Aromatic Etiojervane Derivatives

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The C-nor-D-homo sapogenin **1a** may be catalytically dehydrogenated to the D-ring aromatic sapogenin **2a**, a compound which undergoes ready pseudomerization with aqueous acid (to **3a**). Similar dehydrogenation of the acetate **1b** effects concomitant dehydroxymethylation (of C-26) to provide the norpseudomer **5a**. Oxidation of either pseudomer (**3, 5**) followed by hydrolysis provides the acetyl phenol **9a**. The 16-deoxy analog **14a** is prepared by a facile aromatization of the unsaturated C-nor-D-homopregnenone **13b**; the same compound (**14a**) is also synthesized by degradation of dihydroveratramine (**16a**).

A continuing exploration of etiojervane derivatives produced from hecogenin[1] led to the preparation of compounds which contain an aromatic D-ring, as is found in veratramine (**16b**). An attractive method of forming the terminal ring of alkaloids of this type entails direct utilization of the eight-carbon sapogenin side chain with its two protected functional groups (C-22, C-26).[2] Initial D-ring aromatization of an intermediate such as the olefin **1a**[3] might involve elimination of the 16-oxygen to afford, for example, compound **7**.

Although several oxidizing agents failed to aromatize ring D in olefin **1a**, heating this compound with palladium-on-charcoal catalyst effected a disproportionation to the known saturated derivative **1d**[1] and to an aromatic compound **2a**. Suppression of disproportionation was accomplished by use of a solvent with the catalyst or by oxidation with sulfur, either method affording increased yields of the aromatic derivative. That the expected elimination of the 16-oxygen function had not occurred was shown by the presence of a single aromatic proton signal at 388 c.p.s. in the n.m.r. spectrum and from the subsequent chemical reactions of this product.

Dilute mineral acid caused facile pseudomerization of the aromatic sapogenin **2a** to the diol **3a** (Chart I), a compound whose structure was clearly shown by its strong ultraviolet absorption as well as by its degradation products. The same compound was obtained as a by-product in varying yields in the preparation of **2a**, apparently as a result of minor acidic contamination. Direct hydrolysis of the total dehydrogenation mixture afforded the diol in 55% over-all yield. The unusual reversal of sapogenin–pseudosapogenin stabilities as compared to those found in the saturated sapogenin systems may be attributed to the strong resonance stabilization obtained in producing the benzofuran ring system.

Dehydrogenation of the acetate **1b** with palladium in refluxing cymene followed a different course than the corresponding C-3 alcohol **1a**. This was presumably a result of the presence of acetic acid split from the A-ring during the lengthy period necessary to complete the reaction. The total product, hydrolyzed and chromatographed, afforded only small amounts of the expected diol **3a** and the saturated sapogenin **1d**. A major portion (40%) of the product was a new compound (**5a**) exhibiting an ultraviolet spectrum identical with that of **3a**. A final component of this mixture was a highly aromatic substance whose structure (**4**) was assigned tentatively on the basis of its spectra, analytical data, and its presumed formation from **5a** acetate.

The major product (**5a**) from the above reaction was shown by elemental and spectral analysis to have lost both the C-26 oxygen and carbon. To prove the structure of this compound, the monoacetate **3c**, prepared by alumina hydrolysis[4] of the diacetate **3b** or by aluminum chloride opening of the sapogenin **2b**, was converted to its tosylate. Since dehydrotosylation to **5d** did not proceed smoothly, the tosylate was converted to the aldehyde **5b** with dimethyl sulfoxide–sodium bicarbonate at 150°.[5] Isoamyl nitrite and base afforded the oxime **5c** which was converted by direct Wolff–Kishner reduction to the desired styrene **5a**. This reduction of oximes was first explored in a model system, pregnenolone oxime, which provided the 17β-ethyl derivative[6] in good yield. Dehydroxymethylation with Raney nickel has been described earlier by Pines and co-workers[7]; despite the difference in catalyst employed here, the mechanism of the reaction is almost certainly the same.

More definitive evidence of the structure of the benzofuran derivatives **3** and **5** was obtained by oxidative fission of the C-20–C-22 bond using either ozone or chromic acid. Subsequent hydrolysis yielded the acetyl derivative **9a** which showed a characteristic n.m.r. signal for each of the four D-ring substituents. Removal of the 16-hydroxyl function *via* reduction of its phosphite ester was abandoned because of accompanying hydrogenolysis at C-20. The 16-methyl ether formed readily and oxidation of its 3-hydroxyl proceeded normally. Wolff–Kishner reduction of **9c** afforded a mixture of the ether **8b** and the phenol **8a**, the latter a result of base-catalyzed ether cleavage. The ether **8b** was also formed as the major crystalline product of lithium–ammonia reduction of the methyl ether **9c**.

The infrared spectrum of the phenol **9a** shows a hydrogen-bonded carbonyl (6.13 μ), implying the acetyl group is in the plane of the benzene ring. In agreement with this, the n.m.r. spectrum shows the signal of the 21-methyl, as well as of the 18-methyl, subjected to the paramagnetic shift from both the carbonyl

(1) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964); W. F. Johns and I. Laos, *ibid.*, **30**, 123 (1965).

(2) Examples of this utilization of the sapogenin side chain are found in the work of F. C. Uhle, *ibid.*, **27**, 656 (1962), and references cited there.

(3) The structures of olefin **1a** and its derivatives have been recently clarified by J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron Letters*, 119 (1965); *Australian J. Chem.*, **18**, 759 (1965).

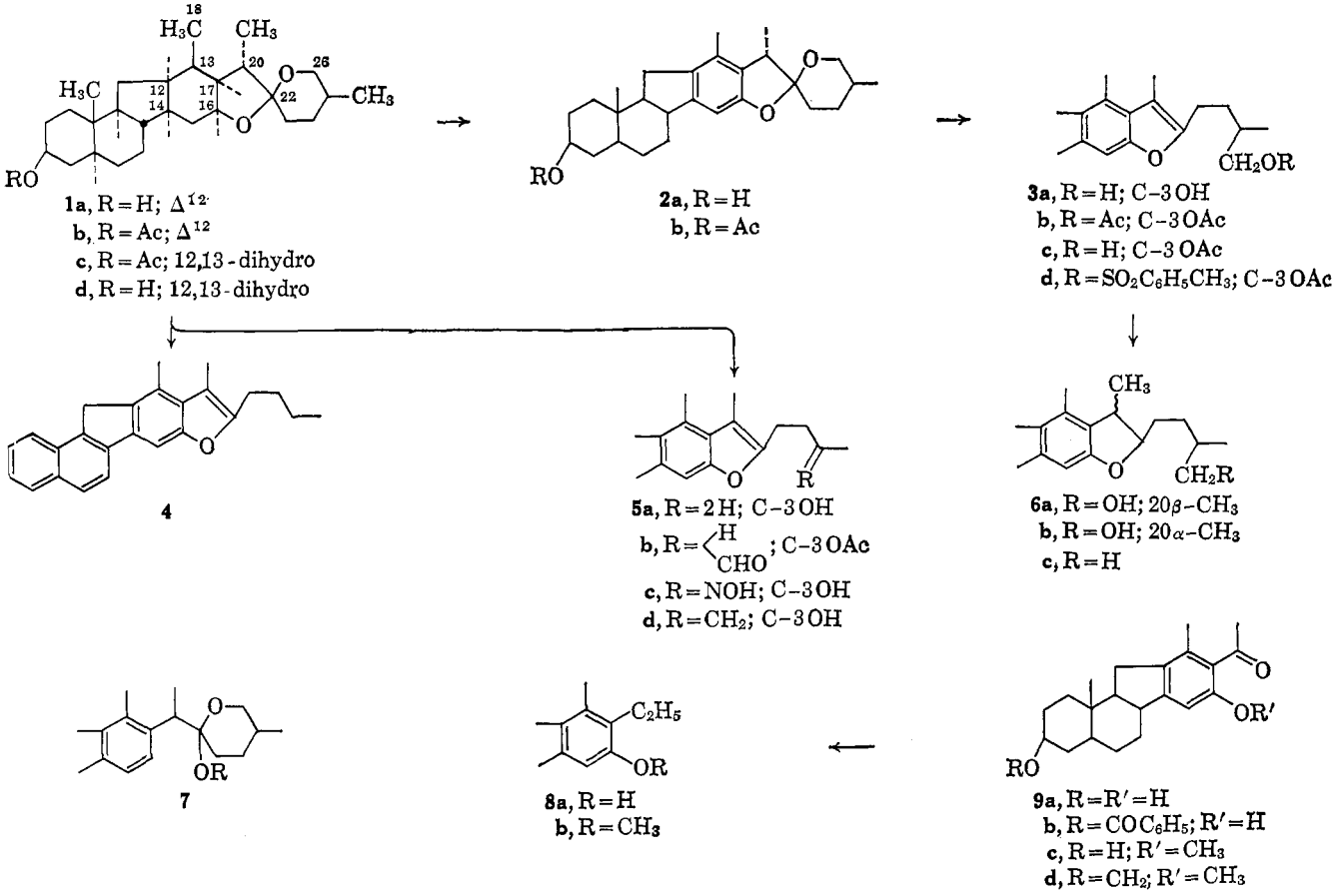
(4) W. F. Johns and D. M. Jerina, *J. Org. Chem.*, **28**, 2922 (1963).

(5) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959).

(6) This sample was kindly afforded by Dr. C. W. Marshall of these laboratories, prepared by the method of Huang-Minlon, *ibid.*, **71**, 3301 (1949).

(7) H. Pines, M. Shamaiengar, and W. S. Postl, *ibid.*, **77**, 5099 (1955).

CHART I



function and the benzene ring.[8a] In the methyl ether **9c**, an interesting change is seen, indicative of an apparent lack of conjugation of the 20-carbonyl with the aromatic ring: the infrared maximum is at 5.86 μ, the ultraviolet absorption is of low intensity, and the n.m.r. spectrum shows the 18- and 21-methyl absorptions at 127 and 147 c.p.s., respectively (*vs.* 146 and 157 c.p.s. in the phenol). This phenomenon is a result of steric inhibition of resonance,[8b] the acetyl group having been forced from the plane of the phenyl ring by the adjacent methyl and methoxyl groups; this subjects the 18-methyl group to a diamagnetic shift by being above the plane of the carbonyl group, and the 21-methyl to a similar shielding by being above the plane of the phenyl ring. The same phenomenon was seen in the diethyl phosphite ester and to a lesser extent in the acetate.

Formation of the eight carbon atoms attached to C-17 into a veratramine-like E-ring or any analogous structure necessitates utilization of the latent 22-carbonyl group. The large inherent stability of the furan ring in **3a** (or **5a**) was amply demonstrated by the failure of this system to open or react with a variety of acidic or basic reagents. To decrease the stability of this system, the conjugated double bond of **3a** was reduced. Catalytic or lithium–ammonia reduction yielded a crystalline epimer (**6a**) as the major product. The remainder of the material (amorphous) was believed to contain the stereoisomer **6b** because of (a) its spectral similarity to **6a**, and (b) the production of the same material by direct catalytic reduction of the sapogenin **2b**. By analogy to the hydrogenations in the normal sapogenins, **6a** would have a 20β-methyl, and **6b** a 20α-methyl. No useful E-ring opening of these reduced materials was found.

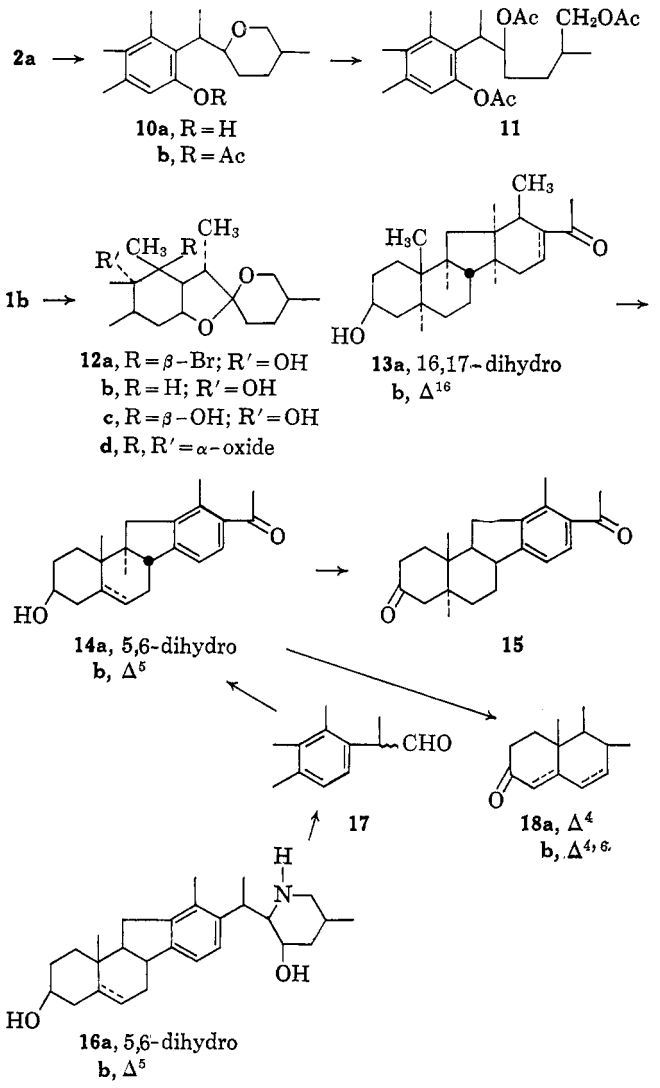
A successful attempt to free the 22-oxygen function entailed an alternate opening of the sapogenin side chain (see Chart II) by use of lithium aluminum hydride–aluminum chloride on **2a**.[9] The resulting amorphous phenol was tentatively assigned the structure **10a** on the basis of its analytical data and the following reactions: the product formed a methyl ether with methyl iodide, a diacetate **10b** with acetic anhydride–pyridine, and an amorphous tetraacetate **11** with acetic anhydride–boron trifluoride. Further investigation of this intermediate was frustrated by the low over-all yields involved.

Concurrent attempts to utilize the carbon atoms of the sapogenin side chain involved a study of the acid-catalyzed reactions of olefin **1a** which possibly would lead to any of a number of valuable intermediates. Although the initial studies involved pseudomerization conditions, it soon was recognized that such severe treatment was neither necessary or productive. Under relatively mild conditions the sapogenin side chain opened, affording mixtures which showed ultraviolet maxima of moderate intensity in the 250–270-mμ region. That this absorption was not due to a homoannular diene was indicated by failure to aromatize

(8) (a) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p. 25; (b) E. A. Braude and E. S. Waight, *Progr. Stereochem.*, 1, 144 (1954). A close analogy has also been noted by Dr. W. M. Hoehn of these laboratories in the spectra of 4-acetylestrone derivatives: *cf.* Abstracts, 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1958, p. 66P.

(9) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4553 (1961), and references cited there.

CHART II



the product under oxidizing or dehydrogenating conditions. The complexity of the products obtained precluded use of this direct approach.

The elimination of two molecules of water and/or hydrogen bromide from an appropriately substituted adduct of olefin **1** could lead to the formation of an intermediate homoannular diene or aromatized compound (*e.g.*, **7**). Accordingly, the known *trans* (**12c**) and *cis* glycols[3,10] were prepared as well as the dibromo derivative. Also, the bromohydrin **12a** was prepared by addition of hypobromous acid to olefin **1b**. The position of the substituents in **12a** was seen by inspection of the n.m.r. spectrum: the 18-methyl signal was a singlet at 107 c.p.s., indicative of a bromine atom at C-13. The configurations of the bromine (13β) and hydroxyl (12α) were deduced from the formation of the known α-oxide by mild base treatment of the bromohydrin. Attempts to debrominate **12a** with Raney nickel led to dehydrobromination, affording the exocyclic methylene derivative (C-18 protons at 294 and 308 c.p.s.). Catalytic reduction of this olefin led only to an amorphous alcohol (**12b**?) which could not be related to the known monoalcohols.[3,10]

(10) This oxide and its derivatives were first described by J. Elks, G. H. Phillipps, D. A. H. Taylor, and L. J. Wyman, *J. Chem. Soc.*, 1739 (1954). See also ref. 3.

Prolongation of the hypobromous acid treatment produced the *trans* glycol **12c**, identical with the product obtained from peracetic acid treatment of the olefin **1b**. A number of attempts to convert the bromohydrin, glycol, or dibromo derivatives of **1a** to a diene failed to yield a discrete product, nor were the mixtures produced oxidizable to aromatic etiojervane derivatives.

Dehydrogenation of the unsaturated ketone **13b** with palladium catalyst in refluxing cymene led to a disproportionation mixture containing the saturated ketone **13a** and the aromatic ketone **14a**[11] (structural assignment by spectral analysis) in a 1:2 ratio. The time and severity of the reaction conditions were reduced and the yield of the aromatic ketone was increased to 50% by addition of the hydrogen acceptor, cyclohexenone. The ease of the final conditions—1 hr. in refluxing xylene—is an indication of the steric strain found in the starting material. Other attempts at aromatization by direct oxidation or addition–elimination sequences were unrewarding with one exception: sulfur in refluxing cymene produced 40% of the aromatic ketone **14a** from **13b**.

The same aromatic ketone **14a** was prepared from dihydroveratramine[12] by application of the degradation of Johnson and Franck.[13] Since the initial synthesis stems from hecogenin, a correlation of the stereochemistry at carbons 8, 9, and 10 is afforded,[14,15] assuming no inversion has occurred during the mild dehydrogenation of the unsaturated ketone **13b**.

The aromatic compound ketone **14a** was oxidized to the 3-ketone **15** which in turn readily formed a 3-ketal with methanol. The unsaturated ketone **18a** was prepared by Oppenauer oxidation of the alcohol **14b**.[13] An attempt to prepare the diene **18b** by the procedure of Kalm and Dryden[16] led to a product in which the 19-methyl n.m.r. absorption had been lost, probably owing to halogenation of this group; since reductive removal of the bromine from this material failed to regenerate the tertiary methyl group, rupture of the C-9–C-10 bond is postulated to have occurred also.

Experimental Section[17]

C-Nor-D-homo-5α-spirosta-12,14,16-trien-3β-ol (2a).—The olefin **1a**[1,3] (10 g.) and 5% palladium-on-charcoal catalyst (1.0 g.) were stirred in 100 ml. of refluxing cymene for 65 hr. The mixture was filtered and the catalyst was washed with 50 ml. of hot chloroform. The combined filtrates were concentrated to

(11) An alternate synthesis of this material from rockogenin has recently been described by H. Mitsuhashi and K. Shibata, *Tetrahedron Letters*, 2281 (1964).

(12) K. Saito, *Bull. Chem. Soc. Japan*, **15**, 22 (1940).

(13) R. W. Franck and W. S. Johnson, *Tetrahedron Letters*, 545 (1963).

(14) Two recent papers have dealt with this correlation, applying in part the same reaction sequence: *cf.* R. W. Franck, G. P. Rizzi, and W. S. Johnson, *Steroids*, **4**, 465 (1964); T. Masamune, M. Takasugi, and Y. Mori, *Tetrahedron Letters*, 489 (1965).

(15) Other papers dealing with the configuration of the B–C juncture of the jervanes include D. M. Bailey, D. P. G. Hamon, and W. S. Johnson, *ibid.*, 555 (1963); S. M. Kupchan and S. D. Levine, *J. Am. Chem. Soc.*, **86**, 701 (1964).

(16) M. J. Kalm and H. L. Dryden, Jr., patent pending.

(17) We wish to thank Dr. R. T. Dillon and staff for the analytical and spectral data reported here. The infrared spectra were determined in chloroform solution, ultraviolet spectra in methanol, rotations in chloroform (1%), and n.m.r. spectra in deuteriochloroform ($\Delta\nu$ = 0 c.p.s. with tetramethylsilane as an internal standard on a Varian A-60 spectrometer). The melting points were taken on a Fischer-Johns apparatus and are uncorrected.

dryness and chromatographed.[18] The early crystalline fractions eluted with 3% ethyl acetate in benzene were combined and recrystallized from acetonitrile (Darco) to yield 1.25 g. of the aromatic sapogenin **2a**: m.p. 190–195°; λ_{max} 2.72, 6.35 (ms), 11.30 (s) μ; λ_{max} 289 mμ (log ϵ 3.64); $\Delta\nu$ 131 (18-CH_3), 388 (14-H) c.p.s.[19]

Anal. Calcd. for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.64; H, 9.53.

Subsequent fractions eluted with 3% ethyl acetate–benzene yielded 2.4 g. of starting material **1a**. Addition of nitrobenzene as hydrogen acceptor to the reaction mixture gave lower yields of **2a**.

The aromatic compound **2a** failed to be reduced with hydrogen using either rhodium or ruthenium catalysts at 100° and 1200 p.s.i.[20] The standard lithium–ammonia reaction effected reduction but, after acid hydrolysis and chromatography, afforded only intractable products.

C-Nor-D-homo-5a-spirosta-12,14,16-trien-3β-ol acetate (2b) was prepared from the alcohol **2a** in pyridine–acetic anhydride at 100° for 10 min. and purified by recrystallization from methylene chloride–methanol. The acetate **2b** had m.p. 172–175°, λ_{max} 5.78 μ, λ_{max} 289 mμ (log ϵ 3.67).

Anal. Calcd. for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 77.01; H, 8.99.

C-Nor-D-homo-5α-furosta-12,14,16,20(22)-tetraene-3β,26-diol (3a). A. By Dehydrogenation.—The dehydrogenation procedure described above for the preparation of **2a** was repeated starting with 9.5 g. of **1a** and continuing the reaction for a total of 5 days. The mixture was filtered and the catalyst was washed with hot chloroform. The combined filtrates, concentrated to half-volume and cooled, afforded 3.80 g. of the diol **3a**, m.p. 197–199°. Recrystallization from methylene chloride–methanol afforded the pure sample: m.p. 202–203°; λ_{max} 3.02, 6.32 (mw) μ; λ_{max} 216 mμ (log ϵ 4.43), 255 (4.18), 263 (4.18), 284 (3.85), 289 (3.82), 294 (3.86); $\Delta\nu$ 138 (18-CH_3), 158 (21-CH_3), 418 (14-H) c.p.s.; $[\alpha]_D$ 5°.

Anal. Calcd. for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.85; H, 9.14.

The relative amounts of the two principal products of this dehydrogenation (**2a** and **3a**) varied from run to run, apparently owing to traces of acid.

B. By Pseudomerization.—A solution of 0.10 g. of the sapogenin **2a** in 20 ml. of ethanol and 1 ml. of concentrated hydrochloric acid was boiled for 1 hr. and then was diluted with water. The resulting precipitate was separated by filtration, washed with water, and dried, yielding 0.10 g. of the pure diol **3a**, m.p. 198–200°.

C-Nor-D-homo-5a-furosta-12,14,16,20(22)-tetraene-3β,26-diol diacetate (3b), prepared from the diol **3a** with acetic anhydride–pyridine, was recrystallized from acetone–petroleum ether (b.p. 60–70°) to yield the pure diacetate, m.p. 139–140°, λ_{max} 5.76 μ.

Anal. Calcd. for $C_{31}H_{42}O_5$: C, 75.27; H, 8.56. Found: C, 75.16; H, 8.51.

C-Nor-D-homo-5α-furosta-12,14,16,20(22)-tetraene-3β,26-diol 3-Acetate (3c). A. Anhydrous Pseudomerization.—A solution of 0.10 g. of the sapogenin **2a** in 20 ml. of ether was added to 0.4 g. of aluminum chloride in 50 ml. of ether. The mixture was heated at reflux in a nitrogen atmosphere for 3 hr., cooled, and diluted by the dropwise addition of water. The product was isolated by ether extraction, yielding 0.10 g. of the pure monoacetate **3c**: m.p. 182–184°; λ_{max} 2.74, 5.78 μ.

Anal. Calcd. for $C_{29}H_{40}O_4$: C, 76.96; H, 8.91. Found: C, 77.16; H, 9.09.

B. Alumina Hydrolysis.[4]—A solution of 23 g. of the diacetate **3b** in benzene was adsorbed on 600 g. of alumina (Merck Chromatographic grade). After 3.5 days the column was eluted with 5% ethyl acetate–benzene, affording 4.6 g. of starting material **3b**. Later fractions, weighing 15 g., were combined and recrystallized from acetone to yield 9.7 g. of the monoacetate **3c**, m.p. 181–182°.

Catalytic Disproportionation of Olefin 1b.—A mixture of the olefin acetate **1b** (5.0 g.) and 5% palladium-on-charcoal catalyst (3.0 g.) was heated in a carbon dioxide atmosphere. The mixture evolved hydrogen gas at 180° and was held at this temperature for 1 hr. The product was extracted with methylene chloride and crystallized from acetonitrile. The resulting crystals (0.85 g.) were recrystallized from methylene chloride–methanol to yield 0.48 g. of the saturated acetate **1c**, m.p. 176–181°.[1] Chromatography[18] of the mother liquors afforded fractions (eluted with benzene) which were recrystallized to yield 1.15 g. of the aromatic compound **2b**, m.p. 166–168°. Closely following this material were fractions which provided an additional 0.25 g. of the saturated acetate **1c** as well as 0.9 g. of a mixture of **1c** and **2b**.

Sulfur Dehydrogenation of Olefin 1b.—An intimate mixture of 142 g. of the acetate **1b** and 20.0 g. of sulfur in a flask was heated in an oil bath at 185–210° for 3 hr. A solution of the resulting clear yellow glass in 3.3 l. of 2B ethanol was consecutively filtered, acidified with 190 ml. of concentrated hydrochloric acid, boiled for 2 hr., distilled to half-volume, and diluted with water. The resulting precipitate was collected by filtration, yielding 71.5 g. (55%) of diol **3a**, m.p. 198–200°.

Omission of the acid hydrolysis in favor of direct chromatography of the crude product afforded varying amounts of the aromatic compounds (**2b**, **3c**) as the readily separable 3-acetates.

As the relative amount of sulfur was increased, a new component was indicated by signals (141, 152 c.p.s.) in the n.m.r. spectrum and an altered ultraviolet spectrum [λ_{max} 285 mμ (log ϵ 4.25)]. Isolation of a pure sample of this compound was not achieved.

Direct oxidation of the olefin **1b** with chromic acid, selenium dioxide, dichlorodicyanoquinone, or N-bromodimethylhydantoin afforded no useful products. The last gave an unstable adduct with bromotrichloromethane as indicated by elemental analysis.

C-Nor-D-homo-26-nor-5α-furosta-12,14,16,20(22)-tetraen-3β-ol (5a).—A solution of 24 g. of the acetate **1b** in 300 ml. of cymene was stirred at reflux with 10 g. of 5% palladium-on-charcoal catalyst for 5 days. The solution was filtered and concentrated to dryness. An aliquot (1 g.) was chromatographed.[18] Fractions eluted with 100% benzene were combined and recrystallized from acetonitrile to yield 0.25 g. of crystals, m.p. 149–153°, and then from methylene chloride–methanol to yield 0.20 g. of **C-nor-D-homo-26-nor-5α-furosta-12,14,16,20(22)-tetraen-3β-ol acetate (5a acetate)**: m.p. 153–155°; λ_{max} 255 mμ (log ϵ 4.18), 263 (4.18), 283 (3.79), 289 (3.76), 294 (3.81).

Anal. Calcd. for $C_{28}H_{38}O_3$: C, 79.58; H, 9.06. Found: C, 79.76; H, 9.11.

The bulk of the dehydrogenation product (20 g.) was boiled in 200 ml. of ethanol and 10 ml. of concentrated hydrochloric acid for 4 hr. The ethanol was distilled and the resulting mixture, diluted with water, was extracted with chloroform. The product, which crystallized on trituration with ether, was recrystallized from methylene chloride–acetone to afford 0.48 g. of the diol **3a**, m.p. 194–197°. Chromatography[18] of the mother liquors yielded fractions (4.5 g., eluted with benzene) which were recrystallized from petroleum ether to yield 1.0 g. of **C-nor-D-homo-19,26-dinorfurosta-1,3,5(10),6,8,12,14,16,20(22)-nonaene (4)**: m.p. 141–143°; λ_{max} 6.15, 12.39 (s), 13.49 (s) μ; λ_{max} 243 mμ (log ϵ 4.60), 273 (4.45), 282 (4.35), 316 (4.61), 331 (4.67); $\Delta\nu$ 56 and 62 (25-CH_3), 132 (18-CH_3), 148 (21-CH_3), 224 (11-H_2) c.p.s., as well as seven aromatic protons at 430–455 c.p.s.

Anal. Calcd. for $C_{27}H_{26}O$: C, 88.48; H, 7.15. Found: C, 88.25; H, 7.12.

Fractions eluted with 5% ethyl acetate–benzene were recrystallized from methylene chloride–methanol to yield 7.4 g. of the benzofuran **5a**: m.p. 139–140°; λ_{max} 2.75 μ; $\Delta\nu$ 55 and 60 (19- and 26-CH_3), 135 (18-CH_3), 148 (21-CH_3), 412 (14-H) c.p.s.; $[\alpha]_D$ −6°.

Anal. Calcd. for $C_{26}H_{30}O_2$: C, 82.06; H, 9.54. Found: C, 82.06; H, 9.84.

Fractions eluted with 10% ethyl acetate–benzene were combined and crystallized from methanol to yield 0.15 g. of the saturated alcohol **1d**.[1] More polar eluents brought small additional amounts of the diol **3a**.

C-Nor-D-homo-26-nor-5α-furosta-12,14,16,20(22)-tetraen-3β-ol benzoate (5a benzoate), prepared with benzoyl chloride–pyridine at 100°, was recrystallized from 2-propanol and had m.p. 145–146°, λ_{max} 5.82 μ.

Anal. Calcd. for $C_{33}H_{40}O_3$: C, 81.78; H, 8.32. Found: C, 81.80; H, 8.29.

C-Nor-D-homo-5α-furosta-12,14,16,20(22)-tetraene-3β,26-diol 3-Acetate 26-Tosylate (3d).—A solution of 0.85 g. of the monoacetate **3c** and 0.60 g. of *p*-toluenesulfonyl chloride in 20 ml. of

(18) We are grateful to Dr. E. G. Daskalakis and staff for the chromatographies reported. These were run on a weight of silica gel 60 times that of the material being chromatographed.

(19) We wish to acknowledge several informative discussions with Dr. R. H. Bible, Jr., of these laboratories, pertaining to the interpretation of some of the n.m.r. spectra presented here.

(20) Mr. W. M. Selby and staff kindly performed all hydrogenations described herein.

pyridine was allowed to stand at 5° for 19 hr. The solution was then stirred with excess aqueous potassium bicarbonate solution for 10 min., and the product was isolated by benzene extraction. Chromatography[18] of this material provided fractions (at 2% ethyl acetate in benzene) which afforded 0.68 g. of the tosylate **3d**, m.p. 132–134°, on recrystallization from methylene chloride–methanol.

Anal. Calcd. for $C_{36}H_{46}O_6S$: C, 71.25; H, 7.64. Found: C, 71.42; H, 7.67.

The methylene derivative **5d** was not isolable when the tosylate **3d** was boiled in collidine or treated with potassium *t*-butoxide in dimethyl sulfoxide.

Degradation of the Tosylate 3d.—The tosylate **3d** (2.9 g.) and 3 g. of sodium bicarbonate were heated in 30 ml. of dimethyl sulfoxide at 150–155° for 2 min. with stirring.[5] The mixture was cooled quickly, diluted with water, and extracted with methylene chloride, yielding 2.3 g. of the aldehyde mixture **5b**: λ_{max} 3.66 μ, $\Delta\nu$ 576 c.p.s.

To a solution of 2.1 g. of the crude aldehyde **5b** in 100 ml. of *t*-butyl alcohol at 5° was added 3 g. of potassium *t*-butoxide powder with stirring in an atmosphere of nitrogen. A solution of 5 ml. of isoamyl nitrite in 15 ml. of *t*-butyl alcohol was added over 10 min. After 18 hr. at 5° and 2 hr. at room temperature the reaction was poured into aqueous hydrochloric acid. The product was extracted with methylene chloride, yielding 2.1 g. of a dark foam. The amorphous oxime **5c** (0.70 g.) was obtained by chromatography[18] (eluted with 20% ethyl acetate–benzene) and exhibited $\Delta\nu$ 128 (27-CH_3), 138 (18-CH_3), and 149 (21-CH_3) c.p.s.

A solution of 0.55 g. of the crude oxime **5c**, 2 g. of potassium hydroxide, and 3 ml. of hydrazine hydrate in 50 ml. of diethylene glycol was heated with stirring in an atmosphere of nitrogen. After 30 min. at 100–110° and 2 hr. at 190–195° (allowing the water to distil) the solution was cooled and diluted with 5% hydrochloric acid. The product was isolated by benzene extraction and was chromatographed. Fractions (0.10 g.) eluted with 2% ethyl acetate–benzene were combined and recrystallized to give 40 mg. of the pure norfurostenol **5a**.

Wolff–Kishner Reduction of Pregnenolone Oxime.—A solution of 0.5 g. of the oxime of 3-hydroxypregn-5-en-20-one and 2 g. of potassium hydroxide in 50 ml. of diethylene glycol and 3 ml. of hydrazine hydrate was treated as described in the preceding experiment. The reaction mixture, cooled and diluted with water, afforded a precipitate which was collected and washed on a filter. Recrystallization of this material from aqueous acetone afforded 0.35 g. of 5-pregnen-3β-ol, m.p. 125–128°, identical with an authentic sample[6] by comparison of infrared spectra.

17-Acetyletiojerva-12,14,16-triene-3β,16-diol (9a). A. Ozonolysis.—A stream of oxygen containing 1 mole equiv. of ozone was passed through a solution of 1.0 g. of the hydroxy compound **3a** in 80 ml. of methylene chloride and 15 ml. of methanol at −70°. Zinc dust (1 g.) and 1 ml. of acetic acid were then added to the solution and the resulting mixture was stirred in an ice bath for 15 min. The mixture was filtered, and the filtrate was washed with water and aqueous bicarbonate solution. An aliquot (0.37 g.) of the total product (0.95 g.), obtained by distillation of the solvent, was dissolved in 15 ml. of methanol and 2 ml. of 10% aqueous hydrochloric acid. The solution was boiled for 1 hr., cooled, and diluted with water, providing 0.24 g. of crystals, m.p. 100–105°. Recrystallization of the product from methanol gave the phenol **9a**: m.p. 108–110°, 192–194°; λ_{max} 2.74, 6.13 μ; λ_{max} 263 mμ (log ϵ 3.62), 305 (3.38); $\Delta\nu$ 146 (18-CH_3), 157 (21-CH_3), 396 (14-H), 735 (16-OH) c.p.s.; $[\alpha]_D$ 31°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.15, 76.46; H, 8.59, 8.48.

Similarly, 0.82 g. of the alcohol **5a**, ozonized, hydrolyzed, and purified gave 0.25 g. of phenol **9a**, m.p. 107–109°, 192–194°.

An analogous ozonolysis of the 3-benzoate of **5a** gave **17-acetyletiojerva-12,14,16-triene-3β,16-diol 3-benzoate** (**9b**), recrystallized from methylene chloride–methanol to yield the pure sample: m.p. 158–160°; λ_{max} 5.82, 6.12 μ.

Anal. Calcd. for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46. Found: C, 77.50; H, 7.33.

The acetate of **9b** was an amorphous material showing n.m.r. signals at 134 (18-CH_3) and 146 (21-CH_3) c.p.s.

The diethyl phosphite ester of **9a** [$\Delta\nu$ 147 (18-CH_3), 157 (21-CH_3) c.p.s.] was prepared in the normal manner; lithium–ammonia reduction of this molecule was accompanied by removal of the 20-oxygen function, however. Introduction of an 11-acetoxyl group into **9a** with lead tetraacetate was unsuccessful.

B. Chromic Acid Oxidation.—Chromic anhydride (10.5 g., 1.1 mole equiv.) in 20 ml. of water and 80 ml. of acetic acid was added over a period of 1 hr. to a solution of 35 g. of the diacetate **3b** and 7.0 g. of sodium acetate in 70 ml. of chloroform and 350 ml. of acetic acid at 10°. The mixture was stirred at this temperature for 1 hr. more and at ambient temperature for 2 hr. The reaction was then cooled, and 1.4 g. of sodium bisulfite dissolved in 15 ml. of water was added over a 10-min. period. A solution of the product (43 g.), isolated by ether extraction, and 45 g. of potassium hydroxide in 50 ml. of water and 350 ml. of methanol was boiled under an atmosphere of nitrogen. After 3 hr. the product (19.1 g.) was isolated by methylene chloride extraction and was chromatographed.[18] The fractions (12.0 g.) eluted with 12% ethyl acetate–benzene were recrystallized from methanol to yield 9.1 g. of the phenol **9a**, m.p. 98–103°, identical spectrally with the sample obtained above. Later fractions in the chromatogram showed appreciable amounts of unoxidized diol **3a**.

Attempts to form a 20,22 epoxide or glycol derivative of **3b** by use of perbenzoic acid or osmium tetroxide yielded no homogeneous material.

17-Acetyletiojerva-12,14,16-triene-3β,16-diol 16-Methyl Ether (**9c**).—A mixture of 0.20 g. of the phenol **9a** and 1 g. of anhydrous potassium carbonate in 10 ml. of 2B ethanol and 3 ml. of methyl iodide was stirred at the reflux temperature for 3 hr. Half the solvent was distilled and the remaining mixture was diluted with water. The resulting precipitate (0.19 g., m.p. 164–166°) was collected on a filter, dried, and recrystallized from ether–petroleum ether leading to the pure ether **9c** with unchanged melting point: λ_{max} 2.74, 5.86 μ; λ_{max} 260 mμ (log ϵ 3.44), 287 (3.44); $\Delta\nu$ 127 (18-CH_3), 147 (21-CH_3), 227 (OCH_3) c.p.s.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.16; H, 9.07.

17-Acetyletiojerva-12,14,16-triene-3β,16-diol 16-methyl ether 3-acetate (**9d**) was an amorphous solid prepared by acetylation of **9c** with pyridine–acetic anhydride at 100°.

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.36.

Attempted oxidation of the benzylic carbon (11) of **9d** with chromic acid gave mixtures of acidic products and starting material.

17-Acetyletiojerva-12,14,16-trien-16-ol-3-one 16-Methyl Ether.—To a solution of 0.82 g. of the methyl ether **9c** in 80 ml. of acetone at 10°, was added 2.0 ml. of 4 *N* chromic acid[21] over a 5-min. period. After 15 min. the solution was diluted with 2-propanol (1 ml.) and water. The product, isolated by extraction with ethyl acetate, was recrystallized twice from acetone–petroleum ether to give 0.56 g. of the pure 3-ketone: m.p. 148–150°; λ_{max} 5.83, 6.23 μ; λ_{max} 259 mμ (log ϵ 3.44), 288 (3.44); $[\alpha]_D$ 62°.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.49; H, 8.07.

Wolff–Kishner Reduction of the Ether 9c.—Hydrazine monohydrate (0.9 ml.) and 1.88 g. of the methyl ether **9c** were added to a solution of 1.1 g. of potassium hydroxide pellets in 10 ml. of diethylene glycol. The solution was heated at 140–150° for 1.5 hr., and at 190° for an additional 3.5 hr. The reaction mixture was cooled, poured into 100 ml. of dilute cold hydrochloric acid solution, and extracted with ether to give 1.52 g. of crude solid. Chromatography[18] of this material gave fractions, eluted with 5% ethyl acetate in benzene, which were combined and recrystallized from acetone–petroleum ether to yield **17-ethyletiojerva-12,14,16-triene-3β,16-diol 16-methyl ether** (**8b**): m.p. 138–139°; λ_{max} 2.75, 6.24, 6.31 μ; λ_{max} 279 mμ (log ϵ 3.53), 284 (3.52); $\Delta\nu$ 132 (18-CH_3), 228 (OCH_3), 394 (14-H) c.p.s.; $[\alpha]_D$ 28°.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.57; H, 9.87.

Further elution with 5% ethyl acetate in benzene furnished **17-ethyletiojerva-12,14,16-triene-3β,16-diol** (**8a**), which was recrystallized from methanol to give the analytically pure sample: m.p. 123–126°; λ_{max} 2.75, 6.23, 6.30 μ; λ_{max} 2.85 mμ (log ϵ 3.70); $\Delta\nu$ 132 (18-CH_3), 388 (14-H) c.p.s.; $[\alpha]_D$ 35°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.22; H, 9.38.

(21) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

The ether **8b** was also obtained (20% yield) as the only crystalline product from the lithium–ammonia reduction of **9c**.

C-Nor-D-homo-5α,20β-furosta-12,14,16-triene-3β,26-diol (6a).—A solution of 0.45 g. of the diacetate **3b** in 50 ml. of acetic acid and 0.30 g. of platinum oxide were stirred in an atmosphere of hydrogen. After 26 hr. the theoretical amount of hydrogen had been absorbed. The mixture was filtered and the filtrate was concentrated to dryness. Chromatography[18] of the product failed to yield a crystalline material. The center fractions (0.30 g., eluted with 3% ethyl acetate in benzene), were boiled in 30 ml. of methanol containing 5 ml. of 10% aqueous potassium hydroxide for 2 hr. The solution was cooled and diluted with water. The resulting precipitate was separated by filtration and was recrystallized from acetone, yielding 0.17 g. of the dihydro derivative **6a**: m.p. 202–208°; λ_{max} 2.72 μ; λ_{max} 289 mμ (log ε 3.68); Δν 385 (14-H) c.p.s.; $[\alpha]_D$ 7°.

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.43; H, 9.87.

Attempted hydrogenation of **3b** over palladium catalyst led to no reaction. However, lithium–ammonia (see below) or lithium–propylamine reduction led to mixtures from which 30% of the dihydro compound **6a** could be obtained. The remainder of the product presumably contained the stereoisomer **6b** (as judged from the similarity of the ultraviolet and infrared spectra to those of the crystalline material). No unsaturated ketone component was produced after acid hydrolysis even though vigorous reduction conditions had been used.

Hydrogenation of the aromatic sapogenin **2b** with platinum in acetic acid was complete in 6 hr. The product was saponified and was identical in the infrared and ultraviolet with the noncrystalline material (**6b**) obtained from the lithium–ammonia reduction of **3a**. The material failed to crystallize even after chromatography.

Attempted cleavage of the furan ring with hydrochloric acid, pyridine hydrochloride, boron trifluoride, or alcoholic potassium hydroxide (at 200°) failed to give tractable products.

C-Nor-D-homo-26-nor-5α-furosta-12,14,16-trien-3β-ol (6c).—A solution of 1.0 g. of the alcohol **5a** in 50 ml. of tetrahydrofuran was added with stirring to 150 ml. of ammonia containing 50 ml. of *t*-butyl alcohol and 2 g. of lithium wire. After 4 hr. the solution had become colorless. The ammonia was distilled, the mixture was diluted with water, and the product was isolated by extraction with benzene. The residue (1.1 g.) on chromatography[18] yielded the amorphous product, eluted with 1% ethyl acetate–benzene: λ_{max} 2.75, 6.25 μ; λ_{max} 290 mμ (log ε 3.69).

Anal. Calcd. for $C_{27}H_{40}O_2$: C, 81.76; H, 10.17. Found: C, 81.63; H, 9.90.

Reduction of alcohol **5a** with platinum in acetic acid afforded a spectrally similar amorphous product. The stability of the dihydrofuran ring in **6c** was the same as that of the 26-hydroxy analog **6a**.

C-Nor-D-homo-cholesta-12,14,16-triene-3,16,22,26-tetraol 22,26-Ether (10a).—A solution of 3.0 g. of the aromatic sapogenin **2a** in 80 ml. of ether was added over a 10-min. period to a solution of 0.8 g. of lithium aluminum hydride and 3.2 g. of aluminum chloride in 50 ml. of ether. The mixture was stirred at reflux temperature for 2 hr. and then was treated consecutively with ethyl acetate (dropwise), water, and excess dilute hydrochloric acid. The product (3.2 g.) was isolated by ether extraction and was chromatographed.[18] Fractions eluted with 3% ethyl acetate–benzene yielded 2.7 g. of the amorphous ether **10a**: λ_{max} 2.73, 3.11 μ; λ_{max} 287 mμ (log ε 3.54); Δν 130 (18-CH_3) c.p.s.

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.80; H, 9.57.

The phenol gave a strong positive Folin–Denis test for phenols, but formed no phenylhydrazone derivative. Methyl iodide–potassium carbonate in ethanol produced an amorphous phenol ether (226 c.p.s.).

C-Nor-D-homo-cholesta-12,14,16-triene-3,16,22,26-tetraol Tetraacetate (11).—To a mixture of 0.75 g. of the ether **10a** in 10 ml. of acetic anhydride at 5° was added 0.5 ml. of boron trifluoride etherate. After 30 min. at 5° and 1.5 hr. at ambient temperature, the solution was poured into iced aqueous potassium bicarbonate, and the product was isolated by benzene extraction. Chromatography[18] of the residue (1.05 g.) provided 0.16 g. of the amorphous diacetate **10b**: λ_{max} 5.75 μ. This product was identical with that obtained by direct pyridine–acetic anhydride treatment of the diol **10a**.

Anal. Calcd. for $C_{31}H_{44}O_5$: C, 74.96; H, 8.93. Found: C, 74.72; H, 9.23.

Continued elution of the column with 10% ethyl acetate–benzene yielded fractions containing 0.25 g. of the amorphous tetraacetate **11**: λ_{max} 5.76 μ.

Anal. Calcd. for $C_{35}H_{50}O_8$: C, 70.20; H, 8.42. Found: C, 70.26; H, 8.40.

Acid-Catalyzed Isomerization of Olefin 1b.—A solution of 2.0 g. of the olefin **1b** and 0.9 g. of *p*-toluenesulfonic acid in 25 ml. of acetic anhydride was heated at 90° for 35 min. The solution was cooled to 50° and was diluted slowly with water. The product (2.1 g.), isolated by extraction with benzene, showed an ultraviolet maximum at 272 mμ (log ε 3.80). Chromatography of this substance led to separation of an amorphous material: λ_{max} 5.77, 6.00 (m) μ; λ_{max} 272 mμ (log ε 3.94).

Anal. Calcd. for $C_{33}H_{48}O_6$: C, 73.30; H, 8.95. Found: C, 73.54; H, 8.71.

A variety of other acidic reagents afforded similar results. Oxidation of these materials with chromium trioxide–pyridine caused no change in the ultraviolet spectrum.

13β-Bromo-C-nor-D-homo-5α-spirostan-3β,12α-diol (12a).—Aqueous 1 *N* perchloric acid (52 ml.) was added to a solution of 8.4 g. of the olefin **1b** and 3.2 g. of N-bromosuccinimide in 300 ml. of *t*-butyl alcohol and 40 ml. of water at 15° with stirring. Another 0.8 g. of N-bromosuccinimide was added after the solution gave a negative starch–iodide test (5 min.). After a total of 15 min. the solution was diluted with water and the product was extracted with benzene. A portion (2.3 g.) of the crystalline residue (11.7 g.) was recrystallized quickly from ether–methanol to yield 0.68 g. of the pure bromohydrin **12a**: m.p. 143–146° dec.; λ_{max} 2.75, 5.78 μ; Δν 41 and 48 (27-CH_3), 47 (19-CH_3), 63 and 68 (21-CH_3), 107 (18-CH_3) c.p.s.; $[\alpha]_D$ −33°.

Anal. Calcd. for $C_{29}H_{45}BrO_5$: C, 62.92; H, 8.19; Br, 14.44. Found: C, 62.68; H, 7.96; Br, 14.37.

Chromatography of 0.5 g. of the crystalline bromohydrin on Florex gave a small amount of the known oxide **12d**.[3,10] (The same oxide was also formed in good yield by allowing a pyridine solution of the bromohydrin to stand at room temperature for 4 hr.)

Elution with 2% ethyl acetate–benzene afforded material, recrystallized from methanol to yield 0.12 g. of the glycol **12c**, m.p. 217–223°, spectrally identical with the material prepared below.

C-Nor-D-homo-5α-spirost-13(18)-ene-3β,12α-diol 3-Acetate.—A solution of 0.35 g. of the bromohydrin **12a** in 20 ml. of 3A ethanol was stirred with 1 teaspoon of Raney nickel (freshly washed with dilute acetic acid and then with water) at room temperature for 2 hr. and at the reflux point for 1 hr. The solution was filtered and the filtrate was diluted with water. The resulting precipitate was collected on a filter, dried, and recrystallized from aqueous methanol to yield 0.13 g. of the diol, m.p. 160–165°. Recrystallization from ether–petroleum ether gave the pure material: m.p. 215–217°; λ_{max} 2.75, 5.76 μ; Δν 41 and 49 (27-CH_3), 47 (19-CH_3), 62 and 68 (21-CH_3), 294 and 308 (18 CH_2=) c.p.s.; $[\alpha]_D$ −33°.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.24; H, 9.39.

Hydrogenation of this compound afforded an amorphous material (**12b**) which could not be related to the known oxide reduction products described in the literature.[3,10]

Dehydrohalogenation of the Bromohydrin 12a.—A solution of 1.85 g. of the bromohydrin **12a** in 40 ml. of xylene was added slowly to 200 ml. of refluxing xylene resulting in the immediate evolution of hydrogen bromide. The solution was distilled slowly for 28 hr. and then was concentrated to dryness. The crude product (1.75 g.) showed a maximum at 258 mμ (log ε 3.87). An aliquot (0.60 g.) of the residue was chromatographed. Fractions eluted with 1% ethyl acetate in benzene were combined to yield one component: λ_{max} 2.75, 5.78 μ; λ_{max} 258 mμ (log ε 3.54). The n.m.r. spectrum showed no clear aromatic proton absorption.

Anal. Calcd. for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.43; H, 9.55.

Oxidation of this substance with chromium trioxide–pyridine or dehydrogenation with palladium on carbon in acetic acid failed to effect a change.

Similar materials were obtained from the bromohydrin on treatment with mineral acid–methanol, thionyl chloride in pyridine, or chromatography on silica.

C-Nor-D-homo-5α-spirostan-3β,12α,13β-triol 3-Acetate (12c).

—The olefin acetate **1b** (4.3 g.) was treated in the same manner as in formation of the bromohydrin **12a**. After 4 days the reaction was worked up and the product (3.8 g.) was chromatographed. The fractions eluted with 8% ethyl acetate in benzene were combined and recrystallized from methanol, giving 1.04 g. of crystals, m.p. 212–215°. Further recrystallization from methanol gave the pure diol **12c**: m.p. 221–224°; λ_{max} 2.72, 5.78 μ.

Anal. Calcd. for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found: C, 71.22; H, 9.17.

Fractions eluted with 20 and 40% ethyl acetate–benzene were combined and triturated with ether. The crystalline material which separated was recrystallized from acetone–petroleum ether to yield 80 mg. of **C-nor-D-homo-5a-spirostan-3β,12α,13β-triol**, m.p. 262–265°, λ_{max} 2.72 μ.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 72.22; H, 10.01.

The same triol was prepared by saponification of the 3-monoacetate **12c** or alternatively by treatment of the olefin **1b** with peracetic acid and subsequent reduction of the amorphous product with ethereal lithium aluminum hydride at room temperature.

Treatment of the *trans* glycol **12c** or the known *cis* glycol[10] with acidic reagents or with thionyl chloride gave complex mixtures of amorphous compounds similar to those obtained from the bromohydrin. Similar results were obtained from reaction of the olefin **1b** dibromide with collidine.

17-Acetyletiojerva-12,14,16-trien-3β-ol (14a). A. Palladium–Cyclohexenone Dehydrogenation.—17-Acetyletiojerv-16-en-3β-ol acetate[1] (5.0 g., **13b** acetate), cyclohexenone (5 ml., technical), and 30% palladium-on-carbon catalyst (1.0 g.) in 50 ml. of xylene were heated at reflux with stirring for 2 hr. (Later results indicated that a 1-hr. period was sufficient for complete reaction.) The mixture was cooled and filtered. The filtrate yielded a residue on concentration, shown by its n.m.r. spectrum to contain mainly the aromatic ketone (–$COCH_3$, 145 c.p.s.) and about 10% of the saturated ketone (127 c.p.s.); no starting material was apparent (no signal at 138 c.p.s.). The mixture was chromatographed.[18] The amorphous material (5.3 g.) contained in the fractions eluted with 2 and 5% ethyl acetate–benzene was saponified in 100 ml. of methanol and 10 ml. of 10% aqueous potassium hydroxide at reflux for 1 hr. The product (3.0 g.) was precipitated by dilution with aqueous acetic acid and was recrystallized from acetone to afford 1.98 g. of the pure aromatic ketone **14a**: m.p. 176–178°; λ_{max} 2.73, 5.93 μ; λ_{max} 258 mμ (log ϵ 4.10); $\Delta\nu$ 145 (18-CH_3), 153 (21-CH_3), 418, 425, 449, 457 (14,15-H_2) c.p.s.; $[\alpha]_D$ 39°.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.97; H, 9.14.

A second crop of 0.45 g. of the ketone **14a**, m.p. 174–177°, was also obtained. Chromatography[18] of the mother liquors afforded material, eluted with 5% ethyl acetate–benzene, which consisted of 0.92 g. of a 2:1 mixture of aromatic (**14a**) and saturated (**13a**) ketones, m.p. 126–130° (analysis by n.m.r.).

A similar dehydrogenation of the 3-hydroxy derivative afforded by direct crystallization 40% of the aromatic ketone **14a**. The mother liquors consisted of a mixture of approximately equal amounts of the saturated (**13a**) and aromatic ketones (**14a**) from which the former was obtained in a pure state by chromatography and fractional crystallization.

B. Palladium Dehydrogenation.—The unsaturated ketone **13b** (1.0 g.) and 1.0 g. of 30% palladium-on-carbon catalyst in 40 ml. of xylene were stirred at reflux for 26 hr. The crude product, as analyzed by n.m.r. spectroscopy, was a 2:1 mixture of aromatic and saturated ketones. In earlier experiments in which refluxing cymene was used as solvent, the reaction was complete within 3 hr. The product composition was essentially the same (2:1 **13a**:**14a**).

C. Sulfur Dehydrogenation.—Sulfur (2.3 g.) and 2.3 g. of the unsaturated ketone **13b** acetate were boiled in 80 ml. of cymene for 48 hr. (12 hr. was shown later to be sufficient). The cymene was distilled *in vacuo* and the residue was chromatographed.[18] The material eluted with 5% ethyl acetate in benzene was saponified in aqueous methanol, as described above, yielding 0.88 g. of the aromatic ketone **14a**, m.p. 162–166°, by recrystallization of the product from acetone–petroleum ether.

D. Other Aromatization Attempts.—Neither the desired aromatic ketone **14a** nor any other homogeneous products were produced by treatment of the unsaturated ketone **13a** with dichlorodicyanobenzoquinone, 30% palladium-on-carbon catalyst–benzoquinone, cupric chloride–lithium chloride in dimethylformamide, or N-bromosuccinimide. The last of these caused substitution at C-21 as indicated by the disappearance of the acetyl absorption in the n.m.r. spectrum. Dehydrobromination of the 16,17-dibromide of **13a** with magnesium oxide in refluxing dimethylformamide yielded no discrete products.

Degradation of Dihydroveratramine.—The procedure of Johnson and Franck,[13] described for veratramine (**16b**), was applied to dihydroveratramine (**16a**) without essential modification. A solution of 0.80 g. of dihydroveratramine,[12] m.p. 168–172°, and 0.27 g. of N-chlorosuccinimide in 200 ml. of ether was stirred at room temperature. After 20 min., the solution was concentrated under reduced pressure (temperature less than 30°). The residue was treated with 60 ml. of methanol in which had been dissolved 1 g. of sodium. After 1.5 hr. at room temperature, the solution was boiled for 1 hr., cooled, diluted with excess aqueous hydrochloric acid, and stirred at room temperature for 20 min. The solution was diluted with water and extracted with ether yielding 0.74 g. of a foam (aldehyde proton at 585 c.p.s.). Chromatography failed to yield a crystalline sample of the aldehyde **17**. A solution of 0.46 g. of the crude aldehyde **17** in 20 ml. of *n*-butyl alcohol at 5° under nitrogen was mixed with 10 ml. of *t*-butyl alcohol containing 0.5 g. of potassium *t*-butoxide. To the stirred solution was added 2 ml. of isoamyl nitrite. After 20 hr. at 5° the solution was poured into aqueous hydrochloric acid and the product was extracted with benzene. That partial hydrolysis of the oxime had occurred was shown by a 5.93-μ band of medium intensity in the infrared spectrum. The material was crystallized from ether–petroleum ether to yield a sample of **14a** identical in the infrared and n.m.r. with ketone **14a** as obtained by direct dehydrogenation of the unsaturated ketone **13a**.

17-Acetyletiojerva-12,14,16-trien-3-one (15).—Chromic acid solution[21] (3 ml., 4 *N*) was added to 1.63 g. of the hydroxy compound **14a** in 100 ml. of acetone at 5° over a 5-min. period. The solution was diluted with water and a little methanol. The resulting precipitate was filtered, yielding 1.58 g. of solvated crystals, m.p. 143–145°. Recrystallization from acetone–petroleum ether gave an unsolvated form: m.p. 136–138°; λ_{max} 5.85, 5.92 μ; λ_{max} 258 mμ (log ϵ 4.09); $[\alpha]_D$ 86°.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.26; H, 8.41.

17-Acetyletiojerva-12,14,16-trien-3-one 3,3-Dimethyl Ketal (15 Ketal).—To a slurry of 0.90 g. of the ketone **15** in 10 ml. of methanol was added 50 mg. of *p*-toluenesulfonic acid. The crystals dissolved quickly and a new material precipitated within 5 min. After a total of 10 min. the mixture was diluted with aqueous potassium bicarbonate and filtered, yielding 0.93 g. of crystals. Recrystallization of this material from methanol containing a trace of pyridine afforded 0.77 g. of the pure ketal: m.p. 128–130°; λ_{max} 5.94 μ; $\Delta\nu$ 188 and 192 (OCH_3) c.p.s.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.54; H, 9.18.

17-Acetyletiojerva-4,12,14,16-tetraen-3-one (18a).—A stirred, boiling solution of 0.75 g. of the unsaturated alcohol **14b**[13] in 80 ml. of toluene and 5 ml. of cyclohexanone (freshly redistilled) under nitrogen was treated over a 5-min. period with a solution of 1.0 g. of aluminum isopropoxide in 20 ml. of toluene. After an additional 15-min. reflux period the solution was cooled, diluted with Rochelle salt solution, and steam distilled for 1 hr. The mixture was extracted with benzene, yielding 0.80 g. of residue. The unsaturated ketone **18a**, obtained by chromatography[18] of this material, was eluted with 5% ethyl acetate in benzene and recrystallized from acetone–petroleum ether to yield the pure sample: m.p. 168–172°; λ_{max} 5.94 μ; λ_{max} 246 mμ (log ϵ 4.35); $[\alpha]_D$ 127°.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.58; H, 7.75.

An attempt to transform the unsaturated alcohol **14b** into the 4,6-diene **18b** by the procedure of Kalm[16] resulted in loss of the C-19 methyl group absorption in the n.m.r. spectrum. Removal of residual bromine by zinc–acetic acid treatment failed to regenerate the tertiary methyl group, implying ring cleavage had occurred, presumably at C-9–C-10.