TABLE III

ULTRAVIOLET ABSORPTION DATA OF SEVERAL FUSED *s*-TRIAZOLE SYSTEMS

	Solvent[a]	λ_{max}, mμ (log ε)							
3-Methyl-*s*-triazolo[4,3-*a*]pyridine	E	209 (4.38)	244 (sh) (3.14)	249 (sh) (3.26)	252 (sh) (3.30)	258 (3.39)	262 (3.41)	268 (3.47)	288 (3.47)
2-Methyl-*s*-triazolo[2,3-*a*]pyridine	C	217.5 (4.58)					273 (3.57)	281 (i) (3.52)	294 (i) (3.20)
s-Triazolo[4,3-*a*]pyrimidine	E	209 (4.04)	213 (sh) (3.98)				250 (3.20)	266 (sh) (3.08)	298 (3.31)
s-Triazolo[2,3-*a*]pyrimidine	E	208 (4.50)							273 (3.56)
s-Triazolo[4,3-*b*]pyridazine[c]	*b*			240 (4.22)					305 (3.81)
3-Phenyl-*s*-triazolo[4,3-*a*]pyridine	C		221 (4.23)	243 (4.16)				287.5 (3.97)	
2-Phenyl-*s*-triazolo[2,3-*a*]pyridine	C		244.5 (4.56)	252.5 (4.56)			281 (i) (3.88)	292.5 (i) (3.73)	306 (3.58)

[a] E = 95% ethanol; C = cyclohexane. [b] Solvent not given. [c] S. Takahayashi, *J. Pharm. Soc. Japan*, **76**, 765, 1296 (1956).

B. Trichloroacetonitrile.—A mixture of the amine (0.62 g., 0.005 mole), aluminum chloride (0.8 g., 0.006 mole), and trichloroacetonitrile (3 ml.) was heated in a sealed tube at 180° for 5 hr. Extraction of the resulting solid material with ethanol gave a colorless, crystalline product (0.91 g.) which separated from aqueous ethanol as colorless needles, m.p. 91–92°. This product was identified as 2,4,6-tri(trichloromethyl)-*s*-triazine (lit.[12] m.p. 91–92°) by no depression in the mixture melting point and by identical infrared spectra.

Anal. Calcd. for $C_6N_3Cl_9$: Cl, 16.6; N, 9.7. Found: Cl, 16.8; N, 9.4.

It was not possible to isolate any further products from the reaction mixture.

Attempted Reaction of 2-Amino-3,6-dimethylpyrazine with Ethyl Acetimidate Hydrochloride.—A mixture of the amine (0.6 g., 0.005 mole), ethyl acetimidate hydrochloride[13] (0.6 g., 0.005 mole), and ether was heated under reflux for 10 hr. The insoluble material was collected by filtration, and the filtrate evaporated to dryness. The residue (0.45 g.) consisted of unreacted 2-amino-3,6-dimethylpyrazine. The insoluble material was dissolved in water; the solution was made basic with aqueous sodium hydroxide. No further compounds were obtained by extracting this solution with ether. Condensation was not effected by changing the solvent to a more polar one with a higher boiling point or by the use of longer reaction periods.

3,5,6-Triphenyl-*s*-triazolo[4,3-*a*]pyrazine.—Phosphorus pentoxide (35 g.) and orthophosphoric acid (17 ml.) were heated together on a steam bath for 3 hr. N-Benzoyl-2,3-diphenyl-6-hydrazinopyrazine[2] (3.8 g.) was added and the reaction mixture was heated at 150° for 3 hr. After cooling, water was added carefully and the solid material collected and recrystallized from ethanol. 3,5,6-Triphenyl-*s*-triazolo[4,3-*a*]pyrazine (3.0 g., 83%) separated as colorless needles, m.p. 240–241°.

Anal. Calcd. for $C_{23}H_{16}N_4$: C, 79.3; H, 4.6; N, 16.1. Found: C, 79.0; H, 4.6; N, 16.2.

(12) A. Weddige, *J. prakt. Chem.*, [2]**28**, 188 (1883).

(13) S. M. McElvain and J. W. Nelson, *J. Am. Chem. Soc.*, **64**, 1825 (1942).

Degradation of a C-Nor-D-homosapogenin

WILLIAM F. JOHNS

Division of Chemical Research, G. D. Searle & Co., Skokie, Illinois

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The olefins **3** and **4**, produced by modified syntheses, were hydrogenated to a single compound, **5**. This sapogenin was converted to the unsaturated ketone **12a** and the lactone **11** by degradation of the side chain. Attempted ozonolysis of the pseudo-sapogenin **6** yielded in part the C-20 hydroxy derivatives **17** and **18**; these are postulated to have arisen from an epoxide intermediate (**15**).

The intricacies of the structural elucidation,[1] stereochemical determination,[2] and synthetic problems[3] presented by the C-nor-D-homo steroids and their more elaborate derivative alkaloids have stimulated a great deal of chemical research. A further incentive to these studies is provided by the strong hypotensive activity of some of these molecules, notably protoveratrine and its close relatives.[4] The intriguing aspects of these compounds led us to investigate a practicable route to some of their simpler analogs.[5] Three formally similar rearrangements recorded in the literature[6] provide an excellent method for synthesis of the basic skeleton starting from hecogenin, an abundantly available sapogenin. Projected degradation of the sapogenin side chain of the resultant C-nor-D-homo derivative would lead to molecules such as the unsaturated ketone **12**, in turn serving as intermediates to a variety of etiojervane derivatives.[7] These compounds would

(1) (a) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 867; (b) K. A. Jaeggi, E. Weiss, and T. Reichstein, *Helv. Chim. Acta*, **46**, 694 (1963), and references cited there.

(2) *Inter alia*, D. M. Bailey, D. P. G. Hamon, and W. S. Johnson, *Tetrahedron Letters*, 555 (1963); H. Mitsuhashi and Y. Shimizu, *Tetrahedron*, **19**, 1027 (1963); S. Okuda and K. Tsuda, *Chem. Ind.* (London), 512 (1961).

(3) P. W. Schiess, D. M. Bailey, and W. S. Johnson, *Tetrahedron Letters*, 549 (1963); R. A. Barnes and M. Sedlak, *J. Org. Chem.*, **27**, 4562 (1962).

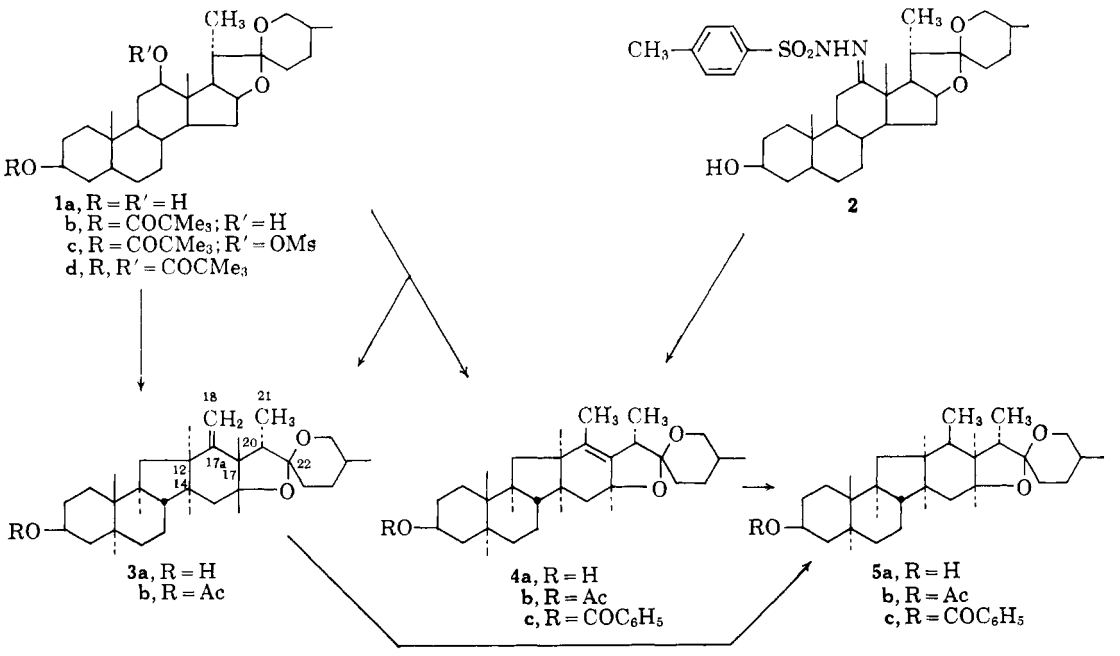
(4) See L. C. Weaver, W. R. Jones, and S. M. Kupchan, *J. Pharm. Sci.* **51**, 1144 (1962), and references cited there.

(5) (a) H. Mitsuhashi, K. Shibata, T. Sato, and Y. Shimizu [*Chem. Pharm. Bull.* (Tokyo), **12**, 1 (1964)] have reported work along similar lines; (b) S. M. Kupchan and S. D. Levine [*J. Am. Chem. Soc.*, **86**, 701 (1964)] have recently described derivatives of this general type.

(6) (a) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *ibid.*, **76**, 4013 (1954); (b) J. Elks, G. H. Phillips, D. A. H. Taylor, and L. J. Wyman, *J. Chem. Soc.*, 1739 (1954); (c) R. Anliker, O. Rohr, and H. Heusser, *Helv. Chim. Acta*, **38**, 1171 (1955).

(7) The designation "etiojervane" will be used to describe 17aα-methyl-C-nor-D-homo-18-nor-5α,12α-androstane. *Cf.* J. Fried and A. Klingsberg, *J. Am. Chem. Soc.*, **75**, 4934 (1953), and ref. 5b.

CHART I



be possible precursors to the natural products, would have potential biological interest, and would furnish answers to some of the stereochemical uncertainties in this area.

The exocyclic olefin **3**[6] was chosen as the first synthetic target. The initial step in its preparation was the conversion of hecogenin to rockogenin (**1a**). Of a number of reagents investigated, two led to stereospecific preparations of rockogenin (**1a**): potassium–alcohol and lithium–ammonia[8] reductions afforded rockogenin containing 5–10% and 3–5%, respectively, of the 12α-epimer. Lithium tri-*t*-butoxyaluminohydride[9a] or sodium borohydride–sodium hydroxide[9b] yielded much larger amounts of 12-epirockogenin. The subsequent steps in the literature preparation of olefin **3** were modified by use of the selective formation of the C-3 monopivalate of rockogenin (**1b**). The corresponding mesylate (**1c**) on treatment with base led to the exocyclic olefin **3a** (Chart I) in yields comparable with those published.[6a,b]

Simultaneous investigation of the production of the endocyclic olefin **4** provided an alternate (and preferred) synthetic route. The original preparation,[6] involving the treatment of hecogenin-*p*-toluenesulfonylhydrazone with sodium ethylene glycolate, was simplified and improved by the substitution of potassium hydroxide as the base. An over-all yield of 65% of the olefin **4a** from hecogenin was obtained. The modified reaction condition also provided a new crystalline diol ($C_{27}H_{44}O_5$) of uncertain structure; no Δ^{11}-tigogenin was found however.[6]

Reduction of the olefin **3** over a palladium catalyst proceeded readily to give a dihydro compound (**5**) in which the exocyclic methylene group had been reduced and the side chain left intact. With the endocyclic isomer **4** as substrate the same conditions gave a slow, erratic reduction. Use of platinum oxide proceeded too far, effecting hydrogenation of the sapogenin side chain in agreement with results reported earlier.[6b] Rhodium–alumina catalyst however, effected the smooth addition of 1 equiv. of hydrogen to provide in high yield the same saturated compound (**5**) obtained from reduction of the exocyclic olefin.

All of the asymmetric centers common to compounds **3–5** and hecogenin (carbon atoms 5, 8, 9, 10, 14, 16, 20, 22, and 25) have the same stereochemistry, since these centers would undergo no changes in the reactions used to produce compound **5** from hecogenin. The same reasoning applies to the configuration of C-17 in **3**, **5**, and hecogenin. Two configurations, those at C-12 and C-17a, remain in doubt, although the former has been assigned previously on mechanistic grounds.[6c,10] The stereochemistry at C-17a could not be predicted from inspection of the molecular models; hydrogenation might occur from either face of the olefin **4** since the molecule is planar.[11] This geometry is a result of a modified boat conformation of ring D imposed by the adjacent *cis*-fused 5-membered rings.

Pseudomerization of the saturated sapogenin **5** was most successfully accomplished by a short treatment with octanoic anhydride[12] or with acetic anhydride–methylamine hydrochloride.[13] Less satisfactory in the pseudomerization of **5** was the use of acetic anhydride at 180°[14] or lactide.[15] The product, the noncrystalline pseudo-diester **6c**, was oxidized to the keto ester **9** with chromic acid and this in turn was cleaved to the unsaturated ketone **12** with base or acetic acid, following the procedures well

(8) J. W. Huffman, D. M. Alabran, and T. W. Bethea, *J. Org. Chem.*, **27**, 3381 (1962).

(9) (a) O. H. Wheeler and J. L. Mateos, *Chem. Ind.* (London), 395 (1957); J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959). (b) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 870 (1955); *cf.* ref. 6a and 6b for lithium aluminum hydride reduction of hecogenin.

(10) At this point the C-12α and C-17aα assignments must be regarded as tentative. However, a forthcoming publication will cite rotatory dispersion data supporting these configurations.

(11) *Cf.* ref. 1a, p. 876.

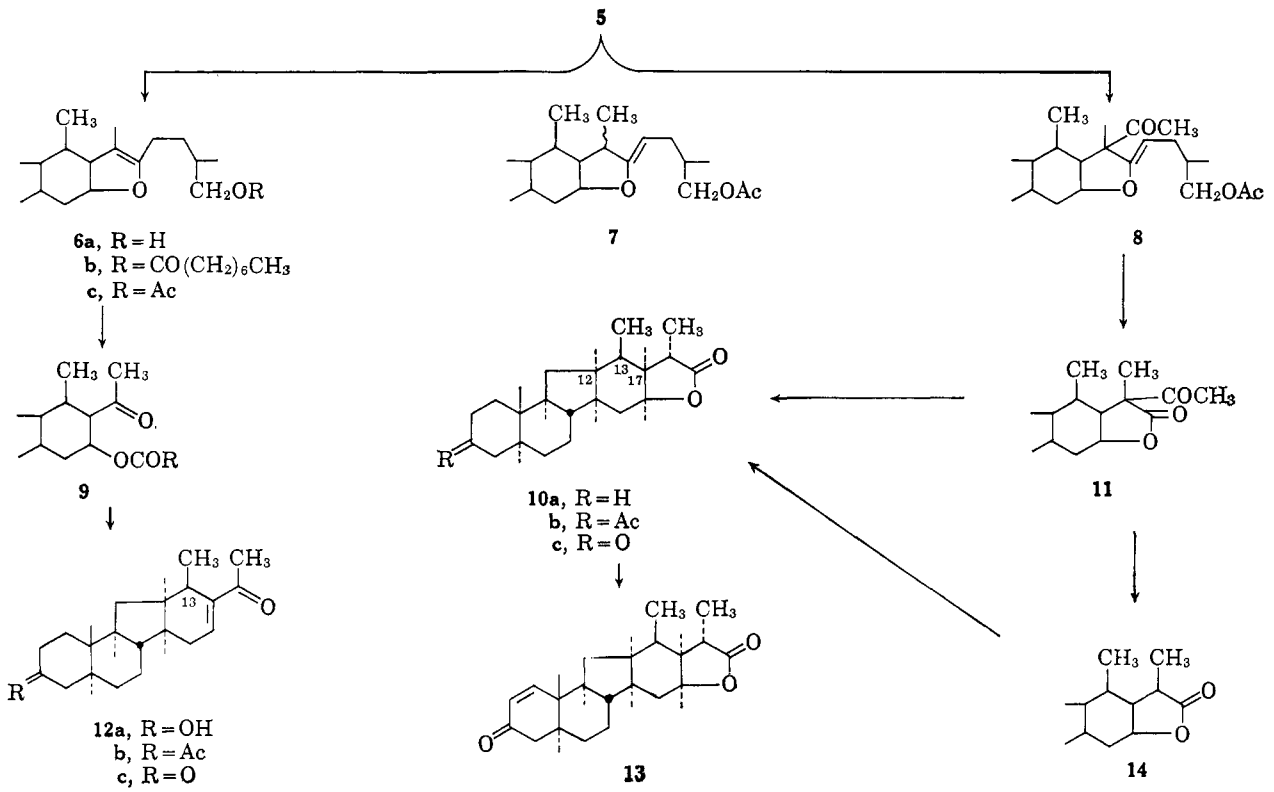
(12) A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, and A. G. Long, *J. Chem. Soc.*, 2807 (1955).

(13) D. N. Kirk and V. Petrow, *ibid.*, 2091 (1961).

(14) M. E. Wall and S. Serota, *Tetrahedron*, **10**, 238 (1960); M. E. Wall, H. E. Kenney, and E. S. Rothman, *J. Am. Chem. Soc.*, **77**, 5665 (1955).

(15) K. H. Hauptmann and K. Zeile, German Patent 1,086,352.

CHART II



worked out in the degradation of the normal sapogenins.[14] Chromatography of the mother liquors of the unsaturated ketone **12a** revealed that the isomeric (Δ^{17}) or epimeric (C-13β methyl) ketones had not been formed in detectable amounts. A separate treatment of pure **12a** in methanolic base produced neither of these ketones nor the C-16 methoxy derivative.[16] Oxidation of the C-3 hydroxyl to the ketone (**12c**) proceeded normally. (See Chart II.)

Pseudomerization with acetic anhydride–pyridine hydrochloride[17] yielded approximately 30% of a new component (**8**) besides a normal amount of the expected olefin **6c**. Evidence for the presence of this compound was obtained by inspection of the oxidation products of the crude pseudo-sapogenin. A lactone (**11**, λ_{max} 5.65 μ) was isolated which contained an additional acetyl group. Removal of this acetyl group with base occurred readily, yielding a new lactone (**14**) which contained no extra hydroxyl group; this result is best explained by postulating the starting material to have an acetyl function on the carbon atom adjacent to the lactone carbonyl. The lactone ring itself can be reasonably formed only from a C-16 hydroxyl and a C-22 carboxyl group.[18] Thus the acetyl group is attached at C-20. The second lactone (**14**) on further base treatment yielded an isomeric lactone (**10a**), presumably the more stable epimer of its precursor. The pair was readily interdistinguishable by a shift in the n.m.r. doublet attributable to the secondary methyl group adjacent to the labilizing lactone carbonyl.[18] Since **10**, **11**, and **14** are formed through planar intermediates, logical assignment of configuration of the pair of epimers **10** and **14** on mechanistic grounds is precluded. However, inspection of the molecular models shows a C-21–C-18 interaction when the C-21 methyl group is in the β-position. On this basis and by analogy to the normal steroids,[19] the unstable isomer **14** is assigned the β-configuration.

The origin of lactone **11** and its precursor **8** is clearly a result of the effectiveness of acetic anhydride–pyridine hydrochloride (as contrasted to, *e.g.*, octanoic anhydride) in causing acylation and its concomitant double-bond isomerization. Little double-bond migration (to compound **7**) is seen without C-20 acetylation as indicated by the relative absence of lactones **10** or **14** before base treatment. It is of interest to compare the formation of the acetyl lactone **11** with the normal steroids where acetylation occurs to an appreciable extent only with more potent catalysts and the product is a C-23-acetyl derivative.[20] The saturated lactone **10** was converted to its C-3 keto derivative and then by bromination–dehydrobromination to the unsaturated ketone **13** without unusual event.

The use of ozone was investigated as an alternative to chromic acid cleavage of the double bond in the pseudomerization product (as prepared by the acetic anhydride–pyridine hydrochloride method). One equivalent of ozone was smoothly absorbed and the zinc–acetic acid method was used to reduce the "ozonide." That the ozonlysis had not proceeded by simple cleav-

(16) The pregn-16-en-20-ones react readily to give the C-16 methoxyl derivatives [D. F. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951); G. P. Mueller, R. E. Stobaugh, and R. S. Winniford, *ibid.*, **75**, 4888 (1953)].

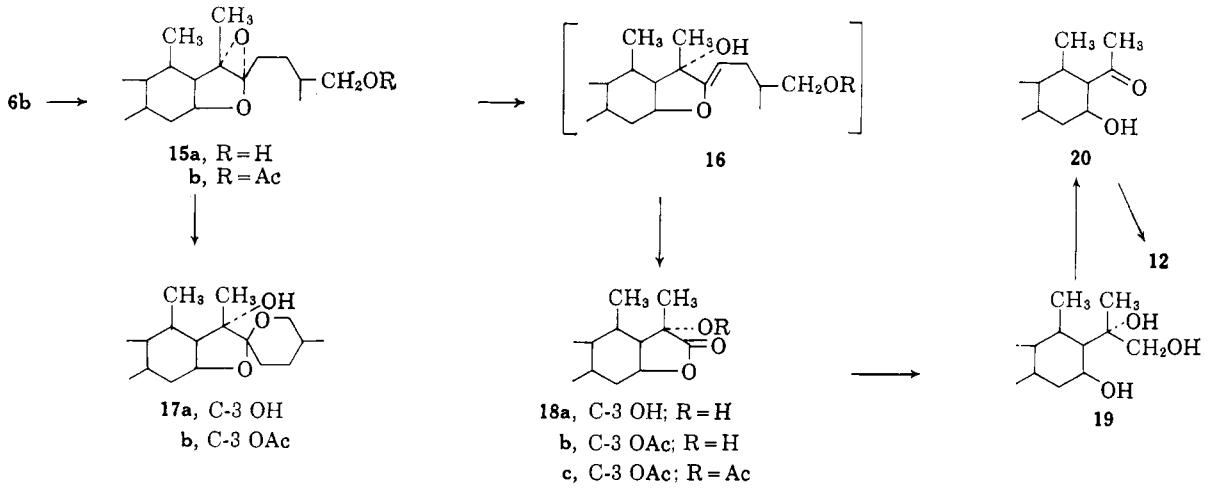
(17) W. G. Dauben and G. J. Fonken, *ibid.*, **76**, 4618 (1954).

(18) The structure and stereochemistry of similar lactones in normal steroids has been rigorously defined. It should be noted, however, that they arise by a different pathway (oxidation of an olefin analogous to **7**, not **8**). See D. H. Gould, H. Staeudle, and E. B. Hershberg, *ibid.*, **74**, 3685 (1952).

(19) J. W. Corcoran and H. Hirschmann, [*ibid.*, **78**, 2325 (1956)] have described the marked instability of the C-21β methyl group in the lactone derived from tigogenin.

(20) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); J. A. Zderic, L. Cervantes, and M. T. Galvan, *J Am. Chem. Soc.*, **84**, 102 (1962); see also ref. 12 and 18.

CHART III



age of the double bond was made clear when the standard base treatment failed to give the expected amount of the desired unsaturated ketone **12** (less than 15% was formed). Instead the major crystalline component was a new compound (**17a**) containing a tertiary hydroxyl group (inert to standard acetylation conditions) and an intact sapogenin side chain (as suggested by elemental analysis and spectral data). Although direct chromic acid oxidation of **5** failed to produce **17a**, epoxidation of the pseudo-diol **6a** did produce this material. By analogy to the epoxidation of other pseudo-sapogenins,[21] compound **17** can be formulated as a C-20α hydroxy sapogenin.

Further attempts to convert the ozonolysis product to the unsaturated ketone **12** involved acid treatment and also a more vigorous reduction with zinc in acetic acid (followed by base treatment); these methods gave no additional **12a**. The expected yield of unsaturated ketone (**12**) was obtained only when the ozonized material was oxidized with chromic acid (followed by base treatment). Chromatography of the entire product yielded fractions containing lactone **10a** (35%), unsaturated ketone **12a** (25%), and a new crystalline compound (**18a**). Two plausible explanations can account for the increased yield of the unsaturated ketone **12a** in this manner. The first is that a portion of the starting material escaped reaction during the ozonolysis and was transformed to the keto ester **9** only after chromic acid oxidation. This explanation is unlikely because of the excess ozone present in the homogeneous reaction mixture; it becomes more unlikely when it is noted that the ozonolysis product, on base treatment and acidification, yielded no detectable **5a**, a necessary product of any unreacted **6**. A preferred interpretation of the experimental results is that a part of the pseudo compound **6** was transformed to an oxidation state lower than that of the keto ester **9**; only on further oxidation would the C-20–C-22 bond cleavage become complete. The nature of this intermediate is discussed below.

The third crystalline component (**18a**) of the above reaction sequence was a γ-lactone (λ_{max} 5.65 μ) containing a tertiary hydroxyl (inert to normal acetylation). A proof of structure was accomplished by reduction of the lactone (**18a**) with lithium aluminum hydride to the tetrol **19**, cleavage with periodate to the hydroxy ketone **20**, and dehydration to the known ketone **12a**. Synthesis of the hydroxylactone **18** by oxidation of the lactone **10** failed. However, epoxidation of the pseudo compound **6b** followed by chromic acid treatment gave the desired product (although in low yield). The epoxide **15** in the acidic chromate solution, presumably undergoes epoxide opening, partial dehydration (to **16**), and oxidation of the resulting exocyclic double bond.[22] (See Chart III.)

The C-20 hydroxylated by-products **17** and **18** may arise from the same intermediate responsible for the increased yield of keto ester **9** on chromic acid oxidation of the ozonolysis product. Attempts to isolate this material failed and thus verification of its structure by routine analytical procedures was not possible. However, its structure may be surmised from its derivatives, **17** and **18** as well as the unsaturated ketone **12a**. This intermediate necessarily has a C-20 oxygen substituent and an intact C-20–C-22 bond. The most probable compound of this type is the epoxide **15**.[23] This epoxide, synthesized by routine[21] perbenzoic acid treatment of the pseudo-sapogenin **6**, has been demonstrated to form the compounds **17** and **18** under the same conditions used to produce them from the ozonolysis product. The final product expected, the unsaturated ketone **12a**, also could be produced from the epoxide **15** in the same manner and yield as formed from the ozonolysis product, namely by chromic acid oxidation and base treatment. The rupture of the C-20–C-22 bond in the epoxide **15** represents direct chromate oxidation of the epoxide or its derivative glycol (formed by oxide opening in the acidic medium). Thus, although a portion of the pseudo-sapogenin is cleaved with ozone, an appreciable amount does not undergo carbon–carbon rupture, but is postulated to form the epoxide **15** instead.[24]

(21) M. E. Wall, H. A. Walens, and F. T. Tyson, *J. Org. Chem.*, **26**, 5054 (1961).

(22) Precedent for facile dehydration of the C-22 hydroxyl group and oxidation of the resulting olefin is provided by H. Hirschmann and F. B. Hirschmann, *Tetrahedron*, **3**, 242 (1958).

(23) Epoxide formation by reaction of ozone with hindered olefins is an occasional occurrence. See, *e.g.*, K. Tanabe, R. Takasaki, and R. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **9**, 7 (1961), and references cited there.

(24) A more quantitative investigation of the ozonolysis of pseudo-sapogenins was possible in the normal steroids and will be presented in a future communication.

Experimental[25,26]

Reduction of Hecogenin A. Metal–Alcohol.—A solution of 300 g. of hecogenin in 0.5 l. of tetrahydrofuran and 2.5 l. of 2-propanol was heated to 60° with stirring under a slight positive pressure of nitrogen. Potassium metal bars (*ca.* 12 g. each) were introduced to this solution at 5–10-min. intervals until 16 bars (190 g.) had been added. (The reaction mixture became homogeneous after addition of the first 3 bars.) After a total of 2 hr., the addition of metal was complete and the solution was heated at reflux an additional 15 min. The reaction mixture was diluted slowly with 1 l. of 50% aqueous acetic acid and then poured with stirring into 6 l. of water. The resulting crystal mass was filtered, washed with water, dried, and recrystallized from aqueous ethanol, yielding 280 g. of rockogenin (**1a**), m.p. 210–213°, λ_{max}^{KBr} 2.75 μ (no carbonyl absorption); lit.[6a] m.p. 209–211°. Analysis by thin layer chromatography showed the crude product to contain 5–10% of the 12α-isomer.

B. Metal–Ammonia.—A solution of 10 g. of hecogenin in 150 ml. of tetrahydrofuran was added to 150 ml. of *t*-butyl alcohol and 300 ml. of ammonia, causing rapid precipitation of the hecogenin. Lithium wire (4 g.) was added to the suspension. The mixture was stirred for 3 hr. and 1 ml. of methanol was added dropwise to decompose the excess metal. The reaction was diluted with water and sufficient hydrochloric acid to acidify the mixture. The resulting precipitate was collected on a filter and washed with water, yielding 10.0 g. of rockogenin, m.p. 185–195°. Analysis of this material by thin layer chromatography showed the presence of 3–5% of the 12α-isomer.

C. Lithium Tri-*t*-butoxyaluminohydride.—To a stirred solution of 55 g. of lithium tri-*t*-butoxyaluminohydride in 0.7 l. of tetrahydrofuran at 5° was added 43 g. of hecogenin. After being stirred at ambient temperature for 20 hr., the mixture was poured into 2 l. of ice–water containing excess acetic acid. The product was isolated by chloroform extraction[27] yielding 38 g. of material. Analysis of the product by thin layer chromatography indicated that it contained 15–25% of the 12α-isomer, the remainder being the 12β-derivative **1a**.

D. Sodium Hydroxide–Sodium Borohydride.—Hecogenin (50 g.) in boiling methanolic sodium hydroxide was treated with a sodium hydroxide–sodium borohydride mixture as described by Adams, *et al.*[9b] After 2 hr., the product was isolated by distillation of half the methanol and dilution with aqueous acetic acid. The product was filtered and dried. Analysis of the product by thin layer chromatography indicated a 6:4 ratio of C-12β–C-12α-isomers.

Rockogenin 3-Pivalate (1b).—The crude rockogenin (280 g., m.p. 210–213° as obtained from the potassium–alcohol reduction) was dried by toluene azeotrope and was dissolved in 2.5 l. of pyridine. Pivaloyl chloride (82 g., a 5% excess) was added and the solution was heated at 100° for 2 hr. The solution, concentrated to a 1.5-l. volume, was diluted with 1 l. of water, and the product was isolated by extraction with benzene. The washed and dried extract was concentrated to a 2-l. volume and allowed to stand at room temperature for 18 hr. The resulting precipitate was collected on a filter yielding 31.9 g. of crystals, m.p. 276–280°. Recrystallization of a portion of this material from methylene chloride provided pure epirockogenin 3-pivalate (C-12α-isomer of **1b**), m.p. 297–299°, λ_{max} 2.72 and 5.81 μ, $[\alpha]_D$ −42°.

Anal. Calcd. for $C_{32}H_{52}O_5$: C, 74.37; H, 10.14. Found: C, 74.20; H, 9.97.

Two additional crops were obtained: 68 g., m.p. 253–257°, $[\alpha]_D$ −56°; and 84 g., m.p. 248–251°, $[\alpha]_D$ −59°. Recrystallization of a portion of this material from acetone gave the pure rockogenin 3-pivalate (**1b**), m.p. 255–257°, λ_{max} 2.75 and 5.82 μ, $[\alpha]_D$ −60°.

Anal. Found: C, 74.61; H, 10.41.

If an excess of pivaloyl chloride was used under the same conditions **rockogenin 3,12-dipivalate (1d)** was formed. Recrystallization from petroleum ether and from methylene chloride–methanol gave the analytical sample, m.p. 240–246°, λ_{max} 5.80 μ, $[\alpha]_D$ −61°.

Anal. Calcd. for $C_{37}H_{60}O_6$: C, 73.96; H, 10.07. Found: C, 73.69; H, 10.03.

Rockogenin 3-Pivalate 12-Mesylate (1c).—To 32.1 g. of the crude 3-pivalate **1b**, m.p. 246–254°, was added 200 ml. of pyridine, and the resulting mixture was stirred at room temperature for 10 min. The insoluble 12α-isomer (1.1 g., m.p. 275–280°) was removed by filtration, and the filtrate, cooled to 5°, was treated with 20 ml. of methanesulfonyl chloride. The solution was allowed to warm slowly to room temperature. After 18 hr. the solution was cooled and treated slowly with dilute sodium bicarbonate. The resulting granular precipitate was filtered and washed with water, giving 34.7 g. of mesylate **1c**, m.p. 134–137°. Recrystallization from methylene chloride–methanol caused some decomposition as evidenced by the resultant acidity of the mother liquors and the lowered melting point of the product, m.p. 128–130°, λ_{max} 5.82 μ, $[\alpha]_D$ −54°.

Anal. Calcd. for $C_{33}H_{54}O_7S$: C, 66.63; H, 9.15. Found: C, 66.60; H, 9.18.

In subsequent runs the crystalline material was used without recrystallization. The base-catalyzed rearrangement of this material to the exocyclic olefin **3a** and the subsequent acetylation to give C-3 acetate (**3b**) proceeded in the manner described by the earlier workers[6] and in comparable yields.

Rearrangement of Hecogenin *p*-Toluenesulfonylhydrazone.—To a solution of 130 g. of potassium hydroxide in 2 l. of ethylene glycol (or diethylene glycol) at 45° was added 130 g. of hecogenin *p*-toluenesulfonylhydrazone (**2**), m.p. 260–263°.[6] The mixture was stirred with heating in an inert atmosphere. Evolution of nitrogen started at 80° causing some foaming. When the temperature had reached 160° (in about 45 min.), the heating was discontinued and the solution was cooled to room temperature. The cooled reaction mixture was poured into 6 l. of water with stirring. The resulting solid, separated by filtration and washed with water, was dissolved in 2 l. of methylene chloride. The solution was washed with water until neutral; the solvent was distilled, being replaced with 1 l. of acetonitrile. Filtration of the cooled solution afforded 59 g. of **17a-methyl-C-nor-D-homo-18-nor-5α,12α,22α-spirost-17(17a)-en-3β-ol (4a)**, m.p. 108–118° (65%). The product was solvated, resulting in a broad melting point, lit. m.p. 113–123°[6a] and 120–125°.[6b] (In some runs it was necessary to concentrate the methylene chloride extract to dryness and to triturate the residue with hot petroleum ether; a varying amount of insoluble crystalline material, hecogenin, was separated by filtration, the filtrate providing the olefin **4a** as described above.) Chromatography of 3.9 g. of the mother liquors of this reaction provided additional endocyclic olefin **4a** (0.7 g.) plus a noncrystalline contaminant (1.1 g.) eluted with 2% ethyl acetate in benzene. In this chromatogram neither these fractions nor any others contained Δ^{11}-tigogenin as seen from the lack of olefinic protons in their n.m.r. spectra. Later eluates (10% ethyl acetate in benzene) yielded 0.30 g. of hecogenin (identification by infrared correlation). Elution with 40% ethyl acetate in benzene gave 1.4 g. of material, which was crystallized and recrystallized from acetone to give a pure compound of unknown structure, m.p. 231–234°, λ_{max} 2.75 μ, $[\alpha]_D$ 16°.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.26; H, 9.89. Found: C, 72.36; H, 9.91.

This material formed an amorphous diacetate on treatment with acetic anhydride in pyridine at room temperature or at 100°; λ_{max} 5.78 μ (no hydroxyl). The molecular weight was 543 as determined in methylene bromide by the Rast method.

Anal. Calcd. for $C_{31}H_{48}O_7$ (533): C, 70.56; H, 8.88. Found: C, 70.93; H, 8.92.

This unknown was stable to hydrogenation with palladium–acetic acid and to refluxing hydrochloric acid in ethanol. The oxidation products from chromic acid–acetone treatment were noncrystalline. That this compound was not initially present was ascertained by chromatography of the starting material (hecogenin).

17a-Methyl-C-nor-D-homo-18-nor-5α,12α,22α-spirost-17(17a)-en-3β-ol Benzoate (4c).—The alcohol **4a** (22 g.) in 150 ml. of pyridine and 15 ml. of benzoyl chloride was heated at 100° for 20 min. The solution was cooled, diluted with 25 ml. of water, and heated at 100° for 30 min. The solution was diluted fur-

(25) We wish to thank Dr. R. T. Dillon and staff for the spectra and analyses reported and Dr. E. G. Daskalakis and staff for the chromatography described. We are indebted to Mr. Ivar Laos for competent technical assistance.

(26) Infrared spectra were determined in chloroform, ultraviolet spectra in methanol, and rotations in chloroform (1%). Petroleum ether refers to the fraction with b.p. 63–68°. Melting points are uncorrected. N.m.r. spectra were determined in deuteriochloroform on a Model A-60 spectrometer, Varian Associates, Inc., at 60 Mc., using tetramethylsilane as an internal standard ($\Delta\nu$ = 0 c.p.s.).

(27) The normal extraction procedure involved washing a solution of the reaction product with water and aqueous potassium bicarbonate (for acidic reactions), drying the extract over anhydrous magnesium sulfate, and concentrating under reduced pressure (temperature less than 50°).

ther with water and the product was extracted with chloroform.[27] The crystalline residue was recrystallized from chloroform–methanol, yielding the benzoate **4c**, 8.3 g., m.p. 240–243°, and 12.7 g., m.p. 240–244°. The analytical sample was obtained by recrystallization from acetone, m.p. 247–248°, λ_{max} 5.82 μ.

Anal. Calcd. for $C_{34}H_{46}O_4$: C, 78.72; H, 8.94. Found: C, 78.69; H, 9.24.

17aβ-Methyl-C-nor-D-homo-18-nor-5α,12α,22α-spirostan-3β-ol Acetate (5b). A. Reduction of the Exocyclic Olefin 3b.—A mixture of 9.12 g. of the olefin acetate **3b**, m.p. 205–220°, and 8 g. of 5% palladium–charcoal catalyst in 500 ml. of acetic acid absorbed 1 equiv. of hydrogen in a 6 hr. period.[28] The filtered solution was concentrated to dryness. The resulting residue was dissolved in methylene chloride and crystallized from methanol and then from acetonitrile yielding 4.4 g. of the acetate **5b**, m.p. 175–177°. Recrystallization of a portion from methylene chloride–methanol yielded a pure sample, m.p. 179–181°, λ_{max} 5.72 μ, $[\alpha]_D$ −112°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found C, 76.01; H, 10.01.

A major component of the mother liquors was seen to be the endocyclic olefin **4b**, separated by chromatography on silica; it was shown by a separate experiment to be a contaminant of the starting material which had not undergone reduction under these conditions.

B. Reduction of the Endocyclic Olefin 4b.—A solution of 200 g. of the olefin acetate **4b**[6a] (m.p. 140–145°) in 900 ml. of acetic acid and 25 g. of 5% rhodium on alumina were shaken in an atmosphere of hydrogen at 45°. One equivalent of gas was absorbed in 7 hr. The catalyst was filtered and was washed with benzene to remove the crystallized product. The combined filtrates on concentration to dryness (rotary still) yielded a crystalline residue which was dissolved in methylene chloride and decolorized with charcoal. Replacement of the methylene chloride with methanol afforded 165 g. of crystals, m.p. 177–183°, and 9.4 g., m.p. 173–177° (87%), identical in the infrared and n.m.r. with the above material (**5b**). Chromatography of the mother liquors on silica afforded a small amount of starting material, eluted from silica immediately after the product **5b** with 0.5% ethyl acetate in benzene. No isomeric saturated compound could be detected. In other runs, slower reductions made necessary addition of fresh catalyst to complete the reaction. It was also determined that mixtures of the exocyclic olefin and the endocyclic isomer were hydrogenated smoothly to the single saturated acetate **5b** in the presence of rhodium–alumina catalyst.

In earlier attempts to produce the saturated compound **5b** from the endocyclic benzoate **4c**, 5% palladium on charcoal in acetic acid was used as catalyst. The reduction was very slow, several changes of catalyst being insufficient to effect complete hydrogenation. Raney nickel catalyst at 2000 p.s.i. and 100° in ethanol caused no reduction.

17aβ-Methyl-C-nor-D-homo-18-nor-5α,12α,22α-furostan-3β,26-diol (dihydro derivative of 6a).—A solution of 0.48 g. of compound **4a** in 60 ml. of acetic acid was stirred with 0.10 g. of platinum oxide in an atmosphere of hydrogen. After 20 hr. 2 mole equiv. of hydrogen gas had been absorbed. The catalyst was filtered and the solvent was evaporated. The residue was hydrolyzed in methanol containing aqueous potassium hydroxide and the resulting product was chromatographed on silica. Recrystallization of the material eluted with 50% ethyl acetate in benzene from ether–petroleum ether afforded the pure dihydro derivative of **6a**, m.p. 139–141°, λ_{max} 2.74 μ.

Anal. Calcd. for $C_{27}H_{46}O_3$; C, 77.46; H, 11.08, Found: C, 77.30, H, 11.22.

17aβ-Methyl-C-nor-D-homo-18-nor-5α,12α,22α-spirostan-3β-ol (5a).—A solution of 0.32 g. of the acetate **5b** in 10 ml. of methanol and 2 ml. of 10% aqueous potassium hydroxide was heated at reflux for 1 hr. Dilution of the reaction mixture with water gave a precipitate which was collected on a filter, washed with water, and dried in a stream of air. Recrystallization of the product from methylene chloride–methanol gave 0.17 g. of the alcohol **5a** as a methanol solvate, m.p. 155–158°; on occasion a second crystalline form, m.p. 172–174°, was obtained. Recrystallization of this material from acetone–petroleum ether gave an unsolvated sample, m.p. 148–151°, λ_{max} 2.75 μ, $[\alpha]_D$ −49°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 77.83; H, 10.65. Found: C, 78.05; H, 10.85.

An alternate preparation of this compound entailed direct hydrogenation of the olefin **4a** as described for the preparation of **5b**.

The benzoate was prepared with the method used in the preparation of **4c**. The product was recrystallized from methylene chloride–methanol to give **17aβ-methyl-C-nor-D-homo-18-nor-5α,12α,22α-spirostan-3β-ol benzoate (5c)**, m.p. 155–158°, λ_{max} 5.82 μ, $[\alpha]_D$ −14°.

Anal. Calcd. for $C_{34}H_{48}O_4$: C, 78.42; H, 9.29. Found: C, 78.57; H, 9.40.

Side-Chain Degradation of the Saturated Acetate 5b. A. Pseudomerization.—The saturated acetate **5b** (134 g.) in 105 ml. of octanoic acid and 80 ml. of acetic anhydride was heated to 240° over a 15-min. period and between 240 and 250° for 20 min.[12] The volatile components were allowed to distil during this time. The reaction mixture was cooled and diluted with 0.5 l. of ether, 200 ml. of water, and excess 10% aqueous potassium hydroxide. The solution was stirred vigorously at room temperature for 20 min. to hydrolyze the anhydride. The layers were separated and the organic layer was washed twice with water, twice with dilute potassium hydroxide, and again with water. The solution was concentrated to dryness yielding 170 g. of a mobile oil. A portion (1.8 g.) of this material, chromatographed on 130 g. of silica, afforded 0.80 g. of the noncrystalline pseudo-diester **6b** on elution with 1% ethyl acetate in benzene. No crystalline products were found.

B. Oxidation.—To a solution of the crude pseudo-diester **6b** (167 g.) in 1 l. of acetic acid and 1 l. of ethylene dichloride at −5° was added over a 20-min. period a solution of 90 g. of chromic acid in 0.8 l. of 90% aqueous acetic acid.[14] The mixture was stirred for an additional hour at 0° and then was treated slowly with 100 g. of sodium bisulfite in 0.4 l. of water. The solution was diluted with 1 l. of water and extracted with ether. The extract was washed three times with water and, without drying, was concentrated to dryness (rotary still, temperature less than 60°). The product was dissolved in ether and filtered. The filtrate was washed with aqueous potassium bicarbonate, dried, and concentrated, yielding 174 g. of a mobile oil containing the keto ester **9**. Chromatography of 2.4 g. of this material on 150 g. of silica afforded, by elution with 2% ethyl acetate in benzene, 0.10 g. of the unsaturated ketone **12a**, m.p. 145–148°, identical with an authentic sample (see below). This was a result of partial chain cleavage that had occurred during the isolation. No other crystalline products were isolated.

C. Elimination of the Side Chain.—A solution of 174 g. of the keto ester **9** in 1.3 l. of *t*-butyl alcohol and 0.5 l. of 20% aqueous potassium hydroxide was stirred at the boiling point in a nitrogen atmosphere for 90 min. The organic solvent was distilled; the resulting mixture was diluted with water and extracted with ether three times. The extract was washed thoroughly with water and dried. An aliquot was concentrated to dryness and was shown to contain approximately 45% of the unsaturated ketone **12a** [λ_{max} 237 mμ (log ϵ 3.89)]. On concentrating the total solution to 200 ml. and cooling, the solution deposited 29.4 g. of crystals, m.p. 164–168°. Pure **17-acetyl-13β-etiojerv-16-en-3β-ol (12a)**[7] was obtained by recrystallization from ether; m.p. 165–168°; λ_{max} 2.75, 6.02, and 6.12 μ; λ_{max} 237 mμ (log ϵ 4.05); $[\alpha]_D$ +54°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.58; H, 10.39.

17-Acetyl-13β-etiojerv-16-en-3β-ol acetate (12b) was prepared by treatment of the alcohol **12a** with acetic anhydride–pyridine at 100° for 10 min. The product, recrystallized from acetone–petroleum ether, had m.p. 143–145°, λ_{max} 236 mμ (log ϵ 4.06).

Anal. Calcd. for $C_{23}H_{34}O_3$; C, 77.05; H, 9.56. Found: C, 77.34; H, 9.81.

Additional unsaturated ketone could be obtained from the semicrystalline mother liquors (39 g.) by triturating with a minimum volume of ether; the resulting crystals (8.8 g.) were filtered and recrystallized from acetone–petroleum ether to yield 4.9 g. of **12a**, m.p. 164–166°, λ_{max} 237 mμ (log ϵ 4.02). Chromatography of the mother liquors on silica afforded first, eluted at 5% ethyl acetate in benzene, the starting sapogenin **5a** (infrared comparison). Further elution with the same solvent provided the unsaturated ketone **12a**. The ultraviolet spectra of several of the nearby chromatographic fractions showed no shift in maxima implying the absence of isomeric unsaturated ketones.

(28) We are indebted to Mr. W. M. Selby and staff for the hydrogenations in this work.

Small amounts of lactone were found in these fractions as indicated by a weak band at 5.65 μ in the infrared.

A separate experiment, designed to test the stability of **12a** to methanolic base (1- and 18-hr. reflux periods), showed a small amount of deconjugation of the double bond (weak infrared maximum at 5.85 μ) but no formation of C-16 methoxyl (no n.m.r. signal near 200 c.p.s.).

The side chain of the keto ester **9** could also be eliminated by boiling in acetic acid for 6 hr., providing directly the acetate **12b** in yield comparable with that from the above procedure. The pure unsaturated ketone **12b** underwent no change in boiling acetic acid after 5 hr.

17-Acetyl-13β-etiojerv-16-en-3-one (12c).—Alcohol **12a** (1.0 g.) was oxidized with an excess of 4 *N* chromic acid solution[29] at room temperature for 10 min. After the addition of 2 ml. of 2-propanol the solution was diluted with water and extracted with ethyl acetate.[27] The extract yielded a crystalline residue, recrystallized from acetone–petroleum ether to give the pure diketone **12c**, m.p. 114–5°; λ_{max} 5.85, 6.02, and 6.14 μ; λ_{max} 235 mμ (log ϵ 4.05); $[\alpha]_D$ +85°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.34; H, 9.67.

Other Pseudomerizations. A. Methylamine Hydrochloride–Acetic Anhydride.[13]—A solution of 4.0 g. of **5a** and 1.4 g. of methylamine hydrochloride in 4 ml. of pyridine and 8 ml. of acetic anhydride was heated at reflux for 2.5 hr. The product, after isolation, showed none of the starting material to be present. Oxidation and side-chain elimination followed the procedure as described above and yielded 1.9 g. of product; the intensity of the maximum at 237 mμ (log ϵ 3.81) corresponded to a 40% over-all yield of **12a**. The infrared spectrum showed little lactone (5.65 μ). The product was not investigated further.

B. Acetic Anhydride.[14]—The acetate **5b** (10.0 g.) in 50 ml. of acetic anhydride and 0.1 ml. of acetic acid was heated at 180° in a glass-lined pressure vessel for 25 hr. The standard work-up, oxidation, and elimination of the side chain gave a final product shown by ultraviolet spectrum to contain 35% of unsaturated ketone **12a**; a new impurity was also present as evidenced by secondary absorption at 270 mμ. The infrared showed a 5.65-μ (lactone) band of medium intensity.

C. Lactide.—Lactide[30] (11 g., m.p. 126–128°) and the acetate **5b** (3.50 b.) were heated at 240–245° under nitrogen for 8 hr.[15] The product was saponified, acetylated with acetic anhydride–pyridine, oxidized, and saponified in the routine manner, yielding a product containing 15% of the unsaturated ketone **12a** (by ultraviolet analysis). The same sequence was run also with the addition of a little acetic anhydride, a change that did not improve the yield.

D. Acetic Anhydride–Pyridine Hydrochloride.—A solution of 72 g. of the saturated acetate **5b** in 700 ml. of acetic anhydride and 28 g. of pyridine hydrochloride was heated at reflux for 9 hr. and then was poured into 1 l. of hot (80°) water with efficient stirring. (A 6-hr. reflux period was insufficient as seen by direct isolation of crystalline starting material at that time.) The product was isolated by benzene extraction[27] and a portion was chromatographed on silica; fractions eluted with 3% ethyl acetate in benzene yielded amorphous material having an n.m.r. signal at 134 c.p.s., characteristic of the C-20 acetyl group (see below). The remainder of the pseudo-sapogenin mixture was submitted to the standard chromic acid oxidation and base-catalyzed elimination as described above. The resulting mixture was shown by ultraviolet analysis to contain 30% of the desired material, **12a**.

2-(3β,16β-Dihydroxy-20-acetyl-13β-etiojervan-17β-yl)propanoic Acid Lactone (11). A. Ozonolysis.—The crude pseudo-diacetate **6c** (7.7 g., prepared by the acetic anhydride–pyridine hydrochloride method) in 60 ml. of methylene chloride containing 2 ml. of pyridine was saturated with ozone at −70°, approximately 1 mole equiv. being absorbed. To the resulting light blue solution was added 5 g. of zinc dust and 5 ml. of acetic acid in 5 ml. of methylene chloride. The mixture was stirred in an ice bath for 40 min. and then was filtered. The filtrate was washed with water and aqueous potassium bicarbonate, dried, and concentrated, yielding 8.8 g. of foam (preparation A). A portion (1.9 g.) of this material was chromatographed on 150 g. of silica. Elution with 2% ethyl acetate in benzene afforded 0.32 g. (30%) of crystalline material, recrystallized from methylene chloride–methanol to give 0.18 g. of the pure lactone **11**, m.p. 225–228°; λ_{max} 5.62 and 5.78 μ; $\Delta\nu$ 88 (C-21 CH_3), 121 (C-3 OAc), and 137 (C-20 $COCH_3$) c.p.s.; $[\alpha]_D$ 17°.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.24; H, 8.70.

Lithium aluminum hydride reduction of this compound gave an amorphous tetrol, stable to periodic acid.

Later eluates (10% ethyl acetate in benzene) afforded 0.74 g. of an amorphous solid, λ_{max} 2.80 and 5.75 μ, $\Delta\nu$ 234 and 239 (C-26 CH_2O) c.p.s. The remainder of the material was not eluted from the silica even though acetone was used as eluent.

Several attempts were made to transform preparation A into the unsaturated ketone **12a**. (For base treatment, see below.) These included treatment of the material in refluxing acetic acid for 20 hr. or in refluxing methanol containing a little concentrated hydrochloric acid for 2 hr. The product contained no appreciable unsaturated ketone (ultraviolet and infrared analyses). Also, treatment of preparation A with granular zinc in refluxing acetic acid for 2 hr., followed by treatment with aqueous potassium hydroxide in refluxing *t*-butyl alcohol, gave as the only crystalline product the lactone **10a** (see below), m.p. 210–225°, in 5% yield, identical in the infrared with the material described below.

B. Chromic Acid Oxidation.—The pseudo compound **6c** (9.2 g., prepared by the acetic anhydride–pyridine hydrochloride method) was oxidized in ethylene dichloride at −10° with chromic acid in 90% acetic acid as described for the preparation of **9**. A portion (3.3 g.) of the resulting product (8.0 g.) was chromatographed on 150 g. of silica. Elution with 2% ethyl acetate in benzene provided 0.41 g. of material containing essentially pure acetyl lactone, identical in the infrared with the lactone **11**.

Increasing the pseudomerization reaction time to 23 hr. did not increase the proportion of the intermediate **8** as evidenced by this oxidative analysis.

17aβ-Methyl-C-nor-D-homo-18-nor-5α,12α,22α-spirostan-3β,-20α-diol (17a). A. Ozonolysis.—The unpurified ozonolysis product (3.9 g. of preparation A) in 40 ml. of *t*-butyl alcohol was stirred and heated to reflux under nitrogen with a solution of 8 g. of potassium hydroxide in 14 ml. of water. After 2 hr. the solution was cooled, diluted with excess aqueous acetic acid, and extracted with methylene chloride.[27] The extract yielded 2.2 g. of foam, λ_{max} 235 mμ (log ϵ 3.30) (corresponding to no more than 15% of unsaturated ketone **12a**), which was chromatographed on 120 g. of silica. Elution with 5% ethyl acetate in benzene gave 1.26 g. of crystalline material, recrystallized from acetone to yield 0.24 g. of analytically pure **17a**, m.p. 178–181°, λ_{max} 2.70 and 2.80 μ.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.83; H, 10.12.

Acetic anhydride–pyridine at 100° produced a monoacetate, recrystallized from methanol to give pure **17aβ-methyl-C-nor-D-homo-18-nor-5α,12α,22α-spirostan-3β,20α-diol 3-acetate (17b)**, m.p. 225–228°.

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.57; H, 9.73.

The hydroxy compound **17a** was labile to methanolic hydrochloric acid (4 hr. at reflux) yielding a mixture with a spectral characteristics [λ_{max} 239 mμ (log ϵ 3.63), λ_{max} 6.02 μ] similar to an anhydrogenoic acid.[31]

The remainder of the material eluted from the column was noncrystalline, showing only poorly defined bands for unsaturated ketone and lactone groups in the infrared spectra.

B. Perbenzoic Acid Oxidation.—A solution of 1.8 g. of the crude pseudo-diester **6b** in 60 ml. of *t*-butyl alcohol and 15 ml. of 10% aqueous potassium hydroxide was stirred at reflux for 20 hr. The solution was diluted with water and the alcohol was distilled. Extraction of the product with benzene[27] afforded 1.45 g. of oil. The entire sample in 100 ml. of benzene was treated with 1.2 mole equiv. of 0.4 *M* perbenzoic acid solution. After 15 min., 15 g. of calcium hydroxide was added to the solution and the resulting mixture was stirred for 20 min. The filtered solution was concentrated to dryness and the residue, 1.15 g. of an amorphous material, was chromatographed on 90 g. of silica. A total of 0.66 g. of material, eluted with 10% ethyl acetate in benzene, was recrystallized from acetone yielding 0.35

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

(30) The lactide, obtained from Clinton Corn Processing Co., Clinton, Ohio, was freshly recrystallized from carbon tetrachloride–acetone.

(31) See ref. 1a, p. 817.

g. of lustrous plates, m.p. 176–178°, identical in the infrared with pure **17a**.

Chromatography of the pseudo-diol **6a** on alumina (Merck chromatographic) gave a single crystalline component which was recrystallized from acetone–petroleum ether to yield pure **17aβ-methyl-C-nor-D-homo-18-nor-5α,12α,20β,22α-spirostan-3β-ol** (the cyclopseudo derivative[32] corresponding to **5a**), m.p. 155–157°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 78.02; H, 10.54.

Treatment of this material in boiling ethanol containing concentrated hydrochloric acid gave the C-20α-isomer **5a** (by infrared correlation).

2-(3β,16β-Dihydroxy-13β-etiojervan-17β-yl)propanoic Acid Lactone (10a).—To a solution of 7.2 g. of preparation A (the crude "ozonide") in 50 ml. of acetic acid and 80 ml. of ethylene dichloride at 5° was added a solution of 3.0 g. of chromium trioxide in 10 ml. of water over a 20-min. period. After an additional 20 min. at ambient temperature, there was added 100 ml. of 36% aqueous formaldehyde. The solution was stirred for 40 min., diluted with water, and the product was isolated by extraction with ethylene dichloride,[27] yielding 8 g. of oil (preparation B). A portion (2 g.) of this material was chromatographed on 160 g. of silica. Elution with 2% ethyl acetate in benzene afforded 0.38 g. of material; recrystallization from methylene chloride–methanol gave 0.23 g. of the pure acetyl lactone **11**, m.p. 224–226°, identical in the infrared with an authentic sample. Also eluted from this column, at 5% ethyl acetate in benzene, was 20 mg. of the hydroxy lactone **18a**, m.p. 273–278° (satisfactory infrared correlation).

A solution of 4.4 g. of preparation B in 100 ml. of *t*-butyl alcohol was stirred with 10 g. of potassium hydroxide in 25 ml. of water at reflux under nitrogen for 2 hr. The crude product (2.1 g.), isolated by ethylene dichloride extraction,[27] showed that the desired ketone **12a** was present in a 25% over-all yield from **5b**. Chromatography of the product on 70 g. of silica gave first, by elution with 10% ethyl acetate–benzene, 0.64 g. of the crude unsaturated ketone. Recrystallization gave readily 0.18 g. of **12a**, m.p. 155–167°, identical with an authentic sample in the infrared. The next product, 0.96 g., was eluted with the same solvent and was purified by recrystallization from methylene chloride–acetone, yielding 0.23 g. of material, m.p. 224–227°. Further recrystallization from acetone gave the analytical sample of **10a**, m.p. 225–227°, λ_{max} 2.75 and 5.75 μ.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.43; H, 9.65.

The acetate was prepared with acetic anhydride–pyridine at 100° for 20 min. Dilution of the reaction mixture and recrystallization of the precipitate from cyclohexane, gave pure **2-(3β-acetoxy-16β-hydroxy-13β-etiojervan-17β-yl)propanoic acid lactone (10b)**, m.p. 192–194°; λ_{max} 5.67 and 5.78 μ; $\Delta\nu$ 48 (C-19 CH_3), 54 and 61 (C-18 CH_3), 75 and 83 (C-21 CH_3) c.p.s.; $[\alpha]_D$ −39°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.04; H, 9.07.

Barbier–Wieland degradation of the lactone failed, probably owing to the inability of the intermediate diphenyl carbinol to dehydrate properly.

2-(3β,16β,20α-Trihydroxy-13β-etiojervan-17β-yl)propanoic Acid Lactone (18a). A. Ozonolysis.—Elution of the chromatographic column (from the preceding experiment) with 20% ethyl acetate in benzene afforded a total of 0.18 g. of semicrystalline material. Recrystallization from methyl ethyl ketone and ethyl acetate gave the pure lactone **18a**, m.p. 301–305°; λ_{max}^{KBr} 2.85, 3.03, and 5.68 μ.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.73; H, 9.35.

Treatment of the lactone in refluxing acetic acid with zinc dust for 6 hr. led to no change.

2-(3β-Acetoxy-16β,20α-dihydroxy-13β-etiojervan-17β-yl)propanoic acid lactone (18b) was prepared with acetic anhydride–pyridine at 100° and had m.p. 272–276° after recrystallization from acetone–petroleum ether.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.39; H, 8.99.

B. Perbenzoic Acid Oxidation. Five grams of the pseudo compound **6b** in 200 ml. of benzene at 20° was treated with 2 g. of *m*-chloroperbenzoic acid. After a total of 45 min., 20 g. of calcium hydroxide was added to the solution and the resulting mixture was stirred for 20 min. The solution was filtered and concentrated to dryness yielding 5 g. of the crude epoxide **15**. This product, in 20 ml. of ethylene dichloride and 20 ml. of acetic acid, was cooled to 0°. A solution of 2.5 g. of chromic acid in 25 ml. of 90% aqueous acetic acid was added over a 5-min. period. The mixture was stirred at 5° for 30 min. and at ambient temperature for 30 min. Sodium bisulfite (5 g.) in 20 ml. of water was added and the product was isolated by ether extraction.[27] Trituration of the residue with petroleum ether gave 0.35 g. of the hydroxy lactone **18a**, m.p. 260–268°, identical in the infrared with the authentic sample.

The mother liquors were chromatographed on silica, but afforded no additional lactone. The total product was recombined in 80 ml. of *t*-butyl alcohol containing 10 ml. of 10% aqueous potassium hydroxide. The mixture was stirred at the boiling point for 3 hr., then cooled, and diluted with water. Extraction with benzene[27] afforded 1.8 g. of an oil which was chromatographed on 100 g. of silica. The fractions eluted with 2% ethyl acetate in benzene yielded 0.52 g. of the unsaturated ketone **12a**, identical in the infrared with an authentic sample.

2-(3β,20α-Diacetoxy-16β-hydroxy-13β-etiojervan-17β-yl)propanoic Acid Lactone (18c).—The lactone **18a**, in acetic anhydride containing a little *p*-toluenesulfonic acid, was heated at 80° for 4 hr., providing the diacetate **18c**. This compound was recrystallized from acetone–petroleum ether to yield the pure material, m.p. 211–213°, λ_{max} 5.59 and 5.72 μ.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.81; H, 8.64.

Reduction of the diacetate **18c** with calcium in liquid ammonia led to amorphous products lacking lactone absorption in the infrared.

2-(3β,16β,20α-Trihydroxy-13β-etiojervan-17β-yl)propanol (19).—A solution of 0.33 g. of the lactone acetate **18b** in 30 ml. of tetrahydrofuran was added to a solution of 0.70 g. of lithium aluminum hydride in 30 ml. of boiling tetrahydrofuran. After 20 hr. the solution was cooled and 4 ml. of water was added cautiously followed by the addition of 1 ml. of 10% aqueous potassium hydroxide. The solution was filtered through Super-cel and the filter cake was washed well with hot ethanol. The filtrate was concentrated to dryness. The resulting product was washed with chloroform and the remaining insoluble material was taken up in 30 ml. of boiling ethanol. A small amount of inorganic salts was removed by filtration, and the filtrate was concentrated and diluted with a little water. The resulting product was 0.11 g. of the pure tetrol **19**, m.p. 238–243°, λ_{max}^{KB} 3.03 μ.

Anal. Calcd. for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 72.16; H, 10.35.

17β-Acetyl-13β-etiojervan-3β,16β-diol (20).—To a slurry of 80 mg. of tetrol **19** in 3 ml. of methanol and 0.5 ml. of pyridine was added a solution of 0.10 g. of periodic acid in 1 ml. of water. The solution became homogeneous within 10 min.; after 30 min. it was diluted with water yielding 70 mg. of crystalline material. Recrystallization of this compound from aqueous acetone afforded 60 mg. of the hydroxy ketone **20**, m.p. 160–164°, λ_{max} 2.75 and 5.89 μ, $\Delta\nu$ 132 c.p.s. ($COCH_3$).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.44; H, 10.40.

Treatment of this compound in methanol containing aqueous potassium hydroxide at room temperature for 10 min. gave in good yield the unsaturated ketone **12a**, identical in the infrared with the authentic sample.

Base Cleavage of the Acetyl Lactone 11.—A solution of 0.30 g. of the acetyl lactone **11** in 30 ml. of *t*-butyl alcohol and 5 ml. of 10% aqueous potassium hydroxide was stirred at reflux under nitrogen for 2 hrs. The solution was cooled and diluted with 2% aqueous hydrochloric acid. The resulting crystal mass was filtered and washed with water yielding 0.25 g. of crystals, m.p. 208–212°. Recrystallization from acetone gave 0.16 g. of lactone, m.p. 211–213°. To obtain an n.m.r. spectrum of this chloroform-insoluble material the acetate was prepared from acetic anhydride–pyridine. Recrystallization of 90 mg. of acetate gave 70 mg., m.p. 182–185°. Careful fractional crystallization from cyclohexane gave pure **2α-(3β-acetoxy-16β-hydroxy-13β-etiojervan-17β-yl)propanoic acid lactone (14)**, m.p. 198–201°; λ_{max} 5.65 and 5.79 μ; $\Delta\nu$ 48 and 55 (C-18 CH_3), 49 (C-19 CH_3), and 73 and 79 (C-21 CH_3) c.p.s.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.02; H, 9.47.

(32) J. B. Ziegler, W. E. Rosen, and A. C. Shabica, *J. Am. Chem. Soc.*, **77**, 1223 (1955); see also ref. 1a, p. 825.

Increasing the period of reflux with base to 18 hr. gave 0.34 g. of product, m.p. 212–235°, from 0.40 g. of the acetyl lactone **11**. The entire product was acetylated, giving 0.33 g., m.p. 178–182°. The n.m.r. spectrum of this material showed no distinct peaks for the C-21α methyl, but only shoulders on the major peaks at 75 and 83 c.p.s. Recrystallization from cyclohexane gave readily the pure C-20β methyl compound identical in the n.m.r. and infrared with authentic **10b**.

2-(16β-Hydroxy-3-keto-13β-etiojervan-17β-yl)propanoic Acid Lactone (10c).—A slurry of 1.0 g. of hydroxy lactone **10a** in 50 ml. of acetone was treated with 1.0 ml. of 4 *N* chromic acid[29] in a water bath at 20°. The crystals dissolved immediately and a green gum precipitated. After a total of 4 min. the solution was diluted with 5 ml. of methanol followed by water. The resulting precipitate was collected on a filter and was recrystallized from acetone–petroleum ether to yield 0.75 g. of the pure ketolactone **10c**, m.p. 183–186°, λ_{max} 5.68 and 5.85 μ, $[\alpha]_D$ −13°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.52; H, 9.34.

2-(16β-Hydroxy-3-keto-13β-etiojerv-1-en-17β-yl)propanoic Acid Lactone (13).—A solution of 0.40 g. of the ketolactone **10c** in 20 ml. of acetic acid was treated with a drop of hydrogen bromide in acetic acid and then with a solution of 1.0 mole equiv. of 0.23 *M* bromine in acetic acid solution. The bromine, added dropwise over a 3-min. period, was consumed immediately. The solution was diluted with water and the resulting crystalline precipitate was collected on a filter and washed with water, yielding 0.47 g. of crude bromide, m.p. 175–183°, λ_{max} 5.64 and 5.78 μ.

The bromo ketone (0.45 g.) was dissolved in 20 ml. of dimethyl formamide to which was added 10.0 g. of magnesium oxide. The mixture was heated at reflux for 90 min. and then cooled and diluted with excess aqueous hydrochloric acid. The mixture was extracted with benzene, washed three times with water dried, and concentrated to dryness. The residue, 0.37 g., was chromatographed on 30 g. of silica. Fractions eluted with 5% ethyl acetate in benzene were combined and recrystallized from acetone–petroleum ether to yield the unsaturated lactone **13** as an acetone solvate, m.p. 175–180°, λ_{max} 5.67 and 5.97 μ, λ_{max} 233 mμ (log ϵ 3.98).

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.28; H, 8.84.

Sesquiterpene Lactones. Coronopilic Acid

T. A. GEISSMAN AND RICHARD J. TURLEY

Contribution No. 1644 from the Department of Chemistry, University of California, Los Angeles, California

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Coronopilin, the sesquiterpenoid lactone of *Ambrosia psilostachya* DC., undergoes an acid-catalyzed dehydration–rearrangement that provides additional evidence for the structure assigned to it, and demonstrates the "abnormal" placement of the angular methyl group at C-5.

The structure of coronopilin (I), the major sesquiterpenoid constituent of *Ambrosia psilostachya* DC., has been established by Herz and Högenauer,[1] who showed that coronopilin is a dihydroparthenin. We had isolated coronopilin at about the same time from *A. psilostachya* and from *Franseria dumosa* Gray, and had reached the same conclusion regarding its structure, but on grounds that were quite different and which provide additional evidence concerning certain features of the chemistry of this compound.

In view of the results of Herz and Högenauer we need not describe the properties of coronopilin further than to say that a combination of analytical, spectrometric, and chemical diagnostic procedures established that coronopilin is a perhydroazulenic lactone that contains a cyclopentanone ring, an α,β-unsaturated γ-lactone with an exocyclic methylene group, and a hydroxyl group that is resistant to acylation and to chromic acid oxidation. The n.m.r. spectrum confirms the presence of a quaternary methyl group and a methyl group attached to a secondary carbon atom. The n.m.r. spectrum showed that the structure of coronopilin was that of the "abnormal" type typified by ambrosin.[2] These observations, coupled with reasonable inferences drawn from considerations of the numerous congeners of the type that are now known, left only the location of the hydroxyl and carbonyl groups in doubt, although their location as in I was regarded as likely.

Although Herz and his co-workers[3] record the failure of attempts to dehydrate coronopilin, treatment of the compound with acetic acid containing a small amount of sulfuric acid resulted in our hands in its smooth conversion in about 50% yield into a carboxylic acid with the composition of a monodehydration product of coronopilin. This compound, coronopilic acid, showed an intense ultraviolet absorption at 310 mμ (log ϵ 4.22) and formed a deep brown-red dinitrophenylhydrazone. It was clearly a dienone, showing that not only had the hydroxyl group of coronopilin been removed, but an additional double bond had been introduced with concomitant opening of the lactone ring. The new dienone system was isolated from the exocyclic methylene grouping of the lactone and of the acid, for the latter retained the characteristic absorption maximum of an α,β-unsaturated acid at 203 mμ (log ϵ 4.10) and could be converted into a pyrazoline (methyl ester) by the action of diazomethane. Ozonolysis of coronopilic acid yielded 35% of the theoretical amount of formaldehyde, and a Kuhn–Roth determination showed 1.74 C-linked methyl groups.

The unusual opening of the lactone ring under acidic conditions was taken as an indication that the hydroxyl group of coronopilin was located in such a position as to be uniquely involved in this reaction. Since this hydroxyl group was tertiary, and because the methyl group at C-10 was known (by n.m.r.) to be attached to a secondary carbon atom, only two positions for the hydroxyl group could be considered—C-1 and C-7—and, because the exocyclic methylene grouping of coronopilic acid was separate from the dienone system, position 7 was ruled out of consideration.

The first interpretation of the rearrangement that must have occurred during the dehydration reaction was that the opening of the lactone ring was accompanied by the migration of the methyl group from C-5 to C-6 (II), but it is now known that the structure of coronopilic acid is III.

(1) W. Herz and G. Högenauer, *J. Org. Chem.*, **26**, 5011 (1961).

(2) W. Herz, M. Miyazaki, and Y. Kishida, *Tetrahedron Letters*, **No. 2**, 82 (1961).

(3) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).