[JOINT CONTRIBUTION FROM THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO AND THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroidal Sapogenins. XXXVI.[1] Partial Synthesis of Gitogenin[2]

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22a,5α-Spirostane-2α,3β-diol (VIa) and 22a,5α-spirostane-2β,3β-diol (XIa) have been synthesized by the routes shown in the formula chart. The identity of the former of these compounds with gitogenin firmly establishes the orientation of the hydroxyl groups in this sapogenin, as well as in kammogenin, manogenin, yuccagenin and lilagenin.

Gitogenin was first obtained in 1913 by Windaus and Schneckenburger[3] by acid hydrolysis of gitonin, an amorphous saponin which usually accompanies digitonin.[4] Twenty-three years later Tschesche and Hagedorn[5] showed the sapogenin to be a 2-hydroxytigogenin (now known to be 22a,5α-spirostane-2ξ,3ξ-diol), the stereochemistry of the 2,3-diol system not being determined. Recently partial syntheses of 22a,5α-spirostane-2α,3α-diol and of the corresponding 2β,3α-diol, were carried out in these laboratories.[6] The non-identity of these gitogenin isomers with the natural product taken together with the fact that gitogenin does not form an acetonide and is therefore presumably a *trans*-glycol, strongly suggested that the sapogenin possesses the 2α,3β-diol structure VIa.[7] We now report the partial synthesis of the last-named isomer, as well as of the fourth possible one, the 2β,3β-diol XIa. As expected, the 2α,3β-compound VIa proved to be identical with gitogenin. The synthesis not only establishes the 2α,3β-structure for gitogenin, but also for kammogenin (Δ⁵-22a-spirostene-2α,3β-diol-12-one), manogenin (22a,5α-spirostane-2α,-3β-diol-12-one), yuccagenin (Δ⁵-22a-spirostene-2α,-3β-diol) and lilagenin (Δ⁵-22b-spirostene-2α,3β-diol), since all these sapogenins have been interrelated by Marker, *et al.*[8]

Diosgenin was employed as starting material for the synthesis of the 2α,3β-isomer VIa. The Oppenauer oxidation leading to Δ⁴-22a-spirosten-3-one (I)[9] and the subsequent C-6 bromination with N-bromosuccinimide[10] have been described previously. The resulting 6-bromo-Δ⁴-22a-spirosten-3-one (II) was treated with potassium acetate in boiling acetic acid. This type of acetolysis reaction is now known to yield the 2α-acetoxy-Δ⁴-3-ketones,[11] and the product was therefore assigned structure III. The M_D contribution of the 2α-acetoxy grouping was found to be −44°,[12] in good agreement with the values ranging from −30° to −53° in other series.[11a]

Hydrogenation of the 2α-acetoxy-Δ⁴-3-ketone III over a palladium–charcoal catalyst led mainly to 22a,5α-spirostan-2α-ol-3-one acetate (IV). The 5α ("allo") configuration of this compound[13] was demonstrated through hydrolysis and oxidation to 22a,5α-2,3-secospirostane-2,3-dioic (gitogenoic) acid (V),[3] a transformation which also confirmed that rearrangement from C-6 to C-2 had taken place in the acetolysis step. Finally lithium aluminum hydride reduction of IV smoothly furnished a glycol, which differed from the known[6] 2α,3α-diol, and which must therefore possess the 2α,3β-configuration VIa since inversion of the equatorial grouping at C-2 would not have occurred. The substance proved to be identical with gitogenin in all respects, including the typical purple coloration with concentrated sulfuric acid.[6] Similarly, the diacetate VIb was identical with gitogenin diacetate.

The starting material for the synthesis of the 2β,-3β-diol XIa was tigogenin (22a,5α-spirostan-3β-ol) acetate (VII). Bromination at C-23[14] followed by saponification at C-3 led to 23-bromo-22a,5α-spirostan-3β-ol (VIIIb), which on chromic acid oxidation yielded 23-bromo-22a,5α-spirostan-3-one (IX). Reaction of the latter with lead tetraacetate (the 23-brominated side-chain is unattacked by this reagent) and subsequent zinc debromination afforded a compound, the elemental analysis of which showed that one acetoxy group had been introduced. In view of the well known enolization of C-3 ketones of the 5α ("allo") configuration to the C-2 position,[15] it was to be expected that acetoxylation had occurred at C-2, and this was confirmed by the obtention of gitogenoic acid at a later stage (*vide infra*). The product, however, differed from the 2α-acetoxy-3-ketone III, and consequently must be assigned the 2β-acetoxy-3-keto structure Xb.

Reduction of 22a,5α-spirostan-2β-ol-3-one acetate (Xb) by means of lithium aluminum hydride furnished a diol, which differed from the 2β,3α-

(1) Paper XXXV, J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).

(2) A preliminary announcement of part of this work has appeared in *Chem. and Ind.*, 824 (1953).

(3) A. Windaus and A. Schneckenburger, *Ber.*, **46**, 2628 (1913).

(4) *Cf.* A. Windaus and K. Weil, *Z. physiol. Chem.*, **121**, 62 (1922).

(5) R. Tschesche and A. Hagedorn, *Ber.*, **69**, 797 (1936); *cf.* reference 4.

(6) J. Pataki, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 5375 (1951).

(7) *Cf.* N. L. Wendler, H. L. Slates and M. Tishler, *ibid.*, **74**, 4894 (1952), there footnote 9.

(8) *Cf.* L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, Chapter VIII. It must be pointed out that the assignment of configuration of the hydroxy groups in these other sapogenins rests solely on these interrelationships, independent confirmation of which has not yet been reported.

(9) R. E. Marker, T. Tsukamoto and D. L. Turner, THIS JOURNAL, **62**, 2525 (1940).

(10) J. Romo, H. J. Ringold, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 1873 (1951).

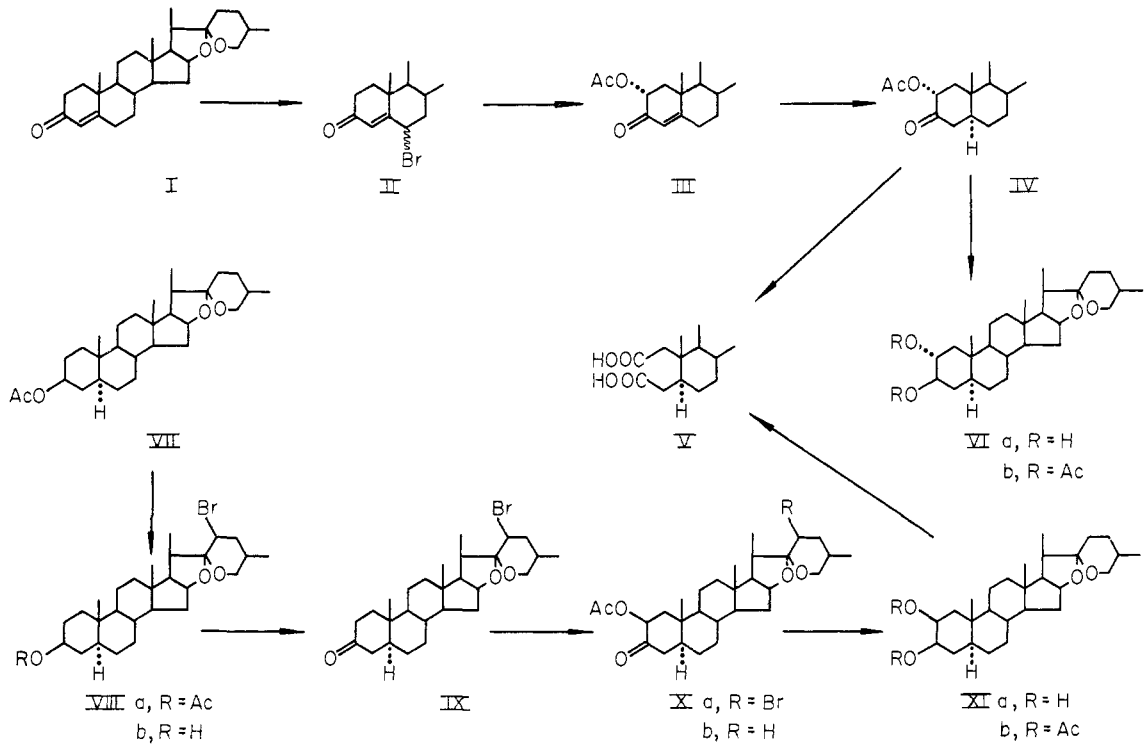
(11) (a) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, THIS JOURNAL, **75**, 4712 (1953); (b) L. F. Fieser and M. A. Romero, *ibid.*, **75**, 4716 (1953).

(12) Δ⁴-22a-Spirosten-3-one (I): $[\alpha]_D$ −10°, M_D −41 (determined in these laboratories).

(13) Catalytic reduction of a 2α-acetoxy-Δ⁴-3-ketone to a compound with the 5α-configuration in the cholestane series has been reported by E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944).

(14) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 1516 (1939).

(15) *Cf.* A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).



diol[6] (as well as from the 2α,3α-[6] and 2α,3β-diols, which might have been formed in the unlikely[16] event of inversion of the axial grouping at C-2) and which we therefore believe to be the remaining 2β,3β-diol XIa. The substance yielded the diacetate XIb on acetylation, and gitogenoic acid (V) on chromic acid oxidation. It is of interest to note that the 3-keto grouping both in the 2α-acetoxy-3-ketone IV and the 2β-acetoxy-3-ketone Xb is reduced with lithium aluminum hydride predominantly to the 3β-alcohol and consequently that the substituents at C-2 do not markedly influence the steric course taken by the reaction in their absence.[17]

Experimental[18]

Δ⁴-22a-Spirosten-2α-ol-3-one Acetate (III).—6-Bromo-Δ⁴-22a-spirosten-3-one (42 g., m.p. 185–186° dec.)[10] was refluxed with 96 g. of anhydrous potassium acetate in 500 cc. of glacial acetic acid for 24 hours. Dilution with water and crystallization of the precipitate from acetone furnished 10.1 g. (25%) of the 2α-acetoxy compound III with m.p. 238–241°. The analytical sample exhibited m.p. 245–246°, $[\alpha]_D$ −18°, M_D −85, λ_{max} 240 mμ, log ε 4.23, $\nu_{max}^{CHCl_3}$ 1736 and 1684 cm.⁻¹.

Anal. Calcd. for $C_{29}H_{42}O_5$[19a]: C, 74.01; H, 9.00. Found: C, 73.74; H, 9.18.

22a,5α-Spirostan-2α-ol-3-one Acetate (IV).—The unsaturated ketol acetate III (2.00 g.) dissolved in 150 cc. of ethyl acetate was hydrogenated over 0.20 g. of a 5% palladium–charcoal catalyst at atmospheric pressure and room temperature. After 1 hour 1.02 moles of gas had been absorbed and uptake ceased. The catalyst and solvent were removed, and the residue was chromatographed on 80 g. of neutral alumina. Crystallization of the fractions eluted with benzene–hexane (3:2) from methanol–ethyl acetate yielded 1.05 g. (52%) of the 5α-compound IV with m.p. 218–221°. The analytical specimen showed m.p. 226–228°, no appreciable absorption in the ultraviolet, $\nu_{max}^{CHCl_3}$ 1736 cm.⁻¹.

Anal. Calcd. for $C_{29}H_{44}O_5$[19b]: C, 73.69; H, 9.38. Found: C, 73.55; H, 9.50.

22a,5α-Spirostane-2α,3β-diol (Gitogenin) (VIa).—The saturated ketol acetate IV (250 mg.) dissolved in 75 cc. of dry tetrahydrofuran was added slowly to a solution of 250 mg. of lithium aluminum hydride in 50 cc. of tetrahydrofuran. The mixture was refluxed for 15 minutes, and the excess hydride was then destroyed with ethyl acetate. Addition of dilute sulfuric acid, extraction with benzene and crystallization from benzene afforded 185 mg. (81%) of gitogenin with m.p. 270–272°, $[\alpha]_D$ −64°, $\nu_{max}^{CHCl_3}$ free hydroxyl band only. An authentic specimen[6] exhibited m.p. 272–273°, $[\alpha]_D$ −63°, and identity was established through mixture m.p. determination and infrared comparison. The synthetic compound developed the same deep purple coloration when wetted with concentrated sulfuric acid as did the natural material.[6]

The diacetate VIb (acetic anhydride–pyridine, steam-bath, 1 hour) was crystallized from acetone–hexane and showed m.p. 240–242°, $[\alpha]_D$ −93°. Identity with an authentic sample (m.p. 240–242°, $[\alpha]_D$ −90°)[6] was demonstrated in the usual way.

23-Bromo-22a,5α-Spirostan-3-one (IX).—Saponification of 60 g. of 23-bromotigogenin acetate (VIIIa) (prepared by the bromination of tigogenin acetate (VII) as described previously[14]) was carried out by refluxing a solution in 12 l. of methanol with 20 g. of potassium hydroxide for 1 hour. Crystallization of the product from methanol–ethyl acetate furnished 51.2 g. of crude 23-bromotigogenin (VIIIb) with m.p. 184–186° dec. This material, dissolved in 1.8 l. of glacial acetic acid, was oxidized by the gradual addition of 7.2 g. of chromic acid dissolved in 20 cc. of water and 200 cc. of acetic acid, the temperature being maintained at 20°. The solution was stirred for a further 20 minutes after the addition was complete, and was then diluted with water. Crystallization from acetone yielded 40.6 g. of 23-bromo-

(16) *Cf.* D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950).

(17) *Cf.* C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950); W. G. Dauben, R. A. Micheli and J. F. Eastham, THIS JOURNAL, **74**, 3852 (1952).

(18) Melting points are uncorrected. Unless noted otherwise rotations were determined (at 20°) in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We would like to thank Mrs. P. Lopez for these measurements as well as for the infrared spectra, which were determined on a Perkin–Elmer model 12C single beam spectrophotometer with sodium chloride prism. Thanks are due to Mrs. A. Gonzalez for the microanalyses.

(19) In our preliminary communication (reference 2) the empirical formula was erroneously given (a) as $C_{29}H_{44}O_5$; (b) as $C_{29}H_{46}O_5$.

22a,5α-spirostan-3-one (IX) with m.p. 214–216°, $[\alpha]_D$ −45°, $\nu_{max}^{CHCl_3}$ 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}O_3Br$: C, 65.70; H, 8.37; Br, 16.19. Found: C, 65.75; H, 8.42; Br, 16.55.

22a,5α-Spirostan-2β-ol-3-one Acetate (Xb).—23-Bromo-22a,5α-spirostan-3-one (40 g.) dissolved in 1.4 l. of glacial acetic acid was heated on the steam-bath with 49 g. of lead tetraacetate for 5 hours. Addition of water, extraction with chloroform and crystallization from benzene–hexane yielded 20.8 g. of crude 23-bromo-22a,5α-spirostan-2β-ol-3-one acetate (Xa) with m.p. 215–220°. This material was refluxed in 2 l. of ethanol with 200 g. of zinc dust for 24 hours, another 100 g. of zinc having been added after the first 10 hours. The metal was removed, most of the alcohol was evaporated, and the product was extracted with chloroform. Chromatographic purification on 800 g. of neutral alumina, and crystallization of the fractions eluted with benzene–hexane (3:2) from acetone–hexane afforded 5.7 g. of 22a,5α-spirostan-2β-ol-3-one acetate (Xb) with m.p. 225–228°. The analytical sample was crystallized from methanol and showed m.p. 230–231°, $\nu_{max}^{CHCl_3}$ 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.96; H, 9.67.

The compound differed from the 2α-isomer IV as evidenced by a depression in m.p. on admixture and by differences in the infrared spectra.

22a,5α-Spirostane-2β,3β-diol (XIa).—The ketol acetate Xb (1.30 g.) dissolved in 400 cc. of dry tetrahydrofuran was reduced with 1.30 g. of lithium aluminum hydride in 100 cc. of tetrahydrofuran as described above for the 2α-isomer. The product, obtained by benzene extraction, was purified by chromatography on alumina followed by crystallization from acetone. This procedure yielded 0.76 g. of the 2β,3β-diol XIa with m.p. 266–267°, $\nu_{max}^{CHCl_3}$ free hydroxyl band only.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 75.11; H, 10.45.

The compound was shown to differ from gitogenin as well as from the corresponding 2β,3α- and 2α,3α-diols described previously[6] through depressions in m.p. on admixture and differences in the infrared spectra. The pure diol XIa, as well as the total reduction product before purification, gave only a light yellow color with sulfuric acid.

The diacetate XIb was crystallized from acetone and showed m.p. 237–238°, $\nu_{max}^{CHCl_3}$ 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.11; H, 9.33.

22a,5α-2;3-Secospirostane-2,3-dioic (Gitogenoic) Acid (V). (a) From IV.—The saturated ketol acetate IV (200 mg.) was saponified by refluxing a solution in 40 cc. of methanol with 300 mg. of sodium carbonate for 1 hour. The free ketol was isolated with ether, and without purification was oxidized with 200 mg. of chromic acid in chloroform–acetic acid for 1 hour at room temperature. Crystallization of the acidic product from dilute acetic acid furnished 85 mg. of gitogenoic acid with m.p. 240–242°, $\nu_{max}^{CHCl_3}$ 1700 cm.$^{-1}$. No depression in m.p. was observed on admixture with an authentic sample[6] (m.p. 241–243°), and the infrared spectra were identical.

(b) From XIa.—The 2β,3β-diol XIa (200 mg.) was oxidized with chromic acid as described under (a). Crystallization of the acidic product from dilute acetic acid yielded 120 mg. of gitogenoic acid with m.p. 239–242°, identified with authentic material in the usual way. Gitogenin on oxidation under the same conditions yielded the acid in comparable yield.

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Steroidal Sapogenins. XXXVII.[1] Experiments in the Hecogenin Series. (Part 6).[2] Conversion to Cortisone

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The conversion of hecogenin to the cortisone intermediate 22a,5α-spirostan-3β-ol-11-one is described. The key reaction involves bismuth oxide oxidation of 22a,5α-spirostane-3β,12β-diol-11-one to the corresponding 11,12-dione followed by removal of the 12-keto function.

The widely distributed[4,5] hecogenin (22a,5α-spirostan-3β-ol-12-one) (I) appears to be the only naturally occurring ring C oxygenated steroidal sapogenin worthy of consideration as a potential raw material for cortical hormone synthesis. In an earlier communication[6] we reported the conversion of hecogenin to 22a,5α-spirostan-3β-ol-11-one (Va), a compound which previously had been transformed[7] into allopregnan-3β-ol-11,20-dione and thence to cortisone.[8] We now wish to report at greater length on the conversion of I into C-11 oxygenated intermediates.

The method of Borgstrom and Gallagher[9] employed in the bile acid series for removal of a 12-hydroxyl function from an 11-keto-12β-hydroxy compound, involving treatment of the ketol with phosphorus tribromide, is inapplicable in the sapogenin series because of reaction of the reagent with the spiroketal side chain. It has now been observed that bismuth oxide, a specific oxidizing agent for acyloins,[10] does not attack tigogenin (22a,5α-spirostan-3β-ol) VII, but reacts smoothly with a ketol such as methyl 3α,12β-dihydroxy-11-ketocholanate (Marker–Lawson acid)[11] to afford, after acetylation, the known[12] enol acetate of methyl 3α-acetoxy-11,12-diketocholanate.

Similarly, treatment of 22a,5α-spirostane-3β,12β-diol-11-one (IIa)[13] for 30 hours in boiling acetic acid

(1) Paper XXXVI, J. Herran, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 5531 (1954).

(2) Part 5, C. Djerassi, A. J. Lemin, H. Martinez, G. Rosenkranz and F. Sondheimer, *ibid.*, **75**, 4485 (1953).

(3) Department of Chemistry, Wayne University, Detroit, Mich.

(4) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).

(5) R. K. Callow, J. W. Cornforth and P. C. Spenseley, *Chem. and Ind.*, 699 (1951).

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

(7) (a) E. M. Chamberlin, 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); (b) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *ibid.*, **74**, 3634 (1952).

(8) G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951); J. M. Chemerda, E. M. Chamberlin, E. H. Wilson and M. Tishler, *ibid.*, **73**, 4058 (1951).

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

(10) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(11) *Cf.* T. F. Gallagher, *J. Biol. Chem.*, **162**, 539 (1946).

(12) O. Wintersteiner and M. Moore, *ibid.*, **162**, 725 (1946).

(13) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951).