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JERVINE—XV

HYDROGENATION OF THE 13,17a-DOUBLE BOND

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Abstract—The α,β-unsaturated ketone XIa, produced from N-acetyl-tetrahydroisojervine (Xa) by alkali-catalyzed double bond shift, gave on catalytic hydrogenation with platinum in acetic acid and subsequent acetylation the 13β,17aα-dihydro compound VIII rather than the product of *cis*(α, α)-hydrogen addition, VIIb, which is the more stable member of this pair of 13-epimers (VIII $\xrightarrow[93\%]{HO^-}$ VII).[6] The formation of VIII as the kinetically favoured product is explained by the predominance of stereoelectronic over purely steric control of proton addition at C-13 in the re-ketonization of an enolic intermediate arising by 1,4-addition of hydrogen to the enone system of XIa.

The observation[1] that the hydrogenation of jervine (Ia) under these conditions affords (in poor yield) tetrahydrojervine (IIIa) by *cis*(α, α)-addition has been confirmed. With O,N-diacetyljervine (Ib), however, the primary event is the hydrogenolysis of the 17,23-ether linkage resulting in the establishment of a free 23-hydroxyl group. This may be accompanied by de-conjugation of the enone grouping (leading to 3,N-diacetyl-tetrahydroisojervine, isolated as the triacetate Xb), or followed by hydrogenation of the double bond (leading by *trans*(13β,17aα)-addition to the 3,N-diacetate of compound IX, and to a configurationally as yet undefined new stereoisomer (XII) of the latter). These results are discussed in terms of their dependence on the ease of protonation of the 17,23-ether oxygen, and the direction of polarization of the enone system before and after cleavage of the 17-oxygen bond.

THE catalytic reduction of the two double bonds present in jervine (Ia) was first studied by Jacobs *et al.*[1,2] The simultaneous reduction of both double bonds could be accomplished with Pt-catalyst in acetic acid,[1] but the resulting tetrahydrojervine (IIIa) was obtained in very low yield and in impure state. More satisfactory was a two-step procedure using the same catalyst in which the more reactive 13,17a-double bond was first reduced in neutral (ethanol) solution, whereupon the dihydrojervine (IIa) thus obtained could be converted in good yield to tetrahydrojervine by hydrogenation in acetic acid.[2] The rather slow rate of hydrogen uptake in the first step Ia → IIa could be somewhat improved by conducting the hydrogenation under pressure (4 atm).[3] The use of 0·1N ethanolic potassium hydroxide as the solvent has also been reported to speed up the reaction and to afford dihydrojervine in 75% yield.[4] An attempt to use Pd-catalyst in acetic acid gave a mixture of starting material and non-crystalline products.[5] In 10% aqueous acetic acid, Pd- black and hydrogen effected migration of the 13,17a-double bond into the 13,14-position with the formation of Δ^{13}-jervine (IV).[5]

Evidence for the α-orientation of the 13- and 17a-hydrogen atoms in dihydrojervine and tetrahydrojervine has been presented in paper XIII of this series.[6] It derives from the fact that the acetolysis product V[3] of O,N-diacetyl-tetrahydrojervine

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

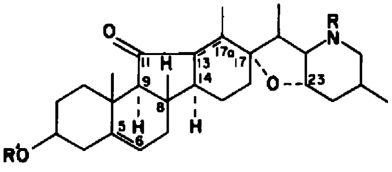
[2] W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.* **170**, 635 (1947).

[3] O. Wintersteiner, M. Moore and B. M. Iselin, *J. Amer. Chem. Soc.* **76**, 5609 (1954).

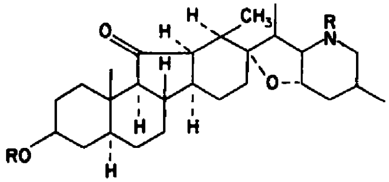
[4] R. Anliker, H. Heusser and O. Jeger, *Helv. Chim. Acta* **35**, 838 (1952).

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

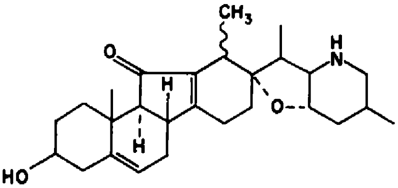
[6] O. Wintersteiner and M. Moore, *Tetrahedron* **20**, 1947 (1964).



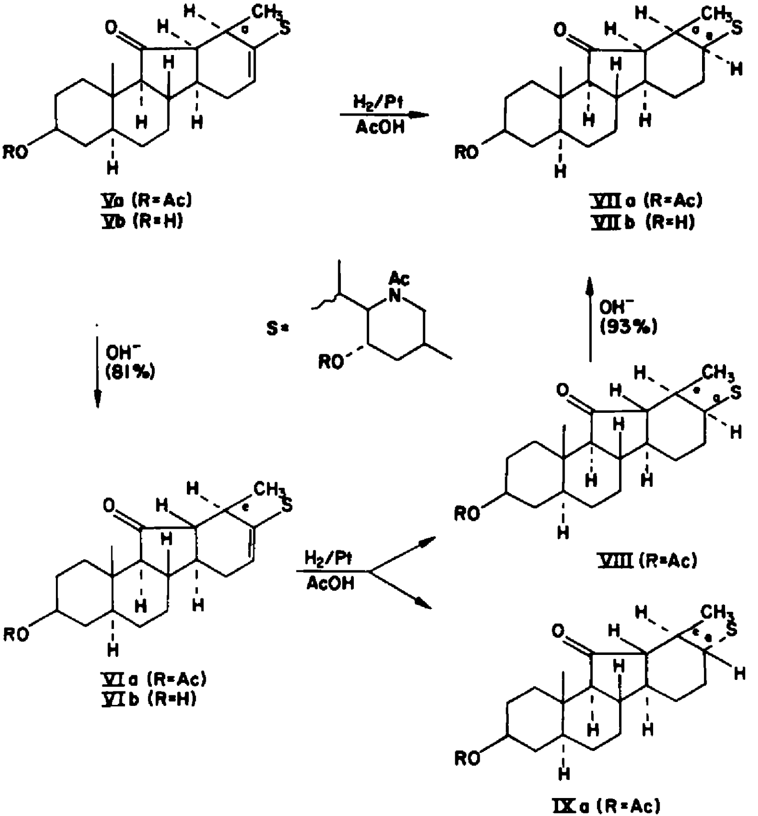
Ia (R=R'=H, Δ^{13-17a})
Ib (R=R'=Ac, Δ^{13-17a})
II (R=R'=H), no Δ^{13-17a}



IIIa (R=H)
IIIb (R=Ac)



IV



(IIIb) is epimerized at C-13 by alkali at room temperature to the extent of 81% to its 13-epimer VI, and that this parallels the behaviour on equilibration of *cis*-7-methylhydrind-5-en-1-one in which the 7-methyl group is situated *trans* to the hydrogen atom at the ring junction carbon atom 3a[7] (corresponding to C-14 in V). Since from the excellent work of Mitsuhashi and Shimizu[8] culminating in the conversion of hecogenin to a degradation product of jervine it is known that the 14-hydrogen is α-oriented, compound V, and hence also III, must be written with the 13 and 14 hydrogens α and the 17a- methyl group β to make it correspond to the model hydrindenone. These configurational assignments are furthermore supported by the behaviour on equilibration with alkali of the 16,17-dihydro derivative VII of V, and of the two 17-epimeric dihydro derivatives VIII and IX obtained from VI (VII: VIII = 93:7; IX completely stable), if the assumption is made that the degree of stability in each pair of 13-epimers is for the most part determined by the conformation of the bulky 17-substituent.[9]

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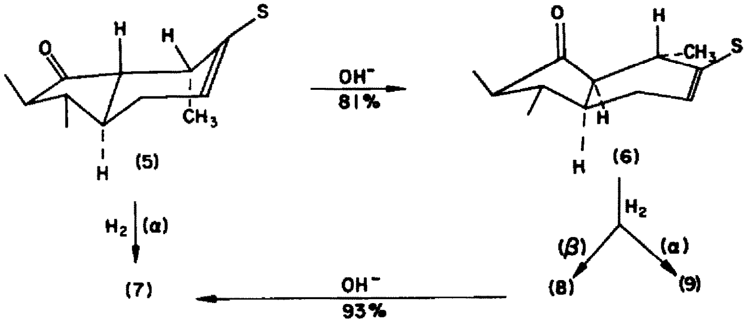
[7] H. O. House and G. A. Rasmussen, *J. Org. Chem.* **28**, 31 (1963).

[8] H. Mitsuhashi and Y. Shimizu, *Tetrahedron Letters* No 21, 777 (1961); *Tetrahedron* **19**, 1027 (1963).

[9] It is true the evidence summarized above in support of the stereostructures assigned to compounds V–IX, and hence of *cis* (α,α) addition of H_2 to the 13,17α-double bond in the formation of tetrahydrojervine from jervine, would, with the restrictions noted below, be consistent also with the occurrence of *cis* (β,β) addition in this reaction. We refrain from developing here in its entirety the argument based on this alternative interpretation except for showing below the conformational formulae (5 and 6) which would then have to be assigned to the acetolysis product V and its 13-epimer VI. The driving force in the epimerization of 5 to 6 would in this case be the tendency of



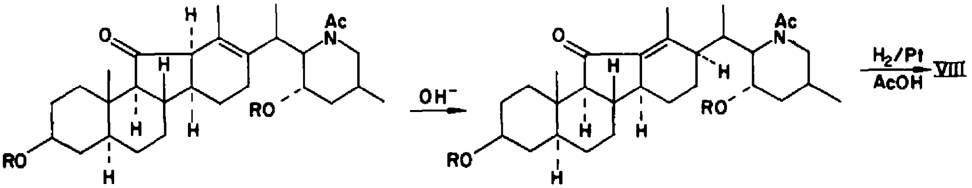
the *pseudo*-axial 17a-methyl group of 5 to become equatorial in 6. This, however, would also mean that ring D would have to change from the *hemi*-chair conformation to the energetically unfavourable boat conformation, which is the form which it probably assumes in a *cis*-hydrindenone of this type.[6,7] It seems questionable that 6, in which there are 3 major unfavourable interactions (1,4-diaxial between 17a and 15β hydrogens, and eclipsing of the 13α and 14α-hydrogens as well as of the methyl group and the bulky 17-substituent S) would be greatly favoured under equilibrating conditions over 5, in which the only major element of instability is the 1,3-diaxial relationship between the methyl group and the 14α-hydrogen, the former being skewed in respect to the S-group ($\phi = 45°$).

Among other arguments favouring V and VI over 5 and 6 we regard one presented farther below (Footnote 12) as nearly conclusive.

It might be mentioned in this context that the ORD curves of IIIb, Vb to IXb, and of the hydrogenolysis product XIIc to be described later—which data we owe to the kind cooperation of Dr. W. S. Klyne in London—do not differentiate between the 13-epimeric compounds (negative Cotton effect in all cases). Interpretation of the amplitude magnitudes in terms of the quadrant rule is confused by the fact that, in contrast, the curve of the C/D *cis*-linked triacetyl-tetrahydroisojervine (Xb) shows a strong positive Cotton effect.

On the basis of the above assignments hydrogen addition to the 13,17a-double bond of jervine must occur at both ethylenic carbons from the α-side. It was then somewhat disconcerting to find that the hydrogenation of this double bond with Pt-catalyst in acetic acid took a different steric course in the case of a closely related compound, the unsaturated ketone XI, which may be regarded as having arisen from jervine by hydrogenolytic opening of the ether linkage in ring E and saturation of the 5,6-double bond, but was actually obtained by a different route.

In our investigation of isojervine[10] it was observed that treatment of N-acetyl-5,6,8,9-tetrahydroisojervine (Xa) with methanolic potassium hydroxide at room temperature resulted in the slow emergence of an UV absorption band at 247 mμ which reached intensity after 5 days at a value indicating that about half of the starting product had been converted to the α,β-unsaturated isomer XIa.[10b] In following up this reaction preparatively we have now found that a solution of Xa in 5% methanolic potassium hydroxide on short heating at reflux temperature deposited the new isomer XIa in crystalline, almost pure state and in nearly quantitative yield. The pure compound (m.p. 274–276°, $[\alpha]_D$ −27°) showed UV characteristics (λ_{max} 255, 352 mμ, ε 15,000, 90) similar to but not identical with those of jervine (λ_{max} 250, 360 mμ, ε 15,000, 60].[11] The new ketone was further characterized by conversion with acetic anhydride and pyridine to the 3,23-N-triacetate XIb (m.p. 262–264°, $[\alpha]_D$ −27·4°). The reason for assigning to the side chain attached at C-17 the β-configuration will become clear farther below.



Xa (R=H)
Xb (R=Ac)

XIa (R=H)
XIb (R=Ac)

Hydrogen addition in the catalytic hydrogenation of the 13,17a-double bond of XI could be expected to occur from the rear as in the formation of 13,17a-dihydrojervine and hence lead to the stereoisomer VII. The ketone XIa proved to be completely resistant to platinum-catalyzed hydrogenation in ethanol solution even at 4 at., and the same was true when Pd black was used with dioxane as the solvent. In acetic acid, on the other hand, uptake of hydrogen by XIa proceeded at a reasonable rate but did not stop at one mole, and when allowed to progress till reduction of the double bond was complete (UV), resulted in the formation of difficultly separable mixtures. However, in an experiment in which the reaction was interrupted after the uptake of 1·1 moles most of the unreduced starting material could be removed by

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[10] O. Wintersteiner and M. Moore, [a] *Tetrahedron Letters* No. 18, 795 (1962); [b] *J. Org. Chem.* **29**, 262 (1964).

[11] A compound having similar UV characteristics but differing from XIa by the presence of a 5,6-double bond has recently been obtained by T. Masamune, M. Takasugi, M. Gohda, H. Suzuki, S. Kawahara and T. Irie (*J. Org. Chem.* **29**, 2282 (1964), Footnote 26) from triacetyl-8,9-dihydroisojervine with hot methanolic potassium hydroxide.

direct crystallization of the crude product. Acetylation of the amorphous remainder then yielded a crystalline substance which after purification melted at 226–229° and was identified as the C/D *trans*-linked isomer VIII, still contaminated (UV) with about 7% of starting material (now present as XIb). By chromatographing the mother liquor material only additional amounts of VIII containing from 5 to 12% of XIb could be isolated. A part of the hydrogenation product was equilibrated in alkaline solution under the conditions used in our previous study.[9] The characteristic shape of the mutarotation curve (cf. Exptl) and the isolation from the equilibrium mixture of the C/D *cis*-linked isomer VII (as the N-acetyl derivative VIIb) left no doubt as to the identity of the hydrogenation product with isomer VIII. It follows from this finding that the side chain in the parent ketone XI must be β-oriented,[12] and furthermore that *trans*-addition of hydrogen to the double bond of XIa has occurred under

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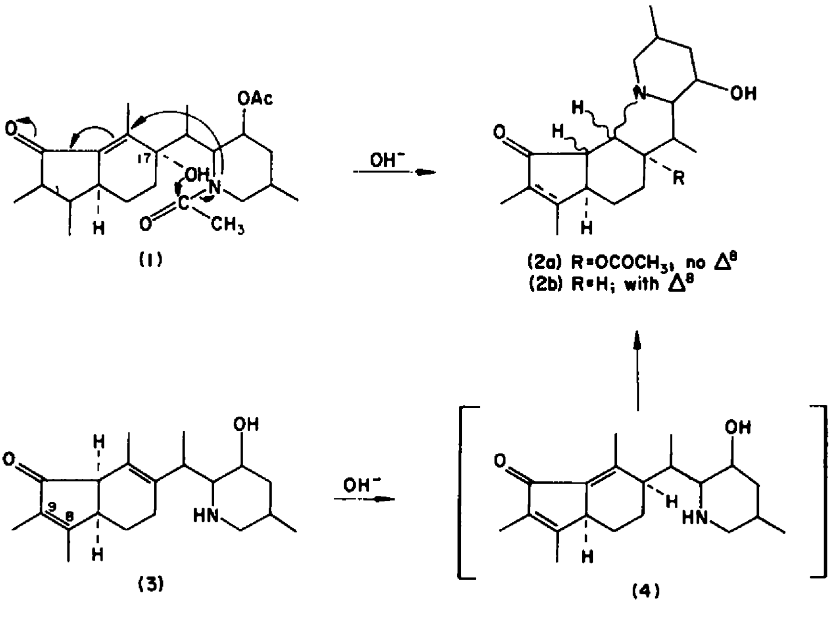
[12] The contention that the axial character of the side chain in VIII, which is the cause of the latter's instability relative to its 13-epimer VII, is due to this substituent being β-oriented in the $13\beta,14\alpha$-*trans*-linked 1-hydrindanone system attributed to VIII (and hence that V, and not the alternative formula 5 of footnote 9, correctly expresses the steric structure of the acetolysis product of tetrahydrojervine) is also supported by the following facts:

All the available evidence[10b] indicates that in the "second acetolysis product" from diacetyljervine (O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.* **75**, 4938 (1953)) the side chain is β-oriented as shown in the partial formula 1 below. On treatment with warm methanolic potassium hydroxide. this compound is isomerized to the weak tertiary base jervisine 17-monoacetate (2a) with retention of configuration at C-17 (*loc. cit.*). Now, Masamune *et al.*[11] have found that 5,6-dihydroisojervine (3) is transformed by potassium *t*-butoxide to a base having similar properties which is undoubtedly 8-dehydro-17-deoxyjervisine (2b). This reaction, as they point out, must have involved the dienone (4) as an intermediate, and this means that the side chain assumes the β-configuration when the 17,17a-double bond of 3 migrates into the 13,17a-position. Since the reaction 3 → 4 is analogous to the reaction Xa → XIa in our work, it follows that the enone XI, and hence also its hydrogenation product VIII, has the 17β-configuration.



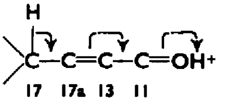
(1)

(2a) $R = OCOCH_3$, no Δ^8
(2b) $R = H$; with Δ^8

(3)

(4)

these conditions.[13] Such *trans*-addition to fully substituted olefinic bond of α,β-unsaturated ketones has been observed with steroidal Δ^8-7-ketones[14,15], Δ^{8-14}-7-ketones[16], and Δ^8-7-,11-diketones,[17] with the reaction in all these cases establishing the "natural" (8β,9β,14α) configurations at the bridge head carbon atoms involved. Most commentators on these findings lean to the view that the *trans*-dihydro products arise by 1,4-addition to the enone system[18] or by reduction of an enol or enolate,[19,17b] which is equivalent to saying that the decisive step is the protonation of the α-carbon in the re-ketonization of the intermediate 1,4-hydrogen adduct or enol from the side opposite to that at which the catalyst is attached (in the above cases β-approach to C-8). For our case (XI → VIII) the 1,4-addition mechanism initiated by the formation of the oxygen:C-17a di-anion or di-radical perhaps deserves preference on the grounds that acetic acid is too weak a proton donor to promote to a substantial degree dienol formation via the conjugate ion



The reaction XI → VIII differs from the above cases in that the dihydro product formed represents the less stable of the two isomers differing by epimerism at the α-carbon (VIII $\xrightarrow[93\%]{\text{OH}^-\text{r.t.}}$ VII). On the premise that the protonation of the α-carbon (C-13) in the re-ketonization of the enolic intermediate formed by 1,4-addition from the rear is the rate-determining step[20] in the overall process, VIII is clearly the kinetically favoured product. The situation is thus analogous to that in the many examples uncovered by Zimmerman[21] in which ketonization of enols by protonization of the α-carbon leads to the kinetically favoured but thermodynamically less stable ketonic end product. The 1959 paper quoted is particularly pertinent to our case insofar as it deals with the 1,9-enol of 1-decalone, i.e., with a bicyclic system in which the protonation occurs at a bridge carbon atom. The results (37–73% formation of the less stable *cis*-decalone, depending on the size of the proton donor, as against about 5% under equilibrating conditions) are discussed in terms of the stability of the possible enol-ketone transition states (approaching in all cases the enol form), steric factors favouring or impeding the approach of the proton donor, the size of the latter as influencing the stereoselectivity of this approach, and finally stereoelectronic

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[13] This conclusion is valid no matter whether or not the 13- and 17a-configurations assigned to VII and VIII are correct, if it is granted that the hydrogenation of the 13,17a-double bond of jervine in ethanol solution (Ia → IIa) almost certainly involves normal *cis*-addition. This follows from the fact that the sequence tetrahydrojervine (III) → V → VI → VIII includes a reaction (V → VI) in which only *one* of the two originally olefinic carbon atoms (C-13) suffers inversion of configuration.

[14] H. E. Stavely and G. N. Bollenback, *J. Amer. Chem. Soc.* **65**, 1290 (1942).

[15] C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *J. Amer. Chem. Soc.* **74**, 1712 (1952).

[16] O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.* **65**, 1507 (1943).

[17a] C. Dorée, J. F. McGhie and F. Kurzer, *J. Chem. Soc.* 988 (1948);

[b] F. J. McQuillan and W. O. Ord, *Ibid.* 2902 (1959).

[18] P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton and G. H. Thomas, *J. Chem. Soc.* 2921 (1953).

[19] C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 3496 (1953).

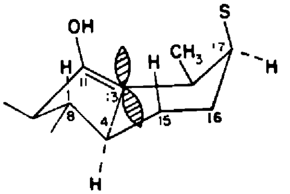
[20] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **78**, 6269 (1956).

[21] H. E. Zimmerman and A. Mais, *J. Amer. Chem. Soc.* **81**, 3044 (1959), and previous papers cited there.

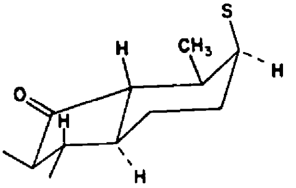
factors such as the need for continued p-orbital overlap in the transition state as first emphasized by Corey.[20]

Now, application to the postulated enol precursor of VIII (VIII-E below) of the concept of (predominantly) steric control would lead to the prediction that the ketonic end product should be the 13a-epimer VII rather than the 13β-epimer VIII. The model of VIII-E, written below as being in the enol-ketone transition state to which it makes the main contribution, shows that the approach to the β-face is hindered by the large axial side chain substituent at C-17, as well as by the axial hydrogens at C-15 and C-8, all in 1–3 relationship to the reacting trigonal carbon atom 13, whereas the approach to the latter carbon atom from the α-face is relatively unimpeded. It is, of course, possible that the 17-side chain, seeking escape from the *gauche*-interactions with C-13 and C-15, forces ring D into a twist conformation making the dihedral angle between S and these carbon atoms 120° instead of 60°, but this would make the formerly equatorial 17a-methyl group *pseudo*-equatorial and bring it into a position above the plane of ring D where it could effectively interfere with the β-approach to C-13. No other conformational factors are apparent which would favour the β- over the α-approach even for a small, less discriminating proton donor such as acetic acid.

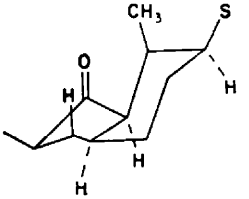
A better case for β-approach can be made by applying Corey's concept of stereoelectronic control, which stresses the need for continued overlap between the p-orbitals of the α-carbon and of the labile donor proton, a requirement best satisfied by axial approach in respect to the ring carrying the ketonic oxygen. (It is implicit in this concept that the transition state reflects to some extent also the stereostructure of the ketonic end product.) In our case, as formulae VIII-K and VII-K below show, the β-approach of the proton would be *pseudo*-axial, and the α-approach *pseudo*-equatorial, in respect to ring C,[22] and the former approach should then be favoured by the orbital overlap criterion. Furthermore, VIII-K closely resembles the transition state VIII-E in regard to the conformation of ring D (14-hydrogen and 17β-substituent axial in both), whereas a flip of that ring would be required in the enol-ketone transition to achieve VII-K, the more stable of the two possible C/D *cis*-linked conformations of VII (14-hydrogen and 17β-substituent equatorial). The activation energy required for going from VIII-E to VIII-K would thus presumably be smaller than that for going to VII-K.



VIII-E



VIII-K



VII-K

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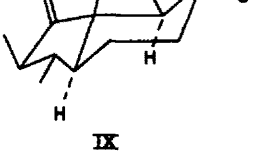
[22] The scale model of VIII-K shows that ring C is a half chair with C-13 and C-8 above, and C-14 and C-9 below the ring plane (the plane formed by C-11 and the mid points of the 13,14- and 8,9-linkages); whereas in VII-K ring C is an envelope, with the tip of the flap at C-8 and above the near plane formed by C-14, C-13, C-11 and C-9; the ring plane in this case is the plane intersecting the mid points of the 13,14-, 8,14-, 8,9- and 9,11-linkages (cf. E. L. Eliel, *Stereochemistry of Carbon Compounds* pp. 249, 250. McGraw-Hill, New York (1962)). "*Pseudo*-axial" and "*pseudo*-equatorial" are then meant in relation to the ring planes as defined.

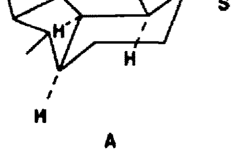
The anomalous behaviour of ketone XIa on catalytic reduction in acetic acid prompted a reinvestigation of the hydrogenation under the same conditions of jervine and diacetyljervine, the latter resembling XIa more closely than the former in that the basic group is acetylated.

The experiment with jervine confirmed in general the early observations of Jacobs and Craig.[1] Hydrogen uptake was slow and required one change of catalyst to reach 2 moles. The crystalline product isolated directly in 22% yield appeared to be a mixture of tetrahydrojervine and 13,17a-dihydrojervine. Only by chromatography of the acetylated mother liquor material could tetrahydrojervine be obtained in pure form as the diacetate. The main impurity was a rather polar amorphous product still containing one isolated olefinic bond (peracid titration) which was not further investigated.

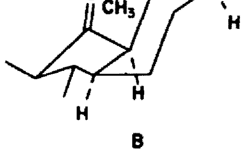
The hydrogenation of diacetyljervine (Ib) took an entirely different course. Hydrogen uptake was comparatively rapid and exceeded 2 moles. The product obtained in about 15% yield by direct crystallization was not diacetyltetrahydrojervine but a hexahydro derivative (m.p. 240–243°, $[\alpha]_D$ −26·7°) in which not only the two double bonds had been reduced but also the 17,23-ether linkage hydrogenolyzed with the formation of a free hydroxyl group at C-23. On acetylation this 3,N-diacetate formed an amorphous triacetate ($[\alpha]_D$ −23·3°), and on treatment with hot methanolic alkali a crystalline N-acetyl derivative (m.p. 220–221°, $[\alpha]_D$ −27·3°) differing by these constants and the IR spectrum from the N-acetyl derivatives VIIb and IXb with which it is structurally identical. The latter conclusion derives, *inter alia*, from the presence of a 5·78 μ band in the IR spectrum of the N-acetyl derivative (11-keto group still present), the absence of a vinylic proton signal in the NMR spectrum of the diacetate (5,6-double bond reduced), and the lack of reactivity of the diacetate towards *m*-chloroperbenzoic acid (no 17,17a-double bond). From the only slight rotation change attending the conversion of the diacetyl- to the N-acetyl derivative in alkaline solution under equilibrating conditions (−35° → −38·9°) and the identity of the IR spectra of the amorphous triacetates obtained from the diacetate and the N-acetyl derivative it may be concluded that the new isomer is stable to alkali and hence that the 17-side chain substituent and the 17a-methyl group are both equatorial. This complete stability to alkali is also exhibited by isomer IX, which for this reason has been accorded the C/D *trans*-linked stereostructure shown in the conformational formula below.



IX



A



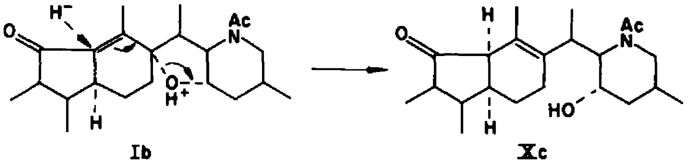
B

On the premise that in the new isomer the 13 and 17a hydrogens had been added from the rear as in the formation of tetrahydrojervine, this isomer could then be the 13α-epimer of IX stabilized in the conformation of ring D shown in A. However, A can be approximated in the model only in a form in which ring D is distorted in such a way that the hydrogens at the ring junction carbon atoms 13 and 14 are nearly eclipsed, (ϕ about 20°), and hence this ring tends to change into one of the possible boat forms.[23] Moreover, there is in A the unfavourable 1,3-interaction between the carbonyl oxygen and the equatorial 17a-methyl group, the latter lying almost in a plane with the former, and with C-11, C-13 and C-17a. It thus seems likely that A, if it were formed and stable enough to be isolated, would be epimerized by alkali to IX, and therefore cannot represent the new stable isomer. The only other steric structure which would satisfy the stability criterion is B, which differs from isomer VII by having the configuration of C-17a reversed. However, for want of any experimental evidence supporting this expression we prefer to leave the configurations of C-13, C-17a and C-17 of the new isomer, to which we shall refer in the following as XII, undefined.

The mother liquor material from the diacetate XIIc was acetylated and chromatographed on alumina. The crystalline fractions eluted with hexane-benzene 1:1, amounting to about 20% of the weight of the starting material, afforded on purification triacetyltetrahydroisojervine (Xb), identified by its physical and spectral properties and conversion with alkali to the conjugated ketone XIa. Of the subsequent fractions, which were all amorphous, the ones eluted with more polar solvent mixture yielded on hydrolysis with alkali substantial amounts of compound IX as the N-acetyl derivative IXb. There was no sign for the presence of diacetyltetrahydrojervine, which should have been eluted before the triacetylated olefin Xb.

It is evident from these findings that when the basic group of jervine is acylated the dominant event in the catalytic reduction is the hydrogenolysis of the 17,23-ether linkage, accompanied or followed by either hydrogenation or migration of the 13,-17a-double bond, whereas with the free base it is the normal *cis*-addition of hydrogen to the double bond. Clearly, in the latter case the positive charge on the basic nitrogen, which is separated from the ether oxygen by two carbon atoms, prevents the protonation of the latter which must precede the hydrogenolysis, much in the way the free amino group of a 2-amino sugar glycoside impedes protonation of the glycosidic oxygen and thus increases resistance to acid hydrolysis. With the persistence of the 17-oxygen bond the tendency of the α,β-unsaturated keto system to become polarized toward the ketonic oxygen and hence of C-17a to assume a partial positive charge, is counteracted by the electron pull exerted in the opposite direction by the ether oxygen, formation of an 1,4-di-anion or di-radical is thereby cut short, and normal *cis*-addition of hydrogen can take place.

On the other hand, in the case of jervine diacetate, with the access of protons to the ether oxygen unimpeded by a positive charge on the nitrogen, polarization in this direction gains predominance. The formation of tetrahydroisojervine (as the 3,N-diacetate Xc) is thus readily explained by the electron shift pictured below followed by hydride ion addition at C-13 from the α-side:



Ib Xc

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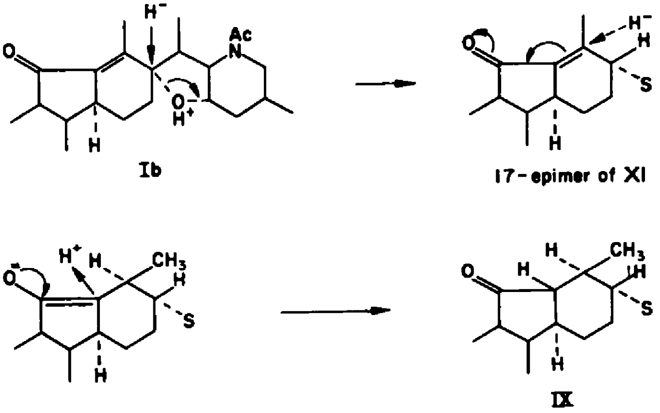
[23] In contrast, in the other C/D *cis*-linked form (as represented by VII-K above) ring D is an only moderately distorted, quite stable chair in which the dihedral angles between the 13- and 14-hydrogens approximate 45°.

However, Xc cannot be an intermediate in the formation of the completely saturated hydrogenation products IX and XII, since the 17,17a-double bond of N-acetyl tetrahydroisojervine (Xa) is inert to Pt-catalyzed hydrogenation in acetic acid. Moreover, since we have found that the 17,22-ether linkage in diacetyl tetrahydrojervine (IIIb) likewise remains unattacked under these conditions, it is clear that the hydrogenolysis of this linkage must precede reduction of the ethylenic bond in the formation of IX and XII, i.e., this phase of the over-all reduction is dependent on allylic activation of the oxygen by this bond. The over-all process leading to IX may then be pictured as follows:



In the intermediate so formed (the 17-epimer of XI) polarization towards the ketonic oxygen is now possible, paving the way for 1,4-addition of hydrogen via a di-anion or di-radical as suggested for the formation of isomer VIII from XI (though in the sequence above the process is pictured for simplicity's sake as involving transfer from the catalyst of hydride ion instead of electrons to C-17a). In the final reketonization step the proton would then add to C-13 from the β-side as discussed for the reaction XI → VIII.

EXPERIMENTAL

The m.ps were taken in open pyrex glass capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1 dm semi-micro tube, with $CHCl_3$ as the solvent, unless indicated otherwise. The UV spectra were measured in absolute ethanol in a Cary self-recording instrument Model 11 M. The IR spectra were determined on nujol mulls in the Perkin-Elmer double beam self-recording spectrophotometer Model 21. The characteristics of the IR bands are expressed in the text as follows: (s), strong; (m), medium; (l), low; (v.l.), very low; (br), broad; (sh), shoulder.

Ketone XIa *from* N-*acetyl-tetrahydroisojervine* (Xa).[10] A solution of the latter compound (503 mg) in 5% methanolic KOH was boiled under reflux for 1 hr while a stream of N_2 was passed through the vessel. The crystalline product which had deposited was collected after short standing at room temp, washed well with water and dried (416 mg, m.p. 274–278°). After recrystallization from MeOH–ethyl acetate (364 mg) it melted at 276–279°; $[\alpha]_D^{22}$ $-12{\cdot}7°$ (*c*, 0·883), λ_{max}^{alc} 255, 352 mμ (ε, 15,400, 91); λ_{max}^{nujol} 2·94 (m), 5·88 (m), 6·15 (s) μ. (Found: C, 73·74; H, 9·64. Calc. for $C_{29}H_{45}O_4N$ (471·7): C, 73·84; H, 9·62%).

The *triacetate* XIb was prepared in the usual manner with acetic anhydride and pyridine at room temp. After recrystallization from ethyl acetate–hexane it melted at 262–264°; $[\alpha]_D^{27}$ $-27{\cdot}4°$ (*c*, 0·948); λ_{max}^{alc} 254, 350 mμ (ε, 16,100, 102); λ_{max}^{nujol} 5·77 (s), 5·88 (m), 6·08 (s) 6·12 (sh, s), 8·01–8·06 (s) μ. (Found: C, 71·34; H, 8·89. Calc. for $C_{33}H_{49}O_6N$ (555·7): C, 71·32; H, 8·89%).

Hydrogenation of ketone XIa. A solution of XIa (149 mg) in acetic acid (15 ml) containing 80 mg of pre-reduced PtO_2 catalyst (Engelhard Ind., Inc.) suspended in the same solvent (2 ml), was shaken under H_2 gas at 1 atm. H_2 uptake still proceeded at the rate of 0·4 ml/hr when the reaction was interrupted after 5 hr with 8·2 ml (1·07 mole equiv) consumed. The solution was filtered from the catalyst, brought to dryness, and the residue was taken up in a small volume of 50% aqueous EtOH. The crystalline material which deposited on standing overnight (70 mg, m.p. 140–219°) on two recrystallizations from ethyl acetate gave 12 mg starting material (m.p. 275–278°) by analysis, the UV spectrum, and conversion to the triacetate XIb.

The residue from the combined mother liquors was acetylated. The crystals obtained from the crude product from warm aqueous EtOH (68 mg, m.p. 211–217°) after recrystallization from the same medium and then from ethyl acetate–hexane (37 mg) melted at 226–229° and did not depress the m.p. of VIII (lit.[6] m.p. 227–229°), although according to the UV spectrum they still contained 7% of starting ketone; $[\alpha]_D^{22}$ $-8·6°$ (c, 1·059 in MeOH–tetrahydrofurane 1:1; lit.[6]: $-6·8°$). Mutarotation in this solvent mixture containing 2% KOH: $c = 1·075$: $[\alpha]_D^{21}$ $+12·0°$ (initial), $+14·3°$ (1 h), $+1·6°$ (3 h), $-14·8°$ (7 h), $-24·2°$ (23 h); lit.[6]: $+9·1°$ (initial), $+11·3°$ (1 h), $-2·4°$ (3 h), $-10·7°$ (7 h), $-22·6°$ (23 h).

The product isolated from the solution containing the equilibrated mixture after recrystallization from ethyl acetate (7·5 mg) melted at 268–270° and did not depress the m.p. (273–274°) of a pure specimen of VIIb; $[\alpha]_D^{21}$ $-39°$; lit.[6]: $-46°$.

The residue of the combined mother liquors from VIII (ca. 80 mg) was chromatographed in the usual manner (initial solvent hexane–benzene 1:1) on Merck acid-washed alumina (3·5 g). The fractions eluted with benzene (41 mg) and with benzene–ether 95:5 (15 mg) both yielded on recrystallization VIII (m.p. 225–228°, undepressed on admixture of authentic material). The purified product (14 mg) from the benzene–ether 9:1 elutes showed a lower m.p. (210–212°) and $[\alpha]_D$ ($-10·4°$), but the mutarotation curve indicated that it contained substantial amounts of VIII ($+14·2°$ (initial,) $+18·9°$ (1 h), $+7·1°$ (3 h), $-8·7°$ (24 h)). The nature of the more dextrorotatory impurity present is obscure, as all the known stereoisomers of VIII show in this medium $[\alpha]_D$s more negative than the above 24 h equilibrium value.

In another hydrogenation experiment starting with 75 mg of XIa the reaction was allowed to proceed till the UV absorption at 255 mμ had completely disappeared. This necessitated two changes of catalyst and resulted in a total uptake of 1·9 mole equivs of H_2. The product was acetylated, but since the crystalline material thus obtained was grossly inhomogenous (m.p. 206–224°) after 2 recrystallizations, it was recombined with the mother liquors and chromatographed on acid-washed alumina. However, only the benzene elutes yielded on purification a small amount of VIII, m.p. 225–228°, whereas the m.ps of the other eluates remained low and unsharp. That they contained substantial amounts of this isomer was evident from the trend of the mutarotation of the combined fractions (initial, $+1·6°$; 24 h, $-19°$), and from the isolation from the equilibrated mixture of VIIb (m.p. 275–277°, $[\alpha]_D^{25}$ $-48·5°$, lit.[6] $-46°$) in 68% yield. It is possible that the main impurity was the triacetate of the latter isomer, VIIa, formed from VIII by epimerization at C-13 during the prolonged contract with the catalyst.

Hydrogenation of jervine. Jervine (1·5 g) dissolved in acetic acid (150 ml) was hydrogenated in the presence of prereduced Pt–catalyst (756 mg). In order to attain the theoretical uptake of 2 molar equivs (172 ml) the catalyst had to be replaced once, and since the product at this state still showed UV absorption at 248 mμ indicating the survival of 7% of the original chromophor, the hydrogenation was continued with new catalyst till the specific absorption in that region had disappeared (total uptake about 2·5 mole equivs). However, no pure tetrahydrojervine could be obtained from the three crops of crystals isolated in about 20% yield from the crude reduction product. The main impurity seemed to be, to judge from the rotation values, 13,17α-dihydrojervine.

The mother liquor from the 3rd crop was acetylated and chromatographed on acid-washed alumina. The crystalline benzene–ether eluates 95:5, 9:1 and 3:1, accounting together for 36% of the wt of the starting material, on repeated recrystallization all afforded diacetyltetrahydrojervine, identified by m.p. (214–217°, undepressed by authentic sample) and the IR spectra.

The remainder of the material (ca. 15%) could be eluted only with ether containing 2% MeOH. It was amorphous, had $[\alpha]_D$ $-13·6°$, and analyzed well for $C_{33}H_{49}O_6N$, i.e., for an isomer of Xb. The presence of an unconjugated double bond was also indicated by the uptake of one molar equiv. of *m*-chloroperbenzoic acid (6 h) by the likewise amorphous product obtained from it with cold alkali.

Hydrogenation of diacetyljervine

Hexahydro derivative XII. Diacetyljervine (3·06 g) was hydrogenated in acetic acid (300 ml) with pre-reduced Pt catalyst (1·54 g). After 6 hr, 2·4, and overnight (22 hr) 3·0 molar equivs had been consumed. The residue of the filtered solution was taken up in a small volume of ethyl acetate. On addition of hexane a crystalline substance was obtained (461 mg), which was recrystallized first from warm ethyl acetate (removal of a small amount of insoluble material before concentrating), then from MeOH–ethyl acetate, and finally from acetone (168 mg m.p. 240–244°). Chromatography on alumina, from which it was almost quantitatively recovered in the ether–MeOH 98:2 elutes, showed the final product to be homogeneous (m.p. 240–243°). This compound is the 3,N-*diacetate* XIIc of a hexahydro derivative stereoisomeric with VII, VIII and IX; $[\alpha]_D^{28}$ −27·8° (c = 1·148); λ_{max}^{alc} 303 mμ (71); λ_{max}^{nujol} 2·26 (m), 5·78 (s), 6·20 (s), 8·05 (s) μ. (Found: C, 72·23; H, 9·53. Calc. for $C_{31}H_{49}O_5N$ (515·7): C, 72·19; H, 9·58%).

The *triacetate* XIIa was amorphous; $[\alpha]_D^{30}$ −23·3; λ_{max}^{nujol} 5·78 (s) 6·09 (m) 8·10 (s) μ. Hydrolysis of the diacetate XIIc with boiling 5% methanolic KOH (0·5 h) afforded the N-*acetyl derivative* XIIb needles from warm ethyl acetate, m.p. 220–221°, $[\alpha]_D^{31}$ −27·3° (c, 0·952); λ_{max}^{nujol} 2·96 (m), 5·79 (ms), 6·20 (s). (Found: C, 73·45; H, 9·97. Calc. for $C_{29}H_{47}O_4N$ (473·7): C, 73·53; H, 10·00%).

Acetylation of XIIb gave an amorphous product, the IR spectrum of which was identical with that of the triacetate obtained from the diacetate XIIc.

Mutarotation of diacetate XIIc in MeOH–THF 1:1, 2% KOH, c = 1·389: $[\alpha]_D^{30-31}$ −35·0° (initial), −37·3° (1 h), −38·2° (2 h) −38·5° (4 h) −38·9° (5 h, constant). Work-up of the mixture yielded the N-acetyl derivative XIIb.

The material remaining in the mother liquor of the crude diacetate XIIc (ca, 2·5 g) was acetylated and chromatographed on acid-washed alumina from hexane–benzene 1:1. The crystalline fractions eluted with this solvent mixture (430 mg) and the first 3 benzene eluates (484 mg), which a previous small scale experiment had shown to contain Xb, were combined and recrystallized from ethyl acetate–hexane and aqueous EtOH. Since the m.p. remained low (162°), the top fraction (ca. 300 mg), was rechromatographed and then yielded in the hexane–benzene 1:1 eluates (105 mg) after two recrystallizations almost pure *triacetyl-tetrahydroisojervine* (Xb) m.p. 170–172°, $[\alpha]_D^{30}$ +66·3° (c = 1·033), lit.[10] m.p. 173–175°, $[\alpha]_D^{22}$ +63°, IR spectrum identical with that of an authentic sample.

The subsequent eluates were all amorphous. Those obtained with benzene–ether 1:1 (255 mg) showed $[\alpha]_D^{28}$ −14·7° in $CHCl_3$, and in the alkaline MeOH:THF mixture −21·5° → −21·9° (24 h). That this material was IX-triacetate (IXa) was confirmed by hydrolysis of the remainder with 5% methanolic KOH (reflux 0·5 h) which gave the N-*acetyl derivative* IXb, (106 mg, m.p. 235–239°, $[\alpha]_D^{25}$ −13° (c = 1·192) lit.[6] m.p. 240–243°, $[\alpha]_D$ −15·7°. The ether–MeOH 99:1 and 97:3 eluates (265 mg), suspected to contain an unsaturated product similar to the polar material obtained in the hydrogenation of jervine, were rechromatographed on Woelm alumina, neutral, grade II. However, the two main fractions, eluted with hexane–benzene 1:1 and benzene, hardly differed in rotation (−17·2° and −20·0°) and the latter fraction proved to be inert towards *m*-chloroperbenzoic acid. On hydrolysis with alkali it likewise yielded IXb, m.p. 234–238° after 2 recrystallizations, $[\alpha]_D^{28}$ −15·3°, identity confirmed by IR spectrum.