Studies in the Synthesis of Cortisone. Part XII. Improvements in the Conversion of Sapogenins into Pregnan-20-ones.*

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The conversion of steroidal sapogenins (I) into pregnan-20-ones (VI) by way of the ψ-sapogenins (II) is improved, particularly for 11-oxotigogenin and its esters (I*c*). In the first step furost-22-ens are evidently formed as well as the desired ψ-sapogenins, but this difficulty and others are avoided by methods described.

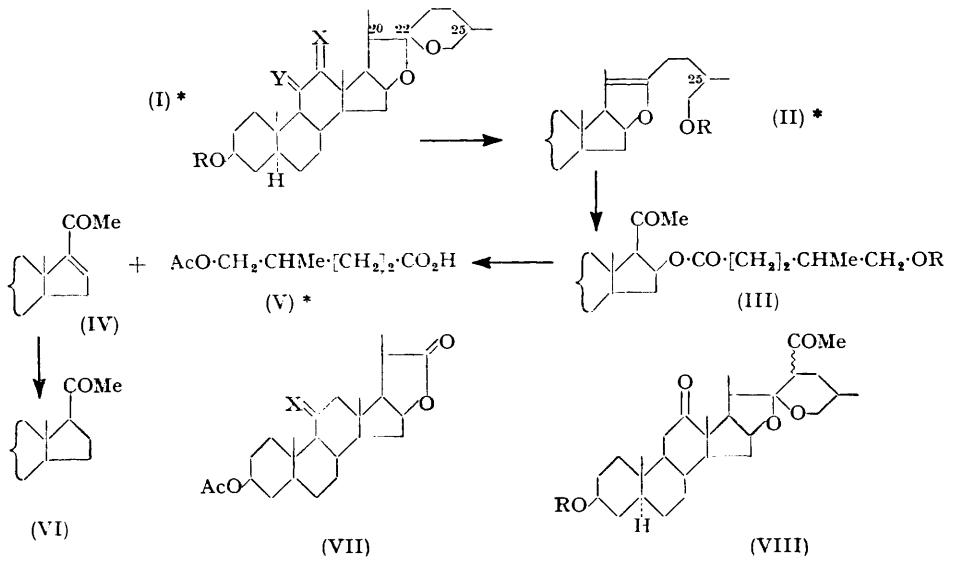
THE development of practicable means of making 11-oxotigogenin and its esters (I*c*) from hecogenin (I*b*; R = H) (Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241; Cornforth, Osbond, and Phillipps, *J.*, 1954, 907) has prompted us to try to improve the published methods for converting 11-oxosapogenins into 3β-acetoxy-5α-pregnane-11 : 20-dione (VI*c*; R = Ac), from which cortisone can be derived (Part VII, *J.*, 1954, 747; Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615; Rosenkranz, Djerassi, Yashin, and Pataki, *Nature*, 1951, **168**, 28).

The first stage of this conversion (in which the ψ-sapogenin is generated) has entailed heating the sapogenin in acetic anhydride at 200° (Djerassi, Batres, Romo, and Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 3634; Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *ibid.*, 1953, **75**, 3477); as the reaction mixture corrodes stainless steel, special apparatus is needed for work on a large scale. Marker and Rohrmann (*ibid.*, 1940, **62**, 518; cf. Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 578; Shoppee and Shoppee, "Chemistry of Carbon Compounds," edited by Rodd, Elsevier, Amsterdam, 1953, Vol. IIB, p. 1035), who devised this method for the degradation, claimed good yields when it was applied to simple sapogenins of the normal and *iso*-series, and they and later workers also used refluxing *n*-butyric anhydride at ordinary pressures (Mueller, Stobaugh, and Winniford, *J. Amer. Chem. Soc.*, 1953, **75**, 4888; Uhle, *ibid.*, 1954, **76**, 4245). We found octanoic anhydride (b. p. 285°) more effective (experiments with acetic anhydride in sealed tubes succeeded best at >200°). At these temperatures fatty acids generate small proportions of their anhydrides (and therefore presumably of the active acetylium ions) (Davidson and Newman, *ibid.*, 1952, **74**, 1515); accordingly we found acetic acid nearly as efficient as its anhydride in the degradation of 11-oxotigogenin acetate (I*c*; R = Ac) at 270°, although Marker and Rohrmann (*loc. cit.*) had dismissed it as ineffective at 200° on sarsasapogenin acetate (I*e*; R = Ac). Further, in *n*-octanoic acid (b. p. 237°), the desired change took less than 2 hr., and 3β : 26-dihydroxy-5α : 25*D*-furost-20-en-11-one (II*c*; R = H) was obtained, after hydrolysis, in 85—90% yield. The water generated in this conversion can be removed by distillation or, better, by addition of an acid anhydride (*e.g.*, acetic or octanoic anhydride). This method was successful also for the degradation to their ψ-isomers of the genins (I*a*; I*d*; I*e*; I*f*; and I*b*; R = H), and can be adapted readily to a large scale. Benzoic acid and aliphatic dicarboxylic acids are less suitable reagents than the simple fatty acids.

Gould, Staeudle, and Hershberg (*ibid.*, 1952, **74**, 3685; Rust, U.S.P. 2,623,053) have also studied alternatives to the method invented by Marker and Rohrmann. Although refluxing acetic anhydride does not perceptibly promote the required breakdown, Gould *et al.* found that Friedel–Crafts catalysts converted diosgenin acetate (I*f*; R = Ac) in refluxing acetic anhydride into ψ-diosgenin diacetate (II*f*; R = Ac). Using 11-oxotigogenin acetate (I*c*; R = Ac), we tried milder catalysts, *e.g.* zinc acetate, with slightly better success, and with trichloroacetic acid achieved the conversion in refluxing acetic acid containing only enough of the anhydride to esterify the hydroxyl groups. For

* Part XI, *J.*, 1955, 2017.

reasons discussed below unwanted changes militate against high yields of the ψ-compounds by these methods.



Series (*a*) **X** = Y = H_2; (*b*) X = O, Y = H_2; (*c*) X = H_2, Y = O; (*d*) 5β-H, X = Y = H_2; (*e*) 5β-H, X = Y = H_2; normal sapogenin; * (*f*) Δ^5, X = Y = H_2.

* The formulæ are not intended to specify the configurations at $C_{(20)}$, $C_{(22)}$, and $C_{(25)}$ in (I) or (VIII), at $C_{(25)}$ in (II), at $C_{(20)}$ in (VII), or at the asymmetric centre in (V). The stereochemistry of these sapogenins at $C_{(25)}$ and of the acid (V) can now be deduced (see Callow *et al.*, *J.*, 1955, 1966). Except for (I*e*) and (II*e*) all the spirostan and furosten derivatives described in this paper have the 25*D*-configuration.

Dauben, Eastham, Micheli, Takemura, Mandell, and Chemerda (*J. Amer. Chem. Soc.*, 1953, **75**, 3255) noticed degradation of the *spiro*ketal side chain of a sapogenin in pyridine–acetyl chloride, and Dauben and Fonken (*ibid.*, 1954, **76**, 4618) found acetic anhydride and pyridine hydrochloride to be efficient with diosgenin acetate (I*f*; R = Ac). Conditions of the former type gave poor results with our compounds; we have not tried the latter.

The pure ψ-sapogenins behave as expected of furost-20-ens: they give brown or yellow colours with tetranitromethane, and their cyclic vinyl ether chromophore endows them with an absorption maximum at about 216 mμ. Dihydrofurans with the >C=CH·O– chromophore have maxima at about 211 mμ (Eglinton, Jones, and Whiting, *J.*, 1952, 2873); therefore the shift of about 5 mμ (denoting the further alkyl substituent in the ψ-sapogenins on the carbon atoms joined by the double bond) resembles cognate effects in the absorption of conjugated dienes and αβ-unsaturated ketones (cf. Fieser and Fieser, *op. cit.*, p. 184). In their infrared absorption the ψ-sapogenins show a C=C stretching band at about 1690 $cm.^{-1}$ (Hayden, Smeltzer, and Scheer, *Analyt. Chem.*, 1954, **26**, 550), whereas other cyclic vinyl ethers show a maximum between 1600 and 1680 $cm.^{-1}$, and the nearest analogue to the furost-20-en structure, 2 : 3-dihydro-5-methylfuran at *ca.* 1675 $cm.^{-1}$ (Bader, *Helv. Chim. Acta*, 1953, **36**, 215; Rosenkranz and Gut, *ibid.*, p. 1000; Meakins, *J.*, 1953, 4170; Barr and Rose, *J.*, 1954, 3766). Other peaks at about 960 and 1025 $cm.^{-1}$ in the absorption spectra of the ψ-sapogenins are possibly due to C–O stretching vibrations, for similar maxima appear in the spectra of dihydrosapogenins and of many derivatives of tetrahydrofuran and tetrahydropyran (cf., *e.g.*, Burket and Badger, *J. Amer. Chem. Soc.*, 1950, **72**, 4397; Barker, Bourne, Stephens, and Whiffen, *J.*, 1954, 171, 3468, 4211; Callow, Dickson, Elks, Evans, James, Long, Oughton, and Page, *J.*, 1955, 1966; Meakins, *loc. cit.*).

The desired degradation of the sapogenins is continued by the opening of ring E in the ψ-sapogenin diesters (II). Of the oxidising agents suggested for this purpose (Marker and Rohrmann, *loc. cit.*; Marker, Jones, *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 2532; 1942,

64, 468; Mueller *et al.*, *loc. cit.*) we found chromic acid in acetic acid the best. The resulting 16β-acyloxy-20-oxo-steroid (III) cannot be easily purified, and is generally best used crude for the next stage. We chose acetic acid as agent for the elimination of the 16-acyloxy-substituent, after poor results with the acids and bases suggested by other workers (*e.g.*, Marker, Turner, Wagner, Ulshafer, Crooks, and Wittle, *ibid.*, 1941, **63**, 774, 779; Djerassi *et al.*, *loc. cit.*; Chamberlin *et al.*, *loc. cit.*), and in this way avoided hydrolysis of the 3β-acetate and addition of nucleophilic groups to the 16 : 17-double bond (Fukushima and Gallagher, *ibid.*, 1950, **72**, 2306), which are probable faults in the other methods. We were able to overcome such difficulties in other ways: thus, although elimination in the ester (III*c*) was almost imperceptible in refluxing solutions in benzene, the addition of an acidic earth such as silica promoted it; an anion-exchange resin or alumina also promoted it, even in the cold (cf. Gould *et al.*, *loc. cit.*; Mueller *et al.*, *loc. cit.*).

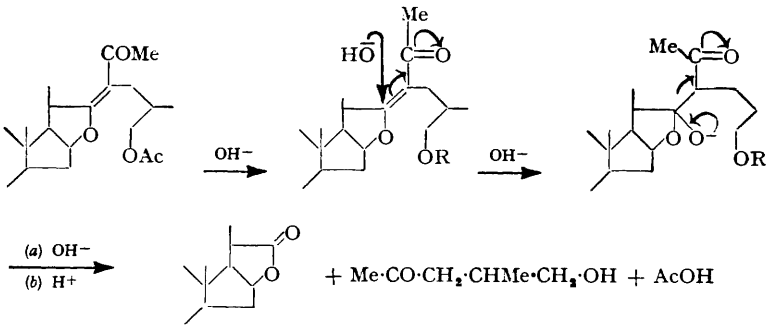
By the preferred methods mentioned above we made the enones (IV*a*, *c*, and *b*; R = Ac) from the genins (I*a*, *c*, and *b*; R = H) or certain of their 3-esters. Catalytic hydrogenation readily furnished the corresponding saturated pregnan-20-ones (VI*a*, *c*, and *b*; R = Ac) in average yields of 40, 65, and 55% from the three *iso*sapogenins. Shortcomings in the degradation of the side-chain of tigogenin seem to spring from the intractability of ψ-tigogenin (II*a*; R = H), for we made the ketone (VI*a*; R = Ac) in about the same yield from the hecogenin (I*b*; R = H) by converting the latter into ψ-hecogenin (II*b*; R = H), reducing this by the Wolff–Kishner method to ψ-tigogenin (II*a*; R = H) and then completing the degradation in the ordinary way.

In an appraisal of the effects of catalysts in refluxing acetic anhydride on the conversion of diosgenin (I*f*; R = H) into its ψ-isomer (II*f*; R = H) Gould *et al.* (*loc. cit.*) attributed some of their loss in yield to the formation of two by-products, namely, the Δ^{22}-isomer of the latter steroid, and a substance that they took to be an α-diketone, owing to its $\lambda_{max.}$ at 275 mμ, although they did not explain the origin of this chromophore. We agree that the furost-22-endiols may accompany the desired ψ-sapogenins if the initial ring cleavage is inadequately controlled. They are manifested by a trend of the optical rotation to the negative side. Moreover, ψ-sapogenin diesters contaminated with these isomers consume more oxidant than is required for rupture of a ditertiary double bond in ring E, and γ-lactones then accompany the desired 16-oxo-steroids in the products. We have been unable to isolate a pure specimen of a furost-22-en, but have segregated and identified a little of the lactone (VII; X = O, 5α-H) after oxidising the product from an experiment carried out with cold acetic anhydride containing phosphoric acid as catalyst. Like the pure ψ-sapogenin diacetates (II), 11-oxo*cyclo*-ψ-tigogenin acetate (11-oxo*ana*tigogenin acetate) afforded on oxidation hardly perceptible quantities of lactone. In acid solution the *cyclo*-ψ-compound would generate the isomeric 3β-acetoxyfurost-20-en-26-ol, in which form it becomes oxidisable (cf. Wall, Eddy, and Serota, *J. Amer. Chem. Soc.*, 1954, **76**, 2849; Callow *et al.*, *loc. cit.*).

We also noticed among our products substances with $\lambda_{max.}$ *ca.* 275 mμ, but we think that these contain not an α-diketone, but the chromophore $-C_{(22)}(OR)=C_{(23)}(COMe)-$ (cf. Attenburrow, Elks, Elliott, Hems, Harris, and Brodrick, *J.*, 1945, 571; Meek, Turnbull, and Wilson, *J.*, 1953, 2891; Szmuszkovicz, *J. Org. Chem.*, 1954, **19**, 1424; Gillam and Stern, "Electronic Absorption Spectroscopy," Arnold Ltd., London, 1954, p. 98), arising by *C*-acylation of the furost-22-en (cf. Henne and Tedder, *J.*, 1953, 3628; Burton and Praill, *Chem. and Ind.*, 1954, 75). After treating hecogenin acetate (I*b*; R = Ac) with perchloric acid in acetic anhydride at room temperature, we isolated yet another type of compound, which behaved as a *C*-acetylsapogenin, probably 23ξ-acetylhecogenin (cf. Marker, Turner, Shabica, and Ulshafer, *J. Amer. Chem. Soc.*, 1941, **63**, 1032; Mueller, Norton, Stobaugh, Tsai, and Winniford, *ibid.*, 1953, **75**, 4892). Its infrared absorption between 800 and 1100 cm.$^{-1}$ befits a sapogenin of this type rather than an *iso*sapogenin carrying the substituent in a position remote from rings E and F (Dickson and Page, *J.*, 1955, 447). It is possibly generated by cyclisation of a 23-acetylfurosten of the type just discussed.

23-Acetylfurost-22-ens are probably decomposed in alkali, owing to influences like those that determine the instability in such conditions of γ-pyrones ("Organic Chemistry," edited by Gilman, Wiley and Sons, Inc., New York, 1953, p. 824). This observation

helps to explain the generation of the γ-lactone (VII; X = H_2, 5β-H) as well as ψ-sarsasapogenin (II*e*; R = H) when sarsasapogenin acetate (I*e*; R = Ac) was degraded in acetic anhydride at 200°, and, after hydrolysis, the alkali-soluble part acidified (Marker and Rohrmann, *loc. cit.*), since it now seems reasonable that the annexed changes could lead to this result:



The possibility of side reactions originating in the furost-22-ens stresses the importance of control in the first stage of the degradations discussed in this paper.

Experimental

Unless stated otherwise, solutions as follows were used for measurements of the physical constants of the compounds described herein: in CS_2 and EtOH for infrared and ultraviolet spectra respectively, and in $CHCl_3$ for optical rotation. The apparatus used for obtaining the infrared spectra has been described elsewhere (Dickson, Page, and Rogers, *loc. cit.*). Owing to overlapping absorption by CS_2 the C=C stretching band for αβ-unsaturated ketones could be descried only in the spectra of CCl_4 solutions. Absorption bands were usually assigned by reference to Jones and Dobriner (*Vitamins and Hormones*, 1949, **7**, 293) and Jones and Herling (*J. Org. Chem.*, 1954, **19**, 1252) for the infrared, and Dorfman (*Chem. Reviews*, 1953, **53**, 47) for the ultraviolet, region.

We used a Kofler m. p. apparatus.

n-*Octanoic Anhydride.*—*n*-Octanoic acid (317 ml.) and acetic anhydride (275 ml.) were refluxed for 18 hr. Distillation through a 6-in. Vigreux column under a reduced pressure of anhydrous nitrogen gave the pure anhydride (180 g., 71%), b. p. 183—186°/16 mm., 280°/760 mm., m. p. −0·5°, n_D^{15} 1·4405, $\nu_{max.}$ 1818 and 1752 cm.$^{-1}$ (acid anhydride) [Found: equiv. (by hydrolysis), 137·5. Calc. for $C_{16}H_{30}O_3$: equiv., 135]. Krafft and Rosiny (*Ber.*, 1900, **33**, 3576), Autenrieth (*Ber.*, 1901, **34**, 183), and Holde and Genter (*Ber.*, 1925, **58**, 1422) record b. p. 186°/15 mm., 280—285°/760 mm., m. p. −1°, $n_D^{17.5}$ 1·4358.

Use of Anhydrides in the Conversion of 11-*Oxotigogenin Acetate* (I*c*; R = Ac) *into* 11-*Oxo-ψ-tigogenin* (II*c*; R = H).—The ψ-sapogenin was isolated as described below. Acetic anhydride at 200°, used as described by Chamberlin *et al.* (*loc. cit.*) and Djerassi *et al.* (*loc. cit.*), gave the ψ-compound (II*c*; R = H) in 45—50% yield. When the mixture was heated to 270° (in 105 min.) and cooled immediately (25—30 min.) the yield was raised to 71%. Use of only a theoretical quantity of the anhydride and dilution with acetic acid (0·5—5 vol.) gave a 52% yield; when light petroleum (b. p. 118—122°; critical temp. >300°; free from aromatic hydrocarbons) was used as diluent the yield was 68%. Pure acetic anhydride becomes black in these circumstances, but the colour could be removed from the crude product (as its ester) by filtration of its ethereal solution through alumina.

When 11-oxotigogenin acetate (I*c*; R = Ac) (1 g.) was treated with refluxing *n*-octanoic anhydride (4 ml.) or succinic anhydride (4 g.) at ordinary pressure, a change occurred that finished in 30 or 7 min. respectively (assessed polarimetrically). 11-Oxo-ψ-tigogenin (II*c*; R = H) was obtained therefrom in a yield of 58 or 82%.

Use of Acids.—11-Oxotigogenin acetate (I*c*; R = Ac) was treated with refluxing acids (2—5 vol.) and the products were worked up as described below. Except for the experiment with acetic acid these reactions were done at ordinary pressure, and the course of the conversion was studied polarimetrically, the water formed during the reaction being distilled off. The acid used, temperature and time of reaction, and yield of 11-oxo-ψ-tigogenin (II*c*; R = H)

were: acetic, 270°, 105 min. (see above), 35%; *n*-hexanoic, 205°, 6 hr., 81%; *iso*hexanoic, 207°, 6 hr.. 79%; *n*-octanoic, 237°, 2 hr., 83%; decanoic, 268°, 0·5 hr., 78%; myristic, 310°, 0·5 hr., 66%; oleic, 270°, 1 hr., 67%.

Phenylacetic, benzoic, and adipic acid furnished impure products in low yield.

Similar experiments, in which enough of the anhydride of the acid was added to take up the water produced, gave the following results: *n*-butyric acid, 169°, 24 hr., 80%; *n*-octanoic acid, 247°, 2 hr., 92%. During these times the rotations of the solutions had reached their maxima; on further refluxing, the rotation decreased, for reasons mentioned in the introduction.

For preparation of ψ-sapogenins the following was typical. 11-Oxotigogenin acetate (I*c*; R = Ac) (10 g.) was heated for 2 hr. in refluxing *n*-octanoic acid (13·2 ml.) containing *n*-octanoic anhydride (6·8 ml.) or acetic anhydride (5 ml.). In the latter instance the low-boiling fractions were distilled off until the temperature reached 240°, and the refluxing continued for 2 hr. thereafter. If octanoic acid is used without the anhydrides the result is as good, but the initial azeotropic removal of the water causes uneven boiling. The reaction mixture was cooled and extracted with ether or benzene. This extract was washed with 2N-sodium hydroxide and then with water. Evaporation of the organic phase left a gum that was hydrolysed in 0·5 hr. in refluxing methanol (100 ml.) containing potassium hydroxide (5 g.); addition of hot water then precipitated a white solid that was washed with plenty of water containing a little pyridine or alkali. The product (8·59 g., 94%) had m. p. 181—189°, $[\alpha]_D^{21}$ +74° (*c*, 1·0), and was suitable for most purposes. Crystallisation from methanol afforded an analytical specimen of 11-*oxo*-ψ-*tigogenin* (II*c*; R = H) (see below). In this manner the alcohol (I*c*; R = H) and benzoate (I*c*; R = Bz) were similarly converted into the foregoing ψ-compound. The yields of ψ-sapogenins when other sapogenins were similarly treated were: tigogenin acetate (I*a*; R = Ac) 98%; hecogenin acetate (I*b*; R = Ac) 92%; smilagenin (I*d*; R = H) 86%; sarsasapogenin acetate (I*e*; R = Ac) 27%, and diosgenin (I*f*; R = H) 87%. The properties of the products appear below. The 3 : 26-diacetates were obtained nearly quantitatively (except for ψ-tigogenin diacetate, which arose in *ca.* 60% yield) in 20—30 min. by acetylation of the ψ-sapogenins with acetic anhydride and pyridine (equal vols.) on the steam-bath.

(i) ψ-Tigogenin (II*a*; R = H), plates or needles (from methanol), m. p. 179—189°, $[\alpha]_D^{20}$ +24° (*c*, 0·47), $\lambda_{max.}$ 214 mμ (ε 5900), $\nu_{max.}$ see Dickson, Page, and Rogers, *J.*, 1955, 443 (Found: C, 77·9; H, 10·5. Calc. for $C_{27}H_{44}O_3$: C, 77·8; H, 10·65%). Marker and Rohrmann (*J. Amer. Chem. Soc.*, 1940, **62**, 898) give m. p. 193—196°. 3 : 26-Diacetate (II*a*; R = Ac), plates (from methanol), m. p. 68—70°, $[\alpha]_D^{20}$ +3·5° (*c*, 1·0), $\nu_{max.}$ 1735 and 1238 (acetate), and 1690 cm.$^{-1}$ (vinyl ether) (Found: C, 74·7; H, 9·7. Calc. for $C_{31}H_{48}O_5$: C, 74·4; H, 9·7%). Rosenkranz, Djerassi, Nussbaum, and Sandoval (*J. Org. Chem.*, 1952, **17**, 426) give m. p. 70—72°, $[\alpha]_D^{20}$ +7°.

(ii) ψ-Hecogenin (II*b*; R = H), plates (from aqueous acetone), m. p. 190—191°, $[\alpha]_D^{20}$ +103° (*c*, 1·5), +96° (*c*, 1 in dioxan), $\lambda_{max.}$ 213 mμ (ε 6400), $\nu_{max.}$ (Nujol) 3320 (hydroxyl), 1706 (ketone) and 1688 cm.$^{-1}$ (vinyl ether) (Found: C, 75·5; H, 10·0. Calc. for $C_{27}H_{42}O_4$: C, 75·3; H, 9·8%). Mueller, Stobaugh, and Winniford (*loc. cit.*) give m. p. 186—188°, $[\alpha]_D^{20}$ +84° (in dioxan). 3 : 26-Diacetate (II*b*; R = Ac), plates (from methanol), m. p. 92·5—94°, $[\alpha]_D^{20}$ +74° (*c*, 1·8), $\nu_{max.}$ 1738 and 1238 (acetate), 1710 (ketone), and 1688 cm.$^{-1}$ (vinyl ether) (Found: C, 72·55; H, 9·0. Calc. for $C_{31}H_{46}O_6$: C, 72·35; H, 9·0%). Mueller, Stobaugh, and Winniford (*loc. cit.*) give m. p. 92—94°, $[\alpha]_D^{20}$ +69° (dioxan).

(iii) 11-*Oxo*-ψ-*tigogenin* (II*c*; R = H), prisms (from methanol) or needles (from acetone), m. p. 194—196°, $[\alpha]_D^{20}$ +76° (*c*, 2), $\lambda_{max.}$ 215 mμ (ε 4950), $\nu_{max.}$ see Dickson, Page, and Rogers (*loc. cit.*) (Found: C, 75·0; H, 9·7. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%). 3 : 26-*Diacetate* (II*c*; R = Ac), m. p. 75—78°, $[\alpha]_D^{23}$ +45° (*c*, 1·23), $\lambda_{max.}$ 218 mμ (ε 5150), $\nu_{max.}$ 1732 and 1240 (acetate), 1708 (ketone), and 1690 cm.$^{-1}$ (vinyl ether) (Found: C, 72·4; H, 9·0. $C_{31}H_{46}O_6$ requires C, 72·35; H, 9·0%).

(iv) ψ-Smilagenin (II*d*; R = H) (from aqueous methanol), m. p. 158—161°, $[\alpha]_D^{22}$ +24° (*c*, 0·98), $\nu_{max.}$ (Nujol) 3300 (hydroxyl) and 1690 cm.$^{-1}$ (vinyl ether). Scheer, Kostic, and Mosettig (*J. Amer. Chem. Soc.*, 1953, **75**, 4871) give m. p. 158—161°, $[\alpha]_D^{20}$ +24°.

(v) ψ-Sarsasapogenin (II*e*; R = H) (from methanol), m. p. 165—168°, $[\alpha]_D^{24}$ +12° (*c*, 0·73), $\lambda_{max.}$ 215 mμ (ε 6050), $\nu_{max.}$ (Nujol) 3300 (hydroxyl) and 1688 cm.$^{-1}$ (vinyl ether). Scheer *et al.* (*loc. cit.*) give m. p. 167—169°, $[\alpha]_D^{20}$ +12°.

(vi) ψ-Diosgenin (II*f*; R = H) (from aqueous methanol), m. p. 157—163°, then 174—177°, $[\alpha]_D^{18}$ −36° (*c*, 1·7), $\lambda_{max.}$ 202 mμ (ε 9200) and 217 mμ (ε 6100), $\nu_{max.}$ 3300 (hydroxyl) and 1690 cm.$^{-1}$ (vinyl ether) (Found: C, 78·1; H, 10·4. Calc. for $C_{27}H_{42}O_3$: C, 78·2; H, 10·2%). Ziegler, Rosen, and Shabica (*ibid.*, 1954, **76**, 3865) give m. p. 165—168°, $[\alpha]_D^{25}$ −39°, $\nu_{max.}$ 1693 cm.$^{-1}$

for this compound. Earlier workers reporting different properties had probably overlooked the ease of the cyclisation to compounds with a high negative rotation (Marker, Tsukamoto, and Turner, *ibid.*, 1940, **62**, 2525; Kaufman and Rosenkranz, *ibid.*, 1948, **70**, 3502; cf. Callow *et al.*, *loc. cit.*). 3 : 26-Diacetate (II*f*; R = Ac) sublimed at 130—140°/10^{-5} mm. and crystallised from methanol as rhombs, m. p. 102—104°, $[\alpha]_D^{20}$ −39° (*c*, 1·01), $\lambda_{max.}$ 206 (ε 8860) and 215 mμ (ε 7010), $\nu_{max.}$ 1732 and 1240 (acetate) and 1690 cm.$^{-1}$ (vinyl ether) (Found: C, 74·8; H, 9·3. Calc. for $C_{31}H_{46}O_5$: C, 74·7; H, 9·3%). The ultraviolet maxima given by these two compounds at the shorter wavelengths are presumably due to the 5 : 6-double bond. Kaufman and Rosenkranz (*loc. cit.*) give m. p. 97—98°, $[\alpha]_D$ −31°, Gould *et al.* (*loc. cit.*) m. p. 98·5—100·5°, $[\alpha]_D$ −47°, and Dauben and Fonken (*loc. cit.*), m. p. 95—98°, $[\alpha]_D^{25}$ −48°.

All of these ψ-sapogenins and their diacetates gave brown or yellow colours with tetranitromethane in chloroform. Their conversions into *cyclo*-ψ-compounds and thence into the parent sapogenins are described elsewhere (Callow *et al.*, *loc. cit.*). Mother-liquors from the crystallisations and purifications of ψ-sapogenins could in this way be made to yield usefully recoverable material.

Preparation of ψ-Tigogenin (II*a*; R = H) *from ψ-Hecogenin* (II*b*; R = H).—A solution of ψ-hecogenin (10 g.) in diethylene glycol (100 ml.) containing sodium hydroxide (10 g.) and hydrazine hydrate (6 ml.) was heated to 145° for 1 hr. under reflux. The condenser was then removed and the mixture heated during 5 hr. up to 205°. The product was left to cool under oxygen-free nitrogen. Methanol (100 ml.) was added, and the solution poured into water (500 ml.) and then set aside overnight; the precipitated ψ-tigogenin (II*a*; R = H) (9·06 g.), m. p. 180—185°, had no infrared carbonyl absorption. Acetylation and crystallisation of the product therefrom yielded the diacetate (II*a*; R = Ac) (8·0 g., 64%), m. p. and mixed m. p. 67—70°, $[\alpha]_D^{20}$ +3° (*c*, 1·0).

3β-*Acetoxy*-16β-γ-*acetoxymethylvaleroyloxy*-5α-*pregnane*-11 : 20-*dione* (III*c*; R = Ac).—To a solution of 3β : 26-diacetoxy-5α : 25*D*-furost-20(22)-en-11-one (11-oxo-ψ-tigogenin diacetate) (II*c*; R = Ac) (4·3 g.) in "AnalaR" acetic acid (30 ml.) was added 1·39N-chromium trioxide in 90% acetic acid (31·5 ml.; 30% excess). The temperature was kept below 30°, and after 1·5 hr. the excess of oxidant (corresponding approximately to the calculated excess) was destroyed with methanol or sodium metabisulphite. Extraction of this solution with benzene or ether (from which the water-soluble and acidic materials were then removed with aqueous sodium hydrogen carbonate) and subsequent evaporation gave a dry residue that could be used for the next stage. Crystallisation from ethanol yielded needles (3·44 g., 76%) of the 16β-ester (III*c*; R = Ac), m. p. 133—134°, $[\alpha]_D^{24}$ +38°. A specimen crystallised to analytical purity had m. p. 131—133°, $[\alpha]_D^{23}$ +35° (*c*, 1·04), $\nu_{max.}$ 1736, 1240 and 1162 (esters), and 1714 cm.$^{-1}$ (ketone) (Found: C, 68·2; H, 8·3. Calc. for $C_{31}H_{46}O_8$: C, 68·1; H, 8·5%). Djerassi, Batres, Romo, and Rosenkranz (*J. Amer. Chem. Soc.*, 1952, **74**, 3635) give m. p. 128—130°, $[\alpha]_D^{20}$ +47°.

The acetic acid used as solvent in the above experiments could be diluted with ethylene dichloride without spoiling the efficiency of the reaction. Slightly inferior yields were obtained when potassium dichromate in acetone and dilute sulphuric acid, hydrogen peroxide in acetic acid (Mueller, Stobaugh, and Winniford, *loc. cit.*), or potassium permanganate in acetic acid (Marker, Jones *et al.*, *locc. cit.*) were used for the oxidation. These statements were also confirmed by comparing the respective yields of the Δ^{16}-20-ketone (IV*c*; R = Ac) when the crude ester (III*c*; R = Ac) was used after each oxidation for the next stage.

3β-*Acetoxy*-16β-γ-*acetoxymethylvaleroyloxy*-5α-*pregnan*-20-*one* (III*a*; R = Ac).—This was made from ψ-tigogenin diacetate (II*a*; R = Ac) in 74% yield by oxidation in the above manner with chromic acid. It crystallised from methanol as plates, m. p. 99—100°, $[\alpha]_D^{20}$ +14° (*c*, 1·0), $\nu_{max.}$ 1736, 1238, and 1164 (esters), and 1715 cm.$^{-1}$ (ketone) (Found: C, 69·9; H, 8·9. Calc. for $C_{31}H_{48}O_7$: C, 69·9; H, 9·1%). Marker, Turner, Wagner, Ulshafer, Crooks, and Wittle (*J. Amer. Chem. Soc.*, 1941, **63**, 774) give m. p. 102—104°. It seemed to be necessary to use pure specimens of this compound for successful conversion into the Δ^{16}-20-keto-steroid (IV*a*; R = Ac).

3β-*Acetoxy*-5α-*pregn*-16-*ene*-11 : 20-*dione* (IV*c*; R = Ac).—(*a*) To the 16β-ester (III*c*; R = Ac) (0·25 g.) in benzene (2·5 ml.) and light petroleum (b. p. 40—60°; 7·5 ml.) was added alumina (Spence Grade H; 2·5 g.; cf. Mueller, Stobaugh, and Winniford, *loc. cit.*). The slurry was shaken or stirred at room temperature, for 2 hr., then filtered, and the alumina washed with ether–methylene chloride (1 : 1; *ca.* 50 ml.). Evaporation of the combined filtrate and eluate, and crystallisation of the residue from ether, gave the enone (IV*c*; R = Ac) (0·16 g., 94%), m. p. 178—181°, $[\alpha]_D^{14}$ +64° (*c*, 1·3), $\lambda_{max.}$ 235 mμ (ε 9150). Similar results were achieved when a solution of the ester (III*c*; R = Ac) in benzene containing silica (B.D.H. "pure precipitated")

was refluxed for 5 hr., or when a benzene solution of the ester containing the anion-exchange resin A 3 (sold by Colborne Engineering Co. Ltd., London, W.3) was kept for 24 hr. at room temperature with occasional shaking. The product from the experiment with silica was washed with aqueous sodium hydrogen carbonate to remove acidic by-products.

(*b*) The 16β-ester (III*c*; R = Ac) (5 g.) was refluxed in glacial acetic acid (50 ml.) for 2 hr. The solvent was then removed *in vacuo*, and the residue dissolved in methylene chloride. Washing with sodium hydrogen carbonate solution and then several times with water, and evaporation of the dried ($MgSO_4$) lower phase left a residue that crystallised from ether as rods of the Δ^{16}-20-ketone (IV*c*; R = Ac) (3·2 g., 94%), m. p. 178—181°, $[\alpha]_D^{20}$ +64° (*c*, 1·0), $\lambda_{max.}$ 235 mμ (ε 9300). Recrystallisation from methanol gave an analytical specimen as rods, m. p. 182—184°, $[\alpha]_D^{20}$ +65° (*c*, 2), $\lambda_{max.}$ 235 mμ (ε 9150), $\nu_{max.}$ 1730 and 1288 (acetate), 1706 (ketone), 1670 and 1592 (αβ-unsaturated ketone), and 822 cm.$^{-1}$ (trisubstituted ethylene). The 1592-cm.$^{-1}$ peak could be discerned only in spectra of solutions in CCl_4 (Found: C, 74·25; H, 8·6. Calc. for $C_{23}H_{32}O_4$: C, 74·2; H, 8·7%). The properties of this material agree with those given by, *e.g.*, Djerassi *et al.* and Chamberlin *et al.* (*locc. cit.*). The use of sodium hydroxide in tetrahydrofuran (*idem*, *loc. cit.*), of potassium hydrogen carbonate in *tert.*-butanol (Mueller Stobaugh, and Winniford, *loc. cit.*) or of methanolic hydrogen chloride (Marker, Turner, *et al.*, *locc. cit.*) for the conversion of the ester (III*c*; R = Ac) into the foregoing Δ^{16}-ketone (IV*c*; R = Ac) resulted in poor yields.

Tigogenin acetate (I*a*; R = Ac), hecogenin acetate (I*b*; R = Ac), 11-oxotigogenin (I*c*; R = H), and the acetate (I*c*; R = Ac) and benzoate (I*c*; R = Bz) of the last-named were converted into the corresponding Δ^{16}-20-keto-steroids (IV) by the sequence (I) ⟶ (II) ⟶ (III) ⟶ (IV) + (V), without purification of the furostendiols or their acetates (II), or of the esters (III). A slightly increased uptake of oxidant (5—10%) was then observed in the oxidation of the furosten diesters, and the mother-liquors from the crystallisation of the Δ^{16}-keto-steroids contained a compound with $\nu_{max.}$ 1780 cm.$^{-1}$ (γ-lactone). We made the enones (IV*a*, *b*, and *c*; R = Ac) in this way from the three *iso*sapogenins and their esters. Analytical specimens were obtained, as follows.

(i) 3β-Acetoxy-5α-pregn-16-en-20-one (IV*a*; R = Ac), leaflets (from methanol), m. p. 166°, $[\alpha]_D^{20}$ +35° (*c*, 0·51), $\lambda_{max.}$ 239 mμ (ε 10,600), $\nu_{max.}$ 1735 and 1238 (acetate), 1668 (αβ-unsaturated carbonyl), and 816 cm.$^{-1}$ (trisubstituted ethylene) (Found: C, 77·05; H, 9·4. Calc. for $C_{23}H_{34}O_3$: C, 77·05; H, 9·55%). Plattner, Ruzicka, Heusser, and Angliker (*Helv. Chim. Acta*, 1947, **30**, 385) give m. p. 166—167°, $[\alpha]_D$ +42°, and Klyne, Schachter, and Marrian (*Biochem. J.*, 1948, **43**, 231) m. p. 165—167°, $[\alpha]_D$ +36·3°.

(ii) 3β-Acetoxy-5α-pregn-16-ene-12 : 20-dione (IV*b*; R = Ac), plates (from ether), m. p. 178—180°, $[\alpha]_D^{20}$ +128° (*c*, 2), $\lambda_{max.}$ 228 mμ (ε 10,100), $\nu_{max.}$ 1730 and 1240 (acetate), 1718 (ketone), 1678 (αβ-unsaturated ketone), and 824 cm.$^{-1}$ (trisubstituted ethylene). Mueller, Stobaugh, and Winniford (*loc. cit.*) give m. p. 179—181°, $[\alpha]_D^{25}$ +124° (in dioxan), $\lambda_{max.}$ 227·5 mμ (ε 8500) for this compound. On one occasion crystallisation of the above compound from methanol afforded material, m. p. 173—175°, $[\alpha]_D^{20}$ −11° (*c*, 2), $\lambda_{max.}$ 242 mμ ($E_{1cm.}^{1\%}$ 303), $\nu_{max.}$ at 3350 (hydroxyl), 1735 and 1240 (acetate), and 1654 cm.$^{-1}$ (αβ-unsaturated ketone). This result could not be repeated, even with methanol containing added traces of acid or alkali, anhydrous or containing a little water. Attempts to acetylate the hydroxyl group with cold pyridine and acetic anhydride decomposed the compound, and only the Δ^{16}-20-ketone (IV*b*; R = Ac) was isolated. We believe that a hemiketal group may have formed at the 12-position, inasmuch as peaks in the infrared absorption at 1185, 1148, 1120, 1075, and 1057 cm.$^{-1}$ might denote absorption of this type (Page, *J.*, 1955, 2017). The possibility that the novel compound is an aldol arising from interaction of the 12-keto-group with the activated 21-methyl (cf. Fieser and Fieser, *op. cit.*, p. 667; Arigoni, Riniker, and Jeger, *Helv. Chim. Acta*, 1954, **37**, 878) seems to be discredited by the position of the carbonyl absorption band, which is not appropriate for a cyclic ketone.

Conversion of 11-*Oxo*cyclo-ψ-*tigogenin Acetate into* 3β-*Acetoxy*-5α-*pregn*-16-*ene*-11 : 20-*dione* (IV*c*; R = Ac).—The 11-oxo*cyclo*-ψ-sapogenin (2 g.) (Callow *et al.*, *loc. cit.*) was dissolved in acetic acid (50 ml.) and oxidised with 1·39N-chromic oxide in 90% acetic acid (30·5 ml.). The solution was set aside for 3·5 hr. The excess of oxidant was removed by the addition of aqueous sodium metabisulphite, and the steroid extracted into benzene. Treatment with alumina as described heretofore yielded the pure Δ^{16}-20-oxo-steroid (IV*c*; R = Ac) (0·518 g., 33%), m. p. 180—182°, $[\alpha]_D^{21}$ +64° (*c*, 1·2), $\lambda_{max.}$ 235 mμ (ε 9200). The material in the mother-liquors contained no more than a trace of γ-lactone (on the basis of the infrared spectrum), but was contaminated with a neutral substance of low rotation and ultraviolet absorption.

Hydrogenation of the Foregoing Δ^{16}-20-*Keto-steroids*.—Each of the enones was hydrogenated

almost quantitatively with 5% palladised charcoal in ethyl acetate under hydrogen at atmospheric pressure and temperature. In this way we obtained the following 20-keto-steroids derived from tigogenin, hecogenin, and 11-oxotigogenin.

(i) 3β-Acetoxy-5α-pregnan-20-one (VI*a*; R = Ac), plates (from acetone), m. p. 144—145°, $[\alpha]_D^{20}$ +75° (*c*, 1·0), $\nu_{max.}$ 1732 and 1242 (acetate), 1706 (ketone), and 1356 cm.$^{-1}$ (methyl ketone) (Found: C, 76·5; H, 10·1. Calc. for $C_{23}H_{36}O_3$: C, 76·6; H, 10·1%). Barton and Cox (*J.*, 1948, 791) give m. p. 143·5—144·5°, $[\alpha]_D$ +77°.

(ii) 3β-Acetoxy-5α-pregnane-12 : 20-dione (VI*b*; R = Ac), crystals (from ethyl acetate), m. p. 188—190°, $[\alpha]_D^{20}$ +140° (*c*, 1·0), $\nu_{max.}$ 1738 and 1240 (acetate), and 1710 cm.$^{-1}$ (ketones). Mueller, Stobaugh, and Winniford (*loc. cit.*) give m. p. 189—190°, $[\alpha]_D$ +139° (in dioxan).

(iii) 3β-Acetoxy-5α-pregnane-11 : 20-dione (VI*c*; R = Ac), see next paragraph.

Physical Properties of 3β-*Acetoxy*-5α-*pregnane*-11 : 20-*dione* (VI*c*; R = Ac).—Crystallisation from aqueous methanol afforded needles, m. p. 127—128°, solidifying and remelting at 143—145°. Material fused at 130—135° and crystallised from aqueous methanol gave plates, m. p. 142—144°. Crystallisation of either form in the presence of the other gave mixed crystals. Each of the two forms had $[\alpha]_D^{20}$ +89° (*c*, 2), and their solutions gave identical infrared spectra (see Dickson, Page, and Rogers, *loc. cit.*) (Found: C, 73·8; H, 9·2. Calc. for $C_{23}H_{34}O_4$: C, 73·75; H, 9·2%). The ketone obtained from ergosterol (Cameron *et al.*, *loc. cit.*) behaved similarly. Djerassi *et al.* (*loc. cit.*) give m. p. 143—145°, $[\alpha]_D$ +87°, and Chamberlin *et al.* (*loc. cit.*), m. p. 124—127° (needles), 141—143° (plates), $[\alpha]_D$ +86°.

Hydrolysis of either form (1 g.) with potassium hydroxide (0·5 g.) for 0·5 hr. in refluxing methanol (10 ml.), and subsequent dilution with water yielded white needles (0·8 g.), m. p. 185—191°, $[\alpha]_D^{23}$ +106° (*c*, 0·6). Recrystallisation from ethyl acetate–*cyclo*hexane and acetone furnished needles, m. p. 192—196°, $[\alpha]_D^{22}$ +110° (*c*, 0·6), $\nu_{max.}$ (Nujol) at 3470 and 3400 (hydroxyl), 1698 (ketone) and 1352 cm.$^{-1}$ (methyl ketone), of 3β-hydroxy-5α-pregnane-11 : 20-dione (VI*c*; R = H) (Found: C, 76·2; H, 9·7. Calc. for $C_{21}H_{32}O_3$: C, 75·9; H, 9·7%). Cameron, Hunt, Oughton, Wilkinson, and Wilson (*J.*, 1953, 3864) give m. p. 188—190°, $[\alpha]_D$ +109°, and Stork, Romo, Rosenkranz, and Djerassi (*J. Amer. Chem. Soc.*, 1951, **73**, 3546) m. p. 192—194°, $[\alpha]_D$ +99°. By reacetylation it yielded the acetate (VI*c*; R = Ac), the form of which depended on the method of crystallisation.

It seems likely that catalytic hydrogenation occurs only on the " after " face of the molecule of the enone (VI*c*; R = Ac) (Shoppee and Shoppee, *op. cit.*, p. 901) and, as epimerism at $C_{(17)}$ is marked by large rotational differences (Fieser and Fieser, *op. cit.*, p. 390), the two forms cannot be 17-epimers and must be dimorphous (cf. Dickson, Page, and Rogers, *loc. cit.*).

3β-n-*Octanoyloxy*-5α-*pregn*-16-*ene*-11 : 20-*dione* (IV*c*; R = C_7H_{15}·CO).—11-Oxotigogenin (I*c*; R = H) (5 g.), *n*-octanoic anhydride (6·9 ml.) and acid (2 ml.) were refluxed together for 2 hr. The crude furosten diester was isolated without hydrolysis and then oxidised and treated with alumina as described above. The above 3-*octanoate* was obtained as a crystalline mass (4·76 g., 90%). Crystallised from light petroleum–ether it had m. p. 94—99°. The specimen for analysis separated from methanol as plates, m. p. 99—101°, $[\alpha]_D^{20}$ +51° (*c*, 0·9), $\lambda_{max.}$ 235 mμ (ε 9700), $\nu_{max.}$ 1728 and 1175 (ester), 1708 (ketone), 1672 (αβ-unsaturated ketone), and 821 cm.$^{-1}$ (trisubstituted ethylene) (Found: C, 76·1; H, 9·8. $C_{29}H_{44}O_4$ requires C, 76·3; H, 9·7%).

3β-n-*Octanoyloxy*-5α-*pregnane*-11 : 20-*dione* (VI*c*; R = C_7H_{15}·CO).—The foregoing Δ^{16}-20-ketone (3·3 g.) was hydrogenated as described above with the catalyst (0·7 g.) in ethyl acetate (70 ml.). Uptake of hydrogen being very slow, more catalyst (1·4 g.) was added, and the reduction was then completed in 1 hr. The steroidal product crystallised as rhombs (2·5 g., 75%), m. p. 40—50°, from methanol. Recrystallisation afforded the saturated 11 : 20-*dione* (1·79 g.), m. p. 55—60°, $[\alpha]_D^{20}$ +69° (*c*, 0·8), $\nu_{max.}$ 1725 and 1166 (ester), and 1707 cm.$^{-1}$ (ketone) (Found: C, 76·0; H, 9·95. $C_{29}H_{46}O_4$ requires C, 75·9; H, 10·1%).

Hydrolysis yielded the diketone (VI*c*; R = H), m. p. 185—190°, $[\alpha]_D^{20}$ +110° (*c*, 1·2), identified by mixed m. p. and infrared spectroscopy with a specimen described above.

Degradations in Refluxing Acetic Anhydride containing Catalysts.—11-Oxotigogenin acetate (I*c*; R = Ac) (5 g.) (which is not changed in refluxing acetic anhydride) was heated for 23 hr in the refluxing anhydride (165 ml.) containing zinc acetate (2·5 g.). The product was filtered, and the filtrate extracted into ether, and washed therein with sodium hydrogen carbonate solution and water. Evaporation of the washed and dried ($MgSO_4$) ether phase left a gum that was oxidised with chromic oxide and treated with alumina in the usual manner. Isolation of the final product yielded the enone (IV*c*; R = Ac) (1·72 g., 45%), m. p. 173—179°, $[\alpha]_D^{20}$ +65° (*c*, 2), $\lambda_{max.}$ 235 mμ (ε 9300). After similar experiments in which concentrated hydrochloric acid (3 ml.) and dichloroacetic acid (16 g.) (severally) were used as catalysts, the enone (IV*c*;

R = Ac) was isolated in yields of 11 and 9%. When acetic acid with the theoretical amount of anhydride to combine with the hydroxyl groups was used as solvent, with trichloroacetic acid (2·25 g.) as catalyst, the yield was 36%. Aluminium chloride in acetic anhydride promoted a change in the sapogenin (assessed polarimetrically), but no Δ^{16}-20-ketosteroid could be obtained. A mixture of acetic anhydride and β-picoline failed to change the sapogenin. In the conditions described by Dauben *et al.* (*loc. cit.*, 1953) excessive darkening occurred.

After the formation of the furosten diacetate (II*c*; R = Ac) in the successful catalysed conversions another change set in, marked by a trend in the rotation to the negative side. Thus, cooled aliquot parts of a refluxing solution of the sapogenin (I*c*; R = Ac) in acetic anhydride made N with respect to dichloroacetic acid had $[\alpha]_D$ +40° and −20° after 1·5 hr. and 6 hr. respectively, and solutions of the ψ-sapogenin diacetate (II*c*; R = Ac) behaved similarly. The significance of these changes is manifest in the results of catalysed conversions taking place in cool acetic anhydride (see below).

Tigogenin acetate (I*a*; R = Ac) was more stable in conditions of the foregoing type: for instance, it was recovered after 23 hours' refluxing with acetic anhydride containing zinc acetate in suspension.

Lactone (VII; X = O, 5α-H) *of* 3β-*Acetoxy*-16β-*hydroxy*-11-*oxobisnor*-5α-*cholanic Acid*.—11-Oxotigogenin acetate (I*c*; R = Ac) (5 g.) was treated with acetic acid (125 ml.) and acetic anhydride (125 ml.) containing "AnalaR" phosphoric acid (2·7 ml.; *d*, 1·74; final concn. 0·11M), and kept in the dark for 40 days (the rotation was then constant). The solution was extracted with chloroform, washed with water, and evaporated. The residual gum, dissolved in acetic acid (60 ml.), was oxidised with 1·39N-chromic acid in 90% acetic acid (40 ml.) for 2·5 hr.; methanol was then added, and the solvents were distilled off *in vacuo*. Extraction of the steroid with ether (with salting of the aqueous phase), washing with water, and evaporation of the dried ($MgSO_4$) ether phase left a residue that gave a white solid when triturated with ether. Crystallisation from ethanol yielded the *lactone* (VII; X = O, 5α-H) (0·150 g., 3%), m. p. 250—262°. An analytical specimen was obtained by subliming this product at 220°/10^{-4} mm. and subsequently crystallising the sublimate from ethanol as laminæ, m. p. 266—268°, $[\alpha]_D^{21}$ −23° (*c*, 1·2), $\nu_{max.}$ (in $CHBr_3$) 1762 (γ-lactone), 1710 and 1250 (acetate), and 1710 cm.$^{-1}$ (ketone) (Found: C, 71·5; H, 8·3. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%). A solution of this lactone in CS_2 gave lactonic carbonyl absorption at $\nu_{max.}$ 1780 cm.$^{-1}$, as did the lactone of the 16β-hydroxybisnor-5α-cholanic acid (VII; X = H_2, 5α-H) (derived from tigogenin) and its 5β-isomer (VII; X = H_2, 5β-H) (derived from sarsasapogenin and smilagenin) (Tschesche and Hagedorn, *Ber.*, 1935, **68**, 1412; Farmer and Kon, *J.*, 1937, 414).

23ξ-*Acetylhecogenin* (VIII; R = H).—Hecogenin acetate (I*b*; R = Ac) (10 g.) in alcohol-free chloroform (100 ml.) was treated with 60% perchloric acid (2 ml.) in acetic anhydride (20 ml.). The solution became warm and reddened. It was left for 20 min., and washed with aqueous sodium hydroxide and water. The dried ($MgSO_4$) organic phase, on evaporation, left a yellow glass (11·32 g.) that was hydrolysed in 2·5 hr. in refluxing 10% ethanolic sodium hydroxide (100 ml.). Precipitation of the product with water and subsequent crystallisation from aqueous ethanol (charcoal) yielded 23ξ-*acetylhecogenin* (VIII; R = H) (2·04 g., 20%), m. p. 243—246°. It crystallised from acetonitrile as fine needles, m. p. 247—251°, $[\alpha]_D^{20}$ −14° (*c*, 0·42), $\nu_{max.}$ (Nujol) 3580 (hydroxyl), 1708 (ketone), and 1352 cm.$^{-1}$ (methyl ketone), and a pattern of bands (see below) that distinguish this compound from an ordinary *iso*sapogenin (Found: C, 73·2; H, 9·3. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%). This compound gave an immediate positive test for a ketone with 2:4-dinitrophenylhydrazine (cf. Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof, *J. Amer. Chem. Soc.*, 1947, **69**, 2167) and for a methyl ketone with sodium nitroprusside (Feigl, "Qualitative Analyse mit Hilfe von Tüpfelreaktionen," Akademische Verlagsgesellschaft m.b.H., Leipzig, 1935, p. 375). 3β-*Acetoxy*-23ξ-*acetylhecogenin* (VIII; R = Ac), made from the above compound (0·5 g.) with pyridine (2·5 ml.) and acetic anhydride (2·5 ml.) in 1 hr. at 90°, crystallises as fluffy needles (0·45 g.) (from aqueous acetone), m. p. 213—216°, $[\alpha]_D^{20}$ −22° (*c*, 1·06), $\nu_{max.}$ 1732 and 1240 (acetate), 1708 (ketone), 1352 (methyl ketone), 1010, 955, 935, and 900 cm.$^{-1}$ (23-substituted sapogenin; cf. Dickson and Page, *loc. cit.*) (the intensity of the peak at 1708 cm.$^{-1}$ suggested the presence of two carbonyl groups) (Found: C, 72·9; H, 8·9. $C_{31}H_{46}O_6$ requires C, 72·3; H, 9·0%).

Treatment of hecogenin acetate (I*b*; R = Ac) or 11-oxotigogenin acetate (I*c*; R = Ac) at 0° or room temperature with *ca.* 0·1N-perchloric acid in acetic anhydride for 1 hr. made the rotation negative, its magnitude depending markedly on the dilution and diluent. After the addition of potassium acetate, water precipitated the two products with indefinite m. p.s,

$[\alpha]_D^{20}$ +7·5° (*c*, 1·0), $\lambda_{max.}$ 274·5 mμ ($E_{1cm.}^{1\%}$ 174), $\nu_{max.}$ 1735 and 1238 (acetate), 1710 (ketone) and (weak) 1666 cm.$^{-1}$ (αβ-unsaturated ketone), and $[\alpha]_D^{25}$ +19° (*c*, 1·0), $\lambda_{max.}$ 275 mμ ($E_{1cm.}^{1\%}$ 117), $\nu_{max.}$ 1735 and 1240 (acetate), 1709 (ketone), and (weak) 1671 cm.$^{-1}$ (αβ-unsaturated ketone). Neither substance could be got pure. Each presumably contains the 23-acetylfurost-22-en. The second substance, derived from the 11-ketone (I*c*; R = Ac), was not appreciably changed by attempted oxidation with chromic oxide in acetic acid and the usual working up with alumina (see above); it gave a 2 : 4-dinitrophenylhydrazone, $\lambda_{max.}$ (in $CHCl_3$) 372 mμ ($E_{1cm.}^{1\%}$ 293).

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