Solvolytic Cyclization of Pseudosapogenin Derivatives[1]

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Solvolysis of pseudodiosgenin 27-iodide in aqueous ethanolic silver nitrate proceeds with participation of the ring-E dihydrofuranoid olefinic bond to afford 85% of a novel hexacyclic hemiketal. Pseudodiosgenin 27-*p*-toluenesulfonate gives rise to lower yields of the ring-closure product when subjected to solvolysis in aqueous acetone, aqueous ethanol, or aqueous dioxane. Refluxing formic acid reductively converts the hemiketal to a cyclic ether while refluxing acetic acid leads to opening of the ring system to furnish an acetoxy ketone. Solvolysis of kryptogenin 27-iodide and of kryptogenin 27-*p*-toluenesulfonate occurs without rearrangement to supply 16α-alkoxydiosgenin derivatives.

The rapid hydrolysis of cholesteryl 3β-*p*-toluenesulfonate in refluxing aqueous acetone was described in 1932.[2] This observation, which later received theoretical interpretation,[3] found practical issue in development of selective hydrolysis of the 3β-homoallylic ester function of pseudodiosgenin 3β,27-di-*p*-toluenesulfonate (**1**) to afford the 27-*p*-toluenesulfonate (**2**).[4]

Monosubstituted pseudosapogenin derivatives of the class of **2** were needed as intermediates in the synthesis of ring-F nitrogen[5] and sulfur[4] counterparts of the spiroketal sapogenins. Suitable specific attack at the C-27 primary function appeared infeasible since the pseudomer side chain and nuclear hydroxyl groups, despite their differing degree, do not display sharply divergent behavior with most reagents.[6] 27-Iodo derivatives of pseudosarsasapogenin and of pseudoneotigogenin were secured in 40% yields, nevertheless, by chromatographic separation after tosylation with a limited quantity of *p*-toluenesulfonyl chloride in pyridine, followed by treatment with sodium iodide.[5]

In early work,[7] isolation of the pseudosapogenin 27-*p*-toluenesulfonates as crystalline entities had not been attempted. Continued experience, however, engendered conviction that fears for their stability had been groundless, emboldening exploration of partial hydrolysis of 3β,27-disulfonate esters as a route to C-27 derivatives of genins possessing a homoallylic olefinic bond in ring B. This approach proved eminently justified.

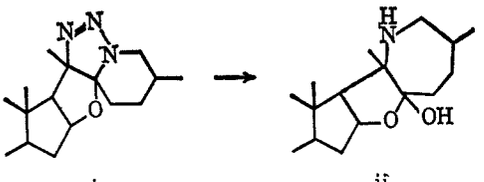
Esterification of pseudodiosgenin with 4 equiv of *p*-toluenesulfonyl chloride in pyridine at 0° gave 90% of ditosylate **1**. Subjection of **1** to hydrolysis in refluxing aqueous acetone during 2 hr afforded 80% of pseudodiosgenin 27-*p*-toluenesulfonate (**2**) which separated directly from the reaction medium in nicely crystalline form.[4]

Treatment of **2** with sodium iodide,[4] with potassium phthalimide,[8] potassium acetate,[8] potassium thioacetate,[4] potassium azide,[9] and methylamine[8] gave normal displacement products. Provocative observations during study of the reaction with methylamine, however, inaugurated an investigation of the behavior of **2** under conditions of solvolysis.

The ester proved remarkably stable when aqueous acetone solutions were heated during prolonged periods. Substantial amounts of unchanged tosylate could be detected after as long as 100 hr. Solvolysis seemed less sluggish in aqueous ethanol, or in aqueous dioxane, although collection of crystalline products, often ill defined, rarely exceeded 35%. When acetic acid showed scant promise, formic acid, a solvent of superior ionizing power,[10] was tried as a medium. While no change was evident at low temperatures, formic acid solutions of **2** rapidly assumed a royal purple color when heated. Interruption of the process after a few minutes, followed by alkaline hydrolysis, permitted isolation of a crystalline product melting at 248–253° whose properties offered no structural clues. Under optimal circumstances, 20% of the new substance was obtained after 3 min at reflux temperature in the presence of 10 equiv of potassium formate.

Meanwhile, in search of conditions favoring a smoother course, experiments were begun with pseudodiosgenin 27-iodide (**3**), readily prepared from **2** with sodium iodide in butanone.[4] When an ethanolic solution of **3** was treated with aqueous silver nitrate, the theoretical quantity of silver iodide deposited within a few minutes at ambient temperature. Recrystallization of the product from methanol furnished 85% of needles melting at 220–225°. Treatment of **3** with silver acetate in acetic acid, followed by crystallization from methanol, gave the same compound.

This substance was shown to be a methyl ketal which appears to possess structure **5**, arising from participation of the ring-E enol ether olefinic bond in the solvolytic process. Aqueous acetic acid at 25° promptly converted **5** to the hemiketal **4** while ethanolic acetic acid at 25°, or refluxing absolute ethanol alone,



i ii

(1) Preliminary communication: F. C. Uhle, *Tetrahedron Letters*, **No. 42**, 3039 (1964).

(2) W. Stoll, *Z. Physiol. Chem.*, **207**, 47 (1932).

(3) S. Winstein and R. Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948); R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948); E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347, 4354 (1956).

(4) F. C. Uhle, *J. Org. Chem.*, **27**, 2797 (1962).

(5) F. C. Uhle, *J. Am. Chem. Soc.*, **83**, 1460 (1961).

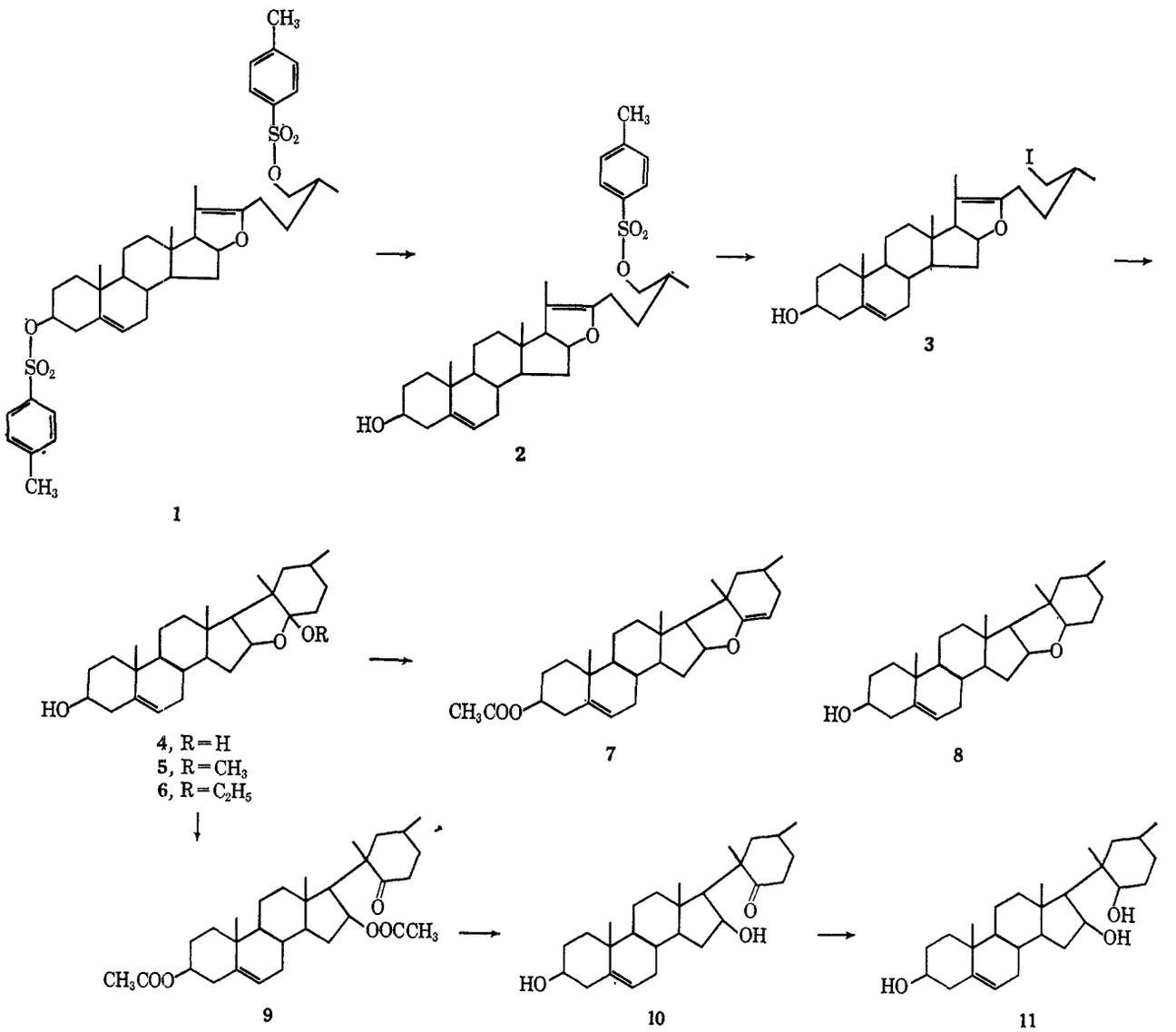
(6) *Cf.* W. F. Johns and D. M. Jerina, *J. Org. Chem.*, **28**, 2922 (1963); R. T. Blickenstoffe and F. C. Chang, *J. Am. Chem. Soc.*, **80**, 2726 (1958); I. Scheer, M. J. Thompson, and E. Mosettig, *ibid.*, **78**, 4733 (1956).

(7) F. C. Uhle, *ibid.*, **75**, 2280 (1953); **76**, 4245 (1954); F. C. Uhle and J. A. Moore, *ibid.*, **76**, 6412 (1954).

(8) To be described elsewhere.

(9) Displacement with potassium azide in dimethylformamide at 100° was followed by a 1,3-dipolar cycloaddition to the ring-E olefinic bond affording the heptacyclic triazoline i. Treatment of i with mineral acids promptly induced evolution of nitrogen to furnish a secondary amine tentatively formulated[1] as an expected 20-hydroxysolasodine derivative. On the basis of new evidence to be described elsewhere, however, this substance appears to be the hemiketal ii.

(10) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948).



furnished ethyl ketal **6**. Methyl ketal formation from the hemiketal appeared virtually instantaneous, dissolution in methanol sufficing for quantitative conversion. The ethyl ketal, on the other hand, could not be prepared from the hemiketal in the absence of acid catalysis. If isolated without exposure to methanol, the solvolysis product proved to be the hemiketal itself, preferably crystallized from acetone or from dichloromethane.

Comparison of the rich infrared spectra of **4** and of **5** with spectra given by crystalline fractions from solvolysis of the 27-*p*-toluenesulfonate **2** in aqueous acetone, aqueous ethanol, or aqueous dioxane, now revealed the cyclic hemiketal to have been formed in these slower, less decisive reactions as well. Despite the indefinite melting range of many of the early products, spectroscopic evidence in retrospect warranted estimates of 18–35% yields in the best cases.

The nuclear magnetic resonance spectrum of **5** showed a signal at 193 cps attributable to the methoxyl function, together with signals at 62, 67, and 71 cps associated with the angular methyl groups. The signal at 62 cps may be ascribed to the C-19 methyl hydrogens since the C-19 methyl resonance of diosgenin occurs at 62 cps. The signals at 67 and 71 cps arise from the C-18 and C-21 angular methyl groups although respective attribution is uncertain. Observation of these resonances at unusually low fields appears to suggest that the methoxyl group occupies the β configuration since the oxygen atom, thus placed, is situated near the sterically crowded C-18 and C-21 methyl groups. A doublet at 48 and 54 cps probably stems from the secondary methyl group of ring F.[11]

Acetylation of the hemiketal **4** with acetic anhydride in pyridine at 25° or with acetic anhydride containing 2% boron trifluoride etherate[12] at 25°, led only to esterification of the 3β-hydroxyl group. Treatment of the 3β-acetate with acetic anhydride in refluxing pyridine[13] afforded the unsaturated ether **7**. Evidence for the anhydro structure of **7** was provided by the elemental analysis as well as by the infrared spectrum which showed a sharp band of medium intensity at 5.9 μ characteristic of enol ethers. Dehydration was accompanied by a marked negative rotation shift. In

(11) Comments on the nuclear magnetic resonance spectrum of **5** were made by Dr. George Slomp to whom the author is greatly indebted.

(12) This combination of reagents leads to acetylation of the hemiketal hydroxyl group of methyl 3α-hydroxy-9α,11α-oxidocholenate and of related compounds: H. Heymann and L. F. Fieser, *J. Am. Chem. Soc.*, **73**, 5252 (1951).

(13) The hemiketal tertiary hydroxyl group of cevine is acetylated under these conditions: D. H. R. Barton, C. J. W. Brooks, and J. S. Fawcett, *J. Chem. Soc.*, 2137 (1954).

the presence of *p*-toluenesulfonic acid, methanol added to the enol ether olefinic bond, affording the 3β-acetate of the methyl ketal **5**.

Treatment of **5** with boiling acetic acid, a reagent which generally promotes dehydration of hemiketals,[14] led to opening of the ring system to afford the acetoxy ketone **9**. Yields of 30–40% realized with acetic acid alone rose to 80% when refluxing acetic acid containing acetic anhydride was employed. Isopropenyl acetate in the presence of *p*-toluenesulfonic acid converted **9** to an enol acetate.

Alkaline hydrolysis of **9** gave the hydroxy ketone **10** which formed an oxime and a *p*-nitrophenylhydrazone. Both the hemiketal **4** and the methyl ketal **5** failed to react with hydroxylamine or with *p*-nitrophenylhydrazine under the conditions used for preparation of carbonyl derivatives of **10**.

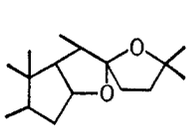
Although the hydroxy ketone **10** proved stable in acidified aqueous solutions, treatment with refluxing anhydrous methanol containing 0.5% *p*-toluenesulfonic acid caused reversion to the methyl ketal **5**. Similar treatment with *p*-toluenesulfonic acid in refluxing acetone returned the hemiketal **4**. Sodium borohydride reduced the hydroxy ketone **10** to the triol **11** which gave a triacetate with refluxing acetic anhydride. Oxidation of **11** with chromium trioxide in acetone, followed by acidification, afforded a triketone whose infrared spectrum showed three distinct carbonyl bands at 5.75 (C-16), 5.90 (C-22), and 5.98 μ (C-3).

Exposure of the methyl ketal **5** to boiling formic acid promptly gave rise to a purple coloration reminiscent of that observed during formolysis of the *p*-toluenesulfonate **2**. Within a few minutes, a white, crystalline deposit began to separate from the hot solution. Quenching with water discharged the color and led to isolation of 85% of a formate ester. Alkaline hydrolysis of the sparingly soluble formate gave a sterol of composition $C_{27}H_{42}O_2$ identical with the substance of mp 248–253° secured in 20% yield after formolysis of **2**. This compound, which presented no reactive function other than the 3β-hydroxyl group, appears to be the hydrogenolysis product **8**.[15] Reduction of **5** with ethereal lithium aluminum hydride in the presence of anhydrous aluminum chloride afforded the same substance (**8**), confirming the tetrahydrofuran formulation.[16] Supplementing the 3β-formate, the 3β-acetate, the 3β-benzoate, the 3β-*p*-toluenesulfonate, and the 3β-chloride were prepared as derivatives.

Treatment of **4**, of **5**, or of **7** with refluxing acetic anhydride alone furnished 10–20% of a refractory compound whose infrared spectrum displayed a band at 5.62 μ of intensity comparable with that of the acetate band at 5.8 μ. Traces of this substance frequently were noted during preparation of **7** with acetic anhydride in refluxing pyridine. Aqueous ethanolic potassium hydroxide produced a hydrolysate which retained the source of the 5.62-μ band while sodium borohydride in isopropyl alcohol led to its disappearance. *p*-Nitrophenylhydrazine gave a *p*-nitrophenylhydrazone. The compound appears to be a strained carbonyl derivative, possibly a bridged ketone, arising from an enol ether rearrangement. Clarification of its nature must await further work.

Since the hemiketal **4** and its transformation products represent new ring systems which cannot be degraded to known reference compounds by any straightforward scheme, classical structure proof is precluded. Although the stereochemistry of rings E and F has not been established, both the C-21 methyl group and the C-22 substituent provisionally are considered to occupy β configurations.

Initially, study of the solvolysis of **2** had been undertaken to ascertain whether a 1,2-hydrogen migration at least in part accompanied reaction.[17] In fact, the ring-F furanoid diosgenin isomer **12** expected from acid-catalyzed cyclization of a C-25 tertiary alcohol has been isolated as the predominant product after decomposition of N-nitrososolasodine in aqueous ethanolic acetic acid.[18] Hence, when solvolysis of **2** and of **3** was found to proceed with ring-E olefinic bond participation, the expression **13**, as well as structure **4**, required consideration. The hypothetical isomer **13** appeared excluded, however, when the infrared spectrum of the hydroxy ketone **10** in potassium bromide showed a carbonyl maximum at 1700 cm^{-1}, inconsistent with a cyclopentanone formulation. Moreover, the nmr spectrum of **5** offered support for only three tertiary methyl groups.



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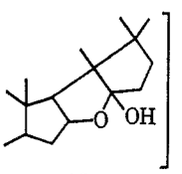

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Additional evidence for retention of side-chain integrity was sought, nevertheless, in examination of solvolysis of kryptogenin 27-iodide (**14**). This γ-diketone, an intermediate in the synthesis of solasodine from kryptogenin,[5] had been obtained by a process analogous to preparation of **3**. Selective hydrolysis of the 3β ester function of kryptogenin 3β,27-di-*p*-toluenesulfonate had given 80% of kryptogenin 27-*p*-toluenesulfonate which was transformed to **14** with sodium iodide in butanone.[19]

Treatment of **14** with aqueous ethanolic silver nitrate at 25° gave a heterogeneous product which afforded only 35% of kryptogenin after chromatography on alumina. The leading eluate was composed of material whose infrared spectrum showed no carbonyl absorption, suggesting spiroketal formation across the 16,22-diketo system. Hydrogen chloride in aqueous dioxane converted this nonketonic fraction to kryptogenin.

(14) (a) *Cf.* H. Hirschman and F. B. Hirschman, *Tetrahedron*, **3**, 234 (1958); Y. Sato and N. Ikekawa, *J. Org. Chem.*, **25**, 789 (1960); (b) F. C. Uhle, *ibid.*, **27**, 656 (1962).

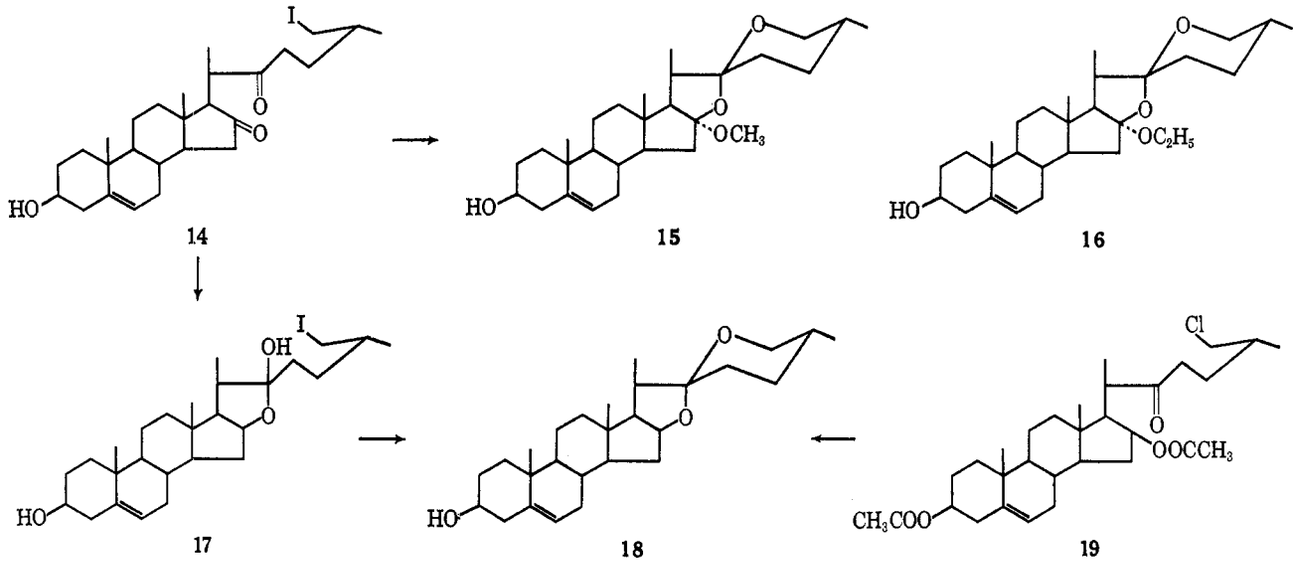
(15) Formic acid reduction of presumed carbinolamine intermediates in the Leuckart reaction provides some analogy: M. L. Moore, *Org. Reactions*, 301 (1949).

(16) For hydrogenolysis of ketals with this reagent complex see R. M. Doukas and T. D. Fontaine, *J. Am. Chem. Soc.*, **73**, 5917 (1951); **75**, 5355 (1953); E. L. Eliel and M. N. Rerick, *J. Org. Chem.*, **23**, 1088 (1958); G. R. Pettit and W. J. Bowyer, *ibid.*, **25**, 84 (1960); E. L. Eliel, *Rec. Chem. Progr.* (Kresge-Hooker Sci. Lib.), **22**, 129 (1961); E. L. Eliel, V. G. Bedding, and M. N. Rerick, *J. Am. Chem. Soc.*, **84**, 2371 (1962).

(17) Rearrangements of isobutyl systems into *t*-butyl systems have been recognized for nearly a century. E. Linnemann [*Ann.*, **162**, 12 (1872)], for example, found that reaction of isobutyl iodide with silver acetate in acetic acid gave *t*-butyl acetate as the principal product.

(18) Y. Sato, H. G. Latham, Jr., L. H. Briggs, and R. N. Seelye, *J. Am. Chem. Soc.*, **79**, 6089 (1957).

(19) After esterification of kryptogenin with 2 equiv of *p*-toluenesulfonyl chloride in pyridine at 0°, the 27-*p*-toluenesulfonate can be isolated directly in 40% yields.[5]



Solvolysis of **14** with silver nitrate in anhydrous methanol afforded 93% of bethogenin (16α-methoxydiosgenin) (**15**), a hexacyclic methyl ketal readily prepared from kryptogenin with refluxing methanolic mineral acids. Ethanolysis of **14** with silver nitrate in absolute ethanol furnished the ethyl counterpart 16α-ethoxydiosgenin (**16**), a new substance which cannot be acquired directly from kryptogenin in ethanolic acid solution. Methanolysis of kryptogenin 27-*p*-toluenesulfonate in refluxing absolute methanol during 20 hr gave 85% of bethogenin (**15**).[20]

Sodium borohydride in isopropyl alcohol preferentially reduced the C-16 keto group of kryptogenin 27-iodide (**14**), affording 30% of the 22-hydroxyfurostene derivative **17**.[23] Treatment of **17** with aqueous ethanolic silver nitrate at 25°, followed by acidification, furnished 29% of diosgenin (**18**). The low-melting material from the diosgenin mother liquors gave an infrared spectrum which showed bands of medium intensity at 5.9 and 6.15 μ, possibly denoting elimination and hemiketal dehydration products.

The 27-chloro derivative **19**, prepared from diosgenin with hydrogen chloride in acetic anhydride,[14b] failed to react at an appreciable rate with aqueous ethanolic silver nitrate at 25°, with sodium iodide in refluxing butanone, or with silver *p*-toluenesulfonate in refluxing acetonitrile. Nonetheless, subjection of **19** to solvolysis in boiling 50% aqueous ethanol in the presence of silver nitrate during 50 hr, followed by successive treatment of the silver chloride filtrate with potassium hydroxide and hydrochloric acid, gave 78% of diosgenin (**18**).[24]

Regeneration of normal sapogenin structures in high yield from kryptogenin 27-*p*-toluenesulfonate, from kryptogenin 27-iodide (**14**), and from the chloro ketone **19** thus serves to demonstrate the virtual absence of rearrangement propensity during solvolysis of side-chain sulfonates and halides.

While incursion of homoallylic unsaturation in solvolytic reactions has been recognized for many years,[25] closing of five- and six-membered rings through participation of olefinic bonds more remotely situated from the ionizing center has been discovered only recently.[26] Construction of the novel framework represented by the hemiketal **4** appears to provide the first example of a solvolytic ring closure involving a neighboring enol ether.

(20) Bethogenin was first isolated as an artifact from Beth root (*Trillium erectum*) by Noller and collaborators.[21] Marker and co-workers demonstrated its ketal structure through partial synthesis from kryptogenin with boiling methanolic hydrogen chloride.[22] While crystallizing readily in long needles, bethogenin exhibits a perplexing, erratic behavior on recrystallization or storage. The melting point, which may extend from 130 to 185°, offers a wholly unreliable criterion of identity or homogeneity since after recrystallization it may rise or fall unpredictably. After storage, lower values usually are seen. Noller and Marker observed the ostensible deterioration and apparently ascribed it to reversal of ketal formation, recommending recrystallization from 2% methanolic potassium hydroxide. However, infrared spectra of all samples examined in this laboratory have been practically identical, even the poorest specimens showing no trace of carbonyl absorption. Moreover, the melting point of bethogenin 3β-acetate, though never sharpening, remains constant at 205–220° after recrystallization. The phenomenon must therefore be associated with the physical state, possibly with a weak crystal lattice, rather than with an intrinsic, molecular lability. Claims,[21,22] presumably derived from capillary tube measurements, of mp 193–194° for bethogenin after recrystallization from alkaline methanol, and of mp 230–232° for its 3β-acetate, cannot be substantiated when the more sensitive microhot stage is used. Like the methyl compounds, the ethyl ketal and its 3β-acetate are well-crystalline substances. The ethyl ketal survives repeated recrystallization from hot, aqueous ethanol. Its melting point covers a wide range but does not fluctuate after recrystallization. Both ketals and their 3β-acetates give complex, distinctive infrared spectra which serve to identify the compounds.

(21) S. Lieberman, F. C. Chang, M. R. Barusch, and C. R. Noller, *J. Am. Chem. Soc.*, **64**, 2581 (1942); C. R. Noller and M. R. Barusch, *ibid.*, **65**, 1435, 1786 (1943).

(22) R. E. Marker, R. B. Wagner, C. H. Ruof, P. R. Ulshafer, and D. P. J. Goldsmith, *ibid.*, **65**, 1658 (1943); R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith, and C. H. Ruof, *ibid.*, **69**, 2210 (1947).

(23) *Cf.* the sodium borohydride reduction of 3β-hydroxy-27-phthalimido-25α-cholest-5-ene-16,22-dione and of kryptogenin itself.[5]

(24) Treatment of **19** with silver acetate in refluxing acetic acid gives 3β,16β,27-triacetoxy-25α-cholest-5-en-22-one, a precursor of diosgenin: R. S. Miner, Jr., and E. S. Wallis, *J. Org. Chem.*, **21**, 715 (1956).

(25) B. Capon, *Quart. Rev.* (London), **18**, 93 (1964); A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw Hill Book Co., Inc., New York, N. Y., 1962, pp 153–157, 182–187.

(26) G. LeNy, *Comp. Rend.*, **251**, 1526 (1960); R. G. Lawton, *J. Am. Chem. Soc.*, **83**, 2399 (1961); P. D. Bartlett and S. Bank, *ibid.*, **83**, 2591 (1961); H. L. Goering and W. D. Closson, *ibid.*, **83**, 3511 (1961); S. Winstein and P. Carter, *ibid.*, **83**, 4487 (1961); P. D. Bartlett, *Ann.*, **653**, 45 (1962); W. Herz and G. Caple, *J. Am. Chem. Soc.*, **84**, 3517 (1962); E. L. Allred and M. J. Maricich, *Tetrahedron Letters*, 949 (1963); G. E. G. Gream and D. Wege, *ibid.*, 535 (1964); M. Hanack and W. Kaiser, *Angew. Chem. Intern. Ed. Engl.*, **3**, 583 (1964); W. D. Closson and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **86**, 1887 (1964); W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jaques, and J. K. Crandall, *ibid.*, **86**, 1959 (1964); W. S. Johnson and R. Owyang, *ibid.*, **86**, 5593 (1964); W. S. Johnson and J. K. Crandall, *J. Org. Chem.*, **30**, 1785 (1965); P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *J. Am. Chem. Soc.*, **87**, 1288 (1965); P. D. Bartlett and G. D. Sargent, *ibid.*, **87**, 1298 (1965); P. D. Bartlett, W. D. Closson, and R. J. Cogdell, *ibid.*, **87**, 1308 (1965); P. D. Bartlett, W. S. Trahanovsky, D. A. Balan, and G. H. Schmid, *ibid.*, **87**, 1314 (1965).

Experimental Section[27]

3β-Hydroxy-27-*p*-toluenesulfonyloxy-25α-5,20(22)-furostadiene (Pseudodiosgenin 27-*p*-Toluenesulfonate)[4] (2, $C_{34}H_{48}SO_5$, 568.78).—Hydrolysis of 0.05 *M* pseudodiosgenin 3β,27-di-*p*-toluenesulfonate (1)[4] in refluxing 70% aqueous acetone during 2 hr consistently gives about 80% of nicely crystalline precipitate depositing directly from the chilled reaction mixture, mp 155–165°; the highest yield attained has been 83%. Recrystallization from acetone furnishes long, colorless needles of mp 165–170° (melt rapidly darkens). These constants supercede those given previously.[4] Recrystallized or well-washed material may be stored indefinitely without discoloration.

3β-Acetoxy-27-*p*-toluenesulfonyloxy-25α-5,20(22)-furostadiene (Pseudodiosgenin 27-*p*-Toluenesulfonate 3β-Acetate) (2 3β-Acetate).—A mixture of 57 mg (0.0001 mole) of **2**, 0.3 ml of acetic anhydride and 1 ml of anhydrous pyridine was kept at 25° during 1 hr, followed by 45 hr at 0°. The solution was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from isopropyl alcohol gave 35 mg (57%) of prismatic needles: mp 82–84°; infrared spectrum 5.78, 8.0 (acetate), 5.9 (m) (enol ether), 6.25 (m) (phenyl), 7.4, 8.2, 8.4, 8.5 $(OSO)_2$, 9.7, 10.4, 10.8, 11.0, 12.3, 14.9 μ.

Anal. Calcd for $C_{36}H_{50}O_6S$ (610.83): C, 70.78; H, 8.25. Found: C, 70.45; H, 8.30.

3β-Hydroxy-27-iodo-25α-5,20(22)-furostadiene (Pseudodiosgenin 27-Iodide)[4] (3, $C_{27}H_{41}O_2I$, 524.51).—Treatment of a 0.05 *M* solution of **2**, during 2 hr, with 3 equiv of sodium iodide in refluxing butanone magnetically stirred to prevent troublesome bumping, followed by recrystallization of the product from dichloromethane–methanol, gives 90% yields. Material prepared in this way does not always exhibit the lower component of the double melting point previously reported.[4,5] Instead, the microscopic crystalline plates are transformed near 100°, without visible melting, to highly characteristic, minute needle clusters which melt finally at 125–138°.

3β-Hydroxy-22β-methoxy-25α-20,27-cyclofurost-5-ene (5). A.—To a solution of 524 mg (0.001 mole) of pseudodiosgenin 27-iodide (**3**) in 60 ml of absolute ethanol was added a solution of 510 mg (0.003 mole) of silver nitrate in 3 ml of water. A yellow precipitate of silver iodide began to separate at once. After 20 hr at 25° the silver iodide was removed by filtration. The filtrate was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Crystallization of the residue from a mixture of dichloromethane and methanol afforded 365 mg (85%) of rods, mp 210–225°. Further recrystallizations gave the analytical sample: mp 220–225°; [α] −3°; infrared spectrum rich finger-print region with 36 bands between 7 and 14 μ of which the most prominent are 9.05, 9.3, 9.5, 9.8, 10.1, 10.15, 10.3, 10.8, 11.0, 11.5, and 11.9 μ; nmr (deuterochloroform with tetramethylsilane as internal standard) 193 (OCH_3), 62 (C-19), 67 and 71 (C-18 and C-21), 48 and 54 cps (C-25).

Anal. Calcd for $C_{28}H_{44}O_3$ (428.63): C, 78.45; H, 10.35; OCH_3, 7.24. Found: C, 78.16; H, 10.26; OCH_3, 7.00.

B.—To a solution of 105 mg (0.0002 mole) of **3** in 4 ml of glacial acetic acid was added a solution of 40 mg (0.00024 mole) of silver acetate in 6 ml of acetic acid. A yellow precipitate of silver iodide which began to separate promptly was removed by filtration after 30 min at 25°. The filtrate was diluted with water to give a deposit which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and methanol gave 65 mg (75%) of needles, mp 204–218°, whose infrared spectrum was identical with that of the compound from procedure A.

3β-Acetoxy-22β-methoxy-25α-20,27-cyclofurost-5-ene (5 3β-Acetate).—A solution of 129 mg (0.0003 mole) of **5** and 1 ml of acetic anhydride in 3 ml of anhydrous pyridine was kept at 25° during 20 hr. The mixture was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and methanol gave 95 mg (67%) of needles: mp 173–198°; the broad, rather uncharacteristic range does not sharpen after repeated recrystallization from methanol or from acetone; [α] −7°; infrared spectrum 5.8, 8.05 (acetate), 9.1, 9.4, 9.6, 10.1, 10.3, 10.8, 10.9 μ.

Anal. Calcd for $C_{30}H_{46}O_4$ (470.67): C, 76.55; H, 9.85. Found: C, 76.35; H, 9.52.

3β-Hydroxy-22β-ethoxy-25α-20,27-cyclofurost-5-ene (6). A.—To a suspension of 86 mg (0.0002 mole) of **5** in 3 ml of absolute ethanol was added 0.6 ml of acetic acid. Dissolution of **5** became complete upon manual stirring during 10 min. After an additional 30 min at 25°, the mixture was added to a solution of 1.5 g of potassium bicarbonate in 20 ml of water. The precipitate was collected by filtration, washed with water, dried, and recrystallized from acetone to give 65 mg (74%): mp 153–160°. Additional recrystallizations gave needles melting at 163–173°; [α] 0°; infrared spectrum 27 bands between 7 and 14 μ of which the most prominent are 9.1, 9.3, 9.4, 9.8, 10.0, 10.1, 10.3, 10.7, 10.9 μ.

Anal. Calcd for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.47; OC_2H_5, 10.18. Found: C, 78.46; H, 10.45; OC_2H_5, 10.24.

B.—A mixture of 86 mg (0.0002 mole) of **5** and 5 ml of absolute ethanol was heated under reflux during 3 hr. Dissolution of **5** was complete after 1 hr. The solution was concentrated to give a residue which was recrystallized from acetone to afford 71 mg (80%) of long needles, mp 163–173°, whose infrared spectrum was identical with that of the compound prepared with ethanolic acetic acid.

C.—When a suspension of 10 mg of **4** in 1 ml of absolute ethanol was treated with 0.2 ml of acetic acid, the hemiketal rapidly dissolved. After 1 hr at 25°, the solution was diluted with water to give a precipitate whose infrared spectrum was identical with that of **6**.

When a solution of 41 mg (0.0001 mole) of **4** in 3 ml of absolute ethanol was heated under reflux during 3 hr and concentrated to give a residue which was recrystallized twice from acetone, 13 mg of needles of unchanged **4** was collected. The infrared spectrum of the total mother liquor material was identical with that of **4**.

Heating of a methanolic solution of the ethyl ketal (**6**) during 45 min led to isolation of the methyl ketal (**5**).

3β,22β-Dihydroxy-25α-20,27-cyclofurost-5-ene (4).—A suspension of 86 mg (0.0002 mole) of **5** in 15 ml of 80% aqueous acetic acid was stirred. After 10 min, when dissolution of the methyl ketal was nearly complete, the product began to precipitate. The mixture was stirred for an additional 1 hr at 25° and was diluted with 15 ml of water to give a deposit which was collected by filtration, washed with water, and dried. Recrystallization from 16 ml of acetone gave 63 mg (76%) of needles: mp 203–204°; [α] −32°; infrared spectrum 40 bands between 7 and 14 μ of which the most prominent are 9.05, 9.3, 9.4, 9.5, 9.6, 9.8, 10.1, 10.3, 10.7, 11.05 μ.

Anal. Calcd for $C_{27}H_{42}O_3$ (414.61): C, 78.21; H, 10.21. Found: C, 78.18; H, 10.27.

When the product from treatment of pseudodiosgenin 27-iodide (**3**) with aqueous ethanolic silver nitrate, as described above for preparation of **5**, was crystallized from acetone, 80–85% yields of **4** were obtained directly. Because of the very sparing solubility of **4** in acetone, as well as in dichloromethane, trituration with refluxing solvent, rather than complete dissolution, may be used for purification in large runs.

3β-Acetoxy-22β-hydroxy-25α-20,27-cyclofurost-5-ene (4 3β-Acetate). A.—A mixture of 50 mg (0.00012 mole) of **4**, 1 ml of acetic anhyride, and 3 ml of anhydrous pyridine was kept at 25° during 20 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, dried, and crystallized from a mixture of dichloromethane and acetone to afford 33 mg (60%) of needles, mp 195–207°. Recrystallization gave needles: mp 202–222°; [α] −22°; infrared spectrum 2.9 (hydroxyl), 5.8, 8.05 (acetate), 9.1, 9.5, 9.65, 9.8, 10.1, 10.3, 10.75, 11.05 μ.

Anal. Calcd for $C_{29}H_{44}O_4$ (456.64): C, 76.27; H, 9.71. Found: C, 76.10; H, 9.80.

B.—A solution of 21 mg (0.00005 mole) of **4** in 1 ml of acetic anhydride containing 20 mg of boron trifluoride etherate was kept at 25° during 20 hr. The dark blue solution was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration and dissolved in ether. The ethereal

(27) Melting points were observed on a calibrated micro hot stage and are corrected. Ethereal solutions were dried over anhydrous magnesium sulfate. Solvents were removed under diminished pressure with a rotating evaporator. Woelm nonalkaline aluminum oxide was used for chromatography. Infrared spectra were recorded from potassium bromide disks with a Perkin-Elmer spectrophotometer, Model 137. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass. Rotations were measured at concentrations of 1% in chloroform by Huffman Laboratories, Inc., Wheatridge, Colo.

solution was washed with water, dried, and concentrated. Crystallization of the residue from acetone gave 15 mg (65%) of needles, mp 178–188°, whose infrared spectrum was identical with that of **4** 3β-acetate.

3β-Acetoxy-25α-20,27-cyclofurosta-5,22(23)-diene (7).—A mixture of 83 mg (0.0002 mole) of **4** 3β-acetate, 1 ml of acetic anhydride, and 5 ml of pyridine was heated under reflux during 1 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and methanol gave 56 mg (63%) of plates, mp 146–165°. A second recrystallization gave 36 mg of plates: mp 155–165°; [α] −153°; infrared spectrum 5.8, 8.05 (acetate), 5.92 μ (m) (enol ether).

Anal. Calcd for $C_{29}H_{42}O_3$ (438.63): C, 79.40; H, 9.65. Found: C, 79.14; H, 9.82.

Preparation of **7** was erratic with frequent inexplicable failures returning only unchanged **4** 3β-acetate. In some runs, **7** was accompanied by significant amounts of the product exhibiting an infrared band at 5.62 μ (see below under reaction of **4** with refluxing acetic anhydride). In these cases, crystallization from acetone was preferable, favoring removal of the 5.62-μ contaminant which cannot be eliminated by repeated recrystallization from methanol or from ethanol. In preparations free of the strained ketone, on the other hand, crystallization from methanol or from ethanol is more effective in removing unchanged **4** 3β-acetate when present in minor amounts.

Warming of a methanolic solution of **7** in the presence of a trace of *p*-toluenesulfonic acid led to the isolation of **5** 3β-acetate.

An attempted diimide reduction[28] of **7** with hydrazine and hydrogen peroxide in the presence of copper ion in methanol at 0° returned **4** as the only identifiable product. Treatment of **7** with sodium borohydride in isopropyl alcohol during 24 days likewise returned **4**. Presumably, hydration of the olefinic bond intervened at some stage, most likely during work-up procedures. In model experiments, attempted diimide reduction of pseudosarsasapogenin failed; pseudodiosgenin was recovered unchanged after exposure to sodium borohydride in isopropyl alcohol during 8 days.

Treatment of 4 with Refluxing Acetic Anhydride.—Exposure of **4**, of **5**, or of the total product after treatment of **4** with acetic anhydride in boiling pyridine, as in preparation of **7**, to refluxing acetic anhydride during 1 hr, followed by decomposition with water and crystallization of the product from dichloromethane–ethanol, gave 24–38% of needles whose infrared spectrum showed a sharp band at 5.62 μ of intensity equal to, or slightly greater than that of the acetate band at 5.8 μ. Although melting commenced at 218°, crystals persisted abundantly in the melt beyond 300°. Repeated, sacrificial recrystallization failed to sharpen the melting point. Suspicion of inhomogeneity was reinforced by low yields after alkaline hydrolysis.

Treatment of 16 mg of first crystallizate with 2% potassium hydroxide in refluxing aqueous ethanol, followed by crystallization of the product from acetone, afforded 6 mg of glistening plates: mp 233–238°, infrared spectrum 5.62 μ. *Anal.* Found: C, 78.27; H, 9.52. Reacetylation of this material with acetic anhydride in pyridine at 25°, followed by crystallization from dichloromethane–ethanol, gave tiny cubes, mp 227–233°, whose infrared spectrum did not differ greatly from that of the original product which melted at 218–>300°. *Anal.* Found (different preparations): C, 76.32, 76.99; H, 9.17, 8.63.

Treatment of first crystallizate with sodium borohydride in isopropyl alcohol gave material whose infrared spectrum no longer showed the carbonyl band at 5.62 μ.

Treatment of 10 mg of first crystallizate with *p*-nitrophenylhydrazine in refluxing ethanolic acetic acid, followed by crystallization of the product from dichloromethane–methanol, gave 6 mg of needles: mp 218–228°; infrared spectrum 5.8, 8.05 (acetate), 6.25 (C=N), 7.6, 9.0, 11.8, 13.3, 14.3 μ.

At least traces of the compound appear to be formed during preparation of **7** with acetic anhydride in refluxing pyridine since infrared spectra of the total precipitated product frequently showed an incipient or moderately well-developed band at 5.62 μ.

In early phases of the work, treatment of **4** or of **5** with refluxing acetic anhydride had given **9** exclusively. The aged reagent used must have contained sufficient acetic acid to induce ring opening.

(28) Conditions used were those of E. J. Cory and A. G. Hortmann, *J. Am. Chem. Soc.*, **87**, 5740 (1965).

Solvolysis of Pseudodiosgenin 27-*p*-Toluenesulfonate (2). A. In Aqueous Acetone.—A mixture of 228 mg (0.0004 mole) of **2**, 45 mg (0.00044 mole) of lithium acetate hydrate, 10 ml of water, and 30 ml of acetone was heated under reflux during 95 hr. The solution was acidified with 0.5 ml of 6 *N* aqueous hydrochloric acid,[29] heated under reflux during 5 min, neutralized with 350 mg of potassium bicarbonate, and concentrated to give a precipitate which was collected by filtration, washed with water, and dried. When the precipitate was triturated with dichloromethane, 20 mg (12%) of crystalline material remained undissolved. Recrystallization from dichloromethane–methanol gave needles, mp 206–209°, whose infrared spectrum was identical with that of **5**. The dichloromethane filtrate was concentrated to give a residue which was chromatographed over 5.25 g of aluminum oxide. Elution with ether–dichloromethane (9:1) gave 100 mg. Crystallization from dichloromethane–methanol furnished 80 mg, mp 105–150°. When further recrystallizations effected no improvement, all fractions and mother liquors were combined and twice recrystallized from acetone to afford 15 mg (9%), mp 190–196°, whose infrared spectrum was identical with that of **5**. The acetone mother liquors were concentrated to give a residue which was twice recrystallized from isopropyl alcohol, affording 25 mg (11%), mp 135–153°, whose infrared spectrum was identical with that of **2**.

B. In Aqueous Ethanol.—A mixture of 228 mg (0.0004 mole) of **2**, 510 mg (0.005 mole) of lithium acetate dihydrate, 12 ml of water, and 28 ml of ethanol was heated under reflux during 95 hr. The solution was concentrated to give an aqueous residue which was extracted with ether. The ethereal solution was washed with water, dried, and concentrated. Two crystallizations of the residue from a mixture of dichloromethane and methanol gave 58 mg (34%) of needles, mp 203–223°, whose infrared spectrum was identical with that of **5**.

In a similar experiment with 163 mg (0.0016 mole) of lithium acetate dihydrate heated during 44 hr, chromatography on 5 g of aluminum oxide gave an eluate of 140 mg with ether–dichloromethane (4:1). Two recrystallizations from acetone afforded 56 mg (34%) of **4**, mp 190–203°, identified by infrared spectrum.

C. In Aqueous Dioxane.—A mixture of 114 mg (0.0002 mole) of **2**, 1 ml of water, and 4 ml of dioxane was heated under reflux during 5 hr. The mixture was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and methanol gave 57 mg (50%) of plates, mp 138–148°, whose infrared spectrum was identical with that of **2**. When the reaction was allowed to proceed for 25 hr, recrystallization of the product from dichloromethane–methanol gave 18 mg (21%) of needles, mp 196–206°, whose infrared spectrum was identical with that of **5**.

3β,16β-Diacetoxy-17β-(1′,3′-dimethyl-5′-oxocyclohexyl)-5-androstene (9).—A mixture of 86 mg (0.0002 mole) of **5**, 1 ml of acetic anhydride, and 2 ml of acetic acid was heated under reflux during 1 hr. The cooled solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and methanol afforded 80 mg (80%), mp 179–187°. Additional recrystallizations gave needles: mp 187–189°; [α] −125°; infrared spectrum 5.8, 8.05 (acetate), 5.88 μ (C=O).

Anal. Calcd for $C_{31}H_{46}O_5$ (498.68): C, 74.66; H, 9.30. Found: C, 74.54; H, 9.36.

Preparations carried out with **5** in refluxing acetic acid alone gave 35–50% yields.

3β,16β-Diacetoxy-17β-(1′,3′-dimethyl-5′-acetoxycyclohex-4′-enyl)-5-androstene (9 5′-Enol Acetate).—A mixture of 50 mg (0.00001 mole) of **9**, 100 mg of *p*-toluenesulfonic acid hydrate, and 10 ml of isopropenyl acetate was heated under reflux during 20 hr. The cooled solution was diluted with ether and was extracted with aqueous potassium bicarbonate. The ethereal phase was washed with water, dried, and concentrated. Crystallization of the residue from acetone gave 27 mg (50%) of plates, mp 233–245°. Two additional recrystallizations from acetone

(29) Early isolation procedures had included a final treatment with mineral acid designed to effect ring closure to diosgenin, or to a diosgenin isomer, provided solvolysis had taken a simple hydrolytic course. The nature of the products did not appear to be influenced by omitting this acidification step, however, even when solvolysis had been conducted in highly buffered media. Absence of the 5.92-μ enol ether absorption band from the infrared spectra, which were nearly congruent regardless of the manner of work-up, offered the first hint that olefinic participation had prevailed.

gave hexagonal plates: mp 249–251°; [α] −102°; infrared spectrum 5.68, 8.35 (enol acetate), 5.78 (sh), 5.8, 8.05 (acetate), 6.0 (m) (C=C), 9.05, 9.35, 9.7 μ; in chloroform solution the shoulder at 5.78 μ was not evident.

Anal. Calcd for $C_{33}H_{48}O_6$ (540.71): C, 73.30; H, 8.95. Found: C, 73.35; H, 8.98.

3β,16β-Dihydroxy-17β-(1′,3′-dimethyl-5′-dimethyl-5′-oxocyclohexyl)-5-androstene (10).—A mixture of 100 mg (0.0002 mole) of **9**, 560 mg (0.01 mole) of potassium hydroxide, 2 ml of water, and 8 ml of ethanol was heated under reflux during 15 min. The solution was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal phase was washed with water, dried, and concentrated. Crystallization of the residue from methanol gave 75 mg (90%) of needles, mp 178–183°. Additional recrystallizations from dichloromethane–methanol afforded needles: mp 182–187°, [α] −4°, infrared spectrum 5.88 μ (C=O).

Anal. Calcd for $C_{27}H_{42}O_3$ (414.61): C, 78.21; H, 10.21. gund: C, 78.22; H, 10.36.

When crystallized from aqueous ethanol, **10** appeared to deposit as a hydrate which melted initially at 145–150° followed by resolidification to tiny needles melting finally at 182–187°.

Cyclization of 10 to 4.—A solution of 21 mg (0.00005 mole) of **10** and 5 mg of *p*-toluenesulfonic acid hydrate in 1 ml of acetone was heated under reflux during 3 hr. After 20 hr at 0°, the deposit was collected by filtration to give 9 mg (43%) of rods, mp 199–203°, whose infrared spectrum was identical with that of **4**. The filtrate was heated under reflux during 3 hr to give an additional 6 mg (28%) of **4**.

Cyclization of 10 to 5.—A solution of 10 mg (0.000025 mole) of **10** and 5 mg of *p*-toluenesulfonic acid hydrate in 1 ml of methanol was heated under reflux during 2 hr. After 20 hr at 0°, the precipitate was collected by filtration to give 4.5 mg (45%) of rods, mp 221–228°, whose infrared spectrum was identical with that of **5**.

3β,16β-Dihydroxy-17β-(1′,3′-dimethyl-5′-oxocyclohexyl)-5-androstene Oxime (10 Oxime).—A mixture of 42 mg (0.0001 mole) of **10**, 139 mg (0.002 mole) of hydroxylamine hydrochloride, 1 ml of pyridine, and 4 ml of absolute ethanol was heated under reflux during 4 hr. The solution was concentrated to give a residue which was diluted with water. The precipitate was collected by filtration, washed with water, dried, and crystallized from methanol to give 25 mg (58%), mp 241–249°. Two additional recrystallizations from methanol afforded large, broad needles: mp 243–253°, (darkens early on heating); [α] +9°; infrared spectrum 6.0 (w) (C=N), 10.4 μ.

Anal. Calcd for $C_{27}H_{43}NO_3$ (429.62): C, 75.48; H, 10.09; N, 3.26. Found: C, 75.34; H, 9.95; N, 3.36.

When a mixture of 41 mg (0.0001 mole) of **4**, 347 mg (0.005 mole) of hydroxylamine hydrochloride, and 510 mg (0.005 mole) of lithium acetate hydrate in 5 ml of 80% ethanol was heated under reflux during 20 hr, methanol recrystallization of the product precipitated by water gave 9 mg of needles of **5**, mp 205–225°. The infrared spectrum of the total material from the mother liquors gave no evidence for the presence of the oxime of **10**.

Similar treatment of **5** with hydroxylamine hydrochloride and pyridine in ethanol likewise returned about 25% of the methyl ketal.

3β,16β-Dihydroxy-17β-(1′,3′-dimethyl-5′-oxocyclohexyl)-5-androstene *p*-Nitrophenylhydrazone (10 *p*-Nitrophenylhydrazone).—A mixture of 21 mg (0.00005 mole) of **10**, 11 mg (0.00007 mole) of *p*-nitrophenylhydrazine, 5 drops of acetic acid, and 2 ml of ethanol was heated under reflux during 1 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from methanol gave 19 mg (69%) of yellow, dense, prismatic needles: mp 170–175°; infrared spectrum 6.21 (s), 7.6, 9.0, 11.9, 13.3 μ.

Anal. Calcd for $C_{33}H_{47}N_3O_4$ (549.73): N, 7.64. Found: N, 7.53.

When a mixture of 42 mg (0.00001 mole) of **4**, 22 mg (0.00014 mole) of *p*-nitrophenylhydrazine, 10 drops of acetic acid, and 4 ml of ethanol was heated under reflux during 4 hr, recrystallization from methanol, after precipitation of the product with water, gave 36 mg (85%) of **5**, mp 220–230°. Similar treatment of **5** with *p*-nitrophenylhydrazine likewise returned the methyl ketal.

3β,16β-Dihydroxy-17β-(1′,3′-dimethyl-5′-hydroxycyclohexyl)-5-androstene (11).—A mixture of 83 mg (0.0002 mole) of **10**, 38 mg (0.001 mole) of sodium borohydride, and 20 ml of isopropyl alcohol was stirred magnetically during 70 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried to give 83 mg (100%) of tiny rods, mp 154–156°. The melting point was unchanged after several recrystallizations from aqueous ethanol. Recrystallization from methanol gave poor recovery of long, transparent needles of the same melting point; [α] −79°; infrared spectrum showed no functional bands other than hydroxyl, uneventful fingerprint region.

Anal. Calcd for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.65. Found: C, 77.71; H, 10.80.

3β,16β-Diacetoxy-17β-(1′,3′-dimethyl-5′-acetoxycyclohexyl)-5-androstene (11 3β,16β,5′-Triacetate).—A solution of 42 mg (0.0001 mole) of **11** in 3 ml of acetic anhydride was heated under reflux during 1 hr. The cooled mixture was added to water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of dichloromethane and methanol gave 42 mg (78%) of rods, mp 223–227°. Three additional recrystallizations afforded 33 mg of long needles: mp 227–229°; [α] −122°; infrared spectrum 5.8, 8.05 μ (acetate).

Anal. Calcd for $C_{33}H_{50}O_6$ (542.73): C, 73.03; H, 9.29; CH_3CO, 23.79. Found: C, 72.97; H, 9.12; CH_3CO, 23.75.

3,16-Dioxo-17β-(1′,3′-dimethyl-5′-oxocyclohexyl)-4-androstene (11 Triketone).—To a solution of 26 mg (0.000062 mole) of **11** in 2.5 ml of acetone at 0° was added dropwise a solution of 19 mg (0.000186 mole) of chromium trioxide and 35 mg of sulfuric acid in 0.5 ml of water. After 15 min at 0°, the solution was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Recrystallization of the residue from acetone gave 3 mg of plates, mp 240–253°, whose infrared spectrum showed bands at 5.75 and 5.9 μ. Since the olefinic bond appeared to have been retained at the 5.6 position in this material, the entire reaction product was recombined, dissolved in 5 ml of ethanol, acidified with 5 drops of 6 *N* aqueous hydrochloric acid, and heated under reflux during 15 min. Condensation, followed by extraction with ether, washing with water, drying, and evaporation gave a residue which was recrystallized from acetone to afford 2 mg of plates: mp 257–264°; infrared spectrum 5.78 (C-16), 5.9 (C-22), 5.98 (C-3), 6.2 μ (m) (C-4=C-5).

3β-Formyloxy-25α-20,27-cyclofurost-5-ene (8 3β-Formate).—To a boiling solution of 690 mg (0.005 mole) of potassium carbonate in 10 ml of formic acid (prepared by cautious addition in the cold) was added 215 mg (0.0005 mole) of **5**. The solution promptly assumed a royal purple color; after 3 min at reflux temperature a white precipitate began to separate. After 5 min of over-all heating the mixture was cooled and diluted with water, discharging the color, and giving a crystalline deposit which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of dichloromethane and acetone furnished 182 mg (85%) of dense, gem-like plates, mp 239–244°. Additional recrystallizations gave gems: mp 248–250°; [α] −72°; infrared spectrum 5.8, 8.4 (formate), 9.3, 9.5, 9.7, 10.05, 10.2, 10.4, 10.7, 11.0 μ.

Anal. Calcd for $C_{28}H_{42}O_3$ (426.62): 78.82; H, 9.92. Found: 78.78; H, 9.99.

3β-Hydroxy-25α-20,27-cyclofurost-5-ene (8). A. From Alkaline Hydrolysis of 8 3β-Formate Produced by Formic Acid Reduction of 5.—A mixture of 182 mg (0.000425 mole) of **8** 3β-formate, 500 mg of potassium hydroxide, 5 ml of water, and 45 ml of ethanol was heated under reflux during 2 hr. The solution was concentrated to give an aqueous residue which was extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Crystallization of the residue from a mixture of dichloromethane and acetone gave 140 mg (79%) of rods, mp 248–253°. Recrystallization from acetone sometimes gives plates. On the micro hot stage the crystals characteristically grow to long spikes which cross the entire field; [α] −51°; infrared spectrum showed no functional bands other than hydroxyl, numerous bands of medium intensity between 7 and 14 μ.

Anal. Calcd for $C_{27}H_{42}O_2$ (398.61): C, 81.35; H, 10.62. Found: C, 81.12; H, 10.62.

B. From Formolysis of Pseudodiosgenin 27-*p*-Toluenesulfonate (2).—To a boiling solution of 552 mg (0.004 mole) of potassium carbonate in 10 ml of formic acid (prepared by cautious addition in the cold) was added 228 mg (0.0004 mole) of **2**. After 5 min at reflux temperature the purple solution was cooled and concentrated. A solution of the residue in 3 ml of ethanol was made basic by addition of 560 mg of potassium hydroxide in 2 ml of water. After 1 hr at reflux temperature, the mixture was

concentrated to give a residue which was extracted with ether. The ethereal extract was washed with water, dried, and concentrated. A solution of the residue (165 mg) in ether–dichloromethane (4:1) was chromatographed over 5 g of aluminum oxide. The eluate (110 mg) was crystallized twice from acetone to afford 33 mg (20%), mp 238–243°, whose infrared spectrum was identical with that of **8** prepared by aqueous ethanolic potassium hydroxide hydrolysis of the formic acid reduction product of **5**.

Recrystallization of the first mother liquor from methanol gave 15 mg of crystals melting at 155–175°. A second recrystallization furnished 5 mg (3%) of material, mp 173–193°, whose infrared spectrum was identical with that of diosgenin.

When formolysis of **2** was first studied, before the structure of the product was known, a series of experiments was run in the presence of varying amounts of buffer, other variables (10 ml of formic acid, 5-min reflux period) remaining constant, with the following results: 1 equiv of potassium formate, 10% of **8**; 2 equiv, 12%; 4 equiv, 17.5%; 8 equiv, 18%, 10 equiv, 17.5%; 10 equiv, 20%; 20 equiv, 20%. With refluxing formic acid alone, in the absence of potassium formate, **8** was not isolated. In a single experiment with 20 equiv of potassium formate in 50 ml of 80% aqueous formic acid, 15% of **8** was produced.

C. From Lithium Aluminum Hydride–Aluminum Chloride Reduction of 5.—To a magnetically stirred mixture of 45 mg (0.0012) of lithium aluminum hydride and 15 ml of anhydrous ether at 0° was added a solution prepared by cautious addition of 640 mg (0.0048 mole) of anhydrous aluminum chloride to 10 ml of anhydrous ether. After 15 min, a solution of 43 mg (0.0001 mole) of **5** in 25 ml of anhydrous ether was added. The mixture was stirred for 30 min at 0° and then was heated under reflux during 4 hr. The reagents were decomposed by cautious dropwise addition of water to the chilled mixture, followed by dropwise addition of dilute, aqueous hydrochloric acid. The ethereal phase was washed with water and with aqueous potassium bicarbonate, dried, and chromatographed over 1.2 g of aluminum oxide. The material which eluted with ether was crystallized twice from acetone to afford 10 mg (25%) of needles, mp 215–240°, whose infrared spectrum was identical with that of **8**. Acetylation with acetic anhydride in pyridine at 25°, followed by crystallization of the product from methanol afforded fine needles, mp 240–245°, whose infrared spectrum was identical with that of **8** 3β-acetate. The reaction was studied only cursorily; the modest yield is probably ascribable to the relatively low activity of the lithium aluminum hydride sample used.

3β-Acetoxy-25α-20,27-cyclofurost-5-ene (8 3β-Acetate).—A mixture of 42 mg (0.0001 mole) of **8**, 2 ml of acetic anhydride, and 5 ml of anhydrous pyridine was kept at 25°. (The starting compound failed to dissolve in a lesser volume.) After 20 hr, the solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of dichloromethane and methanol gave 38 mg (86%) of needles: mp 256–258°; [α] −57°; infrared spectrum 5.8, 8.05 μ (acetate).

Anal. Calcd for $C_{29}H_{44}O_3$ (440.64): C, 79.04; H, 10.07. Found: C, 78.93; H, 10.08.

3β-Benzoyloxy-25α-20,27-cyclofurost-5-ene (8 3β-Benzoate).—A mixture of 52 mg (0.00013 mole) of **8**, 0.5 ml of benzoyl chloride, and 5 ml of anhydrous pyridine was kept at 25° during 5 days. The dark red solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of dichloromethane and methanol gave 48 mg (75%), mp 231–239°. Additional recrystallizations (without heating) gave rods: mp 235–240°; [α] −34°; infrared spectrum 5.8, 7.9, 14.0 (s) μ (benzoate).

Anal. Calcd for $C_{34}H_{46}O_3$ (502.71): C, 81.23; H, 9.22. Found: C, 81.37; H, 9.12.

3β-*p*-Toluenesulfonyloxy-25α-20,27-cyclofurost-5-ene (8 3β-*p*-Toluenesulfonate).—A mixture of 8 mg of **8**, 100 mg of *p*-toluenesulfonyl chloride, and 1 ml of anhydrous pyridine was kept at 0° during 20 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried, mp 191–193°. Recrystallization from acetone gave 7 mg of fine needles: mp 194–196° (melt rapidly darkens); infrared spectrum 6.25 (m), 7.4, 7.5, 8.45, 8.55, 10.8, 11.6, 14.6 μ. Brief hydrolysis in refluxing 70% aqueous acetone returned **8**.

3β-Chloro-25α-20,27-cyclofurost-5-ene (8 3β-Chloride).—Treatment of 6 mg of **8** with a few drops of thionyl chloride at 25° during 40 min, followed by crystallization of the product from acetone, gave 4 mg of plates, mp 238–243°; the infrared spectrum included prominent bands at 11.5, 12.15, 13.0, and 13.8 μ.

Bethogenin (16α-Methoxydiosgenin, 15). A. From Kryptogenin 27-Iodide (14).—To a solution of 108 mg (0.0002 mole) of **14** in 3 ml of methanol was added a solution of 102 mg (0.0006 mole) of silver nitrate in 7 ml of methanol; a yellow precipitate of silver iodide began to separate at once. After 3 days at 25°, the filtrate from the silver iodide was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. The residue was crystallized from a mixture of dichloromethane and methanol to afford 83 mg (93%) of long needles. On the micro hot stage the crystals began to soften at 150°; after partial resolidification, melting was complete at 185°; [α] −102°. The infrared spectrum was identical with that given by a sample of bethogenin prepared from kryptogenin with methanolic hydrogen chloride: 32 bands between 7 and 14 μ of which the most prominent are 9.05, 9.2, 9.6, 9.75, 10.2, 10.5, 10.8, 11.1, 11.3 μ.

The crystals were combined with material from the mother liquors and dissolved in 3.5 ml of dioxane. To the solution was added 1.5 ml of water and 1 drop of 6 *N* aqueous hydrochloric acid. After 20 hr at 25°, the mixture was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from acetone afforded 66 mg (77%) of tiny rods, mp 178–187°. Recrystallization gave 55 mg of rods, mp 178–187°; [α] −211°; mixture melting point with a sample of natural kryptogenin (mp 183–189°) 181–189°; infrared spectrum identical with that of kryptogenin 5.8 (C-16 C=O), 5.88 μ (C-22 C=O).

B. From Kryptogenin 27-*p*-Toluenesulfonate.—A solution of 117 mg (0.0002 mole) of kryptogenin 27-*p*-toluenesulfonate[5] in 50 ml of methanol was heated under reflux during 23 hr. After 100 mg of potassium hydroxide in 1 ml of water had been added to the cooled solution, the mixture was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Crystallization of the residue from 2 ml of 2% methanolic potassium hydroxide afforded 76 mg (85%) of rods, mp 158–180°; recrystallization from 3 ml of 2% methanolic potassium hydroxide gave 67 mg of rods, mp 153–188°, whose infrared spectrum was identical with that of bethogenin prepared from kryptogenin with methanolic hydrogen chloride.

Bethogenin 3β-Acetate (16α-Methoxydiosgenin 3β-Acetate) (15 3β-Acetate). A. From Kryptogenin 27-Iodide (14).—The total product from silver nitrate methanolysis of 108 mg of **14**, as described above, was dissolved in 2 ml of pyridine and acetylated with 0.5 ml of acetic anhydride. After 20 hr at 25°, the mixture was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and methanol gave 80 mg (82%) of tiny rods, mp 207–219°. Recrystallization furnished 76 mg: mp 203–220°; [α] −107°; infrared spectrum 5.8, 8.05 (acetate), 30 bands between 7 and 14 of which the most prominent are 9.0, 9.05, 9.2, 9.6, 10.2, 10.9, 11.1, 11.3 μ.

Anal. Calcd for $C_{30}H_{46}O_5$ (486.67): C, 74.03; H, 9.53. Found: C, 73.99; H, 9.52.

B. From Kryptogenin.—A solution of 86 mg (0.0002) mole of kryptogenin and 60 mg of *p*-toluene sulfonic acid hydrate in 3 ml of methanol was heated under reflux 4 hr, diluted with water, and extracted with ether. The ethereal extract was washed with aqueous potassium bicarbonate and with water and was dried. Concentration gave a residue which was dissolved in 2 ml of pyridine and acetylated with 0.5 ml of acetic anhydride. After 3 days at 25°, the solution, containing a deposit of long needles, was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and methanol gave 72 mg (74%) of rods, mp 205–219°, whose infrared spectrum was identical with that of the product prepared from **14**.

16α-Ethoxydiosgenin (16).—To a solution of 108 mg (0.0002 mole) of kryptogenin 27-iodide (**14**) in 3 ml of absolute ethanol was added a solution of 102 mg (0.0006 mole) of silver nitrate in 7 ml of absolute ethanol. After 20 hr at 25°, the silver iodide (47 mg, 100%) was removed by filtration. The filtrate was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. The product failed to crystallize satisfactorily from any single solvent; separation from acetone was slow with poor recovery. Recrystallization from

aqueous ethanol afforded 67 mg (73%) of needles, mp 136–146°. Two additional recrystallizations from hot aqueous ethanol gave rods: mp 144–158°; [α] −84°; infrared spectrum 32 bands between 7 and 14 of which the most prominent are 8.6, 9.2, 9.3, 9.4, 10.2, 10.8, 11.2 μ.

Anal. Calcd for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 75.91; H, 10.33.

16α-Ethoxydiosgenin 3β-Acetate (16 3β-Acetate).—The total product from silver nitrate ethanolysis of 108 mg of **14**, as described above, was dissolved in 3 ml of pyridine and acetylated with 1 ml of acetic anhydride. After 20 hr at 25°, the mixture was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from acetone gave 40 mg (40%), mp 158–168°. Two additional recrystallizations from acetone afforded dense, glistening plates: mp 166–176°; [α] −97°; infrared spectrum 5.8, 8.05 (acetate), 26 bands between 7 and 14 of which the most prominent are 9.0, 9.2, 9.5, 9.7, 10.2, 10.55, 10.85, 11.1, 11.4, 11.5 μ.

Anal. Calcd for $C_{31}H_{48}O_5$ (500.69): C, 74.36; H, 9.66; OC_2H_5, 8.99. Found: C, 74.30; H, 9.75; OC_2H_5, 8.75.

Solvolysis of Kryptogenin 27-Iodide (14) in Aqueous Ethanol.—To a solution of 108 mg (0.0002 mole) of **14** in 15 ml of ethanol was added a solution of 136 mg (0.0006 mole) of silver nitrate in 2 ml of water. After 20 hr at 25°, the silver iodide was removed by filtration. The filtrate was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Recrystallization from acetone gave 40 mg, mp 155–170°. The crystals were combined with material from the mother liquors and chromatographed over 2.4 g of aluminum oxide. Crystallization of the ether eluate from acetone gave material melting at 140–150° whose infrared spectrum showed no carbonyl absorption. Acetone recrystallization of the product which eluted with 1% methanol in ether gave 28 mg of needles (32%), mp 176–186°, whose infrared spectrum was identical with that of kryptogenin. In another experiment in which the total product from 54 mg of **14** was treated with hydrochloric acid in aqueous dioxane at 25° during 48 hr, 30 mg (70%) of kryptogenin was isolated.

3β,22-Dihydroxy-27-iodo-25α-5-furostene (17).—A mixture of 324 mg (0.0006 mole) of kryptogenin iodide (**14**), 90 mg (0.0024 mole) of sodium borohydride, and 36 mg of isopropyl alcohol was stirred magnetically during 48 hr. The solution was concentrated to give a residue which was diluted with water and extracted with ether. The dried ethereal extract was chromatographed over 9 g of aluminum oxide. The material (200 mg) which eluted with ether was recrystallized twice from acetone to give 98 mg (30%) of plates, mp 108–118°. Further recrystallizations from acetone gave dense plates: mp 115–125°; [α] −60°; infrared spectrum showed no function bands other than hydroxyl.

Anal. Calcd for $C_{27}H_{43}IO_3$ (542.54): C, 59.77; H, 7.99; I, 23.39. Found: C, 59.95; H, 7.94; I, 23.72.

Solvolysis of 3β,22-Dihydroxy-27-iodo-25α-5-furostene (17).—To a solution of 54 mg (0.0001 mole) of **17** in 9 ml of ethanol was added a solution of 51 mg (0.0003 mole) of silver nitrate in 1 ml of water; a yellow precipitate of silver iodide began to separate within a few minutes. After 1 hr at 25°, the mixture was acidified with 5 drops of 6 *N* aqueous hydrochloric acid and was warmed briefly. The silver salts were removed by filtration to give a filtrate which was neutralized with aqueous potassium bicarbonate and was concentrated. The residue was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Crystallization of the residue from methanol gave 12 mg (29%) of needles, mp 180–200°, whose infrared spectrum was identical with that of diosgenin (**18**).

Dilution of the mother liquors with water afforded needles, mp 110–180°, whose infrared spectrum showed a sharp band of medium intensity at 5.9 and a somewhat weaker band at 6.15 μ. Conjugated dienes were not present since the ultraviolet spectrum showed no absorption. The infrared spectrum offered no evidence for the presence of terminal methylene resulting from simple elimination.

Treatment of **17** with refluxing acetic anhydride, followed by crystallization of the product from ethanol, gave material melting at 112–115° whose infrared spectrum showed acetate bands at 5.8 and 8.05 μ as well as a sharp band of medium intensity at 5.92 μ characteristic of enol ethers. This substance doubtless is the 3β-acetate of pseudodiosgenin 27-iodide, produced by hemiketal dehydration. The claim[24] that boiling acetic anhydride converts the 27-chloro analog of **17** to 3β,16β-acetoxy-27-chloro-25α-cholest-5-en-22-one (**19**) appears questionable.

Solvolysis of 3β,16β-Diacetoxy-27-chloro-25α-cholest-5-en-22-one (19).—To a boiling solution of 107 mg (0.0002 mole) of **19**[14b] in 10 ml of ethanol was added a hot solution of 102 mg (0.0006 mole) of silver nitrate in 10 ml of water. After 50 hr at reflux temperature (the starting compound had dissolved completely after 4 hr), the dark purple precipitate was collected by filtration to afford 20 mg (70%) of silver chloride (quantitative recovery difficult). The filtrate was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water and was concentrated to give a residue which was dissolved in 10 ml of 80% aqueous ethanol containing 100 mg of potassium hydroxide. After 30 min at reflux temperature, the solution was acidified with 0.5 ml of 6 *N* aqueous hydrochloric acid and heated during 5 min. The cooled mixture was neutralized with potassium bicarbonate and was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Recrystallization of the residue from a mixture of dichloromethane and methanol afforded 65 mg (78%) of needles, mp 195–201°, whose infrared spectrum was identical with that of diosgenin (**18**). A second recrystallization gave 58 mg: mp 201–204°, [α] −129°.

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