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

STEROIDAL SAPOGENINS. XXIV.[1] SYNTHESIS AND SIDE CHAIN DEGRADATION OF Δ^{7}-22a-SPIROSTEN-3α-OL

M. VELASCO, J. RIVERA, G. ROSENKRANZ, FRANZ SONDHEIMER,
AND CARL DJERASSI[2]

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All of the syntheses of 11-oxygenated steroids from ring C unsubstituted precursors which have so far been reported from this and other laboratories (1) involve the oxidation of a $\Delta^{7,9,(11)}$-diene of the 5α (*allo*) series. It seemed of interest to investigate similar oxidations in the 5β (*normal*) series, particularly as applied to sapogenin derivatives, and it was necessary, therefore, to examine synthetic approaches to such dienes. The only hitherto described preparation[3] of a 5β-$\Delta^{7,9,(11)}$-diene from a steroid devoid of substituents in ring C is that of $\Delta^{7,9,(11)}$-22a-spirostadien-3α-ol[4] (2) and involved catalytic hydrogenation of $\Delta^{4,7,9,(11)}$-22a-spirostatrien-3-one followed by lithium aluminum hydride reduction. The present article is concerned with the investigation of an alternate approach through a Δ^{7}-en-3α-ol of the 5β-configuration (III).

It has recently been reported (3, 4) that catalytic hydrogenation of Δ^{4}-3-ketones of the sapogenin series in the presence of base affords in excellent yield the corresponding 3-keto-5β-dihydro derivatives. A similar hydrogenation of $\Delta^{4,7}$-22a-spirostadien-3-one (I) (2) now produced Δ^{7}-22a-spirosten-3-one (II), which upon reduction with lithium aluminum hydride[5] led to the desired Δ^{7}-22a-spirosten-3α-ol (IIIa), further characterized by the formation of a benzoate (IIIb) and acetate (IIIc). Degradation of the side chain *via* the oily $\Delta^{7,20,(22)}$-furostadiene-3α,26-diol diacetate was carried out in the usual manner (5), and yielded $\Delta^{7,16}$-pregnadien-3α-ol-20-one acetate (IV) which was hydrogenated catalytically to Δ^{7}-pregnen-3α-ol-20-one acetate (Va). Saponification and oxidation with chromium trioxide in acetone solution (6) gave Δ^{7}-pregnene-3,20-dione (Vc) which proved to be completely different from the corresponding 5α-derivative prepared by a similar oxidation from the known (5) Δ^{7}-allopregnen-3β-ol-20-one. Further confirmation of the 5β-configuration of the diketone Vc (and hence of II, III, and IV) was provided by catalytic hydrogenation of $\Delta^{4,7}$-pregnadiene-3,20-dione (VI) (7) which afforded Δ^{7}-pregnene-3,20-dione

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[1] Paper XXIII, Sondheimer, Yashin, Rosenkranz, and Djerassi, *J. Am. Chem. Soc.*, **74**, 2696 (1952).

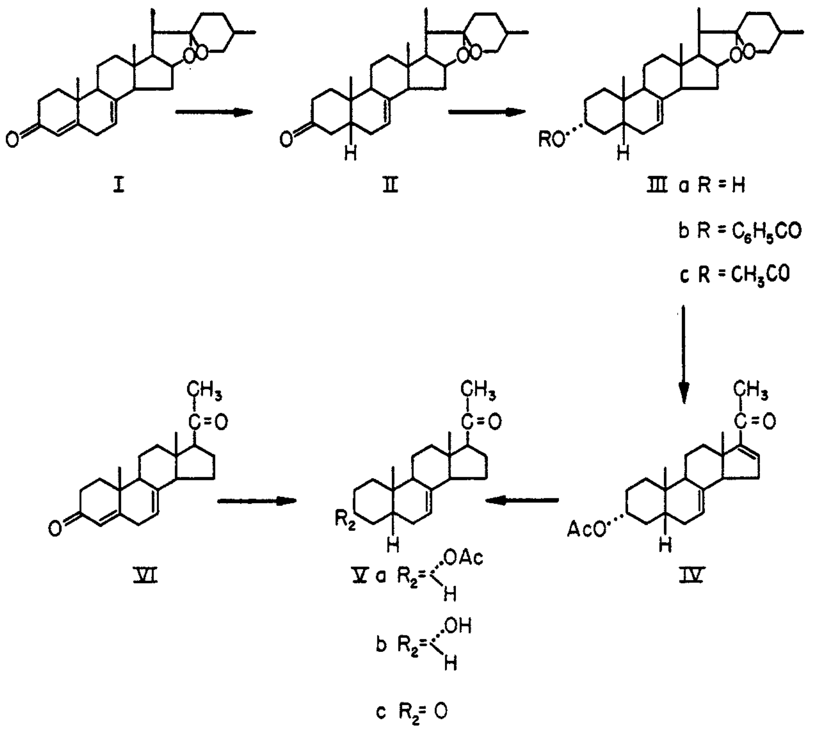
[2] Present address: Department of Chemistry, Wayne University, Detroit, Mich.

[3] Such dienes have, however, been prepared from 12-oxygenated steroids (cholic acid) by Fieser, Rajagopalan, Wilson, and Tishler [*J. Am. Chem. Soc.*, **73**, 4133 (1951)] and by Heusser, Eichenberger, Kurath, and Daellenbach [*Helv. Chim. Acta*, **34**, 2106 (1951)].

[4] Our sapogenin nomenclature [Rosenkranz and Djerassi, *Nature*, **166**, 104 (1950)] has been changed slightly ("22a" for "22-iso"; "5α" for "allo") in conformance with the recommendations of the Ciba Conference on Steroid Nomenclature (*Chemistry & Industry*, pp. SN1–11) (June 23, 1951).

[5] Such reductions of 5β-3-ketosteroids are known to lead essentially quantitatively to 3α-alcohols [*cf.* Shoppee and Summers, *J. Chem. Soc.*, 687 (1950)].

(Vc), identical in all respects with a specimen prepared by the first route. All attempts to introduce the 9–11 double bond into the Δ^7-mono-unsaturated derivatives III and V by means of mercuric acetate failed (starting material recovered), in marked contrast to the behavior of the corresponding Δ^7-5α-derivatives examined earlier (5, 8). This failure seems to be associated with the configuration at C-5; the alternate explanation that the Δ^7-double bond migrated during the catalytic hydrogenation in a *basic* medium to the $\Delta^{8,14}$-position appears extremely unlikely since even the *acid*-catalyzed migration of such a double bond in the 5β-series proceeds unsatisfactorily (9).



EXPERIMENTAL[6]

Δ^7-22a-Spirosten-3-one (II). A solution of 61 g. of $\Delta^{4,7}$-22a-spirostadien-3-one (I) (2) in 1.2 l. of purified dioxane containing 1.24 g. of potassium hydroxide in 30 cc. of methanol was shaken in an atmosphere of hydrogen at room temperature under a slightly positive pressure for 3 hours with 12 g. of 5% palladized charcoal (American Platinum Works, Newark, N. J.). Filtration of the catalyst, concentration, and dilution with water yielded 51 g. of colorless crystals with m.p. 198–201°, $[\alpha]_D^{20}$ −34°. The analytical sample was recrystallized from methanol; m.p. 201–203°, $[\alpha]_D^{20}$ −33°, no selective absorption at 240 mμ, $\nu_{\max.}^{CS_2}$ 1716 cm.$^{-1}$ (saturated 3-ketone).

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[6] All melting points are uncorrected. Rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque for these measurements as well as for the infrared spectra (Perkin-Elmer model 12C spectrometer with sodium chloride prism) and to Srta. Amparo Barba for the microanalyses.

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

Found: C, 78.57; H, 10.02.

The *oxime* after recrystallization from methanol exhibited m.p. 229–231°.

Anal. Calc'd for $C_{27}H_{41}NO_3$: C, 75.82; H, 9.67.

Found: C, 75.78; H, 9.85.

Δ^7-*22a-Spirosten-3α-ol* (IIIa). A solution of 14 g. of the ketone II in 200 cc. of tetrahydrofuran was added dropwise to a solution of 7 g. of lithium aluminum hydride in 20 cc. of the same solvent. After refluxing was continued for one-half hour and working up in the usual manner, there was obtained 12.6 g. of colorless crystals with m.p. 206–209°. Further recrystallization from chloroform-methanol and acetone raised the m.p. to 214–215°, $[\alpha]_D^{20}$ −20°.

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

Found: C, 78.25; H, 10.35.

The *benzoate* IIIb was recrystallized from methanol; m.p. 200–201°, $[\alpha]_D^{20}$ +16°.

Anal. Calc'd for $C_{34}H_{46}O_4$: C, 78.71; H, 8.94.

Found: C, 78.59; H, 9.05.

The *acetate* IIIc was recrystallized from chloroform-methanol; m.p. 171–173° (capillary), 178–180° (Kofler), $[\alpha]_D^{20}$ +7°.

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

Found: C, 76.41; H, 9.92.

$\Delta^{7,16}$-*Pregnadien-3α-ol-20-one acetate* (IV). The conversion to the furostadiene derivative was accomplished by heating 5.0 g. of IIIa with 40 cc. of acetic anhydride at 200° for 8 hours in a sealed tube and the crude product was oxidized with 2.4 g. of chromium trioxide and hydrolyzed exactly as reported for the 5α-isomer (5); yield, 1.65 g., m.p. 128–130°. The analytical sample crystallized from methanol as colorless crystals with m.p. 131–133°, $[\alpha]_D^{20}$ +163°, $\lambda_{max.}^{EtOH}$ 238 and 318 mμ, log ε 4.11, 1.83, $\nu_{max.}^{CS_2}$ 1736 (acetate) and 1670 cm.$^{-1}$ (Δ^{16}-20-ketone).

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

Found: C, 77.27; H, 8.91.

Δ^7-*Pregnen-3α-ol-20-one acetate* (Va). The catalytic hydrogenation of the unsaturated ketone IV (2.25 g.) in 100 cc. of ethyl acetate was carried out at room temperature and atmospheric pressure for 2 hours with 0.4 g. of 10% palladized charcoal in the presence of 1 cc. of piperidine (*cf.* 5). Crystallization from pentane-chloroform afforded 1.85 g. of Va with m.p. 112–113°, $[\alpha]_D^{20}$ +140°, $\lambda_{max.}^{EtOH}$ 284 mμ, log ε 1.81, $\lambda_{max.}^{CS_2}$ 1736 (acetate) and 1708 cm.$^{-1}$ (20-ketone).

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

Found: C, 77.41; H, 9.82.

Saponification (methanolic potassium carbonate, 1 hour, steam-bath) proceeded in nearly quantitative yield and after recrystallization from pentane-chloroform produced colorless crystals of Δ^7-*pregnen-3α-ol-20-one* (Vb) with m.p. 187–189°, $[\alpha]_D^{20}$ +126°, $\nu_{max.}^{nujol}$ 1700 cm.$^{-1}$ and free hydroxyl band.

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

Found: C, 79.93; H, 10.28.

Δ^7-*Pregnene-3,20-dione* (Vc). (*a*) *By oxidation of* Δ^7-*pregnen-3α-ol-20-one* (Vb). To a solution of 500 mg. of Vb in 50 cc. of acetone was added dropwise at 35° over a period of 3 minutes 1 cc. of a chromium trioxide stock solution (6) (6.6 g. of chromium trioxide, 5 cc. of water, and 5.3 cc. of conc'd sulfuric acid made up to 25 cc. with water) and stirring was continued for an additional minute. After addition of methanol, water was added and the product was extracted with ether, washed with water until neutral, dried, and evaporated. Crystallization from chloroform-pentane afforded 0.28 g. of the diketone Vc with m.p. 157–158°, $[\alpha]_D^{20}$ +110°, $\nu_{max.}^{nujol}$ 1718 and 1700 cm.$^{-1}$

Anal. Calc'd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62.

Found: C, 79.91; H, 9.35.

(*b*) *By hydrogenation of* $\Delta^{4,7}$-*pregnadiene-3,20-dione* (VI). The catalytic hydrogenation of 0.5 g. of the diketone VI (7) was carried out as described above for I with 20 cc. of dioxane, 10 mg. of potassium hydroxide, and 0.5 cc. of methanol and 50 mg. of palladized charcoal; yield, 0.44 g.; m.p. 154–156°, undepressed upon admixture with a specimen prepared according to (*a*), $[\alpha]_D^{20}$ +105°. The infrared spectra of samples prepared according to (*a*) and (*b*) were identical.

Δ^7-Allopregnene-3,20-dione. When 0.5 g. of Δ^7-allopregnen-3β-ol-20-one (5) was oxidized with chromium trioxide in acetone solution exactly as described above for Vb, there was isolated after crystallization from pentane-chloroform 0.34 g. of the diketone with m.p. 189–191° $[\alpha]_D^{20}$ +72°.

Anal. Calc'd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62.
Found: C, 80.50; H, 9.82.

SUMMARY

Catalytic hydrogenation of $\Delta^{4,7}$-22a-spirostadien-3-one followed by reduction with lithium aluminum hydride produces Δ^7-22a-spirosten-3α-ol, which upon degradation of the side chain leads to $\Delta^{7,16}$-pregnadien-3α-ol-20-one acetate. Catalytic hydrogenation of the Δ^{16}-double bond, saponification, and oxidation yields Δ^7-pregnene-3,20-dione, which can also be obtained by hydrogenation of $\Delta^{4,7}$-pregnadiene-3,20-dione. The Δ^7-unsaturated derivatives with the 5β-configuration cannot be dehydrogenated with mercuric acetate to the corresponding $\Delta^{7,9(11)}$-dienes.

LAGUNA MAYRAN 413
MEXICO CITY 17, D. F., MEXICO

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