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STEROIDAL SAPOGENINS. XIV.[1] $\Delta^{4,6}$-22-ISOSPIROSTADIEN-3β-OL AND $\Delta^{2,4,6}$-ISOSPIROSTATRIENE[2]

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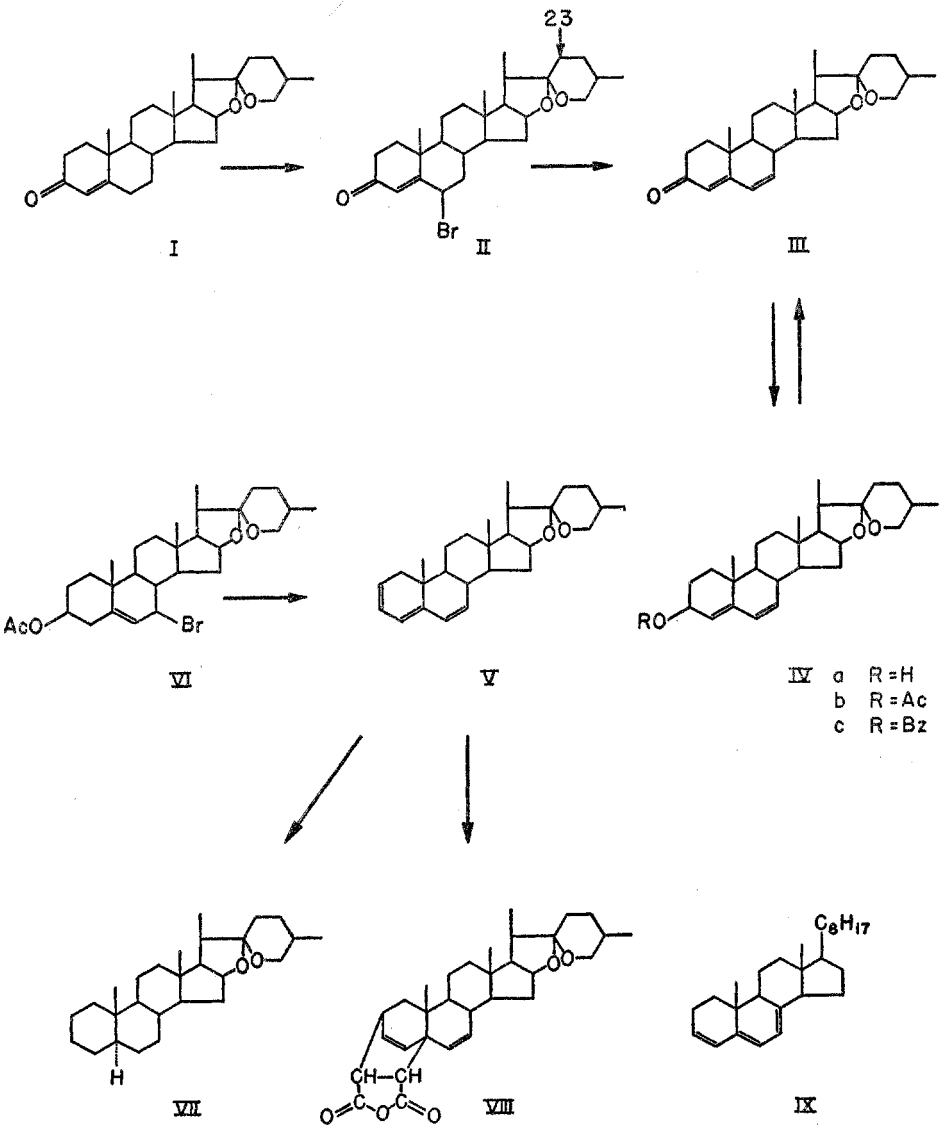
A number of syntheses have been developed (1) during the past twenty years for $\Delta^{5,7}$-dien-3β-ols, notably of the cholesterol series, since such compounds represent provitamins D. Recently, such $\Delta^{5,7}$-dien-3β-ols have achieved renewed importance, since they represent the starting materials (2, 3) for the synthesis of 11-oxygenated steroids and ultimately cortisone from ring C unsubstituted steroids (4–6). In view of the ease of degradation of the sapogenin side chain to pregnane derivatives, $\Delta^{5,7}$-22-isoallospirostadien-3β-ol (7) plays a particularly important role, and the present paper is concerned with the nature of two of the by-products obtained in the preparation of this compound.

In the earlier synthesis (7), Δ^{5}-22-isospirosten-3β-ol acetate (diosgenin acetate) was brominated with N-bromosuccinimide and the resulting 7-bromo derivative VI was dehydrobrominated with collidine to afford the desired $\Delta^{5,7}$-dien-3β-ol acetate. As has already been observed in the cholesterol series (8), there is always simultaneously produced the isomeric $\Delta^{4,6}$-dien-3β-ol acetate (IV). Such a by-product was isolated (7) in the synthesis of $\Delta^{5,7}$-22-isospirostadien-3β-ol but while the spectroscopic results were fully consistent with the $\Delta^{4,6}$-dien-3β-ol structure, the molecular rotation data were not, and an independent synthesis of this compound was considered desirable. $\Delta^{4,6}$-22-Isospirostadien-3-one (*III*) has already been prepared (9) by quinone Oppenauer oxidation of Δ^{5}-22-isospirosten-3β-ol, but this reaction is troublesome on a large scale (10). As an alternate path, there was carried out the Wohl-Ziegler bromination (11) of Δ^{4}-22-isospirosten-3-one (I) (12), which yielded the 6-bromo derivative II without any notable bromination at position 23, and upon dehydrobromination, the desired dienone III. In contrast to the lithium aluminum hydride reduction of Δ^{4}-3-ketosteroids such as Δ^{4}-cholesten-3-one (13), which yields an equimolar mixture of the epimeric alcohols, similar treatment of the dienone III afforded almost exclusively the desired β-isomer, $\Delta^{4,6}$-22-isospirostadien-3β-ol (IVa), further characterized by the formation of an acetate (IVb) and benzoate (IVc). A similar, stereospecific reduction has recently been observed (14) with $\Delta^{4,6}$-cholestadien-3-one. The synthetic $\Delta^{4,6}$-dien-3β-ol and derivatives (IVa–c) agreed fairly well in their properties with the by-products isolated earlier (7) in the dehydrobromination of VI, and the dextrorotatory shift of the synthetic dienol IVa as compared to the $\Delta^{5,7}$-isomer coincided with that reported in the literature for other series (3, 8, 14, 15). As has already been demonstrated with $\Delta^{4,6}$-cholestadien-3β-ol (16), Oppenauer oxidation of the dienol IVa regenerated the dienone III.

[1] For paper XIII see Djerassi, Yashin, and Rosenkranz, *J. Am. Chem. Soc.*, in press.

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

The second by-product in the earlier synthesis (7) of $\Delta^{5,7}$-22-isospirostadien-3β-ol proved to be a triene, to which is now assigned the structure of $\Delta^{2,4,6}$-22-isospirostatriene (V). Such a triene in the cholesterol series has been isolated



originally by Eckhardt (17), who proposed the $\Delta^{3,5,7}$-triene (IX) formulation for it.[3] The correct $\Delta^{3,5,7}$-cholestatriene was recently prepared by Gould, *et al.*, (18) who showed that such a compound was characterized by a strongly negative

[3] This structure has already been questioned earlier on spectroscopic grounds by Fieser and Fieser (Ref. 1, p. 189) and by Barton, *J. Chem. Soc.*, 2178 (1949).

rotation ($[\alpha]_D$ −122°), ultraviolet absorption maxima at 302.5, 315, and 330 mμ, and by the uptake of only two moles of hydrogen upon catalytic hydrogenation (the 7,8-double bond not being reduced). Eckhardt's triene (17), on the other hand as was recently confirmed by Schmutz, Schaltegger, and Sanz (14), exhibits a much more positive rotation ($[\alpha]_D$ −13.5°), and ultraviolet absorption maxima at 295, 305 mμ, and an inflection at 320 mμ, in excellent agreement with the maxima observed for our triene V. As pointed out by the Swiss workers (14), the physical data, the fact that the triene takes up three moles of hydrogen, and that it forms an adduct with maleic anhydride, all support a $\Delta^{2,4,6}$-cholestatriene structure. We have independently reached the same conclusion with regard to the structure of the triene isolated in the sapogenin series, since the latter (V) takes up three moles of hydrogen with formation of 22-isoallospirostan (VII) (19) and also yields a well crystallized adduct (VIII) with maleic anhydride. The coincidence of the molecular rotation differences in the sapogenin and cholesterol series further confirm the presence of the identical $\Delta^{2,4,6}$-triene system in both instances.

The importance of $\Delta^{5,7}$-dien-3β-ols in general, and of $\Delta^{5,7}$-22-isospirostadien-3β-ol in particular, for the synthesis of 11-oxygenated steroid hormones, emphasizes the need to characterize and possibly minimize the formation of by-products in the synthesis of such dienes. Lowenbein (20), in a recent patent has claimed extremely high yields of crystalline 7-dehydrocholesterol, by treatment of 7-bromocholesterol esters with alkaline earth hydroxides in a mixture of xylene and nitrobenzene. This claim could not be duplicated by Schmutz, Schaltegger, *et al.*, (14), who in addition to 7-dehydrocholesterol always isolated appreciable amounts of $\Delta^{2,4,6}$-cholestatriene. We have had similar experiences on applying some of Lowenbein's conditions to 7-bromo-Δ^5-22-isospirosten-3β-ol acetate (VI) and in the experimental section there is reported an experiment with magnesium oxide, in which $\Delta^{2,4,6}$-22-isospirostatriene (V) was the principal product. A similar observation was made in an attempt to hydrolyze the bromo derivative VI with dioxane-water at 90°, the triene V being formed in 60% yield. Successful conversions of the 7-bromo compound VI to the corresponding 7-hydroxy epimers and thence $\Delta^{5,7}$-22-isospirostadien-3β-ol, together with a discussion of the stereochemistry of those intermediates, will be reported in a subsequent paper of this series.

EXPERIMENTAL[4]

$\Delta^{4,6}$-22-Isospirostadien-3-one (III). A solution of 20 g. of Δ^4-22-isospirosten-3-one (I) (12) in 300 cc. of dry carbon tetrachloride was refluxed with 9.4 g. of N-bromosuccinimide for ten minutes with exposure to strong light (G. E. RSP2 lamp). The succinimide was filtered, the filtrate was concentrated under reduced pressure to near dryness, and pentane was added. The faintly pink solid (16 g.) was collected and after two recrystallizations from hexane-acetone afforded colorless crystals of the *6-bromo derivative II* with m.p. 185–187°

[4] 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 indebted to Srta. Paquita Revaque for these measurements and to Srta. Amparo Barba of our microanalytical department for the analyses.

(dec.), $[\alpha]_D^{20}$ −26°, ultraviolet absorption maximum at 238 mμ (log ε 4.26). In view of its instability, the compound was carried directly through the next step by refluxing with 50 cc. of collidine for 30 minutes. After the usual work-up (extraction with ether, washing with dilute acid and alkali, drying, and evaporating), the product was crystallized from acetone-methanol to yield 7.0 g. (35%) of $\Delta^{4,6}$-22-isospirostadien-3-one (III) with m.p. 198–200°. The analytical sample crystallized as brilliant plates with m.p. 205–207°, $[\alpha]_D^{20}$ −55°, ultraviolet absorption maximum at 284 mμ (log ε 4.48); reported (9): m.p. 205–207°, but no rotation or spectrum.

Anal. Calc'd for $C_{27}H_{38}O_2$: C, 78.98; H, 9.33.
Found: C, 78.61; H, 9.06.

$\Delta^{4,6}$-22-Isospirostadien-3β-ol (IVa). The above dienone III (10 g.) in 40 cc. of dry tetrahydrofuran was added dropwise to a mixture of 4 g. of lithium aluminum hydride in 50 cc. of the same solvent and then refluxed for 15 minutes. After decomposing the excess reagent with acetone, diluting with water, and acidifying *slightly*, the product was filtered and recrystallized twice from methanol; yield, 7.5 g., m.p. 179–181° (capillary), 171–173° (Kofler), $[\alpha]_D^{20}$ −106°, ultraviolet absorption maxima at 232 (log ε 4.37), 240 (log ε 4.42), and 248 mμ (log ε 4.23).

Anal. Calc'd for $C_{27}H_{40}O_2$: C, 78.59; H, 9.77.
Found: C, 78.16; H, 9.96.

The infrared spectra of the alcohol (IVa), acetate (IVb), and benzoate (IVc) were indistinguishable from those of the corresponding derivatives isolated (7) as by-products in the dehydrobromination of VI.[5]

The *acetate* IVb was prepared in the usual manner (acetic anhydride—pyridine, one hour, steam-bath) and after recrystallization from methylene chloride-methanol exhibited m.p. 179–181° (Kofler or capillary), $[\alpha]_D^{20}$ −133°, ultraviolet absorption maxima at 232 (log ε 4.37), 238 (log ε 4.41), and 248 mμ (log ε 4.20).

Anal. Calc'd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31.
Found: C, 76.68; H, 9.44.

The *benzoate IVc* showed m.p. 190–191°, $[\alpha]_D^{20}$ −125°.

Anal. Calc'd for $C_{34}H_{44}O_4$: C, 79.02; H, 8.58.
Found: C, 78.73; H, 8.42.

Oppenauer oxidation of $\Delta^{4,6}$-22-isospirostadien-3β-ol (IVa). A solution of 3.0 g. of the dienol IV in 200 cc. of toluene was dried by distilling off 70 cc.; 50 cc. of cyclohexanone and 4.0 g. of aluminum *tert*-butoxide were added and the mixture was refluxed for 45 minutes. After diluting with water and washing with 5% hydrochloric acid, the mixture was distilled with steam and the residue was filtered. Recrystallization from chloroform-methanol afforded 2.05 g. (68%) of $\Delta^{4,6}$-22-isospirostadien-3-one (III) with m.p. 198–201°, undepressed upon admixture with a specimen prepared from I, $[\alpha]_D^{20}$ −53°, ultraviolet absorption maximum at 284 mμ (log ε 4.43).

$\Delta^{2,4,6}$-22-Isospirostatriene (V). (*a*) *By collidine dehydrobromination of 7-bromo-Δ^5-22-isospirosten-3β-ol acetate* (VI) As mentioned earlier (7), the hexane eluates of the chromatogram of the mother liquors from the dehydrobromination of the 7-bromo acetate VI afforded crystals with m.p. 186–188°, corresponding to 7–10% of the total dehydrobromination mixture. Further recrystallization from ethyl acetate did not change the m.p. of the shiny plates, which exhibited $[\alpha]_D^{20}$ −107°, ultraviolet absorption maxima at 296 (log ε 4.27), 306 (log ε 4.33), and an inflection at 320 mμ (log ε 4.15), and gave a brown color with tetranitromethane.

Anal. Calc'd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.70.
Found: C, 82.26; H, 9.91.

(*b*) *By magnesium oxide treatment of 7-bromo-Δ^5-22-isospirosten-3β-ol acetate* (VI). A solution of 25 g. of the bromo acetate VI in 140 cc. of xylene was stirred at 125° for three hours with 60 g. of magnesium oxide. The cooled solution was filtered, the precipitate was washed

[5] As pointed out in Ref. 7 (p. 292, note 3a), the melting point values differ very considerably depending upon the method of determination and also rate of heating.

thoroughly with benzene, and the solvent was removed by steam-distillation in the presence of 5 g. of sodium bicarbonate. The residue was extracted with ethyl acetate, dried, evaporated, and crystallized from benzene-ethanol affording 8.0 g. (44%) of the triene V with m.p. 182–185°, $[\alpha]_D^{20}$ −101°, ultraviolet maxima at 296 (log ε 4.28), 306 (log ε 4.33), and inflection at 320 mμ (log ε 4.15).

(c) *By dioxane-water treatment of 7-bromo-Δ⁵-22-isospirosten-3β-ol-acetate* (VI). The bromo acetate VI (5.0 g.) was dissolved in 40 cc. of dioxane and water was added at 30° until the solution was turbid. After heating on the steam-bath for two hours, water was added, the product (3.4 g.) was filtered and chromatographed on 85 g. of ethyl acetate-washed alumina. Recrystallization of the hexane eluates gave 2.2 g. (60%) of triene with m.p. 181–183°, $[\alpha]_D^{20}$ −100°, ultraviolet absorption maxima at 296 (log ε 4.26), 306 mμ (log ε 4.32), and inflection at 320 mμ (log ε 4.13).

Anal. Found: C, 81.96; H, 9.76.

The infrared spectra (carbon disulfide) of the three specimens, prepared according to (a), (b), and (c), were identical.

22-Isoallospirostan (VII) *from Δ²,⁴,⁶-22 Isospirostatriene* (V). A mixture of 1.0 g. of the triene V in 100 cc. of ethyl acetate upon shaking in an atmosphere of hydrogen with 100 mg. of pre-reduced platinum oxide catalyst consumed three moles of hydrogen in two hours. Filtration of the catalyst, concentration, and cooling produced 0.7 g. of crystals with m.p. 163–168°, which after two recrystallizations afforded the analytical sample of 22-isoallospirostan (VII) with m.p. 176–177°, undepressed upon admixture with an authentic specimen (19), $[\alpha]_D^{20}$ −74°, no color with tetranitromethane.

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07.

Found: C, 81.08; H, 11.29.

Maleic anhydride adduct of Δ²,⁴,⁶-22-isospirostatriene (VIII). After refluxing a solution of 3.0 g. of the triene V and 3.0 g. of maleic anhydride in 100 cc. of xylene for five hours and removing the solvent by steam-distillation, there was obtained a crystalline precipitate (3.0 g.), which after one recrystallization from acetone afforded the analytical sample with m.p. 288–290°, $[\alpha]_D^{20}$ −8°; the substance gave a yellow color with tetranitromethane.

Anal. Calc'd for $C_{31}H_{40}O_5$: C, 75.57; H, 8.18.

Found: C, 75.86; H, 8.39.

SUMMARY

The importance of Δ⁵,⁷-22-isospirostadien-3β-ol as starting material for the preparation of 11-oxygenated steroids has prompted an investigation of the by-products formed in its synthesis. Δ²,⁴,⁶-22-Isospirostatriene (V) was identified as one of the contaminants in the collidine dehydrobromination of 7-bromo-Δ⁵-22-isoallospirosten-3β-ol acetate and conditions are described in which triene formation represents the predominant reaction. Its structure was confirmed by the physical data, hydrogenation to 22-isoallospirostan (VII) and formation of a maleic anhydride adduct. Δ⁴,⁶-22-Isospirostadien-3β-ol (IV), a second by-product, has now been synthesized by lithium aluminum hydride reduction of Δ⁴,⁶-22-isospirostadien-3-one (III), which in turn was prepared by Wohl-Ziegler bromination of Δ⁴-22-isospirosten-3-one (I), followed by dehydrobromination of the intermediate 6-bromo derivative (II).

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