl 5,6,8,9-tetrahydro derivative (Xc) and the latter's 17β,17aβ-oxide (XIa) to the enone (XIV) and thence to 5,6-dihydrojervisine 17-monoacetate (XIX) and to triacetyl-5,6-dihydro-11-ketoveratramine (XVII). The abnormal ultraviolet spectrum of isojervine is due to inhibition of resonance in the $\Delta^{8,9}$-11-keto system by the 5,6-double bond, an effect also exerted by the 4,5-double bond in N-acetyl-Δ^4-isojervone (V). Configurational assignments have been made for the asymmetric carbon atoms in rings C and D of isojervine, 5,6,8,9-tetrahydroisojervine, and the latter's derivatives, XI, XII, XIV, and XVIII.

In 1944, Jacobs and Craig[1] recorded the observation that the native veratrum alkaloid jervine, on treatment with hydrochloric acid or methanolic hydrogen chloride, is transformed into an isomer, isojervine, which markedly differs in its properties from the native alkaloid. Thus the hydrochloride and sulfate of isojervine are far more soluble in water or ethanol than the corresponding salts of jervine; in contrast to jervine the isomer is unstable to caustic alkali at room temperature (immediate formation of red pigment); in its ultraviolet absorption spectrum the high maximum at 250 mμ (ε 15,000) characteristic for jervine is replaced by strong end absorption showing only a shoulder of much lower ε (~3000) in that region, while the low intensity maximum at 360 mμ (ε ~60) is hypsochromically shifted to 330 mμ (ε ~250).[2] On short warming with acetic anhydride isojervine formed a N-acetyl derivative and, on more prolonged heating with this reagent, a triacetate.[2]

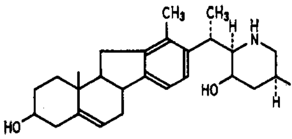
Concurrently with the investigation which led to the establishment in 1951 of structure I[3] for jervine, a limited amount of work on isojervine was carried out in this laboratory. The results, supplemented by more recent findings, have led us to assign to isojervine, structure IVa. In this paper we present the facts immediately relevant to the structure proof,[4] while other, more tangential aspects of the work will be presented in the following two papers of this series.



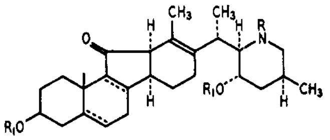
I



II



III

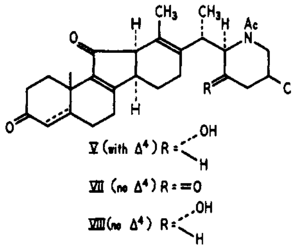


IV (with Δ^5, Δ^8)
a) R = R₁ = H
b) R = R₁ = Ac
c) R = Ac, R₁ = H
d) R = CH₃, R₁ = H

VI (no Δ^5)
a) R = R₁ = H
b) R = R₁ = Ac
c) R = Ac, R₁ = H

IX (no Δ^8)
a) R = R₁ = H
b) R = R₁ = Ac

X (no Δ^5, Δ^8)
a) R = R₁ = H
b) R = R₁ = Ac
c) R = Ac, R₁ = H



Isojervine conforming in its properties with the description of Jacobs and Craig[1] showed in its infrared spectrum a strong carbonyl band at 5.92 μ and a medium high band at 6.10 μ indicative of a conjugated C═C bond. In this respect isojervine resembles Δ^{13}-jervine (II)[5] which exhibits a corresponding band at 5.94 and

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[1] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **155**, 565 (1944).

[2] W. A. Jacobs and C. F. Huebner, *ibid.*, **170**, 635 (1947).

[3] The stereochemical features of formula I derive from evidence adduced in the following papers: (a) C-17, C-23, ref. 9; (b) C-22:C-23, J. Sicher and M. Tichy, *Tetrahedron Letters*, **12**, 6 (1959); (c) C-25, S. Okuda, K. Tsuda, and H. Kataoka, *Chem. Ind.* (London), 512 (1961); (d) C-22:C-25, R. L. Augustine, *ibid.*, 1448 (1961); (e) C-8, C-9, C-14, H. Mitsuhashi and Y. Shimizu, *Tetrahedron Letters*, **21**, 777 (1961); *Tetrahedron*, **19**, 1027 (1963).

[4] A brief account of this phase of the work has been published [O. Wintersteiner and M. Moore, *Tetrahedron Letters*, **18**, 795 (1962)]. T. Masamune, M. Takasugi, H. Swzuki, S. Kawahar, M. Godha, and T. Irie [*Bull. Chem. Soc. Japan*, **35**, 1749 (1962)] and W. G. Dauben, W. W. Epstein, M. Tanabe, and B. Weinstein [*J. Org. Chem.*, **28**, 293 (1963)] have independently arrived at the same conclusion regarding the structure of isojervine. We are indebted to Professor Masamune and Professor Dauben for making available to us prepublication copies of their manuscripts.

The communication by R. Ikan and H. Conroy [*Bull. Res. Council Israel*, **11A**, 33 (April, 1962)] postulating the same structure is based almost entirely on our own data to which R. Ikan had access in 1960 through Professor Conroy, who has meanwhile informed us that he never authorized the use of these data and of his name for publication.

[5] B. M. Iselin and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 5318 (1955).

6.12 μ, rather than jervine (5.88, 6.16 μ).[6] Since isojervine, like jervine, is completely inert to ketone reagents, the keto group indicated by the infrared data must occupy its original position 11.

Isojervine triacetate (IVb) could be prepared in good yield either by the method of Jacobs and Huebner[2] or with acetic anhydride and pyridine. However, when the preparation of N-acetylisojervine we tried to take advantage of the selective N-acetylation in methanol which we have used routinely with jervine and its reduced derivatives,[7] the base was recovered unchanged. Since the secondary base veratramine (III) behaves in the same manner,[8] it could be assumed that the oxide ring of jervine has been opened with the establishment of a hydroxyl group at C-23, a supposition which later was rigidly proved by the conversion of isojervine to a known derivative of this alkaloid (*vide infra*). We have already reported[9] that N-acetylisojervine (IVc) can be readily obtained by treating N-acetyljervine with methanolic hydrogen chloride. The hitherto undescribed N-methylisojervine (IVd) could be prepared similarly from N-methyljervine.[10] These observations clearly ruled out participation of the nitrogen atom in the isomerization reaction.

The presence of the 5,6-double bond was established by Oppenauer oxidation of N-acetylisojervine to the strongly dextrorotatory N-acetylisojervone (V), $[\alpha]_D$ +199°; $\lambda_{\max}$ 230 mμ (ϵ 22,300), 331 (200). The new Δ^4-3-ketone chromophor is evidenced by $\lambda_{\max}$ 235 mμ (ϵ 16,500) of the curve obtained by subtraction of the isojervine curve from that of oxidation product.[11] The molecular rotation change accompanying the formation of the ketone has an abnormally high positive value (+806°), as is the case in the corresponding reaction of jervine (+742°) and of N-acetyl-11-ketoveratramine (+733°).[12]

Contrary to the experience of Jacobs and Huebner[2] we found that isojervine consumed hydrogen on catalytic reduction with platinum oxide in acetic acid as well as with palladium on charcoal in ethanol, and is thereby transformed into a 5,6-dihydro base (VIa) which differs from isojervine by showing typical α,β-unsaturated ketone absorption in the ultraviolet range, with maxima at 238 mμ (ϵ 9500) and 333 mμ (ϵ 210); furthermore the absorption curve, in contradistinction to those of jervine and Δ^{13}-jervine,[5] exhibited a minimum at 225 mμ with $\epsilon \backsim 7000$, a feature obviously referable to the absence of the 5,6-double bond. Strong bands at 5.92 and 6.15 μ are in evidence in the infrared spectrum. For the reasons given later we place the ethylenic bond of the α,β-unsaturated ketone chromophor thus clearly revealed in the 8,9-position. The base forms addition compounds with the common solvents and, hence, was characterized analytically as the triacetate VIb and as the N-acetyl derivative VIc, which is obtained most conveniently by catalytic reduction of N-acetylisojervine. Since 5,6-dihydroisojervine differs from isojervine by being stable to strong base, the latter derivative also could be prepared by O-deacetylation of the triacetate.

To make sure that it was the 5,6-double bond of isojervine which had been reduced in the formation of the dihydro derivatives, N-acetyl-5,6-dihydrojervine was oxidized with chromium trioxide in acetone.[13] The resulting 3,11,23-triketone (VII) (infrared bands at 5.84, 5.94, and 6.09 μ, no hydroxyl band) showed in its ultraviolet spectrum end absorption with a shoulder at 230 mμ (ϵ 11,500) which undoubtedly represents the 238-mμ band of the starting product VIc superimposed on the end absorption originating in the two new keto groups (N-acetyl-22,26-iminojervane-3,11,23-trione,[14] at 225 mμ, $\epsilon \sim 3000$). Since VII was recovered unchanged after short refluxing in methanolic potassium hydroxide solution, it cannot be the Δ^5-unsaturated ketone.[13b] The marked negative molecular rotation shift accompanying the oxidation (−458°) parallels those for the formation of N-acetyldihydroveratramine-3,23-dione[8] and N-acetyl-22,26-iminojervane-3,11,23-trione[14] from the corresponding 3,23-diols (−425° and −256°, respectively).

N-Acetyl-Δ^4-isojervone (V) on catalytic reduction with palladium yielded in facile reaction N-acetyl-4,5-dihydroisojervone (VIII) exhibiting the ultraviolet spectrum typical of the 5,6-dihydro derivatives [$\lambda_{\max}^{\text{alc}}$ 237 mμ (ϵ 9690), 332 (186)]. Saturation of the 4,5-double bond in V has, therefore, the same normalizing effect on the isojervine chromophore as that of the 5,6-double bond in isojervine itself.

It is evident from the ultraviolet absorption data of the new isojervine derivatives described in the foregoing that the inhibition of resonance in the α,β-unsaturated ketone system of isojervine (IV) which must be responsible for its abnormal ultraviolet absorption characteristics still obtains in N-acetyl-Δ^4-isojervone (V), but that this restraint disappears when either the 5,6-double bond in IV or the 4,5-double bond in V is reduced. The disappearance of the spectral abnormality in the reaction IV → VI is paralleled by a similar phenomenon in the transition of simple compounds having a system such as that represented by rings B and C of IV, to their reduction products lacking the "opposed" isolated double bond (1-acetyl-1,4-cyclohexadiene,[15] 1,4-cyclohexadiene-1-carboxylic acid[16]).

Since this matter has already been briefly mentioned by us[4] and more fully discussed by Dauben, *et al.*,[4] we refrain from further elaborating on it here, except for making reference to a finding to these authors relating

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(6) The C═C bands of isojervine and Δ^{13}-jervine are of considerably lower intensity than their carbonyl bands, while in jervine this relationship is reversed; *cf.* R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *ibid.*, **76**, 4013 (1954), and ref. 9.

(7) B. M. Iselin and O. Wintersteiner, *ibid.*, **76**, 5616 (1956).

(8) Ch. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952).

(9) O. Wintersteiner and M. Moore, *ibid.*, **78**, 6193 (1956).

(10) K. Saito, H. Suginome, and M. Takaoto, *Bull. Chem. Soc. Japan*; **11**, 172 (1936).

(11) The absorption spectrum of N-acetyl-Δ^4-13,17a-dihydrojervone, the preparation of which is described in the Experimental section, exhibits the same characteristics ($\lambda_{\max}$ 234 mμ, ϵ 16,300). The marked hypsochromic shift from the position this band occupies in the spectrum of normal Δ^4-3-keto steroids (241 mμ) must be ascribed to the influence of the skeletal abnormality and/or of the 11-keto group, probably mostly of the latter, since this shift is not nearly so pronounced in the case of N-acetyl-Δ^4-veratraminone.

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

(13)(a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(14) O. Wintersteiner, M. Moore, and B. M. Iselin, *J. Am. Chem. Soc.*, **76**, 5609 (1954).

(15) K. Bowden and E. R. H. Jones, *J. Chem. Soc.*, 52 (1946); E. A. Braude, E. R. H. Jones, F. Sondheimer, and J. B. Toogood, *ibid.*, 607 (1949).

(16) L. S. Emerson and J. Meinwald, *J. Org. Chem.*, **21**, 375 (1956).

to the absorption spectrum of Δ^4-isojervone which is at variance with our own.[17]

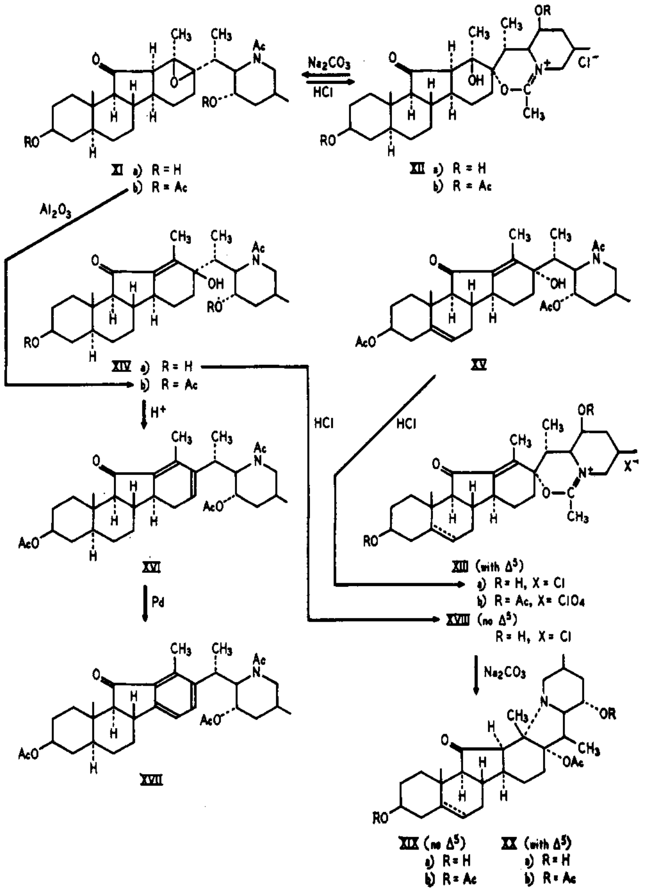
The 8,9-double bond in isojervine (IVa) and 5,6-dihydroisojervine (VIa) could be reduced with lithium in liquid ammonia. The resulting crystalline bases, 8,9-dihydroisojervine (IXa) and 5,6,8,9-tetrahydroisojervine (Xa), obtained in moderate yield only, were always contaminated with small amounts of the starting bases as evidenced by the survival, in low intensity, of the infrared bands at 5.92 and 6.10 (6.15) μ. These impurities could be removed for the most part by acetylation and chromatography of the triacetates (IXb and Xb). More satisfactory in regard to yield and purity of the product was the reduction of N-acetyl-5,6-dihydroisojervine (VIc) to N-acetyl-5,6,8,9-tetrahydroisojervine (Xc), which was needed for the conversions described later. The presence of a strong band at 5.78 (5.76) μ in the infrared spectra of the bases IXa and Xa and the N-acetyl derivative (Xc) showed that the 11-keto group is still situated in a five-membered ring C. The ultraviolet spectra of IXa and Xa and of their respective acetyl derivatives differ from that of tetrahydrojervine or 13,17a-dihydrojervine (λ_{max} 305 mμ, ϵ ~30) in that they showed two or three not too well-defined maxima in the 300–330-mμ region with higher than usual intensity [for instance Xc, 311 mμ (ϵ 168), 320 (159), 330 (100)]. The stereochemical significance of this abnormality, which is characteristic for certain types of β,γ-unsaturated ketones,[18] will be discussed later.

The presence of a third double bond in isojervine followed from the fact that N-acetyl-5,6,8,9-tetrahydroisojervine (Xc) reacted with 1 mole of perbenzoic acid with the formation of an oxide (XIa) the reactions and further transformations of which leave no doubt as to the location of this double bond in the 17,17a-position. Its ultraviolet spectrum no longer exhibited the abnormal features seen in that of the parent olefin Xc (only one poorly defined maximum at 305 mμ, ϵ 28). The acetylation product of XIa, the triacetate (XIb), could not be obtained in crystalline form. The reasons for assigning to the oxidic oxygen bonds the β configuration will become apparent later.

On short treatment at room temperature with one equivalent of hydrochloric acid in 90% methanol, the oxide XIa was transformed to the chloride of a quaternary base to which we ascribe the dihydrometoxazine structure XIIa in analogy to the quaternary base chloride (XIIIa) formed along with N-acetylisojervine from N-acetyljervine with methanolic hydrogen chloride.[9] The spectral properties of XIIa are consonant with this assignment [λ_{max}^{alc} 303 mμ (ϵ 71); λ_{max}^{Nujol} 3.00, 5.78 (11-keto group), 6.06 (>C=N⁺<) μ]. The amorphous triacetate (XIIb) obtained from XIIa by acetylation with acetic anhydride was characterized only by rotation and infrared data.

The quaternary chloride (XIIa) reverted instantaneously to the parent oxide (XIa) on treatment with sodium carbonate in aqueous methanol. This suggests a concerted reaction accompanied by inversion at C-17, analogous to the formation of oxides from diaxial *trans* bromohydrins, and make it extremely likely that in XIIa the 17a-hydroxyl group and the ring oxygen attached to C-17 are both axial, and *trans* to each other.

Another but irreversible isomerization occurred when the amorphous oxide triacetate (XIb) was adsorbed on neutral alumina from benzene solution and then eluted with ether containing a little methanol. The resulting crystalline product contained a new, nonacetylatable hydroxyl group and a new double bond conjugated with the 11-keto group as evidenced by the ultraviolet spectrum [maxima at 261 mμ (ϵ 10,300) and 355 mμ (ϵ 120)]. For the reasons given farther on we formulated this substance as the 5,6-dihydro 17-epimer (XIVb) of a compound (XV) which we obtained 10 yr. ago in the sulfuric acid-catalyzed acetolysis of 3,N-diacetyljervine ["second acetolysis product," λ_{max}^{alc} 252 mμ (ϵ 14,000) and 355 (85)][12] and assign to the two compounds the configurations shown (side chain, α in XIVb and β in XV). We have no explanation for the abnormally high λ_{max} of the main band in the spec-



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[17] Dauben, *et al.*,[4] claim that subtraction of the ultraviolet absorption curve of cholestenone from that of 23,N-diacetyl-Δ^4-isojervone (λ_{max} 232 mμ, ϵ 21,450) gives a curve exhibiting a residual maximum at 238 mμ (ϵ not given), thus "showing the presence of two separate chromophores" in this compound. The inference is that, contrary to our own conclusion from the similarity of the subtraction curve (N-acetyl-Δ^4-isojervone − N-acetyl-13,17a-dihydro-Δ^4-jervone) with the isojervine spectrum, the 4,5-double bond (or the whole ring A chromophore) of Δ^4-isojervone does *not* inhibit resonance in the $\Delta^{8,9}$-11-ketone grouping of this compound. We have, therefore, determined the curve obtained by subtraction of the cholestenone curve (λ_{max} 240 mμ, ϵ 17,000) from that of our N-acetyl-Δ^4-isojervone curve (λ_{max} 230 mμ, ϵ 23,000) in which all points on the wave-length scale were moved up by 2 mμ to make it more closely comparable to that of Dauben, *et al.*, with λ_{max} 232 mμ. The subtraction curve showed no sign of a maximum or even a shoulder at 238 mμ, and ϵ was only 4000 at this wave length. As it is most improbable that the curves of the N-acetyl and diacetyl derivatives of Δ^4-isojervone differ substantially from each other, we are forced to conclude that the claim of Dauben, *et al.*, referred to has no basis in fact.

[18] (a) R. C. Cookson and N. S. Wasiyar, *J. Chem. Soc.*, 2302 (1956); (b) H. Labhart and G. Wagnière, *Helv. Chim. Acta*, **42**, 2219 (1959); (c) C. A. Grob and A. Weiss, *ibid.*, **43**, 1390 (1960); (d) A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962).

trum of XIVb and the low ε-value as compared with that of the 252-mμ band of XV.

On hydrolysis with alkali the enone triacetate (XIVb) merely suffered O-deacetylation to give the amorphous N-acetyl derivative (XIVa) exhibiting the same ultraviolet characteristics, whereas the acetolysis product (XV) is thereby transformed into jervisine 17-monoacetate (XXa).[9,12] It is interesting that XIVa cannot be obtained from N-acetyl-5,6,8,9-tetrahydroisojervine oxide (XIa) by adsorption on neutral alumina and elution with methanol–ether as is XIVb from the triacetate (XIb) of the oxide. Indeed, elution of the more polar XIa is effected already with benzene–ether, and merely results in the recovery of a more homogeneous product with a considerably higher melting point.

The structure of the enone (XIV) rests on unambiguous evidence derived from two different reaction sequences. The first of these starts with the dehydration of the 17-hydroxyl group of the triacetate (XIVb), which was effected by prolonged heating in dioxane containing maleic acid.[19] The resulting crystalline compound showed in its ultraviolet spectrum aside from shoulders at 227 mμ (ε 9000) and 260 (5300), a high maximum at 317 mμ (ε 10,500) comparable with that at 314 (7620) of cholesta-2,4-dien-6-one,[20] and hence must be the homoannular dienone (XVI). Conclusive proof for the correctness of this assignment and hence for the structure of the enone was adduced by dehydrogenating XVI with palladium in boiling cymene[21] to the known[22] triacetyl-5,6-dihydro-11-ketoveratramine (XVII).

The other reaction sequence by which the enone (XIV) was correlated with a compound of known structure preserves the asymmetry of C-17 and thus was instrumental in defining the configuration of this carbon atom in XIV. When the amorphous N-acetyl derivative of the enone (XIVa) was treated with one equivalent of hydrochloric acid in aqueous methanol, it was transformed into the chloride of a base, the ultraviolet spectrum of which resembled that of the quaternary base chloride (XIIIa) resulting from the treatment of N-acetyljervine with methanolic hydrogen chloride[9] in that it exhibited a high maximum at 243 mμ (ε 14,800). That this new base chloride from the enone (XIVa) was nothing else but the 5,6-dihydro derivative (XVIII) of the salt (XIIIa) followed from its conversion by sodium carbonate to a weak tertiary base which was identified as 5,6-dihydrojervisine 17-monoacetate (XIXa), as an identical product was obtained by catalytic reduction of the 5,6-double bond of jervisine 17-monoacetate (XXa), the basic rearrangement product formed from the chloride (XIIIa) with sodium carbonate. The identity of the base monoacetate from the salt (XVIII) with that obtained by reduction of jervisine 17-monoacetate (XXa) was confirmed by acetylation of the two specimens to the same triacetate (XIXb).

It will be recalled that the conversion of the amorphous enone (XIVa), in which the 3- and 23-hydroxyl groups are free, to the quaternary chloride (XVIII) was effected with one molar equivalent of hydrochloric acid in aqueous methanol. Strangely, similar treatment of the crystalline enone *triacetate* (XIVb) left this compound unchanged. That the 23-hydroxyl groups must be free before this reaction can proceed also would appear from the fact to be reported in the following paper that the conversion of a compound analogous to XIVb (with the 23-hydroxyl group acetylated) to the corresponding quaternary chloride of type XVIII could be brought about by excess hydrogen chloride in anhydrous methanol, conditions which also effect the loss of the 23-acetyl group.

It was of interest to ascertain how the fully acetylated enone (XV), which must differ from the enone (XIVb) by epimerism at C-17 (and the presence of the 5,6-double bond), would behave in this respect. That XV can be transformed into quaternary salts of type XVIII by acidic reagents was already clear from a study of the perchloric acid-catalyzed acetolysis of diacetyljervine in which it was shown that XV (as well as diacetyljervine) on treatment with acetic anhydride and acetic acid containing perchloric acid form the 3,23-dicetylated dihydrometoxazine perchlorate (XIIIb) in good yield.[12] We have now found that XV behaves like the enone (XIVb) in that it is not changed by aqueous methanolic 0.1 *N* hydrochloric acid, but with methanolic hydrogen chloride gave as expected the acetyl-free quaternary chloride (XIIIa), though in poor yield. There is no doubt then that these quaternary dihydrometoxazine salts are formed under acidic conditions from enones of type XIV, as well as from their 17-epimers, and that an inversion at C-17 must, therefore, occur in this reaction with one class of epimers but not with the other. The reasons for our belief that it is XIV and its congeners which react with inversion will be given subsequently.

Finally, reference should be made to an anomaly apparently at variance with the β,γ-unsaturated ketone structures assigned to 5,6-dihydroisojervine and 5,6,8,9-tetrahydroisojervine, namely, their failure to undergo isomerization, on treatment with strong alkali, to the corresponding α,β-($\Delta^{13,17a}$)-unsaturated ketones (*cf.* preparation of N-acetyl-5,6-dihydroisojervine from the triacetate). Since there was a remote possibility that the enolization of the 11-keto group towards C-13 was reversible, *i.e.*, that proton addition occurred at C-13 instead of at C-17, the ultraviolet spectra of N-acetyltetrahydroisojervine and of triacetyl-5,6-dihydroisojervine were measured in 1% methanolic potassium hydroxide solution kept under nitrogen. In the case of the tetrahydro compound the slow emergence of a maximum at 247 mμ, the intensity of which corresponded to ε 6900 after 24 hr. and became constant in about 5 days at ε 8450, was indeed observed under these conditions. Acidification with hydrochloric acid produced no change in the position and the intensity of this maximum either immediately or on standing. This observation was not follow up preparatively, but there cannot be much doubt that the α,β-unsaturated ketone with the double bond in the 13,17a-position was

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[19] The use of maleic acid for this purpose goes back to an early attempt to aromatize ring D of the Δ^4-isojervone analog of XIVb by simultaneous dehydration and dehydrogenation; the latter reaction was to be effected by palladium in boiling dioxane with maleic acid serving as the hydrogen acceptor. However, only dehydration resulting in homoannular diene formation occurred. Since the yield of dehydration product was reasonably good also in the absence of palladium, the method was subsequently used routinely for the preparation of XVI and of its more unsaturated analogs described in the following paper.

[20] H. Reich, F. E. Walden, and R. W. Collins, *J. Org. Chem.*, **16**, 1953 (1951).

[21] D. Rosenthal, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **84**, 877 (1962).

[22] O. Wintersteiner and N. Hosansky, *ibid.*, **74**, 4474 (1952).

formed. The lower extinction coefficient as compared with that of jervine and the acetolysis product (XV) indicates that the reaction leads to an equilibrium at which the ratio of the two ketones is about 1:1.

In contrast, the spectrum of triacetyl-5,6-dihydroisojervine remained completely unchanged in the presence of alkali for a 24-hr. period. Alkali is, therefore, incapable of promoting the formation of the conjugated trienic system which would result from enolization of the keto group towards C-13 and on reketonization give the $\Delta^{8,9,13-17a}$-cross-conjugated dienone.

Stereochemistry.—There can be no doubt that the C-14 hydrogen atom in tetrahydroisojervine (X) must be α-oriented as it is in jervine,[3e] since both these compounds have been converted to jervisine derivatives (XX and XIX, respectively) by reactions which do not involve this carbon atom. Since the latter statement, as will be shown in the following paper of this series, applies also to 5,6-dihydrojervine and N-acetyl-Δ^4-isojervone, we believe, albeit with the reservations set forth in that paper, that these compounds and hence isojervine itself likewise have the 14α configuration.

The proposition that C-13 in tetrahydroisojervine (and in isojervine itself if the 14α configuration is accepted for this compound) likewise has the α configuration is based on the following evidence indicating that rings C and D are *cis* linked.

(1) The Dreiding models of both isojervine and tetrahydroisojervine show that the C/D system is far more strained in the $13\beta,14\alpha$-*trans* than in the $13\alpha,14\alpha$-*cis* form.[23]

(2) The abnormal ultraviolet absorption characteristics of 8,9-dihydroisojervine (IXa) and 5,6,8,9-tetrahydroisojervine (Xa) and their acetylated derivatives (two or three maxima at 300–330 mμ, ϵ 100–260) are not seen in the spectra of other jervine or isojervine derivatives having an isolated 11-keto group (*e.g.*, 13,17a-dihydrojervine, jervisine, XI, XII, which show λ_{max} ~305 mμ with ϵ 30–70) and are, therefore, connected with the 17,17a-double bond. Similar characteristics (two to three maxima with ϵ-values from 100 to 800) are exhibited by a number of β,γ-unsaturated ketones[18] in which the C=O and C=C elements are noncoplanar and twisted against each other in such a fashion that the p-orbitals of the carbonyl and β-atoms can be assumed to overlap to a greater or lesser extent. The scale models of X shows that the $13\alpha,14\alpha$ isomer conforms with this description much better than the essentially flat $13\beta,14\alpha$-*trans* isomer.

(3) In 1954 we described an acetolysis product of diacetyltetrahydrojervine[14] which differs from triacetyltetrahydroisojervine only by having its single double bond in the 16,17- instead of the 17,17a-position. This strongly levorotatory compound is isomerized by alkali, with concurrent loss of the O-acetyl groups, to a dextrorotatory N-acetyl derivative which on reacetylation furnishes a likewise dextrorotatory isotriacetate. We recently have shown (n.m.r.) that the two isomers are 13-epimers, and from equilibrium studies on the two epimers and their respective 16,17-dihydro derivatives obtained convincing evidence permitting us to formulate the iso compound, which predominates in the equilibrium mixture in the ratio 3:1, as the $13\beta,14\alpha$-*trans* isomer, and the original acetolysis product as the $13\alpha,14\alpha$-*cis* isomer.[24] The "opposed" 16,17-double bond, together with the β-oriented and hence quasi-equatorial 17a-methyl group, thus stabilizes the *trans* junction of rings C and D in the Δ^5-hydrinden-1-one system represented by these rings. This parallels the greater stability of *trans*- *vs.* *cis*-Δ^2-octalins.[25] Since, on the other hand, the double bond in Δ^1-octalins stabilizes the *cis vs.* the *trans* form,[25] it is reasonable to assume that this holds also for the comparable Δ^6-hydrindenone system of tetrahydroisojervine. True, N-acetyltetrahydroisojervine is not stable to alkali as it should be according to this postulate, but this is because the basic reagent promotes the shift of the double bond into conjugation with the 11-keto group. On the other hand, the fact that N-acetyl-5,6-dihydroisojervine (which does not undergo this isomerization) is, in contrast to the abovementioned 16,17-olefin, *not* epimerized at C-13 by alkali in its preparation from the triacetate may be interpreted as supporting the prior proposition that the 17,17a-double bond stabilizes the *cis* junction of rings C and D, and that isojervine, therefore, has the $13\alpha,14\alpha$ configuration.

The configurations of carbon atoms 8 and 9 in 8,9-dihydroisojervine (IX), 5,6,8,9-tetrahydroisojervine (X), and all compounds derived from the latter must be on the basis of the correlation of X with jervisine and veratramine, and likewise be the same as in jervine.[3e] The configurations of carbon atoms 22, 23, and 25[3b–d] follow, of course, from the correlation with veratramine. The configuration of C-20 has as yet not been established experimentally, but may be assumed to be the same as that in rubijervine and hence as in normal sterols since this alkaloid, which possesses a normal steroid skeleton, has been correlated with sarsasapogenin *via* 5β-solanidanol.[26]

There remain to be discussed the configurations assigned to C-17 and C-17a in the transformation products (XI, XII, and XIX) and to C-17 in the enone (XIV) and the quaternary base chloride (XVIII).

The postulate that the oxiran ring in the 17,17a-oxide (XI) and its congeners (paper XII in this series) is β-oriented is based on the following argument which also defines the configuration at C-17 of the enone (XIV). In a previous paper[9] it was proposed for good reasons that all the solvolysis products of jervine including enone XV (the 17-epimer of XIV otherwise differing from it only by the presence of the 5,6-double bond) and the dihydrometoxazine salts (XIIIa and b) correspond to the native alkaloids in regard to the configuration of C-17, and that this is the "natural" configuration with the side chain β-oriented. More direct evidence supporting this view is now at hand with the ultraviolet spectrum of XIV. While the spectra of jervine and XV are very similar [λ_{max} 250 mμ (ϵ 15,000), 252 (14,000)], that of XIV is markedly different [λ_{max}

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(23) In the *cis* form of both compounds two conformations of ring D are possible, both of which resemble a distorted boat rather than a distorted half-chair in that the 13- and the 14-hydrogen atoms are both either quasi-equatorial or quasi-axial in respect to this ring. In the former C-14 and C-15 lie below the plane of carbon atoms 13, 17a, 17, and 16; in the latter, above that plane.

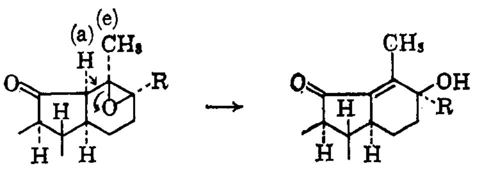
(24) O. Wintersteiner and M. Moore, to be published.

(25) D. A. H. Taylor, *Chem. Ind.* (London), 250, (1954); A. S. Dreiding, *ibid.*, 1419 (1954).

(26) F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945); Y. Sato and W. A. Jacobs, *ibid.*, **179**, 623 (1949).

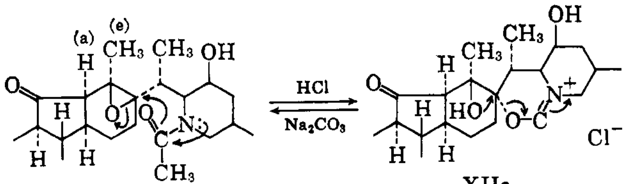
261 $m\mu$ (ϵ 10,300)] from that of jervine.[27] It may then be assumed with some confidence that XIV has the 17-hydroxyl group instead of the side chain β-oriented, and this means that its precursor XIb must be the 17β,17aβ-oxide.

The alumina-catalyzed isomerization XIb → XIVb can then be visualized to proceed by the concerted mechanism shown below to which XI would be predisposed by the near coplanarity of the four reacting centers involved.[28]



XIb XIVb

The nucleophilic displacement of the oxide oxygen at C-17 by the N-acetyl oxygen in the facile formation of the dihydrometoxazine chloride (XIIa) from XIa with hydrochloric acid, as well as the equally facile reverse reaction induced by sodium carbonate, is undoubtedly concerted, so that XIIa must be formulated with the side chain β, and the linkage of the metoxazine oxygen with C-17 α as shown.

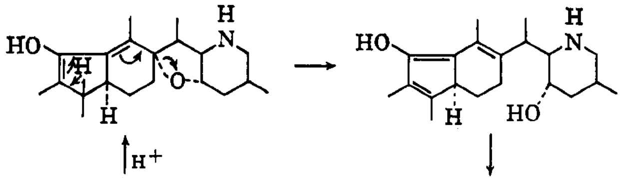


XIa XIIa

In regard to the cyclic quaternary base chloride (XVIII), this compound must have the C-17 stereochemistry depicted (side chain β), because (1) it is transformed by sodium carbonate instantaneously into 5,6-dihydrojervisine 17-monoacetate (XIXa), and (2) jervisine 17-monoacetate (XXa) has been obtained with stronger alkali directly from the enone (XV),[12] in which, as argued further earlier, the side chain is β-oriented. Therefore, it is in the acid-catalyzed reaction leading from the 5,6-dihydro-17-epimer of XV, enone XIV, to XVIII, and not in the analogous reaction XV → XIIIa, where inversion at C-17 must have occurred.

The C-13 and C-17a configurations shown in jervisine derivatives XIX and XX are admittedly postulates unsupported by experimental evidence. They have been chosen for no other reason than that the models of the other three stereoisomers show more unfavorable interactions (or one that is severely so) than that of XIX and that, in one case (the 13β-epimer of XIX), the model cannot be assembled unless ring D is made a boat. Although even in XIX there is a 1,3-diaxial relationship of the 18- and 21-methyl groups, these are tilted away from each other so that their separation in space is greater than it would be in a cyclohexane ring.

Mechanism of Formation of Isojervine.—We visualize the isomerization of jervine to isojervine to proceed by the mechanism depicted.



I IVa

The acid-catalyzed enolization towards C-9, which is assumed to initiate the reaction, would depend, as a prototropic change,[29] on the availability in high concentration of hydrogen ions (to form the conjugated acid at the carbonyl oxygen) and of chlorine ions (the "base" abstracting the 9α-proton), and hence would be expected to proceed only in ionizing solvents. This accords with the fact that the isomerization has so far been found to occur only when water[1] or methanol was used as the solvent, whereas in water-free media (acetic anhydride), acid catalysis merely results in the (acetolytic) cleavage of the oxygen–C-17 linkage in ring E. To reassure ourselves on this point, we have treated N-acetyljervine with hydrogen chloride in chloroform carefully freed from ethanol and moisture and found that, aside from a small amount of the quaternary chloride (XIII), only traces of N-acetylisojervine were formed, in spite of the fact that the reaction was allowed to proceed for as long as 20 hr.

Experimental

The melting points were taken in open Pyrex glass capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semimicrotube, with chloroform as the solvent, unless indicated otherwise. The ultraviolet spectra were measured in absolute ethanol in a Cary self-recording instrument Model 11 M. The infrared spectra were determined on Nujol mulls in the Perkin-Elmer double beam self-recording spectrophotometer Model 21. The characteristics of the infrared bands are expressed in the text as follows: (s), strong; (m), medium; (l), low; (vl), very low; (br), broad; (sh), shoulder. The analytical samples were dried at 110° (2 mm.) unless indicated otherwise.

Isojervine (IVa) was prepared from jervine with methanolic hydrogen chloride (room temperature, 1 hr.) as described by Jacobs and Craig.[1] In a typical experiment starting with 5 g. of jervine, 2.67 g. of the chloroform adduct, m.p. 140–149°, was obtained. Two recrystallizations from acetone of this material with an additional 400 mg. obtained from the mother liquor yielded the acetone compound, m.p. 105–112°, lit.[1] m.p. 105–112°. This preparation, as well as those from other runs, showed somewhat higher levorotation ($[\alpha]^{23}\text{D}$ −36 to 37° in 95% ethanol) than found by Jacobs and Craig (−32°). Contrary to the experience of these authors we could not remove the acetone by drying at 110° (2 mm.), 3 hr., weight loss of 7.1%.

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[27] The scale models of the two "epimers" give no clue as to what these spectral differences may mean in spatial terms. If ring D is made a half-chair, there is no difference in the dihydral angles formed by the two 17-substituents with the plane of the adjacent α,β-unsaturated ketone systems, since not only C-14, C-13, C-17a, and C-17, but also C-16 lie in that plane. If, however, ring D is a boat, then the β-substituent likewise lies in that plane, while the α-substituent becomes truly axial. It is possible that the tendency of the bulky β-oriented side chain in XV to assume a more equatorial conformation might stabilize ring D in a form intermediate between half-chair and boat. The 17α-hydroxyl would then become more truly axial and apt to interact with the π-electrons at the C-terminal of the resonating system.

[28] One of the referees pointed out that the isomerization need not be initiated by base, but could be an acid-catalyzed reaction in which the alumina acts as a Lewis acid. In that event a carbonium ion mechanism would be operative which does not require a *trans*-diaxial relationship of the 13- and 17a-substituents, and hence α-orientation of the 13-hydrogen. While it is true that there is no proof for the concerted mechanism postulated, it must be pointed out that acid catalysis promotes the isomerization of XIb to the cyclic base salt (XIIb), not to the enone (XIVb).

[29] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., p. 553.

Anal. Calcd. for $C_{27}H_{39}O_3N \cdot C_3H_6O$ (483.7): C, 74.49; H, 9.38. Found: C, 74.33; H, 9.46.

The ultraviolet characteristics were identical with those rereported by Jacobs and Huebner[2,30]; chloroform adduct, $\lambda_{\max}^{\text{Nujol}}$ 3.05 (m), 5.92 (s), 6.04 (vl), 6.11 (m) μ.

As noted by Jacobs and Huebner,[2] isojervine immediately produces a wine-red pigment when treated in alcoholic solution with alkali hydroxides. Little or no isojervine could be extracted from such solutions with chloroform after standing overnight and dilution with water.

The preparation of **N-acetylisojervine** (**IVc**) by isomerization of N-acetyljervine has been described in the preceding paper of this series[9]; m.p. 207–210° (lit.[2] m.p. 202–203°); $[\alpha]^{25}\mathrm{D}$ +15° (*c* 0.930); ultraviolet spectrum identical with that of free base; $\lambda_{\max}^{\text{Nujol}}$ 3.00 (s), 5.92 (s), 6.14, 6.20 (doublet, s) μ.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.47; H, 8.84. Found: C, 74.31; H, 8.84.

Addition of alkali hydroxide (but not of ammonia or potassium carbonate) to a methanolic solution of N-acetylisojervine produced an intense cherry-red color which in time turned brown-red. In a preparative experiment a solution of 100 mg. in 6 ml. of 5% methanolic potassium hydroxide which had been allowed to stand overnight was concentrated, diluted with water, and extracted with chloroform. The extract was washed with 2 *N* hydrochloric acid and water, dried, and evaporated, yielding 35 mg. of a yellow gum. The acid phase after alkalinization yielded only 3 mg. of chloroform-extractable bases, while the original alkaline solution was found to contain substantial amounts (27 mg.) of chloroform-soluble acids. The balance appeared to consist of amphoteric products. Similar results were obtained when the potassium hydroxide concentration was reduced to 0.1 *N*. Under the latter conditions, N-acetyljervine was recovered in virtually quantitative yield in the neutral fraction.

The **triacetate** (**IVb**) was obtained from the base by acetylation with acetic anhydride and pyridine in the usual manner (room temperature, 20 hr.), m.p. 187–190°, unchanged after chromatography; $[\alpha]^{25}\mathrm{D}$ +29° (*c* 0.988).

Anal. Calcd. for $C_{33}H_{45}O_6N$ (551.7): C, 71.84; H, 8.22. Found: C, 71.72; H, 7.87.

A specimen prepared in the same manner from N-acetylisojervine melted at 187–189° (no depression in mixture) and had $[\alpha]^{23}\mathrm{D}$ +26°.

N-Methylisojervine (**IVd**).—N-Methyljervine[10] (m.p. 205–209°, $[\alpha]^{24}\mathrm{D}$ −98°, 150 mg.) was dissolved in methanol (4 ml.) which had been saturated at 0° with gaseous hydrogen chloride. The solution was allowed to stand at room temperature for 1 hr. and was then worked up as in the preparation of isojervine.[1] The amorphous crude product (150 mg.), on recrystallization from 33% aqueous ethanol and then from methanol–ethyl acetate, yielded rods (38 mg.) melting with decomposition at 220–224°, $[\alpha]^{25}\mathrm{D}$ 0° (*c* 0.45, ethanol). The ultraviolet spectrum was practically identical with that of isojervine; $\lambda_{\max}^{\text{Nujol}}$ 3.00 (m), 5.92 (s), 6.12 (m) μ. The analytical sample lost no weight on drying at 110° (2 mm.) for 3 hr.

Anal. Calcd. for $C_{28}H_{41}O_3N$ (439.6): C, 76.49; H, 9.40. Found: C, 76.35; H, 9.48.

N-Methylisojervine gave an orange color on treatment with methanolic potassium hydroxide.

N-Acetyl-Δ^4-isojerv-3-one (**V**).—N-Acetylisojervine (1.00 g.) was dissolved in dry benzene (20 ml.) and dry acetone (30 ml.). Aluminum *t*-butylate (4 g.) in benzene (40 ml.) was added, and the mixture was boiled under reflux for 21 hr. After chilling and decomposition of the reagent with cold 1 *N* sulfuric acid the product was recovered by repeated extraction with benzene. The extract was washed successively with dilute sulfuric acid, sodium bicarbonate solution, and water, dried, and freed from solvent *in vacuo*. Since the crystalline product obtained from the residue with acetone appeared to be a mixture, the total material (705 mg.) was subjected to treatment with Girard's reagent T (750 mg.) and separated into ketonic and nonketonic fractions in the usual manner. From the nonketonic fraction 158 mg. of starting material, m.p. 199–202°, was recovered. The ketonic fraction (325 mg.) extracted from the acidified (pH 1) aqueous phase with chloroform yielded on crystallization from ethyl acetate square platelets (252 mg.) melting at 234–239°. On further recrystallization from methanol–ethyl acetate the melting point became constant at 239–241.5°; $[\alpha]^{25}\mathrm{D}$ +199° (*c* 0.983); $\lambda_{\max}^{\text{alc}}$ 230 mμ (ϵ 22,300), 331 (198); $\lambda_{\max}^{\text{Nujol}}$ 3.00 (m), 5.96 (s), (sh, l), 6.16 (sh, m), 6.22 (s) μ.

Anal. Calcd. for $C_{29}H_{39}O_4N$ (465.6): C, 74.80; H, 8.44. Found: C, 74.89; H, 8.35.

When a small sample of V was dissolved in 5% methanolic potassium hydroxide, a pink color developed immediately which turned deep blue on warming.

5,6-Dihydroisojervine (**VIa**).—Isojervine acetonate (983 mg.) was dissolved in benzene (50 ml.) and the solution was brought to dryness to remove the acetone. After two repetitions of the procedure the residue was dissolved in absolute ethanol (20 ml.), and the solution added to a prehydrogenated suspension of 5% palladium-on-charcoal catalyst (1.0 g.) in ethanol (8 ml.). Shaking under hydrogen was continued till the uptake stopped after 2.75 hr. at 56 ml. (calcd. for 1 molar equiv., 50.8 ml.). After filtering off the catalyst the solution was brought to dryness, and the residue (small plates) recrystallized first from aqueous methanol (needles, m.p. 144–147°, 798 mg.) and then from ethyl acetate; (m.p. 155–157°, unchanged after drying at 110° (2 mm.); weight loss, 1.9%; $[\alpha]^{23}\mathrm{D}$ −23° (*c* 0.506, 95% ethanol).

Anal. Calcd. for $C_{27}H_{41}O_3N \cdot {}^1/_2H_2O$ (436.6): C, 74.27; H, 9.70. Found: C, 74.76; H, 9.47.

Prolonged drying at 137° (2 mm.) of the crystals obtained from ethyl acetate, acetone, or chloroform usually raised the melting point to the range 170–176°. Samples dried in this manner, although they gave analyses somewhat too high in carbon, were used for the spectral measurements; $\lambda_{\max}^{\text{alc}}$ 238 mμ (ϵ 9500), 333 (210) $\lambda_{\min}^{\text{alc}}$ 224 (6980); $\lambda_{\max}^{\text{Nujol}}$ 2.95 (sh, s), 3.15 (s), 5.92 (s), 6.15 (s) μ.

In our early experiments the hydrogenation was carried out with prereduced platinum dioxide catalyst in glacial acetic acid. Although the uptake usually exceeded 2 moles, only the dihydro base of the properties described before could be isolated, albeit in somewhat lower yield.

For the preparation of the **triacetate** (**VIb**), a solution of the base (71 mg.) in 1:1 acetic anhydride–pyridine (2 ml.) was allowed to stand overnight, and then worked up in the usual way. The crystalline product (104 mg.) was recrystallized from aqueous ethanol and then twice from ethyl acetate, from which it formed needles melting at 209–211°; $[\alpha]^{20}\mathrm{D}$ +37.5° (*c* 1.05); $\lambda_{\max}^{\text{alc}}$ 238 mμ (ϵ 10,300), 332 (135); $\lambda_{\max}^{\text{Nujol}}$ 5.76 (s), 5.92 (s), 6.12 (s), 8.08 (s) μ.

Anal. Calcd. for $C_{33}H_{47}O_6N$ (553.7): C, 71.58; H, 8.56. Found: C, 71.77; H, 8.41.

A product with nearly identical properties [m.p. 208–210°, $[\alpha]^{21}\mathrm{D}$ +35.7°; $\lambda_{\max}^{\text{alc}}$ 238 mμ (ϵ 9000), 332 (143)] was obtained by catalytic hydrogenation with palladium–charcoal in ethanol of triacetylisojervine (IVb). The catalytic reduction of the latter with platinum oxide in acetic acid likewise led to VIb, in this case in good yield since the uptake was confined to 1 mole. The infrared spectra of all three specimens were identical.

Similarly, hydrogenation of N-acetylisojervine (IVc) in ethanol with palladium black afforded **N-acetyl-5,6-dihydroisojervine** (**VIc**) in satisfactory yield. Thus, 3.035 g. of IVc, after taking up in 2.75 hr. 180 ml. of hydrogen (calcd., 159 ml.), gave 1.71 g. of twice recrystallized VIc as plates from ethyl acetate; m.p. 183–185°; $[\alpha]^{22}\mathrm{D}$ +30.6° (*c* 0.782); $\lambda_{\max}^{\text{alc}}$ 238 mμ (ϵ 9400), 333 (207); $\lambda_{\max}^{\text{Nujol}}$ 3.03 (s), 5.95 (s), 6.11 (s), 6.22 (s) μ.

Anal. Calcd. for $C_{29}H_{43}O_4N$ (469.6): C, 74.16; H, 9.23. Found: C, 74.21; H, 9.14.

On acetylation in pyridine the compound was nearly quantitatively transformed to the triacetate (VIb). Conversely, pure VIc was recovered after one recrystallization from the product obtained by refluxing a solution of VIb in 5% methanolic potassium hydroxide for 0.5 hr.

Triketone VII from N-Acetyl-5,6-dihydroisojervine (**VIc**).—A solution prepared by diluting 0.50 ml. of the chromic acid reagent, specified by Djerassi, *et al.*[13b] (26.72 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid diluted with water to 100 ml.), to 10 ml. with reagent grade acetone was added dropwise from a buret to compound VIc (119 mg., 0.253 mmole) dissolved in pure dioxane (8 ml.). After addition of 4.20 ml. (0.61 matom of oxygen) the solution was allowed to stand for 10 min., treated with a few drops of 95% ethanol, and brought to dryness *in vacuo*. The residue was taken up in chloroform; the latter was washed with bicarbonate solution and water, dried, and evaporated. The residue was recrystallized thrice from ethyl acetate–hexane, yielding rosettes of needles; m.p. 185–187°; $[\alpha]^{22}\mathrm{D}$ −67°

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[30] A measurement carried out in 1951 at the University of Manchester with a Unicum SP-500 instrument showed the absence of maxima in the 200–220-mμ region. The ϵ-values were 6100, 8200, and 9900 at 220, 210, and 203 mμ, respectively. We wish to express our sincere thanks to Dr. H. B. Henbest and Dr. G. W. Wood for making available to us these data.

(*c* 0.488); the ultraviolet absorption curve exhibited a shoulder at 230 mμ (ε 11,500), a maximum at 305 (285), and shoulders at 323 and 335 (228, 150); $\lambda_{\max}^{\text{Nujol}}$ 5.85 (s), 5.95 (s), 6.10 (s), no band at ~3.0 μ.

Anal. Calcd. for $C_{29}H_{39}O_4N$ (465.6): C, 74.80; H, 8.44. Found: C, 74.89; H, 8.56.

The triketone was recovered unchanged after refluxing in 0.1 *N* methanolic potassium hydroxide solution for 5 min.[13b] (melting point infrared spectrum). The shoulder at 230 mμ in the ultraviolet spectrum was, however, somewhat increased in height (ε 13,200), possibly due to contamination of the starting material with the Δ^5-unsaturated compound corresponding to VIc.

N-Acetyl-4,5-dihydroisojerv-3-one (VIII).—N-Acetyl-Δ^4-isojervone (V, 120 mg.) was hydrogenated in pure ethanol (17 ml.) with palladium–charcoal (130 mg.) as the catalyst. The uptake of hydrogen gas stopped after 10 min. with 7.1 ml. of gas consumed (calcd. 6.3 ml.). The residue from the filtered solution was recrystallized twice from ethyl acetate, from which it formed small plates (85 mg.) melting at 216–218°; $[\alpha]^{21}\text{D}$ +37°; $\lambda_{\max}^{\text{alc}}$ 237 mμ (ε 9700), 332 (186); $\lambda_{\min}^{\text{alc}}$ 225 mμ (ε 9100); $\lambda_{\max}^{\text{Nujol}}$ 3.01 (s), 5.84 (s), 5.95 (s), 6.22 (s) μ.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.48; H, 8.84. Found: C, 74.78; H, 8.87.

8,9-Dihydroisojervine (IXa).—Isojervine acetonate (984 mg.) was freed from acetone by distillation with benzene as previously described. The sample, dissolved in tetrahydrofuran (25 ml.), was added slowly with mechanical stirring to a solution of lithium metal (240 mg.) in liquid ammonia (100 ml.) kept at acetone–solid carbon dioxide temperature and protected from outside moisture. After 1.3 hr. ammonium chloride (3 g.) was added in portions, and the ammonia was allowed to evaporate at room temperature. The reduced material, isolated by extraction with chloroform, was dissolved in warm ethanol, from which it deposited as small plates on addition of water to the point of incipient turbidity (534 mg.), m.p. 123–127°, after recrystallization 127–130°. Since the base formed a sparingly soluble chloroformate the rotation had to be measured in ethanol: $[\alpha]^{20}\text{D}$ −16.5° (*c* 0.792). The ultraviolet spectrum showed only end absorption (ε 3360 at 220 mμ) and a plateau between 310 and 323 mμ (ε 195); $\lambda_{\max}^{\text{Nujol}}$ 3.07 (ms, br) 5.78 (ms), 5.90 (l), 6.12 (vl) μ. The presence of a small amount of unreduced isojervine, indicated by the survival of the 5.90-μ band, also revealed itself in the gradual development of a faint pink color on alkalinization of an ethanolic solution.

The analyses, carried out on material dried at 100° (drying at 110° caused decomposition), gave varying results, generally on the low side for both carbon and hydrogen.

For the preparation of the **triacetate (IXb)** 259 mg. of the base were acetylated in the usual manner. The crude product was dissolved in 1:1 benzene–hexane and chromatographed on alumina (Woelm, almost neutral, activity grade I). Most of the material (185 mg.) was recovered in crystalline form in the fractions eluted with the above solvent mixture. It was recrystallized to constant melting point (156–160°, 159–161° after drying) from acetone–hexane and then hexane alone; $[\alpha]^{22}\text{D}$ +49° (*c* 0.860); $\lambda_{\max}^{\text{alc}}$ 310 mμ (ε 270), 320 (265); $\lambda_{\max}^{\text{Nujol}}$ 5.76 (sh, s), 5.80 (vs), 5.92 (vl), 6.10 (s), 8.03 (s) μ.

Anal. Calcd. for $C_{33}H_{47}O_6N$ (553.7): C, 71.58; H, 8.56. Found: C, 71.54; H, 8.89.

5,6,8,9-Tetrahydroisojervine (Xa).—5,6-Dihydroisojervine (VIa, 149 mg.) was reduced with lithium (40 mg.) in liquid ammonia as described above for isojervine. The partly crystalline reduction product was recrystallized three times from aqueous ethanol, yielding 54 mg. of small rods; m.p. 147–149°; $[\alpha]^{21}\text{D}$ +20.4° (*c* 0.961, ethanol); the ultraviolet spectrum showed shoulders at 230 mμ (ε ~2300) and 332 (145) and maxima at 310 (223) and 320 (221); $\lambda_{\max}^{\text{Nujol}}$ 2.91 (s), 3.10 (s, br), 5.78 (s), 5.90 (ml), 6.12 (ml) μ.

Anal. Calcd. for $C_{27}H_{43}O_3N \cdot {}^1/_2C_2H_5OH$ (452.7): C, 74.29; H, 10.25. Found: C, 74.58; H, 9.93.

Since the spectral data indicated contamination with about 20% starting material, the experiment was repeated but with the difference that more lithium metal was added at intervals along with the solution containing the substance. This caused the blue color of the reaction mixture to persist for 1.5 hr. However, the spectral properties of the final product were not appreciably different from those of the first specimen.

The **triacetate (Xb)**, obtained in good yield without chromatography, melted at 173–175° after three recrystallizations from hexane, $[\alpha]^{22}\text{D}$ +63° (*c* 0.894). While the ultraviolet spectrum no longer exhibited the shoulder at 230 mμ, the infrared spectrum showed, aside from the bands at 5.78 (br) and 6.12 (s) μ, still a low band at 5.94 μ indicating contamination with the triacetate (VIb).

Anal. Calcd. for $C_{33}H_{49}O_6N$ (555.7): C, 71.32; H, 8.89. Found: C, 71.75; H, 8.99.

N-Acetyl-5,6,7,8-tetrahydroisojervine (Xc).—A solution of N-acetyl-5,6-dihydroisojervine (458 mg.) in dry tetrahydrofuran (30 ml.) was added dropwise with magnetic stirring and under anhydrous conditions to a solution of lithium (221 mg.) in liquid ammonia (200 ml.) cooled in a bath of acetone–solid carbon dioxide. After 1 hr., ammonium chloride (2 g.) was added slowly and then the ammonia was allowed to evaporate at room temperature. Water was added and the product was isolated by extraction with chloroform which was then washed with hydrochloric acid and water. The residue of the dried chloroform phase was crystallized twice from ethyl acetate, yielding 257 mg. of platelets which melted at 225–228°; $[\alpha]^{20}\text{D}$ +53° (*c* 0.818); $\lambda_{\max}^{\text{alc}}$ 311 mμ (ε 169), 322 (153), 331 (107); $\lambda_{\max}^{\text{Nujol}}$ 2.95 (m), 3.09 (m), 5.76 (s), 5.91 (l), 6.20 (s), 7.92 (m) μ.

Anal. Calcd. for $C_{29}H_{45}O_4N$ (471.7): C, 73.84; H, 9.62. Found: C, 73.95; H, 9.27.

N-Acetyl-5,6,8,9-tetrahydroisojervine 17,17a-Oxide (XIa).—N-Acetyl-5,6,8,9-tetrahydroisojervine (209 mg., 0.44 mmole) was treated with perbenzoic acid (0.690 mmole) in chloroform (50 ml.) at 4° for 48 hr., after which time 1.06 molar equiv. of the reagent had been consumed. The solution, diluted with an equal volume of chloroform, was washed with sodium bicarbonate and water. The glassy residue (253.3 mg.) from the dried and evaporated chloroform solution was twice crystallized from ethyl acetate yielding rods (109 mg.) melting at 195.5–198.5°. The melting point was raised to 231–235° by stirring a chloroform solution of the oxide with Woelm neutral alumina for 20 min., transferring to a chromatographic tube, and eluting with chloroform; $[\alpha]^{20}\text{D}$ −22° (*c* 0.617); $\lambda_{\text{sh}}^{\text{alc}}$ 235 mμ (ε 1020); $\lambda_{\max}^{\text{alc}}$ 305–310 mμ (ε 22); $\lambda_{\max}^{\text{Nujol}}$ 3.00 (m), 5.78 (s), 5.93 (l), 6.20 (s), 7.98 (m) μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$ (487.7): C, 71.42; H, 9.30. Found: C, 71.26; H, 9.32.

The **triacetate (XIb)** prepared from XIa in the usual manner with anhydrous pyridine and acetic anhydride could not be crystallized; $[\alpha]^{20}\text{D}$ −9.4° (*c* 0.682); $\lambda_{\max}^{\text{Nujol}}$ 5.75 (s), 6.08 (m), 8.05 (s) μ.

Dihydrometoxazine Chloride (XIIa) from Oxide XIa.—N-Acetyl-5,6,8,9-tetrahydroisojervine 17,17a-oxide (XIa, 40 mg.) was dissolved in 90% methanol (5 ml.) and treated with 0.1 *N* hydrochloric acid (1 ml.). After 0.75 hr. at room temperature, the reaction mixture was evaporated to dryness *in vacuo* and the residue was twice crystallized from methanol and ethyl acetate, yielding needles (33 mg.) which melted at 197.5–201°; $[\alpha]^{21}\text{D}$ +59° (*c* 0.760, absolute ethanol); $\lambda_{\max}^{\text{alc}}$ 303 mμ (ε 71); $\lambda_{\max}^{\text{Nujol}}$ 3.00 (s), 5.78 (s), 6.06 (s) μ.

Anal. Calcd. for $C_{29}H_{46}O_5NCl \cdot 2CH_3COOC_2H_5$ (700.3): C, 63.45; H, 8.95. Found: C, 62.99; H, 8.95.

A solution of the chloride (12.6 mg.) in 1 ml. of methanol was shaken while being treated dropwise with 5% sodium bicarbonate solution (1.5 ml.). After the addition of water the reaction mixture was extracted with chloroform, the extract was washed with water and dried over sodium sulfate. Crystallization of the residue (7 mg.) from methanol–ethyl acetate yielded plates which were identified as the oxide XIa by the melting point (196°, undepressed in mixture with XIa) and the infrared spectrum.

Quaternary Dihydrometoxazine Chloride (XIIIa) from "Second Acetolysis Product" (XV).—The "second acetolysis product" from diacetyljervine[12] (7.8 mg.) was dissolved in methanol (1 ml.) which had been saturated with hydrochloric acid at 0°. After 20 min. at room temperature, the reaction mixture was evaporated to dryness *in vacuo*. The residue crystallized from methanol–ethyl acetate yielding 2 mg. of the salt (XV); $\lambda_{\max}^{\text{alc}}$ 243 mμ (ε 13,300). The infrared spectrum (potassium bromide) was identical with that of a reference sample.[9]

"Enone" 3,23,N-Triacetate (XIVb).—The 17,17a-oxide of triacetyl-5,6,8,9-tetrahydroisojervine (XIb, 564 mg.) was dissolved in benzene (75 ml.) and stirred with Woelm neutral alumina, grade I (22.6 g.), for 0.5 hr. The mixture was transferred into a chromatographic tube and the alumina column was washed first with benzene and then with ether; both these solvents eluted only minute amounts of amorphous substances. The main fraction (460 mg.), eluted with ether containing 2% of methanol, was crystallized from ethyl acetate yielding rods (334 mg.); m.p. 222–223°; $[\alpha]^{20}\mathrm{D}$ +48° (*c* 0.618); $\lambda_{\max}^{\text{alc}}$ 261 mμ (ε 10,300), 355 (120); $\lambda_{\max}^{\text{Nujol}}$ 2.79 (l), 5.76 (s), 5.80 (s), 5.85 (m), 6.03 (s), 6.11 (m), 7.96 (s) μ.

Anal. Calcd. for $C_{33}H_{49}O_7N$ (571.7): C, 69.32; H, 8.64. Found: C, 69.50; H, 8.55.

The **N-acetylenone (XIVa)**, which could not be prepared by treating N-acetyl-5,6,7,8-tetrahydroisojervine 17,17a-oxide with neutral alumina, was obtained by hydrolyzing the triacetylenone (XIVb) with 5% methanolic potassium hydroxide overnight. The product could not be crystallized; $\lambda_{\max}^{\text{alc}}$ 258 mμ (ε 8975), 335–355 (98); $\lambda_{\max}^{\text{Nujol}}$ 2.96 (m), 5.83 (m), 6.14 (s), 7.95 (m) μ.

Dehydration Product (XVI) from Enone Triacetate (XIVb).—A solution of enone triacetate (56.6 mg.) and maleic acid (107.6 mg.) in dioxane (5 ml.) was refluxed under nitrogen for 15 hr. and was then evaporated to a sirup *in vacuo*. The washed and dried chloroform extract yielded an amorphous residue (57 mg.) from which by chromatography on Woelm neutral alumina, grade I, there was obtained in the ether (10%)-benzene (90%) eluates the dehydration product, (XVI 34 mg.). Two crystallizations from ethyl acetate–hexane yielded needles (15 mg.) melting at 186.5–191°; $\lambda_{\text{sh}}^{\text{alc}}$ 227 mμ (ε 9000), 260 (5300); $\lambda_{\max}^{\text{alc}}$ 317 mμ (ε 10,480); $\lambda_{\max}^{\text{Nujol}}$ 5.75 (s), 5.90 (m), 6.09 (s), 6.36 (l), 8.03 (s) μ.

Anal. Calcd. for $C_{33}H_{47}O_6N$ (553.7): C, 71.58; H, 8.56. Found: C, 71.29; H, 8.31.

5,6-Dihydro-11-ketoveratramine Triacetate (XVII) from XVI.—A solution of the dehydration product, (XVI 14 mg.) in *p*-cymene (1.5 ml.) to which 10% palladium on carbon (15 mg.) had been added was stirred and heated at reflux temperature in a nitrogen atmosphere for 2 hr. After the removal of the catalyst by filtration, the cymene was evaporated *in vacuo* and the residue was crystallized twice from ethyl acetate–hexane. The small needles thus obtained (6.1 mg.) melted at 242–245°; $[\alpha]^{20}\mathrm{D}$ +56° (*c* 0.406) (lit.[22] m.p. 242–245°; $[\alpha]\mathrm{D}$ +57.5°); $\lambda_{\max}^{\text{alc}}$ 212 mμ (ε 3650), 251 (10,800), 300 (1870). The infrared spectrum was identical with that of an authentic specimen.[22]

Dihydrometoxazine Chloride (XVIII) from N-Acetylenone (XIVa).—To a solution of N-acetylenone (298 mg.) in methanol (24 ml.) 0.1 *N* hydrochloric acid (8 ml.) was added. After 1.5 hr., the mixture was evaporated to dryness *in vacuo* and the residue on crystallization from methanol–ethyl acetate yielded very small rods (116.4 mg.) melting at 219–222°; $[\alpha]^{20}\mathrm{D}$ +14° (*c* 0.939, 95% ethanol); $\lambda_{\max}^{\text{alc}}$ 243 mμ (ε 14,800), plateau 306–318 (630); $\lambda_{\max}^{\text{Nujol}}$ 3.00 (sh), 3.09 (m), 5.79 (m), 6.08 (s), 8.00 (l) μ.

Anal. Calcd. for $C_{29}H_{44}O_4NCl$ (506.1): C, 68.82; H, 8.76; Cl, 7.01. Found: C, 68.69; H, 8.67; Cl, 6.97.

5,6-Dihydrojervisine 17-Monoacetate (XIXa). A. From Dihydrometoxazine Chloride (XVIII).—To a solution of the chloride (XVIII, 41 mg.) in methanol (5.5 ml.) a 2 *N* aqueous solution of sodium carbonate (5.5 ml.) was added slowly. The reaction mixture was diluted with water and extracted twice with ether (20 ml.). The residue from the washed and dried ether phase was twice crystallized from ethyl acetate–hexane, yielding 24 mg. of small rods which melted at 276–278°; $[\alpha]^{21}\mathrm{D}$ −61° (*c* 0.7141); $\lambda_{\text{sh}}^{\text{alc}}$ 235 mμ (ε 537); $\lambda_{\max}^{\text{Nujol}}$ 2.85 (l), 5.75 (s) μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$ (487.7): C, 71.42; H, 9.30. Found: C, 71.64; H, 9.01.

B. From Jervisine 17-Monoacetate.—Jervisine 17-monoacetate (100 mg.) was hydrogenated with prereduced PtO_2 (93 mg.) in glacial acetic acid (10 ml.). When 1 mole equiv. of hydrogen had been consumed the uptake came to a standstill. The crude reduction product was twice recrystallized from ethyl acetate–hexane yielding rectangular plates melting at 275–278°; $[\alpha]^{21}\mathrm{D}$ −61° (*c* 0.742); $\lambda_{\text{sh}}^{\text{alc}}$ 235 mμ (ε 331). The infrared spectrum was identical with that of the previous specimen.

The triacetate (XIXb) obtained from the monoacetate prepared according to A by acetylation with acetic anhydride and pyridine crystallized from hexane in small blocks melting at 187–189°; $[\alpha]^{21}\mathrm{D}$ −73.0 (*c* 0.535); $\lambda_{\max}^{\text{Nujol}}$ 5.72 (sh), 5.76 (s), 8.00 (s) μ.

Anal. Calcd. for $C_{33}H_{49}O_7N$ (571.7): C, 69.32; H, 8.64. Found: C, 69.35; H, 8.49.

The specimen prepared from the monoacetate B showed identical properties, inclusive of the infrared spectrum.

N-Acetyl-13,17a-dihydro-Δ⁴-jerv-3-one.—A solution of N-acetyldihydrojervine,[2] m.p. 260–262° (118 mg.), and aluminum *t*-butoxide (500 mg.) in dry toluene (9 ml.) and acetone (1 ml.) was boiled under reflux for 5.5 hr. The solvents were removed *in vacuo*, and the residue was distributed between 1 *N* sulfuric acid and chloroform. After separation of the layers and extraction of the aqueous phase with another portion of chloroform the extract was washed with 1 *N* sulfuric acid, aqueous bicarbonate, and water. The residue from the dried extract was treated with Girard's reagent T and separated into nonketonic and ketonic fractions in the usual manner, except that the former fraction was extracted from the aqueous phase with benzene and the latter fraction with chloroform. The ketonic material (88 mg.) was dissolved in benzene and chromatographed on alumina. The crystalline material eluted with 1:9 ether–benzene (48 mg.) was recrystallized from ethyl acetate–hexane, from which it formed plates melting at 204–206°; $[\alpha]^{21}\mathrm{D}$ +100° (*c* 0.762); $\lambda_{\max}^{\text{alc}}$ 234 mμ (ε 16,400), 295 (132); $\lambda_{\max}^{\text{Nujol}}$ 2.88 (l), 5.79 (s), 6.00, 6.05 (s, doublet), 6.19 (l) μ.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.47; H, 8.84. Found: C, 74.75; H, 8.59.

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Jervine. XII. Transformation Products of 5,6-Dihydroisojervine and N-Acetyl-Δ⁴-isojerv-3-one

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Transformations paralleling those previously performed on N-acetyl-5,6,8,9-tetrahydroisojervine (II) have been carried out on N-acetyl- and triacetyl-5,6-dihydroisojervine (IVa and b) and on N-acetyl-Δ⁴-isojerv-3-one (XII). The results, aside from lending additional support to structure I for isojervine, render it likely that no inversion of carbon atom 14 has occurred during the reduction of the 8,9-double bond in the preparation of the tetrahydro derivative, *i.e.*, that both compounds have the 14α configuration.

The preceding paper of this series[1] delineates the structure proof for isojervine (I) which was brought about by relating N-acetyl-5,6,8,9-tetrahydroisojervine (II) *via* the latter's 17,17a-oxide (III) to known derivatives of jervine, namely, triacetyl-5,6-dihydro-11-ketoveratramine and jervisine 17-monoacetate. Similar transformations *via* epoxides of type III had been performed prior to that work[1] with N-acetyl- and triacetyl-5,6-dihydroisojervine (IVa and b) and with N-acetyl-Δ⁴-isojerv-3-one (XII) as the starting materials and, while these were instrumental for recognizing I as the correct structure, it became clear later that conclusive proof

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[1] O. Wintersteiner and M. Moore, *J. Org. Chem.*, **29**, 262 (1964); preliminary publication, *Tetrahedron Letters*, **18**, 795 (1962).