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

Steroids. LIII.[1] Steroidal Sapogenins. XXXII.[2] The Dehydration of 11α-Hydroxy Steroids

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11α-Hydroxy steroids of the 5α, of the 5β and of the Δ^4-3-one series have been dehydrated by means of phosphorus oxychloride in pyridine, as well as by treating the corresponding 11-*p*-toluenesulfonates with collidine. It was found in all cases that the $\Delta^{9(11)}$-dehydro compounds were produced.

11α-Hydroxy steroids may now be obtained from $\Delta^{7,9(11)}$-dienes and 7-acetoxy-$\Delta^{7,9(11)}$-dienes by chemical oxidation,[3] from 11-ketones by chemical reduction,[4] and, most simply, from ring C-unsubstituted steroids by microbiological oxidation[5] methods. In view of the ready availability of these 11α-hydroxylated compounds, it became of interest to study their dehydration, either by direct or indirect methods.

11β-Hydroxy steroids of the 5β ("normal") configuration on dehydration with phosphorus oxychloride and pyridine are known to yield almost exclusively the $\Delta^{9(11)}$-ethylenes,[6] whereas interaction with boiling hydrochloric acid and acetic acid gives in addition some of the Δ^{11}-compounds.[6b] The phosphorus oxychloride–pyridine method of dehydration is not applicable to 11β-hydroxy steroids containing the Δ^4-3-ketone system, since the latter is attacked by this combination. Such compounds, however, have been dehydrated by the hydrochloric acid–acetic acid procedure,[7] and in this case there are also indications that some of the Δ^{11}-ethylenes may have been formed (*vide infra*). The dehydration of 11β-hydroxy steroids of the 5α ("allo") configuration does not appear to have been studied previously, but has now been shown also to lead to the $\Delta^{9(11)}$-unsaturated compounds.

The predominant formation of $\Delta^{9(11)}$-ethylenes by dehydration of 11β-hydroxy steroids is fully in accord with Barton's postulate that in this type of ionic elimination reaction, the four centers participating in the reaction must lie in one plane for maximal ease of reaction. This state of affairs exists when the groupings that are eliminated (*viz.*, the 9α-hydrogen and 11β-hydroxyl in the present case) are both in the axial orientation.[8]

The dehydration of 11α-hydroxy steroids had not been investigated when the present study was initiated.[9] The first example examined by us was an 11α-hydroxy compound of the 5α ("allo") series, 22a-5α-spirostane-3β,11α-diol 3-monoacetate (I), prepared from the known diol[4a,10] by differential acetylation at C-3. Dehydration with phosphorus oxychloride in pyridine proceeded smoothly, and produced a homogeneous anhydrocompound which proved to be identical with the $\Delta^{9(11)}$-22a-5α-spirosten-3β-ol acetate (II) previously prepared in these laboratories[11] from hecogenin *via* the $\Delta^{9(11)}$-12-ketone III. An alternative dehydration procedure involves conversion of the 3β,11α-diol 3-monoacetate I to the 11-*p*-toluenesulfonate IV, which with boiling collidine yielded the same $\Delta^{9(11)}$-compound II in 72% yield. In neither case could any indications of the formation of the Δ^{11}-compound be found. $\Delta^{9(11)}$-22a-5α-Spirosten-3β-ol acetate (II) could moreover be obtained from 22a-5α-spirostane-3β,11β-diol 3-monoacetate (V)[10] by dehydration with phosphorus oxychloride–pyridine, and the latter dehydrating conditions therefore yield the same product from the equatorial 11α-ol (I) as from the axial 11β-ol (V). The identity of the $\Delta^{9(11)}$-ethylene (II) obtained by these routes with the known compound[11] was further substantiated through conversion to the previously described 9α,11α-oxide (VI).[10,11]

Dehydration experiments were next carried out

(1) Steroids. LII. C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, in press.

(2) Steroidal Sapogenins. XXXI. J. Herrán, G. Rosenkranz and F. Sondheimer, *Chemistry and Industry*, 824 (1953).

(3) *Inter al.* G. Rosenkranz, C. Djerassi, *et al.*, THIS JOURNAL, **73**, 3546, 4496 (1951); **74**, 1712, 3321 (1952); **75**, 3505 (1953); H. Heusser, R. Anliker, K. Eichenberger and O. Jeger, *Helv. Chim. Acta*, **35**, 936 (1952); F. S. Spring, *et al.*, *Chemistry and Industry*, 1035 (1951); 1102 (1952); *J. Chem. Soc.*, 2892, 2901, 4874 (1952); 778 (1953).

(4) (a) F. Sondheimer, G. Rosenkranz, C. Djerassi, *et al.*, THIS JOURNAL, **74**, 2696 (1952); **75**, 1282 (1953); (b) H. Heusser, R. Anliker and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952); (c) K. Heusler and A. Wettstein, *ibid.*, **37**, 398 (1953); (d) K. Heusler, H. Heusser and R. Anliker, *ibid.*, **36**, 652 (1953); (e) H. L. Herzog, E. B. Hershberg, *et al.*, THIS JOURNAL, **74**, 4470 (1952); **75**, 269, 1505 (1953); (f) S. Bernstein, R. Littell and J. H. Williams, *ibid.*, **75**, 1481 (1953).

(5) (a) D. H. Peterson and H. C. Murray, *ibid.*, **74**, 1871 (1952); (b) S. H. Eppstein, D. H. Peterson, H. M. Leight, H. C. Murray, A. Weintraub, L. M. Reineke and P. D. Meister, *ibid.*, **75**, 421 (1953), and previous papers in the series; (c) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 3711 (1952); (d) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, *ibid.*, **74**, 3962 (1952); (e) F. W. Kahnt, C. Meystre, R. Neher, E. Vischer and A. Wettstein, *Experientia*, **8**, 422 (1952).

(6) *Inter al.* (a) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943); (b) H. Reich and T. Reichstein, *ibid.*, **26**, 562 (1943); (c) A. Lardon and T. Reichstein, *ibid.*, **28**, 1420 (1945).

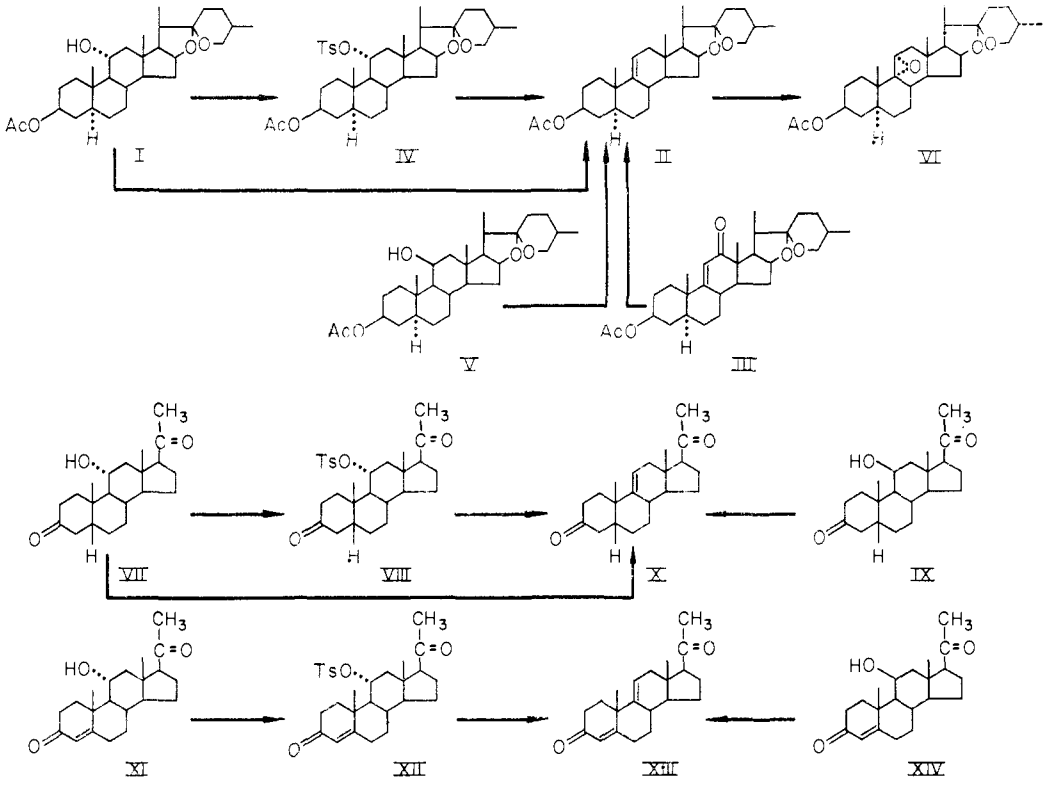
(7) Dehydration of 11β-hydroxyprogesterone: (a) C. W. Shoppee and T. Reichstein, *ibid.*, **24**, 351 (1941); (b) *cf.* P. Hegner and T. Reichstein, *ibid.*, **26**, 715 (1943). Dehydration of corticosterone 21-acetate: (c) C. W. Shoppee and T. Reichstein, *ibid.*, **26**, 1316 (1943).

(8) D. H. R. Barton, *Experientia*, **6**, 316 (1950); D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951). The suggestion made by D. H. R. Barton, O. Hassel, K. S. Pitzer and V. Prelog [*Nature*, **172**, 1096 (1953); *Science*, **119**, 49 (1954)] to substitute "axial" for "polar" has been adopted.

(9) After completion of the work described in this paper, J. Fried and E. F. Sabo (THIS JOURNAL, **75**, 2273 (1953)) reported that treatment of Δ^4-pregnene-11α,21-diol-3,20-dione 21-acetate 11-*p*-toluenesulfonate and of Δ^4-pregnene-11α,17α,21-triol-3,20-dione 21-acetate 11-*p*-toluenesulfonate with sodium acetate in boiling acetic acid yield the corresponding $\Delta^{4,9(11)}$-dienes. These results are in accord with our findings that *p*-toluenesulfonates of 11α-hydroxy steroids with boiling collidine furnish the $\Delta^{9(11)}$-ethylenes.

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

(11) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).



with pregnan-11α-ol-3,20-dione (VII),[5c,12] an 11α-hydroxy steroid of the 5β ("normal") series, and the results obtained were very similar to those in 5α-series. Thus, direct dehydration with phosphorus oxychloride and pyridine yielded a substance (though in this case only in poor yield), which was identical with that obtained *via* the 11-*p*-toluenesulfonate (VIII) through boiling with collidine, as well as with the phosphorus oxychloride–pyridine dehydration product of pregnan-11β-ol-3,20-dione (IX),[13] and which must therefore be $\Delta^{9(11)}$-pregnene-3,20-dione (X).

Finally the dehydration of 11α-hydroxy steroids was carried out with 11α-hydroxyprogesterone (XI),[5a,5c,5d,5e,14,15] a substance containing the Δ^4-3-ketone moiety. In this case the direct phosphorus oxychloride–pyridine method was inapplicable due to interaction with the unsaturated keto grouping, and the 11-*p*-toluenesulfonate (XII) was therefore prepared. The latter compound with boiling collidine furnished in 74% yield a dehydroprogesterone, assigned the $\Delta^{9(11)}$-structure (XIII) in analogy to the products obtained in the 5β- and 5α-series, and since the properties of the product differed from those of the alternative Δ^{11}-dehydroprogesterone.[7b,16] The properties of XIII agreed only approximately with those of the $\Delta^{9(11)}$-dehydroprogesterone prepared previously[7a] from 11β-hydroxyprogesterone (XIV) with boiling hydrochloric acid and acetic acid. The latter reaction was therefore repeated; the carefully purified product appeared to be very similar to that derived from 11α-hydroxyprogesterone as indicated by the similarity of infrared spectra and non-depression of melting points on admixture. Paper chromatographic analysis, however, showed the acid dehydration product to be inhomogeneous. The major constituent was identical with the pure $\Delta^{9(11)}$-dehydroprogesterone prepared from 11α-hydroxyprogesterone. The minor constituent is probably Δ^{11}-dehydroprogesterone,[7b,16] although the $\Delta^{8(9)}$, $\Delta^{8(14)}$ or Δ^{14} structures cannot definitely be excluded at present.[17]

It is apparent that in all cases studied the dehydration of 11α-hydroxy steroids, either directly or *via* the *p*-toluenesulfonates, gives rise to the $\Delta^{9(11)}$-ethylenes rather than the Δ^{11}-ethylenes, and in fact represents a useful preparative method for the obtention of the former type of unsaturated compound. An explanation of the observed direction of dehydration may be found in the fact that dehydration in the opposite direction (to the Δ^{11}-ethylene), though it could proceed by *trans*-elimination, would involve the unfavorable removal of two groups in the equatorial configuration. *cis*-Elimination involving the 9α (axial) hydrogen atom is equivalent electronically to *trans*-

(12) D. H. Peterson, A. H. Nathan, P. D. Meister, S. H. Eppstein, H. C. Murray, A. Weintraub, L. M. Reineke and H. M. Leigh, THIS JOURNAL, **75**, 419 (1953); O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, **75**, 1286 (1953); E. P. Oliveto, H. L. Herzog and E. B. Hershberg, *ibid.*, **75**, 1505 (1953).

(13) G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.*, **17**, 290 (1952); E. P. Oliveto, T. Clayton and E. B. Hershberg, THIS JOURNAL, **75**, 486 (1953).

(14) O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 1066 (1952).

(15) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister and H. M. Leigh, THIS JOURNAL, **74**, 5933 (1952).

(16) J. v. Euw and T. Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946); C. Meystre, E. Tschopp and A. Wettstein, *ibid.*, **31**, 1463 (1948).

(17) *Cf.* T. Reichstein, U. S. Patent 2,409,798 (*C. A.*, **41**, 1397 (1947)).

elimination with the 12β (equatorial) hydrogen atom, but here is favored because it leads to the more highly substituted olefin. This case is related to that reported recently by Cristol and Hause,[18] who found that *trans*-11,12-dichloro-9,10-dihydro-9,10-ethanoanthracene underwent dehydrohalogenation considerably more rapidly than the *cis* compound, although in the former case *cis*-elimination of hydrogen chloride was involved.

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Experimental[19]

22a-5α-Spirostane-3β,11α-diol 3-Monoacetate (I).—A solution of 22a-5α-spirostane-3β,11α-diol[4a,10] (5 g.) in 125 cc. of glacial acetic acid containing 2.5 cc. of concentrated hydrochloric acid was allowed to stand at room temperature for 18 hours. Addition of water and filtration afforded a solid product which was purified chromatographically on 200 g. of ethyl acetate washed alumina. The first fractions, eluted with hexane–benzene, yielded 1.60 g. of the 3,11-diacetate,[4a,10] m.p. 172–175°; the fractions eluted with benzene–ether on crystallization from chloroform–methanol furnished 1.76 g. of the desired 3-monoacetate, m.p. 200–202°, $[\alpha]^{20}D$ −76°, $\nu_{max}^{CHCl_3}$ 1718 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.52; H, 10.00.

22a-5α-Spirostane-3β,11α-diol 3-Acetate 11-*p*-Toluenesulfonate (IV).—A solution of 0.5 g. of the 3-monoacetate I and 0.5 g. of *p*-toluenesulfonyl chloride in 5 cc. of anhydrous pyridine was kept for 5 days at room temperature. Addition of water and filtration gave a product, m.p. *ca.* 96–120°, which was chromatographed on 30 g. of ethyl acetate washed alumina. The fractions eluted with hexane–benzene were crystallized from acetone–hexane and yielded 0.41 g. of the *p*-toluenesulfonate with m.p. 126–128°, $[\alpha]^{20}D$ −49°, $\nu_{max}^{CHCl_3}$ 1718 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{36}H_{52}O_7S$: C, 68.76; H, 8.33; S, 5.10. Found: C, 68.89; H, 8.03; S, 4.68.

Δ$^{9(11)}$-22a-5α-Spirosten-3β-ol Acetate (II). (a) By Treatment of 22a-5α-Spirostane-3β,11α-diol 3-Acetate 11-*p*-Toluenesulfonate (IV) with Collidine.—A solution of 0.40 g. of the *p*-toluenesulfonate IV in 10 cc. of collidine was refluxed for 30 minutes, cooled, and poured into water. Isolation with ether, chromatography of the product on 30 g. of ethyl acetate washed alumina, and crystallization of the fractions eluted with hexane–benzene from chloroform–methanol gave 0.21 g. (72%) of the Δ$^{9(11)}$-compound, m.p. 197–199°, $[\alpha]^{20}D$ −50°, $\nu_{max}^{CHCl_3}$ 1718 cm.$^{-1}$, no free hydroxyl band. Identity with the compound (m.p. 197–199°, $[\alpha]^{20}D$ −53°) derived from hecogenin[11] was established through mixture m.p. and infrared comparison.

(b) By Direct Dehydration of 22a-5α-Spirostane-3β,11α-diol 3-Monoacetate (I).—A solution of 0.20 g. of 22a-5α-spirostane-3β,11α-diol 3-monoacetate in 2 cc. of dry pyridine was cooled to 0° and 0.6 cc. of redistilled phosphorus oxychloride was added. The mixture was kept overnight at room temperature, cooled, and cautiously decomposed with ice. Isolation with ether and crystallization from chloroform–methanol afforded 0.10 g. of the Δ$^{9(11)}$-compound, m.p. 195–197°, $[\alpha]^{20}D$ −51°. The substance was identified with samples obtained from hecogenin and by method a through mixture m.p. and infrared comparison.

(c) By Dehydration of 22a-5α-Spirostane-3β,11β-diol 3-Monoacetate (V).—The dehydration of 0.30 g. of 22a-5α-spirostane-3β,11β-diol 3-monoacetate (V)[10] in 3 cc. of pyridine was carried out with 0.8 cc. of phosphorus oxychloride, exactly as described under b for the 3β,11α-isomer. Crystallization of the solid product from chloroform–methanol furnished 0.19 g. of the Δ$^{9(11)}$-compound with m.p. 198–199°, $[\alpha]^{20}D$ −48°, identified with the previously described products in the usual way.

9α,11α-Oxido-22a-5α-Spirostan-3β-ol Acetate (VI).—The Δ$^{9(11)}$-compound (II) (0.17 g.), obtained from the *p*-toluenesulfonate IV (route a), dissolved in 10 cc. of ether, was mixed with 15 cc. of an ether solution containing 0.10 g. of perphthalic acid. After 48 hours at room temperature the oxide VI (0.11 g.) had separated as large hexagonal plates, m.p. 247–252°, $\nu_{max}^{CS_2}$ 1736 cm.$^{-1}$, no free hydroxyl band. Another 0.065 g. (total yield, 99%) with the same melting point could be obtained by washing the filtrate with sodium carbonate and water, evaporating, and crystallizing the residue from chloroform–methanol. Identity with the sample (m.p. 248–252°)[11] obtained (in 56% yield) by perbenzoic acid oxidation of the Δ$^{9(11)}$-ethylene II derived from hecogenin, and with that[10] obtained by elimination of the keto group from the corresponding 7-ketone, was established through mixture m.p. and infrared comparison.

Identical results were obtained when the perphthalic acid oxidation was carried out with the Δ$^{9(11)}$-ethylene II obtained from 22a-5α-spirostane-3β,11β-diol 3-acetate (V) (route c).

Pregnan-11α-ol-3,20-dione *p*-Toluenesulfonate (VIII).—A solution of 0.50 g. of pregnan-11α-ol-3,20-dione (VII)[5c,12] in 3.5 cc. of anhydrous pyridine was mixed with 0.5 g. of *p*-toluenesulfonyl chloride and allowed to stand for 3 days at room temperature. Addition of water, isolation with ether and crystallization from acetone–hexane afforded 0.37 g. of the *p*-toluenesulfonate with m.p. 159–160°, $[\alpha]^{20}D$ +74°, $\nu_{max}^{CHCl_3}$ 1700 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{28}H_{38}O_5S$: C, 69.10; H, 7.87. Found: C, 69.51; H, 7.80.

Δ$^{9(11)}$-Pregnene-3,20-dione (X). (a) By Treatment of Pregnan-11α-ol-3,20-dione *p*-Toluenesulfonate (VIII) with Collidine.—A solution of the *p*-toluenesulfonate VIII (200 mg.) in 2 cc. of collidine was refluxed for 30 minutes, cooled, and diluted with water. The product was isolated with ether and chromatographed on 10 g. of ethyl acetate washed alumina. The fractions eluted with hexane–benzene were crystallized from acetone–hexane, and yielded 72 mg. (56%) of Δ$^{9(11)}$-pregnen-3,20-dione, m.p. 147–149°, $[\alpha]^{20}D$ +58°, $\nu_{max}^{CHCl_3}$ 1700 cm.$^{-1}$, no free hydroxyl band, identified with a sample obtained from pregnan-11β-ol-3,20-dione (IX) (route c) in the usual way.

(b) By Direct Dehydration of Pregnan-11α-ol-3,20-dione (VII).—The dehydration of 300 mg. of pregnan-11α-ol-3,20-dione in 2 cc. of pyridine was effected with 0.8 cc. of phosphorus oxychloride at room temperature for 20 hours. The product was isolated with ether and was chromatographed on 15 g. of ethyl acetate washed alumina. The fractions eluted with benzene–hexane yielded *ca.* 10 mg. of the Δ$^{9(11)}$-compound, m.p. 146–149°, identified with a sample obtained by route c through mixture m.p. and infrared comparison.

(c) By Dehydration of Pregnan-11β-ol-3,20-dione (IX).—Pregnan-11β-ol-3,20-dione (IX) (200 mg.) was dehydrated with 0.6 cc. of phosphorus oxychloride in 1.5 cc. of pyridine for 20 hours at room temperature in the usual way. Isolation with ether, chromatography of the product on 10 g. of ethyl acetate washed alumina, and crystallization of the fractions eluted with hexane–benzene from acetone–hexane, furnished 80 mg. of Δ$^{9(11)}$-pregnene-3,20-dione with m.p. 148–150°, 153–155° (Kofler), $[\alpha]^{20}D$ +61°, $\nu_{max}^{CHCl_3}$ 1700 cm.$^{-1}$ no free hydroxyl band.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.35; H, 9.70.

11α-Hydroxyprogesterone *p*-Toluenesulfonate (XII).—A solution of 1.0 g. of 11α-hydroxyprogesterone (XI)[5a,5c,5d,5e,14,15] and 1.0 g. of *p*-toluenesulfonyl chloride in 10 cc. of anhydrous pyridine was kept at room temperature for 3 days, and then poured into water. Isolation with chloroform, chromatography of the product on 50 g. of neutral alumina, and crystallization of the fractions eluted with benzene from acetone–hexane furnished 1.11 g. (76%) of the *p*-toluenesulfonate, m.p. 154–155°, $[\alpha]^{20}D$ +132°, λ_{max} 230 mμ, log ε 4.53, $\nu_{max}^{CHCl_3}$ 1700 and 1670 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49. Found: C, 69.08; H, 7.69.

(18) S. J. Cristol and N. L. Hause, THIS JOURNAL, **74**, 2193 (1952).

(19) Melting points are uncorrected and were determined in capillaries, unless stated otherwise. Rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Miss P. Revaque (Mrs. P. Lopez) for these measurements as well as for the infrared spectra, which were obtained with a Perkin–Elmer model 12C spectrometer with sodium chloride prism. Thanks are due to Miss A. Barba for the microanalyses and to Miss C. Velasco for valuable technical assistance.

$\Delta^{4,9(11)}$-Pregnadiene-3,20-dione ($\Delta^{9(11)}$-Dehydroprogesterone) (XIII).—11α-Hydroxyprogesterone p-toluenesulfonate (0.50 g.) dissolved in 10 cc. of collidine was refluxed for 30 minutes, and the cooled mixture was then diluted with water. Isolation with ether yielded a solid product (0.33 g.), which was chromatographed on 20 g. of ethyl acetate washed alumina. The fractions eluted with hexane–benzene and benzene were crystallized from acetone–hexane, and yielded 0.24 g. (74%) of $\Delta^{9(11)}$-dehydroprogesterone, m.p. 127–128°, $[\alpha]^{20}D$ +171° (chloroform), +155° (acetone), λ_{max} 240 mμ, log ϵ 4.22, $\nu_{max}^{CHCl_3}$ 1700 and 1666 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.79; H, 9.15.

The dehydration of 11β-hydroxyprogesterone (XIV) with boiling concentrated hydrochloric acid and acetic acid, following Shoppee and Reichstein,[7a] was also carried out. After careful chromatography on alumina, material with m.p. 115–118° was obtained [Shoppee and Reichstein[7a] give m.p. 120–122°, $[\alpha]^{18}D$ +145 ± 5° (acetone)], which was undepressed in m.p. on admixture with the pure $\Delta^{9(11)}$-dehydroprogesterone described above; moreover the infrared spectra were very similar. Paper chromatography[20] of this material showed that it consisted of two compounds of closely similar polarities. The major constituent proved to be identical (mixed paper chromatogram, sulfuric acid curve comparison) with the above $\Delta^{9(11)}$-dehydroprogesterone. The minor constituent, which was not further investigated, may be the Δ^{11}-isomer.

(20) We are indebted to Dr. A. Zaffaroni for this analysis.

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

Steroidal Sapogenins. XXXIII.[1] Aromatization Experiments in the Diosgenin Series

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$\Delta^{1,4,6}$-22a-Spirostatrien-3-one (II) in mineral oil solution on vapor phase aromatization furnished 19-nor-$\Delta^{1,3,5(10),6}$-22a-spirostatetraen-3-ol (IIIa), hydrogenation of which led to the phenol IVa. The 3-methyl ether IVb of the latter on side chain degradation afforded 3-methoxy-17-acetyl-$\Delta^{1,3,5(10),16}$-estratetraene (Vb), a valuable intermediate for the synthesis of 19-nor hormone analogs. The structure of the degradation product Vb was confirmed through hydrogenation to the known 3-methoxy-17β-acetyl-$\Delta^{1,3,5(10)}$-estratriene (VIb). The "dienone phenol" rearrangement of $\Delta^{1,4,6}$-22a-spirostatrien-3-one (II) could be carried out, without attack of the side chain, by means of p-toluenesulfonic acid in acetic anhydride at room temperature. The resulting 1-methyl-19-nor-$\Delta^{1,3,5(10),6}$-22a-spirostatetraen-3-ol acetate (IX) was hydrogenated to the 1-methyl phenol acetate X.

3-Hydroxy-17-acetyl-$\Delta^{1,3,5(10),16}$-estratetraene (Va) and the 3-methyl ether Vb, as well as 3-hydroxy-17β-acetyl-$\Delta^{1,3,5(10)}$-estratriene (VIa) and the ether VIb, are important intermediates for the synthesis of the interesting 19-nor analogs of the C-21 steroidal hormones. Thus, the conversion of these ring A aromatic substances to the highly active progestational hormone 19-norprogesterone has recently been announced from these laboratories.[2] The $\Delta^{1,3,5(10),16}$-tetraenes Va and Vb are of especial utility, since the presence of the Δ^{16}-double bond in these compounds makes possible the application of the convenient Julian bromohydrin procedure[3] for producing the corresponding 17α-hydroxy-20-ketones, from which the 19-nor analogs of the more complex adrenal hormones may be prepared. The phenol Va has been prepared previously from estrone acetate (XI) through hydrogen cyanide addition, dehydration and Grignard reaction,[4] and also from allopregnane-3,20-dione (VII) through successive tribromination and dehydrobromination to $\Delta^{1,4,16}$-pregnatriene-3,20-dione(VIII),[5] followed by pyrolytic aromatization.[6] Neither of these routes is satisfactory in detail and therefore an alternative path to the $\Delta^{1,3,5(10),16}$ tetraene V was sought. An attractive possibility involved the aromatization of ring A of a polyenone containing the intact diosgenin (22a-spirostan), side chain, since degradation of the latter should then lead directly to a ring A aromatic pregnane derivative containing the desired Δ^{16}-20-one system (type V). In this paper we record the accomplishment of this type of transformation.

The conversion of Δ^4-22-spirosten-3-one (I) (the Oppenauer oxidation product of diosgenin[7]) by successive bromination and dehydrobromination to $\Delta^{1,4,6}$-22a-spirostatrien-3-one (II) has been reported previously.[8] It has been shown that steroidal $\Delta^{1,4,6}$-trien-3-ones on vapor phase aromatization at 600° in mineral oil[9] or in tetralin[10] solution furnish the corresponding 3-hydroxy-$\Delta^{1,3,5(10),6}$-tetraenes with the C-19 methyl group eliminated (type III). The trienone II dissolved in mineral oil was therefore subjected to the pyrolysis procedure, but in contrast to the previous cases studied,[9a,9b] the product could not be made to crystallize by chilling the resulting solution. A convenient isolation procedure involved removal of the mineral oil by passage through alumina and elution with hexane, after which the steroidal products could be obtained by the usual chro-

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