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STEROIDS. LV.[1] STEROIDAL SAPOGENINS. XXXV.[2] CHEMICAL INTRODUCTION OF THE 6β-HYDROXY GROUP INTO STEROIDAL Δ^4-3-KETONES BY A TWO STEP SEQUENCE

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The desirability of making available steroidal hormone analogs hydroxylated at C-6 has been pointed out in a recent memoir from these laboratories (1). All the previous methods referred to in that paper for preparing the necessary 6-hydroxy-Δ^4-3-ketones, as well as the new route reported there, employed the corresponding Δ^5-3β-ols as starting materials. Such Δ^5-3β-alcohols, however, are not readily available in some cases, such as in the 11-oxygenated series. For this reason we attempted to find a way for preparing 6-hydroxy-Δ^4-3-ketones from the corresponding Δ^4-3-ketones (*i.e.* the actual hormones of which the 6-hydroxy analogs were required), since the latter are available in all cases. This paper records the realization of this objective by a simple two step reaction sequence.

It has been shown that an 11α-hydroxy group may be introduced into steroidal Δ^8-7-ketones through conversion to the enol acetate, followed by oxidation with a per-acid (2), and it was expected that Δ^4-3-ketones could be transformed to the corresponding 6-hydroxy compounds by a similar route. In fact when a typical Δ^4-3-ketone, Δ^4-22a-spirosten-3-one (I) (3), was converted to the enol acetate (II) with isopropenyl acetate and *p*-toluenesulfonic acid in benzene solution (*cf.* 2)[4] and then oxidized with monoperphthalic acid, a compound was obtained in 25% yield which contained one more oxygen atom than the initial ketone (I). The infrared spectrum and the formation of a monoacetate revealed the presence of a hydroxyl function, and the fact that the latter had been introduced at C-6 was shown through chromic acid oxidation to the known Δ^4-22a-spirostene-3,6-dione (V) (4), through base isomerization to 22a-5α-spirostane-3,6-dione (VI) (4), and by the ultraviolet spectrum ($\lambda_{max.}$ 236 mμ, log ϵ 4.14) which showed the hypsochromic shift of *ca.* 4 mμ to be expected on passing from a Δ^4-3-ketone to the 6(β)-hydroxy analog (*cf.* 5). Finally the compound was identified as Δ^4-22a-spirosten-3-one-6β-ol (III) through direct comparison with a sample prepared by the manganese dioxide route (1), which involved performic acid oxidation of diosgenin (VII) to the 3β, 5α,6β-triol (VIII, R = H) (4a), followed by acetylation to (VIII, R = Ac) (4a), dehydration to the Δ^4-3β,6β-

[1] Paper LIV, Djerassi, Miramontes, Rosenkranz, and Sondheimer, *J. Am. Chem. Soc.*, **76**, August (1954).

[2] Paper XXXIV, Djerassi, Lemin, Rosenkranz, and Sondheimer, *J. Chem. Soc.*, July (1954).

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[4] The acetic-anhydride-*p*-toluenesulfonic acid method [Bedoukian, *J. Am. Chem. Soc.*, **67**, 1430 (1945)] was unsuitable, since the spiroketal side chain is attacked under such conditions [Gould, Staeudle, and Herschberg, *J. Am. Chem. Soc.*, **74**, 3685 (1952), and independent observations from these laboratories].

diacetate (IX, R = Ac), saponification and preferential oxidation at C-3 with manganese dioxide at room temperature.

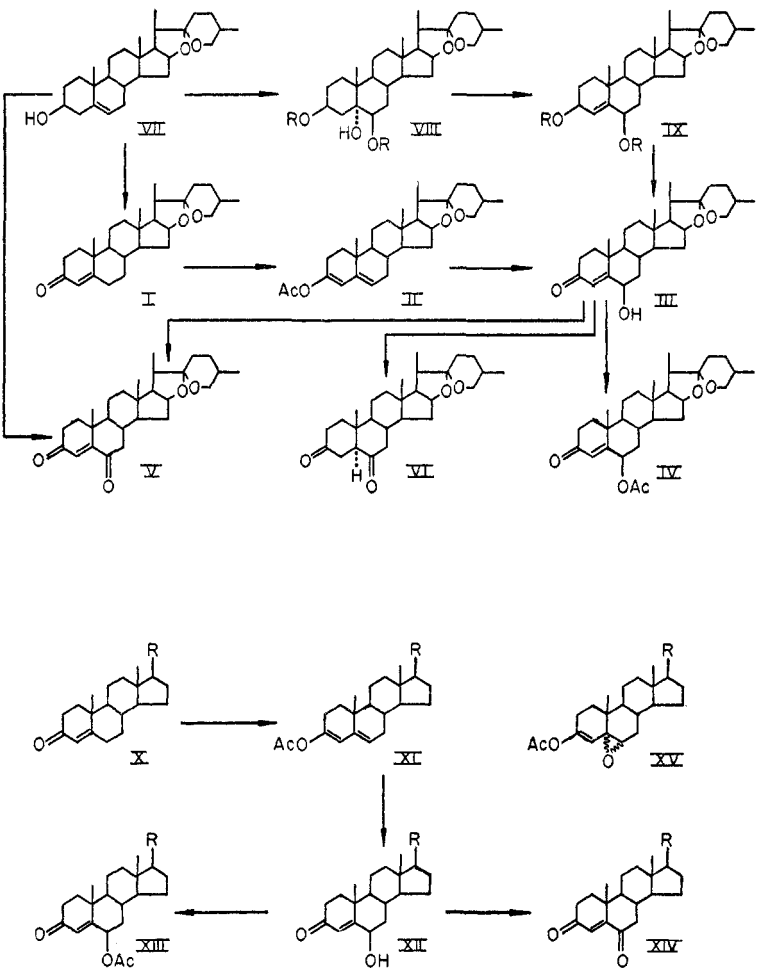

FIG. 1

The generality of the above described method for introducing a 6β-hydroxyl group into Δ^4-3-ketones was demonstrated by its application to the synthesis of 6β-hydroxy-Δ^4-cholesten-3-one (XII, R = C_8H_{17}), 6β-hydroxytestosterone 17-acetate (XII, R = OAc), 6β-hydroxyprogesterone (XII, R = $COCH_3$), and 6β-hydroxydesoxycorticosterone 21-acetate (XII, R = $COCH_2OAc$) by the sequence (X) → (XI) → (XII). These substances were identified by direct comparison with authentic samples where possible, and were further characterized through acetylation to the 6β-acetoxy-Δ^4-3-ketones (XIII), through chromic acid oxidation to the Δ^4-3,6-diones (XIV), and through base isomerization to the saturated (5α)-3,6-diones.

It is of interest that in all the above examples the 6-hydroxy-Δ^4-3-ketones were obtained directly from the per-acid oxidation, as had been the 11-hydroxy-Δ^8-7-ketones from the oxidation of the enol acetates of steroidal Δ^8-7-ketones (2). Only in one case (R = C_8H_{17}) was a small amount of a by-product isolated, which may be the 3-acetoxy-Δ^3-5ξ,6ξ-oxide (type XV) as evidenced by the elemental analysis and absence of an ultraviolet maximum. This finds an an alogy in the formation of the 7-acetoxy-Δ^7-9α,11α-oxide by perphthalic acid oxidation of the enol acetate of the Δ^8-7-ketone in the lanosterol series (6).

In the oxidation of 7-acetoxy-$\Delta^{7,9(11)}$-dienes with per-acids, attack occurs at the rear side of the molecule with the consequent introduction of the 11-hydroxyl group of the α (equatorial) configuration. On the other hand in the presently described oxidations of 3-acetoxy-$\Delta^{3,5}$-dienes (XI), attack apparently takes place mainly from above, thus accounting for the formation of the 6β-(axial)[5]-hydroxy-Δ^4-3-ketones.[6] This is a fortunate fact, for the isomerization of the latter type of substance to the thermodynamically more stable 6α-hydroxy isomers by hydrogen chloride in chloroform containing alcohol has recently been described (7). The present method therefore permits the preparation of both 6β- and 6α-hydroxy hormone analogs.

EXPERIMENTAL[7]

Δ^4-22a-Spirosten-3-one-6β-ol (III) *from Δ^4-22a-spirosten-3-one* (I). A solution of 10 g. of Δ^4-22a-spirosten-3-one (I) (3) in 200 cc. of dry benzene and 40 cc. of isopropenyl acetate containing 1.2 g. of *p*-toluenesulfonic acid was slowly distilled during the course of 4 hours, another 20 cc. of isopropenyl acetate having been added after 2 hours. At the end of the reaction (120 cc. of distillate collected) the cooled solution was poured into ice-water and the product was extracted with ether. Washing with sodium bicarbonate solution and water, drying, evaporation, and crystallization of the residue from acetone—hexane gave 6.9 g. of the crude enol acetate (II), m.p. 172–175°, $\lambda_{max.}$ 236 mμ (log ϵ 4.20).

The crude enol acetate (6.5 g.) was oxidized with 1.05 equivalents of monoperphthalic

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[5] The suggestion made by Barton, Hassel, Pitzer, and Prelog [*Nature*, **172**, 1096 (1953); *Science*, **119**, 49 (1954)] to substitute "axial" for "polar" has been adopted.

[6] Although only the 6β-hydroxy-Δ^4-3-ketones were isolated in all of the examples studied, the formation of some of the 6α-hydroxy-Δ^4-3-ketones (or 3-acetoxy-Δ^3-5α,6α-oxides) is not excluded. In fact the presence of these substances may account for the fact that in some cases the pure 6β-hydroxy-Δ^4-3-ketones were obtained only after careful chromatography or repeated crystallization. The formation of the axial (6β)-hydroxy compound can be explained on the same basis as the initial production [Corey, *Experientia*, **9**, 329 (1953)] of the axial epimer in the bromination of ketones. The isolation of the equatorial 11α-hydroxy derivative (ref. 2) may be either a reflection of the greater hindrance at C-11 resulting in direct attack from the α-side or it may be due to isomerization of the initially formed axial isomer.

[7] Melting points are uncorrected. Ultraviolet absorption spectra were measured in 95% ethanol solution, and infrared spectra in chloroform solution (unless specified otherwise) with a Perkin-Elmer model 12C single beam spectrophotometer with sodium chloride prism. Rotations were determined at 20° in chloroform solution. We are indebted to Miss P. Revaque (Mrs. P. Lopez) for these measurements and to Miss A. Barba (Mrs. A. Gonzalez) for the microanalyses. Thanks are due to Miss Rosa Yashin for valuable technical assistance.

acid in 1 l. of ether for 16 hours in the dark. The acidic materials were then removed by washing with sodium bicarbonate solution, the ethereal extract was dried, evaporated and the residue was crystallized repeatedly from acetone—hexane. In this way, 2.4 g. (25% over-all) of the 6β-hydroxy-Δ^4-3-ketone (III) with m.p. 215–218° was obtained. Further crystallization from the same solvent pair furnished the analytical sample, m.p. 231–233°, $[\alpha]_D$ −64°, $\lambda_{max.}$ 236 mμ (log ε 4.14), $\nu_{max.}$ 1670 cm.$^{-1}$ and free hydroxyl band.

Anal. Calc'd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41.
Found: C, 75.41; H, 9.41.

The *acetate* (IV) was prepared in the usual way (acetic anhydride—pyridine, steam bath, 1 hour) and after crystallization from acetone—hexane showed m.p. 209–211°, $[\alpha]_D$ −48°, $\lambda_{max.}$ 236 mμ (log ε 4.13), $\nu_{max.}$ 1736 and 1674 cm.$^{-1}$, no free hydroxyl band.

Anal. Calc'd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00.
Found: C, 74.11; H, 9.15.

Δ^4-22a-Spirostene-3,6-dione (V). The 6β-hydroxy-Δ^4-3-one (III) (500 mg.) dissolved in 15 cc. of acetic acid was oxidized with 250 mg. of chromium trioxide dissolved in 1 cc. of water for 15 minutes at room temperature. Addition of water, isolation with ether in the usual way, and crystallization from acetone—pentane furnished 420 mg. of the Δ^4-3,6-dione V, m.p. 188–190°. Further crystallization yielded the analytical sample, m.p. 194–195°, $[\alpha]_D$ −115°, $\lambda_{max.}$ 250 mμ (log ε 4.03), $\nu_{max.}$ 1686 cm.$^{-1}$, no hydroxyl group [reported: m.p. 197° (4a); m.p. 192–195° (4b)].

Anal. Calc'd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98.
Found: C, 75.68; H, 8.65.

Identity with an authentic sample, obtained by chromium trioxide oxidation of diosgenin (VII) (4b), was established by mixture m.p. and infrared comparison.

22a-5α-Spirostane-3,6-dione (VI). A solution containing 500 mg. of the 6β-hydroxy-Δ^4-3-ketone (III) and 3 g. of sodium hydroxide in 50 cc. of methanol and 5 cc. of water was heated under reflux for 75 minutes. Water was then added and the product was extracted with ether. Crystallization from chloroform—methanol furnished 340 mg. of the saturated dione, m.p. 232–233°, no appreciable absorption in the ultraviolet, $\nu_{max.}$ 1710 cm.$^{-1}$, no free hydroxyl band [reported: m.p. 233–234° (4a); m.p. 235–237° (4b)].

Anal. Calc'd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41.
Found: C, 75.95; H, 9.60.

Identity with an authentic sample, obtained by zinc reduction of the Δ^4-3,6-dione (V) (4b), was established by mixture m.p. and infrared comparison.

22a-Spirostane-3β,5α,6β-triol (VIII, R = H) (*cf.* 8). A solution of 20 g. of diosgenin (VII) dissolved in 250 cc. of tetrahydrofuran was heated on the steam-bath with 180 cc. of 90% formic acid for 5 minutes, cooled to room temperature, and then treated in portions with 40 cc. of 30% hydrogen peroxide, the temperature being kept at *ca.* 40°. After being allowed to stand at room temperature for 12 hours, water was added, and the solid precipitate was collected and washed well with water. It was then heated under reflux with 15 g. of potassium hydroxide in 500 cc. of methanol and 25 cc. of water for 15 minutes. Evaporation of solvent to small volume, addition of water, filtration and crystallization from methanol furnished 17.1 g. (79%) of the 3β,5α,6β-triol, m.p. 281–283°, $[\alpha]_D$ −74° (dioxane) [reported for the hemihydrate (4a): m.p. 283–284°, $[\alpha]_D$ −83° (ethanol)].

Anal. Calc'd for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89.
Found: C, 72.38; H, 9.75.

The *3,6-diacetate* (VIII, R = Ac) was prepared by heating 41.5 g. of the 3β,5α,6β-triol (VIII, R = H) with 200 cc. of acetic anhydride and 200 cc. of pyridine for 1 hour on the steam-bath. Addition of water, isolation with ether, and crystallization from ether-hexane afforded 39.5 g. (80%) of the diacetate, m.p. 192–194°, $[\alpha]_D$ −105°, $\nu_{max.}$ 1736 cm.$^{-1}$ and free hydroxyl band [reported (4a): m.p. 186–188°, $[\alpha]_D$ −107° (ethanol)].

Anal. Calc'd for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08.
Found: C, 70.21; H, 9.31.

Δ^4-22a-Spirostene-3β,6β-diol diacetate (IX, R = Ac) (*cf.* 9). Thionyl chloride (14 cc.) was added to an ice-cooled solution of 39 g. of the triol diacetate (VIII, R = Ac) in 150

cc. of anhydrous pyridine. After 5 minutes at 0°, the product was precipitated with water, washed well with water, dried, and crystallized from acetone—methanol. In this way 28.1 g. (75%) of the unsaturated diacetate (IX, R = Ac), m.p. 133–136°, was obtained. Further crystallization yielded the analytical sample, m.p. 145–147°, $[\alpha]_D$ −87°.

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

Found: C, 72.09; H, 9.11.

Δ^4-22a-Spirostene-3β,6β-diol (IX, R = H). The unsaturated diacetate (IX, R = Ac) (25.5 g.; m.p. 133–136°) dissolved in 1 l. of methanol was saponified through being refluxed with 25.5 g. of potassium hydroxide in 50 cc. of water for 75 minutes. The solution was concentrated to *ca.* 500 cc. under reduced pressure, water was added, the product was extracted with chloroform, and the organic layer was dried and evaporated to incipient crystallization. The resulting unsaturated diol (19.2 g.; 90%) showed m.p. 272–275°; further crystallization from chloroform furnished the analytical sample, m.p. 286–288°, $[\alpha]_D$ −69°, $\nu_{max.}^{mull}$ free hydroxyl band only.

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

Found: C, 75.71; H, 9.99.

Δ^4-22a-Spirosten-3-one-6β-ol (III) *from the Δ^4-3β,6β-diol* (IX, R = H). A mixture of 18.5 g. of the Δ^4-3β,6β-diol (IX, R = H) and 185 g. of manganese dioxide [prepared as described previously (10)] in 2 l. of chloroform was shaken at room temperature for 20 hours. The dioxide was removed and washed well with hot chloroform. Evaporation of the filtrate and crystallization from chloroform—hexane afforded 15.4 g. (84%) of the 6β-hydroxy-Δ^4-3-ketone (III), m.p. 215–217°. The over-all yield from diosgenin was 36%. Further crystallization yielded 11.8 g. of the analytically pure compound, m.p. 232–234°, $[\alpha]$ −65°, $\lambda_{max.}$ 236 mμ (log ε 4.15), ν_{max} 1670 cm.$^{-1}$ and free hydroxyl band.

Anal. Calc'd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41.

Found: C, 75.77; H, 9.40.

The compound was identical (mixture m.p., infrared comparison) with that derived from the enol acetate (II).

The *acetate* (IV) exhibited m.p. 211–212°, $[\alpha]_D$ −46°, $\lambda_{max.}$ 236 mμ (log ε 4.14), and identity with the previously described compound was established in the usual way.

Δ^4-Cholesten-3-one-6β-ol (XII, R = C_8H_{17}) *from Δ^4-cholesten-3-one* (X, R = C_8H_{17}). Δ^4-Cholesten-3-one (4 g.) was converted to the enol acetate (11) by the isopropenyl acetate *p*-toluenesulfonic acid method, as described above for II. The total enol acetate (XI, R = C_8H_{17}) (4.2 g.; $\lambda_{max.}$ 236 mμ, log ε 4.22) was treated with 1.3 equivalents of monoperphthalic acid in 300 cc. of ether for 20 hours in the dark. Removal of acidic materials and of ether left a residue ($\lambda_{max.}$ 236 mμ, log ε 4.10), which was chromatographed on 160 g. of neutral alumina. The fractions eluted with hexane—benzene on crystallization from acetone—methanol furnished 0.13 g. (3%) of a substance, m.p. 118–119°, $[\alpha]_D$ +42°, no appreciable absorption in the ultraviolet, $\nu_{max.}$ 1746 cm.$^{-1}$, no free hydroxyl band, which may be 5ξ,6ξ-oxido-Δ^3-cholesten-3-ol acetate (XV, R = C_8H_{17}). This compound was not further investigated.

Anal. Calc'd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.48.

Found: C, 78.75; H, 10.35.

Continued elution of the chromatogram with benzene and benzene—ether yielded a crystalline product, which after several crystallizations from acetone—hexane gave 1.3 g. (31%) of Δ^4-cholesten-3-one-6β-ol (XII, R = C_8H_{17}), m.p. 187–190°. A further purified sample showed m.p. 192–194°, $\lambda_{max.}$ 236 mμ (log ε 4.13), $\nu_{max.}$ 1670 cm.$^{-1}$ and free hydroxyl band.

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

Found: C, 81.21; H, 11.36.

Identity with a sample (m.p. 194–195°), prepared (1) by manganese dioxide oxidation of Δ^4-cholestene-3β,6β-diol was established through mixture m.p. and infrared comparison.

The *acetate* (XIII, R = C_8H_{17}), prepared in the usual way, was crystallized from methanol and showed m.p. 101–103°, $\nu_{max.}$ 1736 and 1672 cm.$^{-1}$. It was identified with an authentic sample (m.p. 103–104°) (1) in the usual way.

The 6β-hydroxy-Δ^4-3-ketone (XII, R = C_8H_{17}) was further characterized through chro-

mium trioxide oxidation (12) to Δ^4-cholestene-3,6-dione (XIV, R = C_8H_{17}) [m.p. 120–122°, $[\alpha]_D$ −35°, $\lambda_{max.}$ 250 mμ (log ε 4.03)] and through base rearrangement to cholestane-3,6-dione (m.p. 170–171°, $[\alpha]_D$ +9°, no appreciable absorption in the ultraviolet). These transformation products were identical with authentic samples.

6β-Hydroxytestosterone 17-acetate (XII, R = OAc) *from testosterone acetate* (X, R = OAc). Testosterone acetate was transformed to the enol acetate (11) by the isopropenyl acetate-*p*-toluenesulfonic acid method. The resulting diacetate (XI, R = −OAc) [1.0 g.; m.p. 150–153°, $\lambda_{max.}$ 234 mμ (log ε 4.22)] was oxidized with 1.2 equivalents of monoperphthalic acid in 100 cc. of ether for 72 hours in the dark. Isolation as before and crystallization of the product ($\lambda_{max.}$ 236 mμ, log ε 4.03) from ether—pentane furnished 245 mg. (26%) of 6β-hydroxytestosterone 17-monoacetate (XII, R = OAc), m.p. 211–212°, $[\alpha]_D$ +27°, $\lambda_{max.}$ 236 mμ (log ε 4.14), $\nu_{max.}$ 1718 and 1674 cm.$^{-1}$ and free hydroxyl band.

Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73.

Found: C, 72.78; H, 9.04.

The *6,17-diacetate* (XIII,R = OAc) was crystallized from ether—pentane and exhibited m.p. 137–138°; it was identified with a specimen (m.p. 134–135°) prepared by an independent method (1) through mixture m.p. and infrared comparison.

Base treatment of (XII, R = OAc), as described previously (1) for the corresponding free diol (XII, R = OH), yielded androstane-3,6-dione-17β-ol with m.p. 234–236°, $[\alpha]_D$ +7°. It was identified with authentic specimens (1) (m.p. 235–236°, $[\alpha]_D$ +9°) in the usual manner.

6β-Hydroxyprogesterone (XII, R = $COCH_3$) *from progesterone* (X, R = $COCH_3$). Progesterone (4.0 g.) with isopropenyl acetate and *p*-toluenesulfonic acid in benzene [as described above for (II)] yielded 2.8 g. of the 3-enol acetate (XI, R = $COCH_3$),[8] m.p. 120–125° after crystallization from ether—pentane. A further purified sample exhibited m.p. 134–136°, $\lambda_{max.}$ 234 mμ (log ε 4.21) [reported (11): m.p. 138°].

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

Found: C, 77.25; H, 9.23.

The crude enol acetate (1.9 g.; m.p. 120–125°) was oxidized with 1.3 equivalents of monoperphthalic acid, as before (72 hours). Crystallization of the product from acetone—hexane afforded 0.80 g. (28% over-all) of 6β-hydroxyprogesterone (XII, R = $COCH_3$) with m.p. 163–165°, which on further crystallization was raised to m.p. 175–177°, $[\alpha]_D$ +107°, $\lambda_{max.}$ 236 mμ (log ε 4.14). Identity with an authentic specimen (1) (m.p. 179–180°, $[\alpha]_D$ +105°) was established through mixture m.p. determination.

The compound was characterized further through chromium trioxide oxidation to (XIV, R = $COCH_3$) with m.p. 194–196°, $[\alpha]_D$ +33°, $\lambda_{max.}$ 250 mμ (log ε 4.02), identified with an authentic sample (1) (m.p. 193–194°, $[\alpha]_D$ +30°) through infrared comparison and mixture m.p.

6β-Hydroxydesoxycorticosterone 21-acetate (XII, R = $COCH_2OAc$) *from desoxycorticosterone acetate* (X, R = $COCH_2OAc$). Desoxycorticosterone acetate (4.0 g.) was transformed to the 3-enol acetate (XI, R = $COCH_2OAc$) by the isopropenyl acetate—*p*-toluenesulfonic acid-benzene procedure. The total crude product [4.1 g.; $\lambda_{max.}$ 234 mμ (log ε 4.18)] was oxidized with 1.3 equivalents of monoperphthalic acid in 400 cc. of ether for 72 hours. Chromatographic purification of the product on 160 g. of neutral alumina, and crystallization of the fractions eluted with benzene and benzene—ether from acetone—ether afforded 0.57 g. of 6-hydroxydesoxycorticosterone 21-acetate, m.p. 196–198°, $[\alpha]_D$ +108°, $\lambda_{max.}$ 236 mμ (log ε 4.12), $\nu_{max.}$ 1740, 1718 and 1670 cm.$^{-1}$ and free hydroxyl band; it was identified with an authentic specimen (1) (m.p. 198–199°, $[\alpha]_D$ +105°) in the standard way.

Anal. Calc'd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30.

Found: C, 70.81; H, 8.36.

The *6,21-diacetate* (XIII, R $COCH_2OAc$) crystallized from ether—pentane, m.p. 130–

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[8] It is known that under these conditions the saturated 20-keto grouping is not attacked (ref. 2).

132°, $[\alpha]_D$ +104°, $\lambda_{max.}$ 236 mμ (log ε 4.13), and was identified with an authentic sample (1) (m.p. 130–131°, $[\alpha]_D$ +102°) through mixture m.p. determination and infrared comparison.

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SUMMARY

Δ^4-22a-Spirosten-3-one (I) on conversion to the enol acetate (II), followed by oxidation with monoperphthalic acid, yielded the 6β-hydroxy derivative (III). The structure of the latter was confirmed through an independent synthesis from diosgenin (VII). Similarly 6β-hydroxy-Δ^4-cholesten-3-one (XII, R = C_8H_{17}), 6β-hydroxytestosterone 17-acetate (XII, R = OAc), 6β-hydroxyprogesterone (XII, R = $COCH_3$) and 6β-hydroxydesoxycorticosterone 21-acetate (XII, R = $COCH_2OAc$) were prepared from the corresponding Δ^4-3-ketones (X).

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