tion was basified with ammonia and extracted with 250 cc. of ether in three successive portions. The washed ether solution deposited a sparingly soluble base while it was being evaporated. The colorless prisms, after washing with ether and then with methanol melted sharply at 246° in an evacuated tube. In an open tube this base, which is evidently 2,3-dihydroxy-9,10-demethoxy-6-methyltetrahydroprotoberberine, melted with decomposition at 200–210°.

Anal. Calcd. for $C_{20}H_{23}O_4N$: N, 4.10. Found: N, 4.27.

The crystalline base was dissolved in hot methanol (sparingly soluble) and the rapidly cooled solution treated with an ethereal solution of diazomethane. The brisk evolution of nitrogen ceased after several hours and the non-phenolic base, which was readily isolated from the reaction mixture, crystallized from methanol in the characteristic stout prisms of *d*-corydaline. Either alone or in admixture with an authentic specimen it melted sharply at 135°.

Oxidation of Thalictricavine.—A small amount of the base was dissolved in very dilute hydrochloric acid and the solution then treated with aqueous sodium carbonate until the turbidity was just permanent. An excess of aqueous potassium permanganate was added. After 5 to 6 hr. the excess reagent was destroyed with sulfur dioxide and the acidified mixture then extracted with ether. The residue from the ether extract was dissolved in a small volume of water, the solution filtered to remove a turbidity, treated with excess ethylamine, and evaporated to dryness. The residue thus obtained was sublimed *in vacuo* and the crystalline sublimate washed with ether–hexane, and then recrystallized from dilute methanol. The colorless fine needles thus obtained melted at 168–169° either alone or in admixture with an authentic specimen (m.p. 170°) of the N-ethylimide of hydrastic acid.

ONTARIO, CANADA

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

The Structure of Jervine. III. Degradation to Nitrogen-free Derivatives

BY JOSEF FRIED AND ANNA KLINGSBERG

RECEIVED JUNE 1, 1953

The degradation of jervine by means of acetic anhydride and zinc chloride to a nitrogen-free substance is described. Evidence is presented, on the basis of which structure III is assigned to this substance. The structure of jervine is discussed in the light of this and other available evidence and found to be most satisfactorily expressed by formula II.

Jervine, the main alkaloid of *Veratrum viride*, first isolated by Wright and Luff[1] has recently been the subject of a number of important investigations by Jacobs and his collaborators,[2–5] as a result of which the steroidal structure I was proposed for this interesting alkaloid. This structure if correct would render jervine a valuable starting material in the synthesis of corticoids carrying oxygen in position 11, and it is mainly for this reason that a thorough investigation of this alkaloid has been undertaken in this Laboratory.

The most important arguments advanced by Jacobs and his collaborators in favor of structure I shall be summarized briefly. Jervine has the composition $C_{27}H_{39}O_3N$.[6] Its three oxygen atoms were demonstrated to be present as (1) an acylable secondary hydroxyl group, (2) a keto group, which is inert toward carbonyl reagents but is readily reduced to an acylable hydroxyl group by sodium and butanol (β-dihydrojervinol)[3] and (3) a cyclic ether group cleaved by acids to form an acylable hydroxyl group (isojervine).[3,7] Jervine contains two double bonds demonstrable by catalytic hydrogenation (dihydro- and tetrahydrojervine).[3] The more easily reduced double bond is in conjugation with the keto group as evidenced by the characteristic ultraviolet absorption spectrum of jervine (λ_{max}^{alc} 252 and 360 mμ, ε 14,000 and 70). The second double bond is an isolated double bond, which readily enters into conjugation with the keto group formed by Oppenauer oxidation of the secondary hydroxyl group (Δ^4-jervone).[3] In this and other reactions of the secondary hydroxyl group and of the isolated double bond, jervine closely resembles cholesterol and it is for this reason that rings A and B of jervine were formulated as shown in formula I.[4] This latter conclusion in conjunction with the finding that rubijervine, a companion alkaloid of jervine, possesses a steroidal ring system[8] led Jacobs and his collaborators to postulate the existence of such a ring system in jervine also. The unreactive keto group was then logically placed into the hindered 11-position and the conjugated double bond between carbon atoms 8 and 9, the only position available for conjugation with the keto group. The formulation of the heterocyclic rings E and F the former containing the secondary nitrogen atom[9] is based on the formation of 2-ethyl-5-methylpyridine and 2-ethyl-5-methyl-3-hydroxypyridine in the dehydrogenation with selenium,[2,5] and patterned after the proved attachment of the octahydropyrrocoline system in the tertiary alkaloids rubijervine[8] and solanidine.[10] The attachment of the oxidic oxygen atom at carbon 16 is purely speculative.

Evidence casting doubt on the correctness of structure I was presented by Wintersteiner, *et al.*,[11] who described 7-keto derivatives of jervine and dihydrojervine, the ultraviolet spectra of which, while lending support to the formulation of rings A and B militated against the location assigned by Jacobs to the α,β-unsaturated ketone group. On the basis of the studies reported in this and the subsequent paper,[12] we wish to propose formula II[13]

(1) C. R. A. Wright and A. P. Luff, *J. Chem. Soc.*, **35**, 421 (1879).

(2) W. A. Jacobs, L. C. Craig and G. I. Lavin, *J. Biol. Chem.*, **141**, 51 (1941).

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

(4) W. A. Jacobs and Y. Sato, *ibid.*, **175**, 57 (1948).

(5) W. A. Jacobs and Y. Sato, *ibid.*, **181**, 55 (1949).

(6) W. A. Jacobs and L. C. Craig, *ibid.*, **148**, 51 (1943).

(7) W. A. Jacobs and L. C. Craig, *ibid.*, **155**, 565 (1944).

(8) Y. Sato and W. A. Jacobs, *ibid.*, **179**, 623 (1949).

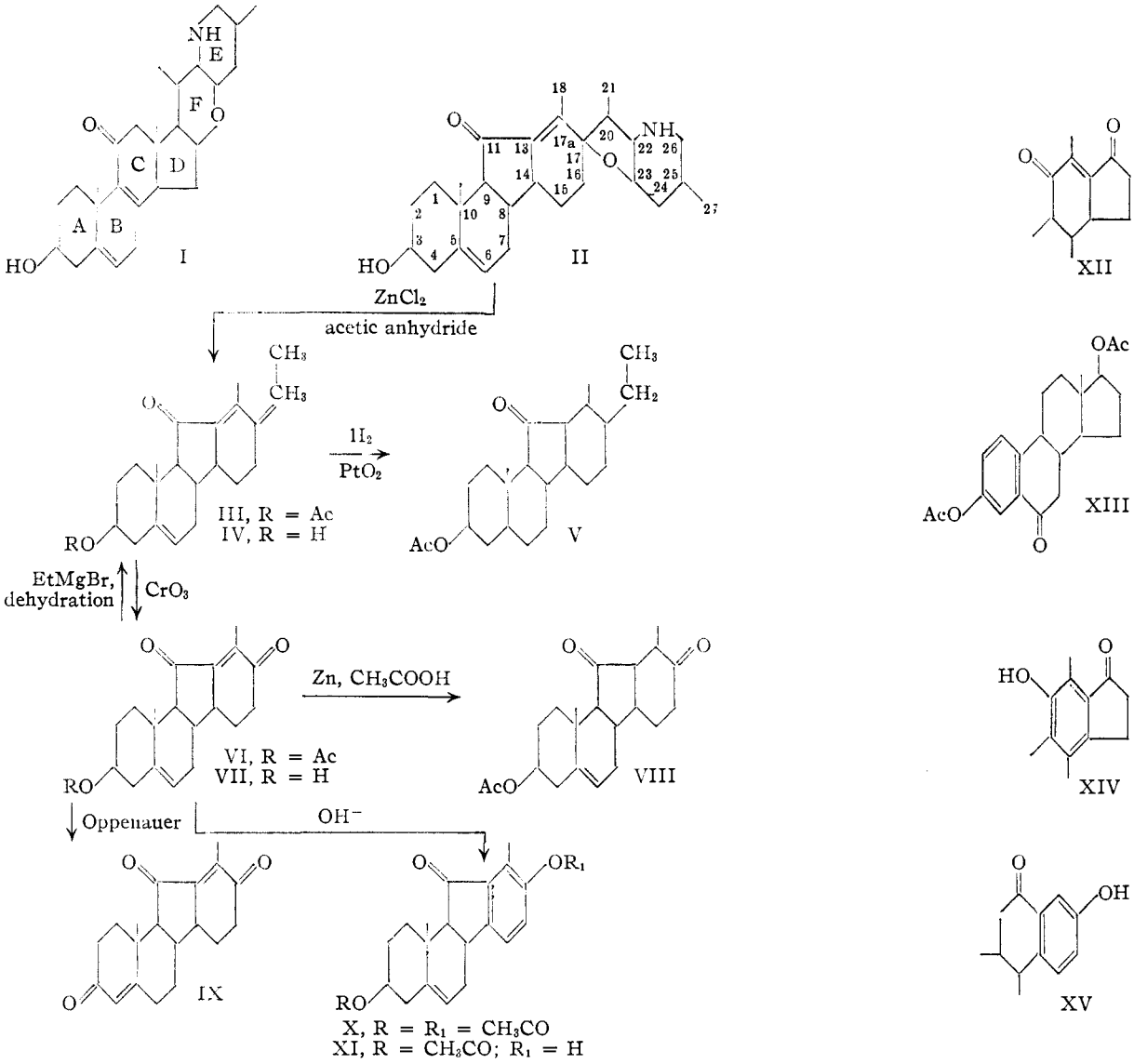
(9) K. Saito, H. Suginome and M. Takaoka, *Bull. Chem. Soc. Japan*, **11**, 172 (1936).

(10) F. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945).

(11) O. Wintersteiner, M. Moore, J. Fried and B. M. Iselin, *Proc. Nat. Acad. Science*, **37**, 333 (1951).

(12) O. Wintersteiner and M. Moore, THIS JOURNAL, **75**, 4938 (1953).

(13) Part of this material has already been presented in a Communication to the Editor by J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, *ibid.*, **73**, 2970 (1951).



possessing a modified steroidal skeleton, as representing the structure of jervine.

The key product in this investigation is a nitrogen-free substance of the composition $C_{23}H_{30}O_3$, to which structure III has been assigned on the basis of its spectral properties and of degradation results to be discussed below. III was obtained when jervine was refluxed with acetic anhydride containing 0.5% zinc chloride under conditions designed to open acetolytically the tetrahydropyran ring F postulated in formula I. The unexpected elimination of the piperidine ring E appears to be contingent upon the presence of at least one of the two double bonds of jervine, since tetrahydrojervine is merely acetylated under these conditions. Acetic anhydride alone had no effect on jervine at 150° (other than acetylation), but produced triacetylisojervine[3,7] at 200°. The latter is stable toward boiling acetic anhydride in the presence of zinc chloride and is therefore not an intermediate in the formation of III from jervine.

The acetolysis product III (m.p. 186–188°, $[\alpha]^{25}D$ − 101°) contains an acetoxy group, which is saponified by methanolic KOH with the formation of the parent alcohol $C_{21}H_{28}O_2$ (IV) (m.p. 150–155°, $[\alpha]^{23}D$ − 111°[14]). The third oxygen atom of III is ketonic and forms part of an $\alpha,\beta,\gamma,\delta$-di-unsaturated ketone grouping as shown by its ultraviolet absorption maximum at 300 mμ (ε 25,000)[15] and infrared maxima at 5.91 and 6.30 μ. This keto group undoubtedly represents the original keto group of jervine, since it parallels the latter in its inertness not only toward carbonyl reagents but also to catalytically activated hydrogen. Thus, III on hydrogenation with PtO_2 in glacial acetic acid consumed 4 moles of hydrogen yielding a mixture of products, from which the hexahydro derivative V (m.p. 114–116°, $[\alpha]^{25}D$ − 8.6°) was isolated in moderate yield. The latter was free from carbon–carbon double bonds as shown by its failure to react with perbenzoic acid, and still contained the original keto group as evidenced by the ultraviolet absorption spectrum (λ^{alc}_{max} 305 mμ (ε 90)) character-

(14) $[M]^{IV}_{D}{}^{-III}$ −12°; $[M]^{O}_{D}{}^{Ac-OH}$ for 3β-Δ⁵-steroids: −35 ± 16°. *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 813 (1945).

(15) Calculated on the basis of structure III: 295 mμ (L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, p. 192).

istic for an isolated carbonyl group, the absence of the characteristic hydroxyl absorption in the infrared and its stability toward chromic acid. The presence of an ethenyl group in III followed from the formation of acetaldehyde, isolated as the *p*-nitrophenylhydrazone, on both ozonolysis (in acetic acid and carbon tetrachloride) and chromic acid oxidation. In the latter case it was necessary to remove the aldehyde as formed by sweeping the solution with nitrogen during the dropwise addition of the chromic acid solution. The latter reaction, in which between 2.5 and 3 atom equivalents of oxygen were consumed within 1.5 to 2 hours, proved of particular interest since it afforded not only the 2-carbon fragment acetaldehyde but furnished the remaining 21-carbon fragment of III as a diketone of the composition $C_{21}H_{26}O_4$ (VI) (m.p. 182–183°, $[\alpha]^{22}D$ − 234°). An attempt to hydrolyze this substance with dilute methanolic alkali caused in addition to deacetylation more deep-seated changes to be discussed below. The desired hydrolysis was readily effected, however, by the use of dilute acid and yielded the parent alcohol $C_{19}H_{24}O_3$ (VII) (m.p. 170–171°, $[\alpha]^{22}D$ − 220°). Two oxygen atoms of VI are thus accounted for as an acetoxy group. The presence of a reactive keto group in VI was demonstrated by the preparation at room as well as reflux temperatures of a monoxime (m.p. 243–244°) and of a monosemicarbazone (m.p. 287–288°), both of which were instrumental in establishing the accurate molecular weight and thus the above composition for VI. The fourth oxygen atom is obviously part of the unreactive keto group. The positions of the two keto groups with respect to each other follows from the ultraviolet spectra of VI and VII, which show an intense band at 267 mμ (ε 14,500) and a low intensity band at 415 mμ (ε 59), the latter being responsible for the deep yellow color of these two substances. Such absorption (and color) is characteristic for the chromophore CO—C=C—CO, examples of which are known in both the steroid and polyterpene literature.[16] The possibility that the low intensity band at 415 mμ might have been due to a 1,2-diketonic structure was ruled out from a study of the reduction products of VI. Of special significance in this respect were the tetrahydro derivative XVIII obtained in the catalytic reduction of VI[17] and a dihydro product VIII (m.p. 171–172.5°, $[\alpha]D$ − 208°, $\lambda^{alc}_{shoulder}$ 295 mμ (ε 90)) prepared by mild reduction of VI with zinc in acetic acid, neither of which showed evidence in its absorption spectrum for a 1,2-diketo grouping.[18] The presence of the $\Delta^{2,3}$-ene-1,4-dione system in VI also follows smoothly from the mode of its formation from the dienonic grouping CO—C=C—C=C present in III, and further confirmation has been obtained by the resynthesis of III from VI in small yield by means of a Grignard reaction with ethylmagnesium bromide followed by dehydration of the resulting mixture of tertiary alcohols with acetic anhydride containing zinc chloride.

In the preceding section we have discussed the nature of the functional groups present in III–VII. In the following we shall consider the structure of the carbon skeleton common to these substances and the position of the functional groups on that skeleton.

The presence of a tetracyclic ring system in the above products was ascertained as follows. The crude mixture resulting from catalytic hydrogenation of VI with PtO_2 in glacial acetic acid was saponified with methanolic KOH, oxidized to the

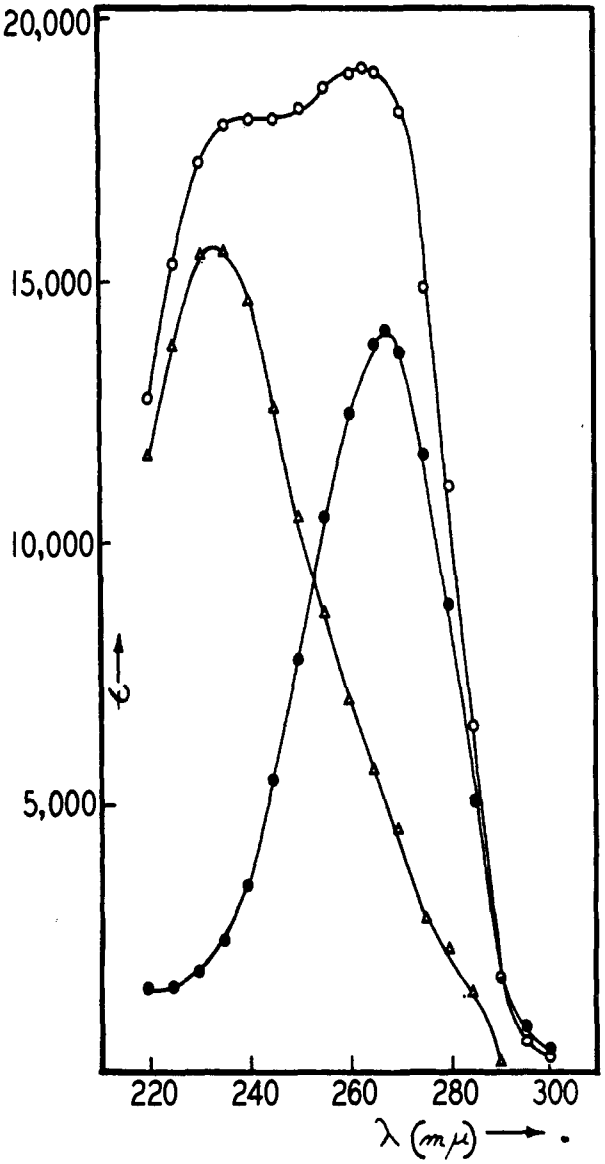


Fig. 1.—Ultraviolet absorption spectra: curve 1, ●—● $\Delta^{5,13(17a)}$-etiojervadiene-3β-ol-11,17-dione (VII) in alcohol; curve 2, O—O, $\Delta^{4,13(17a)}$-etiojervadiene-3,11,17-trione (IX) in alcohol; Δ—Δ, curve 2 − curve 1.

(16) (a) L. F. Fieser, J. E. Herz and Wei-Yuan Huang, THIS JOURNAL, **73**, 2396 (1951); (b) W. Voser, M. Montavon, H. S. H. Günthard, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **33**, 1893 (1950).

(17) The catalytic reduction of VI under a variety of conditions led to a number of products to be described in the Experimental part, some of which were of little structural significance. The likely structures of these products exclusive of their stereochemistry, and some of their properies are listed in Table I.

(18) That both keto groups were still present in VIII and XVIII followed from the fact that like VI they formed monoximes. The ultraviolet spectra of these oximes (λ^{alc}_{max} 300 mμ (ε 80)) were likewise incompatible with a 1,2-diketone structure for VI since α-oximinoketones show intense absorption at about 240 mμ. *Cf.* 16-oximinoisodehydroandrosterone: λ^{alc}_{max} 243 mμ (ε 8000).

ketone(s) with chromic acid and subjected to a rigorous Clemmensen reduction as described by Reichstein for 3,11,17-androstanetrione.[19] The resulting product, which probably consists of a mixture of stereoisomers, after purification by chromatography and distillation in high vacuum (oil, $[\alpha]^{20}D$ + 12.5°) gave analytical figures in close agreement with those calculated for a tetracyclic hydrocarbon of the formula $C_{19}H_{32}$.[20]

It has been pointed out previously that a considerable amount of evidence has been accumulated by Jacobs and his collaborators which tends to show that rings A and B of jervine are constituted as in cholesterol. That the same is true in the present series of degradation products follows from an examination of the ultraviolet spectrum of the triketone IX (m.p. 196–199°, $[\alpha]^{22}D$ + 8°[21]) prepared by Oppenauer oxidation of VII. The curve for IX (Fig. 1), which shows a broad and intense maximum between 240 and 270 mμ and a low intensity band at 415 mμ obviously represents the sum of the curves characteristic of (a) the enedione chromophore present in VI (λ_{max}^{alc} 267 mμ and 415 mμ) and (b) the Δ^4-3-ketone system (λ_{max}^{alc} 236 mμ) produced in the oxidation. This indicates not only that rings A and B have not been affected by the reactions leading to VII, but also that the two chromophores present in IX must be separated by at least one carbon atom. The latter conclusion and the fact that carbon atom 7 in jervine and therefore also in III and VI carries two hydrogen atoms[11] places the chromophore CO—C=C—CO in rings C and D. It is obvious at this point that such an unsaturated system cannot be accommodated in rings C and D of a normal steroid. The simplest modification of the steroid skeleton permitting the accommodation of this grouping would be to shift the angular methyl group to position 12, which would result in the system shown in the partial formula XII. Such a structure containing the unreactive keto group in the hindered 11-position and the reactive keto group in position 17 was considered at first but became untenable for the following reasons. When VI was treated with 0.5 *N* NaOH in 50% methanol at room temperature aromatization[22] of one of the rings occurred. The new product isolated as the crystalline diacetate (X) (m.p. 207–209°, $[\alpha]^{24}D$ − 139°) showed the infrared band (λ_{max}^{nujol} 5.67 μ) characteristic for phenolic acetyl, and exhibited ultraviolet absorption identical in all

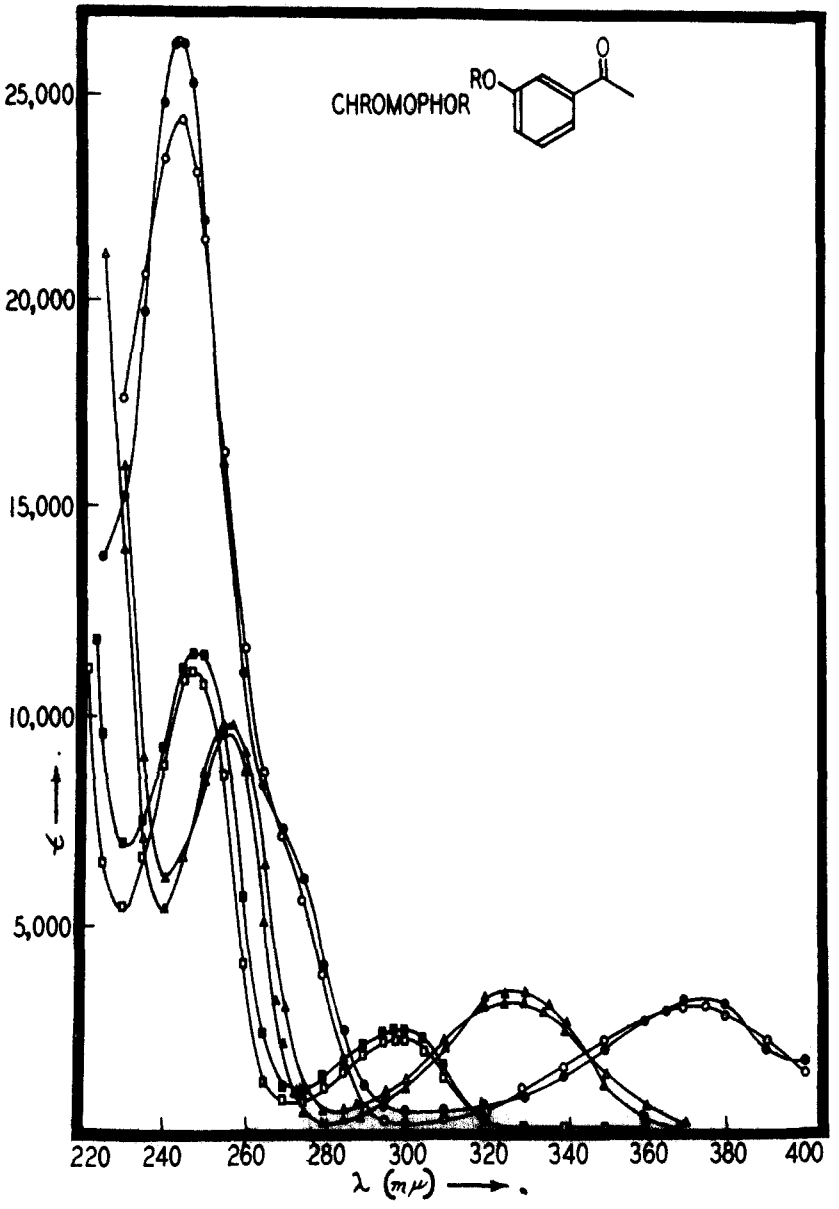


Fig. 2.—Ultraviolet absorption spectra: ▲—▲, $\Delta^{5,13,15,17}$-etiojervatetraene-3β,17-diol-11-one 3-acetate (XI) in alcohol; O—O, XI in 2% KOH in methanol; □—□, $\Delta^{5,13,15,17}$-etiojervatetraene-3β,17-diol-11-one 3,17-diacetate (X) in alcohol; Δ—Δ, 6-keto-α-estradiol in alcohol; ●—●, in 2% KOH in methanol; ■—■, 6-keto-α-estradiol diacetate (XIII) in alcohol.

(19) T. Reichstein, *Helv. Chim. Acta*, **19**, 982 (1936).

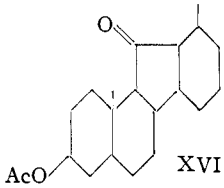
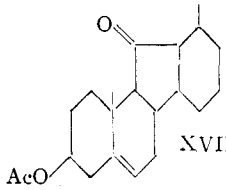
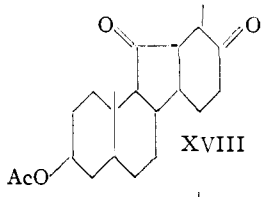
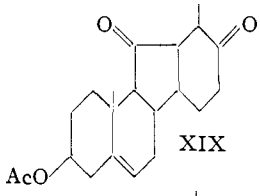
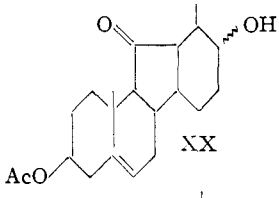
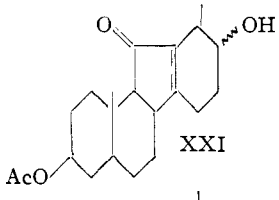
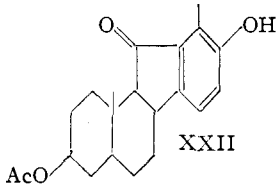
(20) Addition or subtraction of two hydrogen atoms changes both the C and H figures by 0.7%.

(21) The change in molecular rotation attending this oxidation (Δ[M]D +684°) agrees fairly well with that observed in the analogous oxidation of jervine to Δ^4-jervone (Δ[M]D +742°). In contrast oxidation of a Δ^5-stenol to a Δ^4-stenone causes a considerably smaller change (Δ[M]D +480 ± 39°). *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 813 (1945).

(22) Since this reaction, in which two hydrogen atoms are eliminated proceeded equally well in the absence of air it was assumed that intermolecular oxidation-reduction had taken place. The low yields encountered in this reaction are in harmony with this view.

TABLE I

PRODUCTS OBTAINED BY CATALYTIC HYDROGENATION OF VI

Structure	Composition	Reduction conditions	M.p., °C.	$[\alpha]_D$ $CHCl_3$	Coloration with tetranitromethane
 XVI	$C_{21}H_{32}O_3$	PtO_2 CH_3COOH	105–107	−4°	−
 XVII	$C_{21}H_{30}O_3$	Pd-black CH_3COOH	156–158.5	−254	+
 XVIII	$C_{21}H_{30}O_4$	Pd-black CH_3COOH	172–174	+56	−
 XIX	$C_{21}H_{28}O_4$	Pd/charcoal Dioxane	135–136	−12	+
 XX	$C_{21}H_{30}O_4$	Pd/charcoal Dioxane	143–145	−109	+
 XXI	$C_{21}H_{30}O_4$	Pd/charcoal Dioxane	204–205	−118	+
 XXII	$C_{21}H_{26}O_4$	Pd/charcoal Dioxane	225–230	−210	

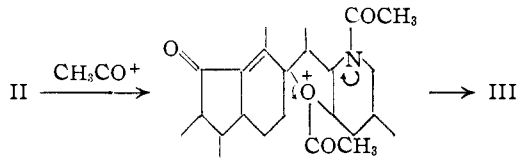
respects with that shown by 6-ketoestradiol diacetate.[23] Figure 2 represents a comparison of the ultraviolet spectra of the two compounds in the form of the free phenols and their acetates in both neutral alcohol and 2% methanolic KOH. The striking similarity of their ultraviolet spectra also holds for the colors produced when the free phenols are coupled with diazotized sulfanilic acid in carbonate alkaline medium. On the basis of formula XII the new phenol would have to be represented by XIV, a formulation which leaves unexplained its coupling properties, unless the methyl group at carbon atom 12 were transferred to a different position. There is a more compelling reason, however, to abandon structure XIV in favor of X, in which ring D is six- and ring C five-membered. Formula XIV as well as the perhydrochrysene structure XV require that the keto-group be of normal reactivity toward carbonyl reagents. This, however, was not found to be the case since treatment of the diacetate X with hydroxylamine acetate in boiling methanol did not yield an oxime but only the monoacetate XI, which no longer contained the phenolic acetyl group. 6-Ketostradiol (XIII),

(23) B. Longwell and O. Wintersteiner, *J. Biol. Chem.*, **133**, 219 1939).

which is entirely comparable to XV as far as rings C and D are concerned, readily formed a semicarbazone[23] and an oxime at room temperature. It must therefore be concluded that a six-membered ring D containing the reactive keto-group has been aromatized, and that ring C, in order to possess a keto group which is both unreactive and in α-position with respect to the phenolic ring, is five-membered. The methyl group corresponding to carbon atom 18 of the steroid nucleus has been placed at C_{17a}[24] in order to account for the ultraviolet absorption maxima of VI and VII at 267 mμ. A hydrogen atom instead of a methyl group at C_{17a} would have resulted in a chromophore similar to that present in Δ^4-3,6-diketosteroids, which show maximum absorption at 252 mμ. Such an assignment of the methyl group is sound also on biogenetic grounds inasmuch as structures III–IX can be visualized as being derived from the conventional steroid skeleton by a simple carbon–carbon rearrangement.[25]

What significance then has the elucidation of the structure of the dienone III for the structure of jervine itself? Could the alkaloid perhaps possess a steroidal skeleton, which under the influence of the acidic reagent used in the acetolysis undergoes rearrangement to form the perhydrobenzfluorene skeleton present in III–IX? All the evidence adduced in this and the following paper[12] indicates that jervine cannot possess a steroidal structure and that if rearrangement had occurred during the acetolysis reaction it could only have involved a change of one non-steroidal to another non-steroidal structure. That such an assumption is unnecessary follows from the direct correlation of derivatives of jervine and veratramine,[26] which permits no other conclusion than that ring D in veratramine, and therefore most likely also in jervine, is six-membered. The early observations by Jacobs, Craig and Lavin,[2] that selenium dehydrogenation of jervine does not yield derivatives of phenanthrene but leads to what from ultraviolet data appear to be homologs of 1,2-benzfluorene, are in full accord with the above conclusions.

There remain to be discussed the implications of this work concerning the position of the conjugated double bond and the attachment of the nitrogenous side chain in jervine. There are two possible sites for this double bond, namely, positions 13,17a and 13,14. The former is preferred for the following reason. The yellow diketone VI on catalytic reduction with Pd-on-charcoal in dioxane forms among other products the keto alcohol XXI (see Table I), in which to judge from the difference of its ultraviolet spectrum (λ_{max}^{alc} 243 mμ (ϵ 9000) from that of jervine (252 mμ (ϵ 14,000)) the conjugated double bond must occupy the alternate available position.[27] According to the Woodward–Fieser generalizations[15] the 13,17a-ene-11-one system possessing an exocyclic double bond should give rise to absorption at a slightly longer wave length than the isomeric 13,14-ene-11-one system. This requirement is fulfilled if the 13,17a-double bond is assigned to jervine and the 13,14-double bond to the isomerization product XXI. The attachment of the nitrogenous side chain at carbon atom 17 follows smoothly from the position of the ethenyl group in the trienone III. On the other hand, the reactions described in this paper offer only circumstantial evidence concerning the attachment at ring D of the oxidic oxygen atom. Such evidence consists of the failure of tetrahydrojervine in contrast to jervine to undergo acetolytic cleavage suggesting the allylic 17-position as the site for this attachment. A similar difference in reactivity between jervine and its tetrahydro derivative has been observed in the case of the isojervine rearrangement, which proceeds only with the former. Moreover, the spirocyclic formula II permits the degradation of jervine to the trienone III to be formulated in a straightforward manner analogous to the well-known transformation of the hydrogen halide adducts of the cinchona alkaloids to the corresponding niquine bases[28]



Experimental

Acetolytic Degradation of Jervine with Acetic Anhydride and Zinc Chloride. ($\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate[29] (III)).—A solution of jervine (10.0 g., m.p. 246–247°,[30] $[\alpha]^{23}D$ −147° (*c* 0.9 in 95% alcohol)) and anhydrous zinc chloride (500 mg.) in acetic anhydride (100 ml.) was heated under reflux for 6 hours. The reaction mixture soon assumed a purple color, which slowly changed to a dark brown. After concentration of the mixture *in vacuo* the resulting thick sirup was dissolved in chloroform (100 ml.) and washed with four 30-ml. portions of water. The

(24) The assignment of the methyl group to position 17a has been fully substantiated by the isolation of benzene-1,2,3,4-tetracarboxylic acid from the products obtained on oxidation of veratramine with permanganate (O. Wintersteiner, M. Moore and N. Hosansky, THIS JOURNAL, **75**, 2781 (1953)). The carbon skeleton of veratramine has been shown to be identical with that of jervine (*cf.* ref. 26).

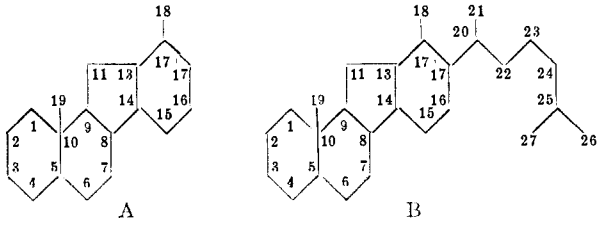
(25) Such a rearrangement has recently been realized by R. Hirschmann, C. S. Snoddy and N. L. Wendler, THIS JOURNAL, **74**, 2693 (1952), who succeeded in preparing a perhydrobenzfluorene derivative by solvolysis of a 12β-mesyloxysteroid.

(26) O. Wintersteiner and N. Hosansky, *ibid.*, **74**, 4474 (1952).

(27) An isomerization product of jervine obtained under similar conditions will be described by Iselin, Moore and Wintersteiner in a subsequent publication.

(28) For an electronic interpretation of this reaction *cf.* the recent paper by H. S. Mosher, R. Forker, H. R. Williams and T. S. Oakwood, THIS JOURNAL, **74**, 4627 (1952). We are indebted to Dr. R. B. Woodward for suggesting this analogy.

(29) The naming of the degradation products described in this paper according to the proposed rules for steroid nomenclature (*Chem. and Ind.*, 1951) is so cumbersome as to invite the use of some less involved system. A simple nomenclature is proposed and used throughout the Experimental part in which the parent tetracyclic hydrocarbon $C_{19}H_{30}$ (A) is named etiojervane, the term jervane signifying the carbon skeleton of jervine (B).



(30) All melting points were taken in capillary tubes and are corrected for stem exposure.

chloroform solution was dried over sodium sulfate and the solvent and residual acetic anhydride removed in a good vacuum. The dark brown residue was taken up in warm acetone (5 ml.) and allowed to crystallize in the refrigerator for 48 hours. The paste-like mixture was thinned down by the addition of a few ml. of cold acetone and the crystals were filtered off with suction and washed with little acetone. The residual very impure crystals (5.4 g.) were dried thoroughly *in vacuo*, dissolved in benzene (15 ml.)–hexane (15 ml.) and chromatographed on sulfuric acid-washed alumina (60 g.). Elution with benzene–hexane yielded in the first 120 ml. the crude trienone (III) (1.552 g.), which after crystallization from acetone appeared as pale yellow heavy prisms melting at 186–188°, $[\alpha]^{25}D$ −101° (*c* 0.72 in $CHCl_3$), λ_{max}^{alc} 300 mμ (ε 25,000), λ_{max}^{Nujol} 5.76 μ (ester carbonyl), 8.03 μ (C–O–C), 5.91 μ (conjugated ketonic carbonyl), 6.30 μ (conjugated double bonds).

Anal. Calcd. for $C_{28}H_{30}O_3$: C, 77.93; H, 8.53; acetyl, 12.15; mol. wt., 354.5. Found: C, 78.14; H, 8.58; acetyl, 11.5; mol. wt. (Rast), 350, 360.

The above described separation of the crude reaction products with acetone into a crystalline and an amorphous fraction prior to chromatography gave better yields of III than direct chromatography of the total reaction products. In an experiment in which the total mixture was chromatographed, benzene–ether 1:1 (preceded by benzene–hexane (1:1) and benzene) eluted a small amount of O,N-diacetyljervine (m.p. 172°). No other crystalline products were obtained by subsequent elution with ether and acetone–benzene (1:1).

An attempt to prepare a dinitrophenylhydrazone of III by heating with Brady reagent yielded only starting material.

Titration of the trienone III (22.7 mg.) with bromine in glacial acetic acid with or without added potassium acetate rapidly consumed 9.8 mg. of bromine; calcd. for 1 mole equivalent: 10.2 mg. In carbon tetrachloride or ether bromine addition was slow and did not stop at the 1-mole mark.

Saponification of $\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate (III).—To a solution of III (200 mg.) in pure dioxane (5 ml.) was added 1 *N* aqueous sodium hydroxide (5 ml.) and the mixture was refluxed for 1.5 hours. After removal of the dioxane *in vacuo* the aqueous mixture was extracted with chloroform, the chloroform solution washed with water, dried over sodium sulfate and the solvent removed *in vacuo*. The residue (150 mg.) was dissolved in benzene (6 ml.) and chromatographed on sulfuric acid-washed alumina (5 g.). Elution with benzene (200 ml.) yielded crystalline material (15 mg.) which was combined with the material (43 mg.) subsequently eluted with benzene–ether (8:2) for recrystallization from acetone. The pure $\Delta^{5,13(17a),17(20)}$-17-ethyletiojervatriene-3β-ol-11-one (IV) melted at 150–155°, $[\alpha]^{23}D$ −111° (*c* 1.12 in $CHCl_3$), λ_{max}^{alc} 300 mμ (ε 28,000).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.60; H, 8.97.

Attempted Acetolysis of Tetrahydrojervine.—Tetrahydrojervine (500 mg., m.p. 216–217°) was treated with acetic anhydride and zinc chloride and the reaction mixture worked up as described above for jervine. Crystallization of the chloroform residue from acetone yielded 316 mg. of diacetyltetrahydrojervine, m.p. 216–218°.

Reaction of Jervine with Acetic Anhydride at 200°.—A solution of jervine (0.5 g.) in acetic anhydride (5 ml.) was heated in a sealed tube at 195–200° for 12 hours. The cooled reaction mixture was evaporated to dryness *in vacuo*, the amorphous residue dissolved in benzene (7 ml.)–hexane (5 ml.) and the resulting mixture chromatographed on alumina (18 g.). A mixture of equal volumes of benzene and hexane (235 ml.) eluted only 4 mg. of material. Elution with benzene furnished at first amorphous material (22 mg. in the first 150 ml.) followed by a crystalline fraction (113 mg. in the next 300 ml.). Several recrystallizations of this latter fraction from aqueous ethanol yielded material melting at 186–187°, which did not depress the melting point of triacetylisojervine when mixed with the latter; ultraviolet spectrum (alcohol): end absorption with inflection at 245 mμ (ε 4400) and maximum at 330 mμ (ε = 200).

Anal. Calcd. for $C_{33}H_{45}O_6N$: C, 71.84; H, 8.22. Found: C, 72.23; H, 8.52.

Subsequent elution with benzene–ether (1:1) furnished a small amount of diacetyljervine, λ_{max}^{alc} 250 mμ (ε 16,400), 360 mμ (ε 80).

Reaction of Isojervine with Acetic Anhydride and Zinc Chloride.—A solution of isojervine (237 mg., m.p. 111–116°) and zinc chloride (15 mg.) in acetic anhydride (3 ml.) was refluxed for 3 hours. The reaction mixture was worked up as described above for jervine. The resulting residue (310 mg.) crystallized readily from acetone yielding 150 mg. of crude crystals, which after two more crystallizations melted at 187–189° and were identified as triacetylisojervine. Chromatography of the mother liquor material (150 mg.) on alumina yielded no trace of III in the benzene–hexane (1:1) eluates. The benzene–ether (1:1) eluate yielded an additional amount (20 mg.) of triacetylisojervine.

Catalytic Hydrogenation of $\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate (III).—A suspension of PtO_2 (200 mg.) in glacial acetic acid (15 ml.) was saturated with hydrogen and to it was added a solution of III (303 mg.) in 15 ml. of glacial acetic acid. Hydrogen uptake was rapid and came to a standstill after one hour when 79 ml. or the equivalent of 4 moles had been absorbed. The catalyst was filtered off and the glacial acetic acid was removed *in vacuo*. The thoroughly dried residue (317 mg.) crystallized readily from methanol and afforded after three crystallizations the pure 17-ethyletiojervane-3β-ol-11-one acetate (V) (97 mg.) melting at 114–116°, $[\alpha]^{25}D$ −8.6° (*c* 0.87 in $CHCl_3$), λ_{max}^{alc} 305 mμ (ε 90), λ_{max}^{Nujol} 5.78 μ) composite of ester-carbonyl (5.75 μ) and saturated 11-keto-carbonyl (5.82 μ)),[31] 8.03 μ, no OH-bands.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07; acetyl, 11.63. Found: C, 76.84; H, 10.38; acetyl, 11.47.

A small additional amount of crystalline reduction product was obtained from the mother liquors, but the bulk of the mother liquors could not be induced to crystallization.

The absence of carbon–carbon double bonds in this substance was demonstrated as follows: 3.9 mg. (0.011 mmole) was dissolved in 1 ml. of 0.031 *M* perbenzoic acid and allowed to stand in the refrigerator for 18 hours. Iodometric titration showed negligible consumption of the reagent. The fact that the keto group of the trienone III had not been reduced to hydroxyl in the hexahydro product V was demonstrated by the isolation of unchanged starting material after allowing a solution of 16.8 mg. of V and 3.4 mg. of chromic acid in 3 ml. of glacial acetic acid to stand at room temperature for 3 hours.

The keto group of V did not react with thiosemicarbazide, as shown by the absence of ultraviolet absorption at 280 mμ after refluxing a solution of V (3.0 mg.) and thiosemicarbazide (1.3 mg.) in alcohol (2 ml.) for 2.5 hours.

Ozonolysis of $\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate. (a) In Acetic Acid.—Oxygen containing 2% ozone was passed for 30 min. through a solution of the trienone III (126 mg.) in glacial acetic acid (6 ml.) maintained at 15–18°. Water (6 ml.) was added and the mixture was distilled at ordinary pressure in a micro-distillation apparatus into an ice-cooled receiver until a total of 4 ml. of distillate had been collected. The addition of excess *p*-nitrophenylhydrazine in dilute acetic acid produced a copious precipitate (23 mg.) melting at 123–125°. Two recrystallizations from hexane gave fine needles m.p. 126–127°. A freshly prepared sample of acetaldehyde *p*-nitrophenylhydrazone melted at 123–126° and did not depress the melting point of the above sample.

A blank experiment carried out in the same manner except that diacetyljervine (100 mg.) was used yielded no acetaldehyde.

(b) In Carbon Tetrachloride.—A solution of the trienone III in carbon tetrachloride (7 ml.) was ozonized at 0°. After about 5 minutes an insoluble gelatinous ozonide began to appear and after 20 minutes the ozonization mixture was carefully evaporated to dryness *in vacuo*. Water (7 ml.) was added and the mixture distilled as described above. Fourteen mg. of acetaldehyde *p*-nitrophenylhydrazone m.p. 123–125° was obtained.

Oxidation of $\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate with Chromic Acid.—To a solution of the trienone III (2.39 g.) in glacial acetic acid (200 ml.) was added dropwise with stirring chromic acid (1.47 g.) in 95%

(31) The position of the saturated 11-ketone band in tetrahydro- and dihydrojervine is at 5.82 μ.

acetic acid (73 ml.). After the addition was complete (0.5 hour) the mixture was allowed to remain at room temperature for another 1.5 hours. Alcohol (2 ml.) was then added and the solution was evaporated to a sirup *in vacuo*. The residue was distributed between chloroform and water and the aqueous phase extracted with additional amounts of chloroform. The combined chloroform extracts were washed with dilute bicarbonate, which removed non-crystallizable acidic products (138 mg.),[32] and water and dried over sodium sulfate. Evaporation of the solvent *in vacuo* yielded a yellow residue (2.5 g.) which could be crystallized directly from acetone, but which was more appropriately chromatographed on sulfuric acid-washed alumina (50 g.) from a solution in benzene (20 ml.) and hexane (7 ml.). Elution of the column with benzene–hexane (3:1) furnished in the first 925 ml., 1.05 g. of crystalline material corresponding to a yield of 45%. Recrystallization of this material from acetone yielded the pure $\Delta^{5,13(17a)}$-etiojervadiene-3β-ol-11,17-dione acetate (VI) as intensely yellow prisms, m.p. 182–183°, $[\alpha]^{22}D$ −234° (*c* 0.67 in $CHCl_3$), λ_{max}^{alc} 267 mμ (ϵ 14,000), 415 mμ (ϵ 49), $\lambda_{max}^{2.5\% \text{ KOH in MeOH}}$ 265 mμ (ϵ 10,000), 390 mμ (ϵ 5000), λ_{max}^{Nujol} 5.81 μ, 5.96 μ, 6.06 μ and 6.14 μ.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65; acetyl, 12.55. Found: C, 73.53, 73.82; H, 7.87, 7.47; acetyl, 13.5.

Further elution of the column with benzene–acetone (1:1) (400 ml.) yielded a considerable amount of non-crystallizable material (770 mg.).

$\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione acetate was recovered unchanged in attempts to effect reaction with lead tetraacetate, periodic acid, *o*-phenylenediamine, pyridine and acetic anhydride at 100° and pyridine and benzoyl chloride at 100°.[33]

Rapid reaction took place with 2,4-dinitrophenylhydrazine, hydroxylamine and semicarbazide.

The monoxime was prepared with hydroxylamine acetate in methanol. Recrystallization from methanol yielded the pure oxime as pale yellow prisms, m.p. 243–244° after sintering at 235°; λ_{max}^{alc} 294 mμ (ϵ 19,000), shoulder at 270 mμ (ϵ 12,000).

Anal. Calcd. for $C_{21}H_{27}O_4N$: C, 70.51; H, 7.62; N, 3.92. Found: C, 70.37; H, 8.01; N, 4.10.

The monosemicarbazone was prepared with semicarbazide acetate in methanol. It was recrystallized from methanol and melted at 287–288° dec., after browning at about 265°.

Anal. Calcd. for $C_{21}H_{29}O_4N_3$: C, 66.10; H, 7.31; N, 10.52. Found: C, 65.73; H, 7.87; N, 10.41.

Isolation of Acetaldehyde from the Chromic Acid Oxidation of $\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate (III).—The oxidation of III (500 mg.) was conducted as described above except that nitrogen was swept through the solution during the dropwise addition of the chromic acid solution. The gases were passed through 3 ml. of ice-cold water and after completion of the reaction *p*-nitrophenylhydrazine acetate was added to the aqueous solution. Immediate precipitation (3 mg.) occurred and the precipitate, m.p. 125–127° after two crystallizations from hexane, was identified as acetaldehyde-*p*-nitrophenylhydrazone.

Deacetylation of $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione Acetate (VI).—$\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione acetate (VI) (200 mg.) was refluxed with a mixture of dioxane (8 ml.), water (6.4 ml.) and concentrated hydrochloric acid (1.6 ml.) for 8 hours. After removal of the dioxane *in vacuo* the residual mixture was extracted with chloroform. The chloroform extract was washed with bicarbonate and water and dried over sodium sulfate. Removal of the solvent *in vacuo* left a yellow residue (190 mg.), which after 2 crystallizations from acetone–hexane yielded the pure $\Delta^{5,13(17a)}$-etiojervadiene-3β-ol-11,17-dione (VII), m.p. 170–171°, $[\alpha]^{22}D$ −220° (*c* 0.44 in $CHCl_3$); λ_{max}^{alc} 267 mμ (ϵ 14,000), 415 mμ (ϵ 55); λ_{max}^{Nujol} 3.21 μ (OH), 5.96 μ (conjugated carbonyls), 6.17 μ (conj. double bond).

(32) Chromatography of the methyl esters of these acids did not furnish crystallizable products.

(33) L. F. Fieser, M. Fieser and S. Rajagopalan, *J. Org. Chem.*, **13**, 800 (1948).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.61; H, 8.57.

Oxidation of $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione (VII) with Aluminum *t*-Butylate.—To a solution of $\Delta^{5,13(17a)}$-etiojervadiene-3β-ol-11,17-dione (80 mg.) in dry acetone (1.5 ml.) was added a solution of aluminum *t*-butylate (300 mg.) in benzene (5 ml.). The mixture was refluxed for 12 hours and then decomposed with 1 *N* sulfuric acid. The benzene layer was separated off and the aqueous layer washed with fresh portions of benzene. The combined benzene extracts were dried over sodium sulfate and evaporated to dryness *in vacuo*. The yellow residue (87 mg.) crystallized readily from acetone affording the pure $\Delta^{4,13(17a)}$-etiojervadiene-3,11,17-trione (IX), m.p. 196–199°, $[\alpha]^{22}D$ +8° (*c* 1.1 in $CHCl_3$); ultraviolet spectrum, see Fig. 1.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.40. Found: C, 76.50; H, 7.78.

Synthesis of $\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate (III) from $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione Acetate (VI).—To a solution of $\Delta^{5,13(17a)}$-etiojervadiene-3β-ol-11,17-dione acetate (80 mg.) in dry ether (10 ml.) was added 0.7 ml. of the Grignard reagent prepared from ethyl bromide (1.6 ml.) and magnesium (500 mg.) in anhydrous ether (10 ml.). The resulting mixture was refluxed for 20 min. and decomposed with dilute hydrochloric acid. The ether solution was washed with water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The crude amorphous product (λ_{max}^{alc} 255 mμ ($E_{1\text{ cm}}^{1\%}$ 280)) (92 mg.) was refluxed with zinc chloride (10 mg.) in acetic anhydride (2 ml.) for five hours. The dark-brown solution was concentrated *in vacuo*, the residue taken up in chloroform and washed with water, dilute bicarbonate and again with water. Evaporation of the solvent left a residue (98 mg.) which was dissolved in benzene (4 ml.) and hexane (4 ml.) and chromatographed on sulfuric acid-washed alumina (4 g.). Elution of the column with benzene–hexane (1:1) afforded a small crystalline fraction, which on recrystallization from acetone melted at 178–182°, λ_{max}^{alc} 300 mμ (ϵ 15,000). The melting point of a mixture of this substance with authentic III was not depressed.

In a duplicate experiment the crude Grignard product (280 mg.) was separated by chromatography on alumina (10 g.) into essentially two fractions. The first was eluted with benzene–ether (3:1) (101 mg., λ_{max}^{alc} 255 mμ ($E_{1\text{ cm}}^{1\%}$ 180)) and the second with ether–acetone (4:1) (46 mg., λ_{max}^{alc} 250 mμ $E_{1\text{ cm}}^{1\%}$ 7)). The benzene–ether fraction, which probably represents a mixture of the 17- and 11-ethylcarbinols could be dehydrated to the trienone III. The ether–acetone fraction presumably represents the 11,17-diethyldicarbinol.

Treatment of $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione Acetate (VI) with Dilute Alkali. $\Delta^{5,13,15,17}$-Etiojervatetraene-3β-17-diol-11-one Diacetate (X).—To a solution of $\Delta^{5,13(17a)}$-etiojervadiene-3β-ol-11,17-dione acetate (VI) (200 mg.) in methanol (5.5 ml.) was added 1 *N* NaOH (5.5 ml.) and the mixture was refluxed for 1.5 hours. After acidification with dilute sulfuric acid the methanol was removed *in vacuo* and the aqueous mixture extracted with chloroform. The chloroform solution was washed, extracted twice with bicarbonate and evaporated to dryness *in vacuo*. Extraction of the acidified bicarbonate solution with chloroform yielded 17 mg. of acidic products which were not further investigated. The neutral fraction (152 mg.) was acetylated with acetic anhydride (1 ml.)–pyridine (1 ml.) overnight and the crude acetylation products dissolved in benzene (4 ml.)–hexane (4 ml.) for chromatography on sulfuric acid-washed alumina (5 g.). Elution with benzene yielded colorless prisms (42 mg.) which were purified by crystallization from methanol. Pure X melted at 207–208.5°, $[\alpha]^{23}D$ −138° (*c* 0.76 in $CHCl_3$); λ_{max}^{alc} 247 mμ (ϵ 11,000), 330 mμ (ϵ 2,200); $\lambda_{max}^{2.5\% \text{ KOH in MeOH}}$ 243 mμ (ϵ 26,700), 370 mμ (ϵ 3,100) (see Fig. 2); λ_{max}^{Nujol} 5.67 μ (phenolic acetyl), 5.87 μ (combined ester and conjugated ketonic carbonyls), 6.26 μ, 6.80 μ (phenyl).

Anal. Calcd. for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85; acetyl, 22.51. Found: C, 72.58; H, 6.94; acetyl, 20.60.

$\Delta^{5,13,15,17}$-Etiojervatetraene-3β,17-diol-11-one diacetate could also be isolated when the reaction with alkali was conducted at room temperature for 6 hours either in the presence or absence of oxygen. The diacetate coupled readily with

diazotized sulfanilic acid in carbonate alkaline medium and produced a deep red color, which changed to yellow upon addition of acetic acid.

$\Delta^{5,13,15,17}$-Etiojervatetraene-3β,17-diol-11-one 3-Acetate (XI).—An attempt to prepare the oxime of X resulted only in the removal of the phenolic acetyl group. The diacetate X (12 mg.) was refluxed for 1.5 hours with hydroxylamine acetate (prepared from 26 mg. of hydroxylamine hydrochloride and 40 mg. of potassium acetate) in methanol (1.2 ml.). The solution was then concentrated and a few drops of water was added. Crystallization occurred rapidly affording 8.5 mg. of material which after one recrystallization melted at 245–247° dec., λ_{max}^{alc} 255 mμ (ϵ 9,500), 330 mμ (ϵ 3,200), $\lambda_{max}^{2.5\%\ KOH\ in\ MeOH}$ 245 mμ (ϵ 24,300), 370 mμ (ϵ 3,100) (see Fig. 2).

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.98; H, 7.25.

An alcoholic solution of XI gave no coloration with ferric chloride. Diazomethane had no effect over a 16-hour period at room temperature.

Reduction of $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione Acetate (VI) with Zinc in Acetic Acid. Δ^{5}-13ξ,17aξ-Etiojervene-3β-ol-11,17-dione Acetate (VIII).—To a warm solution of $\Delta^{5,13(17a)}$-etiojervadiene-3β-ol-11,17-dione acetate (250 mg.) in glacial acetic acid (19 ml.) and water (10 ml.) was added in small portions a total of 1.2 g. of zinc dust until the solution appeared colorless. During the addition, which required about 15 minutes, the solution was warmed on the steam-bath and kept in gentle motion. While still hot the solution was separated from the residual zinc by centrifugation and the zinc washed with glacial acetic acid and chloroform. The acetic acid solution was evaporated to near-dryness and the residue was taken up in water and chloroform. The chloroform extract was washed with bicarbonate and water and dried over sodium sulfate. Evaporation of the solvent *in vacuo* left a residue (193 mg.), which was dissolved in benzene (2 ml.)–hexane (2 ml.) for chromatography on alumina (10 g.). Benzene–hexane (2:1) eluted in the first 175 ml. crude Δ^{5}-13ξ,17aξ-etiojervene-3β-ol-11,17-dione acetate (VIII) (61 mg.) melting at 165–171°, which after crystallization from acetone–hexane melted at 171–172.5°, $[\alpha]^{24}D$ −208° (*c* 0.33 in $CHCl_3$), $\lambda_{shoulder}^{alc}$ 295 mμ (ϵ 100).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.14; H, 7.72.

The monoxime was prepared with hydroxylamine acetate in methanol at room temperature. It was recrystallized from methanol and melted at 226–229° dec., λ_{max}^{alc} 300 mμ (ϵ 65).

Anal. Calcd. for $C_{21}H_{29}O_4N$: N, 3.90. Found: N, 4.21.

Continued elution of the column with the same solvent mixture yielded only lower melting material (100 mg., melting between 142 and 155°), which on rechromatography on 5 g. of alumina yielded with benzene–hexane (2:1) an additional 34 mg. of pure Δ^{5}-etiojervene-3β-ol-11,17-dione acetate (m.p. 170–171°). Subsequent fractions were again lower melting (147–153°, $[\alpha]D$ −123° (*c* 0.68 in $CHCl_3$)) and probably contain a stereoisomer of VIII.

Reduction of $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione Acetate (VI) with PtO_2 in Acetic Acid.—To a suspension of PtO_2 (200 mg.) in glacial acetic acid (12.5 ml.) which had been pre-reduced with hydrogen (42.5 ml.) was added a solution of $\Delta^{5,13(17a)}$-etiojervadiene-3β-ol-11,17-dione acetate (220 mg.) (VI) in glacial acetic acid (12 ml.). During the first 20 min. 54 ml. of hydrogen was taken up and the reduction came to a virtual standstill after two hours when 62.5 ml. of wet hydrogen had been taken up (*ca.* 4 mole equivalents). The catalyst was filtered off and to the filtrate was added a solution of chromic acid (50 mg.) in acetic acid (5 ml.). After 17 hours at room temperature alcohol (1 ml.) was added, the mixture was concentrated to small volume and the residue distributed between water and chloroform. The chloroform solution was washed with dilute bicarbonate and water and dried over sodium sulfate. Evaporation of the chloroform left a residue (164 mg.), which was dissolved in benzene (3 ml.) and hexane (3 ml.) and chromatographed on alumina (11 g.). Elution with benzene–hexane 1:1 yielded in the first 50 ml. amorphous material (25 mg.) followed in the next 75 ml. by a crystalline fraction representing crude 5ξ,13ξ,17aξ-etiojervane-3β-ol-11-one acetate (XVI) (45.0 mg.) which after 2 crystallizations from methanol melted at 105–107°; $[\alpha]^{21}D$ −4.1° (*c* 0.96 in $CHCl_3$).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.29; H, 9.99.

Subsequent elution of the column with benzene yielded in the first 110 ml. a second substance 5ξ,13ξ,17aξ-etiojervane-3β-ol-11,17-dione acetate (XVIII) (40 mg.) which after recrystallization from methanol melted at 172–174°, $[\alpha]^{24}D$ +33° (*c* 0.37 in $CHCl_3$).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.11; H, 8.87.

Reduction of $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione Acetate (VI) to the Parent Hydrocarbon: 5ξ,13ξ,17aξ-Etiojervane.—$\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol,11,17-dione acetate (300 mg.) was reduced with PtO_2 in acetic acid as described above. The crude reduction product (286 mg.) was deacetylated with potassium bicarbonate (290 mg.) in methanol (25 ml.)–water (5 ml.) for 18 hours at room temperature. The methanol was evaporated *in vacuo* and the aqueous residue extracted with chloroform. Evaporation of the sodium sulfate-dried chloroform extract left 266 mg., which was oxidized with chromic acid (200 mg.) in glacial acetic acid (45 ml.) for 18 hours at room temperature. The work-up of the oxidation mixture (see previous experiment) yielded 167 mg. of neutrals and 117 mg. of acids. The neutral fraction was subjected to a Clemmensen reduction[19] as follows: A solution of the neutral fraction in dioxane (23 ml.)–concentrated hydrochloric acid (20 ml.) was heated on the steam-bath with zinc amalgam (prepared from 10 g. of 30 mesh zinc) for two hours. The aqueous mixture was decanted from the zinc amalgam and both phases were extracted with hexane (5 times 30 ml.). The hexane extracts were washed with dilute bicarbonate and water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue (115 mg.) was shaken again with PtO_2 (100 mg.) and hydrogen in acetic acid (10 ml.) to reduce any unsaturated by-products formed in the Clemmensen reduction. The material recovered from the catalytic reduction was dissolved in hexane (3 ml.) and chromatographed on alumina (7 g.). The first 50 ml. of hexane eluted 57 mg. of a colorless liquid which was fractionally distilled in a cold finger sublimation apparatus.

Fraction I: bath temperature 55–60° at 0.04 mm., 17 mg., $[\alpha]^{20}D$ +12.5° (*c* 0.64 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.46; H, 12.16.

Fraction II: bath temperature 60–65° at 0.04 mm., 18 mg., $[\alpha]^{20}D$ +13.3° (*c* 0.45 in $CHCl_3$).

Anal. Found: C, 87.46; H, 12.09.

Reduction of $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione Acetate with Pd-Black in Acetic Acid.—$\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione acetate (VI) (301 mg.) was reduced in glacial acetic (20 ml.) with (pre-reduced) Pd-black (200 mg.). Forty-seven ml. of hydrogen (*ca.* 2.1 mole equivalents) was taken up within two hours (38 ml. within 20 min.). The crude reduction products (292 mg.) were dissolved in benzene (3 ml.)–hexane (3 ml.) and chromatographed on alumina (15 g.). Benzene (50 ml.) eluted at first the monoketone XVII, which after recrystallization from methanol had the following properties: m.p. 156–158.5°, $[\alpha]^{22}D$ −254° (*c* 0.60 in $CHCl_3$).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.56; H, 9.34.

The next 30 ml. of benzene eluted low-melting fractions (16 mg.), which were followed in the subsequent 50 ml. by a fraction (27 mg.), which after 2 crystallizations from methanol melted at 174–175.5°, $[\alpha]^{23}D$ −86° (*c* 0.27 in $CHCl_3$). This material gave a strong depression in the mixture melting point with the subsequent fraction of the same melting point. There was not sufficient material for analytical characterization.

This fraction was followed in the chromatogram by a low-melting mixture (40 mg. in 50 ml. of benzene). The main component of the reduction mixture eluted in the next 175 ml. of benzene (64 mg.) was 5ξ,13ξ,17aξ-etiojervane-3β-ol-11,17-dione acetate (XVIII), which after crystallization from methanol melted at 172–174°, $[\alpha]D$ +56° (*c* 0.78 in $CHCl_3$), λ_{max}^{alc} 298 mμ (ϵ 100).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.20; H, 8.74.

The mixture of this substance with the substance of the same m.p. but lower rotation ($[\alpha]_D$ +33°) obtained in the PtO_2 reduction showed no depression in melting point.

The monoxime of XVIII was prepared with hydroxylamine acetate in methanol: m.p. 221–224°, λ_{max}^{alc} 300 mμ (ε 79).

Anal. Calcd. for $C_{21}H_{31}O_4N$: N, 3.88. Found: N, 4.20.

Reduction of $\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione Acetate (VI) with Palladium-on-charcoal in Dioxane.—$\Delta^{5,13(17a)}$-Etiojervadiene-3β-ol-11,17-dione acetate (VI) (700 mg.) was hydrogenated with pre-reduced 5% Pd-on-charcoal (500 mg.) in pure dioxane (25 ml.) until 80 ml. of hydrogen had been taken up, which required *ca.* 24 hours. The crude reduction product (660 mg.) was dissolved in benzene (5 ml.)–hexane (5 ml.) and chromatographed on alumina (13 g.). Benzene (1000 ml. in 28 fractions) eluted essentially a single substance (242 mg.), which after two crystallizations from ether–hexane melted at 135–136°, $[\alpha]^{23}D$ −12° (*c* 1.27 in $CHCl_3$), λ_{max}^{alc} 300 mμ (ε 110), λ_{max}^{Nujol} 5.81 μ (composite of saturated keto- and ester-carbonyls), 6.05 μ (isolated double bond), no OH-bands. This product appears to be Δ^{5}-13ξ,17aξ-etiojervene-3β-ol-11,17-dione acetate (XIX).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.55; H, 7.94.

Elution with benzene (360 ml.) gave only difficultly separable mixtures. Benzene–ether (8:2) afforded in the first 70 ml. 75 mg. of $\Delta^{13,15,17}$-5-ξetiojervatriene-3β,17-diol-11-one 3-acetate (XXII) which after recrystallization from acetone–hexane melted at 225–230° dec., $[\alpha]^{23}D$ −210° (*c* 1.26 in $CHCl_3$); λ_{max}^{alc} 224 mμ (ε 15,500), 254 mμ (ε 10,400), 327 mμ (ε 2,050).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 74.05; H, 7.48.

This substance was followed by amorphous material (30 mg. in 75 ml. of benzene–ether 8:2) and eventually by a crystalline substance (50 mg. in 275 ml. of the same solvent mixture). Recrystallization from acetone–hexane afforded material melting at 143–144.5°, $[\alpha]^{24}D$ −109° (*c* 1.20 in $CHCl_3$), λ_{max}^{alc} 300 mμ (ε 80); λ_{max}^{Nujol} 2.89 μ (OH), 5.77 μ (composite saturated keto and ester carbonyls), 6.05 μ (isolated double bond). This substance appears to be Δ^{5}-13ξ,17aξ-etiojervene-3β,17ξ-diol-11-one 3-acetate (XX).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.59; H, 8.23.

Benzene–ether 1:1 (175 ml.) eluted a small amount of crystalline material (25 mg.), which could not be crystallized to sufficient purity.

Benzene–acetone 3:1 (125 ml.) eluted 100 mg. of crystalline material, which was readily purified by crystallization from methanol, m.p. 204–205.5°, $[\alpha]^{23}D$ −118° (*c* 1.28 in $CHCl_3$); λ_{max}^{alc} 243 mμ (ε 9000), 318 mμ (ε 45); λ_{max}^{Nujol} 2.93 μ (OH), 5.92 and 5.97 μ (conj. carbonyl); 6.15 μ (conj. double bond). This substance probably represents Δ^{13}-5ξ,17aξ-etiojervene-3β,17ξ-diol-11-one 3-acetate (XXI).

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The Structure of Jervine. IV. The Sulfuric Acid-catalyzed Acetolysis of O,N-Diacetyljervine

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O,N-Diacetyljervine on acetolysis with acetic anhydride–acetic acid containing several molar equivalents of sulfuric acid yielded besides an amorphous sulfonic acid two neutral compounds melting at 240° and 194°, respectively. In their formation the oxidic ring of jervine has been opened with the establishment of an acetoxy group at position 23 in the piperidine ring. The compound m.p. 240° is assigned the indanone structure III on the basis of its ultraviolet absorption spectrum, its reducibility to a product exhibiting benzenoid absorption characteristics, the inertness of its keto group, and the fact that the N-acetate IV prepared from it by O-desacetylation on Oppenauer oxidation gave the α,β-unsaturated ketone V. The formulation of the compound m.p. 194° as VII rests mainly on the similarity of its absorption spectrum to that of jervine and the presence of a new, non-acylatable hydroxyl group. On hydrolysis with alkali VII suffers not only the loss of its two O-acetyl groups, but also a rearrangement resulting in the formation of a weak tertiary base which is best expressed as IX.

In the preceding paper of this series[1] Fried and Klingsberg have described the acetolysis of jervine by means of boiling acetic anhydride and zinc chloride. In this reaction the piperidine ring and the oxidic oxygen atom are eliminated with the formation of a C_{21}-fragment retaining only two carbon atoms of the original side chain. In contrast, the sulfuric acid-catalyzed acetolysis of acetylated jervine derivatives on which we wish to report in this and the following paper does not result in degradation. The side chain moiety including the nitrogenous ring remains intact except for the anticipated opening of the oxidic bridge linking that ring with ring D of the tetracyclic nucleus (*cf.* formulas I and II, representing, respectively, the structure proposed for jervine by Jacobs and Sato[2] in 1949, and the new structure advanced by us). However, in the case of jervine itself the reaction brings about an additional change in ring D which is highly significant in relation to the structure assigned by Fried and Klingsberg to the "yellow diketone" resulting from further degradation of their acetolysis product. The substance of these investigations already has been communicated in preliminary form.[3,4] In this paper we present in detail the work with jervine amplified by some results obtained more recently.

The reaction was carried out by dissolving O,N-diacetyljervine[5] in the acetolysis mixture (acetic

(1) J. Fried and A. Klingsberg, THIS JOURNAL, **75**, 4929 (1953).

(2) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **131**, 55 (1949).

(3) J. Fried, O. Wintersteiner, A. Klingsberg, M. Moore and B. M. Iselin, THIS JOURNAL, **73**, 2970 (1951).

(4) O. Wintersteiner, B. M. Iselin and M. Moore, Abstracts, XIIth Internat. Congress of Chemistry, September 10–13, 1951. Medicinal Chemistry, p. 292.

(5) It was necessary to use the acetylated derivatives as starting materials for this reaction as the free alkaloidal bases combine with the sulfuric acid to form the sulfates which are practically insoluble in the acetolysis mixture.