Anal. Calcd. for $C_{18}H_{25}O_2F$: C, 70.1; H, 8.17; F, 6.16. Found: C, 70.32; H, 8.39; F, 6.05.

10β-Fluoro-2-methyl-Δ¹-dehydro-19-nortestosterone (IVa).—2-Methylestradiol (IIIb, 9 g.) in dimethylformamide (450 cc.) was treated with perchloryl fluoride for 20 hours. After working up in the usual way the product was chromatographed on 270 g. of alumina. Elution with benzene and crystallization from acetone–hexane gave **10β-fluoro-2-methyl-Δ¹-dehydro-19-nortestosterone** (IVa, 3.4 g.), m.p. 169–173°. The analytical sample had m.p. 173–174°, $[\alpha]_D$ −51°, λ_{max}^{EtOH} 246 mμ, log ε 4.14.

Anal. Calcd. for $C_{19}H_{25}O_2F$: C, 74.96; H, 8.28; F, 6.24. Found: C, 74.44; H, 8.35; F, 5.79.

10β-Fluoro-2β-methyl-5β-19-norandrostane-3-one-17β-ol (Vd).—The preceding dienone (2.5 g.) in dioxane (80 cc.) was hydrogenated over 10% Pd/$BaSO_4$ until no further hydrogen was absorbed. After filtering from catalyst on 75 g. of alumina, elution with benzene and crystallization from acetone–hexane gave the saturated ketone (Vd, 1.2 g.) m.p. 194–197°. The analytical sample had m.p. 202–204°, $[\alpha]_D$ +0.5°.

Anal. Calcd. for $C_{19}H_{29}O_2F$: C, 73.99; H, 9.48; F, 6.16. Found: C, 74.22; H, 9.36; F, 5.71.

This m.p. compound (100 mg., m.p. 200–202°) was dissolved in methanolic potassium hydroxide solution (1%, 5 cc.) and allowed to stand for 72 hours at room temperature. The alkali was then neutralized with acetic acid and the solution evaporated to give a crystalline residue, which, after addition of water, was isolated by filtration (98 mg.). This proved to be starting material and had m.p. and mixed m.p. 196–198°, $[\alpha]_D$ 0°. The infrared spectrum was identical with that of the starting material.

2,17α-Dimethylestradiol (IIIc).—2-Methylestrone (IIIa, 22 g.) was dissolved in dry tetrahydrofuran (1.5 l.) and treated with a large excess of ethereal methylmagnesium bromide (4 *N*, 300 cc.), the ether was distilled off and the residue refluxed with good stirring for 3 days. Most of the tetrahydrofuran was then distilled off and the residue treated with ice-water and excess hydrochloric acid and extracted with methylene chloride. Crystallization of the product from acetone–hexane afforded 15.2 g. of **2,17α-dimethylestradiol** (no carbonyl band in the infrared), m.p. 202–204°. Recrystallization from acetone–hexane gave an analytical sample, m.p. 208–210°, $[\alpha]_D$ +53°, λ_{max}^{EtOH} 283 mμ, log ε 3.42.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 79.89; H, 9.47; O, 10.50.

10β-Fluoro-2,17α-dimethyl-Δ¹-dehydro-19-nortestosterone (IVb).—2,17α-Dimethylestradiol (15 g.) in dimethylformamide (750 cc.) was treated with perchloryl fluoride for 18 hours. After working up in the usual way the product was chromatographed on 450 g. of alumina. Elution with benzene and crystallization from acetone–hexane gave the 10β-fluorodienone (IVb, 7.8 g.), m.p. 165–167°. Recrystallization gave a sample with m.p. 176–177°, $[\alpha]_D$ −64°, λ_{max} 246 mμ, log ε 4.17.

Anal. Calcd. for $C_{20}H_{27}O_2F$: C, 75.44; H, 8.55; F, 5.96. Found: C, 75.06; H, 8.56; F, 6.17.

10β-Fluoro-2β,17α-dimethyl-5β-19-norandrostane-3-one-17β-ol (Ve).—The preceding dienone (7.7 g.) in dioxane (230 cc.) was hydrogenated over 10% Pa/$BaSO_4$ (3.75 g.) until no further hydrogen was absorbed. After filtering from catalyst the solvent was removed *in vacuo* and the residue chromatographed on 270 g. of alumina. Elution with benzene and crystallization from methanol gave 3.2 g. of the saturated ketone Vb. m.p. 92–94°, apparently with solvent loss. The substance would not crystallize from other solvents. Recrystallization from methanol gave an analytical sample, m.p. 92–94° (97–99° after drying for 2 days at 60°), $[\alpha]_D$ −18°; rotatory dispersion curve (*c* 0.0763, dioxane); $[\alpha]_{700}$ +4°, $[\alpha]_{584}$ −10.5°, $[\alpha]_{315}$ −292.5°, $[\alpha]_{280}$ +38°.

Anal. Calcd. for $C_{20}H_{31}O_2F.{}^1/_2\ H_2O$ C, 72.47; H, 9.73. Found: C, 72.59; H, 9.93.

Further elution with 5% ether–benzene and crystallization from acetone–hexane gave 0.7 g. of 2,17α-dimethylestradiol, m.p. 199–201°.

Dienone–Phenol Rearrangement of 10β-Fluoro-Δ¹-dehydro-19-nortestosterone.—10β-Fluoro-Δ¹-dehydro-19-nortestosterone (400 mg.) in acetic anhydride (4 ml.) was treated with concentrated sulfuric acid (3 drops) and the solution allowed to stand at room temperature for 3 hours. Ice was then added and the crystalline product filtered. Crystallization from methylene chloride–methanol afforded the fluorophenol diacetate (XVIa) (360 mg.), m.p. 129–132°, $[\alpha]_D$ +149°, λ_{max}^{EtOH} 268 and 274 mμ, log ε 2.85.

Anal. Calcd. for $C_{22}H_{27}O_4F$: C, 70.56; H, 7.09. Found: C, 70.54; H, 7.16.

Saponification of this diacetate with 5% methanolic potassium hydroxide for 18 hours at room temperature afforded the free diol XVIb, m.p. 193–194° (from acetone), $[\alpha]_D$ +183°, λ_{max}^{EtOH} 284 mμ, log ε 3.45.

Anal. Calcd. for $C_{18}H_{23}O_2F$: C, 74.45; H, 7.98. Found: C, 74.29; H, 8.31.

Methylation of the free diol with dimethyl sulfate and potassium hydroxide in the usual way afforded the **methyl ether XVIc**, m.p. 119–120° (from aqueous acetone), $[\alpha]_D$ +202°, λ_{max}^{EtOH} 281 mμ, log ε 3.42.

Anal. Calcd. for $C_{19}H_{25}O_2F$: C, 74.97; H, 8.27; F, 6.24. Found: C, 74.95; H, 7.98; F, 6.34.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL]

The Synthesis of the Steroidal Sapogenins[1,2]

BY YEHUDA MAZUR,[3] NAFTALI DANIELI[4] AND FRANZ SONDHEIMER

RECEIVED MAY 25, 1960

Isoandrosterone (V) is converted by an eighteen-stage process to a mixture of tigogenin (LXIII) and neotigogenin (LXIV). Each of these steroidal sapogenins is obtained in the pure state and is identified with an authentic sample. The synthesis leads to other steroidal sapogenins (smilagenin, gitogenin, diosgenin, chlorogenin, hecogenin) as well as to certain steroidal alkaloids (tomatidine, solasodine).

The steroidal sapogenins are an important group of substances occurring in nature in the form of their glycosides (the steroidal saponins), from which they can be obtained by acid treatment.[5a] Although the chemistry of these compounds has been investigated extensively since the end of the last century, it was only in 1939 that the correct structure of a typical member was proposed.[6] More

(1) For preliminary communications, see N. Danieli, Y. Mazur and F. Sondheimer, *Chemistry & Industry*, 1724, 1725 (1958); Y. Mazur and F. Sondheimer, THIS JOURNAL, 81, 3161 (1959).

(2) Presented in part before the Organic Chemistry Division at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1959 (Asbtracts of Papers, p. 85-P).

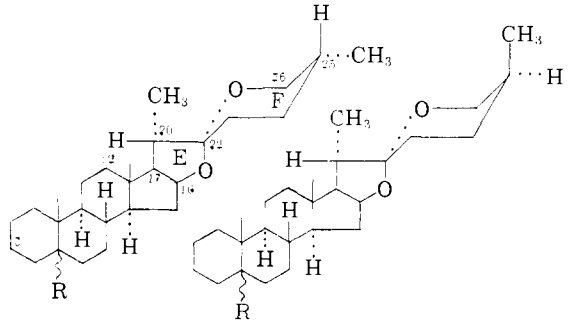
(3) At present Fellow of the School for Advanced Studies, Massachusetts Institute of Technology, Cambridge, Mass.

(4) Part of the material described in this paper has been taken from a Ph.D. thesis presented by Naftali Danieli to the Hebrew University, Jerusalem, June, 1958.

(5) For a review, see L. F. Fieser and M. Fieser, "Steroids," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1959; (a) chapter 21; (b) chapter 10; (c) pp. 343–344; (d) pp. 533–538.

(6) R. E. Marker and E. Rohrmann, THIS JOURNAL, 61, 846 (1939).

recently the remaining stereochemical problems have been solved.[7] As a consequence it is known that of the two main classes of steroidal sapogenins, those belonging to the "iso" series possess structures of type I (25D-spirostanes) and those of the "neo" series structures of type II (25L-spirostanes).[8]

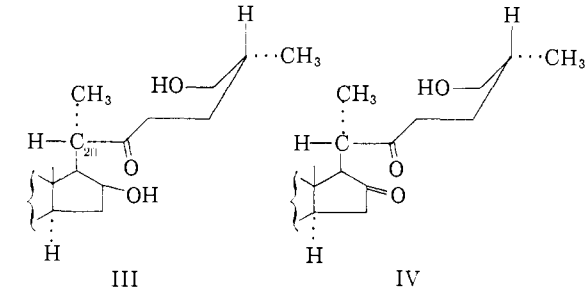


I, R = —H or ...H II, R = —H or ...H

Practically all of the more than thirty different steroidal sapogenins which have been isolated from natural sources in addition possess a 3β-hydroxyl grouping and some contain further oxygen functions and/or double bonds at various positions of the molecule.[5a]

The main importance of the steroidal sapogenins lies in their ready availability from plant sources and in the facility with which the oxygen-containing rings can be degraded to give Δ^{16}-pregnene derivatives which may then be converted to the valuable steroidal sex and adrenal hormones. For this reason considerable work has been carried out on the degradation of the steroidal sapogenins to simpler steroids (as well as on interconversions within the sapogenin series itself). On the other hand, the reverse process, the building up of the steroidal sapogenins from simpler steroids, has been little investigated. This synthetic problem has been studied in our laboratory for some time and we now describe its successful solution.[11]

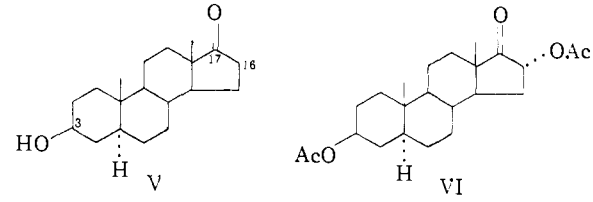
The spiroketal function present in rings E and F of the steroidal sapogenins (type I) may be regarded as the internal ketal of the dihydroxy-ketone III.[12] In fact, 3β,16β,26-trihydroxy-Δ^5-cholesten-20-one (III),[13] formed from kryptogenin



III IV

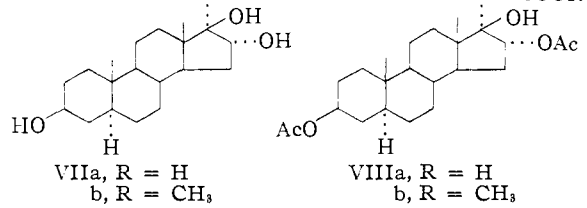
(IV) by the preferential reduction of the 16-keto group[14] or from diosgenin (type I) by a three-step process,[13] is converted to diosgenin by acid treatment.[13,14] We therefore chose to build up a 3,16,-22,26-tetra-oxygenated cholestane derivative of type III as the ultimate intermediate in our synthesis of the steroidal sapogenins.

The starting material was the readily available isoandrosterone (3β-hydroxyandrostan-17-one) (V), the 17-keto group of which could be utilized for the introduction of an oxygen funtion at C-16. Accordingly V was converted to the enol acetate, which on treatment with perbenzoic acid and rearrangement of the resulting oxide with perchloric acid, essentially as described previously,[15] produced 3β,16α-diacetoxyandrostan-17-one (VI) in *ca.* 60% over-all yield.



V VI

The next objective was the construction at the 17-position of an isopropyl unit bearing a terminal oxygen grouping. This was achieved by subjecting the diacetoxy-ketone VI to a Reformatsky reaction with ethyl α-bromopropionate. In order to find out to what extent condensation had taken place, the reaction mixture was saponified and the acidic product was separated. Direct crystallization of the latter produced 36% of the 20-normal-3β,16α,17β-trihydroxy-acid VIIa (m.p. 242-243°). Treatment with diazomethane gave the methyl ester VIIb (m.p. 227-228°), the elemental analysis



VIIa, R = H VIIIa, R = H
b, R = CH_3 b, R = CH_3

(7) I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **75**, 4871 (1953); **77**, 641 (1955); V. H. T. James, *J. Chem. Soc.*, 637 (1955); M. E. Wall, *Experientia*, **11**, 340 (1955); R. K. Callow and P. N. Massy-Beresford, *J. Chem. Soc.*, 4482 (1957); W. E. Rosen, J. B. Ziegler, A. C. Shabica and J. N. Shoolery, THIS JOURNAL, **81**, 1687 (1959).

(8) The two classes can be interconverted by prolonged acid treatment.[5,9] The mechanism of this remarkable reaction has recently been elucidated.[10]

(9) (a) R. K. Callow and V. H. T. James, *J. Chem. Soc.*, 1671 (1955); (b) M. E. Wall, S. Serota and L. P. Witnauer, THIS JOURNAL, **77**, 3086 (1955).

(10) R. B. Woodward, F. Sondheimer and Y. Mazur, *ibid.*, **80**, 6693 (1958).

(11) For preliminary experiments exploring an alternative route to that followed in the present paper, see F. Sondheimer, N. Danieli and Y. Mazur, *J. Org. Chem.*, **24**, 1278 (1959).

(12) In this and subsequent formulas in which C-20 does not form part of a ring, the longest side-chain attached to C-20 has been written to the right and is therefore oriented to the front. Although this convention does not comply with that which requires the longest side-chain to be directed to the rear (see P. A. Plattner, *Chemistry & Industry*, SN 1 (1951); *Helv. Chim. Acta*, **34**, 1693 (1951)), it has been used in the present paper since no change of representation of the stereochemistry at C-20 is necessary when ring E is closed.

(13) This substance appears to exist in a hemiketal form, at least in the solid state (R. S. Miner and E. S. Wallis, *J. Org. Chem.*, **21**, 715 (1956); see also H. Hirschmann and F. B. Hirschmann, *Tetrahedron*, **3**, 243 (1958)).

(14) S. Kaufmann and G. Rosenkranz, THIS JOURNAL, **70**, 3502 (1948).

(15) N. S. Leeds, D. K. Fukushima and T. F. Gallagher, *ibid.*, **76**, 2943 (1954). For the mechanism of the rearrangement, see also W. S. Johnson, B. Gastambide and R. Pappo, *ibid.*, **79**, 1991 (1957).

of which indicated the expected empirical formula $C_{23}H_{38}O_5$, and acetylation of this substance led to the methyl ester diacetate VIIIb (m.p. 172–173°), $C_{27}H_{42}O_7$. Alternatively the trihydroxy-acid VIIa was acetylated to the acid diacetate VIIIa (m.p. 185–186°), which on treatment with diazomethane gave VIIIb. The stereochemistry at C-17 and C-20 in these substances is discussed below.

Since the Reformatsky reaction between VI and ethyl α-bromopropionate appeared to proceed in the expected manner, it was repeated and the resulting material was chromatographed directly on alumina in order to identify all the products of the reaction. This procedure yielded no fewer than five different crystalline substances.

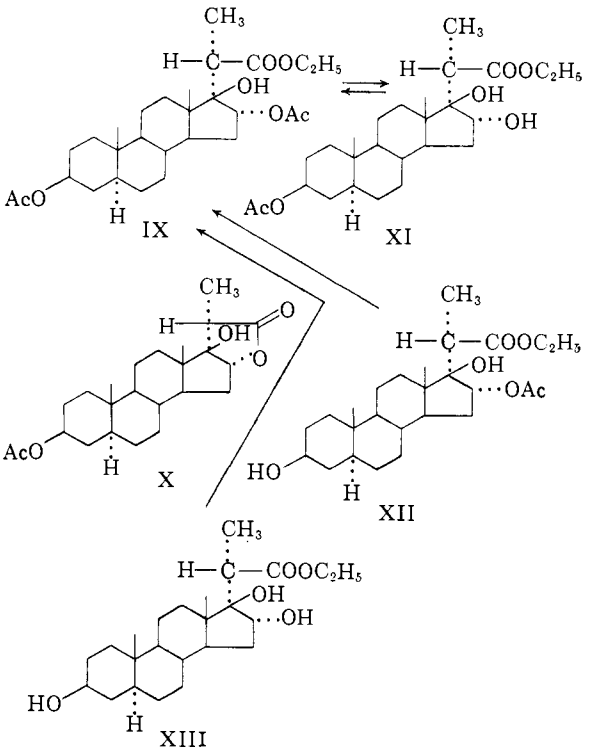
The first compound (m.p. 177–178°) to be eluted, isolated in 6% yield, was assigned the 3β,16α-diacetoxy-17β-hydroxy-ethyl ester structure IX in view of its empirical formula ($C_{28}H_{44}O_7$) and the fact that it was obtained from the above-described acid diacetate VIIIa by conversion to the acid chloride and treatment with ethanol. This interconversion, taken together with the fact that all the five substances from the unsaponified Reformatsky reaction possess the same stereochemical configuration (see below), shows that no inversion at C-20 had taken place during the saponification leading to the trihydroxy-acid VIIa.

The second substance (m.p. 220–222°), eluted from the column in 3% yield, was assigned the hydroxy-γ-lactone structure X, based on the empirical formula ($C_{24}H_{36}O_5$), the presence of one active hydrogen grouping and the existence of a band at 5.64 μ in the infrared.[16a] This formulation was confirmed by the fact that treatment with base led to the trihydroxy-acid VIIa and that the substance was formed from the latter acid by treatment with boiling acetic anhydride or with hydrogen chloride in acetic acid at room temperature. These interconversions also indicated the lactone X to possess the same configuration at C-17 and C-20 as the trihydroxy-acid VIIa and consequently as the ethyl ester diacetate IX.

The third substance (m.p. 167–168°) was the major product of the reaction, being obtained in 34% yield. It had the formula $C_{26}H_{42}O_6$, contained one acetyl and two active hydrogen groupings and on acetylation furnished the diacetate IX. It must therefore be the monoacetate XI or XII and it was assigned the former of these structures for reasons to be discussed below. The fourth compound (m.p. 154–155°), isolated in 4% yield, was isomeric with the preceding one and on acetylation also gave the diacetate IX. It must consequently be the alternative monoacetate XII. Finally a substance (m.p. 201–203°) was obtained in 23% yield, which had the empirical formula $C_{24}H_{40}O_5$ and contained no acetyl groupings. Acetylation once more produced the diacetate IX and it is therefore the trihydroxy-ester XIII.

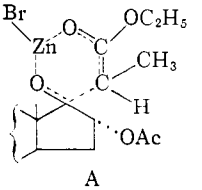
All the Reformatsky products isolated possess the same steric configuration at C-17 and C-20.

(16) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1958; (a) pp. 186–187; (b) pp. 132–136; (c) pp. 181–182; (d) pp. 127–129; (e) pp. 49–51.



The three-carbon side chain at C-17 in these substances is assigned the α-configuration since a model of the diacetoxy-ketone VI reveals the α-side to be less hindered than the β-side and rear-attack would therefore be expected to occur. This stereochemistry at C-17 is confirmed by the comparatively ready formation of the γ-lactone X, described above, since the opposite configuration would require the γ-lactone ring in this substance to be *trans*-fused to the five-membered ring. For steric reasons the latter type of system is expected to be formed only with considerable difficulty, if at all, and in fact all previous attempts to prepare it have given the *cis*-fused system.[17]

Although the stereochemistry at C-20 was not definitely established, the 20-normal configuration is favored through consideration of the cyclic transition state of type A (or a geometrically equivalent one) which is presumably formed in the Reformatsky reaction.[18] Inspection of models shows that of the two configurations possible for the 20-methyl group in this transition state, that leading to the 20-normal compound is unhindered, whereas considerable interference between the 20-



A

methyl and the 12α-hydrogen groups exists in the opposite configuration. These considerations are

(17) (a) W. Hückel and W. Gelmroth, *Ann.*, **514**, 233 (1934); (b) W. E. Grigsby, J. Hind, J. Chanley and F. H. Westheimer, THIS JOURNAL, **64**, 2606 (1942).

(18) H. E. Zimmermann and M. D. Traxler, *ibid.*, **79**, 1920 (1957); see also J. A. Reid and E. E. Turner, *J. Chem. Soc.*, 3365 (1949).

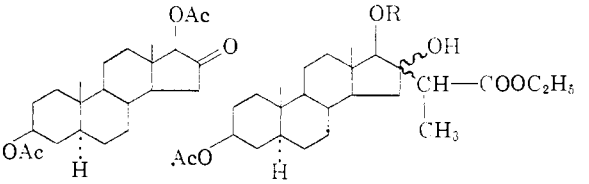
in accord with the fact that the Reformatsky reaction between dehydroisoandrosterone acetate and ethyl α-bromo-(or α-iodo)-propionate is known to yield mainly products with the 20-normal configuration.[19]

In order to determine whether all the five substances IX, X, XI, XII and XIII were formed directly by the Reformatsky reaction or whether some were produced by secondary changes due to the alumina (Merck, acid washed), each of the pure compounds was submitted separately to chromatography. It was found that X, XI and XIII were recovered completely unchanged, but the 3,16-diacetate IX was largely converted to the 3-monoacetate XI and the 16-monoacetate XII yielded the triol XIII. It therefore appears that whereas the cleavage of the 3-acetoxy grouping takes place during the Reformatsky reaction, the cleavage of the 16-acetoxy grouping is effected (at least in part) by the alumina. This facile hydrolysis at C-16 is presumably due to the presence of the neighboring hydroxyl group at C-17. The fact that alumina converts IX to the monoacetate of m.p. 167–168° whereas the monoacetate of m.p. 154–155° gives the triol XIII shows the first monoacetate to be the 3-acetoxy compound XI and the second the 16-acetoxy compound XII. The reverse assignment would require the 3-acetoxy grouping to be cleaved by alumina, whereas in fact authentic 3β-acetoxy-5α-steroids (such as V) were found to be completely unaffected by the alumina employed. Moreover, the results obtained by treatment of the 3-monoacetate XI with potassium bisulfate, described below, show that it does not have the alternative 16-monoacetate structure XII.

The above observations suggested that the most convenient preparative procedure consisted in reacetylating the total Reformatsky product from VI and ethyl α-bromopropionate prior to chromatography. This proved to be the case and the 3,16-diacetate IX (15% yield) and the 3-monoacetate XI (49% yield) were the only substances obtained (a small amount of the lactone X was presumably again formed but was not isolated). Re-acetylation of XI then brought the total yield of the desired diacetate IX to 63%.

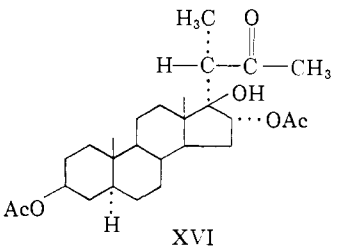
It is of interest to note how well the above-described Reformatsky reaction proceeds and its apparently complete stereospecificity. By comparison the previously studied Reformatsky reaction between the 16-unsubstituted 17-ketone, dehydroisoandrosterone acetate, and ethyl α-halogenopropionates proceeds rather poorly (over 50% of starting material recovered) and gives all four of the possible stereoisomeric products besides some dehydrated material.[19]

The possibility was considered that our Reformatsky products might perhaps possess structures of type XV with the side chain attached at C-16, derived from the 16α-acetoxy-17-one VI by rearrangement to the 17β-acetoxy-16-one XIV prior to condensation. It has previously been shown that the transformation of VI to XIV can be brought about through treatment with base and re-acetylation.[15] In order to rule out this possibility, the 17α-acetoxy-16-ketone XIV, obtained in the indicated manner, was subjected to a Reformatsky reaction with ethyl α-bromopropionate.



Chromatography yielded two stereoisomeric esters, $C_{26}H_{42}O_6$, isomer A (32% yield) showing m.p. 188–189° and isomer B (15% yield) m.p. 123–124°. These appear to be the 3-monoacetates XVa stereoisomeric at the C-16 and/or the "C-20" position, cleavage of the ring D acetoxy group again having occurred. Neither of these substances was identical with the 3-monoacetate XI. On acetylation, XVa (isomer A) gave the corresponding diacetate XVb (m.p. 174–175°) and XVa (isomer B) gave another diacetate XVb (m.p. 125–126°). Both of these diacetates differed from the diacetate XIII and we are therefore dealing with a new series of compounds.

The trihydroxy-acid VIIa and its various esters and acetates contain a superfluous hydroxyl group at C-17 for our purposes. It was decided as the next step to study the transformation of the 22-carboxyl grouping to a 22-ketone, since ready β-elimination of the 17β-hydroxyl function was then expected to occur. As a model experiment, the acid chloride derived from the acid diacetate VIIIa was accordingly treated with dimethylcadmium.[20] The resulting compound (m.p. 190–191°), obtained in 44% yield, is tentatively assigned the 22-ketone structure XVI in view of the elemental analysis and the appearance of a band at 5.86 μ



XVI

in the infrared.[16b] Rather surprisingly, however, all attempts to effect dehydration of XVI to the corresponding $\Delta^{17(20)}$-22-ketone were unsuccessful. Moreover the acid chloride of VIIIa proved to be completely unreactive toward diisoamylcadmium[20] and our attention was therefore turned to attempting dehydration at C-17 prior to carrying out reactions involving the 22-carboxyl grouping.

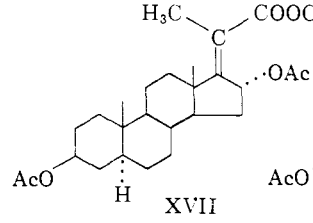
Treatment of the ethyl ester diacetate IX with phosphorus oxychloride in hot pyridine, conditions under which related compounds lacking the 16α-acetoxy grouping had been dehydrated success-

(19) (a) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **24**, 1127 (1941); (b) D. H. Hey, J. Honeyman and W. J. Peal, *J. Chem. Soc.*, 185, 2648 (1954).

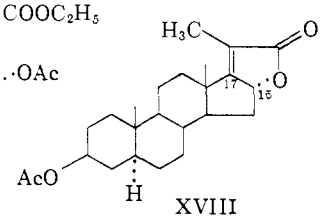
(20) The reaction of a bisnorcholanic acid chloride unsubstituted at C-16 or C-17 with dimethylcadmium as well as with diisoamylcadmium has been shown to give smoothly the corresponding 22-ketones (W. Cole and P. L. Julian, THIS JOURNAL, **67**, 1369 (1945)).

fully,[19b] did not lead to simple dehydration at C-17. The product showed a high-intensity ultraviolet maximum at 272 mμ, indicating that both the oxygen functions at C-16 and C-17 had been lost to give a doubly unsaturated ester. Rather similar results were obtained with boiling acetic anhydride.

The first indications of success were obtained when IX was treated with copper sulfate at 180° (25 mm.), whereby the α,β-unsaturated ester XVII (see below) was formed in 7% yield. After further experimentation it was found that dehydration of IX with potassium bisulfate at *ca.* 170° (25 mm.) for 15 minutes gave 40% of the α,β-unsaturated ester XVII (m.p. 140-141°) and 38% of the α,β-unsaturated γ-lactone XVIII (m.p. 239-240°). Each of these substances had the elemental composition to be expected of the assigned structures.



XVII



XVIII

Furthermore the spectral properties of XVII [ultraviolet maximum at 221 mμ (ε 11,700); infrared band at 5.82 μ (α,β-unsaturated ester)[16c]] as well as of XVIII [ultraviolet maximum at 220 mμ (ε 10,600); infrared band at 5.74 μ (α,β-unsaturated γ-lactone)[16a]] are in accord with the formulations presented.

When the potassium bisulfate dehydration of IX was allowed to proceed for a longer time, the yield of the ester XVII decreased and that of the lactone XVIII increased (only the latter could be isolated after reaction for 1 hour). It appeared therefore that the ester XVII is an intermediate in the formation of the lactone XVIII and this was confirmed by the finding that the former of these substances yields the latter on being heated with potassium bisulfate. Moreover the transformation of XVII to XVIII (in *ca.* 25% yield) could be effected through successive treatment with potassium hydroxide in boiling methanol, acidification and re-acetylation. This interconversion shows the configuration of the double bond in the α,β-unsaturated ester XVII to be as indicated. It was not found possible to effect the reverse reaction, the conversion of the lactone XVIII to the ester XVII.

It is of interest to note that different results were obtained when compounds closely related to the ethyl ester diacetate IX were subjected to treatment with potassium bisulfate. Thus, the acid diacetate VIIIa on being heated with this reagent at *ca.* 170° (1 mm.) gave 76% of the above-described 17β-hydroxy-lactone X and the latter substance could not be dehydrated at C-17 even by prolonged heating with potassium bisulfate.

The ethyl ester 3-monoacetate XI on treatment with potassium bisulfate at *ca.* 170° (20 mm.) gave two new substances. The first (m.p. 165-166°), obtained in 48% yield, on elemental analysis proved to be an isomer of the α,β-unsaturated lactone XVIII. The lack of a high-intensity ultraviolet maximum above 210 mμ, the existence of a band at 5.69 μ in the infrared as well as the presence of a double bond (yellow color with tetranitromethane) which could not be hydrogenated over platinum in acetic acid, at first suggested it to be the $\Delta^{16(17)}$-isomer of XVIII. This enol lactone formulation, however, could be ruled out since the substance was hydrolyzed with potassium hydroxide to the potassium salt of an acid which re-lactonized on acidification and regenerated the original material on acetylation. The second substance (m.p. 250-252°), isolated in 35% yield, was a γ-lactone (infrared band at 5.68 μ^{16a}) and the elemental analysis showed it to be an isomer of the 17β-hydroxy-lactone X. It was recovered unchanged after being heated with potassium bisulfate and it is therefore not an intermediate in the formation of the first compound. It appears most probable that both the substances under discussion are rearrangement products, although their structures have not been elucidated. It may be noted that potassium bisulfate dehydration of 17-hydroxy-steroids has previously been found to be accompanied by rearrangement.[21]

The α,β-unsaturated ester XVII could not be hydrogenated over platinum in ethyl acetate. However the reaction proceeded smoothly when carried out in acetic acid solution and stereospecifically gave one saturated ester (m.p. 129-130° or 159-160°) in 85% yield. This compound is assigned the structure XIXa (natural configuration at C-17, unnatural configuration at C-20), in view of the known usual *cis*-addition of hydrogen through catalytic hydrogenation[22] and the fact that the α-side of the unsaturated ester XVII appears to be considerably more exposed to adsorption on the catalyst surface than the β-side. The saturated diacetoxy-ethyl ester XIXa on saponification yielded the corresponding dihydroxy-acid XXa which with diazomethane gave the dihydroxy-methyl ester XXb (m.p. 181-182°) and then by acetylation the diacetoxy-methyl ester XIXb (m.p. 169-170°).[23]

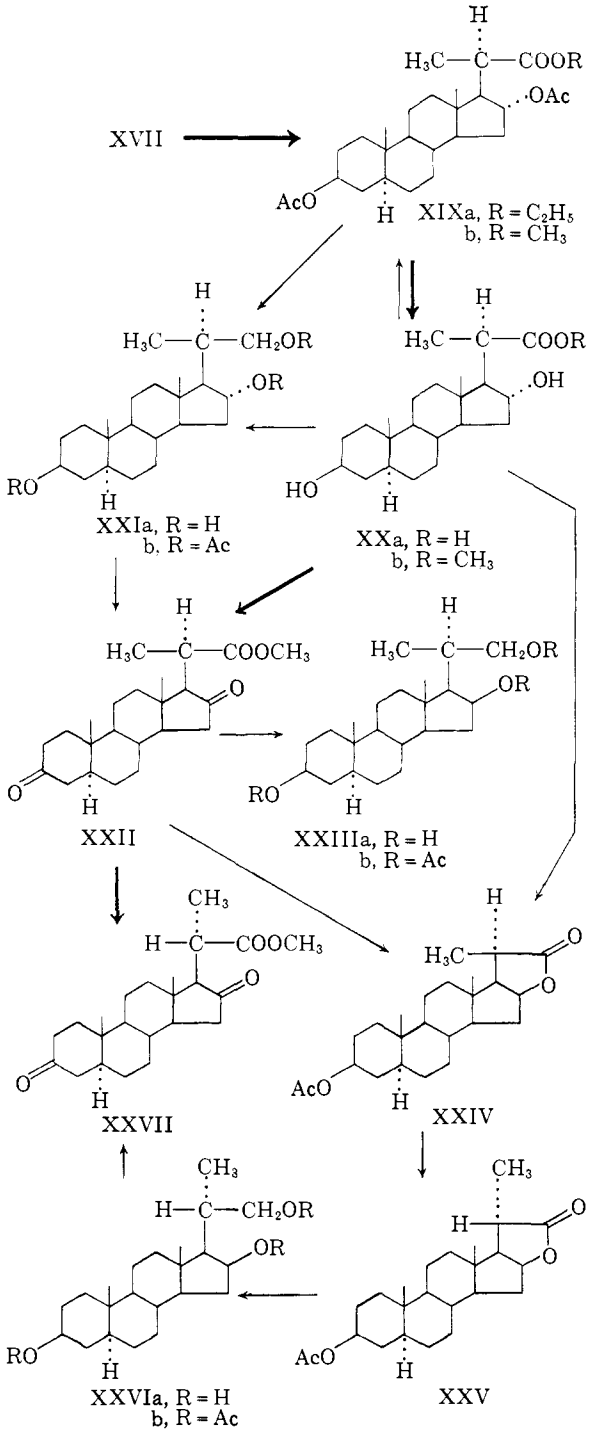
Reduction of the diacetoxy-ethyl ester XIXa with lithium aluminum hydride led to the 20-iso-3β,16α,22-triol XXIa, and then through acetylation to the triacetate XXIb. The same substances were formed by the lithium aluminum hydride reduction of the dihydroxy-methyl ester XXb and no inversion at C-20 had therefore occurred during the saponification of the ethyl ester XIXa.

Oxidation of the dihydroxy-methyl ester XXb with chromium trioxide in acetic acid yielded 68% of the 20-iso-diketo-ester XXII and the same substance was obtained from the triol XXIa by successive chromium trioxide oxidation and esterification with diazomethane. The resulting diketo-ester XXII on reduction with lithium aluminum

(21) See A. Cohen, J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 445 (1935); H. Kägi and K. Miescher, *Helv. Chim. Acta*, **22**, 683 (1939).

(22) See R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, THIS JOURNAL, **64**, 1985 (1942).

(23) Since this part of our work was completed, V. Schwarz, V. Cerny and F. Sorm (*Chem. Listy*, **52**, 1633 (1958)) have reported a different synthesis of a compound which probably possesses structure XIXb, showing physical properties in fair agreement with ours.



hydride gave a triol which differed from XXIa and is assigned the 20-iso-3β,16β,22-triol structure XXIIIa in view of the known formation of the 16β-alcohols by metal hydride reduction of 16-keto-steroids bearing a 17β-substituent.[24,25] It has been found that the change in molecular rotation (M_D) on passing from a 16α- to a 16β-hydroxy steroid is +95 ± 10 (in ethanol) and from a 16α- to a 16β-acetoxy steroid +410 ± 40 (in ethanol).[26] The observed change in M_D on passing from the triol XXIa to the triol XXIIIa is +126 (in pyridine) and from the triacetate XXIb to the triacetate XXIIIb +438 (in chloroform). The molecular rotation data therefore confirm the structural assignments at C-16.

Before proceeding with the synthesis, it appeared desirable at this stage to interrelate one of our synthetic compounds with a steroidal sapogenin degradation product. Tigogenin acetate had previously been oxidized to tigogenin lactone acetate (XXV),[24,27,28] which on lithium aluminum hydride reduction had yielded the 20-normal-3β,16β,22-triol XXVIa[24,27b] and then, by oxidation and esterification, the 20-normal-3,16-diketo-ester XXVII.[24] The latter substance through successive ketal formation, isomerization at C-20, saponification of the ester grouping and acid treatment had given a product containing the 20-iso-diketo-acid corresponding to XXII, since sodium borohydride reduction and acetylation produced the 20-iso-lactone XXIV besides the 20-normal lactone XXV.[24] The synthetic 20-iso-diketo-ester XXII was therefore reduced with sodium borohydride and then treated with acid and acetylated. The resulting substance, isolated in *ca.* 45% yield, showed physical properties in excellent agreement with those reported for the expected 20-iso-lactone XXIV[24] and differed from the 20-normal-lactone XXV.

It has been shown that the 20-iso-lactone XXIV is stable to acids, but can be inverted at C-20 with sodium methoxide, the driving force for the rearrangement being the steric repulsion between the 18β- and 20β-methyl groups in XXIV which does not exist in the normal compound XXV.[24] We have found the inversion of synthetic XXIV to be effected most conveniently by means of potassium hydroxide in boiling methanol, followed by acidification, extraction and acetylation. The resulting tigogenin lactone acetate (XXV), obtained in almost quantitative yield, proved to be identical with an authentic sample.[24,27] This type of lactone, which has played an important part in the elucidation of the constitution of the steroidal sapogenins,[27a,29] is therefore available by synthesis. Moreover the stereochemical course of the synthesis confirms the presently accepted views of the configuration at C-20 of the lactone XXV[24] and hence of the natural steroidal sapogenins[5a] and sterols.[5b]

A shorter synthesis of tigogenin lactone acetate (XXV) was discovered when attempts were made to form the lactone of the dihydroxy-acid XXa in order to ascertain if a γ-lactone *trans*-fused to a five-membered ring could be prepared. Treatment of XXa with boiling hydrochloric acid and acetic acid for 2 hours resulted in inversion at C-16 and after acetylation directly yielded over 50%

(24) J. W. Corcoran and H. Hirschmann, THIS JOURNAL, **78**, 2325 (1956).

(25) H. Hirschmann and F. B. Hirschmann, *ibid.*, **78**, 3755 (1956).

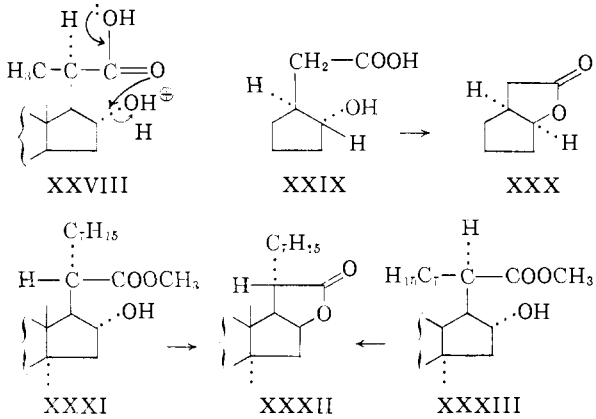
(26) See D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951).

(27) (a) R. Tschesche and A. Hagedorn, *Ber.*, **68**, 1412 (1935); (b) D. L. Klass, M. Fieser and L. Fieser, THIS JOURNAL, **77**, 3829 (1955).

(28) This substance has also been obtained by the chromium trioxide oxidation of tomatidine diacetate (R. Kuhn, I. Löw and H. Trischmann, *Ber.*, **85**, 416 (1952)).

(29) *Inter al.*, S. N. Farmer and G. A. R. Kon, *J. Chem. Soc.*, 414 (1937); R. E. Marker and E. Rohrmann, THIS JOURNAL, **62**, 76 (1940); R. E. Marker, D. L. Turner and P. R. Ulshafer, *ibid.*, **63**, 763 (1941).

of the 20-iso-lactone XXIV. The product was identical to that prepared by the more indirect method and was isomerized at C-20 with base to the 20-normal-lactone XXV. The reaction involving inversion at C-16 presumably proceeds *via* a mechanism of type XXVIII, being similar to that by which *trans*-cyclopentanol-2-acetic acid (XXIX) gives the *cis*-lactone XXX (with boiling dilute sulfuric acid,[17a] with hydrogen chloride in benzene[17a] or by pyrolysis[17b]) and the hydroxy-ester XXXI derived from polyporenic acid C gives the *cis*-lactone XXXII (with thionyl chloride in a boiling hydrocarbon).[30] It is of interest to note however that whereas in our case the reaction proceeds without inversion at C-20 and gives the unstable 20-iso-lactone XXIV, the reaction with the analogous polyporenic acid ester XXXIII (natural C-20 configuration) takes place with inversion at C-20 as well as at C-16 to give the same stable lactone XXXII as had been obtained from XXXI. It has not been determined whether this difference is due to the different reaction conditions employed or to the fact that the lactone XXXII possesses a long alkyl side-chain and in the corresponding 20-unisomerized compound the interaction between the 18β-methyl and 20β-alkyl group would be more pronounced than in the 20-iso-lactone XXIV.



XXVIII XXIX XXX

XXXI XXXII XXXIII

Of the unsaturated ester XVII and the unsaturated lactone XVIII (obtained in similar amounts by dehydration of the Reformatsky product IX), only the former has so far been hydrogenated and then submitted to further transformations. It was of interest now to study the hydrogenation of the lactone XVIII, in order that this substance might also be usable for our synthetic purposes and also because the interesting strained system containing a γ-lactone *trans*-fused to a cyclopentane ring would be obtained if addition of hydrogen proceeded from the α-side as had occurred with XVII.[31] In the event, the lactone XVIII was found smoothly to add hydrogen over platinum in ethyl acetate, the strain in the unsaturated γ-lactone ring presumably being responsible for this reaction to occur under milder conditions than the hydrogenation of the ester XVII. These resulted in 90% yield a saturated γ-lactone (λ_{max} 5.69 μ),[16a] which differed from both the known lactones XXIV and XXV. It was apparent that this was not the strained *trans*-lactone formed by α-addition of hydrogen, as it was not opened to a hydroxy-acid on treatment with potassium hydroxide. More important, lithium aluminum hydride reduction gave a triol which differed from the triol XXIa and subsequent chromium trioxide oxidation and methylation yielded a diketo-ester that was identical neither with the 17-normal-20-iso-ester XXII nor with the 17-normal-20-normal-ester XXVII. The last-mentioned fact clearly indicated that the C-17 side chain in these new compounds is α-orientated and consequently that hydrogenation of XVIII has occurred from the β-side at C-17. Assuming the usual *cis*-addition of hydrogen,[22] the saturated lactone therefore has the 17-iso-20-normal configuration XXXIV, and the derived triol and diketo-ester possess the corresponding structures XXXVa and XXXVI, respectively.

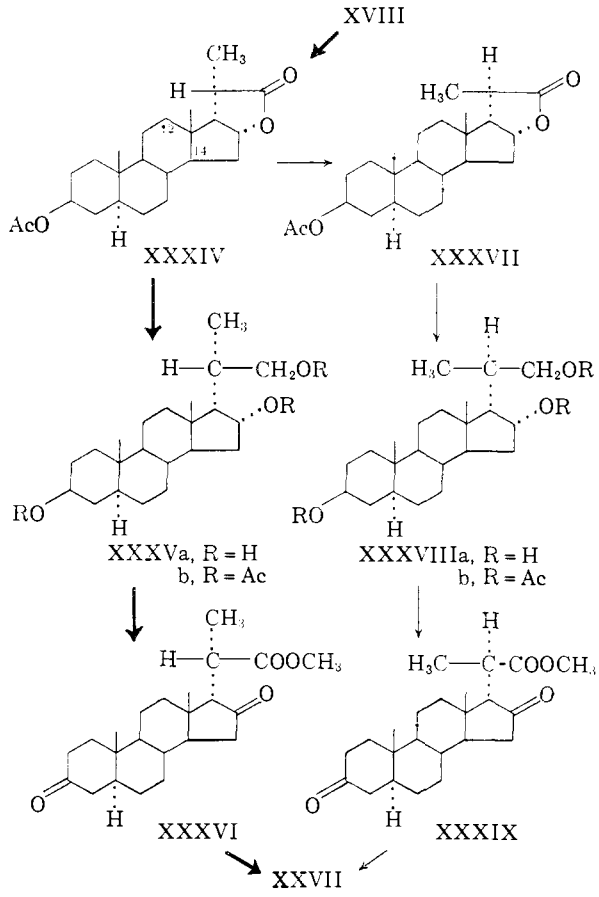
A model of the 17-iso-lactone XXXIV shows there to be considerable steric interference between the 20α-methyl group and the α-hydrogens attached to C-12 and C-14. As expected, treatment of XXXIV with potassium hydroxide in boiling methanol followed by re-acetylation smoothly yielded an isomeric lactone (λ_{max} 5.69 μ),[16a] to which is assigned the 17-iso-20-iso structure XXXVII in which the 20-methyl group is quite unhindered. This rearrangement is comparable to that leading from the 17-normal-20-iso-lactone XXIV to the corresponding 20-normal isomer XXV, except that the shift of the 20-methyl group is in the opposite direction.[32] The isomerized lactone XXXVII was recovered completely unchanged after being subjected to the conditions under which it had been formed. The stability relationship between the two new lactones XXXIV and XXXVII provides strong evidence for the C-20 configurations ascribed to them, since the reversed assignments would not only necessitate *trans*-addition of hydrogen to XVIII to have taken place, but would also require the theoretically stable isomer to have isomerized to the theoretically unstable one. In agreement with the structure XXXVII, the isomerized lactone on lithium aluminum hydride reduction yielded a new triol, which must be the 17-iso-20-iso-3β,16α,22-triol XXXVIIIa, and then by oxidation and methylation the new 17-iso-20-iso-diketo-ester XXXIX.

All the four possible *cis*-fused lactones of the tigogenin lactone acetate type stereoisomeric at C-16, C-17 and C-20 are now known and their physical properties are set out in Table I. It has previously been found[24] that the two 17-normal-lactones XXIV and XXV can be differentiated by

(30) A. Bowers, T. G. Halsall and G. C. Sayer, *J. Chem. Soc.*, 3070 (1954).

(31) It could not be predicted *a priori* from which side of XVIII addition of hydrogen would occur, since a model cannot be made from "Catalin" models and it is difficult to estimate which side of the molecule is more hindered.

(32) It was found that whereas base treatment of the 17-normal-20-iso-lactone XXIV yielded the potassium salt of the corresponding 20-normal-dihydroxy-acid from which the lactone XXV was obtained only after acidification, extraction and acetylation, the 17-iso-20-normal-lactone XXXIV with base directly produced the 17-iso-20-iso-lactone XXXVII (3-hydroxyl instead of 3-acetoxyl) without acidification. Inspection of models shows that the latter phenomenon is most probably due to the fact that isomerization at C-20 of the 17-iso-20-normal-lactone XXXIV proceeds more readily than opening of the lactone ring for steric reasons, and that the 22-carbonyl group in the product is then so shielded that opening of the ring does not take place.



the fact that in their infrared spectra a band ascribable to the acyl–oxygen stretching of the lactone group appears at 8.61 μ in the 20-iso-compound XXIV and at 8.51 μ in the 20-normal-compound XXV (measured in carbon disulfide; the values obtained by us in chloroform are given in Table I). We have observed that the corresponding infrared bands in the two 17-iso-lactones XXXIV and XXXVII show a similar shift (see Table I), in this case the band of the 20-normal-isomer XXXIV being at higher wave length than that of the 20-iso-compound XXXVII. In both series therefore the higher wave length band is shown by the isomer in which there is steric interference between the 20-methyl group and another part of the molecule and consequently in which the lactone ring may well be strained or distorted.

TABLE I

PHYSICAL PROPERTIES OF STEREOISOMERIC TIGOGENIN LACTONE ACETATES

Compound	M.p., °C.	$[\alpha]_D^{CHCl_3}$	$\lambda_{max}^{CHCl_3}$, μ
17-Normal-20-iso (XXIV)[24]	226–228	−36°	8.54
17-Normal-20-normal (XXV)[24,27,28]	219–221	−49	8.45
17-Iso-20-normal (XXXIV)	199–201	+21	8.51
17-Iso-20-iso (XXXVII)	190–191	+13	8.45

In the bisnor-5α-cholane-3β,16,22-triol series, five of the eight possible isomers differing in configuration at C-16, C-17 and C-20 have been prepared. Their physical properties as well as those of the corresponding triacetate are recorded in Table II.

In Table III are summarized the properties of the four possible methyl 3,16-diketobisnor-5α-cholanates stereoisomeric at C-17 and C-20, all of which are now available. The presence of carbonyl groups adjacent to the asymmetric centers at C-17 and C-20 in these substances should permit isomerization to the most stable configurations. The first isomer to be investigated was the natural diketo-ester XXVII, which on treatment with sodium methoxide or with potassium hydroxide and subsequent re-methylation was recovered completely unchanged, no indications of the formation of any 20-iso-ester XXII being obtained. This was rather unexpected, since related 20-normal-bisnorcholanic acid esters either unsubstituted at C-16[33] or carrying a 16-cycloethylenedioxy grouping[24] can be inverted to the 20-iso-compounds, at least in part.

The synthetic 17-normal-20-iso-ester XXII was then heated with potassium hydroxide in methanol and re-methylated, whereby complete isomerization at C-20 took place and the natural isomer XXVII, identical with an authentic sample, was obtained in almost quantitative yield. Moreover both the 17-iso-20-normal-ester XXXVI and the 17-iso-20-iso-ester XXXIX under these conditions were converted in excellent yield to the same natural isomer XXVII, the isomerization of the axial 17α-substituent to the equatorial 17β-position being in keeping with expectation.[34]

The surprising fact that in the methyl 3,16-diketobisnor-5α-cholanate series the 20-normal configuration is the stable one must be connected with the presence of the 16-keto group. This is demonstrated clearly by our observation that whereas the 3β,16α-diacetoxy-20-iso-ester XIXa can be saponified with base without any isomerization at C-20, the corresponding 3,16-diketo-20-iso-ester XXII under the same conditions suffers complete inversion. The unusual stability relationship of 16,22-dicarbonyl steroids has been discussed by us elsewhere[35] and appears to be due to the existence of an intramolecular field effect between the two carbonyl groups which can be detected by the anomalous infrared spectral properties.

The above-described isomerization experiments make available by synthesis the 17-normal-20-normal-diketo-ester XXVII by several different paths. Since it was found subsequently that this synthetic compound can be transformed further to steroidal sapogenins, the two best routes to it are shown by heavy arrows in the formula charts, one proceeding from the unsaturated ester XVII and the other from the unsaturated lactone XVIII. The over-all yield from 3β,16α-diacetoxyandrostan-17-one (VI) is *ca.* 20%.

We have available at this stage a number of bisnor-5α-cholane derivatives oxygenated at the 3-,

(33) H. Wieland, O. Schlichting and R. Jacobi, *Hoppe-Seyler's Z. physiol. Chem.*, **161**, 80 (1926). M. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **27**, 1631 (1944); **28**, 875 (1945).

(34) Attempts made with the 17-iso-20-iso-ester XXXIX under milder basic conditions to effect isomerization only at C-17 to give the 17-normal-20-iso-ester XXII were unsuccessful, either unchanged XXXIX or the 17-normal-20-normal ester XXVII being obtained.

(35) Y. Mazur and F. Sondheimer, *Experientia*, **16**, 181 (1960).

TABLE II

PHYSICAL PROPERTIES OF STEREOISOMERIC BISNOR-5α-CHOLANE-3β,16,22-TRIOLS

Compound	Triol a M.p., °C.	Triol a $[\alpha]_D^{C_5H_5N}$	Triacetate b M.p., °C.	Triacetate b $[\alpha]_D^{CHCl_3}$
17-Normal-20-iso-3β,16α,22-triol (XXI)	269–270	−23°	151–152	−57°
17-Normal-20-iso-3β,16β,22-triol (XXIII)	308–310	+13	163–164	+35
17-Normal-20-normal-3β,16β,22-triol (XXVI)[24,27b]	246–249	+15	117–118	+52
17-Iso-20-normal-3β,16α,22-triol (XXXV)	245–247	−45	100–101	−45
17-Iso-20-iso-3β,16α,22-triol (XXXVIII)	189–191	−19	109–110	−71

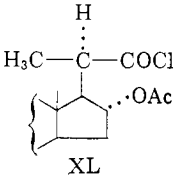
TABLE III

PHYSICAL PROPERTIES OF STEREOISOMERIC METHYL 3,16-DIKETOBISNOR-5α-CHOLANATES

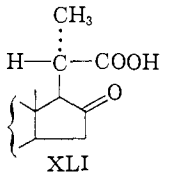
Compound	M.p., °C.	$[\alpha]_D^{CHCl_3}$
17-Normal-20-iso (XXII)	143–145	−110°
17-Normal-20-normal (XXVII)[24]	220–222	−108
17-Iso-20-normal (XXXVI)	131–133	− 67
17-Iso-20-iso (XXXIX)	121–123	−121

16- and 22-positions and we now turned our attention to the construction at C-22 of the missing five-carbon chain. Before the successful method for achieving this was found, several avenues were explored which did not lead to the desired objective and some of which are summarized briefly below.

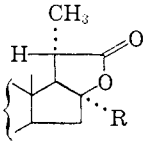
Thus, the 20-iso-3β,16α-diacetoxy-acid chloride XL (infrared band at 5.60 μ; prepared from the dihydroxy-acid XXa by acetylation and subsequent treatment with thionyl chloride) proved to be completely unreactive toward diisoamylcadmium at room temperature,[36] whereas a considerable amount



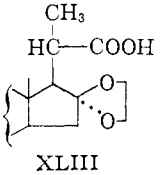
XL



XLI



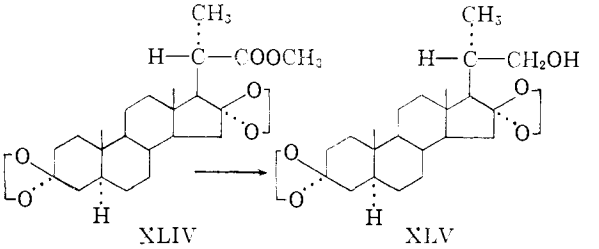
XLIIa, R = Cl
b, R = OMe
c, R = OH



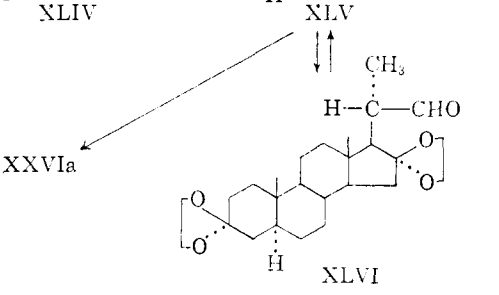
XLIII

of a γ-lactone (infrared band at 5.69 μ) was formed when the reaction was carried out in boiling benzene or toluene. Tigogenin lactone acetate (XXV) when treated with alkyl Grignard reagents or lithium derivatives under various conditions apparently only gave starting material or the tertiary carbinols. The 20-normal-3,16-diketo-acid XLI (obtained by saponification of the methyl ester XXVII) on conversion to the sodium salt and then treatment with oxalyl chloride[37] yielded a chlorine-containing substance which appears to be the chloro-γ-lactone XLIIa rather than the acid chloride, since boiling methanol led apparently to the methoxy-lactone XLIIb (infrared band at 5.68 μ). On attempted enol lactone formation with isopropenyl acetate and sulfuric acid, the diketo-acid XLI gave a compound to which is assigned the hydroxy-γ-lactone structure XLIIc (3-acetoxy-Δ²-grouping in ring A) on the basis of the elemental analysis and infrared spectrum (bands at 5.63 and 5.73 μ). The ester-bisketal XLIV described below on saponification produced the acid-bisketal XLIII (probably as a 20-stereoisomeric mixture),[24] which resisted all attempts at reaction with isoamyllithium,[38] whereas treatment of the corresponding sodium salt with oxalyl chloride[37] resulted in attack of the ketal groupings and did not yield an acid chloride as indicated by the infrared spectrum.

We return now to the main path of our synthesis. The 17-normal-20-normal-3,16-diketo-ester XXVII was converted in *ca.* 60% yield to the 3,16-biscycloethylene ketal XLIV[24] so as to protect the 3- and 16-oxygen functions against attack during the subsequent reactions. Reduction with lithium aluminum hydride then led in 72% yield to the hydroxy-



XLIV XLV



XXVIa XLVI

bisketal XLV (m.p. 235–237°). Oxidation of this alcohol with the chromium trioxide–pyridine complex[39] produced 83% of the aldehyde-bisketal XLVI (m.p. 183–184°), which unlike the starting material XLV showed a carbonyl band (at 5.82 μ) in the infrared. In the last step advantage is taken of the hindered nature of the 22-position, the unusually high yield presumably being due to the slowness of the further oxidation of the aldehyde to the acid. That the aldehyde XLVI still has the 20-normal configuration was shown by the fact that lithium aluminum hydride reduction regenerated

(36) This unreactivity is presumably due to the presence of the 16α-acetoxy grouping in XL, since the related 3β-acetoxy-Δ⁵-bisnorcholenic acid chloride has been found to react smoothly with diisoamylcadmium at room temperature.[29]

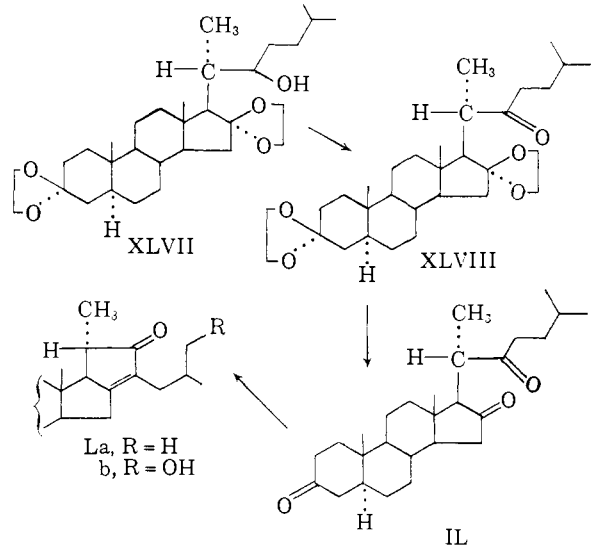
(37) See A. L. Wilds and C. H. Shunk, THIS JOURNAL, **70**, 2427 (1948).

(38) See H. Gilman and P. R. van Ess, *ibid.*, **55**, 1258 (1933); D. A. van Dorp and J. F. Arens, *Rec. trav. chim.*, **65**, 338 (1946).

(39) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

the alcohol XLV, which in turn on cleavage of the ketal groupings with hot aqueous acetic acid and subsequent lithium aluminum hydride reduction produced the 20-normal-3β,16β,22-triol XXVIa.

The aldehyde-bisketal XLVI was now treated with isoamylmagnesium bromide, in order to determine whether the 22-aldehyde grouping would undergo normal condensation with Grignard reagents. The product (m.p. 195–196°), obtained in 72% yield, appeared to have the expected structure XLVII in view of the elemental composition and the disappearance of the carbonyl band and appearance of a hydroxyl band in the infrared. The substance was homogeneous and the reaction therefore proceeded stereospecifically.[40]

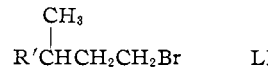


The formulation XLVII was confirmed by the following reaction sequence. Oxidation with the chromium trioxide–pyridine complex[39] produced the corresponding 22-keto-bisketal XLVIII (m.p. 134–135°, infrared carbonyl band at 5.86 μ), the ketal groupings of which were cleaved with hot aqueous acetic acid. The resulting cholestane-3,16,22-trione (IL) (m.p. 176–177°) on treatment with potassium hydroxide in boiling methanol underwent an internal aldol condensation and produced the cyclopentenone La, as indicated by the appearance of an ultraviolet maximum at 246 mμ (ϵ 12,800). This transformation clearly demonstrates the presence of a 16,22-diketo-grouping in IL, the 16,22-diketone kryptogenin (IV) having previously been shown to undergo an analogous reaction with base to give fesogenin (type Lb) [λ_{max} 245 mμ (ϵ 13,700)].[42]

(40) Although the configuration of the newly formed 22-hydroxyl group in XLVII was not determined rigidly, molecular rotation (M_D) data point to the β-configuration (convention of P. A. Plattner).[12] Thus, inspection of the literature[41] shows the shift in M_D on passing from a 22-hydroxycholestane derivative (unsubstituted at C-16) to the corresponding 22-ketone lies in the +20 to −10 range for the 22β-isomer and in the −60 to −80 range for the 22α-isomer; the observed shift in M_D on passing from XLVII to the 22-ketone XLVIII is +20.

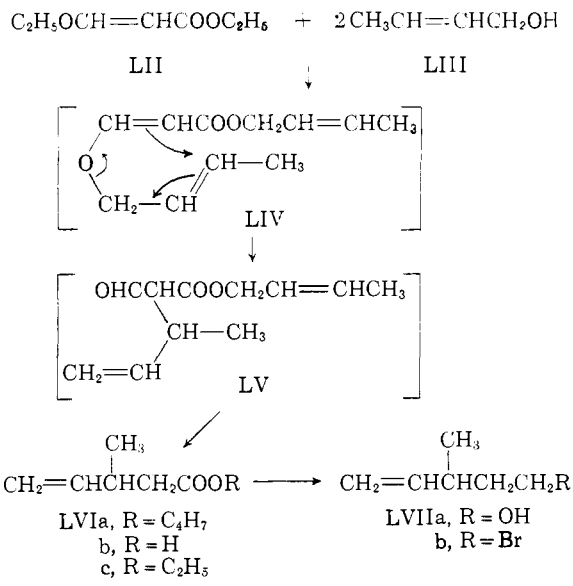
(41) See W. Cole and P. L. Julian, THIS JOURNAL, **67**, 1369 (1945); L. F. Fieser and Wei-Yuan Huang, *ibid.*, **75**, 5356 (1953); A. Stabursvik, *Acta Chem. Scand.*, **7**, 1220 (1953); S. Lieberman, quoted by L. F. Fieser and M. Fieser[5c]; K. Tsuda and R. Hayatsu, THIS JOURNAL, **81**, 5987 (1959).

The stage was now set for the synthesis of a 3,-16,22,26-tetra-oxygenated cholestane derivative (type III and IV), through condensation of the aldehyde-bisketal XLVI with the Grignard derivative of a 3-substituted butyl bromide of type LI in which R′ is a substituent which can subsequently



be converted to a hydroxymethyl grouping. The bromide actually chosen was 1-bromo-3-methyl-4-pentene (LI, R′ = —CH=CH$_2$) = (LVIIb) since its preparation and use promised to involve less complications than a substance of type LI already containing a suitably protected hydroxymethyl function.

3-Methyl-4-pentenoic acid (LVIb) was obtained directly in 30% yield by fractionating a mixture of ethyl β-ethoxyacrylate (LII)[43] and crotyl alcohol (LIII) containing dissolved sodium, followed by saponification with sodium hydroxide in boiling methanol. This reaction sequence, which is based on that whereby methallyl methallylacetate is obtained in one step from LII and methallyl alcohol,[44] proceeds presumably by interchange to crotyl β-crotyloxyacrylate (LIV), which through Claisen rearrangement gives the α-formyl-ester LV and then, by loss of the formyl group, the crotyl ester LVIa. Lithium aluminum hydride reduction of the acid XVIb smoothly gave 3-methyl-4-penten-1-ol (LVIIa), which was converted to 1-bromo-3-methyl-4-pentene (LVIIb) by treatment with phosphorus tribromide and pyridine. The existence of a terminal double bond in this bromide, as well as in the acid LVIb and the alcohol LVIIa was confirmed by the presence of bands at *ca.* 6.09, 10.08



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

(43) Prepared by the condensation of acetylene with ethyl carbonate and subsequent distillation over sodium bisulfate (W. J. Croxall and H. J. Schneider, *ibid.*, **71**, 1257 (1949)).

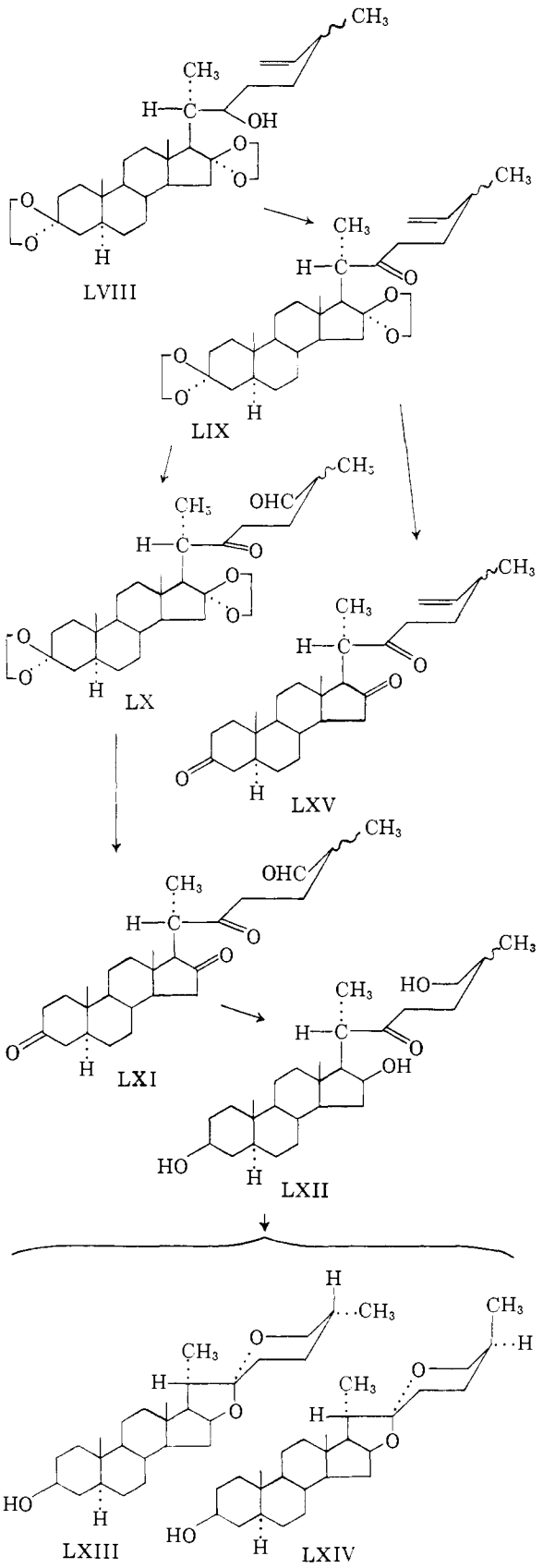
(44) W. J. Croxall and J. O. Van Hook, *ibid.*, **72**, 803 (1950). These authors also reported a three-step synthesis of the ethyl ester LVIc by a method involving the same principle.

and 10.95 μ in the infrared spectra of all three substances.[16e,45]

Condensation of the aldehyde-bisketal XLVI with the magnesium derivative of 1-bromo-3-methyl-4-pentene (LVIIb) yielded 74% of the hydroxy-bisketal LVIII (m.p. 143–157°), the infrared spectrum of which indicated the absence of a carbonyl grouping and the presence of a terminal double bond. The product was inhomogeneous and is undoubtedly a mixture of the two C-25 stereoisomers, the other new asymmetric center at C-22 presumably again having been introduced stereospecifically.[46] Oxidation with chromium trioxide–pyridine[39] gave in 85% yield the corresponding keto-bisketal LIX (m.p. 145–148°; infrared carbonyl band at 5.86 μ), once more as a 25-stereoisomeric mixture.

The 26-oxygen function was now generated through ozonolysis of LIX at −18° in ethyl acetate containing pyridine[47] followed by decomposition with Raney nickel, and the resulting 26-aldehydes LX without purification were submitted to ketal cleavage with hot aqueous acetic acid.[48] The triketo-aldehydes LXI thus obtained were reduced directly with sodium borohydride in isopropyl alcohol–tetrahydrofuran to the 3β,16β,26-trihydroxy-22-ketones LXII (type III)[49] and cyclized through short treatment with hydrochloric acid in methanol. Chromatographic purification then gave 26% (over-all from LIX) of a crystalline product (m.p. 178–182°, $[\alpha]_D$ −71°) which was practically indistinguishable in melting point, mixture melting point, optical rotation and infrared spectrum from a synthetic 1:1 mixture of natural tigogenin (LXIII) and neotigogenin (LXIV), the relative intensities of the infrared bands at 10.87 and 11.11 μ as well as at 11.58 and 11.78 μ (in potassium bromide)[50] having pointed to the presence of comparable amounts of a 25D- and 25L-sapogenin.[51]

Treatment of the synthetic mixture with boiling ethanolic hydrochloric acid for 120 hours[6,9,10] produced pure tigogenin (LXIII) (m.p. 202–204°, $[\alpha]_D$ −68°). On the other hand, slow crystallization of the acetates of the synthetic mixture and



(45) See N. Sheppard and D. M. Simpson, *Quart. Revs. (London)*, **6**, 1 (1952), Table 4.

(46) The 22β-hydroxy configuration was again indicated by the molecular rotation data, the shift in M_D on passing from LVIII to the 22-ketone LIX being +11 (see footnote 40).

(47) See P. Bladon, H. B. H. Henbest, E. R. H. Jones, G. W. Wood and G. F. Woods, *J. Chem. Soc.*, 4890 (1952); D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, J. E. Stafford, R. L. Pederson and A. C. Ott, THIS JOURNAL, **77**, 1212 (1955); G. Slomp and J. L. Johnson, *ibid.*, **80**, 915 (1958).

(48) No attempt was made to effect separation of the two C-25 isomers of the precursors LVIII or LIX, nor to carry out the original Grignard reaction with optically active 1-bromo-3-methyl-4-pentene (when only one isomer of these substances should have been formed), since it is likely that partial inversion at C-25 would take place during the reactions involving the 26-aldehydes. Ready isomerization at C-25 of a related 26-aldehyde has been observed previously.[10]

(49) That sodium borohydride reduction under these conditions reduces the 16- but not the more hindered 22-ketone group was anticipated, as the 16,22-diketone kryptogenin (IV) on being similarly reduced and then treated with acid gave diosgenin (type I).

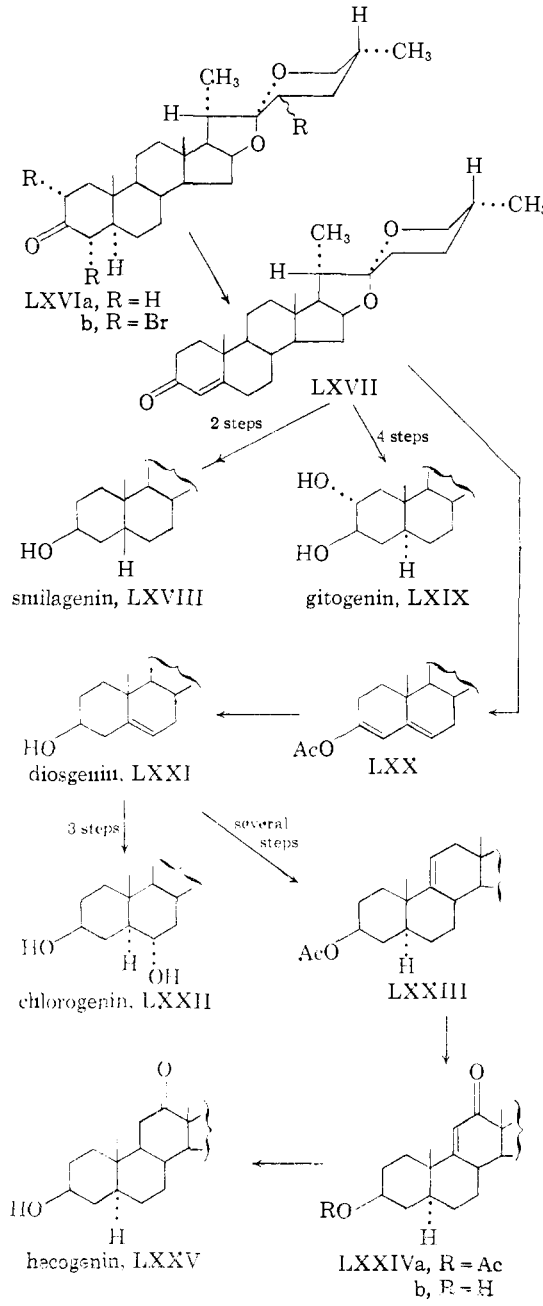
(50) See M. E. Wall, C. R. Eddy, M. L. McClennan and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952); C. R. Eddy, M. E. Wall and M. Klumpp Scott, *ibid.*, **25**, 266 (1953); R. N. Jones, E. Katzenellenbogen and K. Dobriner, THIS JOURNAL, **75**, 158 (1953).

(51) It may be noted that no appreciable amounts of sapogenins were obtained when the ketal groupings of the ethylenic keto-bisketals LIX were cleaved first and the resulting ethylenic triketones LXV (m.p. 161–165°) were then submitted to ozonolysis, sodium borohydride reduction and acid treatment.

mechanical separation[52] led to neotigogenin acetate which on saponification gave pure neotigogenin (LXIV) (m.p. 201–203°, $[\alpha]_D$ −76°). The two sapogenins thus obtained proved to be identical in melting point, mixture melting point and rotation with the respective natural materials. Most important, the very detailed infrared spectra were indistinguishable from those of the respective authentic samples.[50]

With the synthesis of tigogenin and neotigogenin accomplished, the synthesis of other natural steroidal sapogenins was a relatively simple task in view of the large number of interconversions within the sapogenin series carried out previously. Thus, tigogenin (LXIII) has already been oxidized to the corresponding 3-ketone LXVIa.[53] Bromination of the latter with bromine in acetic acid containing hydrogen bromide yielded the 2α,4α,23-tribromoketone LXVIb (m.p. 196–198°), the configuration of the bromo substituents in ring A being assigned by analogy.[54] The tribromo compound was then treated with sodium iodide and iodoacetone in acetone, followed by zinc in acetic acid. This sequence, which is based on the Glaxo modification[55] of the Syntex method[56] for converting a 3-keto-5α-steroid to the corresponding Δ^4-3-ketone, furnished Δ^4-25D-spirosten-3-one (LXVII, m.p. 185–187°), identified with an authentic sample.[57] This unsaturated ketone has already been transformed to smilagenin (LXVIII)[57a] and to gitogenin (LXIX).[58]

Treatment of the Δ^4-3-ketone LXVII with isopropenyl acetate in the presence of sulfuric acid gave the enol acetate LXX (m.p. 181–182°),[59] reduction of which with sodium borohydride smoothly produced diosgenin (LXXI) (m.p. 203–205°).[60] Identity was established by direct comparison with a sample of this important natural sapogenin. The latter has previously been converted to chlorogenin (LXXII).[61] Moreover diosgenin can be transformed by a multi-step process to $\Delta^{9(11)}$-5α,25D-spirosten-3β-ol acetate (LXXIII),[62] which



we have oxidized with chromium trioxide in warm acetic acid to 9(11)-dehydro-hecogenin acetate (LXXIVa, m.p. 217–219°)[63]; the corresponding alcohol LXXIVb is a natural sapogenin.[64] Reduction of LXXIVa with lithium in liquid ammonia and subsequent saponification then yielded hecogenin (LXXV) (m.p. 263–265°), identified with a sample from natural sources.

(52) See L. H. Goodson and C. R. Noller, THIS JOURNAL, **61**, 2420 (1939), and footnote 9a.

(53) *Inter al.*, S. G. Brooks, J. S. Hunt, A. G. Long and B. Mooney, *J. Chem. Soc.*, 1175 (1957).

(54) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).

(55) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).

(56) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(57) *Inter al.*, (a) R. E. Marker, T. Tsukamoto and D. L. Turner, *ibid.*, **62**, 2525 (1940); (b) F. Sondheimer, C. Amendolla and G. Rosenkranz, *ibid.*, **75**, 5930 (1953).

(58) J. Herran, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 5531 (1954). See also C. Djerassi, L. B. High, T. T. Grosnickle, R. Ehrlich, J. A. Moore and R. B. Scott, *Chemistry & Industry*, 474 (1955).

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

(60) This method for converting a Δ^4-3-one to a Δ^5-3β-ol is due to B. Belleau and T. F. Gallagher (THIS JOURNAL, **73**, 4458 (1951)) and to W. G. Dauben and J. F. Eastham (*ibid.*, **73**, 4463 (1951)).

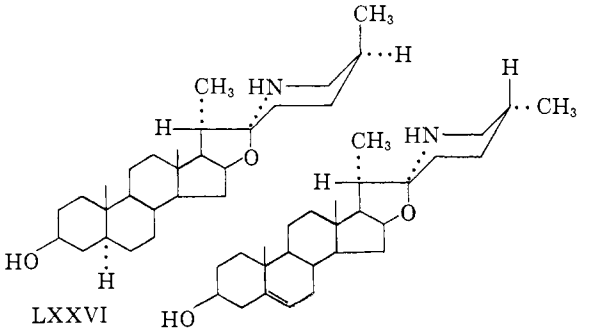
(61) R. E. Marker, E. M. Jones, D. L. Turner and E. Rohrmann, *ibid.*, **62**, 2537, 3006 (1940).

(62) *E.g.*, diosgenin acetate has been converted *via* the corresponding $\Delta^{5,7}$-diene (*inter al.*, G. Rosenkranz, J. Romo and J. Berlin, *J. Org. Chem.*, **16**, 290 (1951)) to the $\Delta^{7,9(11)}$-diene (G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *ibid.*, **16**, 298 (1951)). The latter has been transformed to 5α,25D-spirostane-3β,11α-diol (see C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712 (1952); F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952); F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1282 (1953)) and then to the $\Delta^{9(11)}$-compound LXXIII (G. Rosenkranz, O. Mancera and F. Sondheimer, *ibid.*, **76**, 2227 (1954)).

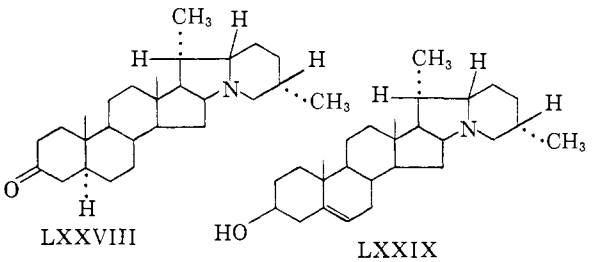
(63) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951); G. P. Mueller, L. L. Norton, R. E. Stobaugh, Lin Tsai and R. S. Winniford, THIS JOURNAL, **73**, 2400 (1951); **75**, 4892 (1953); R. Hirschmann, C. S. Snoddy and N. L. Wendler, *ibid.*, **75**, 3252 (1953).

(64) R. B. Wagner, R. F. Forker and P. F. Spitzer, *ibid.*, **73**, 2494 (1951).

It is to be noted that the work described in this paper formally represents a total synthesis of the steroidal sapogenins, since the starting material, isoandrosterone (V), is available by a number of total synthetic routes.[65] Moreover our work leads to certain of the steroidal alkaloids, in view of known interconversions. Thus, the alkaloid tomatidine (LXXVI) has previously been obtained from neotigogenin (LXIV),[66] while solasodine (LXXVII)



LXXVI LXXVII



LXXVIII LXXIX

has been obtained from diosgenin (LXXI).[67] Finally tomatidine (LXXVI) has been converted further to solanidan-3-one (LXXVIII),[68] a compound closely related to the alkaloid solanidine (LXXIX).[69]

Acknowledgments.—We are indebted to Dr. G. Rosenkranz (Syntex S.A., Mexico City) for a generous gift of dehydroisoandrosterone and to Dr. R. K. Callow (National Institute for Medical Research, Mill Hill, London N.W. 7) for a sample of neotigogenin.

Experimental[70,71]

3β,16α-Diacetoxyandrostan-17-one (VI).—Isoandrosterone (V) was converted by means of isopropenyl acetate and sulfuric acid to Δ[16]-androstene-3β,17-diol diacetate (90%, m.p. 170–172°), which was then treated with excess perbenzoic acid, essentially as described by Leeds, *et al.*[15] The resulting crude epoxide was rearranged directly with perchloric acid in acetic acid for 30 minutes at room temperature, as described in the estrone series.[15] Crystallization from methanol, and chromatography of the mother liquors on alumina followed by elution with pentane–benzene (1:1), gave 3β,16α-diacetoxyandrostan-17-one (VI) (60% over-all from V), m.p. 183–185°, [α]D + 56°; reported[15]: m.p. 184–185°, [α]D + 57°.

Reformatsky Reaction of 3β,16α-Diacetoxyandrostan-17-one (VI) with Ethyl α-Bromopropionate Followed by Saponification.—Granulated zinc (15 g., activated with iodine) was added to a solution of 10 g. of 3β,16α-diacetoxyandrostan-17-one in 100 cc. of dry benzene and *ca.* 20 cc. of solvent was removed by distillation, to remove moisture. The mixture was cooled to room temperature with exclusion of moisture and 40 g. of ethyl α-bromopropionate was then added. The mixture was heated for a short time, when an exothermic reaction occurred, which proceeded for *ca.* 30 minutes without further external heating. The reaction mixture was then boiled under reflux for 30 minutes, cooled, the supernatant liquid was decanted from the excess zinc and the latter was washed with ether. The combined organic extracts were diluted with ether, washed with dilute hydrochloric acid and water, dried and evaporated.

The resulting yellow oil was dissolved in 200 cc. of methanol, 12 g. of potassium hydroxide in 10 cc. of water was added and the solution was boiled under reflux for 3 hr. Most of the solvent was evaporated, water was added and the mixture was extracted well with ether. This "neutral" extract on evaporation yielded 2.9 g. of material which was not investigated further. The basic aqueous layer was then acidified with excess dilute hydrochloric acid and extracted well with ethyl acetate. This "acid" extract on evaporation and crystallization from methanol gave 3.5 g. (36%) of 3β,16α,17β-trihydroxy-17-isobisnor-5α-cholanic acid (VIIa), m.p. 240–242°. A purified sample showed m.p. 242–243°, [α]D − 10° (dioxane).

Methyl 3β,16α,17β-trihydroxy-17-isobisnor-5α-cholanate (VIIb) was prepared from the trihydroxy-acid VIIa in methylene chloride solution by treatment with ethereal diazomethane at 0° for 16 hr. The ester after being crystallized from acetone–hexane showed m.p. 227–228°, [α]D −8° (dioxane).

Anal. Calcd. for $C_{23}H_{38}O_5$: C, 70.01; H, 9.71. Found: C, 69.77; H, 9.55.

3β,16α-Diacetoxy-17β-hydroxy-17-isobisnor-5α-cholanic acid (VIIIa) was prepared from the trihydroxy-acid VIIa by treatment with acetic anhydride and pyridine at room temperature for 16 hr., followed by addition of a little water and heating at 90° for 30 minutes. The diacetate was crystallized from methanol and showed m.p. 185–186°, [α]D −46° (dioxane). It appears to contain methanol of crystallization.

Anal. Calcd. for $C_{26}H_{40}O_7 \cdot CH_3OH$: C, 65.30; H, 8.93. Found: C, 65.30; H, 8.67.

Methyl 3β,16α-diacetoxy-17β-hydroxy-17-isobisnor-5α-cholanate (VIIIb) was prepared both by acetylation[71a] of the trihydroxy-ester VIIb as well as by treatment of the diacetoxy-acid VIIIa with diazomethane in ether solution (16 hr. at 0°). The product from either experiment after crystallization from methanol showed m.p. 172–173°, [α]D −37°.

Anal. Calcd. for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found: C, 67.60; H, 9.15.

Reformatsky Reaction of 3β,16α-Diacetoxyandrostan-17-one (VI) with Ethyl α-Bromopropionate Followed by Chromatography.—The reaction was carried out exactly as described above, on the same scale. The total unsaponified product was then chromatographed on 500 g. of alumina.

Pentane–benzene (2:1) eluted 0.72 g. (6%) of ethyl 3β,16α-diacetoxy-17β-hydroxy-17-isobisnor-5α-cholanate (IX), which after crystallization from ether–hexane showed m.p. 177–178°, [α]D −38°, λ_{max} 5.79 μ (ester).

Anal. Calcd. for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00. Found: C, 68.57; H, 8.92.

Pentane–benzene (1:1) eluted 0.35 g. (3%) of 3β-acetoxy-16α,17β-dihydroxy-17-isobisnor-5α-cholanic 22→16-lactone (X), which after crystallization from methanol

(65) For reviews, see footnote 5d and J. W. Cornforth in "Progress in Organic Chemistry," Ed. J. W. Cook, Butterworths Scientific Publications, London, 1955, Vol. 3, Chapter 1.

(66) F. C. Uhle and J. A. Moore, THIS JOURNAL, **76**, 6412 (1954).

(67) F. C. Uhle, *ibid.*, **76**, 4245 (1954).

(68) Y. Sato and H. G. Latham, *ibid.*, **78**, 3146 (1956).

(69) Another entry into the solanidine series from steroidal sapogenins has been described by F. C. Uhle and W. A. Jacobs (*J. Biol. Chem.*, **160**, 243 (1945)), who converted sarsasapogenin (the 25-epimer of smilagenin (LXVIII)) to 5β-solanidan-3β-ol.

(70) Melting points are uncorrected. Chromatograms were carried out with Merck "acid-washed" alumina, unless otherwise indicated. Rotations were determined at room temperature in chloroform solution, unless stated otherwise. Ultraviolet spectra were measured in 95% ethanol solution on a Unicam model S.P. 500 spectrophotometer and infrared spectra in chloroform solution (unless otherwise stated) on a Baird double-beam recording spectrophotometer with sodium chloride optics. Analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

(71) (a) All acetylations were carried out by means of acetic anhydride and pyridine at room temperature for 16 hr. (b) "Identified in the usual way" signifies that there was no depression in m.p. on admixture and the infrared spectra were identical.

showed m.p. 220–222°, $[\alpha]_D$ −55°, λ_{max} 5.64 (γ-lactone) and 5.80 μ (acetate).

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; act. H (1), 0.25, Found: C, 71.02; H, 9.01; act. H, 0.29.

Benzene eluted 3.92 g. (34%) of ethyl 3β-acetoxy-16α,-17β-dihydroxy-17-isobisnor-5α-cholanate (XI), which after crystallization from acetone–hexane showed m.p. 167–168°, $[\alpha]_D$ −14°, λ_{max} 5.82 μ (ester) and hydroxyl band.

Anal. Calcd. for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40; act. H (2), 0.45; acetyl (1), 9.54. Found: C, 69.87; H, 9.87; act. H, 0.47; acetyl, 9.90.

Acetylation[71a] yielded the ester-diacetate IX, m.p. 176–177°, identified in the usual way.[71b]

Benzene to benzene–ether (9:1) eluted 0.42 g. (4%) of ethyl 16α-acetoxy-3β,17β-dihydroxy-17-isobisnor-5α-cholanate (XII), which after crystallization from acetone–hexane showed m.p. 154–155° (depressed on admixture with XI), λ_{max} 5.81 μ (ester) and hydroxyl band.

Anal. Calcd. for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40. Found: C, 69.45; H, 9.26.

Acetylation[71a] yielded the diacetoxy-ester IX, m.p. 176–177°, identified in the usual way.[71b]

Benzene–ether (1:1) to ether eluted 2.45 g. (23%) of the ethyl 3β,16α,17β-trihydroxy-17-isobisnor-5α-cholanate (XIII), which after crystallization from acetone showed m.p. 201–203°, $[\alpha]_D$ −5°, λ_{max} 5.82 μ (ester) and hydroxyl band.

Anal. Calcd. for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.74; H, 9.95; acetyl, 0.00.

Acetylation[71a] yielded the diacetoxy-ester IX, m.p. 176–178°, identified in the usual way.[71b]

Conversion of the 3,16-Diacetoxy-acid VIIIa to the Ethyl Ester IX.—The above-described diacetoxy-acid VIIIa (200 mg.) was dissolved in 50 cc. of dry ether and 2 cc. of freshly distilled thionyl chloride was added. After being allowed to stand for 2 hr. with exclusion of moisture, the solution was evaporated to dryness under reduced pressure. Dry ethanol (10 cc.) was added to the residual crude acid chloride and the solution was boiled under reflux for 30 minutes. Evaporation to dryness and crystallization from ether–hexane gave 115 mg. of the diacetoxy-ethyl ester IX, m.p. 176–177°, identified in the usual way[71b] with a sample obtained directly by chromatography of the Reformatsky reaction product.

Cleavage of the 16α-Acetoxy Groups of IX and XII with Alumina.—The ester-diacetate IX (200 mg.) was dissolved in pentane–benzene (2:1) and chromatographed on 10 g. of alumina. Elution with this solvent mixture yielded 55 mg. (28%) of unchanged IX, m.p. 175–177°, while elution with benzene gave 125 mg. (68%) of the 3-monoacetate XI, m.p. 165–167°.

Similar chromatography of the ester-monoacetate XII gave the triol ester XIII, m.p. 200–202°, in 60% yield. The substances X, XI and XIII were recovered completely unchanged under these conditions.

3β-Acetoxy-16α,17β-dihydroxy-17-isobisnor-5α-cholanic 22→16-Lactone (X). (a) From the 3,16,17-Trihydroxy-acid VIIa.—A solution of 100 mg. of the trihydroxy-acid VIIa in 25 cc. of acetic anhydride was boiled under reflux for 2 hr., moisture being excluded. The anhydride was then evaporated under reduced pressure and the residue was boiled with water for 15 minutes (to hydrolyze any mixed anhydride or remaining acetic anhydride). Ether was then added and the organic extract, after being washed with sodium carbonate solution and water, was dried, evaporated and crystallized from methanol. The resulting lactone X (62 mg., 58%) showed m.p. 218–220°, $[\alpha]_D$ −56°, and was identified in the usual way[71b] with the lactone X obtained directly from the Reformatsky reaction (see above).

Alternatively, 100 mg. of the trihydroxy-acid VIIa was dissolved in 20 cc. of glacial acetic acid and dry hydrogen chloride was passed in at room temperature for 1 hr. The solution was poured into ice-water and the organic material was extracted with ether. The organic extract was washed with sodium carbonate solution and water and was then dried, evaporated and crystallized from methanol. The resulting lactone X (46 mg., 43%) showed m.p. 219–221°, identified with the above-described sample in the usual way.[71b]

(b) From the 3,16-Diacetoxy-17-hydroxy-acid VIIIa.—The diacetoxy-hydroxy-acid VIIIa (100 mg.) and anhydrous potassium bisulfate (200 mg.) were finely ground together in a mortar and then heated at 170° under reduced pressure (*ca.* 1 mm.) for 10 minutes. The mixture was cooled, water and ether were added and the organic layer was washed with sodium carbonate solution and water. It was then dried and evaporated and the residue was crystallized from methanol or hexane. The resulting lactone X (62 mg., 76%) showed m.p. 220–221° and was identified with the previously described materials in the usual way.[71b] This lactone was recovered unchanged after further treatment with potassium bisulfate.

Hydrolysis of the Lactone X to the 3,16,17-Trihydroxy-acid VIIa.—A solution containing 200 mg. of the lactone X and 1.5 g. of potassium hydroxide in 50 cc. of 95% methanol was boiled under reflux for 2 hr. Water and ether were added and the organic layer after being washed with water, dried and evaporated gave 13 mg. of neutral material, which was not investigated further. The alkaline aqueous layer was acidified with excess dilute hydrochloric acid, extracted well with ethyl acetate and the latter extract was washed with sodium carbonate solution and water. Evaporation of ethyl acetate gave 31 mg. (17%) of a crystalline lactone (λ_{max} 5.64 μ and hydroxyl band), presumably the free 3β-hydroxy compound corresponding to the starting material X, which on acetylation in the usual way regenerated the lactone X. The aqueous sodium carbonate layer was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The latter extract after being washed with water, dried and evaporated yield 137 mg. (73%) of the trihydroxy-acid VIIa which after crystallization from acetone showed m.p. 240–242° and was identified with the previously described material in the usual way.[71b]

Reformatsky Reaction of 3β,16α-Diacetoxyandrostan-17-one (VI) with Ethyl α-Bromopropionate Followed by Reacetylation (Preparative Method).—The reaction was carried out exactly as described previously, but on double the scale. The total unsaponified product was then acetylated by means of 50 cc. of acetic anhydride and 50 cc. of pyridine for 16 hr. at room temperature. The acetylated material was isolated with ether in the usual way and was then dissolved in 50 cc. of pentane–benzene (2:1) and chromatographed on 750 g. of alumina. Elution with pentane–benzene (2:1) followed by crystallization from ether–hexane gave 3.8 g. (15%) of the ester-diacetate IX, m.p. 177–178°, undepressed on admixture with the above-described compound.

Elution with benzene followed by crystallization from acetone–hexane yielded 11.3 g. (49%) of the ester-monoacetate XI, m.p. 165–167°, undepressed on admixture with the aforementioned substance. Acetylation of this material in the usual way[71a] gave 12.1 g. of the ester-diacetate IX m.p. 176–177°. The total yield of the latter was therefore 15.9 g. (63%).

Reformatsky Reaction of 3β,17β-Diacetoxyandrostan-16-one (XIV) with Ethyl α-Bromopropionate.—The Reformatsky reaction was carried out with 2.5 g. of 3β,17β-diacetoxyandrostan-16-one (XIV) (m.p. 180–181°, $[\alpha]_D$ −118°, prepared from the diacetoxy-ketone VI as described by Leeds, *et al.*[15]), 4 g. of activated zinc and 10 g. of ethyl α-bromopropionate in 25 cc. of benzene, exactly as outlined above for the isomeric diacetoxy-ketone VI. The product was isolated with ether and chromatographed directly on 100 g. of alumina.

Elution with benzene yielded 0.91 g. (32%) of the 3-monoacetate XVa (isomer A), m.p. 188–189°, $[\alpha]_D$ + 5°.

Anal. Calcd. for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40. Found: C, 69.12; H, 9.21.

Acetylation[71a] led to the corresponding 3,17-diacetate XVb (isomer A), m.p. 174–175° (depressed on admixture with the starting material as well as with the diacetate IX), $[\alpha]_D$ + 2°.

Anal. Calcd. for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00. Found: C, 68.43; H, 9.04.

Further elution with benzene–ether (4:1) furnished 0.42 g. (15%) of the 3-monoacetate XVa (isomer B), m.p. 123–124°, $[\alpha]_D$ −3°.

Anal. Calcd. for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40. Found: C, 69.35; H, 9.47.

Acetylation[71a] produced the corresponding 3,17-diacetate XVb (isomer B) m.p. 125–126° (depressed on admixture with the starting material), $[\alpha]_D$ −14°.

Anal. Calcd. for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00. Found: C, 68.12; H, 8.95.

3β,16α-Diacetoxy-17β-hydroxy-17-isobisnor-5α-cholan-22-one (XVI).—A solution containing 200 mg. of the diacetoxy-acid VIIIa, 5 cc. of freshly distilled thionyl chloride and 5 cc. of dry benzene was boiled under reflux for 2 hr., moisture being excluded. The solution was then evaporated to dryness under reduced pressure. The residual crude acid chloride was dissolved in 5 cc. of benzene and added under nitrogen to a solution of dimethylcadmium, previously prepared in the usual way[72] from 620 mg. of methyl iodide, 100 mg. of magnesium, 10 cc. of ether and 400 mg. of dry cadmium chloride. The mixture was stirred for 2 hr. at room temperature (nitrogen) and was then allowed to stand for 16 hr. Ice, dilute sulfuric and ether were added, the organic extract was washed with sodium hydroxide solution and water and was then dried and evaporated. The non-crystalline residue (225 mg.) was re-acetylated in the usual way[71a] and the product was chromatographed on 12 g. of alumina. The only crystalline product was a substance, eluted with pentane–benzene (1:1) ,which is tentatively assigned the 22-keto structure XVI. It weighed 82 mg. (44%) and showed m.p. 190–191°, $[\alpha]_D$ −62°; no high-intensity absorption in the ultraviolet; λ_{max} 5.79 (acetate) and 5.86 μ (ketone).

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.07; H, 8.80.

The ketone XVI was unchanged on being allowed to stand in dioxane solution with dilute sulfuric acid. Heating with phosphorus oxychloride and pyridine, or alternatively with acetic anhydride, gave oily products which did not have a high-intensity ultraviolet maximum.

Dehydration of the 3,16-Diacetoxy-17-hydroxy-ester IX. (a) With Potassium Bisulfate. Formation of Ethyl 3β,16α-Diacetoxy-$\Delta^{17(20)}$-bisnor-5α-cholenate (XVII) and 3β-Acetoxy-16α-hydroxy-$\Delta^{17(20)}$-bisnor-5α-cholenic 22→16-Lactone (XVIII) (Preparative Method).—The diacetoxy-ester IX (1 g.) and anhydrous potassium bisulfate (2 g.) were finely ground together in a mortar and heated at 170–175° under reduced pressure (*ca.* 25 mm.) for 15 minutes. The mixture was cooled and ether and water were added. The reaction was repeated twice on the same scale and the combined ether extracts from all three experiments were washed with sodium carbonate solution and water. The residue obtained after drying and evaporation was then chromatographed on 150 g. of alumina.

Pentane–benzene (4:1 to 1:1) eluted 0.33 g. of oily material, λ_{max} 207 and 270–273 mμ (ε 6000 and 3500, respectively, assuming a molecular weight of 492), which was not further investigated.

Benzene to benzene–ether (5:1) eluted material which after crystallization from methanol or ether–hexane gave 1.15 g. (40%) of the unsaturated ester XVII, m.p. 140–141°, $[\alpha]_D$ −73°, λ_{max} 221 mμ (ε 11,700), λ_{max} 5.82 μ (superimposed acetate and α,β-unsaturated ester). It gave no color with tetranitromethane.

Anal. Calcd. for $C_{28}H_{42}O_6$: C, 70.85; H, 8.92. Found: C, 70.80; H, 8.80.

Benzene–ether (4:1) eluted material which after crystallization from acetone–hexane yielded 0.90 g. (38%) of the unsaturated lactone XVIII, m.p. 239–240°, $[\alpha]_D$ −165°, λ_{max} 220 mμ (ε 10,600), λ_{max} 5.74 (α,β-unsaturated γ-lactone) and 5.79 μ (acetate). It also gave no color with tetranitromethane.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.35; H, 8.78.

When the dehydration of IX with potassium bisulfate was allowed to proceed for a longer time, the yield of the unsaturated lactone XVIII increased, while that of the unsaturated ester XVII decreased.

(b) With Copper Sulfate.—A finely ground mixture containing 100 mg. of the diacetoxy-hydroxy-ester IX and 300 mg. of anhydrous copper sulfate was heated at 180° at 25 mm. for 30 minutes. The product was isolated with ether as previously and chromatographed on 5 g. of alumina. Pentane–benzene (4:1 to 1:1) eluted 82 mg. of an oil. λ_{max} 208 and 272 mμ (ε 6000 and 2400, respectively, assuming a molecular weight of 492), the infrared spectrum of which was very similar to that of the least polar material obtained by method a. Benzene–ether (6:1) eluted 7 mg. (7%) of the unsaturated ester XVII, m.p. 138–140°, identified in the usual way[71b] with the substance obtained by method a.

(c) With Phosphorus Oxychloride–Pyridine.—A solution of 3 cc. of phosphorus oxychloride in 5 cc. of pyridine was added to a solution of 100 mg. of IX in 5 cc. of pyridine and the mixture was heated on a boiling water-bath for 30 minutes. Isolation with ether in the usual way yielded 80 mg. of an oil, λ_{max} 272 mμ (ε 8400, assuming a molecular weight of 492).

(d) With Acetic Anhydride.—A solution containing 200 mg. of IX in 30 cc. of acetic anhydride was boiled under reflux for 2 hr. The anhydride then was removed under reduced pressure and the residue was chromatographed on 5 g. of alumina. Benzene eluted 80 mg. of an oil which showed no high-intensity absorption in the ultraviolet. Benzene–ether (9:1) gave 95 mg. of an oil, λ_{max} 262 mμ (ε 16,000, assuming a molecular weight of 492).

Conversion of the Unsaturated Ester XVII to the Unsaturated Lactone XVIII. (a) With Potassium Bisulfate.—A finely ground mixture of 100 mg. of the unsaturated ester XVII and 200 mg. of anhydrous potassium bisulfate was heated at 175° at 25 mm. for 30 minutes. Isolation with ether followed by chromatography on 5 g. of alumina gave 36 mg. of unchanged starting material and then 24 mg. of the unsaturated lactone XVIII, m.p. 236–239°, identified in the usual way[71b] with the above-described material.

(b) With Potassium Hydroxide Followed by Acidification.—A solution containing 120 mg. of the unsaturated ester XVII and 450 mg. of potassium hydroxide in 15 cc. of 95% methanol was boiled under reflux for 2 hr. Water and ether were added and the ether layer was washed with water, dried and evaporated. The neutral residue weighed 15 mg. and could not be crystallized. The alkaline aqueous layer was acidified with dilute hydrochloric acid and extracted with ethyl acetate. Acidic material which had not lactonized was removed by washing the ethyl acetate extract with aqueous sodium carbonate solution and the organic extract was then dried and evaporated. The residual α,β-unsaturated γ-lactone (30 mg.) showed λ_{max} 220 mμ (ε 9,800), λ_{max} 5.73 μ. Acetylation[71a] at C-3 and crystallization from acetone–hexane yielded 24 mg. (25%) of XVIII, m.p. 236–239°, identified in the usual way[71b] with the previously described compound. The acidic product [65 mg., λ_{max} 219 mμ (ε 3600)] could not be induced to crystallize.

Very similar results were obtained when the unsaturated lactone XVIII was treated with potassium hydroxide under the above-described conditions, the recovery after reactylation being 25%.

Dehydration of Ethyl 3β-Acetoxy-16α,17β-dihydroxy-17-isobisnor-5α-cholanate (XI) with Potassium Bisulfate.—A finely ground mixture of 250 mg. of the acetoxy-dihydroxy-ester XI and 500 mg. of anhydrous potassium bisulfate was heated at 170–180° at 20 mm. for 30 minutes. The product was isolated with ether as previously and chromatographed on 12 g. of alumina.

Pentane–benzene (1:1) eluted 103 mg. (48%) of an unsaturated lactone which crystallized from ether–hexane as needles, m.p. 165–166°, $[\alpha]_D$ −49°; no high-intensity ultraviolet maximum above 210 mμ, λ_{max} 5.69 (γ-lactone) and 5.80 μ (acetate). The substance gave a yellow color with tetranitromethane. It could not be hydrogenated with platinum in acetic acid at atmospheric pressure and room temperature.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.35; H, 9.02.

Benzene–ether (4:1) eluted 78 mg. (35%) of a hydroxylactone which after crystallization from acetone–hexane showed m.p. 250–252°, $[\alpha]_D$ −65°; no high-intensity absorption in the ultraviolet; λ_{max} 5.68 μ (γ-lactone), 5.81 μ (acetate) and hydroxyl band. The substance gave no color with tetranitromethane. It was recovered unchanged on further treatment with potassium bisulfate.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.33; H, 8.93.

When 80 mg. of the lactone of m.p. 165–166° was boiled with 300 mg. of potassium hydroxide in 10 cc. of 90% methanol for 2 hr., followed by addition of water and ether, only 12 mg. remained in the neutral fraction. The aqueous alkaline layer was acidified with hydrochloric acid, ex-

(72) See H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

tracted with ethyl acetate and the latter extract was washed with sodium carbonate solution and water and was then dried and evaporated. The resulting lactone (62 mg.) showed m.p. 175–177° (λ_{max} 5.70 μ) and on re-acetylation at C-3 regenerated the starting material (m.p. 163–165°).

Ethyl 3β,16α-Diacetoxy-20-isobisnor-5α-cholanate (XIXa).—A solution of 2 g. of the unsaturated ester XVII in 60 cc. of glacial acetic acid was shaken in hydrogen over 0.3 g. of a pre-reduced platinum oxide catalyst at 24° at 764 mm. After 4 hr., 1.02 molar equivalents of hydrogen had been absorbed and uptake had stopped. The catalyst was removed and the filtrate was evaporated under reduced pressure. Crystallization of the residue from methanol or from hexane gave 1.71 g. (85%) of the saturated ester XIXa, m.p. 129–130°, $[\alpha]_D$ −51°; no high-intensity absorption in the ultraviolet, λ_{max} 5.80 μ (ester). In another experiment a second polymorphic modification, m.p. 159–160°, was obtained. The infrared spectrum was identical with that of the lower melting form and the latter was converted to the higher melting one on being seeded. The higher melting isomer was analyzed.

Anal. Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.63; H, 9.44.

The unsaturated ester XVII was recovered unchanged when the hydrogenation was attempted with platinum in ethyl acetate.

3β,16α-Dihydroxy-20-isobisnor-5α-cholanic Acid (XXa), the Methyl Ester XXb and the Methyl Ester Diacetate XIXb.—A solution of 1.5 g. of the diacetoxy-ethyl ester XIXa and 15 g. of potassium hydroxide in 150 cc. of 85% ethanol was boiled under reflux for 8 hr. Water and ether were added, the alkaline aqueous layer was again extracted with ether and was then acidified with excess dilute hydrochloric acid and extracted well with ethyl acetate. The latter extract was washed with water and was then dried and evaporated. The resulting crude dihydroxy-acid XXa (1.13 g.) was dissolved in 100 cc. of dry methanol, cooled to 0° and excess ethereal diazomethane was added. After being allowed to stand at 0° for 16 hr., the solution was treated dropwise with acetic acid to destroy excess reagent and the solvent was then evaporated. Crystallization from acetone–hexane yielded the methyl ester XXb (0.97 g., 81% from XIXa), m.p. 181–182°, $[\alpha]_D$ −7°, λ_{max} 5.80 μ (ester) and hydroxyl band.

Acetylation of a small sample in the usual way[71a] gave the methyl ester diacetate XIXb, m.p. 169–170°, $[\alpha]_D$ −50°, λ_{max} 5.80 μ (ester). Schwarz, *et al.*,[23] report m.p. 166–167°, $[\alpha]_D$ −42°, for what is probably this substance.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.18; H, 9.28.

In another experiment 200 mg. of the diacetoxy-ethyl ester XIXa was refluxed for 2 hr. with 750 mg. of potassium hydroxide in 25 cc. of 95% methanol. Water and ether were added and the ether layer was washed with water, dried and evaporated. Crystallization from acetone–hexane yielded 76 mg. of the methyl ester XXb, m.p. 181–182°, $[\alpha]_D$ −6°, which was identified with the above-described material in the usual way.[71b] The dihydroxy-acid XXa (68 mg.), obtained by acidification of the aqueous alkaline layer and extraction with ethyl acetate, on treatment with diazomethane yielded XXb, m.p. 180–182°.

20-Isobisnor-5α-cholane-3β,16α,22-triol (XXIa) and Triacetate XXIb. (a) From the Diacetoxy-ethyl Ester XIXa.—A solution of 1.25 g. of lithium aluminum hydride in 60 cc. of ether was added dropwise to a solution of 0.5 g. of the diacetoxy-ethyl ester XIXa in 125 cc. of tetrahydrofuran and the mixture was boiled under reflux for 1 hr. The excess reagent was decomposed by the dropwise addition of ethyl acetate, followed by dilute sulfuric acid. The product was extracted with ethyl acetate and the extract was washed with sodium bicarbonate and water and was then dried and evaporated. Crystallization from methanol gave the 20-iso-3β,16α,22-triol XXIa (0.32 g., 87%), m.p. 269–270°, $[\alpha]_D$ −23° (pyridine), no infrared band in the carbonyl region.

Anal. Calcd. for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.12; H, 10.77.

The triacetate XXIb, prepared by acetylation in the usual manner,[71a] was crystallized from ether–hexane and showed m.p. 151–152°, $[\alpha]_D$ −57°.

Anal. Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.36; H, 9.11.

(b) From the Dihydroxy-methyl Ester XXb.—The dihydroxy-methyl ester XXb (50 mg.) in 10 cc. of tetrahydrofuran was reduced with 125 mg. of lithium aluminum hydride in 10 cc. of ether as described under a. The resulting 20-iso-3β,16α,22-triol XXIa (35 mg., 76%) showed m.p. 267–269° and was identified with the above-described compound in the usual way.[71b]

Methyl 3,16-Diketo-20-isobisnor-5α-cholanate (XXII). (a) From the Dihydroxy-methyl Ester XXb (Preparative Method).—A solution of 1 g. of chromium trioxide in 10 cc. of 90% acetic acid was added during 10 minutes to a cooled solution of 1.1 g. of the dihydroxy-methyl ester XXb in 100 cc. of glacial acetic acid, the temperature being maintained at *ca.* 10° by external cooling. The solution was allowed to stand at 10° for 1 hr. and then at room temperature for a further 1 hr. The excess trioxide was destroyed by addition of methanol and water was then added. The product was extracted with ether, the ether extract was washed with sodium bicarbonate solution and water and was then dried and evaporated. Crystallization from methyl ethyl ketone–hexane yielded 0.74 g. (68%) of the 20-iso-diketo-ester XXII, m.p. 143–145°, $[\alpha]_D$ −110°, λ_{max} 5.78 (superimposed ester and 16-ketone) and 5.84 μ (3-ketone).

Anal. Calcd. for $C_{28}H_{44}O_4$: C, 73.76; H, 9.15. Found: C, 73.66; H, 9.29.

(b) From the 3β,16α,22-Triol XXIa.—A solution of 300 mg. of the triol XXIa in 25 cc. of acetic acid was oxidized with 250 mg. of chromium trioxide in 2.5 cc. of 90% acetic acid as described under a. The ether extract on being washed with sodium carbonate solution yielded 110 mg. of neutral oily material which could be reduced back with lithium aluminum hydride to the starting triol XXIa in *ca.* 40% yield. The acidic product (175 mg.), obtained by acidification of the aqueous carbonate layer and extraction with ethyl acetate, was dissolved in 20 cc. of methylene chloride and treated at 0° with ethereal diazomethane for 16 hr. Chromatography of the resulting material on 10 g. of alumina, followed by elution with benzene–ether (9:1), yielded the diketo-ester XXII (140 mg., 44%) which on crystallization from acetone–hexane showed m.p. 142–144°, identified in the usual way[71b] with the substance obtained by method a.

20-Isobisnor-5α-cholane-3β,16β,22-triol (XXIIIa) and Triacetate XXIIIb.—A solution of 250 mg. of lithium aluminum hydride in 10 cc. of ether was added to 100 mg. of methyl 3,16-diketo-20-isobisnor-5α-cholanate (XXII) in 30 cc. of tetrahydrofuran and the mixture was boiled under reflux for 1 hr. Isolation with ethyl acetate then yielded 75 mg. (80%) of the 20-iso-3β,16β,22-triol XXIIIa, which on crystallization from methanol–ethyl acetate showed m.p. 308–310°, $[\alpha]_D$ + 13° (pyridine), no infrared band in the carbonyl region.

Anal. Calcd. for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.09; H, 10.68.

The triacetate XXIIIb, prepared by acetylation in the usual way,[71a] was crystallized from ether–hexane and showed m.p. 163–164°, $[\alpha]_D$ + 35°.

Anal. Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.41; H, 9.58.

3β-Acetoxy-16β-hydroxy-20-isobisnor-5α-cholanic 22→16-Lactone (20-Isotigogenin Lactone Acetate) (XXIV). (a) From the Diketo-ester XXII.—The diketo-ester XXII (100 mg.) in 20 cc. of methanol was treated with 500 mg. of sodium borohydride in 4 cc. of methanol at room temperature for 16 hr. The solution was poured into 100 cc. of water, 30 cc. of 10% aqueous hydrochloric acid was added and after 30 minutes the organic material was extracted with ethyl acetate. The extract was washed with water, dried, evaporated and the residue (90 mg.) was acetylated in 4 cc. of pyridine with 2 cc. of acetic anhydride at room temperature for 16 hr. The product was isolated with ether and separated into acidic (17 mg.) and neutral (76 mg.) material. The latter was chromatographed on 5 g. of alumina. The fractions eluted with benzene and benzene–ether (9:1) on crystallization from methanol or from hexane yielded 48 mg. (46%) of the 20-iso-lactone XXIV, m.p. 226–228°, $[\alpha]_D$ −36°; λ_{max} 5.68 (γ-lactone), 5.80 (acetate) and 8.54 μ; reported[24]: m.p. 227–229°, $[\alpha]_D$ −34°. On admixture with a sample of tigogenin lactone

acetate (XXV) (m.p. 219–221°), the m.p. was depressed to 207–214°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.30; H, 9.20.

(b) From the Dihydroxy-acid XXa.—A solution containing 100 mg. of the crude dihydroxy-acid XXa, 1 cc. of concd. hydrochloric acid and 1 cc. of water in 20 cc. of glacial acetic acid was boiled under reflux for 2 hr., poured into ice and extracted with ethyl acetate. The organic extract was washed with sodium hydroxide solution and water and was then dried and evaporated. The resulting crude lactone (90 mg., λ_{max} 5.68 μ) was acetylated[71a] and the product was chromatographed on 5 g. of alumina. The fractions eluted with benzene and benzene–ether (9:1) on crystallization from methylene chloride–hexane gave 58 mg. (54% based on XIXa) of the 20-iso-lactone XXIV, m.p. 224–226°, $[\alpha]_D$ −35°, identified in the usual way[71b] with the substance obtained by method a.

When the treatment of the dihydroxy-acid XXa with hydrochloric–acetic acid was carried out at room temperature for 18 hr., no appreciable amount of XXIV was formed, but the product appeared to contain some anhydride (λ_{max} 5.52 and 5.68 μ).[16d]

Isomerization of 3β-Acetoxy-16β-hydroxy-20-isobisnor-5α-cholanic 22→16-Lactone (XXIV) to the 20-Normal Isomer (Tigogenin Lactone Acetate) (XXV).—A solution containing 60 mg. of the 20-iso-lactone acetate XXIV and 750 mg. of potassium hydroxide in 25 cc. of 90% methanol was boiled under reflux for 2 hr. The solution was extracted with ethyl acetate, and was then acidified with dilute hydrochloric acid and again extracted with ethyl acetate. The latter extract was washed with water, dried and evaporated. Acetylation[71a] of the residue yielded 56 mg. (93%) of crude tigogenin lactone acetate (XXV), m.p. 212–216°, the infrared spectrum of which was practically indistinguishable from that of the purified sample. Crystallization from methylene chloride–hexane gave pure material, m.p. 219–221°, $[\alpha]_D$ −49°; λ_{max} 5.68 (γ-lactone), 5.80 (acetate) and 8.45 μ; reported[24]: m.p. 220–222°, $[\alpha]_D$ −48°. The synthetic compound was identified in the usual way[71b] with an authentic sample, prepared by oxidation of tigogenin acetate.[24,27]

Tigogenin lactone acetate (XXV) on being treated under the above-mentioned conditions gave back starting material in over 80% yield.

Alternatively the rearrangement of the 20-iso-lactone XXIV to XXV was carried out with sodium methoxide in benzene at 78° in a sealed tube, as described by Corcoran and Hirschmann.[24]

3β-Acetoxy-16α-hydroxy-17-isobisnor-5α-cholanic 22→16-Lactone (XXXIV).—A solution of 500 mg. of the unsaturated lactone XVIII in 20 cc. of ethyl acetate was shaken in hydrogen over 50 mg. of a pre-reduced platinum oxide catalyst at 27° and 754 mm. After 1.5 hr. 0.98 molar equivalent of hydrogen had been absorbed and uptake had stopped. The catalyst was removed, the filtrate was evaporated and the residue was crystallized from methylene chloride–hexane. The resulting 17-iso-lactone XXXIV (445 mg., 89%) showed m.p. 199–201°, $[\alpha]_D$ + 21°; no high-intensity absorption in the ultraviolet; λ_{max} 5.69 (γ-lactone), 5.80 (acetate) and 8.51 μ.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.26; H, 9.30.

17-Isobisnor-5α-cholane-3β,16α,22-triol (XXXVa) and Triacetate XXXVb.—The 17-iso-lactone XXXIV (200 mg.) in 50 cc. of tetrahydrofuran was reduced with 500 mg. of lithium aluminum hydride in 20 cc. of ether, ad described above for the preparation of XXIa. Isolation with ethyl acetate and crystallization from methanol gave 145 mg. (80%) of the 17-iso-3β,16α,22-triol XXXVa, m.p. 245–247°, $[\alpha]_D$ −45° (pyridine), no infrared band in the carbonyl region.

Anal. Calcd. for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 74.97; H, 10.84.

The triacetate XXXVb, prepared in the usual way,[71a] after crystallization from ether–hexane showed m.p. 100–101°, $[\alpha]_D$ −45°.

Anal. Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.36; H, 9.52.

Methyl 3,16-Diketo-17-isobisnor-5α-cholanate (XXXVI).—A solution of 200 mg. of the 17-iso-3β,16α,22-triol XXXVa in 25 cc. of acetic acid was oxidized with 200 mg. of chromium trioxide in 2 cc. of 90% acetic acid as described above for the preparation of the diketo-ester XXII. The acidic fraction (140 mg.) was dissolved in 20 cc. of methylene chloride and treated with ethereal diazomethane at 0° for 16 hr. Chromatography of the product on 10 g. of alumina, followed by elution with benzene, yielded 115 mg. (54%) of the diketo-ester XXXVI, which after crystallization from methylene chloride–hexane showed m.p. 131–133°, $[\alpha]_D$ −67°, λ_{max} 5.79 (superimposed ester and 16-ketone) and 5.84 μ (3-ketone).

Anal. Calcd. for $C_{28}H_{44}O_4$: C, 73.76; H, 9.15. Found: C, 73.73; H, 9.40.

3β-Acetoxy-16α-hydroxy-17-iso-20-isobisnor-5α-cholanic 22→16-Lactone (XXXVII).—A solution containing 200 mg. of the 17-iso-lactone XXXIV and 1.5 g. of potassium hydroxide in 50 cc. of 90% methanol was boiled under reflux for 2 hr. Water and ether were added and the ether layer was washed with water, dried and evaporated. The resulting lactone (175 mg., λ_{max} 5.70 μ and hydroxyl band) was then acetylated.[17a] Crystallization of the product from acetone–hexane yielded 155 mg. (78%) of the 17-iso-20-iso-lactone XXXVII, m.p. 190–191°, $[\alpha]_D$ + 13°; λ_{max} 5.69 (γ-lactone), 5.80 (acetate) and 8.45 μ. There was a considerable depression in m.p. on admixture with the starting material XXXIV.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.37; H, 9.32.

17-Iso-20-isobisnor-5α-cholane-3β,16α,22-triol (XXXVIIIa) and Triacetate XXXVIIIb.—The 17-iso-20-iso-lactone XXXVII (200 mg.) in 50 cc. of tetrahydrofuran was reduced with 500 mg. of lithium aluminum hydride in 20 cc. of ether, as described above for the preparation of XXIa. Isolation with ethyl acetate and crystallization from methanol–ethyl acetate yielded 135 mg. (75%) of the 17-iso-20-iso-3β,16α,22-triol XXXVIIIa, m.p. 189–191°, $[\alpha]_D$ −19° (pyridine), no infrared bands in the carbonyl region.

Anal. Calcd. for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.11; H, 10.73.

The triacetate XXXVIIIb, prepared in the usual way,[71a] after crystallization from ether–hexane, exhibited m.p. 109–110°, $[\alpha]_D$ −71°.

Anal. Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.47; H, 9.39.

Methyl 3,16-Diketo-17-iso-20-isobisnor-5α-cholanate (XXXIX).—A solution of 100 mg. of the 17-iso-20-iso-3β,16α,22-triol XXXVIIIa in 10 cc. of acetic acid was oxidized with 100 mg. of chromium trioxide in 1 cc. of 90% acetic acid, as described above for the preparation of XXII. The acidic product (48 mg.) was methylated with diazomethane as previously described and then chromatographed on 2 g. of alumina. Benzene eluted 38 mg. (36%) of the diketo-ester XXXIX, m.p. 121–123°, $[\alpha]_D$ − 121°, λ_{max} 5.78 (superimposed ester and 16-ketone) and 5.83 μ (3-ketone).

Anal. Calcd. for $C_{28}H_{44}O_4$: C, 73.76; H, 9.15. Found: C, 73.81; H, 9.31.

Bisnor-5α-cholane-3β,16β,22-triol (XXVIa) and Triacetate XXVIb from Tigogenin Lactone Acetate (XXV).—The 3β,16β,22-triol XXVIa [m.p. 246–249°, $[\alpha]_D$ + 15° (pyridine)] was obtained in *ca.* 80% yield by the lithium aluminum hydride reduction of natural tigogenin lactone acetate (XXV) and crystallization from methanol, essentially as reported.[24,27b] The triacetate XXVIb after crystallization from ether–hexane showed m.p. 117–118°, $[\alpha]_D$ + 52°; reported[27b]: m.p. 247–250°, $[\alpha]_D$ + 15° (pyridine) and m.p. 117–119°, $[\alpha]_D$ + 53°, respectively. The triol XXVIa was different from the four isomeric triols XXIa, XXIIIa, XXXVa and XXXVIIIa described above and the triacetate XXVIb differed from the corresponding four triacetates.

Methyl 3,16-Diketobisnor-5α-cholanate (XXVII) (a) By Isomerization of the 20-Iso-ester XXII (First Preparative Method).—A solution containing 700 mg. of the 20-iso-ester XXII and 9 g. of potassium hydroxide in 300 cc. of 93% aqueous methanol was boiled under reflux for 2 hr., diluted with water, extracted with ethyl acetate, acidified and again extracted with ethyl acetate. The latter extract on evaporation gave 620 mg. of acidic material which was dissolved in 100 cc. of methylene chloride and treated

for 16 hr. at 0° with ethereal diazomethane. The resulting diketo-ester XXVII (640 mg., 91%) showed m.p. 212–218° and after two crystallizations from methyl ethyl ketone had m.p. 219–222°, $[\alpha]_D$ −108°, λ_{max} 5.77 (superimposed ester and 16-ketone) and 5.85 μ (3-ketone). It was identified in the usual way[71b] with the authentic sample (method d).

(b) By Isomerization of the 17-Iso-ester XXXVI (Second Preparative Method).—The 17-iso-ester XXXVI (100 mg.) was treated with base and then remethylated, exactly as described under a. The resulting diketo-ester XXVII (88 mg., 88%) showed m.p. 214–219°, raised by one crystallization from methyl ethyl ketone to m.p. 219–221°. It was identified in the usual way[71b] with the authentic sample (method d).

(c) By Isomerization of the 17-Iso-20-iso-ester XXXIX.—The 17-iso-20-iso-ester XXXIX (20 mg.) was treated with base and remethylated, as described under a. The resulting diketo-ester XXVII (14 mg.) showed m.p. 218–220° and was identified in the usual way[71b] with the sample prepared by method d.

(b) By Oxidation of Bisnor-5α-cholane-3β,16β,22-triol (XXVIa).—The oxidation of the 3β,16β,22-triol XXVIa (from tigogenin lactone acetate (XXV)) with chromium trioxide in acetic acid and subsequent treatment with diazomethane was carried out essentially as described by Corocoran and Hirschmann[24] and yielded *ca.* 40% of the diketo-ester XXVII, m.p. 220–222°, $[\alpha]_D$ −108° (reported[24]: m.p. 220–223°, $[\alpha]_D$ −109°).

The diketo-ester XXVII prepared in this way was recovered essentially unchanged on being treated with base and then remethylated, as described under a.

Methyl 3,16-Biscycloethylenedioxybisnor-5α-cholanate (XLIV).—The following procedure is based on that described by Corcoran and Hirschmann.[24] A mixture of 1 g. of the 20-normal-diketo-ester XXVII, 1.5 g. of *p*-toluenesulfonic acid hydrate, 12 cc. of ethylene glycol and 1.5 l. of benzene was boiled for 5 hr., while 200 cc. of benzene was distilled off through a Vigreux column. Another 1.5 g. of *p*-toluenesulfonic acid was then added and the reaction was continued for an additional 6 hr. while 300 cc. of benzene was distilled off. The warm reaction mixture was then treated for 10 minutes with a solution of 3 g. of sodium hydroxide in 50 cc. of 95% methanol, water was added and the organic layer was washed with water, dried and evaporated. The crystalline residue was chromatographed on 60 g. of alumina (basic, deactivated). The fractions eluted with pentane–benzene (9:1 to 4:1) on crystallization from acetone–hexane gave 0.72 g. (58%) of the bisketal XLIV, m.p. 194–197°. Further crystallization gave the analytical sample, m.p. 196–198°, $[\alpha]_D$ −24°; λ_{max} 5.80 μ (ester); reported[24]: m.p. 198.5–200°, $[\alpha]_D$ −19° (ethanol).

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.14.

3,16-Biscycloethylenedioxybisnor-5α-cholan-22-ol (XLV).—A stirred solution of 1.13 g. of the bisketal XLIV in 300 cc. of tetrahydrofuran was treated dropwise during 15 minutes with a solution of 1.5 g. of lithium aluminum hydride in 75 cc. of ether, under nitrogen. The reaction mixture was stirred for 1 hr., allowed to stand for 16 hr. at room temperature and then decomposed by the careful addition of a saturated sodium sulfate solution until the precipitated began to adhere to the sides of the flask. Solid sodium sulfate was then added, the salts removed by filtration and washed well with tetrahydrofuran. Evaporation of the filtrate and crystallization of the residue from acetone (containing a few drops of pyridine) yielded 0.76 g. of the hydroxy-bisketal XLV, m.p. 235–237°, $[\alpha]_D$ −18°, no infrared band in the carbonyl region.

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.62; H, 9.63.

Bisnor-5α-cholane-3β,16β,22-triol (XXVIa) from the Hydroxy-bisketal XLV.—A solution of 40 mg. of the hydroxy-bisketal XLV in 10 cc. of 90% acetic acid was heated at 90° for 1 hr. Water was then added and the product, isolated by means of ether, was dissolved in 10 cc. of ether and treated with 50 mg. of lithium aluminum hydride in 2 cc. of ether. The mixture was boiled under reflux for 2 hr. and the product was isolated as previously. Crystallization from methanol gave 26 mg. of the 3β,16β,22-triol XXVIa, m.p. 247–250°, $[\alpha]_D$ +14° (pyridine), identified in the usual way[71b] with the above-mentioned sample.

3,16-Biscycloethylenedioxybisnor-5α-cholan-22-al (XLVI).—Chromium trioxide (350 mg.) was added slowly and with cooling to 15 cc. of dry pyridine. A solution of 500 mg. of the hydroxy-bisketal XLV in 15 cc. of pyridine was added dropwise and the reaction mixture was then kept at 37° for 4 hr. The excess reagent was destroyed by the careful addition of methanol and after 15 minutes the solvents were evaporated under reduced pressure and the dark brown residue was extracted well with hot ethyl acetate. The crystalline residue, obtained by evaporation of the organic extract, was dissolved in pentane–benzene (9:1) and chromatographed on 30 g. of alumina (basic, deactivated). Pentane–benzene (9:1 to 4:1) eluted 415 mg. (83%) of the aldehyde-bisketal XLVI, m.p. 175–180°, which on crystallization from ether–pentane showed m.p. 183–184°, $[\alpha]_D$ −21°, λ_{max} 5.82 μ (aldehyde).

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 71.83; H, 9.56.

Reduction of the Aldehyde-bisketal XLVI to the Hydroxy-bisketal XLV.—A solution of 50 mg. of the aldehyde-bisketal XLVI in 10 cc. of tetrahydrofuran was reduced with 50 mg. of lithium aluminum hydride in 2 cc. of ether for 2 hr. at room temperature. Crystallization of the product from acetone yielded 41 mg. of the hydroxy-bisketal XLV, m.p. 235–237°, identified in the usual way[71b] with the sample described above.

3,16-Biscycloethylenedioxycholestan-22-ol (XLVII).—A solution containing 80 mg. of the aldehyde-bisketal XLVI in 7.5 cc. of benzene was added dropwise to a stirred solution of isoamylmagnesium bromide (prepared from 18 mg. of magnesium and 122 mg. of isoamyl bromide in 7.5 cc. of ether), under nitrogen. The mixture was boiled under reflux for 4 hr. and was then cooled and decomposed by addition of ammonium chloride solution. Extraction with ethyl acetate, followed by crystallization from acetone–hexane, gave 67 mg. (72%) of the hydroxy-bisketal XLVII, m.p. 195–196°, $[\alpha]_D$ −20°; hydroxyl, but no carbonyl band in the infrared.

Anal. Calcd. for $C_{31}H_{52}O_5$: C, 73.76; H, 10.38. Found: C, 73.80; H, 10.32.

3,16-Biscycloethylenedioxycholestan-22-one (XLVIII).—Chromium trioxide (40 mg.) was added to 2 cc. of dry pyridine and a solution of 40 mg. of the hydroxy-bisketal XLVII in 2 cc. of pyridine was then added. The mixture was kept at 37° for 48 hr., when a few drops of methanol were added. The solvents were evaporated and the dry residue was extracted well with hot ethyl acetate. The product in benzene solution was passed through a small column of basic alumina and was then crystallized from ether–pentane. The resulting keto-bisketal XLVIII (27 mg.) showed m.p. 134–135°, $[\alpha]_D$ −16°, λ_{max} 5.86 μ (22-ketone).

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 73.84; H, 10.21.

Cholestane-3,16,22-trione (IL) and the Unsaturated Ketone La.—A solution of 20 mg. of the keto-bisketal XLVIII in 5 cc. of 80% acetic acid was heated at 90° for 1 hr. The product was extracted with ether and then chromatographed on 3 g. of alumina. Elution with benzene–ether (9:1) gave 11 mg. of cholestane-3,16,22-trione (IL) as plates, m.p. 176–177°, λ_{max} 5.78 (16-ketone) and 5.83 μ (superimposed 3- and 22-ketone).[35]

The trione IL (5 mg.) was boiled under reflux for 1 hr. with 2 cc. of 5% methanolic potassium hydroxide (containing 0.2 cc. of water), under nitrogen. Isolation with ether yielded the crude unsaturated ketone La as an oil, λ_{max} 246 mμ (ϵ 12,800).

3-Methyl-4-pentenoic Acid (LVIb).—A mixture of 108 g. (0.75 mole) of ethyl β-ethoxyacrylate (LII)[43] and 115 g. (1.6 moles) of crotyl alcohol (LIII) containing 1 g. of dissolved sodium was fractionated through a 60-cm. packed column (maximum bath temperature 220°), when ethanol distilled and carbon monoxide was evolved. When the evolution of gas had ceased, the residue was dissolved in 500 cc. of methanol and boiled under reflux for 2 hr. with 50 g. of sodium hydroxide in 100 cc. of water. Water was then added and the basic solution was extracted with ether. The aqueous layer was acidified with dilute hydrochloric acid, extracted well with ether and the latter extract was washed with water, dried and evaporated. The residue was fractionated through a Vigreux column. The fraction (34.5 g.), b.p. 70–85° (25 mm.), on redistillation gave 25.8 g. (30%) of pure 3-methyl-4-pentenoic acid, b.p. 78–80°

(25 mm.), $n^{20}D$ 1.4366; λ_{max} 5.85 (acid), 6.09, 10.06 and 10.91 μ (monosubstituted ethylene).[16e,45]

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.53; H, 8.93.

3-Methyl-4-penten-1-ol (LVIIa).—A stirred solution of 20 g. of 3-methyl-4-pentenoic acid LVIb in 200 cc. of ether was treated dropwise with a solution of 8 g. of lithium aluminum hydride in 400 cc. of ether. After being stirred at room temperature for 2 hr., the reaction mixture was decomposed by careful addition of dilute hydrochloric acid. The product was extracted with ether and the organic extract was washed with sodium carbonate solution and water. Drying, evaporation of ether and distillation of the residue yielded 13.8 g. (79%) of 3-methyl-4-penten-1-ol (LVIIa), b.p. 63–64 mm. (25 mm.), $n^{20}D$ 1.4369; λ_{max} 6.10, 10.09 and 10.98 μ (monosubstituted ethylene) and strong hydroxyl band.

Anal. Calcd. for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.60; H, 12.06.

1-Bromo-3-methyl-4-pentene (LVIIb).—Phosphorus tribromide (4.5 cc.) was added dropwise during 30 minutes to an ice-cooled mixture of 12 g. of 3-methyl-4-penten-1-ol (LVIIa) and 2.25 cc. of pyridine. The mixture was stirred at room temperature for 30 minutes and was then poured on ice. Isolation with ether and distillation of the product through a small Vigreux column gave 8.2 g. (42%) of 1-bromo-3-methyl-4-pentene (LVIIb), b.p. 138–140° (764 mm.), $n^{20}D$ 1.4680; λ_{max} 6.08, 10.07 and 10.93 μ (monosubstituted ethylene).

Anal. Calcd. for $C_6H_{11}Br$: C, 44.18; H, 6.79. Found: C, 44.85; H, 6.79.

3,16-Biscycloethylenedioxy-26-methylenecholestan-22-ol (LVIII).—A solution of 300 mg. of the aldehyde-bisketal XLVI in 10 cc. of benzene was added dropwise at room temperature to a stirred solution of 3-methyl-4-pentenylmagnesium bromide (prepared from 68 mg. of magnesium and 650 mg. of 1-bromo-3-methyl-4-pentene in 10 cc. of ether), under nitrogen. The clear reaction mixture was boiled under reflux for 2 hr., cooled and an aqueous solution of ammonium chloride was added. The product, isolated with ether in the usual way, was then chromatographed on 18 g. of alumina (basic, deactivated). The fractions eluted with benzene and benzene–ether (9:1) after crystallization from ether–pentane yielded 265 mg. (74%) of the hydroxy-bisketal LVIII as a mixture of C-25 isomers, m.p. 143–157°, $[\alpha]D$ −18°; λ_{max}^{KBr} 6.08, 10.04 and 10.99 μ (monosubstituted ethylene) and hydroxyl band.

Anal. Calcd. for $C_{32}H_{52}O_5$: C, 74.37; H, 10.14. Found: C, 74.07; H, 10.32.

3,16-Biscycloethylenedioxy-26-methylenecholestan-22-one (LIX).—Chromium trioxide (400 mg.) was added slowly with cooling to 20 cc. of dry pyridine. A solution of 400 mg. of the hydroxy-bisketal LVIII in 20 cc. of pyridine was then added gradually and the mixture was kept at 37° for 48 hr. The excess reagent was decomposed by the careful addition of methanol and the solvents were evaporated under reduced pressure. The dry residue was extracted well with ethyl acetate. Evaporation of the solvent, followed by one crystallization from ether, yielded 340 mg. (85%) of the keto-bisketal LIX as a mixture of C-25 isomers, m.p. 145–148°, $[\alpha]D$ −16°, λ_{max} 5.86 μ (22-ketone); λ_{max}^{KBr} 6.09, 10.02 and 10.99 μ (monosubstituted ethylene).

Anal. Calcd. for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.25; H, 9.71.

26-Methylenecholestane-3,16,22-trione (LXV).—A solution of the keto-bisketal LIX (30 mg.) in 15 cc. of 90% acetic acid was heated at 90° for 1 hr. The product, isolated with ether in the usual way, was chromatographed on 4 g. of alumina. Elution with benzene–ether (9:1) yielded 18 mg. of the triketone LXV as a mixture of C-25 isomers, which after one crystallization from ether–pentene showed m.p. 161–165°, λ_{max} 5.78 (16-ketone) and 5.83 μ (superimposed 3- and 22-ketone).[35]

Ozonolysis of this compound, followed by successive treatment with Raney nickel, reduction with sodium borohydride and cyclization with hydrochloric acid in methanol, as described directly below for the bisketal LIX, did not lead to any appreciable amounts of tigogenin and neotigogenin.

Tigogenin (5α,25D-Spirostan-3β-ol) and Neotigogenin (5α,25L-Spirostan-3β-ol) (LXIII and LXIV) from the Keto-bisketal LIX.—A stream of 2% ozonized oxygen was passed for 8 minutes at −18° through a solution of 300 mg. of the keto-bisketals LIX in 30 cc. of ethyl acetate containing 3 drops of pyridine.[47] Raney nickel (6 g.) was then added and the mixture was boiled under reflux for 10 minutes. The metal was removed, the filtrate was evaporated to dryness and the residue containing the keto-aldehyde-bisketals LX was heated at 90° in 30 cc. of 80% acetic acid for 30 minutes. Isolation with ethyl acetate yielded 195 mg. of the crude non-crystalline aldehydes LXI (λ_{max} 5.79 and 5.84 μ) which were then dissolved in 90 cc. of dry tetrahydrofuran and treated with a solution of 300 mg. of sodium borohydride in 90 cc. of absolute isopropyl alcohol. The solution was allowed to stand at room temperature for 72 hr. and water was then added. Isolation with ethyl acetate yielded a product which was heated on a boiling water bath with 30 cc. of methanol and 0.3 cc. of 10% aqueous hydrochloric acid for 5 minutes. The product, isolated with ethyl acetate, was dissolved in benzene and chromatographed on 9 g. of alumina. The fractions eluted with benzene–ether (9:1) on crystallization from acetone–hexane and subsequent sublimation at 160° (0.01 mm.) gave 63 mg. (26% from LIX) of needles, m.p. 178–182°, $[\alpha]D$ − 71°. The infrared spectrum (in KBr) was typical for steroidal sapogenins,[50] the relative intensities of the bands at 10.87 and 11.11 μ as well as at 11.58 and 11.78 μ indicating the presence of comparable amounts of a 25D- and a 25L-sapogenin.

A 1:1 mixture of tigogenin (LXIII) and neotigogenin (LXIV) (prepared from a solution by evaporation to dryness) showed m.p. 177–182°, $[\alpha]D$ − 72°. There was no depression in m.p. on admixture with the synthetic material and the infrared spectra were practically identical.

Tigogenin (LXIII).—A solution of 15 mg. of the synthetic mixture of tigogenin and neotigogenin in 25 cc. of ethanol and 6 cc. of concd. hydrochloric acid was boiled under reflux for 48 hr., in nitrogen. Another 3 cc. of concd. hydrochloric acid was then added and boiling was continued for 72 hr.[6,9,10] The product was isolated with ethyl acetate and was then chromatographed on 3 g. of alumina. Elution with benzene–ether (9:1) followed by crystallization from acetone–hexane gave 9 mg. of tigogenin, m.p. 202–204°, $[\alpha]D$ − 68°. The m.p. was undepressed on admixture with an authentic sample (m.p. 203–205°, $[\alpha]D$ −68°) and the infrared spectra (in KBr) were identical in every respect.

Neotigogenin (LXIV).—The synthetic mixture of tigogenin and neotigogenin (45 mg.) was acetylated in the usual way,[71a] followed by isolation with ethyl acetate. The resulting mixture of acetates on being allowed to crystallize very slowly from a relatively dilute ethanol solution yielded two different types of crystals.[52] The well-defined octahedra were separated and crystallized twice from isopropyl alcohol. The process was then repeated with the combined mother liquors. The resulting neotigogenin (10 mg., m.p. 175–178°) was boiled under reflux for 1 hr. with 20 cc. of a 3% solution of potassium hydroxide in 90% methanol. Addition of water, isolation with ethyl acetate, followed by crystallization from acetone–hexane, then gave 7 mg. of neotigogenin, m.p. 201–203°, $[\alpha]D$ − 76°. The m.p. was undepressed on admixture with an authentic sample (m.p. 202–204°, $[\alpha]D$ − 77°) and the infrared spectra (in KBr) were identical in every respect. The m.p. was depressed by *ca.* 15° on admixture with a sample of tigogenin.

2α,4α,23-Tribromo-5α,25D-spirostan-3-one (LXVIb).—A solution containing 1 g. of 5α,25D-spirostan-3-one (LXVIa) (obtained by the potassium dichromate oxidation of tigogenin[53]) in 150 cc. of glacial acetic acid was treated with 1 cc. of a saturated solution of hydrogen bromide in acetic acid. A solution of 1.3 g. of bromine in 20 cc. of acetic acid was then added during 3 minutes at room temperature, with stirring. After being allowed to stand for 10 minutes, the yellow solution was poured into 2 l. of water and the resulting precipitate was collected, washed with water and dried. Two crystallizations from methylene chloride–acetate afforded 0.88 g. (56%) of the tribromide LXVIb, m.p. 196–198° dec., $[\alpha]D$ − 23°.

Anal. Calcd. for $C_{27}H_{39}O_3Br_3$: Br, 36.81. Found: Br, 36.65.

Δ⁴-25D-Spirosten-3-one (LXVII).—Bromine (200 mg.) was added to 15 cc. of acetone and when the solution became colorless, 1 g. of sodium carbonate was added. The mix-

ture was shaken for 20 minutes and was then filtered. The filtrate was added to a solution of 5 g. of sodium iodide in 100 cc. of acetone and the resulting solution was boiled under reflux for 30 minutes. The tribromide LXVIb (850 mg.) was then added and refluxing was continued for 12 hr. Water and ethyl acetate were added and the organic extract was washed successively with water, sodium carbonate and sodium thiosulfate solutions. The dried extract was evaporated and the residue was boiled under reflux for 3 hr. with 10 g. of zinc dust in 100 cc. of acetic acid. The cooled mixture was then filtered, the filtrate was diluted with ethyl acetate and washed with water and sodium carbonate solution. Drying and evaporation of the solvent gave a solid residue [λ_{max} 240 mμ (ϵ 7800)] which was chromatographed on 40 g. of alumina. Elution with benzene produced 280 mg. of the saturated ketone LXVIa, m.p. 202–205°. Elution with benzene and benzene–ether (9:1) and crystallization from chloroform–ether yielded 165 mg. (31%) of the unsaturated ketone LXVII, m.p. 185–187°, $[\alpha]_D$ − 7°, λ_{max} 240 mμ (ϵ 15,800). It was identified in the usual way[71b] with an authentic sample (m.p. 185–186°, $[\alpha]_D$ − 8°) prepared by the Oppenauer oxidation of diosgenin.[57a]

$\Delta^{3,5}$-25D-Spirostadien-3-ol Acetate (LXX).—A solution of 150 mg. of the unsaturated ketone LXVII in 50 cc. of isopropenyl acetate was treated with 2 drops of concd. sulfuric acid and was then boiled under reflux for 3 hr. Water and ether were added to the cooled solution and the organic extract was washed with sodium carbonate solution and water. Crystallization of the product from ether–methanol gave 115 mg. (70%) of the enol acetate LXX, m.p. 181–182°, $[\alpha]_D$ − 113°. The crude compound (m.p. 172–175°) has been reported.[59]

Anal. Calcd. for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.58; H, 9.25.

Diosgenin (Δ^5-25D-Spirosten-3β-ol) (LXXI).—A solution of 100 mg. of the enol acetate LXX in 200 cc. of ethanol was added dropwise during 2 hr. to a stirred solution of 1 g. of sodium borohydride in 50 cc. of 70% ethanol kept at 5° by ice-cooling. After being kept at 5° for a further 1 hr., the solution was treated with a solution of 1 g. of sodium hydroxide in 10 cc. of water and was then heated under reflux on a boiling water-bath for 30 minutes. Water was added and the crystalline material, isolated with ethyl acetate, was boiled under reflux for 1 hr. in 50 cc. of ethanol containing 3 drops of concd. hydrochloric acid. The product was again isolated with ethyl acetate and then chromatographed on 6 g. of alumina. The fractions eluted with benzene–ether (9:1) on crystallization from methanol yielded 66 mg. (72%) of diosgenin, m.p. 205–207°, $[\alpha]_D$ − 119°. It was identified with an authentic sample (m.p. 207–209°, $[\alpha]_D$ − 122°) in the usual way.[71b]

3β-Acetoxy-$\Delta^{9(11)}$-5α,25D-spirosten-12-one (LXXIVa) from $\Delta^{9(11)}$-5α,25D-Spirosten-3β-ol Acetate (LXXIII).—A solution of 75 mg. of chromium trioxide in 5 cc. of 85% acetic acid was added to 75 mg. of the $\Delta^{9(11)}$-compound LXXIII (m.p. 197–198°)[62] in 15 cc. of acetic acid. The solution was allowed to stand at 37° for 48 hr. and the excess reagent was then destroyed through addition of methanol. Isolation with ethyl acetate yielded material [λ_{max} 238 mμ (ϵ 4300)] which was chromatographed on 6 g. of alumina. The fractions eluted with pentane–benzene (1:1) on crystallization from ether–pentane yielded 22 mg. of the starting material LXXIII, m.p. 195–197°. The fractions eluted with benzene–ether (9:1) on crystallization from methanol gave 18 mg. (24%) of the unsaturated ketone LXXIVa, m.p. 217–219°, $[\alpha]_D$ −9°, λ_{max} 238 mμ (ϵ 13,200). Identity with an authentic sample (m.p. 218–220°, $[\alpha]_D$ − 8°)[63] was established in the usual way.[71b]

Hecogenin (3β-Hydroxy-5α,22D-spirostan-12-one) (LXXV).—A solution of 50 mg. of the unsaturated ketone LXXIVa in 20 cc. of dry ether was added dropwise during 5 minutes to a stirred solution of 100 mg. of lithium in *ca.* 30 cc. of liquid ammonia. The mixture was stirred for a further 5 minutes, and 2 g. of ammonium chloride was then added. The ammonia was allowed to evaporate, water was added to the residue and the product was isolated with ethyl acetate. The resulting material was boiled for 2 hr. with 20 cc. of a 3% solution of potassium hydroxide in methanol (containing 2 cc. of water). The product was again isolated with ethyl acetate and then chromatographed on 5 g. of alumina. Elution with benzene—ether (5:1) and crystallization from acetone yielded 31 mg. (68%) of hecogenin, m.p. 263–265°, $[\alpha]_D$ + 6°. The compound was identified in the usual way[71b] with an authentic sample (m.p. 264–266°, $[\alpha]_D$ + 8°).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY, STANFORD, CALIF.]

The Isomerization of Thujone[1]

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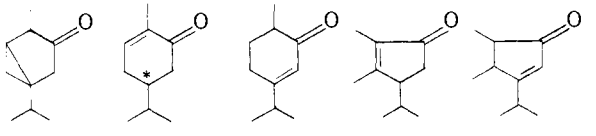
The acid-catalyzed isomerization of thujone has been shown to follow the Markownikoff rule, and the thermal isomerization of thujone has been shown to produce nor-ketones as well as carvotanacetone. The thermal isomerization has been found to proceed at unusually low temperatures and a mechanistic scheme is proposed to account for the fact.

Among the cleavages of the bicyclo[3.1.0]-hexane system,[2] that of thujone (I) by mineral acids presents an anomaly since the reported[3] formation of carvotanacetone (II) involves a violation of the Markownikoff rule as applied to the opening of three-membered rings by acidic agents.[4]

Evidence is presented here to the effect that carvotanacetone (II) is not a product of the acid-catalyzed cleavage; that the products are those predicted by the Markownikoff rule, namely, carvenone (III), 2,3-dimethyl-4-isopropyl-2-cyclopentenone ("isothujone") (IV) and 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V); that these products



I II III IV V

are not in thermodynamic equilibrium under the conditions of the reaction; and, that the production of carvotanacetone (II) in the earlier studies was quite possibly due to fortuitous thermal isomerization of thujone which we have found to proceed at surprisingly low temperatures.[5]

(1) Taken from the Doctoral Dissertation of A. V. Winn in the Department of Chemistry and Chemical Engineering at Stanford University.

(2) For references to previous studies, see R. H. Eastman, P. M. Iloff, Jr., and Hart Isaacs, Jr., THIS JOURNAL, **80**, 1704 (1958).

(3) A. Baeyer, *Ber.*, **27**, 1922 (1894); O. Wallach, *ibid.*, **28**, 1958 (1895); A. Haller, *Compt. rend.*, **140**, 1630 (1905); A. E. Gillam and T. F. West, *J. Chem. Soc.*, 811 (1941).

(4) See G. Büchi and D. M. White, THIS JOURNAL, **79**, 750 (1957), for an example of a non-Markownikoff opening under special conformational requirements.