[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

Configurational Relationship of 11,12-Oxygenated Sapogenins. Rearrangement to the [3.3.0]Bicycloöctane System[1]

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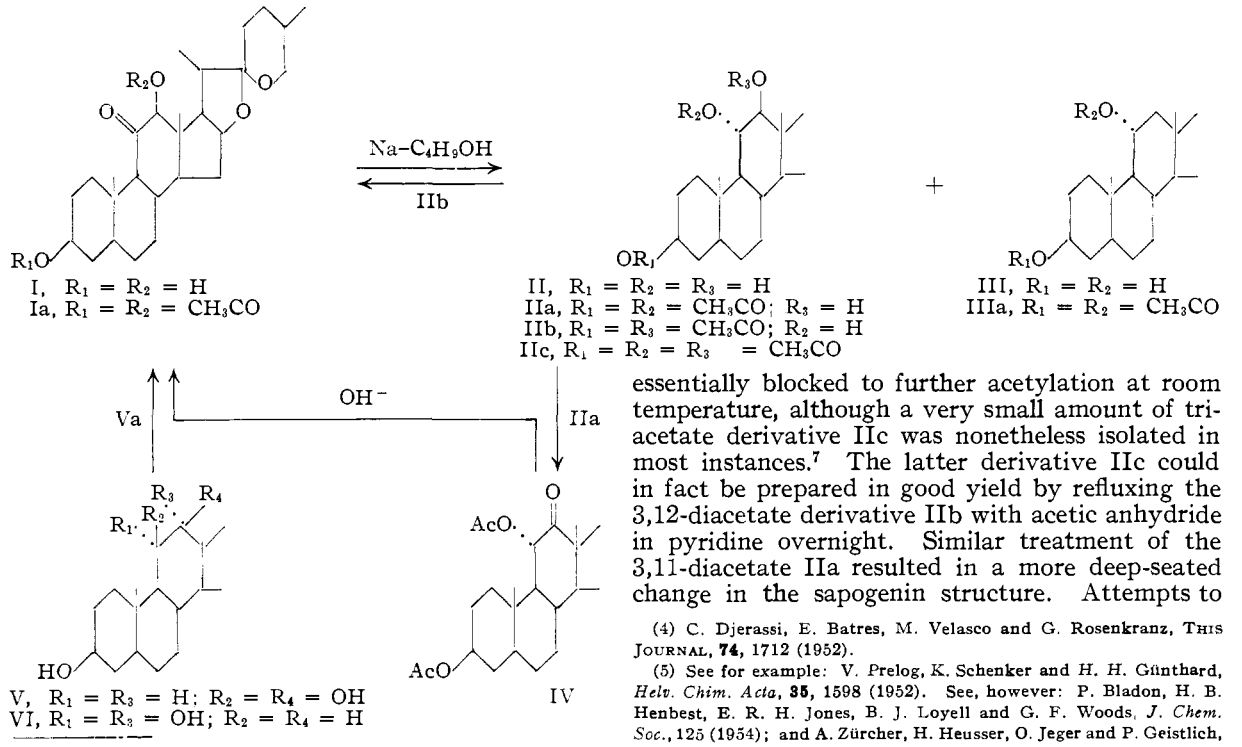
RECEIVED SEPTEMBER 13, 1954

The synthesis of 5α,22a-spirostane-3β,11α,12β-triol (II) has made possible the experimental correlation of configuration of the various 11,12-oxygenated sapogenins. This triol (II) in a derived form was observed to rearrange *via* C-ring contraction to afford the unique [3.3.0]bicycloöctane system exemplified by IX.

The reduction of 11-ketorockogenin (I)[2] with sodium and *n*-butyl alcohol was expected to provide the thermodynamically most stable C_{11},C_{12}-diol configuration.[3] In this instance the 11α,12β or diequatorial configuration was to be anticipated. The actual product from this reduction was a well defined crystalline solid which gave consistently high carbon analyses suggesting reductive loss of oxygen. Acetylation of this reduction product, moreover, under a variety of conditions of varying vigor invariably yielded a non-homogenous derivative exhibiting strong OH absorption in its infrared spectrum. Ultimately, acetylation with acetic anhydride in pyridine at room temperature followed by chromatography on alumina resulted in the isolation of four pure compounds, namely, the diol diacetate IIIa, the isomeric triol diacetates IIa and IIb together with the triacetate derivative IIc.

The formation of the diol III, a known compound,[4] represents the product of reductive scission of the C_{12}-oxygen function in the original sapogenin. The formation of III is noteworthy inasmuch as reductive scissions of this type usually have been observed to occur in general under acid conditions.[5] The proportion of the 3,11- and 3,12-diacetate derivatives IIa and IIb formed on room temperature acetylation was observed in many instances to be nearly statistical at C_{11} and C_{12}. This observed formation of the two isomeric diacetates contrasts with previous experience in the bile acid series. Thus, Wintersteiner, Moore and Reinhardt[6] reported that methyl 3α,11α,12β-trihydroxycholanate on acetylation with acetic anhydride and pyridine at room temperature resulted in the formation of only the corresponding 3,11-diacetate derivative. The present experience in the sapogenin series indicates that the surviving hydroxyl group of each diacetate derivative IIa and IIb is essentially blocked to further acetylation at room temperature, although a very small amount of triacetate derivative IIc was nonetheless isolated in most instances.[7] The latter derivative IIc could in fact be prepared in good yield by refluxing the 3,12-diacetate derivative IIb with acetic anhydride in pyridine overnight. Similar treatment of the 3,11-diacetate IIa resulted in a more deep-seated change in the sapogenin structure. Attempts to



I, $R_1 = R_2 = H$
Ia, $R_1 = R_2 = CH_3CO$

II, $R_1 = R_2 = R_3 = H$
IIa, $R_1 = R_2 = CH_3CO$; $R_3 = H$
IIb, $R_1 = R_3 = CH_3CO$; $R_2 = H$
IIc, $R_1 = R_2 = R_3 = CH_3CO$

III, $R_1 = R_2 = H$
IIIa, $R_1 = R_2 = CH_3CO$

V, $R_1 = R_3 = H$; $R_2 = R_4 = OH$
VI, $R_1 = R_3 = OH$; $R_2 = R_4 = H$

IV

(1) Preliminary announcements of this work appeared in *Chemistry & Industry*, 543, 901 (1954).

(2) 5α,22a-Spirostane-11-one-3β,12β-diol was first described by C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).

(3) Chemical reduction of isolated carbonyl groups have in general been observed to give the alcohol with the more stable configuration. For a leading reference see D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(4) C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712 (1952).

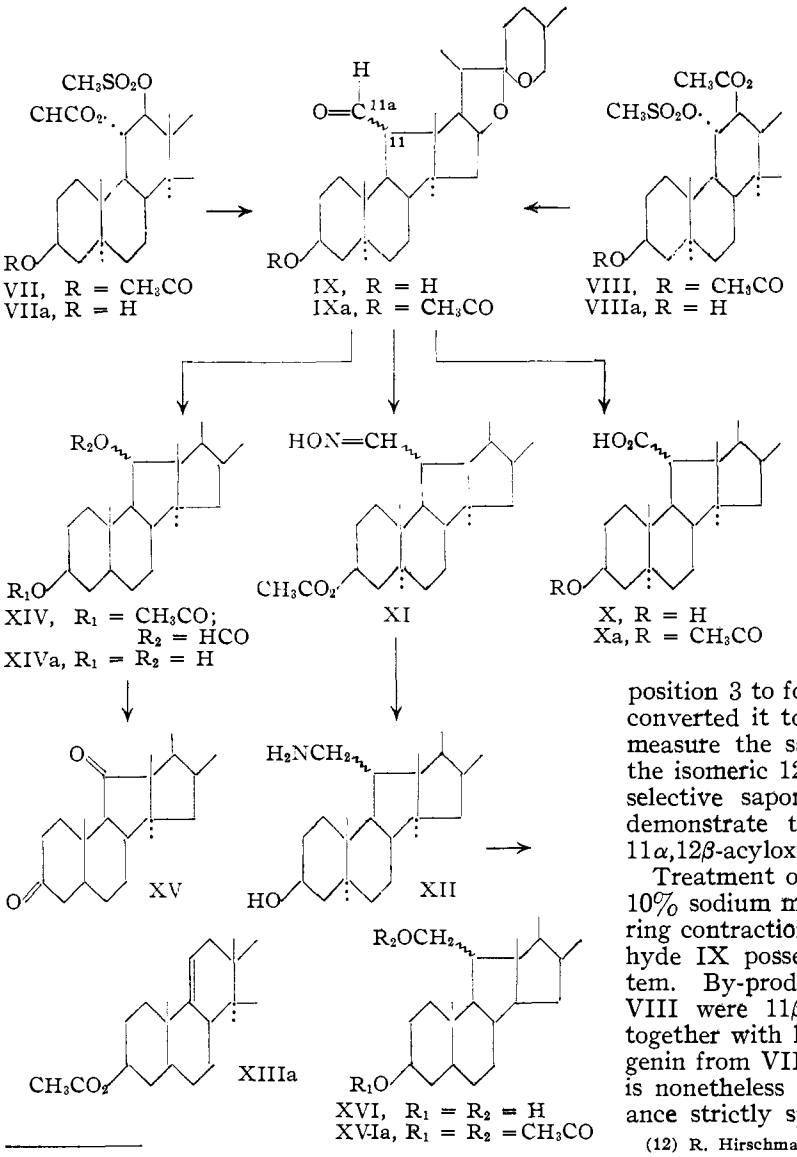
(5) See for example: V. Prelog, K. Schenker and H. H. Günthard, *Helv. Chim. Acta*, **35**, 1598 (1952). See, however: P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Loyell and G. F. Woods, *J. Chem. Soc.*, 125 (1954); and A. Zürcher, H. Heusser, O. Jeger and P. Geistlich, *Helv. Chim. Acta*, **37**, 1562 (1954). These authors have observed that 5α-hydroxy-6-keto steroids undergo reductive loss of the 5-OH group with lithium in liquid ammonia.

(6) O. Wintersteiner, M. Moore and K. Reinhardt, *J. Biol. Chem.*, **162**, 707 (1946); see also T. F. Gallagher, *ibid.*, **162**, 539 (1946).

(7) J. W. Cornforth, J. M. Osbond and G. H. Phillips (*J. Chem. Soc.*, 907 (1954)) recently reported the observation that 11α,23-dibromo-5α,22a-spirostane-3β,12β-diol 3-acetate exhibited a reluctance to acetylation at C_{12}.

prepare the triacetate IIc, moreover, by acetylation of IIa or IIb with acetic anhydride and perchloric acid according to the method of Whitman and Schwenk[8] produced non-crystalline products which exhibited the absence of the characteristic spiroketal side chain peaks[9] in the 10.2 and 11.1 μ regions.[10]

Both diacetate derivatives IIa and IIb could be saponified to the same triol II. Oxidation of IIb with chromic acid gave the known ketol diacetate Ia[2] whereas similar treatment of IIa afforded the isomeric ketol diacetate IV, m.p. 190–192°, $[\alpha]^{chf}D$ −42.2°. The latter[11] on saponification was converted quantitatively to the known 11-ketorockogenin (I). It was further observed that the triol II differed from the triol V obtained from lithium aluminum hydride reduction of I[2]; V moreover has been shown to give the corresponding diacetate which on oxidation yields Ia.[2] The triol II similarly was found not to be identical with 5α,22a-spirostane-3β,11α,12α-triol (VI) prepared by the osmium tetroxide hydroxylation of Δ^{11}-5α,11a-spirostene-3β-ol.[12] Since triol II can be acetylated under mild conditions at C_{11} or at C_{12}, whereas triol V is acetylatable only at C_{12}, and since both the latter diacetate and the diacetate IIb are oxidized to the same ketol diacetate Ia, it follows that II and V are configurationally identical at C_{12} and opposite at C_{11}. These results together with the separate identity of the *cis*-α-triol VI establish the configuration of the triol II as 11α,12β. By the same token the configurations 12β for I and 11β,12β for V as originally assigned by analogy with the bile acids[2] hereby are confirmed experimentally.



Despite the hindrance exhibited by the diacetates IIa and IIb to further acetylation, these compounds nonetheless were smoothly converted to their respective mesylate derivatives VII and VIII on treatment with methanesulfonyl chloride in pyridine at 0°. The 11-mesylate VIII on refluxing with 2% methanolic potassium hydroxide for two hours suffered only hydrolysis of the acetate group at position 3 to form VIIIa; acetylation of VIIIa reconverted it to the original ester VIII. In some measure the same behavior was evidenced with the isomeric 12-mesylate VII giving VIIa. These selective saponifications at C_3 further serve to demonstrate the degree of steric hindrance of 11α,12β-acyloxylated sapogenins.[13]

Treatment of either VII or VIII with refluxing 10% sodium methoxide in methanol resulted in C-ring contraction with formation of the C-nor-aldehyde IX possessing the [3.3.0]bicycloöctane system. By-products formed in minor amounts from VIII were 11β,12β-oxido-5α,22a-spirostane-3β-ol[14] together with hecogenin. The formation of hecogenin from VIII, although only in small amounts, is nonetheless interesting inasmuch as its appearance strictly speaking would have been expected

(8) B. Whitman and E. Schwenk, THIS JOURNAL, **68**, 1865 (1946).

(9) M. E. Wall, C. R. Eddy, M. L. McClennan and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952); R. N. Jones, E. Katzenellenbogen and K. Dobriner, THIS JOURNAL, **75**, 158 (1953).

(10) This observation contrasts with the reported conversion of 11-ketorockogenin to its diacetate derivative under the same conditions by G. P. Mueller, L. L. Norton, R. E. Stobaugh, L. Tsai and R. S. Winniford, *ibid.*, **75**, 4892 (1953).

(11) Recently Mueller, *et al.*, ref. 10, reported the isolation of IV from the bromination-acetoxylation of hecogenin. These authors gave m.p. 230–231°, $[\alpha]^{d1}D$ −24° for this substance, values which are at considerable variance with our own. The reason for this discrepancy is not clear.

(12) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, THIS JOURNAL, **76**, 4013 (1954). As in the bile acid series (ref. 6) Δ^{11}-dehydro sapogenins have been found to follow the "rule of the rear" of T. F. Gallagher and T. H. Kritchevsky, *ibid.*, **72**, 882 (1950).

(13) It is interesting in this connection that A. Fürst and R. Scotoni, Jr. (*Helv. Chim. Acta*, **36**, 1410 (1953)) under the same conditions were able to convert methyl 3α,11β-diacetoxy-12α-mesyloxycholanate to the corresponding 11β,12β-oxide; see also ref. 14.

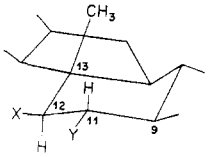
(14) Obtained from the corresponding 11α-Br, 12β-OH halohydrin by (a) J. W. Cornforth and J. M. Osbond, *Chemistry & Industry*, 919 (1953); (b) J. W. Cornforth, J. M. Osbond and G. H. Phillips, *J. Chem. Soc.*, 907 (1954); (c) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **36**, 1241 (1953).

only from a *cis* >C(X)—C(OR)< system.[15] It is furthermore noteworthy that Cornforth, Osbond and Phillips[14] and also Schmidlin and Wettstein[14] do *not* report the formation of any C-nor product from their 11α-Br, 12β-OH halohydrins although the latter are configurationally identical and functionally similar to our triol derivative VIII.

The C-nor-aldehyde IX was isolated as its acetate IXa and identified from the characteristic aldehyde absorption at 5.81 and 3.7 μ.[16] Air oxidation of IXa in ether or acetic acid solution yielded the corresponding **acid Xa**, m.p. 291–295°. Both the aldehyde IXa and the acid X were reduced by lithium aluminum hydride to the same diol XVI, m.p. 216–221°. The aldehyde IXa also formed a yellow **2,4-dinitrophenylhydrazone,** m.p. 176–180°, and an **oxime XI** m.p. 220–225°. Reduction of the oxime with sodium and isopropyl alcohol or with lithium aluminum hydride followed by Demianow rearrangement of the intermediate amine XII caused retrogression of the C-nor system to the normal steroid skeleton with formation of $\Delta^{9(11)}$-dehydrotigogenin; the latter was isolated as its acetate XIII and identified by mixed m.p. and infrared comparison with an authentic specimen. This sequence of transformations thus establishes the *trans*-[3.3.0]bicycloöctane structure of XI and its derivatives. This structure was established further by peracid oxidation of the aldehyde IXa to the formoxy derivative XIV followed by hydrolysis and oxidation of the latter to give the diketone XV. This substance exhibited typical 6-ring and 5-ring ketone absorption at 5.83 and 5.77 μ, respectively, in the infrared.

The C-nor-aldehyde IX and its derivatives are a unique instance of two *trans* locked five-membered carbocyclic rings.[17] On only one previous occasion has such a system been constructed, this being the parent [3.3.0]bicycloöctane prepared by Linstead and Meade.[18] This system, moreover, has long been considered to be a highly strained structural type[19a] and, in fact, its inherent strain has been invoked recently by van Tamelen[19b] to explain the failure of certain neighboring group migrations to occur wherein the transition state to migration would have reasonably approximated two *trans* locked 5-rings. Similar considerations also have been employed as one of the arguments for excluding on theoretical grounds a certain structural possibility in the C/D ring rearrangement of rockogenin.[12]

In conclusion it may be remarked that the geometrical requirements previously discussed and considered as being requisite to ring contraction and expansion phenomena[12] are fulfilled in the case of both VII and VIII. In the structural representation below it is clear that the migrating 9:11 bond



VII, X = CH_3SO_2O; Y = CH_3CO_2
VIII, X = CH_3CO_2; Y = CH_3SO_2O

in VII is *trans* and anti-parallel with respect to the departing function X; likewise in VIII the migrating 12:13 bond is similarly oriented with respect to the departing function Y.

Acknowledgment.—We are indebted to Mr. R. N. Boos and his staff for the analyses reported.

Experimental[20,21]

Reduction of 5α,22a-Spirostane-3β,12β-diol-11-one (I) with Sodium in *n*-Butyl Alcohol.—To a solution of 3 g. of 5α,22a-spirostane-3β,12β-diol-11-one[2] (m.p. 214–217°) in 500 cc. of refluxing *n*-butyl alcohol was added 30 g. of freshly cut sodium metal in three portions. The reaction mixture was refluxed until the sodium had completely dissolved and then concentrated *in vacuo* with occasional addition of water to dissolve precipitated sodium butoxide. The reaction product was ultimately filtered, washed with water and dried in a vacuum desiccator; yield 3 g.

A 100-mg. sample of the above crude triol was acetylated for 15 hours at 25° with 2 cc. of pyridine and 1 cc. of acetic anhydride. The reaction product was extracted with ether and the ether solution washed successively with 5% aqueous hydrochloric acid, 5% aqueous sodium bicarbonate and finally dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude, acetylated reduction product thus obtained was chromatographed on 5 g. of acid-washed alumina to give the following compounds in the order of elution:

A. **5α,22a-Spirostane-3β,11α-diol diacetate** (IIIa) (10 mg.) was eluted with 100% benzene and obtained as rosettes of needles from methanol; m.p. 174–175°. This material exhibited an identical infrared spectrum with an authentic specimen and did not depress the melting point of an authentic specimen of IIIa prepared by sodium and *n*-butyl alcohol reduction of 11-ketotigogenin.[4]

B. **5α,22a-Spirostane-3β,11α,12β-triol triacetate** (IIc) (5–10 mg.) was eluted with 1–2% ether in benzene and crystallized from petroleum ether; m.p. 197–198°, $[\alpha]^{chf}D$ −53.3°.

Anal. Calcd. for $C_{35}H_{52}O_9$: C, 68.98; H, 8.77. Found: C, 69.07; H, 8.68.

This same triacetate, IIc, also was prepared by refluxing the diacetate IIb (see below) with pyridine and acetic anhydride 1:1 for 15 hours. This compound exhibited no band in the OH region of the infrared spectrum.

C. **5α,22a-Spirostane-3β,11α,12β-triol 3,11-diacetate**[22] (IIa) (35 mg.) after elution with 5–10% ether in benzene and obtained as balls of needles from acetone–Skellysolve B, m.p. 206–208°, $[\alpha]^{chf}D$ −64.4°.

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.87; H, 9.08. Found: C, 69.93; H, 9.08.

D. **5α,22a-Spirostane-3β,11α,12β-triol 3,12-diacetate**[22] (IIb) (35 mg.), eluted with 20–50% ether in benzene and crystallized as needle-like prisms, m.p. 231–232°, $[\alpha]^{chf}D$ −55.5°.

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.87; H, 9.08. Found: C, 69.88; H, 9.01.

In another run 120 mg. of crude triol was acetylated for 2 hr. at 100° with acetic anhydride and pyridine and gave

(15) L. F. Fieser and J. A. Dominguez, THIS JOURNAL, **75**, 1704 (1953); L. F. Fieser and W. Huang, *ibid.*, **75**, 4837 (1953). See also ref. 14b.

(16) R. S. Rasmussen, "Fortschritte der Chem. Org. Naturstoffe," Springer-Verlag, Wien, 1948, Vol. 5, p. 331.

(17) No configurational assignment at C_{11} has been indicated in the formulations of these structures; however, model inspection indicates the α-orientation of substituents at this position to be sterically more favorable.

(18) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).

(19) (a) For a leading reference see: W. E. Grigsby, J. Hind, J. Chanley and F. H. Westheimer, THIS JOURNAL, **64**, 2606 (1942); (b) E. E. van Tamelen, *ibid.*, **73**, 3444 (1951).

(20) M.p.'s reported were taken on a micro hot-stage.

(21) Melting paints are corrected unless otherwise specified.

(22) The infrared spectra of the isomeric diacetates IIa and IIb are almost identical differing only in band intensity in the 10–10.5 μ region.

13–15 mg. of triacetate IIc together with 45 mg. each of the 3,11- and 3,12-diacetates IIa and IIb, respectively. On a larger scale involving 4 g. of crude triol, acetylation at room temperature gave 1.5 g. of IIa and over 2 g. of 3,12-diacetate.

5α,22a-Spirostane-3β,11α,12β-triol (II).—Saponification of IIa, IIb or IIc by refluxing for 2 hours with excess 10% methanolic potassium hydroxide followed by crystallization from chloroform–ether afforded the triol II as flat, plate-like prisms, m.p. 256–258°, $[\alpha]^{chf}D$ −65.4°.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 72.12; H, 9.89.

Treatment of the triol II with excess succinic anhydride in pyridine at 100° for 2 hours followed by methylation with diazomethane provided **5α,22a-spirostane-3β,11α,12β-triol 3-methyl succinate**, as needles from ether–petroleum ether m.p. 189–192°.

Anal. Calcd. for $C_{32}H_{50}O_8$: C, 68.29; H, 8.96. Found: C, 68.47; H, 9.17.

Oxidation of the Triol 3,12-Diacetate IIb.—A solution of 50 mg. of IIb in 2 cc. of acetic acid was oxidized with 7.5 mg. of chromic acid at 25° for 15 hours. The product was treated with methanol and evaporated to dryness *in vacuo*. The residue was extracted with ether and the ether solution washed free of acid with aqueous sodium bicarbonate solution. The product was crystallized from methanol; m.p. 228–231°. A m.m.p. with authentic Ia was not depressed and the infrared spectrum was identical with that of an authentic specimen.

5α,22a-Spirostane-3β,11α-diol-12-one 3,11-Diacetate (IV).—A solution of 50 mg. of the 3,11-diacetate IIa in 2 cc. acetic acid was treated with 7.5 mg. chromic acid for 15 hours. The oxidation product was worked up as in the case of IIb (above) and crystallized from petroleum ether or methanol[11]; needles m.p. 190–192°, $[\alpha]^{chf}D$ −42.2°.

Anal. Calcd. for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 69.92; H, 8.58.

The infrared spectrum of IV exhibited a band at 5.75 μ with a shoulder at 5.79 μ of nearly the same intensity. Saponification of a 100-mg. sample of IV by refluxing for 2 hours with 5 cc. of methanol containing 0.5 g. of potassium hydroxide in 0.5 cc. of water followed by crystallization from ethanol afforded 90 mg. of I, m.p. 216–218°. This material showed no depression of m.m.p. with authentic I. The infrared spectrum of this material was likewise identical with that of authentic I.

5α,22a-Spirostane-3β,11α,12β-triol 3,12-Diacetate 11-Methanesulfonate (VIII).—A 0.297-g. sample of the triol diacetate IIb was mesylated with 3 cc. of methanesulfonyl chloride in 20 cc. of pyridine according to a procedure previously described.[12] The product, VIII, was obtained in 94% yield as short needles (acetone–Skellysolve B), m.p. 205° dec.

Anal. Calcd. for $C_{32}H_{50}O_9S$: C, 62.91; H, 8.25; S, 5.25. Found: C, 63.22; H, 8.48; S, 5.12.

Saponification of VIII was effected by addition of a solution of 0.2 g. of VIII in 10 cc. of tetrahydrofuran to 40 cc. of refluxing 2% methanolic potassium hydroxide. After a reflux period of 1.5 to 2 hours the product was isolated in the usual manner and crystallized from acetone–Skellysolve B to give 70 mg. of **5α,22a-spirostane-3β,11α,12β-triol 11-methanesulfonate 12-acetate (VIIIa)**, m.p. *ca.* 191° dec., $[\alpha]^{chf}D$ −38.2; $\lambda\lambda^{Nj}_{max}$ 3–3.1 μ (OH), 5.71 μ (OAc), 7.4 and 8.5 μ (CH_3SO_2).

Anal. Calcd. for $C_{30}H_{48}O_8S$: C, 63.35; H, 8.51. Found: C, 63.68; H, 8.30.

Acetylation of VIIIa with acetic anhydride in pyridine at room temperature reconverted it to VIII identical in all respects with authentic material.

Oxidation of a 108-mg. sample of VIIIa in 6 cc. of acetic acid with 15 mg. of chromic anhydride provided **5α,22a-spirostane-11α,12β-diol-3-one 11-methanesulfonate 12-acetate (VIIIb)**, crystallized from ether, m.p. 185–187° dec., $\lambda\lambda_{max}$ 5.72 and 8.18 μ (OAc), 5.8 μ (C=O), 7.4 and 8.5 μ (CH_3SO_2), 6.95–7.03 μ (6-ring-CH_2-CO-).[23]

(23) The presence of a band in the 7 μ region of its infrared spectrum characteristic of α-methylene bending of 6-membered ring ketones (R. N. Jones and A. R. H. Cole, THIS JOURNAL, **74**, 5648 (1952)) serves to distinguish VIIIb from the alternative isomeric possibility, namely, **5α,22a-spirostane-3β,11α-diol-12-one 3-acetate 11-methanesulfonate.**

Anal. Calcd. for $C_{30}H_{46}O_8S$: C, 63.60; H, 8.13. Found: C, 63.57; H, 8.23.

5α,22a-Spirostane-3β,11α,12β-triol 3,11-Diacetate 12-Methanesulfonate (VII).—Prepared in the same manner as VIII and obtained in 95% yield as hemispherical clusters of needles from ether–petroleum ether, m.p. 165° dec.

Anal. Calcd. for $C_{32}H_{50}O_9S$: C, 62.91; H, 8.25; S, 5.25. Found: C, 62.93; H, 7.97; S, 5.20.

5α,22a,C-nor-Spirostane-3β-ol-11a-al 3-Acetate (IXa).—To a refluxing solution of sodium methoxide, prepared by dissolving 5 g. of sodium metal in 55 cc. of methanol, was added dropwise a solution of 1.9 g. of VII in 13–14 cc. of tetrahydrofuran. After complete addition the reaction mixture was refluxed for 1 hour. At the conclusion of this period the solvent was removed on a steam-bath in a current of nitrogen and the residue extracted with ether. The combined ether extracts were washed free of base with a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated to afford 1.6 g. of a semi-crystalline residue containing IX.

This material (1.6 g.) was acetylated with 3 cc. of acetic anhydride in 10 cc. of pyridine for 15 hours. The acetylated product was evaporated *in vacuo* to near dryness, the residue extracted with ether and the ether solution washed successively with excess dilute aqueous hydrochloric acid, water and sodium carbonate solution. Evaporation of the dried ether solution deposited 0.45 g. of the **C-nor-aldehyde acetate IXa** as prisms, m.p. *ca.* 190°,[24] $[\alpha]^{chf}D$ −10°, $\lambda\lambda^{CS_2}_{max}$ 5.79 and 8.05 μ (OAc), 3.72 and 5.81 μ (CHO).

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.73; H, 9.32. Found: C, 74.06; H, 9.57.

There were no identified by-products isolated from the preparation of IXa derived from the 12-mesylate VII.[25]

The C-nor-aldehyde acetate IXa formed a yellow **2,4-dinitrophenylhydrazone** as needles from ethyl acetate–methanol, m.p. 176–180°.

Anal. Calcd. for $C_{35}H_{48}O_8N_4$: C, 64.36; H, 7.41. Found: C, 64.64; H, 7.60.

Treatment of IXa with hydroxylamine hydrochloride and pyridine in refluxing ethanol for one hour yielded an oxime XI as prisms from benzene–Skellysolve B, m.p. 220–225° with previous softening.

Anal. Calcd. for $C_{29}H_{45}O_5N$: C, 71.42; H, 9.30; N, 2.87. Found: C, 71.56; H, 9.05; N, 2.86.

3β-Acetoxy-5α,22a-C-nor-spirostane-11a-oic Acid (Xa).—A solution of 50 mg. of aldehyde acetate IXa in 4 cc. of acetic acid was treated with 10.7 mg. of chromic anhydride for 15 hours. At the end of this time methanol was added to the reaction mixture and the solvents were removed *in vacuo*. The residue was dissolved in ether and the ether solution washed with water and extracted with 5% aqueous sodium carbonate solution. Acidification of the carbonate extract with dilute hydrochloric acid precipitated the acid Xa; the latter was extracted and crystallized from ether as prisms, m.p. 290–295°, $[\alpha]^{chf}D$ −29.6°.

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08; neut. equiv., 488. Found: C, 71.21; H, 8.95; neut. equiv., 506.

This same acid Xa could be obtained by allowing an ether solution of the aldehyde acetate IXa to stand for several weeks whereupon Xa slowly crystallized. Likewise an acetic acid solution of IXa on standing overnight gave Xa in good yield.[26]

(24) This substance, IXa, exhibited unusual behavior on melting. The well-defined prisms changed crystal structure at *ca.* 185–192° in a manner which suggested a decomposition m.p. and was completely melted at about 230°. The melted material was found to be identical in the infrared with starting IXa and gave the same 2,4-dinitrophenylhydrazone derivative.

(25) The oily mother liquors from this preparation upon chromatography yielded small additional amounts of IXa together with a less polar oil. The latter in one instance exhibited an absorption band in the infrared at 6.05 μ strongly suggesting a C-nor/D-homo structure with an exocyclic methylene group[12]; the companion band for this grouping in the 11.24 μ region, however, was absent. This material was not investigated further.

(26) The infrared spectrum of the acid Xa is noteworthy in that it showed absorption at 3.2 μ (OH) and at 5.79 μ (OAc) but failed to show typical carboxyl absorption in the 5.9 μ region. A morpholine solution of this acid (Xa), furthermore, exhibited a strong peak at 5.79

Treatment of 5α,22a-Spirostane-3β,11α,12β-triol 3,12-Diacetate 11-Methanesulfonate (VIII) with Sodium Methoxide.—A solution of 1.4 g. of VIII in 10–15 cc. of tetrahydrofuran was added dropwise to a refluxing solution of sodium methoxide prepared from 7.5 g. of sodium metal and 75 cc. of methanol. The reaction mixture was refluxed for 2 hours and worked up as in the case of VII. The product was acetylated at room temperature with 5 cc. of pyridine and 2 cc. of acetic anhydride to give 1–1.2 g. of crude acetylated product; 0.2 g. of the latter was chromatographed on acid-washed alumina and gave the following compounds in the order of elution:

A. **11β,12β-Oxido-5α,22a-spirostane-3β-ol acetate**[14] was eluted with benzene–petroleum ether (1:1) and benzene and obtained as needle-like prisms from acetone–Skellysolve B, m.p. 204–206°, $[\alpha]^{chf}D$ −37.7°.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.73; H, 9.32. Found: C, 73.51; H, 9.34.

B. Eluates obtained with 1–10% ether in benzene afforded 110 mg. (55%) of the C-nor-aldehyde acetate IXa identical in all respects with material obtained from sodium methoxide degradation of VII.

C. Elution with 20–50% ether in benzene yielded hecogenin acetate, m.p. 243–245°, identical in all respects with authentic material and further characterized as the **2,4-dinitrophenylhydrazone.**

5α,22a-C-Nor-spirostane-3β-ol 11a-Amine (XII).—A solution of 146 mg. of oxime XI in 5–7 cc. of tetrahydrofuran was added dropwise to a suspension of 200 mg. of lithium aluminum hydride in 15 cc. of tetrahydrofuran and the reaction mixture was refluxed for three hours. At the end of this period an additional 100 mg. of lithium aluminum hydride was added and refluxing continued for 2–3 hours. The reaction mixture was allowed to stand overnight at room temperature and then decomposed with water and evaporated to dryness *in vacuo*. The residue was treated with an excess of 2.5 *N* hydrochloric acid whereupon the aluminum salts dissolved leaving the amine XII as its insoluble hydrochloride in the form of beautiful needles; the latter was crystallized from methanol–ether; m.p. *ca.* 250° dec.

Anal. Calcd. for $C_{27}H_{46}NO_2Cl$: N, 2.95; Cl, 7.79; eq. wt., 468.5. Found: N, 3.05; Cl, 7.50; eq. wt., 478.

Transformation of the Amine XII to $\Delta^{9(11)}$-Dehydrotigogenin Acetate (XIIIa).—The amine XII in the form of its hydrochloride (75 mg.) was suspended in chloroform and shaken with an excess of 6 *N* aqueous ammonium hydroxide. The chloroform solution of liberated amine was evaporated to dryness and the residue dissolved in 10–15 cc. of 50% aqueous acetic acid and treated with 50 mg. of sodium nitrite at 0°. The reaction mixture was allowed to stand at 0° for 1 hour, at room temperature for 1 hour, and finally warmed gently on the steam-bath to complete the reaction. The reaction product which had separated in part during the reaction was diluted with water, extracted with ethyl acetate and the ethyl acetate extract was washed with aqueous bicarbonate solution until neutral. The ethyl acetate solution was evaporated to dryness and the residue acetylated at room temperature with 1 cc. of acetic anhydride and 1 cc. of pyridine. The acetylated reaction product was chromatographed on alumina and afforded material, m.p. 193–198°, which did not depress the m.p. of authentic $\Delta^{9(11)}$-dehydrotigogenin acetate. The infrared spectrum of this material was identical with that of authentic XIII.

5α,22a-C-Nor-spirostane-3,11-dione (XV).—A solution 0.161 g. of the aldehyde IXa in 5.4 cc. of benzene, was allowed to stand with 5.37 cc. of a 0.315 *M* solution of perbenzoic acid in benzene for 3 days at room temperature. The mixture was diluted with ether and washed with sodium thiosulfate solution, water and with a 5% aqueous solution of sodium hydroxide. The alkaline extracts after acidification afforded an acidic fraction which was removed by filtration and washed repeatedly with hot water. The hot water-insoluble residue (22 mg.) proved to be identical with the acid X. The neutral fraction containing XIV was dissolved in 10 cc. of 1:1 tetrahydrofuran–methanol and refluxed for 4 hours with 0.5 cc. of 30% aqueous sodium hydroxide. Removal of the solvents, extraction of the residue with chloroform and removal of excess base by water washing provided, after concentrations, 0.12 g. of crude diol XIVa. The latter was purified by chromatography on alumina to give 0.071 g. of crystalline XIVa which was oxidized directly in 6.5 cc. of acetic acid containing 0.242 g. of chromic anhydride at room temperature for 5 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in ether. The ether solution was washed with dilute sodium hydroxide and water. Evaporation of the dried ether solution afforded 0.063 g. of a partly crystalline residue. The latter was chromatographed on acid-washed alumina and eluted with benzene–Skellysolve B to provide the crystalline diketone XV which was crystallized from methanol, m.p. 205.5–212.5°.

Anal. Calcd. for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.44; H, 9.27.

This substance XV exhibited absorption maxima in the infrared spectrum at 5.77 and 5.83 μ, and showed no absorption in the OH (3 μ) region nor in the acetate and formate companion band regions at 8 and 8.5 μ, respectively.

Preparation of the Diol XVI.—The aldehyde acetate IXa (42 mg.) was reduced with 100 mg. of lithium aluminum hydride in 7 cc. of tetrahydrofuran for 1.5 hours at room temperature to afford 26 mg. of prisms from methanol; m.p. 216–221°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 74.78; H, 10.27.

The same diol was obtained from lithium aluminum hydride reduction of the ester derived from X with diazomethane.

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μ but a band at 6.4 μ characteristic of the carboxylate anion was absent. Esterification of Xa with diazomethane was accompanied by disappearance of OH absorption in the infrared together with intensification of absorption in the 5.8 μ position as well as the appearance of a new band at 8.5 μ in accordance with expectations based on the conversion of Xa to its methyl ester. The hydroxy acid X, obtained by saponification of Xa exhibited typically normal carboxyl absorption in the infrared at 5.86 μ, 3.8–3.9 μ and 3.09 μ (Nujol); in morpholine solution X showed λ_{max} 6.4 μ (CO_2^-).