## 1093. *Steroids Derived from Hecogenin. Part III.*[1] *The Photochemistry of Hecogenin Acetate.*

By Peter Bladon, William McMeekin, and Ivor A. Williams.

Photolysis of hecogenin acetate yields 3β-acetoxy-12,13-seco-5α,25D-spirost-13-en-12-one (lumihecogenin acetate) and 3β-acetoxy-12α,14α-epoxy-5α,25D-spirostan (photohecogenin acetate). The further transformation of these compounds into 14α-hydroxyhecogenin and into $\Delta^{14}$-unsaturated spirostan derivatives is also described.

The action of ultraviolet light on steroid ketones was first studied some twenty-five years ago by Butenandt and his co-workers.[2] They found that 17-oxo-steroids undergo inversion of the angular 18-methyl group adjacent to the carbonyl group. This reaction, now known to be reversible,[3] proceeds by fission of the 13,17-bond, which forms a diradical. Irradiation of 12-oxo-steroids has, apart from our preliminary communication,[4] not hitherto been reported, and it was of interest to compare the behaviour of these compounds in which the carbonyl groups is in a six- rather than a five-membered ring.

During this work, other workers have reported on the behaviour of other steroid ketones on irradiation. In particular photolysis of 11-oxo-[5] and 20-oxo-steroids[6] has afforded routes to compounds substituted on the rather inaccessible angular 19- and 18-methyl group, respectively.

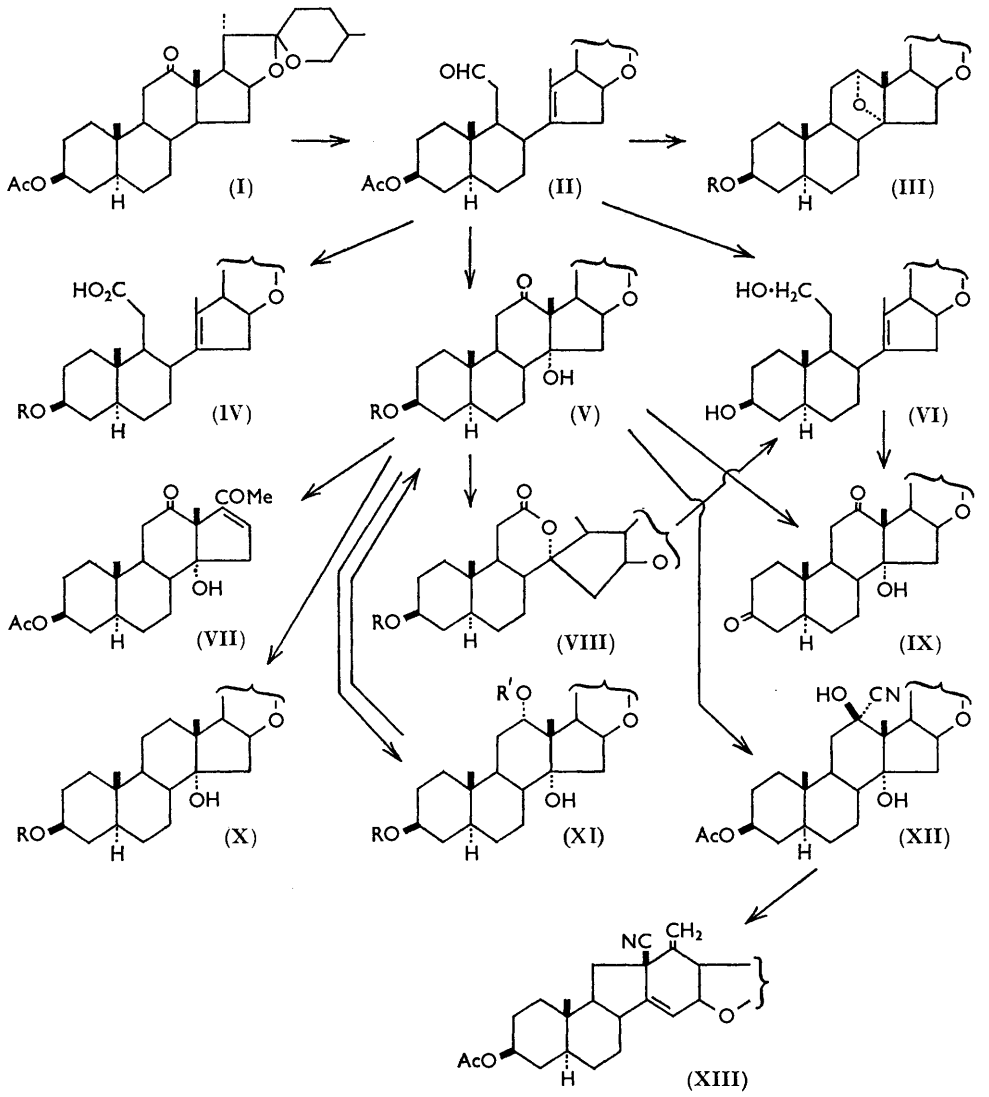
Ultraviolet irradiation of a dioxan solution of hecogenin acetate (I) gave, as the initial product, 3β-acetoxy-12,13-seco-5α,25D-spirost-13-en-12-one (lumihecogenin acetate) (II). By interrupting the reaction at the appropriate time, this product could be obtained in 80% yield. More prolonged irradiation resulted in further isomerisation to 3β-acetoxy-12α,14α-epoxy-5α,25D-spirostan (photohecogenin acetate) (III; R = Ac). The structures of these two photolysis products follow from properties and transformations described below.

*Lumihecogenin Acetate and 14α-Hydroxyhecogenin Acetate.*—The presence of an aldehyde group in lumihecogenin acetate is indicated by the peaks at 2740, 1709, and 1408 cm.$^{-1}$ in the infrared spectrum and the barely resolved triplet at $\tau$ 0·50 in the nuclear magnetic resonance spectrum. Attempts to prepare the corresponding 3β-hydroxy-compound by hydrolysis of the acetate group gave polymeric non-crystalline materials which did not

[1] Part II, Bladon and McMeekin, *J.*, 1961, 3504.
[2] Butenandt, Wolff, and Karlson, *Ber.*, 1941, **74**, 1308; Butenandt, Friedrich, and Poschmann, *Ber.*, 1942, **75**, 1931; Butenandt and Poschmann, *Ber.*, 1944, **77**, 392.
[3] Wehrli and Schaffner, *Helv. Chim. Acta*, 1962, **42**, 385.
[4] Bladon, McMeekin, and Williams, *Proc. Chem. Soc.*, 1962, 225.
[5] Wehrli, Heller, Schaffner, and Jeger, *Helv. Chim. Acta*, 1961, **44**, 2162; Heller, Wehrli, Schaffner, and Jeger, *ibid.*, 1962, **45**, 1261.
[6] Buchschacher, Cereghetti, Wehrli, Schaffner, and Jeger, *Helv. Chim. Acta*, 1959, **42**, 2122; Cereghetti, Wehrli, Schaffner, and Jeger, *ibid.*, 1960, **43**, 354; Wehrli, Cereghetti, Schaffner, and Jeger, *ibid.*, p. 367; Wehrli, Cereghetti, Schaffner, Urech, and Vischer, *ibid.*, 1961, **44**, 1927; Yang and Yang, *Tetrahedron Letters*, 1960, No. 4, 10.

yield the acetate on re-acetylation; presumably the aldehyde group underwent aldol condensation in these conditions.

Reduction of lumihecogenin acetate with lithium aluminium hydride in tetrahydrofuran gave a good yield of anhydrohecolyl alcohol [7] (VI), thus showing that in lumihecogenin acetate, ring c is split between C-12 and C-13. The position of the double bond in lumihecogenin acetate is not proved by the last reaction, since the position of the double bond in anhydrohecolyl alcohol has not hitherto been proved.[7] However, the absences



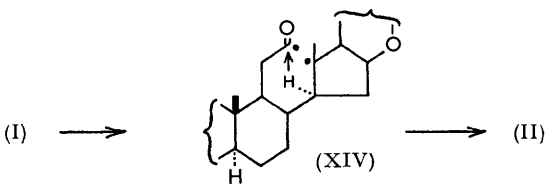

of a C=C stretching peak in the infrared spectrum, and of olefinic proton peaks in the nuclear magnetic resonance spectrum of lumihecogenin acetate, show that the double bond is tetrasubstituted, thus ruling out the remotely possible $\Delta^{14}$-structure. Of the two likely tetrasubstituted double-bond structures, $\Delta^{13}$ and $\Delta^{13(17)}$, we prefer the former,

[7] Rothman, Wall, and Eddy, *J. Amer. Chem. Soc.*, 1954, **76**, 527; Rothman and Wall, *ibid.*, 1955, **77**, 2228.

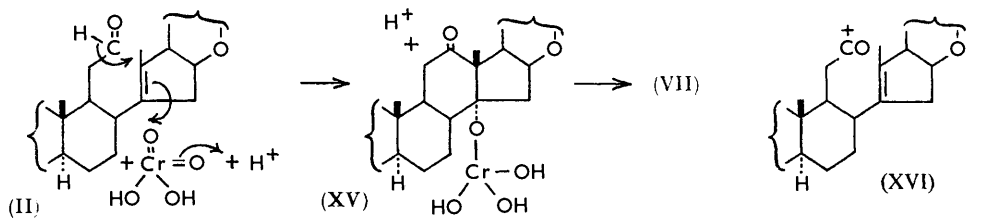
largely on mechanistic grounds: the initial step in the photochemical process is the formation of the diradical (XIV), which is transformed into an aldehyde product by transfer of a hydrogen atom to C-12. Scale models (*e.g.*, Dreiding models) show that of the two hydrogen atoms (at C-14 and C-17), only that at C-14 is sufficiently near C-12 to be transferred.*

Oxidation of lumihecogenin acetate with chromium trioxide in aqueous sulphuric acid and acetone [8] gave the expected anhydrohecolic acid 3-acetate [7] (IV) in only poor yield. The major product was neutral and is formulated as 14α-hydroxyhecogenin acetate (V; R = Ac) for the following reasons. Its infrared spectrum showed peaks at 3550(OH), 1739(OAc), 1706(12-$>$C=O), and 1250 cm.$^{-1}$ (OAc). Its optical rotatory dispersion curve was similar to that of hecogenin acetate, the amplitude of the Cotton effect being rather higher; this indicates that the immediate environment of the carbonyl group, in particular the configuration of the angular methyl group, is the same as in hecogenin acetate.

Unfortunately, the optical rotatory dispersion curve does not allow us to decide the configuration of the hydroxyl group: the Cotton-effect curve of methyl 3β-acetoxy-14-hydroxy-12-oxo-5β,14β-etianate is recorded [9] and the amplitude and sign ($a$ +130°) are similar to those of hecogenin acetate ($a$ +70°). The infrared spectrum of the oxidation product (V) in carbon tetrachloride solution shows that the hydroxyl group is weakly hydrogen-bonded (presumably to the carbonyl group). Models show that this is just possible with a 14α- but not with a 14β-hydroxyl group. (The third possibility, a 17α-hydroxyl group, would be very strongly bonded to a 12-ketone group.) Confirmatory evidence of the 14α-configuration of the hydroxyl group comes from work on photohecogenin acetate (see below).




The introduction of a 14α-hydroxyl group is also effected by oxidative cyclisation of anhydrohecolyl alcohol (VI); in this case concomitant oxidation at C-3 occurs. The product (IX) has also been obtained by oxidation of 14α-hydroxyhecogenin (V; R = H).




We presume that oxidation reaction proceeds as illustrated, the process being consistent with the accepted mechanisms of chromic acid oxidation of double bonds.[10] An alternative mechanism, involving oxidation of the aldehyde to the acid and cyclisation of the

* The reason why the 17-oxo-steroids undergo the inversion of the 13-methyl group on irradiation and not fission of ring D becomes clear on studying the models. With one less methylene group in the ring containing the carbonyl group, fission produces a diradical, which cannot collapse by either of the two hydrogen-transfer processes (14→17 or 16→13) without severe deformation of bond angles. This leaves recombination of the diradical to give starting material or the 13-epimer as the only alternative.

[8] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402; Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

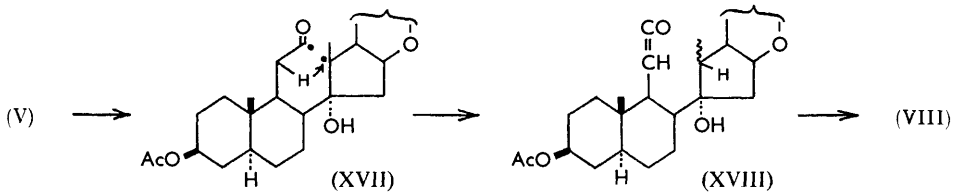
[9] Djerassi, Halpern, Halpern, Schindler, and Tamm, *Helv. Chim. Acta*, 1958, **41**, 250.

[10] Waters, *Quart. Rev.*, 1958, **12**, 277.

derived acylonium ion (XVI), is considered unlikely, since anhydrohecolic acid 3-acetate is recovered unchanged when subjected to the conditions of the oxidation.

In many reactions 14α-hydroxyhecogenin acetate resembles hecogenin acetate. For instance, Wolff–Kishner reduction by the Huang-Minlon procedure [11] gave 14α-hydroxytigogenin (X; R = H) in good yield. It was also possible to prepare an oxime (cf. refs. 1 and 12) and a cyanhydrin (XII), the latter being converted by thionyl chloride in pyridine with loss of both hydroxyl groups into the C-nor-D-homo-derivative (XIII).[13]

In contrast, by the standard method of degrading sapogenins,[14] 3β-acetoxy-14α-hydroxy-5α-pregn-16-ene-12,20-dione (VII) was obtained, in only poor yield. However, the compound had maximal ultraviolet light absorption [$\lambda_{max.}$ 228·5 mμ (ε 7320)] characteristic of a $\Delta^{16}$-12,20-dione.[15] Attempts to degrade the side chain of 14α-hydroxytigogenin acetate failed to give the desired 3β-acetoxy-14α-hydroxy-5α-pregn-16-en-20-one.




Ultraviolet irradiation of 14α-hydroxyhecogenin acetate gave a good yield of an isomeric product, the saturated spirolactone (VIII; R = H). In this case the intermediate diradical (XVII) cannot abstract a hydrogen from C-14; instead it passes into the substituted keten (XVIII), which reacts to form the cyclic ester (VIII). Hydrolysis of the compound served only to remove the 3-acetyl group, the lactone ring being unattacked. The structure of the spirolactone was proved by the formation of anhydrohecolyl alcohol (VI) on successive treatment with lithium aluminium hydride and perchoric acid in methanol.

Reduction of 14α-hydroxyhecogenin acetate with lithium aluminium hydride gave a mixture of triols from which only one compound, the 3β,12α,14α-triol (XI; R = R′ = H), was obtained crystalline. It yielded a crystalline 3-acetate (XI; R = Ac, R′ = H) and a 3,12-diacetate (XI; R = R′ = Ac).

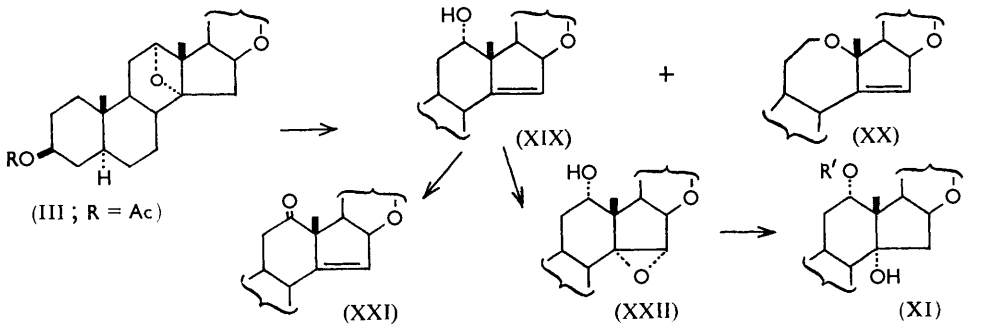
*Photohecogenin Acetate.*—The second irradiation product of hecogenin acetate is also obtained on irradiating lumihecogenin acetate. Its formulation as the 12α,14α-oxide (III; R = Ac), isomeric with hecogenin acetate, was not arrived at quickly since both photohecogenin acetate and its hydrolysis product crystallise in solvated forms. However, ultraviolet light absorption measurements and tests with tetranitromethane show that the compounds are saturated. The infrared spectrum of a carefully dried specimen of the acetate shows the absence of a hydroxyl group. A single acetate-carbonyl group, absent in the spectrum of the corresponding 3β-alcohol, shows the absence of a ketone group.

Treatment of photohecogenin acetate with lithium aluminium hydride resulted in removal of the 3-acetyl group only; the oxide ring was unattacked. The oxide ring also failed to react with sodium thiosulphate, a specific reagent for 1,2-epoxides.[16]

On brief treatment with the boron trifluoride–ether complex, photohecogenin acetate gave a mixture of two compounds, readily separated by chromatography on alumina. The nature of the first compound to be eluted (" Compound A ") is discussed below.

[11] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[12] Anliker, Rohr, and Heusser, *Helv. Chim. Acta*, 1955, **38**, 1171; Mazur, *J. Amer. Chem. Soc.*, 1959, **81**, 1454.
[13] Cf. Hirschmann, Snoddy, Hiskey, and Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013.
[14] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.
[15] Wagner, Moore, and Forker, *J. Amer. Chem. Soc.*, 1950, **72**, 1856.
[16] Ross, Tarbell, Lovett, and Cross, *J. Amer. Chem. Soc.*, 1956, **78**, 4675.

The second compound was recognised as 3β-acetoxyspirost-14-en-12α-ol (XIX; R = Ac). It was readily oxidised to 14,15-didehydrohecogenin acetate (XXI) which had the enhanced light absorption at 290 mμ (ε 252) characteristic of a βγ-unsaturated ketone.[17] The Cotton-effect curve did not show a large amplitude, however, and this is characteristic of such ketones when the double bond and the carbonyl group are in different rings.[18]




Treatment of the 14-en-12α-ol (XIX; R = Ac) with perbenzoic acid gave an epoxide formulated as the 14α,15α-epoxide (XXII) on the basis of a known behaviour of 14,15-double bonds.[19]

Reduction of the epoxide with lithium aluminium hydride afforded the same triol (XI; R = R′ = H) as was obtained by reduction of 14α-hydroxyhecogenin. Further, the triol (XI; R = R′ = H) was oxidised to 14α-hydroxyhecogenone (IX). This sequence of reactions provides additional evidence for the 14α-configuration of the hydroxyl group in 14α-hydroxyhecogenin derivatives.

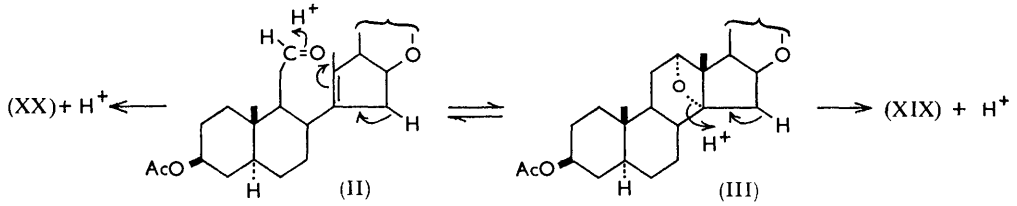
" Compound A " (above) contained no boron or fluorine. It was an isomer of hecogenin acetate, and its ultraviolet spectrum and the formation of a yellow colour with tetranitromethane showed that it was unsaturated. The infrared spectrum showed the absence of hydroxyl and ketonic-carbonyl groups. The nuclear magnetic resonance spectrum had a peak at τ 4·6 of area equivalent to one proton, showing that the double bond was trisubstituted. A broad band at τ 6·5 of area corresponding to four hydrogens is due to the two hydrogen atoms on C-27 and two other hydrogen atoms on carbon bonded to oxygen. On the basis of these observations the structure, 12a-oxa-c-homo-5α,25D-spirost-14-en-3β-yl acetate (XX; R = Ac) is assigned to " Compound A."

Some insight into the mode of formation of this compound was obtained in one of the experiments in which photohecogenin acetate treated with the boron–trifluoride ether complex gave a small quantity of lumihecogenin acetate (II). Lumihecogenin acetate was then treated with this reagent and it afforded " Compound A " (XX; R = Ac) and $\Delta^{14}$-hydroxytigogenin acetate (XIX; R = Ac) in the same proportions as were obtained from photohecogenin acetate. It thus appears that the initial step in this reaction is the establishment of an equilibrium between lumihecogenin acetate and photohecogenin acetate with subsequent transformation of the photohecogenin acetate into the 14-en-12α-ol and of lumihecogenin acetate into " Compound A."

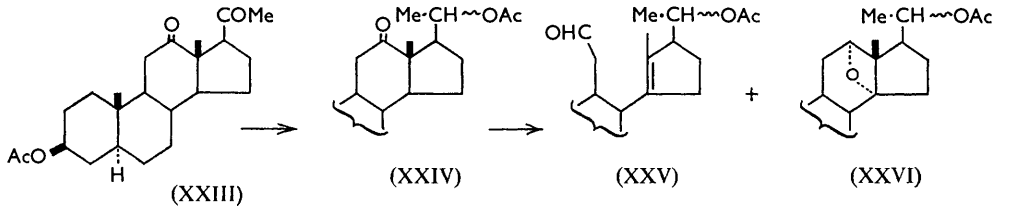
Since the transformations described above offer an easy route to the otherwise inaccessible 14α-hydroxy- and $\Delta^{14}$-unsaturated steroids, it was hoped to make use of them in synthesising 14α(and 14β)-hydroxy-derivatives of hormones. Because poor yields were obtained on degrading 14α-hydroxysapogenins, an alternative approach starting

[17] Cookson and Wariyar, *J.*, 1956, 2302.
[18] Moscowitz, Mislow, Glass, and Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 1945.
[19] Hofer, Linde, and Mayer, *Helv. Chim. Acta*, 1962, **45**, 1041.

from a pregnan-12-one derivative was necessary. Irradiation of 3β-acetoxy-5α-pregnane-12,20-dione [20] (XXIII) gave only non-crystalline products, presumably because simultaneous photolytic reactions involving both the 12- and the 20-ketone [6] groups occurred.




A suitable substrate was found in 3β,20ξ-diacetoxy-5α-pregnan-12-one [21] (XXIV). Irradiation of this in dioxan solution gave a mixture of the 12,13-seco-12-aldehyde (XXV) and




(XXIII) (XXIV) (XXV) (XXVI)

the 12α,14α-oxide (XXVI). The further transformation of the aldehyde (XXV) into a 14α-hydroxy-12-ketone has so far not been successful, and no crystalline materials were obtained on reaction of the oxide (XXVI) with the boron trifluoride–ether complex. We presume that replacement of the sapogenin side chain by the shorter pregnane two-carbon side chain is responsible for these differences in reactions.

## Experimental

Unless otherwise stated, optical rotations were determined for chloroform solutions, ultraviolet spectra were obtained with ethanolic solutions, and infrared spectra with potassium chloride discs on a Grubb-Parsons S4 instrument fitted with sodium chloride optics. M. p.s were determined on a Kofler block.

The alumina used for chromatography was neutralised and deactivated with 10% aqueous acetic acid (5 ml. per 100 g.).

Extracts were dried over anhydrous sodium sulphate before evaporation, unless stated otherwise.

Nuclear magnetic resonance spectra were, unless otherwise atated, obtained for carbon tetrachloride solutions in a Perkin-Elmer instrument operating at 40 Mc./sec. Tetramethylsilane was used as an internal standard and peak positions are recorded on the τ scale.[22]

*Ultraviolet Irradiation of Hecogenin Acetate.*—In preliminary experiments on a small scale, solutions of hecogenin acetate in dry dioxan (5 g. per 100 ml.) were irradiated in quartz flasks by means of a 500-w Hanovia medium-pressure mercury lamp (type U.V.S. 500). Absence of air was found to be essential and was ensured by one of two procedures: (*a*) either the reaction mixture was allowed to reflux by placing the flask over the lamp, and passing a slow stream of purified oxygen-free nitrogen over the surface of the liquid; or (*b*) the reaction was conducted in a closed flask, from which the air had been removed by several evacuations and refillings with purified nitrogen; in this case the flask was placed alongside the lamp and was cooled by a stream of cold water.

On a large scale [procedure (*c*)] a Hanovia photochemical reaction apparatus was used. In this, the 500-w medium-pressure mercury lamp was placed in a double-walled quartz thimble which fits inside the reaction flask and through which cold water circulates. The reaction mixture was stirred and purified oxygen-free nitrogen was slowly bubbled through it. When

[20] Mueller, Stobaugh, and Winniford, *J. Amer. Chem. Soc.*, 1953, **75**, 4888.
[21] Kirk, Patel, and Petrow, *J.*, 1957, 1046.
[22] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.

hecogenin acetate (250 g.) in dioxan (9 l.), was treated thus, the solution showed a change in $[\alpha]_D$ from $\pm 0°$ to $-39·4°$ during 8 hr., $\alpha$ thereafter remaining constant. After 9·25 hr. irradiation the dioxan solution was evaporated, and the solid product crystallised from methanol containing a little pyridine, to give 3β-*acetoxy*-12,13-*seco*-5α,25D-*spirost*-13-*en*-12-*one* (*lumihecogenin acetate*) (II), in three crops, m. p. 140—144° (total yield 201 g., 80%). A sample recrystallised from methanol had m. p. 143—147°, $[\alpha]_D$ −46° (*c* 1·0) (Found: C, 73·7; H, 9·7. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%), $\lambda_{max.}$ 204 mμ (ε 4800), $\nu_{max.}$ 2740 (CHO), 1739 (OAc), 1709 (CHO), 1412 (CHO), 1240 cm.$^{-1}$ (OAc), τ 0·50 (CHO), 5·45 (3α-H + 16α-H), 6·40 and 6·75 (2b-$H_2$), 8·00 ($CH_3$·CO + 13-$CH_3$), 9·18 (10-$CH_3$), R.D. (in MeOH) negative plain curve.

In a similar experiment with hecogenin acetate (100 g.) and dioxan (7 l.) the same change of specific rotation was noted in the first 8 hours' irradiation. Thereafter, the reaction was followed by removing a portion of the solution, evaporating it, and observing the infrared spectrum of the residue in carbon tetrachloride. The peak at 1709 cm.$^{-1}$ decreased in intensity and disappeared completely in 36 hr. The dioxan solution was passed through a column of alumina (not deactivated) to remove traces of peroxides, and evaporated. Crystallisation of the residue from methanol gave 3β-*acetoxy*-12α,14α-*epoxy*-5α,25D-*spirostan* (*photohecogenin acetate*) (III; R = Ac) (30 g.), m. p. 205—206° (from methanol), $[\alpha]_D$ −38·7° (*c* 1·61) (Found: C, 72·4; H, 9·2. $C_{29}H_{44}O_5.0·5CH_3$·OH requires C, 72·55; H, 9·4%), $\nu_{max.}$ 1739 and 1242 cm.$^{-1}$, R.D. (in MeOH) negative plain curve. Identical material was obtained by irradiation of lumihecogenin acetate in dioxan by method (*a*) for 39 hr. or by method (*b*) for 20 hr.

*Derivatives of Lumihecogenin Acetate.*—This acetate (215 mg.) in 2-methyldioxolan (15 ml.) containing toluene-*p*-sulphonic acid was refluxed for 20 hr. Ether was added and the solution washed with aqueous potassium hydrogen carbonate and dried. Evaporation afforded the *ethylene acetal*, prisms (from methanol), m. p. 182—185°, $[\alpha]_D$ −36·2° (*c* 1·27) (Found: C, 72·25; H, 9·35. $C_{31}H_{48}O_6$ requires C, 72·1; H, 9·35%), $\lambda_{max.}$ 206 mμ (ε 4480), $\nu_{max.}$ (in $CCl_4$) 1730 and 1240 cm.$^{-1}$.

Lumihecogenin acetate (195 mg.) in ethanol (10 ml.) was refluxed with semicarbazide hydrochloride (200 mg.) and sodium acetate (300 mg.) for 15 min. Addition of water gave the *semicarbazone*, needles (from aqueous methanol), m. p. 193—196°, $[\alpha]_D$ −13° (*c* 1·23) (Found: C, 68·1; H, 9·0; N, 7·65. $C_{30}H_{47}N_3O_5$ requires C, 68·0; H, 8·95; N, 7·9%).

Attempts to prepare an oxime and a 2,4-dinitrophenylhydrazone gave amorphous products.

*Oxidation of Lumihecogenin Acetate.*—Lumihecogenin acetate (10·5 g.) in acetone (700 ml.) was treated with 8N-chromium trioxide in aqueous sulphuric acid [8] (15 ml.) at room temperature for 5 min. Aqueous sodium hydrogen sulphite and dilute hydrochloric acid were added, and the solution was extracted with ether (3 × 100 ml.). The extracts were washed with water, dilute aqueous potassium hydroxide (three times), and water, and dried. Evaporation gave 14α-hydroxyhecogenin acetate (V; R = Ac), rods (from acetone), m. p. 225—229°, or needles (from methanol), m. p. 231—235°, $[\alpha]_D$ −6° (*c* 0·74) (Found: C, 70·8; H, 8·8. $C_{29}H_{44}O_6$ requires C, 71·3; H, 9·1%), $\nu_{max.}$ (in $CCl_4$) 3540 (bonded OH), 1739 (OAc), 1706 (12-$\rangle$C=O) and 1250 cm.$^{-1}$ (OAc), τ 5·65b (3αH + 16αH), 8·04 ($CH_3$·CO), 9·0 and 9·18 (10- and 13-$CH_3$); R.D. (in MeOH); $[\phi]_{589}$ −8°; $[\phi]_{312·5}$ +62° (peak); $[\phi]_{270}$ −96° (trough); *a* + 158°.

Acidification of the alkaline washings and extraction with ether afforded a syrup, which was boiled with methanol (100 ml.) containing potassium hydroxide (2 g.) and water (10 ml.) for 1 hr. Dilution with water, acidification, and extraction with ether gave a syrup (960 mg.). Crystallisation from aqueous acetone gave anhydrohecolic acid (IV; R = H), m. p. and mixed m. p. 223—226°, having an infrared spectrum identical with that of an authentic sample.

3β,14α-*Dihydroxy*-5α,25D-*spirostan*-12-*one* (V; R = H) prepared by saponification of 14α-hydroxyhecogenin acetate formed prisms (from acetone–isopentane), m. p. 270—272°, $[\alpha]_D$ +16·4 (*c* 0·94) (Found: C, 72·15; H, 9·2. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5%), $\nu_{max.}$ 3520 (OH) and 1708 cm.$^{-1}$ (12-$\rangle$C=O).

*Reduction of Lumihecogenin Acetate with Lithium Aluminium Hydride.*—Lumihecogenin acetate (280 mg.) was refluxed with lithium aluminium hydride (220 mg.) in dry ether for 5 min. The excess of reagent was destroyed by wet ether. Addition of dilute acid and extraction of the product in the usual way gave a syrup, which on trituration with acetone–isopentane gave anhydrohecolyl alcohol (VI), m. p. and mixed m. p. 180—182°, $[\alpha]_D$ −53° (*c* 0·83) (Found: C, 74·9; H, 10·4. Calc. for $C_{27}H_{44}O_4$: C, 74·95; H, 10·25%), having an infrared spectrum identical with that of an authentic specimen. Rothman, Wall, and Eddy [7] report m. p. 174—176°.

14α-*Hydroxy*-5α,25D-*spirostan*-3,12-*dione* (IX).—(*a*) Anhydrohecolyl alcohol (VI) (130 mg.) in acetone (10 ml.) was oxidised with 8N-chromium trioxide in aqueous sulphuric acid [8] (2 ml.), as described above. The *diketone*, crystallised from acetone isopentane, had m. p. 259—261°, $[\alpha]_D$ +31·5° (*c* 1·08) (Found: C, 72·5; H, 8·95. $C_{27}H_{40}O_5$ requires C, 72·95; H, 9·1%), $\nu_{max.}$ 3510 (bonded OH) and 1712 cm.$^{-1}$ (3- and 12- >C=O). (*b*) 14α-Hydroxyhecogenin (V; R = H) (240 mg.) in acetone (50 ml.), treated with the 8N-chromic acid reagent (0·5 ml.) for 5 min., gave the diketone (221 mg.), m. p. 256—259°, identical with material prepared by method (*a*).

14α-*Hydroxyhecogenin Acetate Oxime*.—14α-Hydroxyhecogenin acetate (1·0 g.) and hydroxylamine hydrochloride (1·0 g.) in pyridine (16 ml.) were warmed on a steam-bath for 3 hr. Addition of water and extraction with ether afforded the *oxime*, m. p. (from chloroform–methanol) 287—291° (change of form at 230°), $[\alpha]_D$ ±0° (*c* 0·49) (Found: C, 69·5; H, 9·05; N, 3·2. $C_{29}H_{45}NO_6$ requires C, 69·2; H, 9·0; N, 2·8%), $\nu_{max.}$ 3400 (OH), 1724 (OAc), 1638 (>C=N·OH), and 1240 cm.$^{-1}$ (OAc). Saponification afforded the *oxime* of 14α-hydroxyhecogenin m. p. 232—236° (from methanol), $[\alpha]_D$ −0·8° (*c* 0·51) (Found: C, 69·5; H, 9·6; N, 3·3. $C_{22}H_{43}NO_4$,0·5$CH_3$·OH requires C, 69·2; H, 9·5; N, 2·9%), $\nu_{max.}$ 3425 (OH) and 1638 cm.$^{-1}$ (>C=N·OH).

5α,25D-*Spirostan*-3β,14α-*diol* (X; R = H).—14α-Hydroxyhecogenin acetate (5·73 g.) in ethylene glycol (100 ml.) containing 100% hydrazine hydrate (5 ml.) was boiled for 45 min. After the mixture had been cooled, potassium hydroxide (20 g.) in water (20 ml.) was added and the mixture boiled under reflux for 20 min. The water and the excess of hydrazine were distilled off and the residue was refluxed for 4 hr. After the mixture had cooled, water was added, and the mixture was made acid with dilute hydrochloride acid. The product isolated by chloroform-extraction in the usual way was a solid (5·13 g.). Crystallisation from acetone gave the *diol* (X; R = H), m. p. 211—212°, $[\alpha]_D$ −58·8° (*c* 0·47) (Found: C, 75·2; H, 10·1. $C_{27}H_{44}O_4$ requires C, 75·0; H, 10·25%), $\nu_{max.}$ 3440 cm.$^{-1}$ (OH). Acetylation gave the 3-*acetate* (X; R = Ac), m. p. 187—189° (from methanol, $[\alpha]_D$ −60·8 (*c* 0·56) (Found: C, 73·4; H, 9·4. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·7%), $\nu_{max.}$ (in $CCl_4$) 3590 (OH), 1754 (OAc), and 1242 cm.$^{-1}$ (OAc).

The 3-*benzoate* (X; R = Bz), crystallised from chloroform–acetone, had m. p. 219—224°, $[\alpha]_D$ −59·5° (*c* 0·49) (Found: C, 76·0; H, 9·1. $C_{34}H_{48}O_5$ requires C, 76·1; H, 9·0%), $\nu_{max.}$ 1710, 1600, 1579, and 1277 cm.$^{-1}$.

3β-*Acetoxy*-14α-*hydroxy*-5α-*pregn*-16-*ene*-12,20-*dione* (VII).—14α-Hydroxyhecogenin acetate (2·1 g.) was refluxed with octanoic acid (4 ml.) and octanoic anhydride (2·2 ml.) for 2 hr. Water was added, and the mixture extracted with ether. The extracts were washed with aqueous alkali, dried, and evaporated. The product (2·62 g.) was refluxed with 10% methanolic potassium hydroxide (100 ml.) for 2 hr. The product (1·65 g.), isolated by ether-extraction, was treated with acetic anhydride (4 ml.) and pyridine (25 ml.) at room temperature overnight. The acetylated material (1·66 g.) isolated in the usual way was dissolved in acetic acid (16 ml.) and treated with a solution of chromium trioxide (436 mg.) and sodium acetate (1 g.) in 90% aqueous acetic acid (28 ml.) and kept at room temperature for 2 hr. The excess of oxidant was removed by adding dilute mineral acid and aqueous sodium hydrogen sulphite. Isolation by ether-extraction afforded a brown syrup (1·51 g.). This was dissolved in 1 : 1 light petroleum–benzene (40 ml.) and treated with active alumina (10 g.) at room temperature overnight. The alumina was filtered off and washed with ether. The filtrates were evaporated, to give a yellow syrup (1·30 g.). This was dissolved in benzene and chromatographed on alumina (60 g.). Elution with benzene gave unchanged 14α-hydroxyhecogenin acetate (187 mg.), followed by oily material (812 mg.). Ether eluted 3β-*acetoxy*-14α-*hydroxy*-5α-*pregn*-16-*ene*-12,20-*dione* (VII) (181 mg.) which crystallised from methanol as rods, m. p. 255—256° (change of form at 210° to needles), $[\alpha]_D$ +50·8° (*c* 0·58) (Found: C, 71·7; H, 8·3. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%), $\lambda_{max.}$ 228·5 mμ (ε 7320), $\nu_{max.}$ 3495 (OH), 1740 (OAc), 1693 (12- >C=O), 1670 (20- >C=O) 1609 (C=C), 1235 cm.$^{-1}$ (OAc).

3β-*Acetoxy*-14α-*hydroxy*-12,13-*seco*-5α,25D-*spirostan*-12-*oic Acid Lactone* (VIII; R = Ac).—14α-Hydroxyhecogenin acetate (II; R = Ac) (2·0 g.) was dissolved in dioxan (100 ml.) and irradiated in a quartz flask at the b. p. by a 500-w mercury lamp [method (*a*) above]. The specific rotation changed from −6° to −20° during 5 hr. and thereafter remained constant. After 7 hr. the dioxan was removed *in vacuo* and the residue crystallised from methanol–acetone to yield the *spirolactone* (VIII; R = Ac), m. p. 247—252°, $[\alpha]_D$ −22·3° (*c* 1·26), −21·0° (*c* 0·33 in dioxan) (Found: C, 71·3; H, 9·3. $C_{29}H_{44}O_6$ requires C, 71·3; H, 9·1%), $\nu_{max.}$ (in $CCl_4$) 1738 and 1239 cm.$^{-1}$.

Saponification in the usual way in refluxing methanol gave 3β,14α-*dihydroxy*-12,13-*seco*-5α,25D-*spirostan*-12-*oic acid* 12→14-*lactone* (VIII; R = H), m. p. 195—200° (from chloroform–acetone), $[\alpha]_D$ −19·3°) (Found: C, 71·4; H, 9·5. $C_{27}H_{44}O_5,C_3H_6O$ requires C, 71·4; H, 9·6%), $\nu_{max.}$ 3390 (OH) and 1724 cm.$^{-1}$ (6-membered ring lactone).

*Conversion of the Spirolactone into Anhydrohecolyl Alcohol.*—The spirolactone acetate (VIII; R = Ac) (1·55 g.) in tetrahydrofuran (100 ml.) was treated with lithium aluminium hydride (700 mg.) and refluxed for 3·5 hr. After destruction of the excess of reagent with wet tetrahydrofuran, the product was isolated with ether in the usual way. It formed an amorphous mass (1·36 g.). A portion of this (990 mg.) was dissolved in methanol (50 ml.), 70% aqueous perchloric acid (1 ml.) was added, and the solution was set aside overnight. The product (650 mg.), isolated in the usual way by addition of water and extraction with ether, crystallised from acetone to give anhydrohecolyl alcohol (VI), m. p. and mixed m. p. 173—177°, having an infrared spectrum identical with that of authentic material.

14α-*Hydroxyhecogenin Acetate Cyanohydrin* (XII).—To a solution of 14α-hydroxyhecogenin acetate (V; R = Ac) (6·0 g.) in chloroform (45 ml.) and glacial acetic acid (17 ml.) at 0° was added a suspension of potassium cyanide (20 g.) in methanol (72 ml.), and the mixture was stirred for 2·5 hr. Water was added and the chloroform layer was separated and dried. Evaporation of the chloroform (which still contained some acetic acid) gave 3β-*acetoxy*-12α-*cyano*-5α,25D-*spirostan*-12β,14α-*diol* (XII) (4·6 g.), m. p. (from methanol) 245—267° (decomp.) (change of form at 238°), $[\alpha]_D$ −11·5° (*c* 0·61) (Found: C, 69·5; H, 9·1; N, 2·7. $C_{30}H_{45}NO_6$ requires C, 69·9; H, 8·8; N, 2·7%), $\nu_{max.}$ 3575 and 3370 (OH), 2250 (C≡N), 1710 (OAc), and 1242 cm.$^{-1}$ (OAc).

*Action of Thionyl Chloride in Pyridine on* 14α-*Hydroxyhecogenin Acetate Cyanohydrin.*—The cyanohydrin (XII) (1·2 g.) in dry pyridine (20 ml.) was treated at 0° with pure thionyl chloride (0·8 ml.). The mixture was kept overnight at room temperature, then poured on ice. The precipitate was filtered off and dissolved in chloroform, washed with dilute hydrochloric acid, water, aqueous potassium hydrogen carbonate, and water, dried, and recovered. The residue, crystallised from chloroform–methanol, gave 3β-*acetoxy*-13β-*cyano*-17α-*methylene*-C-*nor*-D-*homo*-5α,25D-*spirost*-14-*ene* (XIII) (0·564 g.), m. p. (from chloroform–methanol) 244—248° (change of form at 230—236°), $[\alpha]_D$ +2·9° (*c* 0·56) (Found: C, 75·0; H, 8·0; N, 2·7. $C_{30}H_{41}NO_4$ requires C, 75·1; H, 8·6; N, 2·9%), $\nu_{max.}$ 3090 (>C=CH$_2$), 2240 (C≡N), 1739 (OAc), 1665 and 1620 (>C=C<), and 1240 cm.$^{-1}$ (OAc).

*Reduction of* 14α-*Hydroxyhecogenin Acetate with Lithium Aluminium Hydride.*—14α-Hydroxyhecogenin acetate (V; R = Ac) (5 g.) and lithium aluminium hydride (2·5 g.) in dry tetrahydrofuran (150 ml.) were refluxed for 3 hr. The excess of the hydride was destroyed by wet tetrahydrofuran, and the product (4·53 g.) was isolated from the acidified solution by ether-extraction. The amorphous solid was treated in pyridine (35 ml.) with acetic anhydride (8 ml.), kept at room temperature for 6 hr., and poured into water. The amorphous product (4·7 g.), isolated in the usual way, was dissolved in benzene and absorbed on a column of alumina (250 g.). Elution with benzene gave tigogenin acetate (191 mg.), m. p. 208—212°, $[\alpha]_D$ −72° (*c* 0·64), a known impurity in the hecogenin acetate used as starting material. Elution with benzene–ether gave material which failed to crystallise (2·93 g.) and was not investigated further. Elution with ether gave 3β-*acetoxy*-5α,25D-*spirostan*-12α,14α-*diol* (XI; R = Ac, R′ = H) (from methanol) (1·35 g.), m. p. 219—222·5° (change of form at 199°),$[\alpha]_D$ −17·4° (*c* 0·98) (Found: C, 70·7; H, 9·3. $C_{29}H_{46}O_6$ requires C, 71·0; H, 9·45%), $\nu_{max.}$ (in $CCl_4$) 3655 (OH), 1735 (OAc), and 1239 cm.$^{-1}$ (OAc).

The above monoacetate (XI; R = Ac, R = H) (1·09 g.) with pyridine (10 ml.) and acetic anhydride (3 ml.) (steam-bath temperature; 3 hr.) gave 3β,12α-*diacetoxy*-5α,25D-*spirostan*-14α-*ol* (XI; R = R′ = Ac) (1·1 g.), m. p. 223—225·5° (from methanol), $[\alpha]_D$ −12·2° (*c* 0·49) (Found: C, 70·05; H, 9·0. $C_{31}H_{48}O_7$ requires C, 69·9; H, 9·1%), $\nu_{max.}$ (in $CCl_4$) 3545 (OH), 1739 (OAc), and 1238 cm.$^{-1}$ (OAc). A mixture of the mono- and di-acetate melted at 193—222°.

Saponification of the monoacetate (XI; R = Ac, R′ = H) gave 5α,25D-*spirostan*-3β,12α,14α-*triol* (XI; R = R′ = H), m. p. 180—184° (from methanol), $[\alpha]_D$ −48·0° (*c* 0·635) (Found: C, 72·6; H, 10·4. $C_{27}H_{44}O_5$ requires C, 72·3; H, 9·9%), $\nu_{max.}$ 3420 cm.$^{-1}$ (OH).

*Oxidation of* 3β-*Acetoxy*-5α,25D-*spirostan*-12α,14α-*diol.*—The diol (XI; R = Ac; R′ = H) (49·5 mg.) in acetone (2 ml.) was treated with 8N-chromium trioxide in aqueous sulphuric acid. After 5 min. at room temperature, the excess of reagent was removed by addition of sodium hydrogen sulphite and hydrochloric acid. The product, isolated by ether-extraction and

crystallised from methanol, gave 14α-hydroxyhecogenin acetate (V; R = Ac) (36 mg.) m. p. and mixed m. p. 231—235°, having an infrared spectrum identical with that of authentic material.

12α,14α-*Epoxy*-5α,25D-*spirostan*-3β-*ol*.—Photohecogenin acetate was saponified in the usual way, to yield 12α,14α-*epoxy*-5α,25D-*spirostan*-3β-*ol* (III; R = H) as diamond-shaped crystals (from acetone–methanol), m. p. 166—170°, $[\alpha]_D$ −41° (*c* 1·4) (Found: C, 74·6; H, 10·0. $C_{27}H_{42}O_4,0{\cdot}5CO(CH_3)_2$ requires C, 74·5; H, 9·9%), $\nu_{max.}$ 3410 and 1720 cm.$^{-1}$ (acetone of crystallisation). Crystallisation from aqueous methanol gave needles, m. p. 204—208°. These had an infrared spectra identical with that of the lower-melting form except for absence of the peak at 1720 cm.$^{-1}$.

Reduction of photohecogenin acetate with lithium aluminium hydride in ether gave photohecogenin, identical with material prepared by saponification.

Acetylation of photohecogenin gave photohecogenin acetate, m. p. 203—206°.

*Action of Boron Trifluoride–Ether Complex on Photohecogenin Acetate*.—A solution of photohecogenin acetate (III; R = Ac) (5·0 g.) in dry benzene (60 ml.) was treated with the boron trifluoride–ether complex (0·4 ml.; freshly redistilled) and kept at room temperature for 5 min. Water was added and the benzene layer was diluted with ether, washed with aqueous potassium hydrogen carbonate, dried, and evaporated. The amorphous residue (5·0 g.) was dissolved in benzene and absorbed on a column of alumina (200 g.). Elution with benzene gave, first, an oil (0·793 g.) and then 12α-*oxa*-c-*homo*-5α,25D-*spirost*-14-*en*-3β-*yl acetate* (*Compound A*) (XX; R = Ac) (1·97 g.), m. p. 313—314° (from methanol), $[\alpha]_D$ +33·2° (*c* 0·71) (Found: C, 73·7; H, 9·2. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·3%), $\nu_{max.}$ (in $CS_2$) 1734 (OAc), 1650 (>C=C<), and 1240 cm.$^{-1}$ (OAc), τ 4·60 (15-H), 5·25 (complex; 16αH + 3α-H), 6·50 (broad, 12-$H_2$ + 26-$H_2$), 8·00 ($CH_3$·CO), 8·98 and 9·23 (10- and 13-$CH_3$). Elution with 19 : 1 benzene–ether gave unchanged photohecogenin acetate (0·533 g.). On one occasion lumihecogenin was isolated at this stage. Elution with ether gave 3β-*acetoxy*-5α,25D-*spirost*-14-*en*-12α-*ol* (XIX; R = Ac) (2·574 g.) (from methanol), m. p. 235° (change of form at 230—233°, $[\alpha]_D$ +47·6° (*c* 0·63) (Found: C, 72·8; H, 9·3. $C_{29}H_{44}O_5,0{\cdot}5CH_3$·OH requires C, 72·55; H, 9·4%), $\nu_{max.}$ (in $CS_2$) 3545 (OH), 3060 (>C=H–), 1735 (OAc), 1645 (>C=C<), and 1240 cm.$^{-1}$ (OAc).

Saponification of 12α-oxa-c-homo-5α,25D-spirost-14-en-3β-yl acetate gave material, m. p. 270—290°, which did not crystallise. Reacetylation gave back the pure 3β-acetate, however.

*Action of Boron Trifluoride–Ether Complex on Lumihecogenin Acetate*.—Lumihecogenin acetate (II) (4·93 g.) in anhydrous benzene (60 ml.) was treated with the boron trifluoride–ether complex (0·4 ml.; freshly redistilled) at room temperature for 5 min. By isolation of the product, followed by chromatography as described in the preceding experiment, there were isolated: (*a*) 12a-oxa-c-homo-5α,25D-spirost-14-en-3β-yl acetate (XX; R = Ac) (1·61 g.), m. p. 280—282° (different crystalline from from that previously described: the infrared spectra were, however, identical): (*b*) hecogenin acetate (0·72 g.) (a known impurity in the lumihecogenin acetate used); and (*c*) 3β-acetoxy-5α,25D-spirost-14-en-12α-ol (XIX; R = Ac) (2·63 g.), identical with that previously described.

*Oxidation of* 3β-*Acetoxy*-5α,25D-*spirost*-14-*en*-12α-*ol*.—3β-Acetoxy-12α-hydroxy-5α,25D-spirost-14-en (XIX; R = Ac) in acetone (80 ml.) was treated with 8N-chromic acid in aqueous sulphuric acid (2 ml.), and the mixture was kept at room temperature for 5 min. Addition of water, aqueous sodium hydrogen sulphite, and dilute hydrochloric acid, followed by ether-extraction in the usual way, gave 3β-*acetoxy*-5α,25D-*spirost*-14-*en*-12-*one* (XXI; R = Ac) (1·82 g.), m. p. 213—215° (from chloroform–methanol), $[\alpha]_D$ +65·4° (*c* 0·69) (Found: C, 74·3; H, 9·0. $C_{29}H_{42}O_5$ requires C, 74·0; H, 9·0%), $\lambda_{max.}$ 294 mμ (ε 252), $\nu_{max.}$ 3030 (>C=H–), 1735 (OAc), 1708 (>C=O), 1635 (>C=C<), and 1238 cm.$^{-1}$ (OAc), τ 4·55 (15-H), 5·25 (complex-16aH + 3αH), 8·00 ($CH_3$·CO); R.D. (in MeOH): $[\phi]_{589}$ + 7°; $[\phi]_{500}$ + 9°; $[\phi]_{408}$ + 15°; $[\phi]_{305}$ + 63° (peak) $[\phi]_{282}$ + 23° (trough); *a* + 40°.

This compound was irradiated in dioxan solution by ultraviolet light in the usual way. Although $[\alpha]_D$ changed from +68·5° to +7·7° in 5 hr., isolation of the product and chromatography gave only amorphous material having $[\alpha]_D$ −17·5°.

*Action of Perbenzoic Acid on* 3β-*Acetoxy*-5α,25D-*spirost*-14-*en*-12α-*ol*.—The steroid (313 mg.) was treated in benzene (8 ml.) with 0·508N-perbenzoic acid in benzene (6 ml.). After 24 hr. at room temperature the solution was diluted with ether and washed with aqueous potassium hydroxide, then water, and dried. Evaporation afforded 3β-*acetoxy*-14α,15α-*epoxy*-5α,25D-*spirostan*-12α-*ol* (XXII; R = Ac), m. p. 270—274° (change of form at 255°) (from methanol),

$[\alpha]_D$ −35·6° (*c* 0·52) (Found: C, 70·9; H, 9·1. $C_{29}H_{44}O_6$ requires C, 71·3; H, 9·1%), $\nu_{max.}$ 3450 (OH), 1725 (OAc), and 1242 cm.$^{-1}$ (OAc).

*Reduction of* 3β-*Acetoxy*-14α,15α-*epoxy*-5α,25D-*spirostan*-12α-*ol with Lithium Aluminium Hydride.*—The foregoing epoxide (1·69 g.) and lithium aluminium hydride (1·61 g.) in tetrahydrofuran were refluxed for 2·25 hr. Isolation by the usual procedure afforded the crude 3β,12α,14α-triol (1·59 g.). A portion of this (50 mg.) in acetone (5 ml.) was oxidised by 8N-chromic acid in aqueous sulphuric acid (0·5 ml.), giving 14α-hydroxy-5α,25D-spirostan-3,12-dione (IX) (26 mg.), m. p. and mixed m. p. 252—257°, having an infrared spectrum identical with that of authentic material.

The remaining crude triol was dissolved in pyridine (20 ml.), and acetic anhydride (2 ml.) was added. The solution was kept overnight at room temperature. Isolation of the product gave 3β-acetoxy-5α,25D-spirostan-12α,14α-diol (XI; R = Ac, R′ = H), m. p. 225—229° (from methanol). This material was a different crystalline form from that already recorded above. The mixture showed no m. p. depression, however, and the infrared spectra were identical.

*Attempted Hydrogenation of* 3β-*Acetoxy*-5α,25D-*spirost*-14-*en*-12α-*ol.*—Subjection of the olefin to hydrogenation in presence of platinum oxide in ethyl acetate or of Raney nickel in dioxan resulted in no uptake of hydrogen and quantitative recovery of starting material. With platinum oxide in acetic acid only part of the starting material was recovered and some polar product, eluted from an alumina column by 99 : 1 ether–methanol, was obtained as an amorphous solid.

*Ultraviolet Irradiation of* 3β,20ξ-*Diacetoxy*-5α-*pregnan*-12-*one.*—The procedure described by Petrow and his co-workers [21] was used for the conversion of 3β-acetoxy-5α-pregnane-12,20-dione (XXIII) into 3β,20ξ-diacetoxy-5α-pregnane-12-one (XXIV). It had m. p. 136—139°, $[\alpha]_D$ +94·2° (in dioxan). A solution of the diacetate (1·766 g.) in dioxan (180 ml.) was irradiated by method (*b*). During 9·5 hr., $[\alpha]_D$ changed from $[\alpha]_D$ +94·2° to +7·9°. Removal of the solvent left a clear gum. This was chromatographed in benzene on alumina (100 g.). Elution with benzene gave, first, 3β,20ξ-*diacetoxy*-C-*seco*-5α-*pregn*-13-*en*-12-*al* (XXV) (511 mg.), m. p. 124—126·5° (from di-isopropyl ether), $[\alpha]_D$ +5·65° (*c* 0·64) (Found: C, 71·8; H, 9·4. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·15%), $\nu_{max.}$ 2720 (CHO), 1725 (>C=O), 1412 (CHO), and 1239 cm.$^{-1}$ (OAc), τ 0·5 (CHO), 5·20 (complex 3α − H + 20-H), 8·05 ($CH_3$·CO + 13-$CH_3$), and 9·15 (10-$CH_3$)

Subsequent benzene fractions eluted 3β,20ξ-*diacetoxy*-12α,14α-*epoxy*-5α-*pregnane* (XXVI) (727 mg.), m. p. 162—167·5° (from di-isopropyl ether), $[\alpha]_D$ −1·8° (*c* 0·54) (Found: C, 71·8; H, 9·3. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·15%), $\nu_{max.}$ 1730 (OAc) and 1240 cm.$^{-1}$ (OAc).

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