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

Steroidal Sapogenins. XXVIII.[1] The Reaction of Peracids with Enol Acetates of Δ^8-7-Keto and Δ^8-11-Keto Steroidal Sapogenins

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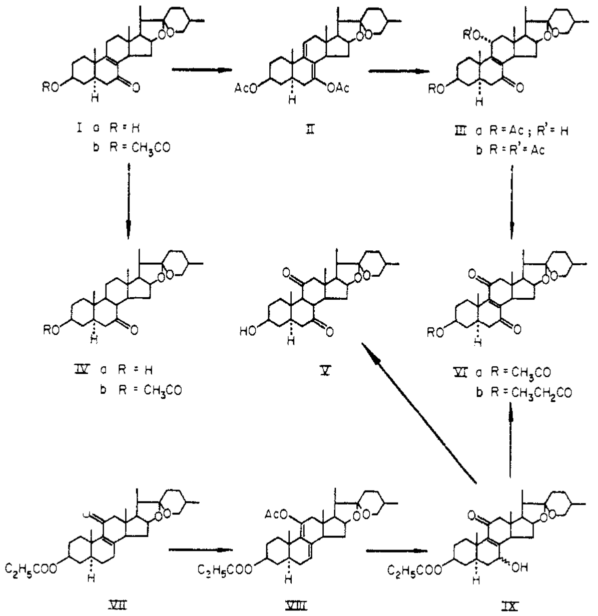
Δ^8-22a,5α-Spirosten-3β-ol-7-one acetate (I) upon conversion to the enol acetate followed by oxidation with perbenzoic acid leads to the corresponding 11α-hydroxy derivative IIIa, which can be oxidized to Δ^8-22a,5α-spirosten-3β-ol-7,11-dione (VI). A similar reaction sequence with the analogous Δ^8-11-ketone (VII) affords the Δ^8-11-one-7-ol IX, which can be either oxidized with sodium dichromate to the Δ^8-7,11-dione VI or isomerized with *t*-butoxide to the saturated 7,11-diketone V.

Recently, there was reported a method for the conversion of Δ^8-7-ketones to the corresponding 11α-hydroxy derivatives involving transformation into the enol acetate and oxidation with perbenzoic or monoperphthalic acid. As illustrated in the allopregnane[3,4] and cholanic acid series,[4] this procedure was applicable to steroids with both the 5α and 5β configuration. We should now like to report on similar experiments in the sapogenin series.

The starting material in the earlier study, Δ^8-allopregnen-3β-ol-7,20-dione, was obtained[3,5] from the mother liquors of the performic acid oxidation[6] of the corresponding $\Delta^{7,9(11)}$-diene. A similar investigation of the mother liquors from the performic acid oxidation[5] of $\Delta^{7,9(11)}$-22a,5α-spirostadien-3β-ol acetate has now resulted in the isolation of Δ^8-22a,5α-spirosten-3β-ol-7-one (Ia) and it has thus been possible to investigate the applicability of the earlier described[3,4] enol acetate–peracid procedure to the sapogenin series. The structure of the starting material Ia was proved readily by catalytic hydrogenation to the known[7] 22a,5α-spirostan-3β-ol-7-one (IVa), and the conversion of I to the oily enol acetate II was carried out in the standard manner[4] with isopropenyl acetate. In contrast to the results obtained in the allopregnane series, oxidation with monoperphthalic acid was quite unsatisfactory, but oxidation with perbenzoic acid readily yielded the expected Δ^8-22a,5α-spirostene-3β,11α-diol-7-one 3-monoacetate (IIIa), further characterized by acetylation to the known 3,11-diacetate IIIb[8] and by oxidation to the yellowish Δ^8-7,11-dione (VIa).[8]



It appeared of interest to examine the course of this reaction with the isomeric Δ^8-11-ketone, the preparation of which (in the form of its propionate VII) has recently been described.[1,9] Conversion to the enol acetate could lead either to the 11-acetoxy-$\Delta^{7,9(11)}$-diene VIII or to the isomeric homoannular $\Delta^{8(14),9(11)}$-diene, and some support for the latter possibility can be found in the observation that the Δ^8-11-ketone VII is readily isomerized at C-14 by means of base.[1,9] However, the oily enol acetate, obtained in the usual manner, possessed an ultraviolet absorption maximum at 240 mμ, thus excluding the homoannular structure and demonstrating that the enol acetate possessed the heteroannular diene system VIII. Reaction with perbenzoic or monoperphthalic acid proceeded in markedly lower yield and furnished an α,β-unsaturated ketone which was shown to possess structure IX, Δ^8-22a,5α-spirostene-3β,7-diol-11-one 3-propionate, on the basis of the following reactions. Oxidation with dichromate led to a yellow diketone VIb with an ultraviolet absorption maximum at 270 mμ, characteristic of Δ^8-7,11-diones, while brief refluxing with potassium *t*-butoxide in *t*-butyl alcohol solution[10] resulted in isomerization to the known[10] 22a,5α-spirostan-3β-ol-7,11-dione (V), as was to be expected on the basis of the known behavior of III.[10] It is of interest to note that while the isomerization of III to the saturated 7,11-diketone V cannot be accomplished with acid since dehydration occurs to a $\Delta^{8(14),15}$-dien-7-one,[11] such

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[1] Paper XXVII, C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **75**, 3496 (1953).

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[3] C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, THIS JOURNAL, **73**, 4496 (1951).

[4] C. Djerassi, O. Mancera, M. Velasco, G. Stork and G. Rosenkranz, *ibid.*, **74**, 3321 (1952).

[5] C. Djerassi, O. Mancera, J. Romo and G. Rosenkranz, *ibid.*, **75**, 3505 (1953).

[6] *Cf.* G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951).

[7] R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **69**, 2178 (1947); R. E. Marker and J. Lopez, *ibid.*, **69**, 2401 (1947).

[8] C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

[9] F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952).

[10] J. Romo, G. Stork, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2918 (1952).

[11] A. J. Lemin, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1745 (1953).

conditions could be used, albeit in poor yield, for the transformation of the Δ^8-11-one-7-ol IX to the 7,11-dione V.

Experimental[12]

Δ^8-22a,5α-Spirosten-3β-ol-7-one (Ia).—The crude crystalline product (m.p. *ca.* 270°) from the performic acid oxidation[5] of $\Delta^{7,9(11)}$-22a,5α-spirostadien-3β-ol acetate[13] was saponified in the usual manner[5,8] and furnished Δ^8-22a,5α-spirostene-3β,11α-diol-7-one[8] in yields of 70–90%. Accumulated mother liquors (125 g.) after removal of the crystalline saponification product were chromatographed on 2.5 kg. of ethyl acetate washed alumina. The benzene–ether and ether eluates afforded 43 g. of the desired unsaturated ketone Ia with m.p. 170–174°, while from the chloroform-acetone eluates there was isolated 56 g. more of Δ^8-22a,5α-spirostene-3β,11α-diol-7-one.[8] The analytical sample of the Δ^8-7-ketone Ia was obtained from chloroform–hexane; m.p. 172–174°, $[\alpha]^{20}\text{D}$ −68°, $\lambda_{\max}^{\text{EtOH}}$ 252 mμ, log ϵ 4.03, $\nu_{\max}^{\text{CHCl}_3}$ 1660 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.32; H, 9.71.

The acetate Ib, prepared in the usual manner (acetic anhydride–pyridine, 1 hour, steam-bath), was recrystallized from acetone–hexane, whereupon it exhibited m.p. 208–210°, $[\alpha]^{20}\text{D}$ −87°, $\nu_{\max}^{\text{CHCl}_3}$ 1736 and 1656 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.75; H, 8.90.

22a,5α-Spirostan-3β-ol-7-one (IVa).—A solution of 3.0 g. of the unsaturated ketone Ia in 200 cc. of ethanol was hydrogenated overnight at room temperature and atmospheric pressure with 0.5 g. of 10% palladized charcoal. Filtration of the catalyst, evaporation of the filtrate to dryness and recrystallization of the residue from chloroform–hexane afforded 2.5 g. of **22a,5α-spirostan-3β-ol-7-one (IVa)** with m.p. 212–214°, $[\alpha]^{20}\text{D}$ −110°, no selective absorption in the ultraviolet, $\nu_{\max}^{\text{CHCl}_3}$ 1700 cm.$^{-1}$ and free hydroxyl band; lit.[7] m.p. 214–215°, no rotation given.

Acetylation and recrystallization from chloroform–methanol furnished the **acetate** IVb with m.p. 208–210°, $[\alpha]^{20}\text{D}$ −100°.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.40; H, 9.65.

Since the literature value[7] for this acetate is m.p. 218°, an authentic sample[7] was prepared by catalytic hydrogenation (palladized charcoal in ethanol solution) of Δ^5-22a-spirosten-3β-ol-7-one acetate.[14] The resulting product exhibited m.p. 209–210°, undepressed upon admixture with a sample of IVb prepared as indicated above, $[\alpha]^{20}\text{D}$ −104°.

Δ^8-22a,5α-Spirostene-3β,11α-diol-7-one 3-Monoacetate (IIIa).—A mixture of 6.0 g. of the unsaturated ketone Ib, 0.9 g. of *p*-toluenesulfonic acid, 20 cc. of isopropenyl acetate and 100 cc. of benzene was concentrated by slow distillation over a period of 4 hours to a volume of *ca.* 60 cc., 5 cc. of isopropenyl acetate having been added at the end of the second hour and an additional 3 cc. at the end of the third hour. The solvent was removed *in vacuo*, the residue was dissolved in ether, washed with sodium bicarbonate solution and water, dried and evaporated, leaving an oil which possessed an ultraviolet absorption maximum at 240 mμ, log ϵ 4.19. The oily enol acetate II was kept at room temperature for 48 hours with 1.2 equivalents of perbenzoic acid in 50 cc. of chloroform. After washing until neutral and evaporating, the residue was crystallized from hexane–acetone yielding 2.5 g. of colorless crystals with m.p. 170–174°. Chromatography of the mother liquors on 100 g. of ethyl acetate washed alumina and elution with benzene–ether yielded an additional 0.96 g. with m.p. 172–177°. The analytical sample of the monoacetate IIIa was obtained from acetone–hexane; m.p. 177–179°, $[\alpha]^{20}\text{D}$ −32°, $\lambda_{\max}^{\text{EtOH}}$ 252 mμ, log ϵ 4.10.

Anal. Calcd. for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.19; H, 8.81.

Acetylation led to the 3,11-diacetate IIIb with m.p. 169–171°, identified with an authentic specimen[8] by a mixture melting point and infrared comparison.

Δ^8-22a,5α-Spirosten-3β-ol-7,11-dione Acetate (VIa).—The above 3-monoacetate IIIa (3.3 g.) in 120 cc. of glacial acetic acid was oxidized at room temperature for 2 hours with a solution of 0.49 g. of chromium trioxide in 25 cc. of 80% acetic acid. Dilution with water, filtration and recrystallization from chloroform–methanol yielded 2.8 g. of yellowish crystals of the unsaturated diketone VIa with m.p. 224–225° (Kofler),[15] undepressed upon admixture with an authentic[8] sample, $\lambda_{\max}^{\text{EtOH}}$ 270 mμ, log ϵ 3.95; identity was further established by infrared comparison.

Δ^8-22a,5α-Spirostene-3β,7-diol-11-one 3-Propionate (IX).—The enol acetate VIII was prepared exactly as described above for IIIa from 2.5 g. of Δ^8-22a,5α-spirosten-3β-ol-11-one propionate (VII)[1,9]; yield, 2.85 g. of pale yellow oil, $\lambda_{\max}^{\text{EtOH}}$ 240 mμ, log ϵ 4.16. The entire crude enol acetate VIII was treated with 1.1 equivalents of monoperphthalic acid in 25 cc. of ether for 48 hours in the above described manner. The crude oily oxidation product possessed $\lambda_{\max}^{\text{EtOH}}$ 248 mμ, log ϵ 3.93 and resisted attempts at crystallization. It was chromatographed on 125 g. of ethyl acetate washed alumina, and the benzene–ether eluates were combined and recrystallized from acetone–hexane, yielding 0.32 g. of colorless crystals of the Δ^8-11-one-7-ol IX with m.p. 197–199° (Kofler), $[\alpha]^{20}\text{D}$ +56°, $\lambda_{\max}^{\text{EtOH}}$ 252 mμ, log ϵ 4.09, $\nu_{\max}^{\text{CHCl}_3}$ 1718, 1700 and 1656 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{44}O_6$: C, 71.97; H, 8.86. Found: C, 71.88; H, 8.77.

Δ^8-22a,5α-Spirosten-3β-ol-7,11-dione 3-Propionate (VIb).—To a solution of 0.25 g. of the above unsaturated ketol IX in 10 cc. of benzene was added dropwise with stirring at 15° a solution of 0.5 g. of sodium dichromate dihydrate in 10 cc. of acetic acid and the mixture was allowed to stand overnight. After dilution with water, addition of ether and washing in the usual manner, the solvent was removed and the residue was recrystallized twice from chloroform–methanol yielding 0.19 g. of the yellowish unsaturated diketone VIb with m.p. 205–207°, $[\alpha]^{20}\text{D}$ −12°, $\lambda_{\max}^{\text{EtOH}}$ 270 mμ, log ϵ 3.96, $\nu_{\max}^{\text{CHCl}_3}$ 1730 and 1684 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{42}O_6$: C, 72.26; H, 8.49. Found: C, 72.11; H, 8.62.

22a,5α-Spirostan-3β-ol-7,11-dione (V). (a) With Potassium *t*-Butoxide.—A solution of 0.5 g. of the unsaturated propionate IX and 0.5 g. of potassium in 60 cc. of *t*-butyl alcohol was refluxed for 30 min., poured into water, acidified, concentrated under reduced pressure and extracted with ether. The ether residue was directly saponified with methanolic potassium hydroxide (1 hour, steam-bath) and the product was isolated by dilution with water, filtration and recrystallization from acetone; yield 0.29 g., m.p. 272–275° (Kofler), undepressed upon admixture with an authentic sample,[10] no selective absorption in the ultraviolet.

(b) With Methanolic Hydrochloric Acid.—A solution of 0.3 g. of the propionate IX in 30 cc. of methanol containing 0.6 cc. of concd. hydrochloric acid was refluxed for 5 hours, concentrated to one-half its volume, diluted with water and extracted with ether. Chromatography of the ether extract on 12 g. of alumina and recrystallization of the benzene–ether (6:4) eluates from acetone afforded 0.05 g. of the saturated 7,11-diketone V with m.p. 272–274°, $[\alpha]^{20}\text{D}$ −59°. The infrared spectrum was identical with that of samples prepared according to (a) or from Δ^8-22a,5α-spirostene-3β,-11α-diol-7-one.[10]

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[12] Melting points are uncorrected except those marked "Kofler," which were determined on the Kofler block. Rotations were measured in chloroform, and ultraviolet absorption spectra in 95% ethanol solution; infrared spectra were obtained with a Perkin–Elmer model 12 C single beam spectrophotometer. Grateful acknowledgment is made to Srta. Paquita Revaque for these measurements and to Srta. Amparo Barba for the microanalyses. We are indebted to Srta. Carmen Velasco and Srta. Mercedes Velasco for technical assistance.

[13] G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1950).

[14] H. J. Ringold, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3318 (1952).

[15] Repetition of the earlier reported (ref. 8) capillary melting point 213–214° on the Kofler block now gave a value of 223–225°.