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THE SYNTHESIS OF 11,19-OXYGENATED PREGNANES FROM OUABAIN

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THE enhancement of biological activity of 11-oxygenated corticoids attending the introduction of oxygen at the C-18 methyl group, as exemplified by aldosterone,[1] has intensified interest in the isolation[2] and synthesis[3] of steroids oxygenated at the complementary C-19 methyl group. The author wishes to report a facile and practical conversion of the complex cardiac glycoside, ouabain,[4] to the hemi-ketal form (VII) of 19-hydroxy-4,5α-dihydro-11-dehydrocorticosterone and the hemi-ketal form (IX) of 19-hydroxy-5α-pregnane-3,11,20-trione.

Quabagenin-1,19-acetonide,[5] obtained readily from ouabain was oxidized with chromium trioxide and pyridine to the crude 3,11-diketone which when treated with a mixture of hot ethanol and basic alumina afforded the known 5α,14,19-trihydroxy-3,11-dioxo-5β-carda-1,20(22)-dienolide (I),[6] in an

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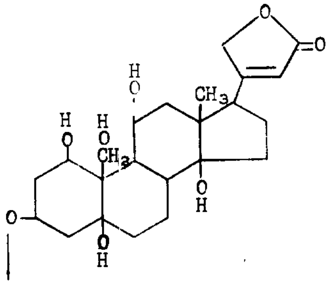
[1] L.F. Fieser and M.Fieser, Steroids pp. 701-708. Reinhold, New York (1959).

[2] [a] R. Neher and A. Wettstein, Helv.Chim.Acta 39, 2062 (1956); [b] G.W. Barber, D.H. Peterson and M. Ehrenstein, J.Org.Chem. 25, 1168 (1960).

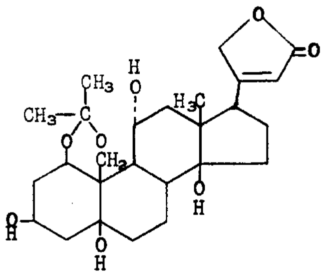
[3] [a] G.W. Barber and M. Ehrenstein, J.Org.Chem. 19, 1758 (1956); [b] G.W. Barber and M. Ehrenstein, Ibid. 20, 1253 (1955) [c] G. Volpp, C. Baumgartner, and Ch. Tamm, Helv.Chim.Acta 42, 1408-1432 (1959); [d] G. Volpp and Ch. Tamm, Tetrahedron Letters No. 27, 31 (1960); [e] D.H.R. Barton and J.M. Beaton, J.Amer.Chem.Soc. 83, 750 (1961).

[4] L.F. Fieser and M. Fieser, ref. 1, p. 768

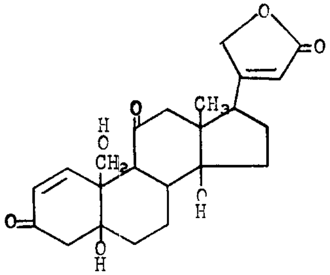
[5] C. Mannich and G. Siewert, Ber.Dtsch.Chem.Ges. 75, 737 (1942).



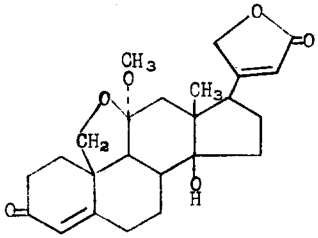
L-Rhamnosyl
Ouabain



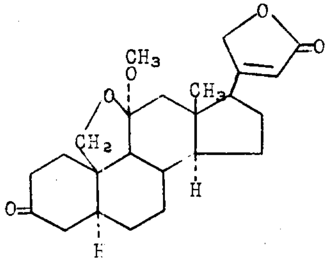
Oubagenin-1,19-acetonide



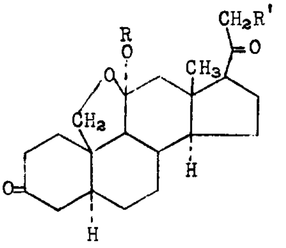
I



III



V



VI (R=CH_3, R' = OH)
VII (R=H, R' = OH)
VIII (R=CH_3, R' = H)
IX (R=H, R' = H)

improved overall yield of 55%. Hydrogenation of I over Pd-C in methanol

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[6] Ch. Tamm, Helv.Chim.Acta 38, 147 (1955).

gave 5β,11α,14-dihydroxy-11,19-epoxy-3-oxo-5β-card-20(22)-enolide (II), m.p. 178-181°, λ_{max}^{MeOH} 218 mμ (ε = 17,300) which is in equilibrium with 5β,14,19-trihydroxy-3,11-dioxo-5β-card-20(22)-enolide. After the catalyst is removed by filtration in the hydrogenation of I, direct treatment of the methanolic solution of II with a catalytic amount of p-toluenesulfonic acid yielded 14-hydroxy-11α-methoxy-11,19-epoxy-3-oxocarda-4,20(22)-dienolide (III), m.p. 258-260°, λ_{max}^{MeOH} 219 mμ (ε = 21,500), λ_{max}^{MeOH} 237 mμ (ε = 19,000), $[\alpha]_D$ + 149.8° $CHCl_3$), (C, 69.77; H, 7.30). Dehydration of III with thionyl chloride and pyridine afforded 11α-methoxy-11,19-epoxy-3-oxocarda-4,14,20(22)-trienolide (IV), m.p. 212-214°, $[\alpha]_D$ +119.5° ($CHCl_3$), (C, 72.43; H, 7.22). Hydrogenation of IV in the presence of Pd-C, ethyl acetate and methanol proceeded rapidly at a constant rate with the absorption of two equivalents of hydrogen to give in greater than 90% yield 11α-methoxy-11,19-epoxy-3-oxo-5α,14α-card-20(22)-enolide (V), m.p. 192-194°, λ_{max}^{MeOH} 217 mμ (ε = 15,000), $[\alpha]_D$ +126.5° ($CHCl_3$), (C, 72.33; H, 8.08). Ozonolysis of the unsaturated lactone in V and hydrolysis of the resulting 21-glyoxylic ester with aqueous methanolic potassium bicarbonate transformed V into 21-hydroxy-11α-methoxy-11,19-epoxy-5α-pregnane-3,20-dione (VI), m.p. 178-180°, $[\alpha]_D$ +134.5° ($CHCl_3$), (C, 70.43; H, 8.28). The overall yield from ouabain to VI was 18%. Hydrolysis of VI with aqueous acetone containing p-toluenesulfonic acid yielded 11α,21-dihydroxy-11,19-epoxy-5α-pregnane-3,20-dione (VII), m.p. 165-167°, $[\alpha]_D$ +107° ($CHCl_3$), (C, 69.70; H, 8.20). The p-toluenesulfonate of VI upon treatment with sodium iodide in acetone yielded the 21-iodo derivative which, when reduced with zinc in acetic acid, gave 11α-methoxy-11,19-epoxy-5α-pregnane-3,20-dione (VIII), m.p. 168-169°, $[\alpha]_D$ +145° ($CHCl_3$), (C, 73.05; H, 8.84). Hydrolysis of VIII afforded 11α-hydroxy-11,19-epoxy-5α-pregnane-3,20-dione (IX), m.p. 156-158°, $[\alpha]_D$ +103° ($CHCl_3$), (C, 72.98; H, 8.67). When VIII was dissolved in methanol containing a catalytic amount of p-toluenesulfonic acid, it was converted to 3,3,11α-trimethoxy-11,19-epoxy-5α-pregnan-20-one (X), m.p. 111-112°, $[\alpha]_D$ +107° (MeOH), (C, 71.04; H, 9.18).

The optical rotatory dispersion curve of X,[7] which exhibits a positive Cotton effect, establishes the configuration of 17-acetyl group as β. The observations that X is not epimerized with warm 1N KOH in methanol and that the optical rotatory dispersion curve of V[8] exhibits a positive Cotton effect verify the conclusion that the product of the hydrogenation of IV has the A/B-<u>trans</u> and C/D-<u>trans</u> configuration.[9]

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[7] The author is most grateful to Dr. W. Klyne for providing the optical rotatory dispersion curve for compound X.

[8] The author is grateful to Dr. W.C. Wildman for providing the optical rotatory dispersion curve of V.

[9] In steroids containing a 14-iso(14β) configuration, the more stable configuration at C-17 is also iso (α) [<u>cf</u>. K. Meyer, <u>Helv.Chim.Acta</u> <u>30</u>, 1976 (1947); A. Lardon, <u>Ibid</u>. <u>32</u>, 1517 (1949); C.P. Balant and M. Ehrenstein, <u>J.Org.Chem.</u> <u>17</u>, 1576 (1952)].