dealing with SN2 reactions on carbon, hydrogen, and heteroatoms. No other valence theory presently makes allowance for L strain although this may come about in the future, since the Linnett theory is complementary to, and not incompatible with, the valence bond and molecular orbital viewpoints. A strong point of the new method is the facility with which it can be applied. Definite structures are easily assigned to molecules and transition states with no need to invoke dotted-bond forms with vague properties. The systematic application of Linnett's theory to other organic reactions will follow in due course.

The 12α,13β-Etiojervane Analog of Testosterone

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The 3-keto-17α-acetoxyetiojervane **1f** was converted *via* the 2,4-dibromide to the unsaturated ketone **5f**; room-temperature formation of the ethylenedioxy ketal **6e** followed by successive saponification, oxidation, and hydride reduction afforded the 17β-hydroxy derivative **6a** (R′ = $-CH_2CH_2-$) which was hydrolyzed to the title compound. Attempts to prepare and use the 2,4-dibromide **4b** in the 17β-acetoxy series were unsuccessful. The corresponding 12β-etiojervanes were prepared from jervine by modification and extension of known methods.

The objective of the research described here was to synthesize, starting from hecogenin, simple etiojervane derivatives which would display some of the potent physiological characteristics of the Veratrum alkaloids.[1] The initial group of etiojervanes (12α, 13α)[2] prepared had both a C/D cis ring fusion and a 13α substituent (methyl) in analogy to the Veratrum alkaloids. These derivatives had no noteworthy physiological activity. The serendipitous preparation[3] (by fermentation) of the corresponding 13β-methyldione **5d** (Δ^1), however, led to the syntheses of a series of compounds with good potency as antialdosterone agents.[4]

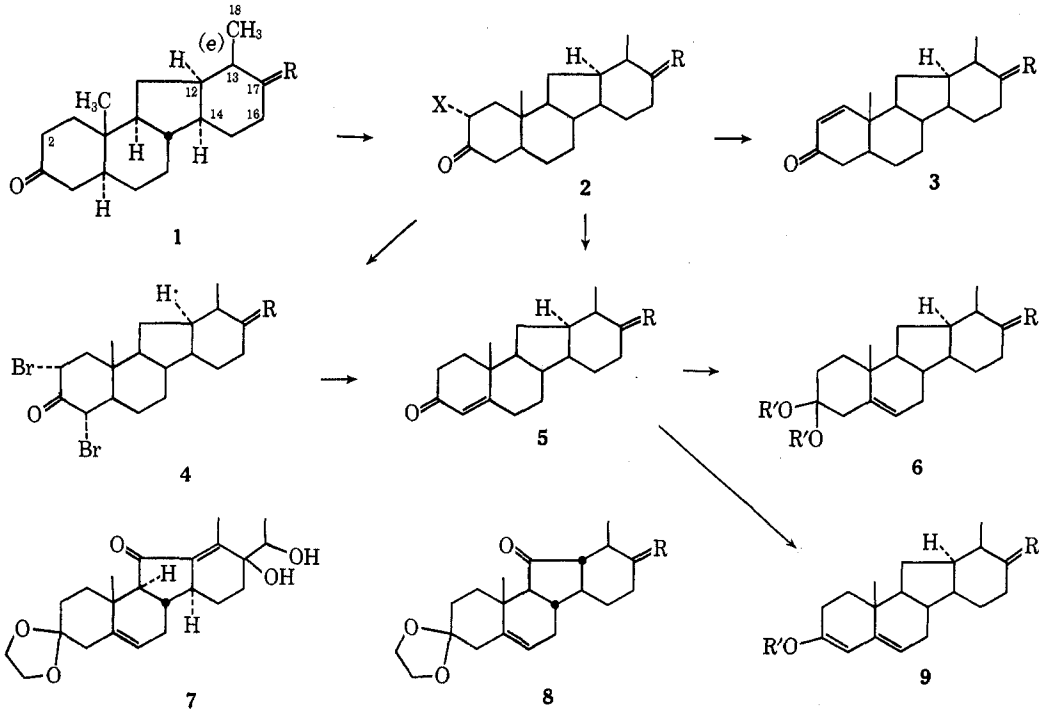
The primary target of our research was a practicable synthesis of the title compound **5a**. One starting material was the saturated 3-ketone **1b**, obtained by rearrangement of hecogenin and subsequent degradation of the sapogenin side chain.[5] The 2-monobromide **2b** was investigated as a possible intermediate to be used in the introduction of the C-4 double bond. The bromide **2b**, a crystalline compound prepared by direct bromination of the ketone **1b**, had both gross structure (C-2 bromine) and configuration (α-bromine) in analogy to the steroidal bromination product, as suggested by nmr and ORD measurements.[6] A chemical confirmation was obtained by zinc–acetic acid reduction to starting material **1b** and by magnesium oxide dehydrohalogenation to give preponderantly the Δ^1 ketone **3b**. A minor by-product of the latter reaction was the Δ^4 ketone **5b** which was separated and characterized. The monobromide **2f** (17α-acetate) underwent analogous reactions, although neither the 17α-acetate **3f** nor its alcohol **3e** was obtained in a crystalline form.

Dehydrobromination of 2-bromo steroids with lithium chloride in dimethylformamide proceeds vinylogously to yield 45% of the Δ^4 derivative.[7] With the etiojervane monobromide **2f**, the same reagent afforded, rather than an elimination product, a displacement product, the monochloride **2f** (X = Cl). The same chloride was produced readily from the monobromide over a wide range of temperatures. Similarly, treatment of the bromide with sodium iodide provided an iodo derivative (**2f**, X = I). The position of the chlorine atom in **2f** was not readily determined because of its stability to relatively vigorous dehydrohalogenation conditions; treatment of the compound in boiling collidine for 7 hr effected little change in the starting material. With magnesium oxide in boiling dimethylformamide, the monochloride **2f** slowly yielded mixtures from which the Δ^1 derivative **3f** could be isolated. In contrast, the iodide underwent a facile elimination to give mainly the Δ^1 ketone, thus supporting directly the assigned position of the iodine atom in the iodo ketone **2f** and indirectly the position of the chlorine atom in the chloro ketone **2f**. The configuration of the chlorine atom in **2f** was determined by ORD and nmr measurements.[8]

The behavior of the 2-monobromo-17β-acetate **2b** on treatment with lithium chloride differed markedly from that of the corresponding 17α-acetate, reacting very slowly in this case and producing an intractable chlorine-containing mixture. Under conditions vigorous enough to remove halogen, the product lacked an unsaturated ketone component (ir analysis). Several other reagents also failed to generate an unsaturated ketone from the lithium chloride product. The difference in behavior between the 17α-acetate and the more strained 17β-acetate[9] on treatment with lithium chloride may be attributed either to a long-range effect (transmission of strain through the carbon–carbon bonds) or to a steric effect (produced by the cupping of the D ring toward the β face of the A ring). Molecular models imply the former to be the more important cause.

Direct dibromination of the 3-keto-17α-acetate **1f** led to the 2,4-dibromide **4f** in good yield. Treatment of this compound sequentially with sodium iodide, acid,

(1) S. M. Kupchan and A. W. By in "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, Chapter 2.
(2) W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 123 (1965).
(3) W. F. Johns, *ibid.*, **35**, 3524 (1970).
(4) The physiological activity of the compounds reported will appear in a forthcoming publication.
(5) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964).
(6) Professor W. Klyne, Westfield College, University of London, kindly supplied this data and its interpretation.
(7) B. J. Magerlein, *J. Org. Chem.*, **24**, 1564 (1959).
(8) Preparation of 2-iodocholestanone from the 2-bromide has been recorded: G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Amer. Chem. Soc.*, **72**, 4077 (1950). The displacement by chloride, however, leads to elimination (ref 7). For displacement of halo ketones at other positions, *cf.*, *inter alia*, G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961).
(9) The 17β derivatives are more strained because of the interaction of the 17β substituents with C-19. See ref 2 for a further discussion of this point.



a, R = β-OH; b, R = β-OAc; c, R = β-OCOPh; d, R = O; e, R = α-OH; f, R = α-OAc

and zinc–acetic acid[10] produced the Δ^4 derivative **5f** in good yield. The dibromide also underwent dehydrohalogenation with magnesium oxide to afford the 1,4-dienone (**5f**, Δ^1). The Δ^4-acetate **5f** was saponified to its alcohol **5e**, and this in turn was oxidized to the ketone **5d**.

Dibromination of the 17β-acetoxy 3-ketone **1b** led to the formation of an amorphous, heterogeneous product. Although the elemental analysis was acceptable, the spectral data were ambiguous as were the subsequent chemical reactions. Direct dehydrobromination of the dibromide with magnesium oxide gave intractable mixtures instead of the expected 1,4-dienone. The sodium iodide procedure gave a nonpolar mixture which crystallized in part to yield a component with an empirical formula of $C_{19}H_{30}O$ (elemental analysis, mass spectrum). The exact structure of this compound was unclear from its spectra, but it is thought to represent D-ring deoxygenated material.

Inversion of the 17α-hydroxy group in the available unsaturated ketone **5e** to provide the desired 17β isomer **5a** was attempted by tosylate formation followed by formolysis. The product was largely olefinic. Inversion by oxidation of the 17α-hydroxyl to a ketone and subsequent reduction to the 17β-hydroxyl had been demonstrated in the A-ring saturated etiojervanes[3] but was complicated in the present case by the unsaturated 3-ketone. Lithium tri-*tert*-butoxyaluminohydride reduction of the 17-carbonyl of **5d** proceeded at a rate slow enough to cause partial reduction of the 4,5 double bond. Lithium aluminum hydride reduction of **5d** afforded the unsaturated diol (**5a**, 3β-OH), but manganese dioxide oxidation to regenerate the unsaturated ketone proceeded only in moderate yields.

Attempts to protect the unsaturated ketone moiety while inverting the 17α-hydroxyl function uncovered a marked instability of the Δ^4-etiojervene in contrast to the normal steroid, presumably due to inherently greater bond strain in the former. Thus acetic anhydride–toluenesulfonic acid treatment of **5f** gave intractable tars instead of the desired enol acetate **9f** (R′ = Ac). Enol ether formation with trimethyl orthoformate provided mixture of dienol ether **9f** (R′ = Me) and ketal **6f** (R′ = Me). Purification of the mixture was abandoned when it was discovered that the dienol grouping was oxidized with the Sarett reagent.[11] Preparation of the ethylenedioxy ketal was successful only through use of a room temperature procedure employing ethylene glycol and triethyl orthoformate.[12] Subsequent oxidation of the 17α-hydroxyl, reduction of the resulting ketone with lithium tri-*tert*-butoxyaluminohydride, and hydrolysis of the ketal group gave the desired 17β-hydroxy compound **5a** in good overall yield.

Despite the modest yields obtained of the 1,4-dienone (**5b**, Δ^1) by direct selenium dioxide oxidation of the saturated ketone **1b**,[2] investigations were also made into the selective reduction of its Δ^1 bond. Brief lithium–ammonia treatment[13] gave the desired 3-keto-4-ene contaminated with appreciable amounts of the saturated ketone. Hydrogenation of the dienone in the presence of tristriphenylphosphorhodium catalyst[14] was highly erratic and very slow, giving in the best instance, less than 30% of the desired 4-ene after a 28-hr period.

The need for biological comparisons between the

(10) K. Schreiber, A. Walther, and H. Rönsch, *Tetrahedron*, **20**, 1939 (1964). Also see ref 8.

(11) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(12) This procedure was developed by H. L. Dryden, Jr., and G. Webber of these laboratories for use on steroidal 17-ketones; *cf.* also British Patent 850,386 (1960); *Chem. Abstr.*, **56**, 8800*b* (1962).

(13) R. E. Schaub and M. J. Weiss, *Chem. Ind. (London)*, 2003 (1961); E. Shapiro, T. Legatt, L. Weber, M. Steinberg, and E. P. Oliveto, *ibid.*, 300 (1962).

(14) (a) A. J. Birch and K. A. M. Walker, *J. Chem. Soc.*, 1894 (1966); (b) C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, **88**, 4537 (1966).

C/D *cis*- and *trans*-etiojervanes dictated the synthesis of the latter. The route chosen involved modification and extension of the known degradation of jervine.[15] Among the changes made was the replacement with manganese dioxide of the chromium trioxide used in the cleavage of the 17,20-glycol **7**, affording a yield of 76% of the crystalline enedione **8d** (Δ^{12}). At a subsequent step, the efficiency of the Wolff–Kishner reduction of the 11-ketone was improved by use of hydrazine dihydrochloride in triethylene glycol to form the hydrazone as a discrete step before the addition of potassium hydroxide. Each of the isomers prepared was hydrolyzed to give the free 12β,13β-testosterone analogs (**5a**, **5e**; 12β-H). Chromic acid oxidation provided the 17-keto derivative **5d** (12β-H).

Experimental Section[16]

2α-Bromo-17β-acetoxy-12α-etiojervan-3-one (2b, X = Br).—Pyridinium bromide perbromide (1.11 g) was added in four portions over a 5-min period to a solution of 0.99 g of the acetate **1b**[3] in 50 ml of acetic acid containing a trace of hydrogen bromide. After 2 min more, the solution was diluted with water and aqueous sodium thiosulfate. The resultant precipitate was collected, washed with water, dried, and recrystallized from acetone–hexane to yield 0.50 g of the bromide **2b**: mp 153–155°; λ_{max} 5.78 μ; Δν 52 and 59 (18-Me), 66 (19-Me) 288 (q, CHBr) Hz; ORD (in 2:1 MeOH/dioxane) $[\phi]^{pk}_{306\ m\mu}$ 2940; $[\phi]^{tr}_{263\ m\mu}$ −3170°; $a = +62$.[6]

Anal. Calcd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60; Br, 19.43. Found: C, 61.63; H, 7.58; Br, 19.36.

Treatment of the monobromo compound **2b** with zinc dust in acetic acid at room temperature for 3 hr gave a good yield of the saturated 3-ketone **1b**.

The 17-benzoate **1c** was prepared by benzoyl chloride–pyridine treatment of the alcohol **1a**.[3] The resulting amorphous compound was monobrominated to provide a chromatographically and spectrally homogeneous, but amorphous, bromide **2c**.

Anal. Calcd for $C_{26}H_{33}BrO_3$: Br, 16.88. Found: Br, 17.04.

17β-Hydroxy-12α-etiojerv-1-en-3-one (3a).—A solution of 0.17 g of the crystalline bromide **2b** in 20 ml of dimethylformamide was added to a stirred, boiling mixture of 1.0 g of magnesium oxide in 30 ml of dimethylformamide under an atmosphere of nitrogen over a 10-min period. After 3 hr the cooled solution was filtered and concentrated to dryness. The residue was chromatographed but failed to crystallize. Similar treatment of the 2α-bromo 17-benzoate **2c** gave again an amorphous product.

A solution of 0.81 g of the benzoate **2c** in 30 ml of *tert*-butyl alcohol containing 5 ml of 10% aqueous potassium hydroxide was boiled in an atmosphere of nitrogen with stirring for 25 hr. The solvent was removed in a stream of nitrogen and the product was extracted with methylene chloride. Chromatography[17] yielded first, by elution with 15% ethyl acetate–benzene, material recrystallized from acetone–hexane to yield the alcohol **3a** as a hemiacetonate: mp 84–87°; λ_{max} 2.72, 5.95 μ; Δν 59 and 68 (18-Me), 62 (19-Me), 350 (d, 1-H), 422 (d, 2-H) Hz.

Anal. Calcd for $C_{19}H_{28}O_2 \cdot {}^1/_2C_3H_6O$: C, 77.56; H, 9.84. Found: C, 77.71; H, 9.81.

The Δ^4 derivative (**5a**, 45 mg), identical with the material prepared below, was obtained by further elution of the column with 20% ethyl acetate–benzene.

Lithium Chloride Treatment of the 2α-Bromo-17β-acetate 2b.—Treatment of the bromide **2b** in dimethylformamide containing lithium chloride at 80° for 2 hr returned 90% of starting material unchanged and no chloro derivatives (halogen analysis). After 20 hr at 95°, an amorphous product was isolated.[18]

Anal. Calcd for $C_{21}H_{31}ClO_3$: Cl, 9.66. Found: Cl, 6.14 (no bromine).

Raising the temperature to the boiling point of dimethylformamide for 2 hr gave a dark product lacking halogen and lacking unsaturated ketone absorption in the ir. Use of lithium chloride–lithium carbonate in the same solvent offered similar results.

Among the reagents used in an attempt to convert the bromide **2b** to the Δ^4 ketone **5b** were ethanolic acid at reflux, collidine at reflux, and semicarbazone formation followed by pyruvic acid reversal. In each of these instances the yield of the desired unsaturated ketone was negligible.

2α-Bromo-17α-acetoxy-12α-etiojervan-3-one (2f).—A solution of bromine in acetic acid (41.4 ml, 0.38 *M*) was added over a 20-min period to a stirred solution of 4.75 g of the ketone **1f** in 200 ml of acetic acid containing a trace of hydrogen bromide at 15°. After an additional 5 min, the solution was diluted with water, and the resulting precipitate was collected, washed with water, dried, and recrystallized from methylene chloride–hexane to yield 4.4 g of the bromide **2f**: mp 142–147°; λ_{max} 5.78 μ; Δν 52 and 58 (18-Me), 64 (19-Me), 287 (q, CHBr) Hz.

Anal. Calcd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60; Br, 19.43. Found: C, 60.44; H, 7.65; Br, 19.60.

Dehydrohalogenation of Bromo Ketone 2f.—Lithium chloride–lithium carbonate dehydrohalogenation of bromide **2f** in boiling dimethylformamide for 1 hr gave an amorphous olefin with the proper spectral characteristics for the Δ^1 ketone **3f**: λ_{max} 232 mμ (ε 5350); λ_{max} 5.78, 5.95 μ; Δν 53 and 59 (18-Me), 60 (19-Me), 350 (d, 1-H), 427 (d, 2-H) Hz.

Saponification of this material in methanol with aqueous potassium hydroxide gave only an amorphous product.

2α-Chloro-17α-acetoxy-12α-etiojervan-3-one (2f).—The bromo ketone **2f** (0.75 g) was added to a solution of 1.0 g of lithium chloride in 20 ml of dimethylformamide with stirring. After 7 hr at room temperature, the solution was diluted with water. The resulting precipitate was collected and dried, yielding 0.55 g of essentially pure chloride **2f**, mp 147–152° (found: 9.44% Cl). Recrystallization of this sample from methylene chloride–hexane gave the pure material: mp 163–167°; λ_{max} 5.78 μ; Δν 52 and 58 (18-Me), 65 (19-Me), 279 (q, CHCl) Hz; ORD[19] (*c* 1.05, dioxane) $[\phi]^{pk}_{313\ m\mu}$ +2720; $a = +71$.

Anal. Calcd for $C_{21}H_{31}ClO_3$: C, 68.74; H, 8.52; Cl, 9.66. Found: C, 68.76; H, 8.35; Cl, 9.64.

Dehydrohalogenation of the Chloro Ketone 2f.—The chloro ketone **2f** was essentially inert to lithium chloride in dimethylformamide at 95° for 3 days or to refluxing collidine for 7 hr. Magnesium oxide in boiling dimethylformamide transformed the chloro ketone **2f**, after 6 hr, into a product containing 20% starting material and the rest a mixture of the Δ^1 ketone **3f** mixed with a small amount of the Δ^1 ketone **5f**. The chloro ketone **2f** displayed a slightly lower stability with lithium chloride and lithium carbonate in boiling dimethylformamide.

Attempts to dehydrochlorinate the chloro ketone **2f** by treatment of its semicarbazone with pyruvic acid[20] were unsuccessful.

Formation and Dehydroiodination of 2α-Iodo-17α-acetoxy-12α-etiojervan-3-one (2f).—Potassium iodide (0.2 g) was added to a solution of 0.20 g of the bromo ketone **2f** in 2 ml of acetone at 5°. After 3 hr at an ambient temperature, the solution was diluted with water and the precipitate collected. The product was recrystallized from aqueous methanol to yield 0.12 g of the iodo ketone: mp 125–134°; λ_{max} 5.75 μ.

Anal. Calcd for $C_{21}H_{31}IO_3$: I, 27.59. Found: I, 29.30 (no bromine).

Treatment of this product with lithium carbonate in hot dimethylformamide afforded the Δ^1 ketone **3f** as the major product (by nmr analysis).

2α,4α-Dibromo-17α-acetoxy-12α-etiojervan-3-one (4f). A. Direct Bromination (Procedure A).—A bromine–acetic acid solution (250 ml, 0.38 *M*) was added over a 25-min period to a solution

(15) (a) S. M. Kupchan and S. D. Levine, *J. Amer. Chem. Soc.*, **86**, 701 (1964). (b) See also an alternate route described in the more recent work of T. Masamune and K. Orito, *Tetrahedron*, **25**, 4551 (1969).

(16) The infrared spectra were determined in chloroform, ultraviolet spectra in methanol, optical rotations in chloroform, and nmr spectra in deuteriochloroform (TMS as an internal standard, Δν = 0 Hz on a Varian A-60 spectrometer). We are indebted to Dr. J. W. Ahlberg and staff for these results as well as for the elemental analyses reported. Melting points were taken on a Fisher–Johns apparatus and are uncorrected.

(17) The chromatographies described in this section were uniformly run on a weight of Davison silica gel 60 times the weight of the compound involved. We thank Mr. R. T. Nicholson and staff for the competent execution of this work.

(18) The isolation procedure used throughout this work involved dilution of the reaction mixture with water, evaporation of water-soluble solvents more volatile than water, and extraction with an immiscible solvent. The extract was routinely dried over magnesium sulfate and the solvent removed under reduced pressure (T <50°).

(19) This ORD was run by N. L. McNiven, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

(20) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

at 15° of 14.5 g of the ketone **1a** in 200 ml of acetic acid containing a trace of hydrogen bromide. The solution was stirred 2 hr more during which time the dibromide precipitated. The mixture was diluted with 2 l. of water and the crystals were collected on a filter, washed with water, and dried, yielding 20.6 g of the dibromide, mp 160–161°. Recrystallization of a portion of this material from aqueous acetone afforded the pure compound **4f**: mp 168–169°; λ_{max} 5.71 (m), 5.80 (s) μ; $\Delta\nu$ 52 and 58 (18-Me), 68 (19-Me), 285 (m, 17-H, 2β-H, 4β-H) Hz.

Anal. Calcd for $C_{21}H_{30}Br_2O_3$: Br, 32.60. Found: Br, 32.75.

Addition of 100 mg of the dibromide **4f** to 0.2 g of lithium carbonate and 0.1 g of lithium chloride in 10 ml of refluxing dimethylformamide led, after 4 hr, to formation of the dienone ($\Delta^{1,4}$ derivative of **1f**) separated by chromatography and identified by its nmr spectrum.[3]

B. Bromination of the Bromide 2f.—Bromination of the 2-bromo compound **2f** (4.3 g) in 90 ml of acetic acid containing 10 g of potassium acetate with 1.3 equiv of bromine in acetic acid at 90° for 10 min caused a disappearance of the bromine color. The resulting product could not be obtained in a crystalline form however. Treatment of this material with hydrogen bromide in acetic acid (2 hr, room temperature) led to a moderate yield of the above crystalline 2,4-dibromide **4f**.

17α-Acetoxy-12α-etiojervan-4-en-3-one (5f, Procedure B).—Iodoacetone[10] was prepared by dropwise addition of 20 ml of bromine over 15 min to 0.6 l. of acetone with cooling. The decolorized solution was stirred well with 200 g of potassium carbonate and filtered into a solution of 2 l. of acetone containing 400 g of sodium iodide. The solution was boiled under nitrogen for 15 min. The dibromo ketone **4f** (45 g) was then added and the solution was distilled slowly for a 2-hr period to a 1.5-l. volume. Oxalic acid (30 g) was added in several portions and the heating continued for an additional 30 min. The reaction mixture was diluted with 2 l. of ethyl acetate and was filtered. The filtrate was washed with water, bicarbonate solution, and water. The combined extracts, after drying, were diluted with 50 ml of acetic acid and then, with stirring and cooling, 100 g of zinc dust was added in several portions. After 0.5 hr, the mixture was filtered and the filtrate washed with water and bicarbonate. The dried extract was concentrated to dryness. Tlc indicated that it was largely the desired unsaturated ketone **5f** contaminated with the starting saturated ketone **1f**. Attempts to purify the product by crystallization or by formation of its sodium bisulfite adduct were unsuccessful. Chromatography of the product yielded first the saturated ketone **1f**, eluted with 3% ethyl acetate–benzene. Eluted shortly after this were fractions which were combined and recrystallized from ether–cyclohexane to yield the pure unsaturated ketone **5f**: mp 84–85°; λ_{max} 5.79, 6.01 μ; λ_{max} 239 mμ (ϵ 17,000); $\Delta\nu$ 52 and 59 (18-Me), 70 (19-Me), 123 (OAc), 346 (C=CH) Hz.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.26; H, 9.34.

More polar fractions contained heterogeneous, amorphous, materials which proved intractable.

17α-Hydroxy-12α-etiojerv-4-en-3-one (5e).—A solution of 100 mg of the acetate **5f** in 2 ml of methanol containing 0.2 ml of 10% aqueous potassium hydroxide was boiled in an atmosphere of nitrogen for 1 hr. The methanol was distilled and the remaining mixture was diluted with water. The resulting precipitate was collected, dried, and recrystallized from acetone–hexane to afford 45 mg of the alcohol **5e**: mp 136–138°; λ_{max} 2.75, 6.02 μ; λ_{max} 239 mμ (ϵ 16,700); $\Delta\nu$ 60 and 67 (18-Me), 70 (19-Me), 347 (4-H) Hz; $[\alpha]_D$ 73°.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.23; H, 9.82.

This compound formed an amorphous tosylate which on treatment with sodium formate in hot dimethylformamide led to intractable products.

12α-Etiojerv-4-ene-3,17-dione (5d, Procedure C).—The 17α alcohol **5e** (0.20 g) was oxidized with the Sarett ragent[11] prepared from 0.2 g of chromium trioxide and 2 ml of pyridine. The reaction mixture was diluted with water after 6 hr at room temperature. The product was isolated by ether extraction and afforded, after recrystallization from ether–cyclohexane, 0.14 g of the diketone: mp 169–172°; λ_{max} 239 mμ (ϵ 16,000); λ_{max} 5.83, 6.00 μ; $\Delta\nu$ 57 and 64 (18-Me), 66 (19-Me) Hz; $[\alpha]_D$ −39°.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.46; H, 9.31.

Attempted Formation of 2,4-Dibromo-17β-acetoxy-12α-etiojervan-3-one (4b).—The dibromination procedure A given above, when applied to the 17β-acetate **1b**, afforded an amorphous mixture (I). Treatment of mixture I with sodium iodide according to procedure B led to an amorphous nonpolar mixture from which was isolated, after chromatography, a small amount of crystalline material: mp 103–110°; λ_{max} 5.80 μ; $\Delta\nu$ 57 Hz (broad methyl signal). The mass spectrum of this component showed a molecular ion of 274, implying the compound has an empirical formula of $C_{19}H_{30}O$.

Direct dehydrobromination of the "dibromide" (mixture I) with magnesium oxide led to intractable mixtures in which the desired dienone (**1b**, $\Delta^{1,4}$) was a negligivele component.

When the dibromination and sodium iodide sequence (procedures A, B) were carried out on the 17β-benzoate **1c**, a nonpolar fraction was again produced, but in this case it was accompanied by a small amount of the desired unsaturated ketone **5c** and the saturated ketone **1c**.

12β-Etiojerv-4-ene-3β,17β-diol (5a, 3β-OH).—A solution of 0.57 g of the dione **5d** in 100 ml of ether and 5 ml of tetrahydrofuran was added to a solution of 0.30 g of lithium aluminum hydride in 100 ml of ether over a 30-min period maintaining the temperature at −10°. After an additional 20 min, excess ethyl acetate was added dropwise followed by 2 ml of 10% aqueous potassium hydroxide. The mixture was filtered through Super-cel and the filtrate was concentrated to dryness. The resulting crystalline residue was recrystallized from ethyl acetate to yield 0.21 g of the diol: mp 187–191°; λ_{max} 3.02, 6.03 (w) μ (KBr); $\Delta\nu$ 51 and 58 (18-Me), 57 (19-Me), 312 (C=CH, 4-H) Hz [$(CD_3)_2SO$].

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.78; H, 10.64.

Oxidation of the diol **5a** (3β-OH) with MnO_2 in chloroform for 22 (or 40 hr) gave the desired unsaturated ketone **5a** in 55% yield.

The reduction of **5d** with lithium tri-*tert*-butoxyaluminohydride was less than half complete after 4 hr at room temperature.

3,3-Ethylenedioxy-12α-etiojerv-5-en-17α-ol (6e, R′ = $-CH_2-CH_2-$).—Concentrated sulfuric acid (0.5 ml) was added to a slurry of 1.35 g of the unsaturated ketone **5e** in 15 ml of ethylene glycol (redistilled) and 1 ml of trimethyl orthoformate (redistilled). The mixture became homogeneous, turned darker in color, and afforded a new precipitate within 1 min. After 5 min, 1 ml of tetramethylguanidine was added followed by dilution of the reaction mixture with water. The crystalline product was collected, washed, dried, and recrystallized from acetone–hexane (darco) to yield 1.16 g of the ethylenedioxy ketal **6e**: mp 163–166°; λ_{max} 2.75 μ; $\Delta\nu$ 61 and 67 (18-Me), 67 (19-Me), 237 (OCH_2-CH_2O-), 325 (m, 6-H) Hz.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.02; H, 9.84.

Treatment of the ketal with acidified aqueous acetone afforded a good yield of the starting material (**5e**).

Treatment of the unsaturated ketone **5e** using the normal ketal procedure (refluxing benzene, ethylene glycol, and toluenesulfonic acid) gave after a short time a dark mixture of intractable products. Use of adipic acid in boiling benzene containing ethylene glycol effected no reaction after 24 hr.

3,3-Ethylenedioxy-12α-etiojerv-5-en-17-one (6d, R′ = $-CH_2-CH_2-$).—The ketal **6e** (R′ = $-CH_2CH_2-$) (1.2 g) was oxidized according to procedure C for 7 hr at room temperature. The product was recrystallized from acetone hexane to afford 0.97 g of the product: mp 170–173°; λ_{max} 5.82 μ; $\Delta\nu$ 57 and 64 (18-Me), 57 (19-Me), 322 (m, 6-H) Hz.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.15; H, 9.06.

3,3-Ethylenedioxy-12α-etiojerv-5-en-17β-ol (6a, R′ = $-CH_2-CH_2-$).—Lithium tri-*tert*-butoxyaluminohydride (15 g) was added to a solution of 6.9 g of **6d** (R′ = $-CH_2CH_2-$) in 250 ml of tetrahydrofuran at 5°. After 20 hr at ambient temperature, the solution was diluted with 2% aqueous acetic acid. The product was extracted with methylene chloride and was recrystallized from ether–hexane, yielding 4.23 g of the ketal **6a** (R = $-CH_2-CH_2-$): mp 113–115°; λ_{max} 2.75 μ; $\Delta\nu$ 62 (19-Me), 59 and 66 (18-Me), 237 (OCH_2CH_2O), 326 (m, 6-H) Hz; $[\alpha]_D$ −56°.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 76.36; H, 9.15. Found: C, 76.05; H, 9.08.

Less than 10% of the 17α-ol was present in the mother liquors (tlc analysis).

17β-Hydroxy-12α-etiojerv-4-en-3-one (5a). A. Hydrolysis of the Ketal 6a (R′ = $-CH_2CH_2-$).—The ketal **6a** (R′ = $-CH_2CH_2-$) (3.0 g) in 100 ml of acetone and 10 ml of water was boiled for 1 hr under an atmosphere of nitrogen. The solution was diluted

with water and the acetone distilled. The resulting precipitate was collected and washed with water. Recrystallization gave the pure unsaturated ketone **5a**: mp 159–160°; λ_{max} 239 mμ (ε 16,300); λ_{max} 2.72, 5.98 μ; Δν 58 and 66 (18-Me), 71 (19-Me), 347 (4-H) Hz; $[\alpha]_D$ +111°.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.03; H, 9.81.

B. Reduction of the Dienone (1a, $\Delta^{1,4}$; Procedure D).—A solution of 0.90 of the dienone **1a** ($\Delta^{1,4}$) in 20 ml of tetrahydrofuran was added to a solution of 0.30 g of lithium metal in 200 ml of distilled ammonia at −70° over a 40-sec period. After an additional 1 min, 2 g of ammonium chloride was added causing discharge of the color within 1 min. The ammonia was distilled and the mixture diluted with water. The product, isolated by ether extraction, crystallized and was recrystallized from ether–hexane to yield 0.55 g of the unsaturated ketone **5a**, mp 148–150°.

The mother liquors consisted of unreduced starting material (**1a**, $\Delta^{1,4}$) and the saturated ketone **1a**.

Several hydrogenations of the dienone (**1a**, $\Delta^{1,4}$) in the presence of tristriphenylphosphorhodium catalyst afforded at best 30% of the monounsaturated ketone **5a** after 28 hr. (The same batch of catalyst reduced Δ^1-testosterone efficiently.)

17β-Acetoxy-12α-etiojerv-4-en-3-one (5b) was an amorphous compound obtained either by acetylation of the corresponding alcohol **5a** with acetic anhydride–pyridine or by use of the lithium reduction (procedure D) on the dienone acetate (**1b**, $\Delta^{1,4}$). The acetate **5b** could be hydrolyzed in good yield with potassium hydroxide to yield the free alcohol **5a**.

Trimethyl Orthoformate Treatment of the Unsaturated Ketone 5e.—Concentrated sulfuric acid (0.2 ml) in 2 ml of methanol was added to a slurry of 1.0 g of the unsaturated ketone **5e** in 8 ml of methanol and 2 ml of trimethyl orthoformate with stirring. The reaction mixture quickly became homogeneous and dark. After 0.5 hr, 1 ml of pyridine was added and the mixture was extracted with methylene chloride. The oily product (mixture II) showed a maximum at 239 mμ (6280), 188 and 193 (OMe:ketal), and 215 Hz (OMe:enol ether) indicating the product was approximately 30% enol ether **9e** (R′ = Me) and 70% ketal **6e** (R′ = Me). In other runs, variations in proportions of solvents and reagents, length of reaction time, or change in the acid used led to no significant change in the relative proportion of products. Triethyl orthoformate gave comparable results. Acid hydrolysis of these mixtures yielded a maximum of 75% of the starting material **5e**.

Use of the Sarett reagent (procedure C) on mixture II at 5° for 5 hr gave a product lacking enol ether absorption but containing the ketal bands: Δν 187 and 193 Hz (OMe), 55 (19-Me), 58 and 66 (18-Me) Hz.

Manganese Dioxide Oxidation of 3-Ethylenedioxy-17,20-dihydroxypregnajerva-5,12-dien-11-one (7).—The diol **7**[21] (2 g) in 100 ml of chloroform was stirred with 4.0 g of activated manganese dioxide (Beacon Chemical Industries) for 3 hr. The mixture was filtered and the solvent distilled, yielding a yellow oil which was crystalled from acetone–cyclohexane to yield 1.35 g, mp 174–177°, and 0.24 g, mp 168–173°, of the 3-ethylenedioxyetiojerva-5,12-diene-11,17-dione, (**8d**, Δ^{12}) with ir and nmr spectra identical with those of an authentic sample.[21]

17β-Hydroxyetiojerv-4-en-3-one (5a, 12β-H; Procedure D).—A solution of 0.5 g of the ketal **8a**, 0.8 g of hydrazine dihydrochloride, and 3.5 ml of hydrazine hydrate in 20 ml of triethylene glycol was distilled slowly until the temperature of the vapors reached 165°. A reflux condenser was then installed above the reaction mixture (care). The temperature was held at 160–165° for 1.5 hr more, the mixture was cooled to 100°, and 1.5 g of potassium hydroxide was added. The reaction mixture was heated to 210° with slow distillation and held at 210–220° for a total of 2 hr. The mixture was cooled and then diluted with ice water. The product, isolated by ether extraction, was hydrolyzed by boiling for 16 hr in 30 ml of acetone, and 3 ml of water containing 35 mg of *p*-toluenesulfonic acid. Water was added, the acetone was distilled, and the product was extracted with ether. The crude extract was recrystallized twice from acetone–cyclohexane to yield the alcohol solvated with 0.25 mol equiv of acetone (**5a**, 12β-H): mp 176–178°; λ_{max} 2.75, 6.02 μ; Δν 57 and 62 (18-Me), 68 (19-Me), 344 (4-H) Hz.

Anal. Calcd for $C_{19}H_{28}O \cdot {}^1/_4C_3H_6O$: C, 78.30; H, 9.82. Found: C, 78.45; H, 9.46.

17α-Hydroxyetiojerv-4-en-3-one (5e, 12β-H).—The ketal **8e**[21] was treated according to procedure D and provided, after recrystallization from acetone–hexane, the unsaturated ketone (**5e**, 12β-H): mp 144–146°; λ_{max} 2.74 and 6.00 μ.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.77; H, 9.67.

12β-Etiojerv-4-ene-3,17-dione (5d, 12β-H).—The alcohol **5e** (12β-H) was oxidized with Sarett reagent (procedure C) for 1 hr. The product was isolated and recrystallized from acetone–hexane, affording 0.13 g of the dione **5d** (12β-H): mp 164–170°; λ_{max} 5.85, 6.00 μ; λ_{max} 239 mμ (ε 16,600); Δν 58 and 65 (18-Me), 69 (19-Me), 346 (4-H) Hz.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.68; H, 8.96.

Registry No.—**2b** (X = Br), 27141-96-4; **2f** bromide, 27141-97-5; **2f** chloride, 27141-98-6; **2f** iodide, 27141-99-7; **3a**, 22785-16-6; **3f**, 27142-01-4; **4f**, 27142-02-5; **5a**, 22782-07-5; **5a** (3β-OH), 27142-04-7; **5a** (12β-H), 3818-35-7; **5d**, 22785-18-8; **5d** (12β-H), 24174-46-7; **5e**, 27142-08-1; **5e** (12β-H), 3818-36-8; **5f**, 22785-15-5; **6a** ketal, 27142-11-6; **6d** ketal, 27141-91-9; **6e** ketal, 27142-12-7; **8d** (Δ^{12}), 27142-13-8.

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(21) This sample was obtained by following exactly the procedure in ref 15a.