[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Jervine. V. The Sulfuric Acid-catalyzed Acetolysis of Diacetyltetrahydrojervine

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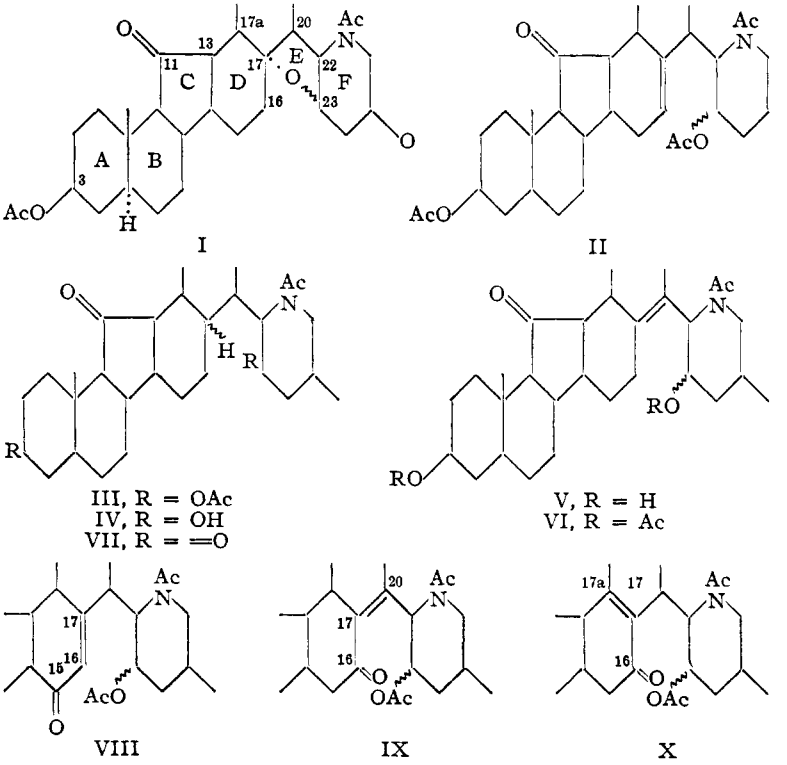
The main product formed in the sulfuric acid-catalyzed acetolysis of O,N-diacetyltetrahydrojervine (I) is an unsaturated triacetate which has been assigned structure II, mainly on the basis of its conversion by means of osmium tetroxide and acetylation to the tetraacetate XI, and to a tertiary base best represented as XIII. The O-desacetylation of II by alkali is accompanied by an isomerization the nature of which remains to be elucidated. While the available facts favor a shift of the 16,17-double bond into the 17,20-position, a purely stereochemical change is not excluded.

The studies described in this and the following paper date back to 1950, and were then undertaken with two objectives in mind: (1) to open the (presumed) oxidic linkage between rings D and F of diacetyltetrahydrojervine and thus to render the doubly heterocyclic side chain moiety more amenable to oxidative degradation and (2) to ascertain the points of attachment of this linkage. Since unequivocal evidence on the latter point as well as on the nature of the tetracyclic nucleus was forthcoming soon thereafter through the parallel acetolysis studies on jervine reported in papers III and IV of this series,[1,2] the present investigation was not carried beyond the structural characterization of the principal products. Nevertheless the results are of interest not only in relation to those presented in the foregoing papers but also because they may contribute to the future elaboration of the stereochemistry of rings D, E and F in jervine.

Acetolysis of Diacetyltetrahydrojervine.—When O,N-diacetyltetrahydrojervine (I) was treated at room temperature with acetic anhydride–acetic acid 7:3 containing 1% of sulfuric acid, there was obtained from the neutral fraction in 40–60% yield a partially crystalline product showing strong specific absorption around 247 mμ. However, on recrystallization the entity responsible for this absorption remained for the most part in the mother liquor, and the pure compound finally obtained in about 20% yield (m.p. 230–231°, $[\alpha]^{24}D$ −72.5°) exhibited only end absorption and the low maximum at 305 mμ characteristic for the isolated 11-keto group of dihydro- and tetrahydrojervine. The analytical composition $C_{33}H_{49}O_6N$ (diacetyltetrahydrojervine + C_2H_2O) indicated that the oxidic ring had been opened with the formation of an acetoxy group and of a double bond. For reasons to be discussed later this unsaturated triacetate is formulated as II. On catalytic reduction with platinum oxide in acetic acid, II readily yielded a dihydro derivative III (m.p. 261–263°, $[\alpha]^{23}D$ −39°). The corresponding N-acetate IV (m.p. 275–278°, $[\alpha]^{22}D$ −45.7°) obtained by alkaline hydrolysis of III, reverted to the latter on reacetylation, as was expected. When, however, the original acetolysis product II was subjected to O-desacetylation with alkali, an isomerization occurred, since reacetylation of the resulting unsaturated N-acetate (m.p. 226–229°, $[\alpha]^{23}D$ +16.7°) led to a new, dextrorotatory triacetate (m.p. 189.5–190.5°, $[\alpha]^{23}D$ +25.1°) isomeric with II. Catalytic hydrogenation of this compound proceeded just as readily as with the original triacetate II, but gave rise to a mixture, only one component of which could be secured in crystalline form by chromatography (m.p. 223–225°, $[\alpha]^{21}D$ −18.5°). This isodihydro triacetate also was obtained by acetylation of the amorphous product formed on hydrogenation of the unsaturated iso-N-acetate, m.p. 229°. The exact nature of the change involved in the isomerization reaction accompanying the hydrolysis of II remains to be clarified. As will be seen later, the available facts are best compatible with a shift of the 16,17-double bond in II to the exocyclic 17,20-position, and though well aware of the inherent improbability of the occurrence of such a shift under alkaline conditions, we have tentatively and for the sake of argument and convenient reference adopted this pos-

CHART I



(1) J. Fried and A. Klingsberg, THIS JOURNAL, **75**, 4929 (1953).
(2) O. Wintersteiner and M. Moore, *ibid.*, **75**, 4938 (1953).

tulate, and accordingly write the iso-N-acetate and the iso-triacetate as V and VI, respectively.

Structure of the Acetolysis Product II.—The ultraviolet spectra of all the compounds described in the foregoing section are indistinguishable from that of tetrahydrojervine (low intensity band at 305 mμ, ε 30–40, originating in the 11-keto group, minimum around 275 mμ, ε 15, and end absorption). The infrared spectra show the expected strong bands in the double bond region, *i.e.*, the N-acetyl band, variously located between 6.06 and 6.16 μ, and the 11-ketone band at 5.80 μ[3] (merged in the O-acetylated compounds with the ester carbonyl band at 5.78 μ). The rotation data will be discussed in conjunction with those of the compounds of the 3-chloro series described in the following paper. However, attention might be called already at this juncture to the close correspondence of the molecular rotation changes accompanying the acetylation of the 3- and 23-hydroxy groups in the saturated N-acetate IV on the one hand, and, on the other, in N-acetyl-11-keto-dihydroveratramine (IV with ring D aromatic),[4] and in N-acetyl-11-keto-veratramine[5] (IV with ring D aromatic, and 5,6-double bond), the Δ[M]D (triacetate − N-acetate) values being, respectively, −218° − (−218°) = 0, +325° − (+320°) = +5°, and −148° − (−149°) = +1°. Since there can be no doubt that the second hydroxyl group in veratramine occupies position 23,[6] and since triacetyl-11-ketoveratramine is one of the products formed in the sulfuric acid-catalyzed acetolysis of diacetyljervine,[2] the above rotational relationships strongly suggest that the acetolysis of diacetyltetrahydrojervine (I) likewise proceeded with the establishment of an acetoxy group at C_{23}, and that this group corresponds configurationally to the hydroxyl group at this carbon atom in veratramine. It may be assumed, on biogenetic grounds, that this is also the configuration of the oxidic bond attached to C_{23} in jervine and in I. As there is some reason to believe that jervine arises in nature from a normal steroid precursor by ring C/D rearrangement,[7] we provisionally write the side chain in I as β-oriented, and hence the oxidic linkage at C_{17} as α-oriented, while that at C_{23} is left sterically undefined.[8]

Concrete chemical evidence for the presence in II of a hydroxyl function at C_{23} was secured by oxidation of the saturated diolone N-acetate IV to the 3,11,23-triketone VII (m.p. 228–231°, $[\alpha]^{22}D$ −101°). Further characterization of this compound was dispensed with, as the properties of the 23-keto group could be assessed more clearly in the 11,23-diketones of the 3-chloro series described in the following paper. However, the rotation and ultraviolet data proved useful in that they revealed certain significant similarities with N-acetyldihydroveratramine-3,23-dione.[5] In both cases the molecular rotation change accompanying the oxidation of the two hydroxyl groups is highly negative (attributable to the even more highly negative Δ[*M*]23-ketone),[5] although quantitatively the agreement is not too good. Thus Δ[*M*] (VII–IV) is −474° − (−218°) = −256°, while the corresponding value for N-acetyldihydroveratraminedione is −58° − (+367°) = −425°. The 11-keto derivative of the latter, which would have been better suited for comparison with VII, is not known. As more significant, however, we regard the similarity of the ultraviolet absorption spectra, particularly with respect to the abnormally high extinction at the maximum, which in both cases is situated at 305 mμ (VII ε 191; N-acetyldihydroveratramine-3,23-dione, ε 230).[5] Although in the case of VII ε includes the contribution of the 11-keto group,[9] the remainder (about 160) still greatly exceeds the values normally observed with isolated keto groups (20–60). The spectra of the 3-chloro-11,23-diketones mentioned above show the same peculiarity.

The evidence for the 16–17-position of the double bond in the acetolysis products II derives from the following observations:

Chromic acid oxidation of the triacetate II afforded two products, both in small yields only: an unsaturated ketone, m.p. 231–233°, of the composition $C_{33}H_{47}O_7N$ (II + O − H_2), λ_{max}^{alc} 230 mμ (ε 10,400), and a compound m.p. 235–237°, $C_{33}H_{47}O_8N$, which lacked α,β-unsaturated ketone absorption (ketoxide?). Of the three possible structures for the unsaturated ketone m.p. 233° (partial formulas VIII, IX and X), the last two are excluded clearly by the location of the ultraviolet absorption maximum at 230 mμ. Even VIII would on first sight seem hardly compatible with this characteristic, as the calculated value for λ_{max} is 239 mμ. However, it is possible that the 11-keto group exerts a hypsochromic effect on the Δ^{16}-ketone chromophore in VIII similar to that of the 12-keto group on the Δ^{16}-20-ketone chromophore in 3β-acetoxy-Δ^{16}-allopregnene-12,20-dione (λ_{max} observed 230 mμ, calcd. 237 mμ).[10] Moreover, two simple cyclohexenones with somewhat comparable alkyl substitution, 3,5-dimethyl-2-cyclohexenone and 3,5,5-trimethyl-2-cyclohexenone, are reported to absorb at 231 and 233 mμ, respectively, with ε in the order of 15,000.[11] The relatively low ϵ_{max} observed with VIII may have its cause in a deviation from coplanarity of the conjugated bonds in consequence of deforming effects exerted by the piperidine ring with its close-by, bulky N- and O-acetyl groups.

Confirmatory evidence for the presence in II of a

(3) As ascertained by measurement in nujol mull of dihydrojervine, tetrahydrojervine and their N-acetyl derivatives. Measurements on dihydrojervine in chloroform or carbon disulfide solution gave the same value. The shift to a higher wave length from the range (5.70–5.76 μ) considered characteristic for an isolated carbonyl in a cyclopentane ring may be due to damping of the C=O stretching vibration frequency in consequence of the steric hindrance exerted by the C_{10}-methyl group.

(4) O. Wintersteiner and N. Hosansky, THIS JOURNAL, **74**, 4474 (1952).

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

(6) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **191**, 71 (1951).

(7) R. Hirschmann, C. S. Snoddy and N. L. Wendler, THIS JOURNAL, **74**, 2693 (1952).

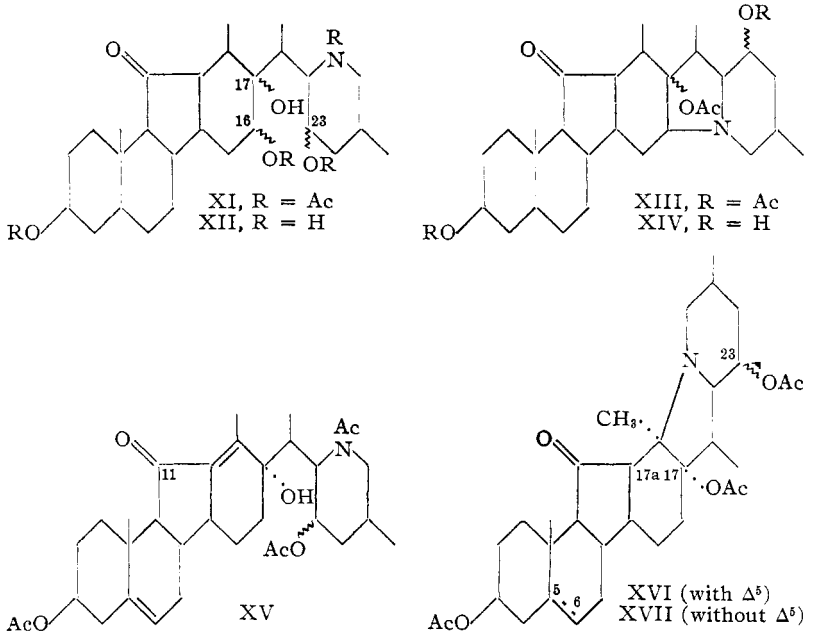
(8) This applies, of course, equally to all other asymmetric carbon atoms of I, except 3, 5, 10, 14 and 20, which on the basis of the above hypothesis may be assumed to have the same configuration as in normal allo-steroids.

(9) The contribution of the 3-keto group is negligible at this wave length; *cf.* cholestanone: λ_{max}. 280 mμ, ε 20.

(10) R. B. Wagner, J. A. Moore and R. F. Forker, THIS JOURNAL, **72**, 1856 (1950).

(11) H. S. French, *ibid.*, **74**, 514 (1952).

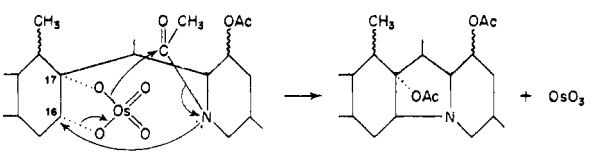
CHART II



trisubstituted ethylenic bond was obtained by hydroxylation with osmium tetroxide. This reaction, followed by reduction of the adduct with sodium sulfite and reacetylation, afforded besides a crystalline triacetate $C_{33}H_{49}O_7N$ (II + O), m.p. 302–305°, $[\alpha]^{20}D$ −114°, an amorphous tetraacetate $C_{35}H_{53}O_9N$ (II + OH + OAc), $[\alpha]^{22}D$ −9.4°, obviously the acetyl derivative of the expected secondary-tertiary glycol, a conclusion also borne out by the infrared data (bands at 3.00 (hydroxyl), 5.79 (ketone + O-acetyl) 6.19 (N-acetyl) and 8.04 μ (ester)). On hydrolysis with methanolic potassium hydroxide at room temperature the tetraacetate yielded instead of the expected N-acetate an acetyl-free base $C_{27}H_{45}O_5N$, m.p. 222–223.5°, $[\alpha]^{22}D$ −64°, which could be converted into a likewise crystalline hydrochloride m.p. 305–315° dec. That this compound was not a rearrangement product of the kind referred to farther below XVI but the normal secondary amine XII followed from the fact that on acetylation it reverted to XI, as evidenced by the identity of the infrared spectrum of the resulting amorphous product with that of the original tetraacetate.

In contrast to XI, the crystalline triacetate, m.p. 305°, obtained in the osmium tetroxide reaction exhibited no hydroxyl and N-acetyl bands in its infrared spectrum, and was found to possess basic properties (perchloric acid titration). This compound is therefore a tertiary base containing three acetoxy groups, one of which must represent a new hydroxyl function introduced in the reaction with osmium tetroxide. This accounts for all the oxygen atoms present, and it is then clear that ring D has maintained the oxidation level acquired in that reaction by accepting the third valence of the nitrogen atom at some activated and sterically feasible site. The new acetoxy group must be tertiary, for on hydrolysis the base yielded a monoacetate $C_{29}H_{45}O_5N$, m.p. 305–307°, $[\alpha]^{22}D$ −134°, in which the remaining acetyl group was demonstrable analytically as well as spectrophotometrically (ester band at 8.15 μ). The simultaneous appearance of a tertiary amino group and of an O-bound acetyl not removable by alkali is reminiscent of the events accompanying the alkali-catalyzed rearrangement of the triacetate XV (an acetolysis product of diacetyljervine) to the tertiary base XVI on which we have reported in paper IV of this series.[2] Now it is reasonable to assume that in the present case the hydroxyl group accepting the acetyl from the nitrogen atom and retaining it in the subsequent hydrolysis is likewise situated at C_{17}. If addition of the nitrogen atom had occurred at C_{17a} as in XVI, the triacetate, m.p. 305°, should be XVII, *i.e.*, the 5,6-dihydro derivative of XVI. However, several considerations militate against this structure: First, it would require the assumption that in a part of II the double bond had migrated into the 17,17a-position prior to the formation of the osmic acid adduct, and this is *a priori* rather unlikely. Secondly, the molecular rotation difference between XVI and the triacetate, m.p. 305° (−112°), and between their respective hydrolysis products (+27°) are not in accord with the values calculated for the contribution to $[M]$ of the 5,6-double bond in N-acetyldihydrojervine (−215°) and in diacetyldihydrojervine (−208°); nor does $\Delta[M]$ accompanying the O-deacetylation at C_3 and C_{23} in XVI (−118°) agree with that for the new base (+2°). (This argument is, of course, predicated on the—not unreasonable—assumption that the rearrangement in both cases takes the same steric course, *i.e.*, that the configurations of carbon atoms 17 and 17a are the same in the two tertiary bases.) Lastly, the tertiary base from II forms a stable, crystalline hydrochloride, whereas the basic strength of XVI is so low that attempts to prepare the hydrochloride and perchlorate resulted in the recovery of the free base.[2] It is this difference in the basic strength of the two compounds which in our opinion militates most strongly against structure XVII for the base m.p. 305°.

These considerations have led us to favor the alternate structures XIII and XIV for the base triacetate and its hydrolysis product, respectively. As shown below, we visualize XIII as arising from the intermediate osmic acid ester XVIII by a concerted mechanism entailing displacement of the osmate at C_{16} by the nitrogen atom in a SN2 reaction



with inversion of configuration, with simultaneous cleavage of the oxygen–osmium bond in the 17-ester linkage, the oxygen in turn displacing the nitrogen from the carbonyl carbon of the N-acetyl group (the configurational assignments for C_{16} and C_{17} are arbitrary). At what stage in the preparation of XIII this reaction might occur is difficult to say. It is conceivable, for instance, that it requires catalysis by hydroxyl ions (the latter having been furnished by hydrolysis of the sodium sulfite in boiling aqueous ethanol), in which case the rearrangement to XIII would simply be a side reaction competing with the normal reductive cleavage of the osmate to the glycol XII. Alternatively it could be assumed that both stereoisomeric osmates are formed initially, and that the one in which the nitrogen atom can more easily approach that side of carbon atom 16 which carries the hydrogen atom is apt to undergo the rearrangement, while the other in which the nitrogen atom is not so disposed survives to furnish XII in the reductive cleavage. This hypothesis is difficult to assess on the model because the relative configurations of the neighboring asymmetric centers (13, 14, 17a, 20, 22, 23) are not known. However, certain reasonable assumptions can be made about at least some of these (C_{14} with α-hydrogen as in normal steroids, rings C/D *cis*, with latter ring in boat conformation, 21-methyl group β in the sense of the current convention for steroids with more than 2 carbon atoms in the side chain[12]), and it appears from models of the two 17-epimeric forms of XVIII constructed on these premises that the closure of the pyrrolidine ring can be effected without difficulty in either case, regardless of what configuration is assigned to carbon atom 22. This does not mean, however, that the respective rate of the displacement reaction at C_{16} could not differ very markedly, since the spatial relationship of the reacting groups to the neighboring groups are actually quite dissimilar in the two forms. Thus the ester oxygen at C_{16} is axial in the isomer with the β-side chain, and equatorial in the isomer with the opposite configuration at C_{17}, and it is conceivable that the former would be more apt than the latter to undergo elimination in the postulated SN2 reaction.

The fact that the N-acetyl group of the tetraacetate XI is lost altogether on alkaline hydrolysis instead of being transferred, as in the formation of XIII and in the even more comparable alkali-catalyzed rearrangement XV → XVI to the 17-hydroxyl group, deserves some comment. We suggest that in this case interaction with the 16-hydroxyl group is involved, and that the resulting cyclic intermediate (*o*-ester-amide?) is decomposed by alkali with the formation of acetic acid. In other words, the 16-hydroxyl group is thought to play, as it were, the role of an internal catalyst promoting the hydrolysis of the N-acetyl linkage which ordinarily is stable toward cold alkali. The disinclination, in this instance, of the tertiary 17-hydroxy to accept the N-acetyl group may mean that this latter reaction can occur only through a concerted mechanism with the participation of a third reactive group (double bond in XV, osmate ester at C_{16} in XVIII), or that this hydroxyl group in XI is less favorably situated sterically than that at C_{16} for interaction with the N-acetyl group.

(12) *Cf.* Pl. A. Plattner, *Helv. Chim. Acta*, **34**, 1693 (1951).

Structure of the Iso Compounds.—It follows from the facts already reported earlier in this paper (ultraviolet and infrared data, presence in the isotriacetate VI of the original functional groups, and of a double bond), that the isomerization accompanying the O-deacetylation by alkali of the acetolysis product II cannot involve a rearrangement of the carbon–nitrogen skeleton or some other profound structural change. It is furthermore clear that the isomerization reaction is contingent on the presence of the double bond in II, since the latter's dihydro derivative III is reconstituted on reacetylation of its hydrolysis product, the saturated N-acetate IV. That tetrahydrojervine itself is stable to alkali is evident from the fact that its N-acetate can be prepared by alkaline hydrolysis of its O,N-diacetate as well as by direct N-acetylation under acidic conditions. The choice is therefore between an alkali-induced shift of the double bond—admittedly a not very likely event—and an inversion of one of the asymmetric centers in the vicinity of the double bond. A third possibility somewhat akin to the first, namely, shift of a proton from C_{13} to C_{16} with the establishment of a 13,17,17a-cyclopropane ring, is excluded by the fact that the isotriacetate VI gave a positive tetranitromethane test.

In an attempt to ascertain the position of the double bond in VI by oxidative cleavage this compound was subjected to prolonged treatment with excess chromic acid at room temperature. The oxidant was consumed at a considerably slower rate than in the case of the isomeric triacetate II. As with the latter most of the material used was recovered in the neutral fraction. Chromatographic fractionation showed this product to be a complex mixture, only one of the components of which, an α,β-unsaturated ketone with λ_{max} 236 mμ (ϵ 8,200), could be secured in amounts permitting further characterization. Though evidently not quite pure (m.p. 229–240°), this substance analyzed sharply for $C_{28}H_{47}O_7N$, *i.e.*, an isomer of the α,β-unsaturated ketone VIII (λ_{max} 230 mμ) obtained in the same manner from II. Like its precursor VI, and in contradistinction to VIII ($[\alpha]D$ −104°), it exhibited dextrorotation ($[\alpha]^{22}D$ +31°). There were also significant differences in the double bond region of the infrared spectra of the two isomeric ketones. While both exhibited the band at 5.79 μ representing the combined absorption of the O-acetyl groups and the 11-keto group, a strong band at 5.94 μ evident in the spectrum of VIII was missing in that of the ketone from VI. Conversely, the N-acetyl band of VIII at 6.06 μ appeared in the spectrum of the isomeric ketone as a doublet with maxima at 6.06 and 6.10 μ. It is true that these differences in the spectral properties do not necessarily preclude structural identity, as they could conceivably be due to vicinal and steric effects. A more serious argument against the proposition that the two ketones differ merely by stereoisomerism is implicit in the fact that the molecular rotation changes attending the introduction of the new keto group into the

two isomeric triacetates are opposite in sign. Thus $\Delta[M]_D$ for passing from II to VIII is $-192°$, while for the corresponding reaction on VI it is $+37°$.

The ketone from VI readily formed a monoxime, but on treatment of mother liquor material with Girard reagent T it was recovered for the most part in the "non-ketonic" fraction, indicating that the keto group was somewhat hindered.

Offhand it would seem then that this isoketone is not a stereoisomer but a structure isomer of VIII. The position of the main ultraviolet maximum at 236 mμ does not conform with the calculated values for either of the two possible structures, IX (254 mμ) or X (249 mμ). However, in the absence of data for comparable model compounds the influence on adsorption of the large substituent at C_{20} cannot be evaluated. In fact the only example in the normal steroid series comparable to IX for which such data are recorded, namely, 3β,22-dihydroxy-22-(26)-oxido-$\Delta^{5,17}$-cholestadiene-16-one,[13] presents an anomaly of precisely this kind, the observed λ_{max}^{alc} 236 mμ being far too low for what one would expect for an α-alkylidene-cyclopentanone.[14] It seems quite plausible that in both this compound and in a structure such as IX the large substituent at C_{20} through steric interference with ring D might bring about deformations resulting in loss of coplanarity of the conjugated atoms. Our preference for IX over X, and consequently for VI over the 17,17a-ethylene, is based on the consideration that the latter structure would hardly be stable under alkaline conditions, since its double bond, being β,γ to the 11-keto group, would be expected to undergo further migration into the α,β position, an event for which there is ample precedent in the steroid series. On the chance that in this particular case acidic conditions might be required to bring about such a shift, the N-acetate V was treated with ethanolic hydrochloric acid at reflux temperature. However, the ultraviolet spectrum showed no alteration, and the compound was recovered substantially unchanged.

There is nothing in the facts so far ascertained to support the alternative postulate, namely, that II and VI are not double bond isomers[15] but stereoisomers differing merely by epimerism at one of the neighboring asymmetric centers. Our sole reason for giving it some consideration is the lack of precedent for an alkali-catalyzed double bond shift. Indeed, it is difficult to imagine that such an epimerization could occur at any other site but at one of the carbon atoms adjacent to the 11-keto group, *i.e.*, C_9 and C_{13}, and of these C_9 is excluded by its remoteness from the double bond, which, as pointed out previously, is somehow involved in the isomerization. On the other hand, there can be no question but that in tetrahydrojervine C_{13} is already in the stable configuration.[16] Since there exists an impressive body of evidence indicating that treatment of 1-ketohydrindanes with alkali leads to the establishment of the *cis* form, it seems probable that rings C and D of tetrahydrojervine are likewise *cis* linked. However, in view of the recent findings of Barton and his collaborators[16a] that in the case of 15-ketosteroids the C/D *trans* linked form is the stable one, the possibility that this might be also the situation with tetrahydrojervine has to be taken into consideration. In either case it would have to be assumed that the introduction of the 16,17-double bond would have the effect of reversing the strain relationships in the system so as to render either carbon 13 or 14 now susceptible to epimerization by alkali. At any rate we feel that in the absence of information on the stereochemistry of the perhydrofluorene part of the molecule and the strain relationships therein the possibility of a purely stereochemical change should not be discounted.

By-products of the Acetolysis.—As mentioned earlier, the crude crystalline fraction which on purification yielded the main acetolysis product II exhibited strong ultraviolet absorption at 245–250 mμ. Although the substance responsible for this property was not obtained in pure form, its structure could be nevertheless deduced from that of the corresponding product in the 3-chloro series (see Discussion in paper VI). Two other by-products obtained in the present work, a neutral compound m.p. 210–212° remarkable for the lack of its ultraviolet spectrum of the 305 mμ band originating in the 11-ketone group, and an amorphous sulfonic acid salt exhibiting jervine-like absorption, are described in the Experimental part.

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. semi-micro tube, with chloroform as the solvent, unless indicated otherwise. The ultraviolet spectra were measured in a quartz Beckman spectrophotometer, model DU, and those of the more important compounds were later checked in a Cary self-recording instrument. The infrared spectra were determined in nujol suspension in a Perkin–Elmer, model 12-B, single beam spectrophotometer and those of compounds II and VI and their respective dihydro derivatives also in a double beam self-recording instrument, model 21. The analytical samples were dried over phosphorus pentoxide at 110° (1 mm.). The alumina used for chromatography (Harshaw) was washed with dilute sulfuric acid and water to *p*H 4.5 and reactivated by heating at 150° for 48 hours.

For the preparation of **tetrahydrojervine** the two-step reduction procedure described by Jacobs and Huebner[17] was used in slightly modified form. In the first step (H_2, PtO_2, ethanol) it was found advantageous to conduct the hydrogenation in a Parr apparatus at an initial pressure of 4 atm.

(13) A. Sandoval, J. R. Romo, G. Rosenkranz, St. Kaufmann and C. Djerassi, THIS JOURNAL, **73**, 3820 (1951).

(14) *Cf.* H. S. French and L. Wiley, *ibid.*, **71**, 3702 (1949): λmax for 2-isopropylidenecylcopentanone, 252 mμ; for 2-isopropylidene-4-methylcyclopentanone, 254 mμ.

(15) Since the double bond in II is trisubstituted and that in VI tetrasubstituted, the infrared spectrum of the former would be expected to show bands in the 11.80 to 12.50 μ region which should be absent in that of the isotriacetate, provided that this compound really has structure VI. However, bands of low to medium intensity in that region are exhibited not only by both unsaturated compounds but also by their respective dihydro derivatives. These measurements were later repeated on the double beam instrument, but the results were equally unrevealing.

(16) On the chance that the epimerization of this carbon atom in tetrahydrojervine may require more severe conditions than those used in the hydrolysis of its diacetate, and of II, the base was subjected to treatment with boiling 20% methanolic potassium hydroxide for one hour. The recovered product was unchanged in respect to melting point and rotation.

(16a) C. S. Barnes, D. H. R. Barton and G. F. Laws, *Chem. and Ind.*, 616 (1953); D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954).

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

and to increase the amount of catalyst (1 g. of Baker platinum oxide catalyst per 5 g. of jervine, the latter suspended in 150 cc. of absolute ethanol, 3–4 days). **The dihydrojervine** obtained in 60–75% yield by concentrating the filtered solution to a sirup and seeding generally melted at 248–251°, had $[\alpha]^{25}D$ −77 to 80° in ethanol (lit.[17] m.p. 250–251°, $[\alpha]D$ −82°), and was practically free from jervine (λ_{max}^{alc} 305 mμ (ε ~30), 250 mμ (ε 4 to 17); λ_{max}^{nujol} 3.03, 5.80 μ position unchanged in $CHCl_3$ or CS_2). **Diacetyldihydrojervine**,[17] prepared with acetic anhydride in pyridine, showed m.p. 210–212°, $[\alpha]^{26}D$ −63° (*c* 1.15), $[\alpha]^{25}D$ −51° (*c* 0.94 in absolute ethanol), lit.[17] m.p. 210–212°. **N-Acetyldihydrojervine**,[17] was obtained by hydrolysis of the diacetate (5% methanolic KOH, 30 minutes reflux temperature) m.p. 255–258°, $[\alpha]^{25}D$ −64.4° (*c* 1.24), lit.[17] (by mild acetylation) m.p. 256–259°.

The preparation of **tetrahydrojervine** by catalytic reduction of dihydrojervine in acetic acid was carried out as described,[17] except that the proportion of platinum oxide catalyst to substance was increased to 1:5, m.p. 214–216°, $[\alpha]^{25}D$ −23° (*c* 0.93 in absolute ethanol); lit.[17] m.p. 216–221°, $[\alpha]^{28}D$ −18°, −23°. λ_{max}^{nujol} 3.03, 5.81μ.

The hitherto undescribed **diacetyltetrahydrojervine (I)** was prepared from the free base (8.5 g.) by acetylation with acetic anhydride (50 cc.) and pyridine (50 cc.). After standing overnight the solution was concentrated *in vacuo* and the resulting crystalline precipitate removed by filtration. Two recrystallizations from 50% aqueous ethanol yielded needles (9.0 g.) melting at 221–223°, $[\alpha]^{25}D$ −2.7° (*c* 2.95); λ_{max}^{nujol} 5.80, 6.04 μ.

Anal. Calcd. for $C_{31}H_{47}O_5N$ (513.7): C, 72.48; H, 9.22; 2 $COCH_3$, 16.8. Found: C, 72.42; H, 9.16; $COCH_3$, 13.7.

Acetolysis of Diacetyltetrahydrojervine; 22,26-Imino-16-jervene-3β,23-diol-11-one 3,23,N-Triacetate[18] (II).—A solution of diacetyltetrahydrojervine (1.0 g.) in a mixture consisting of acetic anhydride (35 cc.), acetic acid (15 cc.) and concentrated sulfuric acid (0.5 cc.) was allowed to stand at room temperature for 22 hours and then poured onto crushed ice. Solid sodium carbonate was added in portions with mechanical stirring till the solution was alkaline. The mixture was extracted with chloroform (3 × 100 cc.). The combined extracts were washed with sodium bicarbonate solution and water, and brought to dryness *in vacuo*. The residue (823 mg.), a yellow resin exhibiting specific ultraviolet absorption at 247 and 330 mμ ($E_{1cm.}^{1\%}$ 85 and 4.1, respectively), yielded from methanol–water a crystalline product (374 mg., m.p. 207–221°) still showing the above absorption characteristics, but with diminished intensity ($E_{1cm}^{1\%}$ 250 mμ, 45). After two more recrystallizations the compound was free of the entity absorbing at 250 mμ (264 mg., m.p. 230–231°); $[\alpha]^{24}D$ −72.5° (*c* 0.775), λ_{max}^{alc} 305 mμ (35), $\lambda_{min.}^{alc}$ 270 mμ (16), end absorption; λ_{max}^{nujol} 5.79, 6.13, 7.98 μ.

Anal. Calcd. for $C_{33}H_{49}O_6N$ (555.7): C, 71.32; H, 8.89; N, 2.52; 3 $COCH_3$, 23.2. Found: C, 71.49; H, 8.71; N, 2.80; $COCH_3$, 16.0.

Variations of the procedure, such as increasing the concentration of starting material or of the sulfuric acid in the acetolysis mixture, or concentrating the latter before the neutralization step, generally gave lower yields of II.

The by-products formed in the acetolysis reaction are described in a later section.

Catalytic Reduction of II; 22,26-Iminojervane-11-3β,23-diol-11-one 3,23,N-Triacetate (III).—The triacetate II (97 mg.) was hydrogenated in acetic acid solution in the presence of platinum oxide catalyst (50 mg.). One mole of hydrogen was consumed in 30 minutes. The filtered solution was taken almost to dryness, diluted with chloroform, washed with bicarbonate solution and water, dried and evaporated. The crystalline residue (94 mg., m.p. 231–237°) was recrystallized several times from ether, yielding needles melting at 241–243°, $[\alpha]^{23}D$ −39° (*c* 1.335).

Anal. Calcd. for $C_{33}H_{51}O_6N$ (557.7): C, 71.06; H, 9.22. Found: C, 71.12; H, 9.08.

Hydrolysis of III; 22,26-Iminojervane-3β,23-diol-11-one N-Acetate (IV).—A solution of the dihydro product III (110 mg.) in 5% methanolic potassium hydroxide (4 cc.) was boiled under reflux for one hour. The product, isolated in the usual manner, was recrystallized from 95% ethanol, from which it formed needles melting at 275–278°, $[\alpha]^{22}D$ −46° (*c* 0.976).

Anal. Calcd. for $C_{29}H_{47}O_4N$ (473.7): C, 73.53; H, 10.00; $COCH_3$, 9.09. Found: C, 73.74; H, 10.23; $COCH_3$, 7.14.

Reacetylation with acetic anhydride–pyridine at room temperature yielded needles, m.p. 240–243° undepressed by III, $[\alpha]^{23}D$ −36.5° (*c* 1.326).

Hydrolysis of II; Iso-N-acetate (V).—The acetolysis product II (761 mg.) was hydrolyzed as described above for its dihydro derivative III. The crude product was recrystallized from 95% ethanol, yielding needles (484 mg.), m.p. 226–229°, $[\alpha]_D^{23}$ + 16.7° (*c* 0.78); λ_{max}^{alc} 305 mμ (35), end absorption; λ_{max}^{nujol} 3.05, 5.80, 6.22 μ.

Anal. Calcd. for $C_{29}H_{45}O_4N$ (471.7): C, 73.84; H, 9.62; $COCH_3$, 9.13. Found: C, 73.63; H, 9.50; $COCH_3$, 3.9.

Treatment of V (25 mg.) with ethanol containing 5 volume percentage of concentrated hydrochloric acid at reflux temperature for one hour did not produce any change in the ultraviolet spectrum. The isolated product melted at 229–231°, undepressed by admixture of V, $[\alpha]^{21}D$ +13°.

Isotriacetate VI ?.—A solution of iso-N-acetate V (290 mg.) in acetic anhydride (4 cc.) and pyridine (4 cc.) was allowed to stand at room temperature for 19 hours and then worked up in the usual manner. The crude acetylation product (342 mg.) on two recrystallizations from ethyl acetate–hexane yielded needles, m.p. 189.5–190.5°, $[\alpha]^{23}D$ +25° (*c* 0.992); λ_{max}^{nujol} 5.79, 6.13, 7.96 μ.

Anal. Calcd. for $C_{33}H_{49}O_6N$ (555.7): C, 71.32; H, 8.89; 3 $COCH_3$, 23.2. Found: C, 71.43; H, 8.85; $COCH_3$, 17.6.

Dihydro Derivative of Isotriacetate VI.—The isotriacetate VI (196 mg.) was hydrogenated in acetic acid solution in the presence of platinum oxide catalyst (100 mg.). The uptake of hydrogen stopped after 20 minutes when 10.1 cc. of the gas had been consumed (calculated for 1 mole 8.69 cc.). The product was freed from solvent as described above for III. Since the once-recrystallized material was obviously inhomogeneous (m.p. 189–217°), it was recombined with the mother liquor fraction and chromatographed in hexane–benzene 1:1 solution on alumina. The fractions eluted with benzene (100 mg.) were recrystallized twice from methanol (64 mg.) and then melted at 223–225°, $[\alpha]^{21}D$ −18.5° (*c* 1.005).

Anal. Calcd. for $C_{33}H_{51}O_6N$ (557.7): C, 71.06; H, 9.22; 3 $COCH_3$, 23.15. Found: C, 71.25; H, 9.08; $COCH_3$, 18.5.

The subsequent fractions eluted with benzene–ether 9:1 could not be crystallized (72 mg., $[\alpha]^{23}D$ −14°).

Hydrogenation of the iso-N-acetate V (100 mg.) followed by acetylation yielded a product with identical properties (31 mg., m.p. 223–225°, $[\alpha]^{22}D$ −16.6° (*c* 0.984)).

22,26-Iminojervane-3,11,23-trione N-Acetate (VII).—The N-acetate IV (103 mg., 0.23 millimole) was dissolved in acetic acid (5 cc.), and a solution of chromium trioxide (38 mg., 2.5 atoms of oxygen per mole) in acetic acid (2.5 cc.) was added. After 90 minutes the mixture was worked up in the usual manner. The partially crystalline neutral fraction was adsorbed in benzene solution on a column of alumina. Continued washing with benzene eluted crystalline material which was recrystallized three times from methanol, yielding rods (14 mg.), m.p. 228–231°, $[\alpha]^{22}D$ −101° (*c* 0.469), λ_{max}^{alc} 303 mμ (191).

Anal. Calcd. for $C_{29}H_{43}O_4N$ (469.6): C, 74.16; H, 9.23. Found: C, 74.23; H, 9.08.

Chromic Acid Oxidation of Acetolysis Product II; 22,26-Imino-16-jervene-3β-23-diol-11,15-dione 3,23-N-Triacetate (VIII).—To a solution of the triacetate II (392 mg., 0.703 millimole) in acetic acid (15 cc.) chromium trioxide (234 mg., 5 atoms of oxygen per mole) in acetic acid (2.5 cc.) was added in portions corresponding to one atom of oxygen per mole. Reduction of the first and second portion was complete in 1.5 and 3 hours, respectively. After addition of the remainder of the oxidant the mixture was allowed to stand overnight (total time 22 hours). The slight excess of chromium trioxide still present was destroyed with methanol, and the mixture was freed *in vacuo* from most of the solvent. The residue was taken up in chloroform and separated in the usual way into neutral (373 mg.) and acidic (21 mg.) products. The sirupy neutral fraction was adsorbed

(18) For nomenclature *cf.* reference 29 in paper III of this series.[1]

in benzene solution on a column of alumina (17 × 60 mm.). Continued washing with benzene eluted 85 mg. of partly crystalline material, which on recrystallization from ethanol afforded rosettes of small needles melting at 235–237°, after drying at 110° (0.1 mm.) m.p. 241–244°, $[\alpha]^{22}D$ −141° (*c* 0.901). The analyses and the ultraviolet spectrum (λ_{max}^{alc} 305 mμ (64)) were suggestive of a ketoxide.

Anal. Calcd. for $C_{33}H_{47}O_8N$ (585.7): C, 67.66; H, 8.09; N, 2.39. Found: C, 67.53; H, 7.96; N, 2.50.

On treatment of material recovered from the mother liquors with Girard reagent T by far the greater part was recovered in the non-ketonic fraction, indicating that the keto group is hindered. The small ketonic fraction exhibited in its ultraviolet spectrum maxima at 250 mμ and 290 mμ ($E_{1cm.}^{1\%}$, 26 and 19.6), suggestive of the conversion of the ketoxide to a dienone during the decomposition of the Girard T derivative with strong acid. Alkaline hydrolysis of the ketoxide likewise produced a change more profound than the expected O-desacetylation, as the resulting crystalline product (m.p. 226–228°) was dextrorotatory ($[\alpha]^{23}D$ +16°), though the ultraviolet spectrum showed no major alteration (λ_{max}^{alc} 300 mμ, $E_{1cm.}^{1\%}$ 0.7). The analysis (C, 66.61; H, 10.03) could not be rationalized.

All but the first two chromatographic fractions eluted with benzene–ether 9:1 were crystalline. They were combined (87 mg.) and recrystallized twice from acetone–ether, yielding 26 mg. of the unsaturated ketone VIII, small needles, m.p. 231–233°, $[\alpha]^{24}D$ −104° (*c* 0.965); λ_{max}^{alc} 230 mμ (10,400), 313 mμ (103); λ_{max}^{nujol} 5.78; 5.94, 6.06, 7.98 μ.

Anal. Calcd. for $C_{33}H_{47}O_7N$ (569.7): C, 69.57; H, 8.32. Found: C, 69.12, 70.15; H, 8.30, 8.22.

Chromic Acid Oxidation of the Isotriacetate VI; Diketone IX ?.—To a solution of the triacetate VI (473 mg., 0.85 millimole) in acetic acid (5 cc.) chromium trioxide (285 mg. 5 atoms of oxygen per mole) was added gradually in portions corresponding to an atom of oxygen per mole. The oxidant was consumed considerably more slowly than in the case of II, the first portion requiring 4 hours for complete reduction, and the second standing overnight. After the remainder of the chromium trioxide had been added, the solution was allowed to stand for an additional 24 hours (incomplete reduction), and then worked up as described for VIII. The separation into neutral and acidic products yielded 344 and 16 mg., respectively, the balance of the material having apparently been converted into amphoteric substances. The neutral fraction was adsorbed in benzene solution on a column (16 × 50 mm.) of alumina. Continued washing with benzene (5 × 100 cc.) eluted only small amounts of oily products. Elution with benzene–ether 9:1 (8 × 100 cc.) yielded crystalline material which, omitting the first, low-melting fraction, was combined (158 mg.) and recrystallized from 95% ethanol (89 mg., m.p. 224–239° dec. after drying at 110°). Two subsequent recrystallizations from the same solvent improved the melting point but slightly (229–240°, dec.); $[\alpha]^{22}D$ +31° (*c* 0.956); λ_{max}^{alc} 236 mμ (8,200), 310 mμ (97); λ_{max}^{nujol} 5.77, 6.06, 6.10 (doublet), 8.01 μ.

Anal. Calcd. for $C_{33}H_{47}O_7N$ (569.7): C, 69.57; H, 8.32; 3 $COCH_3$, 22.7. Found: C, 69.58; H, 8.26; $COCH_3$, 20.1.

For the preparation of the oxime the ketone (26 mg.) was refluxed for 3 hours with excess methanolic hydroxylamine acetate. The crude product was recrystallized twice from aqueous methanol (21 mg., m.p. 250–264° dec. after drying at 110° (2 mm.)).

Anal. Calcd. for $C_{33}H_{48}O_7N_2$ (584.7): N, 4.79. Found: N, 5.12.

Reaction of Acetolysis Product II with Osmium Tetroxide.—To a solution of II (387 mg.) in pure anhydrous dioxane (3.5 cc.) osmium tetroxide (212 mg.) in the same solvent (1.5 cc.) and pyridine (0.2 cc.) were added. The mixture, which darkened quickly, was allowed to stand in the dark for 5 days. The solvent was removed *in vacuo* and the residue dissolved in absolute ethanol (7.5 cc.). After the addition of sodium sulfite (385 mg.) in water (4.5 cc.) the solution was boiled under reflux for 15 minutes, cooled and filtered. The black precipitate on the filter was washed repeatedly with hot ethanol, and the combined filtrate and washings were concentrated *in vacuo*, and then extracted with chloroform (2 × 150 cc.). The residue from the dried extract (401 mg.) was treated with acetic anhydride (4 cc.) and pyridine (4 cc.) at room temperature overnight. The reagents were removed *in vacuo*, and the solution of the residue in chloroform was washed successively with potassium carbonate solution, 1 *N* hydrochloric acid and water and dried over sodium sulfate. The partly crystalline product recovered from the chloroform (433 mg.) was recrystallized twice from methanol and then from absolute ethanol, yielding 75 mg. of the basic rearrangement product ascribed structure XIII (**16,22,26-nitrilo-jervane-3β,17,23-triol-11-one 3,17,23-triacetate**); needles, m.p. 302–304° dec., $[\alpha]^{20}D$ −114° (*c* 0.769); λ_{max}^{alc} 305 mμ (46), end absorption; λ_{max}^{chl} 5.79, 8.0–8.35 μ, no bands in 3.0 (OH), and 6.1 (N-acetyl) regions.

Anal. Calcd. for $C_{33}H_{49}O_7N$ (571.7): C, 69.32; H, 8.64; 3 $COCH_3$, 22.5. Found: C, 69.09; H, 8.72; $COCH_3$, 22.5; neut. equiv., 575 (perchloric acid titration).

The first and second mother liquors from XIII were combined, evaporated (328 mg.) and adsorbed in hexane–benzene 3:1 solution on a column of alumina (17 × 48 mm.). Elution was effected with 75-cc. portions of hexane–benzene 3:1 (225 cc.) and 1:1 (225 cc.); benzene (825 cc.), benzene–ether 95:5 (525 cc.), 9:1 (450 cc.), 3:1 (375 cc.) and ether (300 cc.). The hexane–benzene mixtures eluted only traces. The first 3 benzene eluates were crystalline. The first of these (20 mg.) yielded an additional amount of XIII, and the other two (46 mg.) a low-melting substance which was not further investigated. The material in all the following eluates consisted of an amorphous white solid. Since the infrared spectra of the amorphous benzene and benzene–ether 9:1 eluates were practically identical, these and the intermediate fractions were combined (130 mg.) and lyophilized from benzene. The resulting product XI (**22,26-iminojervane-3β,16,17,23-tetrol-11-one 3,16,23-N-tetraacetate**) was dried at 110° (2 mm.) to constant weight for the analyses and optical measurements (weight loss 2.1%); m.p. 124–141°, $[\alpha]^{22}D$ −9.4° (*c* 0.787); λ_{max}^{nujol} 3.00, 5.79, 6.19, 8.04 μ.

Anal. Calcd. for $C_{35}H_{53}O_9N$ (631.8): C, 66.53; H, 8.46; 4 $COCH_3$, 27.3. Found: C, 66.94; H, 8.49; $COCH_3$, 26.2.

Hydrolysis of Tertiary Base Triacetate XIII; 16,22,26-Nitrilojervane-3β,17,23-triol-11-one 17-Acetate (XIV).—A solution of the triacetate XIII (34.6 mg.) in 5% methanolic potassium hydroxide (6 cc.) was allowed to stand at room temperature for 17 hours. After removal of most of the solvent and addition of water the mixture was extracted with chloroform (3 × 12 cc.). The chloroform extract was washed with water, dried and evaporated. The crystalline residue (34 mg.) was recrystallized from absolute and then from aqueous ethanol, from which it formed small rods, m.p. 305–307° dec., $[\alpha]^{22}D$ −134° (*c* 0.863); λ_{max}^{nujol} 3.02, 5.79, 8.15 μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$ (487.7): C, 71.42; H, 9.30; $COCH_3$, 8.8. Found: C, 71.36; H, 9.37; $COCH_3$, 8.7.

A solution of about 5 mg. of the monoacetate in chloroform (5 cc.) was extracted with small volumes of 2 *N* hydrochloric acid and water. The chloroform phase retained only 1 mg., while the acid extract yielded on evaporation 4.1 mg. of crystalline residue which after recrystallization from methanol–acetone melted at 295–303° and strongly depressed the melting point of the starting base. The Beilstein and silver nitrate tests were positive.

Hydrolysis of Tetraacetate XI. 22,26-Iminojervane-3β,16,17,23-tetrol-11-one (XII).—A solution of the amorphous tetraacetate XI (60 mg.) in 5% methanolic potassium hydroxide (2 cc.) was boiled under reflux for 30 minutes, and then worked up as indicated above for XIV. The chloroform residue (41 mg.) was recrystallized twice from 75% aqueous ethanol from which it formed small needles, probably a hydrate, first melting at 161–172° and then after resolidification at 235–241° dec. However, when the product was recrystallized once more from absolute ethanol, it melted sharply at 222–223.5°, $[\alpha]^{22}D$ −64° (*c* 0.413); λ_{max}^{nujol} 3.04, 3.16 (shoulder) 5.82 μ; no bands in 6.1 μ (N-acetyl) and 8.0–8.20 μ (ester) region.

Anal. Calcd. for $C_{27}H_{45}O_5N$ (463.6): C, 69.94; H, 9.78. Found: C, 70.04; H, 9.50; $COCH_3$, 0.

The base was soluble in 10% acetic acid and was therefrom precipitated by Meyer reagent. For the preparation of the **hydrochloride** a solution of 5.6 mg. of mother liquor material in chloroform was distributed with 2 *N* hydrochloric acid. A fine precipitate of crystals appeared in the aqueous phase. The suspension was brought to dryness. The residue on recrystallization from water yielded fine needles, m.p. 305–315° dec., which gave positive Beilstein and silver nitrate tests.

Acetylation of the base (10.8 mg.) with acetic anhydride–pyridine yielded an amorphous product (15 mg.) which behaved like the tetraacetate XI in that it formed a gelatinous precipitate from warm ethanol. Its infrared spectrum was identical with that of XI.

By-products in the Acetolysis of Diacetyltetrahydrojervine.—The mother liquor from the first recrystallization of the crude acetolysis product II in two instances deposited large square blocks (yield from I about 3 and 5%) which after repeated recrystallization from methanol melted at 210.5–212.5°, $[\alpha]^{25}D$ +51° (*c* 0.921). The ultraviolet spectrum showed only end absorption and no indication of a peak at 305 mμ ($E^{1\%}_{1cm}$ 280–320 mμ, 0.1). The analytical data were best compatible with a tetraacetate $C_{35}H_{51}O_7N$ (II + C_2H_2O).

Anal. Calcd. for $C_{35}H_{51}O_7N$ (597.8): C, 70.32; H, 8.60; 4 $COCH_3$ 28.8, 3 $COCH_3$ 21.6. Found: C, 70.19, 70.76; H, 8.68, 8.45; $COCH_3$, 23.1.

In one run fluffy, felt-like crystals, m.p. 190–202°, $[\alpha]^{25}D$ −35°, also were obtained from such a mother liquor. This product showed strong specific absorption at 250 mμ ($E^{1\%}_{1cm}$ 78) and therefore probably corresponds to the unsaturated ketone obtained as a by-product in the 3-chloro series (*cf.* paper VI). The amount isolated was too small for further investigation.

In one of the early experiments the mother liquors from 5 successive recrystallizations of II were combined and brought to dryness, and the residue was chromatographed in the usual manner on alumina. Except for some additional II eluted with benzene–ether 9:1, no crystalline products were obtained. All the subsequent eluates (benzene–ether 5:1, 1:1, ether, ether–methanol 9:1, 1:1) showed more or less strong specific absorption in the 245–250 mμ region. Pure methanol eluted a sizable amount of amorphous, water-soluble material which the analysis showed to be the (impure) sodium salt of a sulfonic acid; λ^{alc}_{max} 247, 330 mμ ($E^{1\%}_{1cm}$ 149, 7.5).

Anal. Calcd. for $C_{31}H_{46}O_5N{\cdot}SO_3Na$ (615.7): N, 2.28; S, 5.21; Na, 3.73. Found: N, 3.13; S, 5.06; Na, 3.04.

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Jervine. VI. The Sulfuric Acid-catalyzed Acetolysis of N-Acetyl-3-desoxy-3(α)-chlorotetrahydrojervine

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The sulfuric acid-catalyzed acetolysis of N-acetyl-3-desoxy-3(α)-chlorotetrahydrojervine (I) gives rise to a complex mixture of products, three of which have been structurally identified. The normal course of the acetolysis is exemplified by the unsaturated diacetate II, analogous to the main product formed in the same reaction from diacetyltetrahydrojervine.[4] The other two compounds, the α,β-unsaturated 11-ketone VIII and the isomeric tertiary base XI (derived from VIII by rearrangement) are abnormal products, since they represent a higher state of oxidation than I. The probable mode of formation of VIII is discussed.

The work described in this paper was initiated before the nature of the structural abnormality in the steroid-like tetracyclic nucleus of jervine had been elucidated through the acetolysis studies on jervine itself reported in previous papers of this series.[2-3] At that time, the most promising approach open to us seemed to be the oxidative degradation of the acetolysis product of diacetyltetrahydrojervine,[4] in which advantage could be taken of the new hydroxyl function and double bond formed in the acetolytic opening of the oxidic bridge linking rings D and F. In following this line of attack we thought it expedient to replace the hydroxyl function at C_3 by an inert substituent such as chlorine in order to minimize the difficulties likely to arise in the characterization of the expected oxygen-rich degradation products. Accordingly N-acetyl-3-desoxy-3(α)-chlorotetrahydrojervine (I) was prepared from N-acetyltetrahydrojervine[4,5] and subjected to the acetolysis reaction. The results, as far as they pertain to the main acetolysis product II, merely supplement and confirm those obtained with diacetyltetrahydrojervine.[4] However, it was possible in the 3-chloro series to isolate in addition to II a number of by-products of the reaction and to identify structurally the two most important of these, and it is this latter aspect of the study with which we are primarily concerned in this paper.

The starting product I (m.p. 245–247°, $[\alpha]^{23}D$ +18°) was obtained by treatment of N-acetyltetrahydrojervine with phosphorus pentachloride in chloroform solution at 0°, or with phosphorus oxychloride and pyridine at reflux temperature (prolonged exposure to the latter reagents at room temperature gave anomalous results, *cf.* Experimental). The α-configuration is assigned to the halogen substituent in analogy with the behavior of normal 3(β)-stanols toward these reagents. As in the case of diacetyltetrahydrojervine, the crude material obtained from I on treatment with the acetolysis mixture exhibited strong specific ultraviolet absorption in the 245–250 mμ region, while the main

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