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STEROIDAL SAPOGENINS. VI.[1] SYNTHESIS OF Δ^7-22-ISOALLOSPIROSTEN-3β-OL AND UNSATURATED ANALOGS[2]

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Aside from biochemical means (2), C-11 oxygenated corticosteroids have so far only been prepared by partial synthesis from steroids already possessing an oxygen substituent in ring C (positions 11 or 12) (3). In view of the tremendous interest in the biological properties of cortisone and related C-11 oxygenated pregnane derivatives, it seemed important to accomplish the chemical introduction of an oxygen function at C-11 in steroids which possess no substituents in ring C and which comprise the vast majority of readily available, naturally-occurring starting materials. The most obvious approach to this problem appeared to be the initial introduction of double bonds into or adjacent to ring C. Since the steroidal sapogenin side chain can be converted in two steps to the Δ^{16}-20-keto moiety so useful for the elaboration of the dihydroxyacetone grouping characteristic of cortisone and related substances, it was especially desirable to study this approach in the sapogenin series and the present report deals with the synthesis of certain key intermediates.

In the preceding paper of this series (1) there was described the two-step conversion of Δ^5-22-isospirosten-3β-ol (diosgenin) (I), the most abundant, naturally-occurring steroidal sapogenin, into $\Delta^{5,7}$-22-isospirostadien-3β-ol (II). By analogy with transformations in the ergosterol (4) and 7-dehydrocholesterol (5) series, the $\Delta^{5,7}$-spirostadiene II was now found to be hydrogenated smoothly in ethyl acetate solution with platinum oxide to yield Δ^7-22-isoallospirosten-3β-ol (III), which in turn on shaking with a palladium catalyst in the presence of acetic acid underwent bond migration to $\Delta^{8(14)}$-22-isoallospirosten-3β-ol (IV). Further support for the 7–8 position of the double bond in III was adduced by hydroxylation with osmium tetroxide leading, just as with γ-cholestenol (6), to a trihydroxy derivative V in which two of the hydroxyl groups were acylable. Calculation of the molecular rotation differences for the 7–8 isomer III ($\Delta^{Ac} = +8$; $\Delta^{Bz} = +19$) and the 8–14 isomer IV ($\Delta^{Ac} = -46$; $\Delta^{Bz} = -39$) gave results in fair agreement with those reported (7) for similar stenols.[3]

Dehydrogenation of Δ^7-22-isoallospirosten-3β-ol 3-acetate (IIIb) with mercuric acetate led to $\Delta^{7,9(11)}$-22-isoallospirostadien-3β-ol 3-acetate (VIb) and application of the same procedure to the $\Delta^{5,7}$-diene acetate IIb afforded $\Delta^{5,7,9(11)}$-22-isospirostatrien-3β-ol 3-acetate (VIIb). The corresponding benzoates (VIc, VIIc) and free alcohols (VIa, VIIa) were also prepared. The ultraviolet absorption

[1] For paper V, see ref. 1.

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

[3] The Δ-value itself (unsaturated minus saturated compound) does not agree with the literature value, but this is probably due to vicinal action of the sapogenin side-chain attached at C-16 and C-17 (cf. ref. 1).

spectra (Fig. 1) of the diene VI (maxima at 236 and 242 mμ) and the triene VII (main maximum at 324 μu) coincide with those observed for the analogous

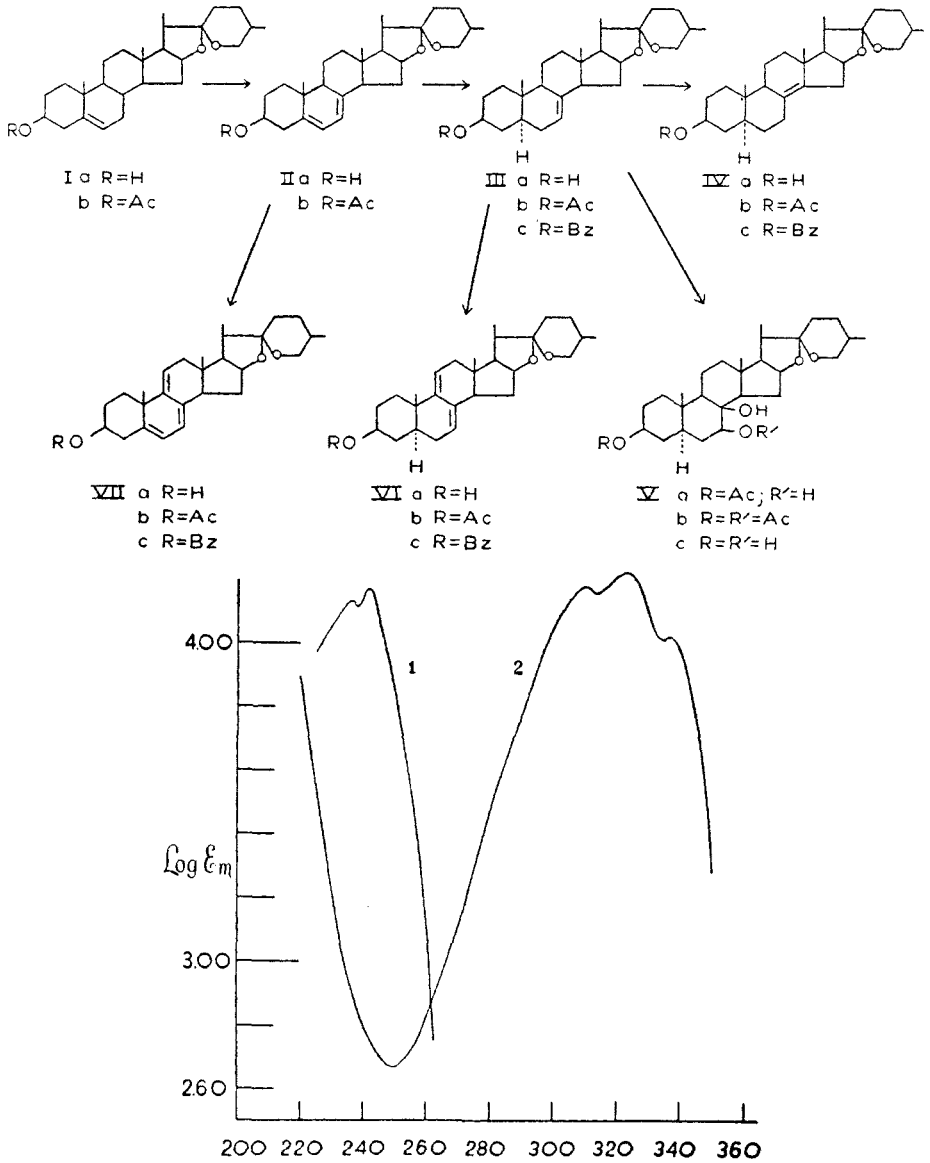

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA (in 95% ethanol solution): curve 1—$\Delta^{7,9(11)}$-22-isoallospirostadien-3β-ol 3-acetate (VIb); curve 2—$\Delta^{5,7,9(11)}$-22-isospirostatrien-3β-ol 3-acetate (VIIb).

ergosterol derivatives (4, 8). The remarkably high Δ^{Ac} = +280 and Δ^{Bz} = +290 values in the triene VII seem to be characteristic for this type of conjugated system (in the ergosterol series, Δ^{Ac} = +260) and deserve comment, since they do not seem to have been noticed before.

The spirostadiene VI and the spirostatriene VII with a double bond at the 9–11 position represent very useful intermediates for the introduction of the oxygen function at C-11 and further transformations of these substances will be reported in the near future.

EXPERIMENTAL[4]

Δ^7-22-Isoallospirosten-3β-ol (III). A solution of 42 g. of $\Delta^{5,7}$-22-isospirostadien-3β-ol 3-acetate (IIb) (1) in 2.1 l. of ethyl acetate was shaken with 2.1 g. of platinum oxide catalyst (American Platinum Works, Newark, N. J.) under 45 p.s.i. of hydrogen for 2–3 hours at which time the hydrogen up-take corresponding to one mole had ceased.[5] After heating to near boiling to dissolve the product which had started to crystallize, the catalyst was filtered and the solution concentrated to incipient crystallization. The long, colorless needles of the *acetate* IIIb were recrystallized from chloroform-methanol: yield, 78–85%, m.p. 222–223°, $[\alpha]_D^{20}$ −66.5°, no absorption between 220–330 mμ, yellow color with tetranitromethane.

Anal. Calc'd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71.
Found: C, 76.45; H, 9.85.

In view of its insolubility, the saponification of the acetate (2.0 g.) had to be carried out in dilute solution by refluxing with 400 cc. of methanol and 2 g. of potassium hydroxide for one hour. Dilution with water and recrystallization of the product from methanol gave 1.6 g. of the free *alcohol* IIIa with m.p. 188–190°, $[\alpha]_D^{20}$ −76.2°.

Anal. Calc'd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.20.
Found: C, 78.29; H, 10.47.

The *benzoate* IIIc, prepared with benzoyl chloride in pyridine solution, was obtained as needles from methanol-ethyl acetate; m.p. 221–223.5°, $[\alpha]_D^{20}$ −56.6°.

Anal. Calc'd for $C_{34}H_{46}O_4$: C, 78.72; H, 8.93.
Found: C, 78.72; H, 8.70.

$\Delta^{8(14)}$-22-Isoallospirosten-3β-ol (IV). The bond migration was accomplished by shaking a solution of Δ^7-22-isoallospirosten-3β-ol 3-acetate (IIIb) in 150 cc. of ethyl acetate and 3 cc. of acetic acid with 100 mg. of 10% palladium-on-charcoal catalyst in an atmosphere of hydrogen for 24 hours. No gas up-take was observed. Filtration of the catalyst, and recrystallization from ethyl acetate-methanol afforded 0.83 g. of the $\Delta^{8(14)}$-spirosten *acetate* (IVb) with m.p. 197–198.5°, $[\alpha]_D^{20}$ −72.4°; yellow color with tetranitromethane.

Anal. Calc'd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71.
Found: C, 76.32; H, 9.42.

When the acetic acid was replaced by a few drops of pyridine, the Δ^7-isomer IIIb was recovered unchanged.

Saponification produced the free *$\Delta^{8(14)}$-22-isoallospirosten-3β-ol* (IVa) which crystallized in prisms from alcohol; m.p. 186–189°, $[\alpha]_D^{20}$ −68.3°.

Anal. Calc'd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.20.
Found: C, 78.12; H, 10.44.

The *benzoate* IVc was recrystallized from ethyl acetate-methanol; m.p. 208–210°, $[\alpha]_D^{20}$ −62.3°.

Anal. Calc'd for $C_{34}H_{46}O_4$: C, 78.72; H, 8.93.
Found: C, 78.47; H, 9.03.

22-Isoallospirostan-3β,7,8-triol (V). A solution of 1.7 g. of Δ^7-22-isoallospirosten-3β-ol

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[4] All melting points were determined on the Kofler block and are corrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are indebted to the Srtas. Paquita Revaque and Maria Eugenia Frontana for these determinations and to Srta. Amparo Barba of our Microanalytical Department for the microanalyses.

[5] The hydrogenation was carried out under slight pressure to reduce the reaction time. In small scale experiments, atmospheric pressure was equally satisfactory.

3-acetate (IIIb) in 300 cc. of dry ether was allowed to stand at room temperature for 12 days with 1.0 g. of osmium tetroxide and 1 cc. of pyridine. At the end of that period, the ether was evaporated and the residue was refluxed for 2½ hours with 80 cc. of ethanol, 6 g. of sodium sulfite heptahydrate, and 25 cc. of water. After filtering and washing the precipitate well with hot ethanol, the filtrate was diluted with water, extracted with ether, washed, dried, and evaporated. The solid residue (0.8 g.) was acetylated with pyridine-acetic anhydride and crystallized from ether-hexane; yield, 0.66 g. (33%), m.p. 220–221°. The analytical sample of *22-isoallospirostan-3β,7,8-triol 3,7-diacetate* (Vb) crystallized as colorless needles with m.p. 221.5–223.5°, $[\alpha]_D^{20}$ −102°, and gave no color with tetranitromethane.

Anal. Calc'd for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08.
Found: C, 70.06; H, 8.90.

In one experiment, a sample of the hydroxylation residue prior to acetylation was chromatographed and recrystallized from ethyl acetate, whereupon colorless crystals of *22-isoallospirostan-3β,7,8-triol 3-monoacetate* (Va) were obtained; m.p. 260–262°.

Anal. Calc'd for $C_{29}H_{46}O_6$: C, 70.97; H, 9.44.
Found: C, 70.91; H, 9.44.

The 3-monoacetate Va on saponification with ethanolic potassium hydroxide followed by recrystallization from ethyl acetate produced *22-isoallospirostan-3β,7,8-triol* (Vc); m.p. 267–269°, $[\alpha]_D^{20}$ −106°.

Anal. Calc'd for $C_{27}H_{44}O_5$: C, 72.29; H, 9.88.
Found: C, 72.11; H, 9.99.

$\Delta^{7,9(11)}$-*22-Isoallospirostadien-3β-ol* (VI). The introduction of the second double bond was carried out in the usual manner (4) by shaking a mixture of 12 g. of the Δ^7-acetate IIIb, 32 g. of mercuric acetate, 400 cc. of chloroform, and 600 cc. of acetic acid for 24 hours at room temperature. The filtered solution was diluted with more chloroform, washed free of acetic acid, dried, evaporated, and the residue crystallized from methanol; yield 8.7 g. (72%), m.p. 201–204°. The analytical sample of the *acetate* VIb crystallized from methanol-ethyl acetate as long needles; m.p. 200–203°, $[\alpha]_D^{20}$ −23°, ultraviolet maxima (Fig. 1) at 236 mμ (log ε 4.13) and 242 mμ (log ε 4.17). The substance gave an orange color with tetranitromethane.

Anal. Calc'd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31.
Found: C, 76.63; H, 9.22.

Alkaline saponification followed by recrystallization from chloroform-methanol gave colorless prisms of $\Delta^{7,9(11)}$-*22-isoallospirostadien-3β-ol* (VIa) with m.p. 177–179°, $[\alpha]_D^{20}$ −36.8°, u.v. maxima at 236 mμ (log ε 4.12) and 242 mμ (log ε 4.16).

Anal. Calc'd for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77.
Found: C, 78.29; H, 10.02.

The *benzoate* Vb exhibited m.p. 206–207°, $[\alpha]_D^{20}$ −26.7°, after recrystallization from methanol-ethyl acetate.

Anal. Calc'd for $C_{34}H_{44}O_4$: C, 79.02; H, 8.58.
Found: C, 79.21; H, 8.33.

$\Delta^{5,7,9(11)}$-*22-Isospirostatrien-3β-ol* (VII). This triene was prepared in a manner similar to that given above by shaking overnight a mixture of 12 g. of $\Delta^{5,7}$-22-isospirostadien-3β-ol 3-acetate (IIb), 20 g. of mercuric acetate, 160 cc. of chloroform, and 250 cc. of acetic acid. The *triene acetate* VIIb after recrystallization from methanol-ethyl acetate was obtained as needles (6.2 g.) with m.p. 178–179°, $[\alpha]_D^{20}$ +170.3°, u.v. maxima at 310 mμ (log ε 4.18), 324 mμ (log ε 4.23), and 338 mμ (log ε 4.02); see Fig. 1.

A deep red color was produced with tetranitromethane.

Anal. Calc'd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.90.
Found: C, 76.79; H, 8.71.

The free *alcohol* VIIa crystallized as plates from methanol, m.p. 187–190°, $[\alpha]_D^{20}$ +119°, u.v. maxima at 310 mμ (log ε 4.12), and 324 mμ (log ε 4.16) and inflection at 338 mμ (log ε 3.95).

Anal. Calc'd for $C_{27}H_{38}O_2$: C, 78.98; H, 9.32.
Found: C, 78.89; H, 9.21.
The *benzoate* VIIc showed m.p. 197–198°, $[\alpha]_D^{20}$ +150°.
Anal. Calc'd for $C_{34}H_{42}O_4$: C, 79.33; H, 8.22.
Found: C, 79.02; H, 8.41.

SUMMARY

$\Delta^{5,7}$-22-Isospirostadien-3β-ol (II), easily obtainable (1) from diosgenin (I), has been reduced catalytically to Δ^{7}-22-isoallospirosten-3β-ol (III), which in turn was dehydrogenated readily with mercuric acetate to $\Delta^{7,9(11)}$-22-isoallospirostadien-3β-ol (VI). Similar treatment of $\Delta^{5,7}$-22-isospirostadien-3β-ol led to $\Delta^{5,7,9(11)}$-22-isospirostatrien-3β-ol (VII). These two sapogenin derivatives (VI and VII) with a double bond at the 9–11 position represent useful intermediates for the partial synthesis of C-11 oxygenated steroids.

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