Tetrahedron Letters No. 27, pp. 31-36, 1960. Pergamon Press Ltd. Printed in Great Britain

1α,11α-EPOXY-STEROIDS FROM OUABAGENIN BY TRANSANNULAR SUBSTITUTION

G. Volpp[1] and Ch. Tamm

Organisch-chemische Anstalt der Universität Basel; Pharmazeutisch-chemisches Laboratorium SANDOZ Basel, and Department of Chemistry, Harvard University, Cambridge, Mass., U.S.A.

(Received 5 December, 1960)

The cleavage of ouabain (I) with HCl-acetone (ca. 10 days at 0°) according to the classical procedure of Mannich and Siewert[2] yields L-rhamnose and 1,19-isopropyliden-ouabagenin (II)[3]. The removal of the acetone group leading to ouabagenin (III) is effected readily by hydrolysing II with 0.6% (= ca. 0.1 N) H_2SO_4 in aqueous ethanol at 0°[2].

We now have found that II does not yield ouabagenin (III) when refluxed with 0.05 N HCl in aqueous ethanol for 30-60 minutes. Instead two new products are formed, namely a monoanhydro-ouabagenin ($C_{23}H_{32}O_7$) with m.p. 274-275° (capillary tube) or 306-316° (micro hot stage), $[\alpha]_D$ + 46° (methanol) and λ_{max} 217 mμ, log ε 4.17 (ethanol) as the main component and, in about 1/10th the amount, tetranhydro-ouabagenin ($C_{23}H_{26}O_4$) with m.p. 238-240°, [α] + 18° (methanol) and λ_{max} 214.5 mμ,

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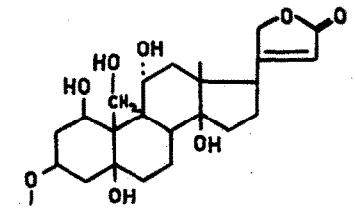
[1] Present address: Department of Chemistry, Harvard University, Cambridge, Mass., U.S.A.

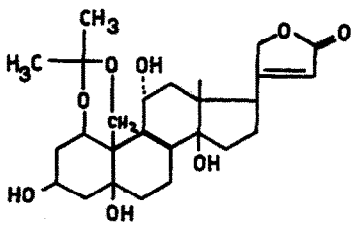
[2] C. Mannich and G. Siewert, Ber.deutsch.chem.Ges. 75, 337 (1942).

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

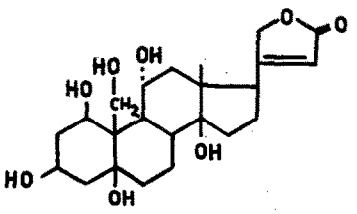


L-Rhamnosyl

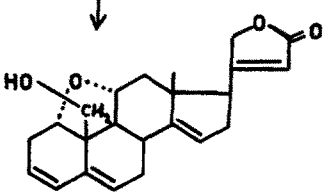
I Ouabain



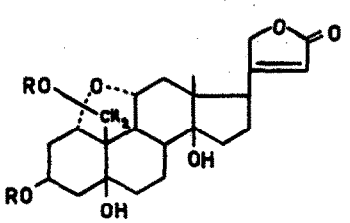
II



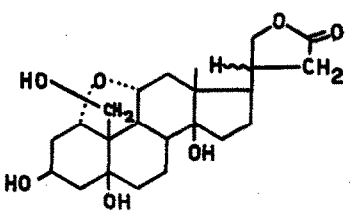
III Ouabagenin



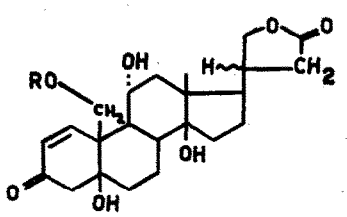
IV



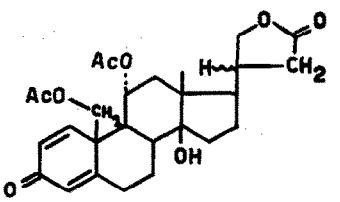
V (R = H) VI (R = Ac)



VII



IX (R = H) X (R = Ac)



XI

log ε 4.42, shoulder at 255-265 mμ, log ε 2.7 (ethanol). The same products are also obtained from ouabagenin (III) itself when hydrolysed under the same conditions. Both structures V and IV are characterized by an 1α.11α-epoxide group and are thus assigned to the monoanhydro and the tetra-anhydro-derivatives respectively on the basis of the following reactions. According to the U.V. spectrum of V the butenolide ring remained unchanged. V gave on treatment with KOH or with K_2CO_3 an iso derivative ($C_{23}H_{32}O_7$, m.p. 267-270°, [α] + 22° (methanol-chloroform (1:1)) indicating the presence of a 14β-hydroxyl in monoanhydro-ouabagenin (V). A chloroform-methanol solution of V gave no yellow colour with tetranitromethane. On catalytic hydrogenation with Pt in acetic acid the dihydro derivative VII ($C_{23}H_{34}O_7$, m.p. 248-252°, $[\alpha]_D$ + 31.5° (methanol), transparent in the U.V.) was obtained. Treatment of V with acetanhydride in pyridine at 60° gave the diacetyl derivative VI ($C_{27}H_{36}O_9$, m.p. 226-230°, $[\alpha]_D$ + 44° (chloroform)).VI was stable against CrO_3 in acetic acid. From these results it is concluded that the dehydration of ouabagenin does not lead to the formation of a C=C bond but gives rise to an ether bridge employing two of the four original hydroxyl groups capable of being acetylated. Since a great number of aglycons of known structure had proved to be stable against an analogous treatment with acid therefore only the five-membered 1α,11α-oxide ring and the four-membered 1β,19-oxide ring remained as sites of location for the oxygen bridge. That the latter could be excluded in favour of the 1α,11β-epoxide ring was adduced by the degradation of monoanhydro-ouabagenin (V) and of the further transformation of the dihydro derivative VII. Selective catalytic dehydrogenation at C-3 of the latter with O_2-Pt^4 in aqueous acetone gave a mixture of the corresponding 3-dehydro derivative VIII (not

isolated) and of the Δ^1-3-ketone IX which both were transformed into the acetylated Δ^1-3-ketone X (amorphous, λ_{max} 232 mμ, log ε 3.95 and λ_{max} 316 mμ, log ε 1.60 (ethanol), I.R. peaks at 5.65 μ, 5.77 μ, 6.20 μ). Thus opening of the oxygen ring took place by base-catalysed rearrangement as observed with β,γ-epoxy-ketones giving γ-hydroxy-α,β-unsaturated ketones[5]. By refluxing with glacial acetic acid the 5-hydroxyl group was removed and the dienone XI was obtained ($C_{27}H_{34}O_8$, m.p. 201-205°, $[\alpha]_D$ + 22° (chloroform), λ_{max} 243 mμ, log ε 4.18 and 330 mμ, log ε 1.61 (ethanol), I.R. peaks at 5.65 μ, 5.76 μ, 6.01 μ, 6.15 μ and 6.23 μ).

Degradation of diacetyl monoanhydro-ouabagenin (VI) with O_3, reductive cleavage of the ozonide and treatment with $KHCO_3$[6] led to the ketol XIII ($C_{21}H_{32}O_7$, m.p. 201-202°, $[\alpha]_D$ + 60° (methanol), λ_{max} 280 mμ, log ε 1.69 (ethanol), I.R. peak at 5.88 μ). After oxidation of VI with $KMnO_4$ in acetone at 22°[7] and methylation of the acid formed with CH_2N_2 and reacetylation amorphous methyl etianate XII was obtained. The two tertiary hydroxyl groups were eliminated with $SOCl_2$-pyridine, the amorphous diene XIV hydrolysed with KOH and remethylated with CH_2N_2. The resulting unsaturated dihydroxy ester XV ($C_{21}H_{28}O_5$, m.p. 189-191°, $[\alpha]_D$

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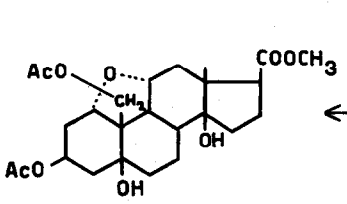
[4] H. Wieland, Ber.deutsch.chem.Ges. 45, 484, 2606 (1912); 46, 3327 (1913); 54, 2353 (1921); R.P.A. Sneeden and R.B. Turner, J.Amer.Chem.Soc. 77, 130, 190 (1955); A. Katz, Helv.Chim.Acta 40, 831 (1957); Ch. Tamm and A. Gubler, Helv.Chim.Acta 41, 297, 1762 (1958); 42, 239 (1959).

[5] Cf.p.ex.: F. Sondheimer, S. Burstein and R. Mechoulam, J.Amer.Chem.Soc. 82, 3209 (1960).

[6] K. Meyer and T. Reichstein, Helv.Chim.Acta 30, 1508 (1947).

[7] M. Steiger and T. Reichstein, Helv.Chim.Acta 21, 828 (1938). F. Hunziker and T. Reichstein, Helv.Chim.Acta 28, 1472 (1945).



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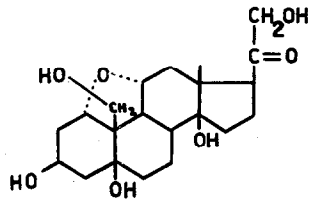

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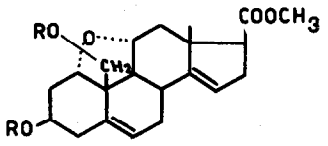
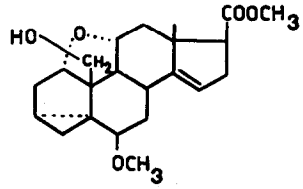


XIV (R = Ac) XV (R = H)



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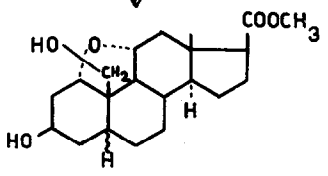

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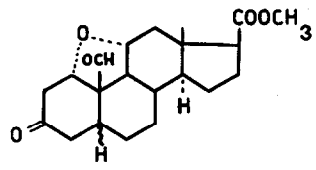
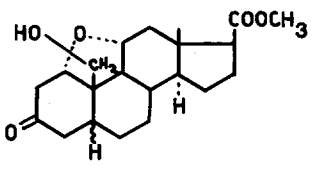


XVIII



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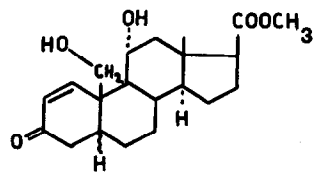

XX

- 23° (chloroform)) gave with tetranitromethane a yellow colour and was transformed readily into the 3,5-cyclo-6β-methoxy derivative XVI ($C_{22}H_{30}O_5$, m.p. 139-142°, [α] - 37° (chloroform)) thus proving the 5-position of one double bond. Hydrogenation of XV with Pt in acetic acid gave the saturated dihydroxy ester XVII ($C_{21}H_{32}O_5$, m.p. 224-227°, $[\alpha]_D$ - 4° (chloroform)). By treatment of XVII with O_2-Pt^4 in aqueous acetone two products were formed, namely XVIII and XIX. Both of them proved to be unstable. The amorphous substance XVII gave on treatment with triethylamine the crystalline ester XX ($C_{21}H_{30}O_5$, m.p. 237-242°, λ_{max} 238 mμ, log ε 3.96 (ethanol)) characterized by a Δ^1-3-ketone group. The proof of structure of the keto aldehyde XVIII relies mainly on its spectroscopic properties. The I.R. spectrum showed no OH bands but peaks at 3.73 μ and at 5.81 - 5.85 μ with the former being assigned to the CH-streching frequency of the aldehyde group. The U.V. spectrum was characterized by a single maximum at 283-285 mμ, log ε 2.01 (ethanol) indicating two isolated carbonyl functions. The presence of the C-19 aldehyde was also shown by the n.m.r. spectrum having a typical peak at 868 c.p.s.

These findings eliminate the 1β,19-epoxide structure as the site of location for the oxygen bridge, and thus leave only the 1α,11α-epoxide ring for monoanhydro-ouabagenin (V) and its derivatives. The ready formation and the spatial arrangement of this ring can be interpreted as a transannular S_N2 type substitution of the axial 1β-hydroxyl group by the 11α-oxygen function. The sequence of reactions described opens a possibility for the synthesis of hormone analogues with an oxygen bridge and of 11-oxygenated $\Delta^{1,4}$-3-keto-steroids starting from ouabagenin.

All substances proved correct upon analysis. A detailed account of this work will be published in Helv.Chim.Acta.