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

Steroidal Sapogenins. XXX.[1] Synthesis and Side Chain Degradation of 22a,5β-Spirostan-3α-ol-11-one Acetate

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

RECEIVED APRIL 13, 1953

The chemical conversion of a ring C unsubstituted steroid ("diosgenin") to cortisone *via* intermediates of the desirable 5β ("normal") series is described. $\Delta^{7,9(11)}$-22a,5β-Spirostadien-3α-ol acetate (I), obtainable from "diosgenin," has been oxidized by Fieser's sodium dichromate procedure to a mixture of Δ^{8}-22a,5β-spirosten-3α-ol-7,11-dione acetate (II) and $\Delta^{9(11)}$-22a,5β-spirosten-3α-ol-7-one acetate (III). The former on zinc reduction yielded the saturated diketone IV, from which the 7-ketone function was removed by conversion to the ethylenethioketal V and nickel desulfurization. The resulting 22a,5β-spirostan-3α-ol-11-one acetate (VI) on side chain degradation furnished Δ^{16}-pregnen-3α-ol-11,20-dione acetate (VII) and thence on hydrogenation pregnan-3α-ol-11,20-dione acetate (VIII). The latter substance had previously been transformed to cortisone by Gallagher and co-workers.

A number of methods for converting steroidal $\Delta^{7,9(11)}$-dienes to 11-oxygenated derivatives have been shown to be applicable to the 5β ("normal") series, as exemplified with methyl $\Delta^{7,9(11)}$-3α-acetoxycholadienate.[3] The latter substance had been derived from a C-12 oxygenated steroid, cholic acid.[3a,e] With the recent synthesis in these laboratories of the 5β-$\Delta^{7,9(11)}$-diene (I) of the 22a-spirostane series[4] from "diosgenin," the way was opened, by use of any of the above mentioned oxygenation methods, to convert a ring C unsubstituted steroid to cortisone chemically by way of intermediates with the desirable 5β-configuration. In this paper we wish to describe the realization of this objective by use of the C-11 oxygen introduction method described by Fieser, *et al.*,[3a,c] in the cholanic acid series.

$\Delta^{7,9(11)}$-22a,5β-Spirostadien-3α-ol acetate (I)[4] on oxidation with sodium dichromate in benzene–acetic acid[3a,5] furnished two crystalline substances. One was easily recognized as the Δ^{8}-7,11-dione II by its yellow color and characteristic ultraviolet maximum at 272 mμ. The other, containing only one additional oxygen atom, showed a saturated carbonyl band in the infrared and no appreciable absorption in the ultraviolet. It was formulated as the $\Delta^{9(11)}$-7-one III by analogy with a similar product obtained by Fieser, *et al.*,[3a,b,c] in the cholanic acid series, and in view of its very ready isomerization with base to an α,β-unsaturated ketone, presumably the Δ^{8}-7-ketone IX.

The Δ^{8}-7,11-dione II on zinc reduction furnished the corresponding saturated diketone IV, from which the superfluous C-7 oxygen function was removed through conversion to the cycloethylene mercaptal V and subsequent nickel desulfurization.

The resulting 22a,5β-spirostan-3α-ol-11-one acetate (VI) was subjected to side chain degradation under the same conditions as had been used for the corresponding 3β,5α-isomer,[6] no attempt being made to characterize the intermediate "furosten" and "diosone." The Δ^{16}-pregnen-3α-ol-11,20-dione acetate (VII) thus obtained was hydrogenated to pregnan-3α-ol-11,20-dione acetate (VIII), the further transformations of which to cortisone had been described previously by Gallagher and co-workers.[7]

Experimental[8]

Δ^{8}-22a,5β-Spirosten-3α-ol-7,11-dione Acetate (II) and $\Delta^{9(11)}$-22a,5β-Spirosten-3α-ol-7-one Acetate (III) by Dichromate Oxidation of $\Delta^{7,9(11)}$-22a,5β-Spirostadien-3α-ol Acetate (I).—A solution of 17.5 g. of sodium dichromate dihydrate in 150 cc. of glacial acetic acid was added dropwise with stirring during *ca.* 30 minutes to 10 g. of $\Delta^{7,9(11)}$-22a,5β-spirostadien-3α-ol acetate (I)[4] dissolved in 150 cc. of benzene kept at 15°. After being allowed to stand overnight at room temperature, the mixture was diluted with water, the aqueous layer washed well with ether, and the combined organic extracts were washed with sodium carbonate solution and water, dried and evaporated. The residue was chromatographed on 500 g. of ethyl acetate-washed alumina, and the fractions eluted with benzene were crystallized from chloroform–methanol. This yielded 1.2 g. (12%) of $\Delta^{9(11)}$-22a,5β-spirosten-3α-ol-7-one acetate (III) with m.p. 223–225°, $[\alpha]^{20}D$ −59°, ν_{max}^{mull} 1736 (ester) and 1700 cm.$^{-1}$ (satd. ketone).

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.23; H, 9.20.

The mother liquors after the removal of III were concentrated and crystallized from methanol. In this way 1.25 g. (12%) of the light yellow Δ^{8}-22a,5β-spirosten-3α-ol-7,11-dione acetate (II) with m.p. 146–148° was obtained. The analytical sample was crystallized from chloroform–methanol and showed m.p. 151–153°, $[\alpha]^{20}D$ −14°, λ_{max} 272 mμ, log ε 3.93, ν_{max}^{mull} 1736 and 1674 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{40}O_6$: C, 71.87; H, 8.32. Found: C, 72.06; H, 8.47.

22a,5β-Spirostan-3α-ol-7,11-dione Acetate (IV).—A solution of 14.8 g. of the Δ^{8}-7,11-dione II in 600 cc. of acetic acid was heated with stirring on the steam-bath (91°) with 0 g. of zinc dust for 3 hours. The metal was removed by filtration, washed with hot acetic acid, and the filtrate was diluted with water. The resulting saturated 7,11-dione IV after crystallization from chloroform–pentane weighed 7.9

(1) Paper XXIX, C. Djerassi, A. J. Lemin, H. Martinez, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **75**, in press (1953).

(2) Department of Chemistry, Wayne University, Detroit 1, Michigan.

(3) (a) L. F. Fieser, J. E. Herz and W. Huang, THIS JOURNAL, **73**, 2397 (1951); (b) L. F. Fieser, J. C. Babcock, J. E. Herz, W. Huang and W. P. Schneider, *ibid.*, **73**, 4053 (1951); (c) L. F. Fieser, W. Huang and J. C. Babcock, *ibid.*, **75**, 116 (1953); (d) L. F. Fieser, W. P. Schneider and W. Huang, *ibid.*, **75**, 124 (1953); (e) H. Heusser, K. Eichenberger, P. Kurath, H. R. Dällenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951); (f) C. Djerassi, O. Mancera, M. Velasco, G. Stork and G. Rosenkranz, THIS JOURNAL, **74**, 3321 (1952).

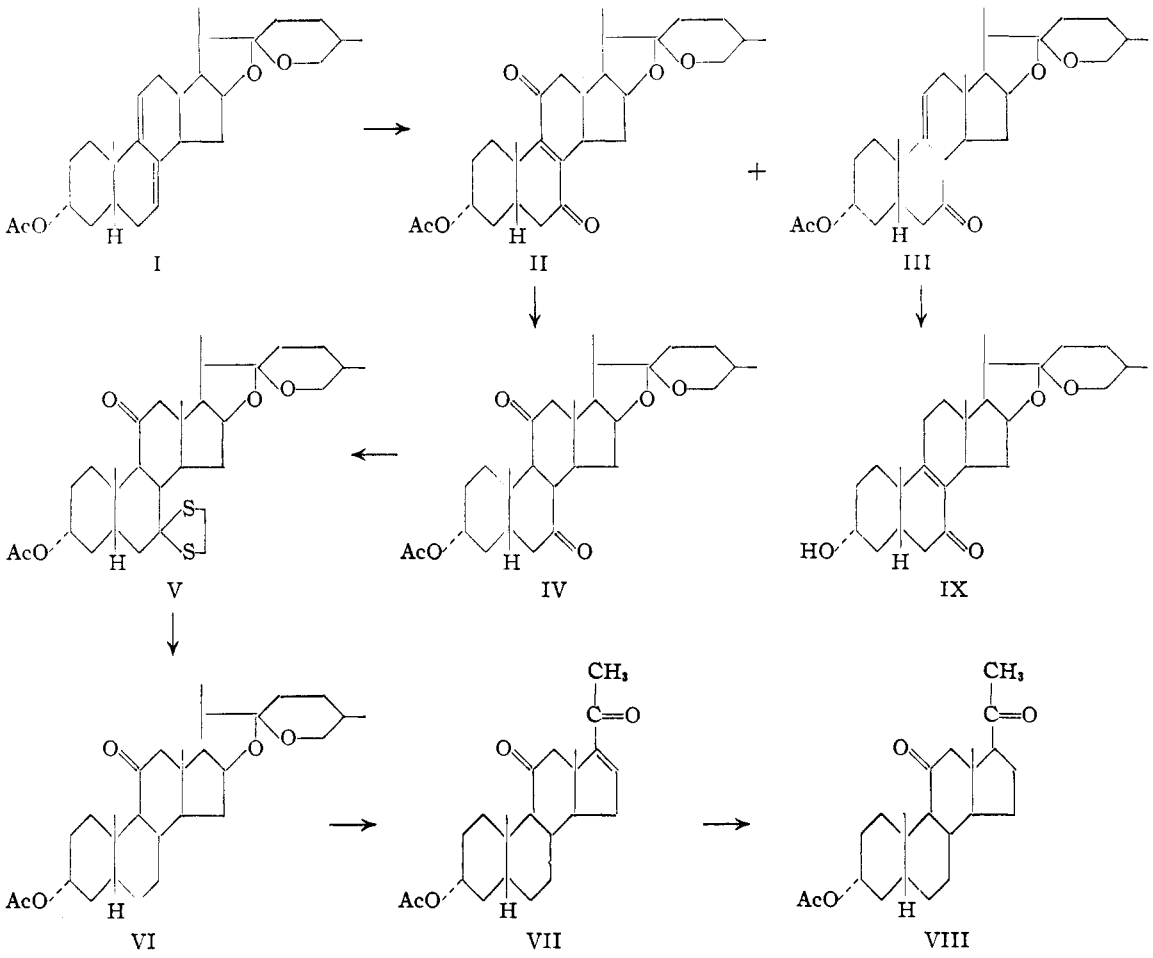
(4) R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 4654 (1951).

(5) L. F. Fieser and J. E. Herz, *ibid.*, **75**, 121 (1953).

(6) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952); *cf.* E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951).

(7) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952).

(8) Melting points are uncorrected, except those marked (Kof.) which were determined on a Kofler micro hot-stage. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution; infrared spectra were obtained with a Perkin–Elmer model 12C single beam spectrophotometer with sodium chloride prism. We are indebted to Srta. Paquita Revaque for these measurements and to Srta. Amparo Barba for the microanalyses.



g. and had m.p. 174–176°. Further crystallization furnished the analytical sample, m.p. 185–186°, no appreciable absorption in the ultraviolet, ν_{max}^{mull} 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.86; H, 8.76.

22a,5β-Spirostan-3α-ol-11-one-7-cycloethylenemercaptal Acetate (V).—A solution of 7.9 g. of the saturated 7,11-diketone IV in 100 cc. of glacial acetic acid containing 7.9 cc. of ethanedithiol and 4 cc. of a saturated solution of hydrogen bromide in acetic acid was allowed to stand at room temperature (21°) for 4 hours. The thioketal which had precipitated was collected; the filtrate was diluted with water, extracted with ethyl acetate, and the washed organic layer was dried, evaporated, and the residue crystallized from ether. This procedure yielded a total of 3.95 g. of the thioketal V with m.p. 275–278°. An additional 0.26 g. was obtained by chromatography of the mother liquors on ethyl acetate-washed alumina. The analytical specimen was crystallized from ether and had m.p. 285–287°, $[\alpha]^{20}D$ −23°, $\nu_{max}^{CS_2}$ 1736 and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{46}O_5S_2$: C, 66.15; H, 8.24; S, 11.39. Found: C, 66.16; H, 8.29; S, 10.97.

22a,5β-Spirostan-3α-ol-11-one Acetate (VI).—A solution of 3.8 g. of the thioketal V dissolved in 3 l. of ethanol (previously distilled over Raney nickel) was boiled under reflux for 6 hours with *ca.* 50 g. of W-2 Raney nickel. The metal was removed by filtration, and washed well with hot alcohol. The filtrate was evaporated to dryness, dissolved in chloroform, and washed with hydrochloric acid, sodium carbonate and water. Drying, evaporation and crystallization of the residue from ether furnished 2.1 g. of the 11-ketone VI with m.p. 172–176°. The analytical sample showed m.p. 179–181°, 186–187° (Kof.), $[\alpha]^{20}D$ +6°, $\nu_{max}^{CS_2}$ 1736 and 1714 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.94; H, 9.39.

Δ^{16}-Pregnen-3α-ol-11,20-dione Acetate (VII).—A solution of 2.3 g. of 22a,5β-spirostan-3α-ol-11-one acetate in 20 cc. of acetic anhydride was heated in a bomb tube at *ca.* 180° for 8 hours, poured into water, extracted with ether, washed well with sodium carbonate solution and water, dried and evaporated. The resulting oily "furosten" was oxidized with chromium trioxide and the oily "diosone" subjected to bicarbonate saponification exactly as described in the degradation of Δ^7-22a,5α-spirosten-3β-ol acetate.[9] Crystallization of the product from chloroform–hexane furnished 0.43 g. of Δ^{16}-pregnen-3α-ol-11,20-dione acetate with m.p. 197–198°, 205–206° (Kof.), λ_{max} 236 and 312 mμ, log ε 4.12 and 1.79, $\lambda_{max}^{CHCl_3}$ 1736, 1718, 1700 and 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.35; H, 8.43.

Pregnan-3α-ol-11,20-dione Acetate (VIII).—The Δ^{16}-dione VII (0.18 g.) in ethyl acetate (20 cc.) was hydrogenated over 0.02 g. of 10% palladized charcoal at room temperature and atmospheric pressure. Crystallization of the product from acetone–hexane yielded 0.14 g. of the saturated dione VIII with m.p. 133–134°, $[\alpha]^{20}D$ +133°, $\nu_{max}^{CHCl_3}$ 1736, 1720 and 1700 cm.$^{-1}$. A sample obtained by an independent route[10] showed m.p. 134–135°, $[\alpha]^{20}D$ +135°, and identity was established by mixture melting point and infrared comparison.

Δ^8-22a,5β-Spirosten-3α-ol-7-one (IX).—The Δ$^{9(11)}$-7-one III (0.30 g.) dissolved in 25 cc. of methanol was heated under reflux for 1 hour with 0.30 g. of potassium hydroxide under an atmosphere of nitrogen. Water was added, the solid product was collected and crystallized from chloroform–methanol. The Δ^8-7-one weighed 0.21 g. and had m.p. 212–214°, 220–221° (Kof.), $[\alpha]^{20}D$ −77°, λ_{max} 252 mμ, log ε 4.12, ν_{max}^{mull} 1674 cm.$^{-1}$ and free hydroxyl band.

(9) C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

(10) O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **75**, 1286 (1953).

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.97; H, 9.28.

The corresponding enol acetate, **$\Delta^{7,9(11)}$-22a-5β-spirostadiene-3α,7-diol diacetate** was obtained by slowly concentrating a solution of 0.40 g. of the Δ^8-7-one IX in 25 cc. of benzene containing 2 cc. of isopropenyl acetate and 0.04 g. of *p*-toluenesulfonic acid to a volume of 10 cc. over a period of 6 hours, 1-cc. portions of isopropenyl acetate having been added after 2 hours and 4 hours refluxing. After evaporating to dryness *in vacuo*, the residue was taken up in ether, washed with sodium bicarbonate solution and water, dried and evaporated. Crystallization of the residue from ethyl acetate–pentane yielded 0.39 g. of the enol acetate with m.p. 165–170°. Further crystallization from this solvent pair gave the analytical sample, m.p. 172–174°, 179–181° (Kof.), $[\alpha]^{20}D$ +76°, λ_{max} 242 mμ, log ϵ 4.20, $\nu_{max}^{CHCl_3}$ 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{44}O_6$: C, 72.62; H, 8.65. Found: C, 72.93; H, 8.81.

MEXICO CITY 17, D.F.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Preparation and Dehydrohalogenation of 4-Halo-3-ketosteroids

BY R. P. HOLYSZ

RECEIVED MARCH 19, 1953

Bromination of 17α-hydroxy-21-acetoxypregnane-3,11,20-trione (dihydrocortisone acetate) in buffered acetic acid solution has been found by subsequent investigators to give lower yields of the corresponding 4-bromo derivative than first reported in the literature. The bromination of dihydrocortisone acetate was improved somewhat by using dimethylformamide as a solvent. Employing this modification 4-bromodihydrocortisone acetate was isolated in 70–80% yields. Brominations of pregnane-3,11,20-trione in the dimethylformamide system and in the buffered acetic acid system were compared. Two monobromopregnanetriones were isolated and characterized. On the basis of analysis, infrared data and dehydrohalogenation studies the two isomers were believed to be relatively pure 4α- and 4β-bromo compounds; the 4α-bromopregnane-3,11,20-trione was obtained in buffered acetic acid solution while the 4β-bromopregnane-3,11-20-trione was obtained in dimethylformamide solution. When certain metal halides, particularly lithium chloride or bromide, and 4-bromo-(or 4-chloro-) dihydrocortisone acetate were heated together in dimethylformamide 60–80% yields of cortisone acetate resulted. Beryllium, magnesium or aluminum chlorides in dimethylformamide or dimethylacetamide dehydrobrominated 4-bromodihydrocortisone acetate almost as well as lithium chloride under the particular conditions investigated; whereas, sodium, ammonium or calcium chlorides in formamide–dimethylformamide, or mercuric chloride in dimethylformamide gave no sigficant amounts of cortisone acetate. Lithium and boron fluorides also failed to effect dehydrohalogenation. Semiquantitative rate studies have been made.

Discussion

The usual method[1] for the bromination of 17α-hydroxy-21-acetoxypregnane-3,11,20-trione in buffered acetic acid solution was reported to give 70% yields of 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione. However, later investigators[2,3] reported somewhat lower yields of 4-bromo compound of quality suitable for subsequent dehydrobromination in good yields. In this Laboratory 4-bromo-17α-hydroxy-21-acetoxypregnane-3,-11,20-trione of $[\alpha]D$ +101° was obtained in about 60% yield from dihydrocortisone acetate when the conditions reported by Mattox and Kendall were used.

In view of these results an investigation was undertaken to discover better conditions and/or better solvent systems for this important step in the cortisone synthesis.

Bromination of dihydrocortisone acetate in dimethylformamide gave 70–80% yields of 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione; however, the specific rotations of the crude 4-bromo compound varied from +103 to +111°, and the bromine content was generally about 1% below the theoretical value. Purification of the crude bromo compound ultimately yielded an analytical sample having an $[\alpha]D$ +112°, some eight to ten degrees higher than the specific rotation reported in the literature.[1-3] The somewhat low bromine content of the crude reaction product may be attributed to the presence of the amide solvent which was difficult to remove under relatively mild drying conditions. In some instances a small amount (*ca.* 5%) of unreacted starting material was detected in the crude bromination product by means of paperstrip chromatography and infrared spectroscopy. Other isomers of monobromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione such as described by Mattox[1] and Hershberg[2] have not been isolated; however, their presence in mother liquors was suggested on the basis of bromine assay and specific rotation data. Examination of these 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-triones of $[\alpha]D$ +112 by phase distribution methods[4] has failed to demonstrate the presence of impurities. Dehydrohalogenation by the method of Mattox and Kendall[5] or by methods described in this report has given good yields of cortisone acetate.

Bromination of pregnane-3,11,20-trione in cold buffered acetic acid solution yielded a mixture of brominated pregnanetriones, from which a 4-bromopregnane-3,11,20-trione ($[\alpha]D$ +95°) was isolated in approximately 35% yield. Bromination of pregnane-3,11,20-trione in dimethylformamide solution at room temperature also resulted in a mixture of bromopregnanetriones, from which a 4-bromopregnane-3,11,20-trione ($[\alpha]D$ +136°) was isolated in comparable yield. The melting points

(1) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **185**, 593 (1950); **188**, 287 (1951).

(2) E. B. Hershberg, C. Gerold and E. P. Oliveto, THIS JOURNAL, **74**, 3849 (1952).

(3) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952).

(4) R. M. Herriott, *Chem. Revs.*, **30**, 413 (1942); A. Findlay, "The Phase Rule and its Applications," Longmans, Green and Co., New York, N. Y., 1938.

(5) V. R. Mattox and E. C. Kendall, THIS JOURNAL, **70**, 882 (1948).