[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

STEROIDAL SAPOGENINS. XI.[1] EXPERIMENTS IN THE HECOGENIN SERIES (PART 2)

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In the first part of this series (1) there was described the conversion of 22-isoallospirostan-3β-ol-12-one[2] (I) (hecogenin) into $\Delta^{9(11)}$-22-isoallospirosten-3β-ol-12-one (II) and 22-isoallospirostan-3β,12β-diol-11-one (III).[3] The present paper deals with further transformations of these two interesting substances (II and III).

Lithium aluminum hydride reduction of the 3,12-diol-11-one (III) readily afforded a triol (IVa), in which only two hydroxyl groups were acetylable, an observation in accord with the expected 22-isoallospirostan-3β,11β,12β-triol (IV) structure. The C-11 keto group is known to yield the 11β-hydroxy derivative (which cannot be acetylated) upon reduction with lithium aluminum hydride (3) and it appears therefore that the 12β-hydroxy group[3] in III does not affect the stereochemical course of this reaction. Marker and co-workers (4) have suggested that 12-ketosapogenins such as 22-isoallospirostan-3β-ol-12-one (I) are artifacts produced during the acid hydrolysis of the saponin, the latter containing an 11,12-dihydroxy grouping with sugar residues attached to it. If this hypothesis were true, then presumably only a *cis*-glycol would suffer dehydration under the usual acid hydrolysis conditions. When tested with the presently described 3β,11β,12β-triol (IV), the starting material was recovered unchanged. Thus if Marker's hypothesis were correct, our observation regarding the stability of the 11β,12β-derivative would leave only the 11α,12α-configuration for such a saponin. The recent isolation (5) from plant sources of $\Delta^{9(11)}$-12-ketosapogenins, which probably arise by the same biogenetic pathway as the saturated 12-ketosapogenins, makes it appear unlikely that a 11,12-dihydroxysaponin represents the common precursor of these substances.

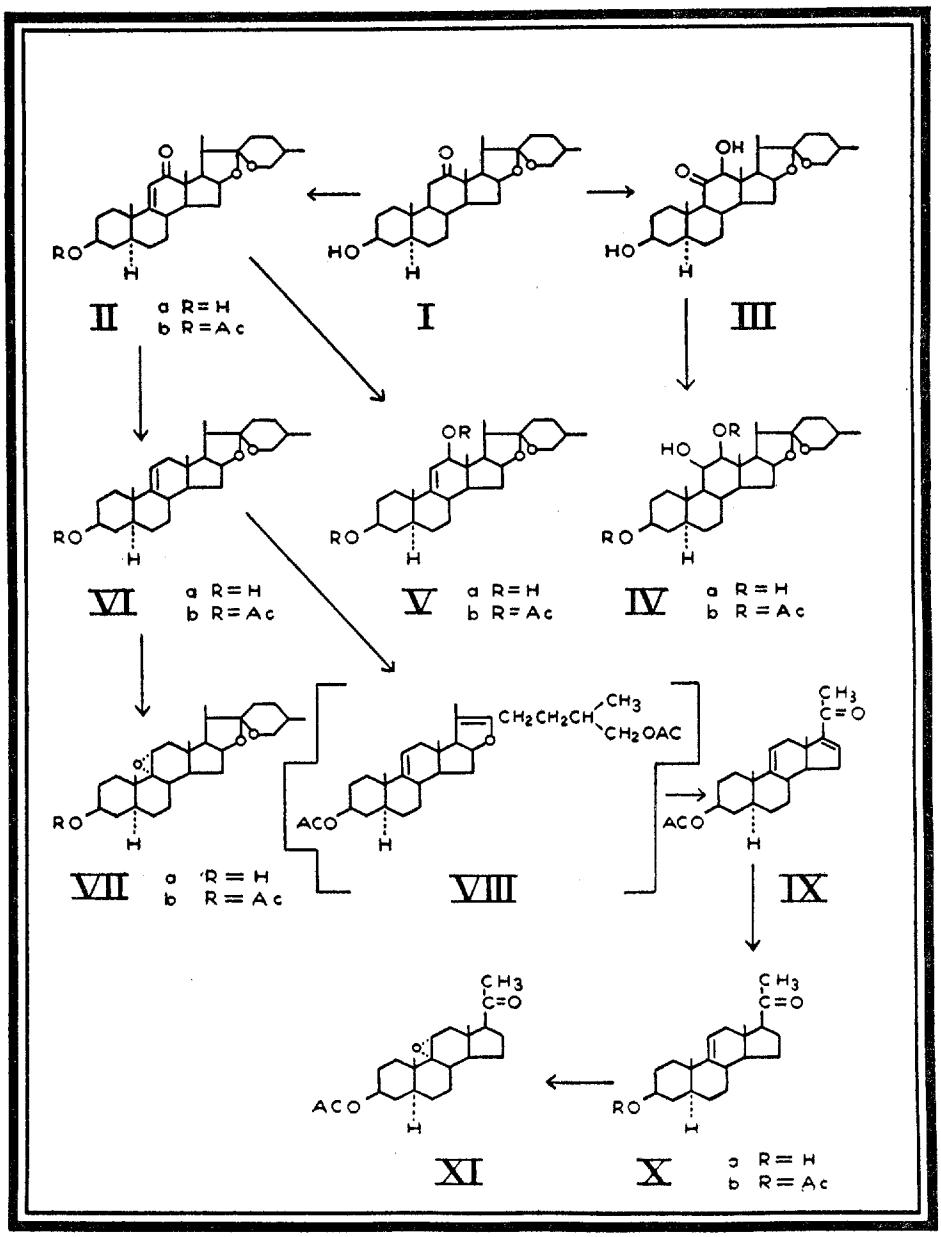
As was to be anticipated, lithium aluminum hydride reduction of the $\Delta^{9(11)}$-12-ketone (II) led to the allylic alcohol $\Delta^{9(11)}$-22-isoallospirosten-3β,12-diol (Va), further characterized by formation of a diacetate (Vb). Wolff-Kishner reduction of the unsaturated ketone II, employing the modification of Huang-Minlon (6), gave the previously undescribed $\Delta^{9(11)}$-22-isoallospirosten-3β-ol (VIa) (9-dehydrotigogenin); in view of its ready crystallizability, the preparation of a pure $\Delta^{9(11)}$-unsaturated steroid appears much easier in the sapogenin series as compared to the bile acids (7, 8). It is of interest to note that the acetate VIb was recovered completely unchanged on treatment with mercuric acetate. This lack of reactivity is the more remarkable if one considers the ready dehydro-

[1] For paper X, see Yashin, Rosenkranz, and Djerassi, in press.

[2] For nomenclature of steroidal sapogenins, see Rosenkranz and Djerassi, *Nature*, **166**, 104 (1950).

[3] The β-configuration of the C-12 hydroxyl group is assumed by analogy to the proved case in the bile acid series (ref. 2).

genation by means of mercuric acetate of the hindered 9–11 position in the case of Δ^7-22-isoallospirosten-3β-ol which led to $\Delta^{7,9(11)}$-22-isoallospirostadien-3β-ol



(9). $\Delta^{9(11)}$-22-Isoallospirosten-3β-ol 3-acetate (VIb) reacted smoothly with perbenzoic acid to afford 9α,11α-oxido-22-isoallospirostan-3β-ol 3-acetate (VIIb). The oxide was not attacked by lithium aluminum hydride or pyridine hydro-

bromide in boiling ethanol.[4] A similar lack of reactivity has recently been observed with methyl 9α,11α-oxidolithocholanate (8).

When heated with acetic anhydride at 200°, $\Delta^{9(11)}$-22-isoallospirosten-3β-ol (VIa) was converted to $\Delta^{9(11),20(22)}$-allofurostadiene-3β,26-diol 3,26-diacetate (VIII), which was oxidized directly to yield $\Delta^{9(11),16}$-allopregnadien-3β-ol-20-one 3-acetate (IX) with an ultraviolet absorption maximum at 238 mμ (log ϵ 4.07) and an infrared band[5] at 1672 cm^{-1}, characteristic of a Δ^{16}-20-keto grouping. Selective hydrogenation of the 16,17-double bond was accomplished by the use of palladium-on-charcoal catalyst in ethyl acetate solution, which did not attack the 9,11-double bond. The resulting $\Delta^{9(11)}$-allopregnen-3β-ol-20-one (X) did not show any maximum at 238 mμ, but still gave a yellow color with tetranitromethane and reacted with perbenzoic acid to yield 9α,11α-oxidoallopregnan-3β-ol-20-one 3-acetate (XI), thus proving the presence of the 9,11-double bond in the hydrogenation product X. $\Delta^{9(11)}$-Allopregnen-3β-ol-20-one (X) represents an interesting substrate for enzymatic and perfusion studies, the results of which will be described elsewhere.

EXFERIMENTAL[6]

22-Isoallospirostane-3β,11β,12β,-triol (IV). A solution of 1.0 g. of the ketol III (1) in 30 cc. of tetrahydrofuran was added dropwise to a suspension of 1.0 g. of lithium aluminum hydride in 100 cc. of tetrahydrofuran and the resulting mixture was refluxed for 30 minutes. After decomposing with water, extracting with ether, washing until neutral, and evaporating to dryness, the residue was triturated with hexane yielding 0.95 g. of solid, m.p. 250–260°. Recrystallization from a small amount of ether afforded the analytical sample of the *triol IVa* with m.p. 262–263° (Kofler), $[\alpha]_D^{20}$ −64°. No ketone band was observed in the infrared.

Anal. Calc'd for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89.
Found: C, 72.41; H, 9.62.

Acetylation of the above triol with boiling acetic anhydride–pyridine afforded in nearly quantitative yield *22-isoallospirostane-3β,11β,12β-triol 3,12-diacetate* (IVb) which after recrystallization from methanol–chloroform showed m.p. 263–264°, (Kofler), $[\alpha]_D^{20}$ −55°. The infrared spectrum[5] showed acetate bands (1736 and 1239 cm^{-1}) as well as a free hydroxyl band.

Anal. Calc'd for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08.
Found: C, 69.76; H, 9.30.

When 0.5 g. of the triol IVa was refluxed with 7 cc. of ethanol and 1.8 cc. of conc'd hydrochloric acid for four hours, followed by acetylation of the product, there was recovered the diacetate IVb, identical with the above specimen by comparison of the infrared spectra, mixture m.p., and analysis.

$\Delta^{9(11)}$-*22-Isoallospirostene-3β,12-diol* (V). The lithium aluminum hydride reduction of 1.21 g. of $\Delta^{9(11)}$-22-isoallospirosten-3β-ol-12-one (IIa) (1) was carried out exactly as described above and yielded 1.04 g. of colorless crystals with m.p. 192–200°, which showed

[4] Pyridine hydrobromide in ethanol solution has proved to be superior to hydrogen bromide for the conversion of oxides to the corresponding bromohydrins (Mancera, Rosenkranz, and Djerassi, to be published).

[5] We are indebted to Dr. K. Dobriner and Mrs. P. Humphries, Sloan-Kettering Institute for Cancer Research, for the infrared spectra.

[6] Melting points are uncorrected unless marked "Kofler", which were determined on the Kofler block. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque and her staff for these measurements and to the Srtas. Amparo Barba and Rachel Cervera for the microanalyses.

no selective absorption in the ultraviolet. The analytical sample of the unsaturated *diol Va* was obtained from hexane–acetone and exhibited m.p. 205–207° (Kofler), $[\alpha]_D^{20}$ −62.5°.

Anal. Calc'd for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83.

Found: C, 75.48; H, 9.87.

The *diacetate Vb* showed m.p. 145–150°, resolidifying at *ca.* 160° and melting at 180–182° (Kofler), $[\alpha]_D^{20}$ −86° after recrystallization from ether–hexane.

Anal. Calc'd for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01.

Found: C, 72.40; H, 8.72.

$\Delta^{9(11)}$-22-Isoallospirosten-3β-ol (VI). A solution of 4.5 g. of the unsaturated ketone IIa (1) was refluxed with 105 cc. of ethylene glycol and 3 cc. of 85% hydrazine hydrate for one hour, cooled, and then treated with 9.2 g. of potassium hydroxide and 10 cc. of water. The open flask was heated until the inside temperature reached 197°, a reflux condenser was attached and refluxing continued for an additional 3½ hours. After dilution with water and hydrochloric acid, the product was extracted with chloroform, washed until neutral, evaporated to dryness and the residue was acetylated by boiling with acetic anhydride–pyridine. The solid residue in hexane-benzene solution was filtered through 100 g. of alumina and then recrystallized from methanol-chloroform; yield, 2.59 g. (54%), m.p. 193–195°, no selective absorption in the ultraviolet. Further recrystallization raised the m.p. of $\Delta^{9(11)}$-22-isoallospirosten-3β-ol *3-acetate* (*VIb*) to 197–199°, $[\alpha]_D^{20}$ −53°. The product gave a yellow color with tetranitromethane.

Anal. Calc'd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71.

Found: C, 76.42; H, 9.50.

Saponification produced the free *alcohol VIa* with m.p. 190–191°, $[\alpha]_D^{20}$ −57°; no carbonyl band was observed in the infrared. [5]

Anal. Calc'd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21.

Found: C, 77.94; H, 10.37.

9α,11α-Oxido-22-isoallospirostan-3β-ol (VII). A solution of 2.0 g. of $\Delta^{9(11)}$-22-isoallospirosten-3β-ol 3-acetate (VIb) in 80 cc. of chloroform was allowed to stand at room temperature with 1.24 g. of perbenzoic acid for 16 hours at which time the peracid consumption corresponded to one mole. After washing with bicarbonate and water, the solution was dried and evaporated. The crystalline residue (2.14 g.) after two recrystallizations from methanol–chloroform afforded 1.16 g. (56%) of the *oxido acetate VIIb* with m.p. 245–253°. Further recrystallizations still gave material with a fairly wide melting range, 248–252° (Kofler), $[\alpha]_D^{20}$ −65°. The substance gave no color with tetranitromethane and showed no hydroxyl band in the infrared.

Anal. Calc'd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38.

Found: C, 74.00; H, 9.45.

Saponification of the acetate with methanolic potassium carbonate solution followed by recrystallization from ether-hexane led to the *free alcohol VIIa* with m.p. 213–215° (Kofler), $[\alpha]_D^{20}$ −70°.

Anal. Calc'd for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83.

Found: C, 75.71; H, 9.96.

The oxide was recovered unchanged on refluxing for three hours with pyridine hydrobromide[4] in ethanol or when treated with lithium aluminum hydride in boiling tetrahydrofuran for two hours. This represents further evidence for the purity of the 9α,11α-oxide and the absence of the 11,12-isomer.

$\Delta^{9(11),16}$-Allopregnadien-3β-ol-20-one 3-acetate (IX). The $\Delta^{9(11)}$-22-isoallospirosten-3β-ol (VIa) (2 g.) was heated for eight hours with 16 cc. of acetic anhydride at 200° and the oily $\Delta^{9(11),20(22)}$-allofurostadiene-3β,26-diol diacetate (VIII), which was not isolated, was oxidized directly with chromium trioxide and hydrolyzed exactly as described earlier (10) for the Δ^7-isomer. Trituration with hexane afforded 0.67 g. (40%) of colorless crystals, m.p. 162–165°. The analytical sample was crystallized from methanol and showed m.p. 164–166° (Kofler), $[\alpha]_D^{20}$ +67°, ultraviolet absorption maximum at 238 mμ (log ε 4.07) and infrared bands[5] (carbon disulfide) at 1672 cm.$^{-1}$ (Δ^{16}-20-ketone), and at 1739 and 1239 cm^{-1} (acetate bands).

Anal. Calc'd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05.
Found: C, 77.56; H, 9.20.

$\Delta^{9(11)}$-*Allopregnen-3β-ol-20-one* (X). The selective reduction of the 16,17-double bond was accomplished by shaking 0.4 g. of the dienolone acetate (IX) in 30 cc. of ethyl acetate with 0.08 g. of 10% palladium-on-charcoal catalyst in an atmosphere of hydrogen until the gas uptake ceased (*ca.* one mole, 45 minutes). The usual work-up followed by recrystallization from dilute methanol afforded 0.32 g. of the *acetate Xb* with m.p. 130–132° (Kofler), $[\alpha]_D^{20}$ +76°, ultraviolet absorption maximum at 280 mμ (log ε 1.89) due to the *un*conjugated carbonyl group. The substance gave a yellow color with tetranitromethane indicating the presence of an isolated double bond.

Anal. Calc'd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56.
Found: C, 76.81; H, 9.59.

The free *alcohol Xa* melted at 192–194° (Kofler) $[\alpha]_D^{20}$ + 105° after recrystallization from dilute methanol.

Anal. Calc'd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19.
Found: C, 79.37; H, 10.55.

9α,11α-Oxidoallopregnan-3β-ol-20-one 3-acetate (XI). As additional proof for the presence of the isolated 9,11-double bond in X, 180 mg. of the acetate Xb in 4 cc. of chloroform was treated with an excess of perbenzoic acid; after 28 hours there was consumed the calculated amount (72 mg.) of perbenzoic acid. On working up in the usual manner, including recrystallization from hexane-ether, colorless crystals of the oxide were obtained with m.p. 149–152°, which gave no color with tetranitromethane.

Anal. Calc'd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15.
Found: C, 73.52; H, 8.83.

SUMMARY

In the present communication are described further transformations of 22-isoallospirostan-3β,12β-diol-11-one (III) and $\Delta^{9(11)}$-22-isoallospirosten-3β-ol-12-one (II), which are readily accessible (1) from 22-isoallospirostan-3β-ol-12-one (hecogenin) (I). Lithium aluminum hydride reduction of the diolone III led to 22-isoallospirostane-3β,11β,12β-triol (IV) while the unsaturated ketone II afforded the allylic alcohol $\Delta^{9(11)}$-22-isospirosten-3β,12-diol (V).

Wolff-Kishner reduction of $\Delta^{9(11)}$-22-isoallospirosten-3β-ol-12-one (II) yielded $\Delta^{9(11)}$-22-isospirosten-3β-ol (VI), which was converted to the corresponding 9α, 11α-oxido derivative VII as well as subjected to side chain degradation leading ultimately to $\Delta^{9(11)}$-allopregnen-3β-ol-20-one (X).

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