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Experiments in the Hecogenin Series.[1a] Part 5.[1b] 22a,5β-Spirostan-3α-ol-12-one

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The naturally occurring sapogenin 22a,5α-spirostan-3β-ol-12-one (hecogenin) upon oxidation at C-3, polybromination, treatment with sodium iodide and dehalogenation yields Δ^4-22a-spirostene-3,12-dione (IVb). Catalytic hydrogenation of this unsaturated ketone leads to a mixture of the C-5 isomeric dihydro ketones which can be separated. While the known 5α-ketone, "hecogenone" (IIa), is reduced preferentially with sodium borohydride to regenerate "hecogenin," the isomeric 5β-ketone, 22a-5β-spirostane-3,12-dione (V) upon similar treatment furnishes 22a,5β-spirostan-3α-ol-12-one (VI) which is the first ring C oxygenated steroidal sapogenin of proved structure possessing the 5β-configuration.

Of the naturally occurring ring C oxygenated steroidal sapogenins, only 22a,5α-spirostan-3β-ol-12-one (Ia) (hecogenin)[5] appears to be sufficiently abundant to be considered as a potential raw material for cortical hormone synthesis and its conversion to cortisone already has been recorded.[6] The fact that "hecogenin" (Ia) belongs to the 5α-series places two stereochemical restrictions upon its transformation to cortisone. Thus, only a modification[6] of Borgstrom and Gallagher's[7] procedure for shifting the C-12 keto group to C-11 is applicable to this series, since methods involving 3α,9α-oxides require a 5β-configuration. Furthermore, it is necessary to introduce the requisite Δ^4-3-keto moiety as the last step by the somewhat involved dibromination–sodium iodide procedure.[8] In contrast to the well characterized and abundant ring C *unsubstituted* sapogenins with the 5β-configuration ("sarsasapogenin" and "smilagenin") only one such sapogenin[9] appears to be known which also carries an oxygen function in ring C. Since such a substance would represent a very desirable starting material for the preparation of 11-oxygenated cortical hormones, the synthesis of one such sapogenin, 22a,5β-spirostan-3α-ol-12-one (VI) has been undertaken and is described in this paper.

Three problems were involved in devising a synthesis for such a 5β-sapogenin from "hecogenin" (Ia): (a) conversion to a Δ^4-3,12-dione, (b) reduction of the Δ^4-double bond to yield the 5β-configuration and (c) preferential reduction of the C-3 keto group without affecting the C-12 carbonyl function. This last aspect was investigated first since there was available as a model the conversion of 22a,5α-spirostane-3,12-dione (IIa) (hecogenone) to the corresponding 3β-ol-12-one (Ia) (hecogenin). This transformation has so far only been accomplished by a somewhat circuitous route[10] involving lithium aluminum hydride reduction of IIa to the 3,12-diol, preferential acylation at C-3, followed by oxidation of the free C-12 hydroxyl function and finally saponification. In view of the facile preferential reduction of a C-3 carbonyl group *vs.* one at C-11,[11,12] C-17[13] and C-20,[12,14] of both the 5α and 5β series by means of sodium borohydride, this ap-

(1) (a) The present paper represents "Steroidal Sapogenins XXIX" in the Syntex series. Paper XXVIII, O. Mancera, L. Miramontes, G. Rosenkranz, F. Sondheimer and C. Djerassi, THIS JOURNAL, **75**, 4428 (1953); (b) Part 4, H. Martinez, H. J. Ringold, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 239 (1953).

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(5) Our sapogenin nomenclature (G. Rosenkranz and C. Djerassi, *Nature*, **165**, 313 (1950)) has been modified slightly in accordance with the recommendations of the Ciba Conference on Steroid Nomenclature (*Chemistry and Industry*, June 23, SN1 (1951)).

(6) C. Djerassi, H. J. Ringold and G. Rosenkranz, THIS JOURNAL, **73**, 5513 (1951).

(7) E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.*, **177**, 951 (1949).

(8) G. Rosenkranz, C. Djerassi, R. Yashin and J. Pataki, *Nature*, **168**, 28 (1951).

(9) "Mexogenin" has been assigned the 22a,5β-spirostane-2,3-diol-12-one structure principally because of its reduction to "samogenin" (*cf.* R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2194 (1947)).

(10) N. L. Wendler, H. L. Slates and M. Tishler, *ibid.*, **74**, 4896 (1952).

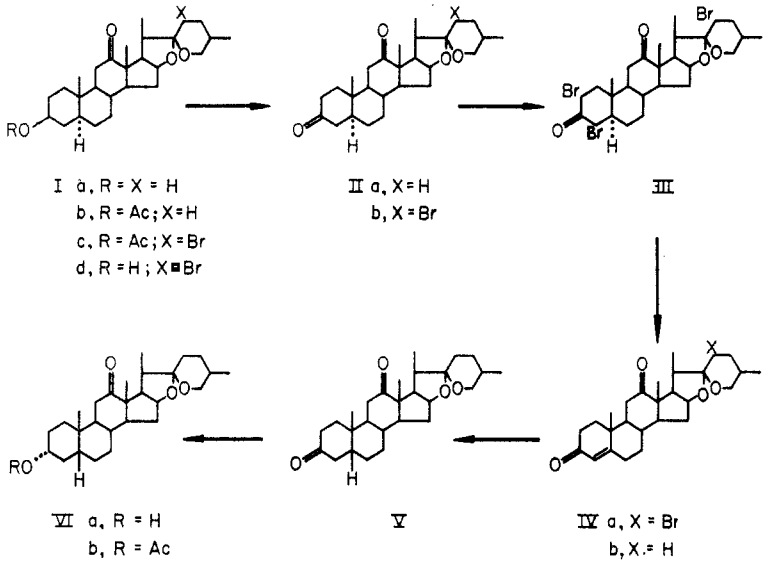
(11) H. Heymann and L. F. Fieser, *ibid.*, **73**, 5252 (1951).

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

(13) E. Elisberg, H. Vanderhaeghe and T. F. Gallagher, *ibid.*, **74** 2814 (1952).

(14) However, a C-20 carbonyl group is reduced preferentially over one at C-11 (E. P. Oliveto and E. B. Hershberg, *ibid.*, **75**, 488 (1953)).

proach was investigated in the case of the 3,12-dione IIa and led in one step in over 60% yield directly to the 3β-ol-12-one Ia (hecogenin).



I a, R = X = H
b, R = Ac; X = H
c, R = Ac; X = Br
d, R = H; X = Br

II a, X = H
b, X = Br

III

VI a, R = H
b, R = Ac

V

IV a, X = Br
b, X = H

In order to introduce the Δ^4-3-keto function required for the catalytic hydrogenation, it was necessary[15] to proceed through the 2,4-dibromo-3-ketone (III) and two syntheses were investigated. The first and longer one started with "hecogenin acetate" (Ib) which was brominated to the 23-bromo derivative Ic[16] saponified to the free alcohol Id[17] and oxidized to the previously unknown 23-bromo-22a-5α-spirostane-3,12-dione (IIb). Bromination with 2.5 molar equivalents[18] of bromine afforded the crude 2,4,23-tribromo derivative III, probably also containing some of the 2,4,11,23-tetrabromo analog, and the crude bromination product was refluxed directly with sodium iodide and deiodinated with sodium bisulfite or chromous chloride. The resulting 23-bromo-Δ^4-3-ketone (IVa), which could be purified readily, was debrominated with zinc to afford the desired Δ^4-22a-spirostene-3,12-dione IVb with the characteristic ultraviolet absorption maximum at 238 mμ and infrared carbonyl bands at 6.01 μ (Δ^4-3-ketone) and 5.88 μ (12-ketone). Subsequently, it was discovered that the entire sequence could be shortened appreciably by brominating 22a,5α-spirostane-3,12-dione (IIa) with 3.5–4.0 moles of bromine and treating the crude product without isolation with sodium iodide and bisulfite.

While it is known that the catalytic hydrogenation (palladium catalyst, preferably in the presence of alkali) of Δ^4-3-keto steroids[19] and sapogenins[20] without substituents in ring C leads predominantly to the 5β,3-ketones, this is not the case with Δ^4-3,11-diketones[21] since hydrogenation there results primarily in the formation of the 5α-isomer. It remained, therefore, to be seen what effect the C-12 keto group would have on the stereochemical course of such a hydrogenation. When the unsaturated diketone IVb was subjected to hydrogenation with palladized charcoal in dioxane solution in the presence of potassium hydroxide, there could be isolated by direct crystallization *ca.* 55% of the relatively insoluble 5α-dione IIa. Chromatography of the mother liquors afforded in 25% yield the desired 22α,5β-spirostane-3,12-dione (V) and the two isomers could be differentiated readily by their infrared absorption spectra, since the 5β-isomer exhibited a marked peak at 9.75 μ. Preferential sodium borohydride reduction of V proceeded at a markedly more rapid rate than that of the 5α-isomer described above, and readily led to the desired 22a,5β-spirostan-3α-ol-12-one (VIa), further characterized by its acetate (VIb). The 3α-configuration of the hydroxyl group, the formation of which was anticipated on the basis of analogy to the work of Shoppee and Summers,[22] was confirmed by the absence of a precipitate with digitonin, the dextrorotatory shift in the molecular rotation upon acetylation,[23] and the presence of only a single band (type A band[24a]) at 8.02 μ in the infrared spectrum of the corresponding acetate VIb. The usually characteristic C–OH stretching band near 9.62 μ[24b] is not very useful in the sapogenin series because of interference by absorption of the spiroketal system.[24c]

Since all of the steroidal sapogenins hitherto isolated from natural sources possess a 3β-hydroxy group, it appears quite unlikely that the presently prepared "3-epi-5-isohecogenin" (VIa) will eventually be encountered in plants; on the other hand, this is quite conceivable with the corresponding 3β,5β-isomer and the above described 22a,5β-spirostane-3,20-dione (V) thus represents a very useful reference compound to which any naturally occurring 3β-hydroxy-5β-12-ketone could be converted by oxidation. From a synthetic standpoint, the presently described 3α-isomer VIa (if obtainable in better yield) would appear to be the most desirable since it should lend itself to both the Kendall[25] and Heymann–Fieser[11] procedures for shifting the C-12 carbonyl group to C-11.

(15) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(16) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **69**, 2180 (1947).

(17) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *ibid.*, **73**, 2400 (1951).

(18) An excess of bromine was used since it had been shown previously (C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16** 303 (1951)) that bromination could also be effected at C-11.

(19) P. L. Julian, "Recent Progress in Hormone Research," Vol. VI, Academic Press, Inc., New York, N. Y., 1951.

(20) C. Djerassi, R. Yashin and G. Rosenkranz, THIS JOURNAL, **74**, 422 (1952).

(21) *Cf.* C. Djerassi, G. Rosenkranz, J. Pataki and S. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952); **195**, 751 (1952).

(22) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).

(23) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 551 (1948).

(24) (a) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **73**, 3215 (1951); (b) A. R. H. Cole, R. N. Jones and K. Dobriner, *ibid.*, **74**, 5571 (1952); (c) R. N. Jones, E. Katzenellenbogen and K. Dobriner, *ibid.*, **75**, 158 (1953).

(25) *Cf.* B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, *J. Biol. Chem.*, **173**, 271 (1948).

Experimental[26]

23-Bromo-22a,5α-spirostane-3,12-dione (23-Bromohecogenone) (IIb).—A solution of 39.4 g. of "23-bromohecogenin acetate" (Ic)[16] in 400 cc. of dioxane and 1600 cc. of methanol was refluxed for one hour with 40 g. of potassium hydroxide and diluted with much water. Filtration and thorough washing with water furnished 35.4 g. of "23-bromohecogenin" (Id)[17] with m.p. 191–194° dec., $[\alpha]^{20}D$ −11°. This material dissolved in 1650 cc. of glacial acetic acid was treated dropwise with stirring at 18° with a solution of 11 g. of chromium trioxide in 6 cc. of water and 165 cc. of acetic acid and then kept at room temperature for 16 hours. Dilution with water and collection of the precipitate afforded 34 g. of the crude dione IIb with m.p. 210–213° dec. One recrystallization from acetone gave 23 g. of crystals with m.p. 225–228° and this material was used in the next step. Further recrystallization from the same solvent led to the analytical sample with m.p. 229–231°, $[\alpha]D \pm 0°$.

Anal. Calcd. for $C_{27}H_{39}O_4Br$: C, 63.89; H, 7.75. Found: C, 63.80; H, 8.03.

Δ⁴-23-Bromo-22a-spirostene-3,12-dione (IVa). (a) From 23-Bromo-22a,5α-spirostane-3,12-dione (IIb).—To a solution of 2 g. of the 23-bromo-3,12-dione IIb in 100 cc. of glacial acetic acid containing two drops of 4 *N* hydrogen bromide in acetic acid was added dropwise at 20° a solution of 2.51 g. of bromine in 25 cc. of acetic acid and the mixture was allowed to stand for 4.5 hours. Dilution with water, filtration and washing with water yielded 2.65 g. of the crude tribromo derivative III with m.p. 165–170° dec. which was refluxed with 9.3 g. of sodium iodide and 310 cc. of acetone for 20 hours. After addition of ether, the solution was washed well with sodium thiosulfate solution, water, dried, evaporated, and the residue, dissolved in 200 cc. of acetone and 20 cc. of dioxane, was treated for 15 minutes with a solution of chromous chloride prepared[15] from 15 g. of chromic chloride. Dilution with water and processing in the usual manner, followed by trituration with ether afforded 1.3 g. of nearly colorless crystals with m.p. 228–232°. The analytical sample was obtained from ether; m.p. 238–240°, $[\alpha]^{20}D$ +34°, λ_{max}^{EtOH} 238 mμ, log ε 4.21, $\lambda_{max}^{CHCl_3}$ 5.88 μ and 6.01 μ. An intense band at 9.48 μ, absent in IVb, may be due to the bromo-spiroketal grouping.

Anal. Calcd. for $C_{27}H_{37}O_4Br$: C, 64.15; H, 7.38. Found: C, 63.98; H, 7.08.

(b) From 22a,5α-Spirostane-3,12-dione (IIa).—22a,5α-Spirostane-3,12-dione (IIa)[16] (13.4 g.) in 600 cc. of glacial acetic acid was brominated with 20.1 g. of bromine in 100 cc. of acetic acid in the manner described above. The crude precipitate thus obtained (17.5 g.) was refluxed for 24 hours with 50 g. of potassium iodide and 1 l. of acetone. Dilution with chloroform and washing in the usual manner afforded 17.0 g. of residue which was dissolved in 300 cc. of dioxane and refluxed for 1 hour with a solution of 10 g. of sodium bisulfite in 60 cc. of water. Three recrystallizations of the crude deiodination product from chloroform–methanol yielded 8.0 g. of the unsaturated bromo ketone IVa with m.p. 226–230°, identified with the above sample by infrared comparison; this material was used directly in the next step.

Δ⁴-22a-Spirostene-3,12-dione (IVb).—The above bromo ketone IVa (8.0 g.) was refluxed with stirring for 24 hours with 600 cc. of ethanol, 100 cc. of glacial acetic acid and 60 g. of zinc dust, filtered, and diluted with much water. The product was extracted with chloroform, the latter was washed with bicarbonate solution, water, dried and evaporated. Chromatography of the residue on 300 g. of alumina and elution with benzene–ether (4:1) followed by crystallization from hexane–acetone furnished 2.1 g. of the desired unsaturated dione IVa with m.p. 230–234°, negative Beilstein test. Further recrystallization led to the analytical sample with m.p. 233–235°, $[\alpha]^{20}D$ +50°, λ_{max}^{EtOH} 238 mμ, log ε 4.20, $\lambda_{max}^{CHCl_3}$ 5.88 and 6.01 μ; the band at 9.48 μ, found in IVa, was absent.

Anal. Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 76.38; H, 9.07.

The corresponding enol acetate, **Δ³,⁵-22a-spirostadien-3-ol-12-one acetate,** was obtained by slowly concentrating a solution of 1.0 g. of IVb in 60 cc. of benzene containing 4 cc. of isopropenyl acetate and 0.16 g. of *p*-toluenesulfonic acid to a volume of 20 cc. over a period of 4 hours, 2-cc. portions of isopropenyl acetate having been added at the end of each hour. After evaporating to dryness *in vacuo*, the residue was taken up in ether, washed until neutral, dried, evaporated and crystallized from ether yielding 0.6 g. of the enol acetate with m.p. 227–231°. Recrystallization from ether–acetone led to a sample with m.p. 234–236°, λ_{max}^{EtOH} 236 mμ, log ε 4.04, $\lambda_{max}^{CHCl_3}$ 5.76 and 5.88 μ.

Anal. Calcd. for $C_{29}H_{40}O_5$: C, 74.32; H, 8.60. Found: C, 74.46; H, 8.90.

22a,5β-Spirostane-3,12-dione (V).—A solution of 2.0 g. of the Δ⁴-3,12-dione IVa in 90 cc. of purified dioxane, to which had been added 0.8 g. of potassium hydroxide in 30 cc. of methanol, was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure with 0.6 g. of pre-reduced 10% palladized charcoal (American Platinum Works, Newark, N. J.). Approximately 2 hours were required for the uptake of one mole of hydrogen at which time the catalyst was filtered, the solution was diluted with much water and the product was extracted with ether. Evaporation of the washed and dried ether extract afforded 1.98 g. of colorless crystals with m.p. 188–199° which exhibited no selective ultraviolet absorption in the region 220–250 mμ. Crystallization from ethyl acetate–methanol gave 1.1 g. of **22a,5α-spirostane-3,12-dione (IIa)** with m.p. 231–235°, identified by infrared spectroscopy with an authentic sample (m.p. 238–240°) prepared by oxidation[16] of Ia. Chromatography of the mother liquors on 100 g. of alumina and elution with benzene–ether (9:1) followed by recrystallization from methanol–chloroform yielded 0.5 g. of **22a,5β-spirostane-3,12-dione (V)** with m.p. 226–228°, $[\alpha]^{20}D$ +10°, $\lambda_{max}^{CHCl_3}$ 5.88 μ and characteristic band at 9.75 μ (latter not shown by 5α-isomer).

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 76.00; H, 9.56.

22a,5β-Spirostan-3α-ol-12-one (VIa).—To a solution of 0.17 g. of the 5β,3,12-dione V in 10 cc. of pyridine was added a solution of 0.05 g. of sodium borohydride in 5 cc. of the same solvent and the mixture was allowed to stand at room temperature for 5 hours. After dilution with 5% hydrochloric acid and extraction with ether, washing, drying and evaporation gave 0.15 g. with m.p. 190–194° which was chromatographed on 20 g. of alumina. Recrystallization of the ether eluates from acetone–hexane furnished 0.08 g. of the desired keto alcohol VIa with m.p. 210–212°, $[\alpha]D$ +9°. The infrared spectrum showed bands at 2.85 μ (free hydroxyl) and 5.88 μ (12-ketone).

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.53; H, 9.72.

The acetate VIb, prepared with acetic anhydride–pyridine at room temperature, was recrystallized from methanol; m.p. 191–194°, $[\alpha]D$ +26°, $\lambda_{max}^{CHCl_3}$ 5.78, 5.88 and 8.02 μ (type A band[24a]).

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 74.04; H, 9.39.

Conversion of 22a,5α-Spirostane-3,12-dione (Hecogenone) (IIa) to 22a,5α-Spirostan-3β-ol-12-one (Hecogenin) (Ia).—A solution of 0.5 g. of the 5α,3,12-dione IIa (m.p. 238–240°) in 5 cc. of pyridine was kept at room temperature for 24 hours with 0.045 g. of sodium borohydride in 1 cc. of pyridine. After working up exactly as above, including chromatography and elution with ether, there was obtained 0.31 g. of pure "hecogenin" (Ia) with m.p. 260–263°, undepressed upon admixture with an authentic specimen from natural sources. Identity was established further by infrared comparison.

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(26) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. The infrared spectra were obtained with a Baird Associates model B double beam recording spectrophotometer. We are indebted to Srta. Amparo Barba (Syntex) and Mr. Joseph F. Alcino (Metuchen, N. J.) for the microanalyses.