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SYNTHESIS OF A NITROGEN-FREE DERIVATIVE OF JERVINE

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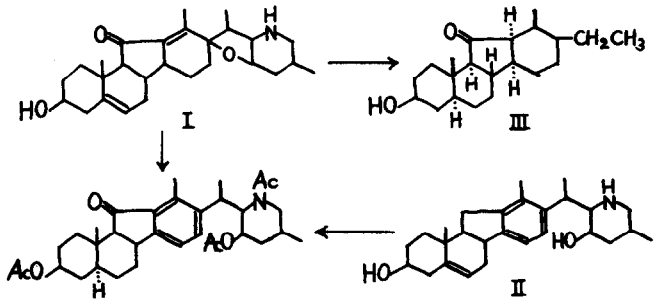
The veratrum alkaloids, jervine (I) and veratramine (II) possess the C-nor-D-homosteroid skeleton as determined by Wintersteiner and co-workers.[1] Recently K. Tsuda, S. Okuda and H. Kataoka have determined the absolute configuration of the methyl group in the piperidine residue,[2] but the correlation of jervine-derived products with derivatives of conventional steroids has been lacking. We have now succeeded in obtaining the degradation product (III) of Fried and Klingsberg[3] in the course of our studies of C-nor-D-homopregnanes derived from hecogenin.



[1] J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, J. Am. Chem. Soc. 73, 2970 (1951).

[2] K. Tsuda, S. Okuda and H. Kataoka, 14th Annual Meeting of Pharmaceutical Society of Japan (Sapporo, July 19, 1961).

[3] J. Fried and A. Klingsberg, J. Am. Chem. Soc. 75, 4929 (1953).

3β-Hydroxy-12,12-ethylenedioxy-5α-pregnan-20-one (IV)[4] prepared in nine steps from hecogenin was reduced to 3β-hydroxy-12,12-ethylenedioxy-5α-pregnane (V) (m.p. 165°) by Huang-Minlon's method in 87% yield. Removal of the ethylenedioxy group by heating in 90% acetic acid gave 3β-hydroxy-5α-pregnane-12-one (VI) (m.p. 186°, 85% yield), which was converted into the acetate (VII) (m.p. 140°, 90% yield). Bromination of VII in benzene readily afforded 3β-acetoxy-11α-bromo-5α-pregnane-12-one (VIII) (m.p. 148°, 50% yield), which was carefully hydrolyzed to 3β,11β-dihydroxy-5α-pregnane-12-one (IX) (m.p. 192-193°, 50% yield). The p-toluenesulfonylhydrazone of IX, (X) (m.p. 235° decomp.), which was obtained on treatment of IX with p-toluenesulfonylhydrazide in acetic acid, was heated with sodium ethyleneglycolate at 170°,[5] to give XI, m.p. 190°, $[\alpha]_D$+34.0°(C, 0.94 $CHCl_3$), Found: C, 79.25; H, 10.85. Compound XI possesses a double bond exocyclic to a five-membered ring because of its relatively strong absorption at 1678 cm^{-1} and its reduction with PtO_2 or Pd-C to a saturated mono-ol with loss of the 11-hydroxyl group suggesting the presence of an allylic structure. Treatment of XI with acetic anhydride-pyridine afforded a monoacetate (XII), m.p. 152°, $[\alpha]_D$+31.2° (C, 1.09 $CHCl_3$), IR: 3580 (11-hydroxyl), 1738 (3-acetyl), 1678 cm^{-1} (double bond), Found: C, 76.50; H, 10.07, in 65% yield. On mild oxidation with CrO_3 in pyridine the acetate XII produced an α,β-unsaturated ketone (XIII), m.p. 143.5°, $[\alpha]_D$-34.2°(C, 1.35 $CHCl_3$), Found: C, 77.01; H, 9.55, in 70% yield.

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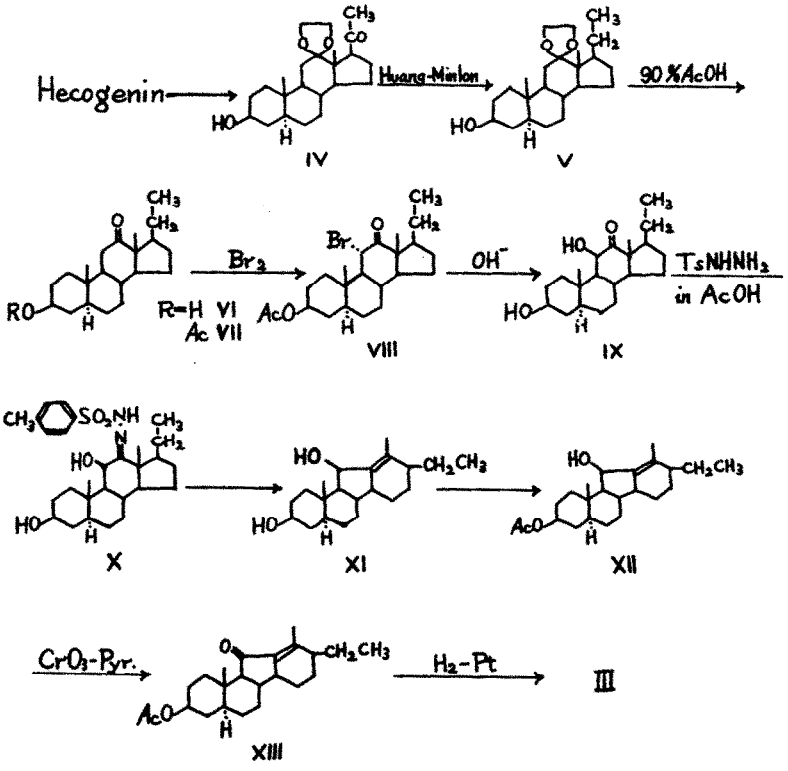
[4] D.N. Kirk, D.K. Patel and V. Petrow, J. Chem. Soc. 1957, 1046.

[5] R. Hirschmann, C.S. Snoddy, Jr., C.F. Hiskey and N.L. Wendler, J. Am. Chem. Soc. 75, 4929 (1953).

This substance has the same chromophore as jervine showing a UV maximum at 255 mμ (log ε=4.1), 354 mμ (log ε=1.89) and an IR spectrum closely resembling that of jervine in the carbonyl region.

Catalytic hydrogenation of XIII with PtO_2 gave a dihydro product, m.p. 118.2-118.9°, $[\alpha]_D$-15.5° (C, 1.55 $CHCl_3$), Found: C, 76.95; H, 10.03, which was proved to be identical with III prepared from jervine[3] by mixed melting point[6] and comparison of IR spectra.



6 J. Fried and A. Klingsberg reported the melting point and specific rotation of III as 114-116°, $[\alpha]_D$-8.6°($CHCl_3$), but present sample from jervine shows m.p. 118-119° and $[\alpha]_D$-15.8° ($CHCl_3$).

Since jervine and veratramine have been correlated with each other,[7] the C-nor-D-homo ring system of both compounds has been confirmed conclusively. Moreover, the stereochemistry at 8, 9 and 14 has been shown to be that of conventional steroids.

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[7] O. Wintersteiner and M. Moore, J. Am. Chem. Soc. 75, 4938 (1953).
Ch. Tamm and O. Wintersteiner, J. Am. Chem. Soc. 74, 3842 (1952).
O. Wintersteiner and N. Kosansky, J. Am. Chem. Soc. 74, 4474 (1952).