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Jervine. VII.[1] 3,5-Cyclo Derivatives of Jervine Degradation Products

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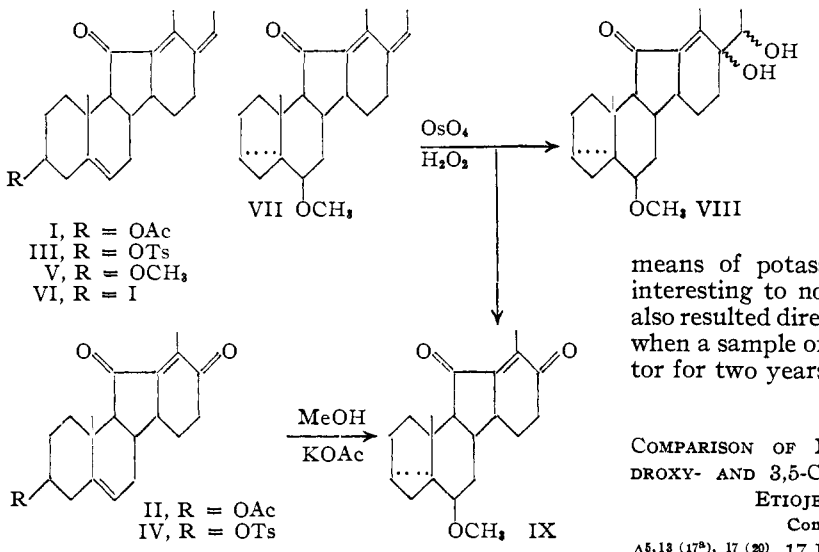
Two degradation products of jervine have been subjected to the *i*-steroid rearrangement and the corresponding 3,5-cyclo derivatives isolated. These conversions offer final proof for the β-orientation of the 3-hydroxyl group in jervine and veratramine. Oxidation of the 3,5-cyclo derivative VII with osmium tetroxide involved only the 17,20-double bond.

In the course of recent studies on the structure of the alkaloid jervine the nitrogen-free degradation products I and II were obtained.[2] The nature and site of the functional groups and particularly the presence of an 11-keto group in these substances recommended their use as intermediates in the synthesis of analogs of cortical hormones, in which the conventional steroidal skeleton is replaced by a C/D rearranged ring system. In order to perform certain operations necessary for the elaboration of the dihydroxyacetone side chain it appeared desirable to protect the hydroxyl group and the 5,6-double bond of I by conversion to a 3,5-cyclo derivative. This latter conversion generally known as the *i*-steroid rearrangement[3,4] is fully stereospecific[5] and is dependent on the presence of a β-oriented 3-hydroxyl group.[6] The 3-hydroxyl group in jervine



and in the acetolysis product I have been assumed mainly on the basis of molecular rotation relationships to be β-oriented,[2,7] but this has not been strictly proved. The formation of a 3,5-cyclo derivative from I, on the other hand, would constitute unambiguous proof for the β-orientation of this hydroxyl group in jervine and, because of degradation results linking the latter with veratramine,[8] also in veratramine.

Treatment of the tosylate III with potassium acetate in methanol[3,4] furnished a mixture of methyl ethers separable by chromatography into a dextrorotatory (m.p. 58–60°, $[\alpha]^{23}D$ +26°) and a levorotatory (m.p. 168–170°, $[\alpha]^{23}D$ −113°) isomer. The composition of these isomers ($C_{22}H_{32}O_4$), their mode of formation and the difference in molecular rotation between them (Table I) leave little doubt that the two substances represent the 3,5-cyclo-6-methyl ether VII and the normal methyl ether V, respectively. In accordance with the 3,5-cyclo structure VII the dextrorotatory ether on treatment with osmium tetroxide and hydrogen peroxide furnished a glycol of the composition $C_{22}H_{34}O_6$, to which structure VIII has been assigned on the basis of its absorption maxima at 250 mμ (ε 12,300) and 355 mμ (ε 72) characteristic of the $\Delta^{13(17a)}$-11-ketone chromophore present in jervine.[9] In addition to the glycol VIII the reaction with OsO_4 afforded the yellow 3,5-cyclo-enedione IX, so formulated on the basis of its ultraviolet absorption spectrum (λ_{max}^{alc} 266 mμ (ε 15,600): CO—C=C—CO) and of its preparation by an independent route from the enedione tosylate IV by means of potassium acetate in methanol. It is interesting to note that the 3,5-cyclo-enedione IX also resulted directly from the 3,5-cyclodienone VII, when a sample of the latter was stored in a desiccator for two years, apparently by autoxidation.[10]

Table I

Comparison of Molecular Rotations of Δ^5-3β-Hydroxy- and 3,5-Cyclo-6-methoxy Derivatives in the Etiojervane and Cholestane Series

Compound	$[M]D$	$\Delta[M]D$
$\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatrien-3β-ol-11-one 3-methyl ether (V)	−369°	
$\Delta^{13(17a),17(20)}$-3,5-Cyclo-17-ethyletiojervadien-6β-ol-11-one 6-methyl ether (VII)	+ 85	+454°
$\Delta^{5,13(17a)}$-Etiojervadien-3β-ol-11,17-dione 3-acetate (II)	−800	
$\Delta^{13(17a)}$-3,5-Cycloetiojerven-6β-ol-11,17-dione 6-methyl ether (IX)	−386	+414
Cholesteryl acetate	−184	
Cholesterol methyl ether	−184	
3,5-Cyclocholestan-6β-ol methyl ether	+220	+404

(1) Jervine. VI: B. M. Iselin and O. Wintersteiner, This Journal, **76**, 5616 (1954).

(2) J. Fried and A. Klingsberg, *ibid.*, **75**, 4929 (1953).

(3) W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

(4) E. S. Wallis, E. Fernholz and F. T. Gephart, This Journal, **59**, 137 (1937).

(5) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(6) B. Riegel and R. M. Dodson, *J. Org. Chem.*, **13**, 424 (1948).

(7) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **175**, 57 (1948).

(8) N. Hosansky and O. Wintersteiner, This Journal, **74**, 4474 (1952).

(9) The most characteristic part of the absorption spectrum of jervine is the unusual position of the low intensity band at 360 mμ. α,β-Unsaturated ketones generally exhibit this band at 300–330 mμ. The C-nor-D-homosteroid prepared by C. F. Hiskey, R. Hirschmann and N. L. Wendler, *ibid.*, **75**, 5137 (1953), which possesses the jervine chromophore shows this band at 350 mμ.

(10) Examination of a sample of the trienone acetate I which had been stored for an equal length of time showed evidence for the presence of the enedione II.

Several attempts have been made to improve the yield of the trienone I from jervine by replacing the zinc chloride previously recommended by other Lewis acids. An alternative procedure using borontrifluoride etherate is described in the Experimental part.

Experimental

The melting points were taken in capillary tubes and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semi-micro tube. The ultraviolet spectra were measured in a quartz Beckman spectrophotometer, model DU, and the infrared spectra in a Perkin–Elmer single beam instrument, model 12-B.

Degradation of Jervine to $\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatrien-3β-ol-11-one Acetate (I).[11]—The procedure described here represents an alternative of the one described previously.[2] A solution of 50 g. of jervine in 500 ml. of acetic anhydride and 5 ml. of BF_3 etherate was refluxed for 24 hours. The reaction mixture was concentrated *in vacuo* until crystals began to appear. After cooling in the refrigerator, the crystals were filtered off and recrystallized from acetone. A yield of 7.2 g. (17%) of I, m.p. 182–188°, was obtained.

The hydrolysis of the acetolysis product I (4 g.) was performed as described previously,[2] 2.8 g. of material melting at 149–151° was obtained, $[\alpha]^{23}D$ −109° (*c* 1.61 in $CHCl_3$). One sample melted at 176–178°, apparently representing a polymorphic modification of the above.

$\Delta^{5,13(17a),17(20)}$-Ethyletiojervatrien-3$\beta$-ol-11-one 3$\beta$-Tosylate (III).—To a solution of the above free alcohol (2.8 g.) in 60 ml. of dry pyridine was added 4 g. of pure *p*-toluenesulfonyl chloride. After 16 hours at room temperature the mixture was warmed on the steam-bath for 15 minutes, diluted with water and the resulting precipitate filtered and recrystallized from acetone–water; 3.2 g. of III, m.p. 167° dec., $[\alpha]^{23}_D$ −92° (*c* 1.16 in $CHCl_3$), was obtained.

Anal. Calcd. for $C_{28}H_{34}O_4S$ (466.61): C, 72.07; H, 7.35; S, 6.87. Found: C, 72.29; H, 7.18; S, 7.05.

Reaction of $\Delta^{5,13(17a),17(20)}$-17-Ethyletiojervatrien-3β-ol-11-one 3β-tosylate (III) with Potassium Acetate in Methanol.—The above tosylate III (2.4 g.) was refluxed with 3 g. of fused potassium acetate in 180 ml. of dry methanol for 5 hours. The solvent was removed *in vacuo*, the residue dissolved in ether and water, and the ether solution washed with dilute bicarbonate and water. An oil was obtained (1.93 g.), which was subjected to chromatography on 40 g. of Merck alumina (weakly basic). A total of 900 ml. of hexane eluted 900 mg. of oil in 9 fractions, the first 4 of which represented the bulk of material and showed the following specific rotations in chloroform: (1) 474 mg., +25.5°; (2) 160 mg., +13.5°; (3) 95 mg.; (4) 61 mg., +4.6°. The first fraction (100 ml. hexane, 474 mg.) on crystallization from acetone–hexane furnished the 3,5-cyclo-6-methyl ether VII as light yellow crystals, m.p. 58–60°, $[\alpha]^{23}_D$ +26° (*c* 0.5 in $CHCl_3$); λ^{alc}_{max} 298 mμ (ϵ 15,700); λ^{nujol}_{max} 5.91 μ, 6.28 μ.

Anal. Calcd. for $C_{22}H_{30}O_2$ (326.46): C, 80.94; H, 9.26. Found: C, 80.90; H, 9.34.

The next fraction eluted with 1000 ml. of 50% benzene-hexane yielded 550 mg. of material, which crystallized from hexane in light yellow needles, m.p. 168–170°, $[\alpha]^{23}_D$ −113° (*c* 0.6 in $CHCl_3$); λ^{alc}_{max} 300 mμ (ϵ 24,400); λ^{nujol}_{max} 5.96 μ, 6.26 μ. It represents the normal methyl ether V.

Anal. Calcd. for $C_{22}H_{30}O_2$ (326.46): C, 80.94; H, 9.26; OCH_3, 9.51. Found: C, 81.01; H, 9.31; OCH_3, 9.57.

A sample of the 3,5-cyclo-6-methyl ether (VII), $[\alpha]D$ +26°, was rechromatographed after having been stored in a desiccator for two years at room temperature. The major portion of this material was now insoluble in hexane; the hexane-soluble portion furnished in the hexane eluates crystals melting at 158–160°, $[\alpha]^{23}D$ −134° (*c* 0.45 in $CHCl_3$); λ^{alc}_{max} 266 mμ (ϵ 15,500), identical in all respects with the 3,5-cyclo-enedione IX.

3β-Iodo-$\Delta^{5,13(17a),17(20)}$-17-ethyletiojervatrien-11-one (VI).—A solution of the trienone tosylate III (250 mg.) and 500 mg. of anhydrous sodium iodide in 15 ml. of anhydrous acetone, was sealed into a tube and heated for 3 hours in the steam-bath. The tube was then allowed to cool to room temperature overnight. The sodium toluenesulfonate was filtered off, the solvent evaporated *in vacuo* and the resulting residue taken up in ether and water. The ether extract was washed with sodium thiosulfate and water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue on crystallization from aqueous acetone afforded the iodo derivative VI, m.p. 186–187° dec., $[\alpha]^{23}D$ −63° (*c* 0.39 in $CHCl_3$); λ^{alc}_{max} 299 mμ (ϵ 24,200).

Anal. Calcd. for $C_{21}H_{27}OI$ (422.35): C, 59.72; H, 6.45. Found: C, 59.71; H, 6.44.

Reaction of $\Delta^{13(17a),17(20)}$-3,5-Cyclo-17-ethyletiojervadien-6β-ol-11-one Methyl Ether (VII) with Osmium Tetroxide.—The 3,5-cyclomethyl ether VII (420 mg.) was dissolved in 25 ml. of dry ether and 9.5 ml. of dry pyridine. A solution of 350 mg. of OsO_4 in 10 ml. of dry ether containing one drop of 30% perhydrol was added and the mixture allowed to remain at room temperature for 21 hours. Alcohol was then added and the mixture evaporated almost to dryness. To the residue was added 25 ml. of ethanol and a solution of 3.3 g. of sodium sulfite in 30 ml. of water and the resulting mixture was refluxed for 15 minutes. The suspension was filtered, the filtrate diluted with water and extracted with chloroform. The crude residue (393 mg.) was dissolved in benzene–hexane 1:4 and chromatographed on 8 g. of sulfuric acid-washed alumina. Thirty-five mg. of a yellow compound, m.p. 154–158°, was eluted with 300 ml. of 50% hexane–benzene. Infrared comparison showed it to be identical with $\Delta^{13(17a)}$-3,5-cyclo-etiojerven-6β-ol-11,17-dione methyl ether obtained by rearrangement of the tosylate IV (*vide infra*).

Continued elution of the column with ether–benzene 1:4 and ether yielded only non-crystallizable material, which was followed by a crystalline fraction (145 mg. in 150 ml. of 10% methanol in ether). Repeated crystallization of this material from acetone afforded the glycol VIII melting at 154–158°, λ^{alc}_{max} 250 mμ (ϵ 12,300), 355 mμ (ϵ 72).

Anal. Calcd. for $C_{22}H_{32}O_4$ (360.48): C, 73.30; H, 8.95. Found: C, 73.25; H, 8.96.

$\Delta^{5,13(17a)}$-Etiojervadien-3β-ol-11,17-dione Tosylate (IV).—To a solution of 2.4 g. of $\Delta^{5,13(17a)}$-etiojervadien-3β-ol-11,17-dione in 30 ml. of pyridine was added 2.5 g. of *p*-toluenesulfonyl chloride. The mixture was allowed to stand at room temperature overnight. The excess acid chloride was destroyed with ice, the mixture diluted with chloroform and washed with 1 *N* HCl, bicarbonate and water. Crystallization fron acetone afforded 2.5 g. of the tosylate IV, m.p. 168–170° dec., $[\alpha]^{23}_D$ −158° (*c* 0.35 in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{30}O_5S$ (454.56): C, 68.70; H, 6.65; S, 7.05. Found: C, 68.93; H, 6.42; S, 7.05.

$\Delta^{13(17a)}$-3,5-Cyclo-etiojerven-6β-ol-11,17-dione 6-Methyl Ether (IX).—A solution of the tosylate IV (65 mg.) and 100 mg. of fused anhydrous potassium acetate was refluxed in 15 ml. of anhydrous methanol for 4 hours. Water was added, the methanol removed *in vacuo*, and the aqueous suspension extracted with chloroform. The chloroform solution was washed, dried and evaporated *in vacuo*. A yellow oil (41 mg.) was obtained, which crystallized from ether when seeded with $\Delta^{13(17a)}$-3,5-cyclo-etiojerven-6β-ol-11,17-dione 6-methyl ether obtained from the osmium tetroxide reaction; m.p. 158–160°, $[\alpha]^{23}_D$ −123° (*c* 0.24 in $CHCl_3$); λ^{nujol}_{max} 5.86μ, 6.14 μ; λ^{alc}_{max} 266 mμ (ϵ 15,600).

Anal. Calcd. for $C_{20}H_{26}O_3$ (314.4): C, 76.40; H, 8.34; OCH_3, 9.87. Found: C, 76.92; H, 8.25; OCH_3, 10.00.

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(11) The nomenclature used here is that outlined in footnote 29 of reference 2.