[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XLII. Partial Synthesis of 11-Ketodiosgenin[2]

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The steroidal sapogenin gentrogenin (3β-hydroxy-22a,25D-spirost-5-en-12-one, I), considered as a suitable cortisone precursor substance, was transformed to 11-ketodiosgenin (3β-hydroxy-22a,25D-spirost-5-en-11-one, VIa) and to 11α-hydroxydiosgenin (22a,25D-spirost-5-en-3β,11α-diol, Va). The route employed involved the tetrabromination of I to 3β-acetoxy-5α,6β,11α,23-tetrabromo-22a,25D-spirostan-12-one (II). This tetrabromide was selectively debrominated to restore the olefinic bond by means of iodide ion to form 3β-acetoxy-11α,23-dibromo-22a,25D-spirost-5-en-12-one (III). Hydrolysis of III formed, after acetylation, 23-bromo-3β,12β-diacetoxy-22a,25D-spirost-5-en-11-one (IVb) which was debrominated with zinc dust in acetic acid to form 3β,12β-diacetoxy-22a,25D-spirost-5-en-11-one (IVc). Selective deacetoxylation of IVc with calcium, sodium or lithium in liquid ammonia gave rise to 11-ketodiosgenin (VIa) or to 11α-hydroxydiosgenin, depending on reaction conditions utilized. Small amounts of 3-desoxy sapogenins also were detected as by-products.

In the course of examination of natural steroidal materials of botanic origin as possible source materials for steroid hormones, we have been studying the 12-ketosteroids hecogenin, gentrogenin[3] and correllogenin.[3] When we read of the discovery by Chapman, Elks and Wyman[4] of the conversion of hecogenin to 11-ketotigogenin by the route of selective deacetoxylation of 3β,12β-diacetoxy-5α,22a,25D-spirostan-11-one by means of calcium in liquid ammonia, it seemed that such a method might be advantageously applied to gentrogenin to prepare the unknown C-11 oxygenated derivatives of diosgenin. Since 11-ketotigogenin is a commercially utilized intermediate for cortisone production, it was reasonable to expect that its 5,6-dehydro derivative, 11-ketodiosgenin, might be similarly used. The present communication describes the preparation of 11-ketodiosgenin and 11α-hydroxydiosgenin.

For this work we had available a ketonic sapogenin fraction obtained from *Dioscorea spiculiflora*[5] containing a mixture of the 25D- and 25L-diastereoisomeric sapogenins gentrogenin and correllogenin, the 25D-isomer greatly predominating in the mixture. Fortunately, separation of isomers is unnecessary for practical work since conversion to derivatives in the C-21 series expels the single differing asymmetric center and leads to a single series of compounds. The constants reported in this paper are for sterically pure 25D-gentrogenin derivatives, although we have carried out the same transformations on the natural mixtures as well.

Bromination of I[6] gave a 90–94% yield of crystalline 3β-acetoxy-5α,6β,11α,23-tetrabromo-22a,25D-spirostan-12-one (II). This crystalline tetrabromide on treatment with zinc in refluxing acetic acid for 1.5 hr. regenerated starting material I essentially completely (95%). However, selective regeneration of the 5,6-olefinic bond with iodide gave only a 48–63% yield of the desired dibromide 3β-acetoxy-11a,23-dibromo-22a,25D-spirost-5-en-12-one (III).[7] The mother liquors were not useful for reconversion to starting material. The speed of the debromination was surprisingly rapid. The reaction in acetone solution was complete in less than six minutes at room temperature.

The hydrolysis of 11α,23-dibromohecogenin acetate had been studied by Mueller, *et al.*,[6] and by Rosenfeld and Gallagher.[8] We applied the conditions of the latter authors to 11α,23-dibromogentrogenin acetate (III) and obtained, after reacetylation and debromination, the desired product 3β,12β-diacetoxy-22a,25D-spirost-5-en-11-one (IV c).[9] The 12β-hydroxyl group adjacent to the 11-ketone group does not reliably acetylate with pyridine and acetic anhydride on the steam-bath so that we used perchloric acid catalysis.[10] When we attempted to carry out the hydrolysis reactions in smaller volumes by using refluxing ethanol in 2-hr. reactions or when we used water-miscible co-solvents (*e.g.*, tetrahydrofuran), the yields were sharply reduced.

A carboxylic acid by-product was obtained in low yields from the hydrolysis reactions. Wendler, Hirschmann, Slates and Walker,[11] working with 11,12-dimesylates, obtained by alkaline treatment a C-ring carboxylic norsteroid.[12] We suspect a

(1) A laboratory of the Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XLI, H. E. Kenney and M. E. Wall, *J. Org. Chem.*, **22**, 468 (1957).

(3) For a preliminary description of these new sapogenins see H. A. Walens, S. Serota and M. E. Wall, THIS JOURNAL, **77**, 5196 (1955). A more complete description has been submitted to *J. Org. Chem.*

(4) J. H. Chapman, J. Elks and L. J. Wyman, *Chemistry & Industry*, 603 (1955).

(5) This material was collected in Chiapas, Mexico, by Drs. H. S. Gentry and D. S. Correll, Horticultural Crops Research Branch, Agricultural Research Service, Beltsville, Md.

(6) The conditions of the bromination were essentially those used by J. W. Cornforth, J. M. Osbond and G. H. Phillips, *J. Chem. Soc.*, 907 (1954), but several differences from results with hecogenin acetate are worth mentioning. We obtained a 37% yield of crystalline 11α,23-dibromohecogenin acetate, melting point 188–190°, rather than the 54% yield reported by Cornforth, *et al.* (See also G. P. Mueller, L. L. Norton, R. E. Stobaugh, L. Tsai and R. S. Winniford, THIS JOURNAL, **75**, 4892 (1953), for yield and melting point data.) The mother liquors from the crystallization were deep green, viscid residues which could be freed of bromine by treatment with zinc and refluxing acetic acid but which yielded only half the calculated content of crystallizable hecogenin acetate.

(7) Attempts to improve the yield of III by treating II with zinc dust in benzene or tetrahydrofuran were not successful since the 11α-bromine atom was more susceptible to reductive attack than the 5,6-bromine atom pair. The direction of attack could be indirectly observed by infrared spectral means since the 11α-bromo ketone absorbs at 1735 cm.$^{-1}$, while the free 11-ketone absorbs in the usual region near 1709 cm.$^{-1}$.

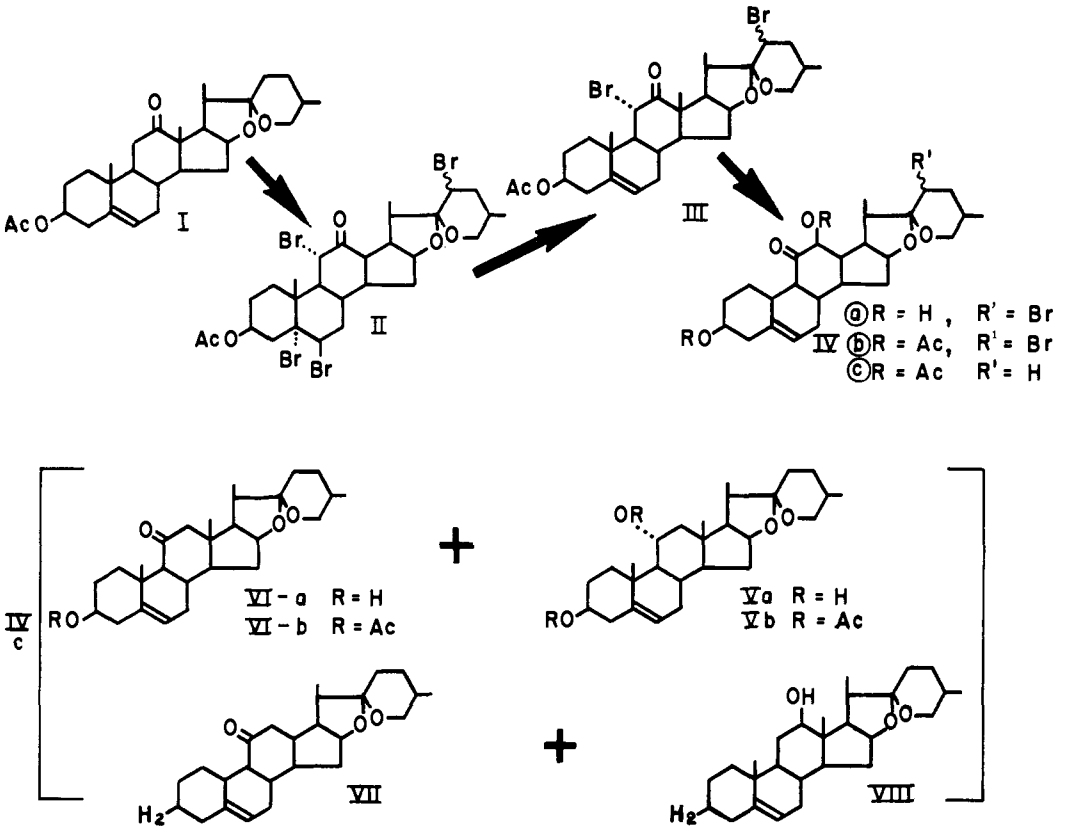
(8) R. S. Rosenfeld and T. F. Gallagher, THIS JOURNAL, **77**, 4367 (1955).

(9) We confirm the 92% yield for 20-hour, room temperature hydrolysis of 11α,23-dibromo hecogenin acetate reported by Rosenfeld and Gallagher; however, identical reaction conditions applied to the closely related III gave IVc in somewhat lower yields averaging 50 to 65%.

(10) See in this connection the observations of Mueller, *et al.*, ref. 6.

(11) N. L. Wendler, R. F. Hirschmann, H. L. Slates and R. W. Walker, *Chemistry & Industry*, 901 (1954).

(12) The carboxylate was obtained by air-oxidation of an intermediate aldehyde.



relationship between these two products but have as yet no experimental verification.

We carried out our preliminary C-12 deacetoxylation experiments of conversion of IVc to 11-ketodiosgenin and to 11α-hydroxydiosgenin on the basis of the communication of Chapman, Elks and Wyman.[4] These authors described the parallel experiments in the hecogenin series but in their preliminary disclosure gave no experimental details. In view of the fact that even closely related sapogenins often have inherent peculiarities that affect direction of reaction and yield it may not be amiss to note here some observations on the metal–ammonia reduction systems as applied to the compound IVc.

The selective deacetoxylations were carried out in liquid ammonia using calcium or *sodium* or *lithium* as the reducing element. The primary product of the reduction was 11-ketodiosgenin, 3β-hydroxy-22a,25D-spirost-5-en-11-one (VIa), which may further react with protonic materials (*e.g.*, water, alcohol) to form 11α-hydroxydiosgenin, 22a,25D-spirost-5-en-3β,11α-diol (Va), in a secondary reaction.[13] When water is used to quench the reaction and decompose excess metal reagent, a greater or lesser amount of 11α-ol is formed. Henry A. Walens of this Laboratory devised an experiment avoiding this quenching operation. The immiscible toluene layer could be separated from the liquid ammonia metal solution phase in a separatory funnel provided with a fritted glass disk. We have also used bromobenzene to quench the reaction as suggested by Chapman, Elks and Wyman.[14] Reduction of IVc gave a 90% yield of products consisting chiefly of 11-ketone VIa but containing about 10–20% of 11α-diol Va. The conversion of gentrogenin to 11-ketodiosgenin is effected in about 35% over-all yield. A further observation in the calcium deacetoxylation experiments is the formation by the reduction system of small amounts of 3-desoxysapogenins by apparently non-specific deacetoxylation. Isolated and identified were 3-desoxy-11-ketodiosgenin (22a,25D-spirost-5-en-11-one, VII) and 3-desoxy-12β-hydroxydiosgenin (22a,25D-spirost-5-en-12β-ol, VIII). The latter compound was characterized by oxidation to the 12-ketone, 3-desoxygentrogenin (22a,-25D-spirost-5-en-12-one). The 12β-configuration is tentatively suggested since the 12β-configuration is the equatorial one usually favored by metal reduction systems. The C-11 ketones can be distinguished from the C-12 ketones not only by reduced chemical reactivity of the former but also by infrared differences. Thus, the 11-ketones show a band at 1704–1710 cm.$^{-1}$ (VIb at 1706 cm.$^{-1}$)[15] while the 12-ketones show the band at 1706–1712 cm.$^{-1}$ (I at 1713 cm.$^{-1}$).[15] In addition the 11-ketones show a band[16] at 970 cm.$^{-1}$ not given by the 12-ketones. Such a band occurs also for ex-

(13) F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953), using calcium, sodium or lithium in liquid ammonia to reduce 3β-propionoxy-5α,22a,25D-spirost-8(9)-en-11-one reported formation of the saturated ketone in the absence of ethanol and the 11α-ol in the presence of ethanol. S. Bernstein, R. Littell and J. H. Williams, *ibid.*, p. 1481, used lithium–ammonia–ethanol to reduce a saturated 11-ketone to an 11α-ol in a similar manner.

(14) Private communication.

(15) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1256 (1954).

(16) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **36**, 1245 (1953); *cf.* Fig. 1 of article for spectra.

ample in the spectrum of tigogenin, diosgenin and 3,5-cyclo-22a,25D-spirostane, but compounds of these types are easily distinguished by other criteria. The relative intensities of the ketone and acetate bands also vary erratically. In hecogenin acetate the acetate band is slightly stronger than the ketone band.[16,17] In gentrogenin and correllogenin, the ketone band[18] is the stronger, while the 11-ketones have a ketone band definitely weaker than the acetate band.

In the course of the identification and structure assignments of the C-11 ketonic products, we observed a substantial deviation of the sapogenin 11-ketone molecular rotation contribution from the mean value of +79° calculated by Barton and Klyne.[19] A check of literature values of 11-ketone molecular rotation contributions in the sterol series gave a value[20] of about +72° in good agreement with Barton and Klyne's value. However, the 11-ketone contribution in 11-ketotigogenin[21] is +150° and in 11-ketotigogenin acetate[16] is +169°. The +207° molecular rotation contribution in 11-ketodiosgenin is even more positive. Similar deviation in a positive direction from the calculated[19] molecular rotation contribution of the 11α-ol also occurs. The calculated value is −29°; the observed value[13] is +35°.

Experimental

Rotations were measured in chloroform in a 2 dm. tube, c = 25 mg./1.5 ml. Melting points were determined on the Kofler block but are otherwise uncorrected.

3β-Acetoxy-5α,6β,11α,23-tetrabromo-22a,25D-spirostan-12-one (II).—Gentrogenin acetate (I), 7.0 g. (0.01486 mole), in 76 ml. of ordinary C.P. chloroform was treated at room temperature with a solution of 0.01486 mole of bromine in 59 ml. of carbon tetrachloride in the course of 5 minutes time. The initial uptake was slow, but the rate of uptake accelerated with time. The bromine was added in batches rather than dropwise. The colorless solution was further treated with 1.9 ml. of liquid bromine dissolved in 15 ml. of chloroform. Various colorations, sometimes yellow-orange, pink or green developed during this second bromination, again carried out in only 5 minutes time despite difficulties in visual observation of the bromine uptake. The solution was stirred, still at room temperature, for an additional 10 minutes, and then all solvents were removed at 30° using water aspiration. The residue was a pale green, glassy froth which on dissolution in 25 ml. of methylene chloride[22] gave a dark green solution. Addition of ethanol incrementally caused color change to a pale pink. Absolute ethanol was then added as rapidly as possible without causing flocculation until a volume of 250 ml. of clear, nearly colorless solution was obtained. Stirring with scratching caused sudden crystallization of 11.1 g. of snow-white product (decomposing at 193° with effervescence and reddening).

Recrystallization was effected by dissolution in a minimal volume of hot methylene chloride, dilution with ether and boiling off the methylene chloride azeotropically. The product formed a mass of felted micro-needles melting suddenly at 199° with browning and effervescence. The analytical sample was recrystallized from methanol to give silky filaments, m.p. 199°, $[\alpha]^{25}D$ −84.5°.

Anal. Calcd. for $C_{29}H_{38}O_5Br_4$: C, 44.30; H, 4.87; Br, 40.66. Found: C, 44.16; H, 5.04; Br, 40.65.

Selective Debromination of II to 3β-Acetoxy-11α,23-dibromo-22a,25D-spirost-5-en-12-one (III).—A sample of II, 11 g., in 250 ml. of ethanol was refluxed for 2 hr. with 14 g. of sodium iodide. The solids went into solution during the course of the reaction. The mixture was cooled, diluted with water and ether was added. A dilute solution of sodium thiosulfate was added in portions to just decolorize molecular iodine, avoiding excess reagent. The ether layer was washed with 1% sodium hydroxide (to remove traces of carboxylic material), with water, with saturated saline solution and after drying with sodium sulfate, was evaporated under reduced pressure at 30° to a pale-orange froth. Stirring with 35 ml. of absolute ethanol caused solution of the froth followed by precipitation of white crystalline III, 63%.[23] The analytical sample was recrystallized from ethanol–methylene chloride to fine hexagonal blades blackening at 152° and melting with effervescence from 160–170°, $[\alpha]^{25}D$ −81.9°.

Anal. Calcd. for $C_{29}H_{38}O_5Br_2$: C, 55.60; H, 6.11; Br, 25.51. Found: C, 54.14; H, 6.18; Br, 24.99.

The compound is not stable in chloroform or methylene chloride solutions for prolonged periods of time. Analytically pure samples let stand overnight in chloroform solution developed deep pink coloration.

23-Bromo-3β,12β-diacetoxy-22a,25D-spirost-5-en-11-one (IVb).—A sample of III, 5 g., suspended in 4.5 l. of 0.3 N 80% ethanolic potassium hydroxide was stirred at room temperature for 20 hr. The mixture was treated with 250 ml. of 6 N hydrochloric acid and was evaporated to 400 ml. under reduced pressure. The residue was diluted with water and extracted with ether. The ether was washed with 2% sodium hydroxide to remove a solid carboxylic acid[11] and was dried with saturated brine and with sodium sulfate. The solid froth obtained by reduced pressure evaporation of the dried ether extract was acetylated in 50 ml. of acetic acid and 15 ml. of acetic anhydride in the presence of 1 ml. of 2.5 N perchloric acid in acetic acid during 1.5 hr. at room temperature. The product was obtained by pouring the acetylation mixture into an excess of cold water and filtering off the flocculent precipitate. Crystallization of the air-dried product from ether gave 3.5 g. of IVb, m.p. 212–215°. The analytical sample, $[\alpha]^{25}D$ −88.7°, crystallized from ether, melted from 214–216° without decomposition, although the colorless melt turned slightly brown soon after melting was completed.

Anal. Calcd. for $C_{31}H_{43}O_7Br$: C, 61.28; H, 7.13; Br, 13.15. Found: C, 61.30; H, 7.02; Br, 13.25.

3β,12β-Diacetoxy-22a,25D-spirost-5-en-11-one (IVc).—The product from the preceding preparation, diminished by the removal of 121 mg. for analytical and reference purposes, was refluxed 6 hr. with zinc dust in acetic acid and the product isolated by dilution with water and extraction with ether and washing in the usual manner. A sample (after removal of zinc halide) gave a positive Beilstein flame test even after multiple crystallizations. The materials were recombined and retreated for an additional 4 hr. without change. Apparently the residual halogen content was vanishingly small since the infrared spectrum of the product was typical of 25D-sapogenins and showed no band at 739 cm.$^{-1}$. The product, 2.13 g., obtained by crystallizing the evaporated ether extract from ethanol, formed feathery, branched masses, m.p. 195–218°. The analytical sample, $[\alpha]^{25}D$ −106°, recrystallized from ethanol, began to undergo transition over 202° to elongated needles, but melting occurred at 221–225° before the transition was completed.

Anal. Calcd. for $C_{31}H_{44}O_7$: C, 70.43: H, 8.39. Found: C, 70.71; H, 8.53.

A. Reduction of 3β,12β-Diacetoxy-22a,25D-spirost-5-en-11-one (IVc) with Calcium and Ammonia to Give a Mixture of Products.—A sample of IVc, 0.85 g., in 9 ml. of tetrahydrofuran was added to a solution of 0.67 g. of calcium in 200 ml. of liquid ammonia. The reactants were stirred 2 hr.

(17) C. R. Eddy, M. E. Wall and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

(18) M. E. Wall, J. J. Willaman, T. Perlstein, D. S. Correll and H. S. Gentry, *J. Am. Pharm. Assoc.*, in press (1957).

(19) D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948).

(20) From K. Tsuda and R. Hayatsu, THIS JOURNAL, **77**, 6582 (1955).

(21) From C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

(22) If isolation of the tetrabromide is not required, the methylene chloride should not be added, but the product should be triturated with ethanol to loosen any crystalline residues from the walls of the flask to pervent scorching during subsequent heating. Debrominative regeneration of the Δ^5-bond with sodium iodide does not require that the tetrabromide be in solution initially.

(23) The yield was about 50–55% when the reaction was carried out with the natural mixture of C-25 diastereoisomers.

during which time the solvent boiled away. The residue was sifted into water to form a flocculent precipitate. The mixture was acidified, extracted with ether and evaporated. The residue was saponified with 5% methanolic sodium hydroxide. The resulting product was dissolved in 50 ml. of ethanol and 5 ml. of acetic acid. Girard reagent T, 2 g., was added and the mixture was refluxed for 1 hr., poured into dilute aqueous sodium carbonate and extracted with ether. The aqueous layer and aqueous washings of the ether on acidification and isolation with ether yielded a negligible quantity of steroid, *i.e.*, the metal–ammonia reduction product was non-reactive with the Girard reagent.[24] The infrared spectrum of the reduction product was similar to that of 11α-hydroxydiosgenin but showed, in addition, the presence of some 11-ketonic material by a weak to medium strength band at 1707 cm.$^{-1}$.

The reduction mixture was resolved in the following manner by chromatography. Seven hundred milligrams of the reduction product was chromatographed on a column of Florisil 20 by $^3/_4$ inches. Benzene, 900 ml., eluted no material. Chloroform–benzene (1:20) eluted 30 mg. of **3-desoxy-11-ketodiosgenin (VII)** (**22a,25D-spirost-5-en-11-one**), m.p. 178–184°, $\bar{\nu}_{max}^{CS_2}$ 1705 and 970 cm.$^{-1}$. Chloroform–benzene (1:10), 600 ml., eluted traces of material not examined. Chloroform–benzene (1:5), 500 ml. eluted 30 mg. of **22a,25D-spirost-5-en-12β-ol (VIII)**.—The infrared spectrum showed the absence of ketone and ester bands and showed absorption bands in the hydroxyl region and olefinic absorption band between 800 and 850 cm.$^{-1}$. Oxidation of VIII with pyridine–chromium trioxide produced **3-desoxygentrogenin (22a,25D-spirost-5-en-12-one IX)**, a monoketone forming a water-soluble Girard T complex. The ketone, m.p. 209–213°, $[\alpha]^{25}D$ −65°, formed prisms from ethanol and underwent sequential transition on the Kofler block to rectangular scales and then to elongated blades. The infrared spectrum of IX, $\bar{\nu}_{max}^{CS_2}$ 1713 cm.$^{-1}$, was different from that of VII and showed Δ^5-unsaturation. Chloroform, 100%, eluted 110 mg. of **11-ketodiosgenin (3β-hydroxy-22a,25D-spirost-5-en-11-one, VIa)** which was unreactive to Girard T complex formation (11-ketone). The infrared spectrum showed bands at 1707 cm.$^{-1}$ (11-ketone) and at 970 and 984 cm.$^{-1}$. The analytical sample recrystallized from hexane melted from 180 to 183°, $[\alpha]^{25}D$ −76.4°. *Anal.* Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.92; H, 9.60. The acetylated substance **11-ketodiosgenin acetate (3β-acetoxy-22a,25D-spirost-5-en-11-one, VIb)**, prepared using pyridine–acetic anhydride at room temperature, formed transparent pearly scales from aqueous methanol, $[\alpha]^{25}D$ −85°, m.p. 221–222° after incomplete transition to rhombic scales. *Anal.* Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.69; H, 9.28. Further elution[25] with chloroform yielded 184 mg. of **11α-hydroxydiosgenin (22a,25D-spirost-5-en-3β,11α-diol, Va)**. Crystallization from hexane and from ether of the unusually soluble material gave thick, hexagonal, bladed or prism-like forms, $[\alpha]^{25}D$ −116°, m.p. 233–235° after incomplete transition over 228° to whips. *Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.37; H, 10.00. Acetylation of Va in pyridine–acetic anhydride on the steam-bath for 0.75 hr. gave **11α-acetoxydiosgenin acetate (3β,11α-diacetoxy-22a,25D-spirost-5-ene, Vb)**. Crystallization from methanol gave the analytical sample, m.p. 195–198°,[26] $[\alpha]^{25}D$ −116°. *Anal.* Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.41; H, 9.33. Elution with 5% ethanol in benzene gave 160 mg. of amorphous, colorless material that did not crystallize even after acetylation and chromatography of the acetylated product.

B. **Reduction of IVc with Calcium–Ammonia to Give Essentially VI.**—Liquid ammonia, 1000 ml., was dried by treating with portions of calcium metal until a persisting blue color developed (1.7 g.) after which point reagent calcium, 4.2 g., was added. The steroid IVc, 14.3 g., was dissolved in 250 ml. of toluene, the volume was reduced somewhat by distillation to remove traces of water and addition was carried out during 8 minutes time. After stirring an additional 5 minutes a solution of 12 ml. of bromobenzene in 50 ml. of toluene was added to decolorize the solution after which 50 ml. of water was added cautiously. The ammonia was allowed to evaporate, the residue was taken up in ether and the ether was evaporated *in vacuo* to dryness. The residue was saponified with 10% sodium hydroxide at reflux for 0.5 hr. and isolated with ether to give a crystalline residue, 10.7 g. (92%), consisting essentially of VIa but containing a small proportion of diol Va. The ketone was eluted from a Florisil column with benzene–hexane 1:1, while chloroform was required to elute the diol. The overall yield of 11-ketodiosgenin from gentrogenin is approximately 35%.

C. **Reduction of IVc with Sodium in Ammonia and with Lithium in Ammonia.**—Treatment of IVc with sodium or with lithium in ammonia under reaction conditions as in procedure B gave the same products. If instead of decomposing the excess calcium metal the reaction flask is opened to the air with access to atmospheric moisture, an essentially quantitative yield of diol Va is obtained after the usual saponification.

Acknowledgment.—The authors wish to express their thanks to H. A. Walens who carried out certain experiments in ketol–acetate reductions with metal–ammonia systems, to R. B. Kelly, D. McClelland and C. L. Ogg for microanalyses, to C. Fenske for infrared spectra and to S. Serota for optical rotation measurements.

PHILADELPHIA 18, PENNA.

(24) W. P. Long and T. F. Gallagher, *J. Biol. Chem.*, **162**, 511, 521 (1946), have noted that 11-hydroxy-12-ketones react normally with ketone reagents.

(25) The diol, Va, gives a sensitive and intense red-black color reaction with sulfuric acid, while the ketone, VIa, gives only a pale yellow color. This difference is useful in locating the point of division in the chromatogram.

(26) It has just come to our attention that J. Romo, *Bol. inst. quim. nacl. auton. Mex.*, **7**, 53 (1955), *C. A.*, **50**, 12088 (1956), has recently prepared this compound from 3β,11α-diacetoxy-5α,22a,25D-spirostan-7-one, but reported m.p. 95–98°, $[\alpha]^{25}D$ −106°. We are unable to account for the melting point difference.