Stereochemistry of the C and D Rings of C-Nor-D-homosteroids. II.[1] Synthesis of Etiojervane Analogs of Pregnan-3β-ol[2]

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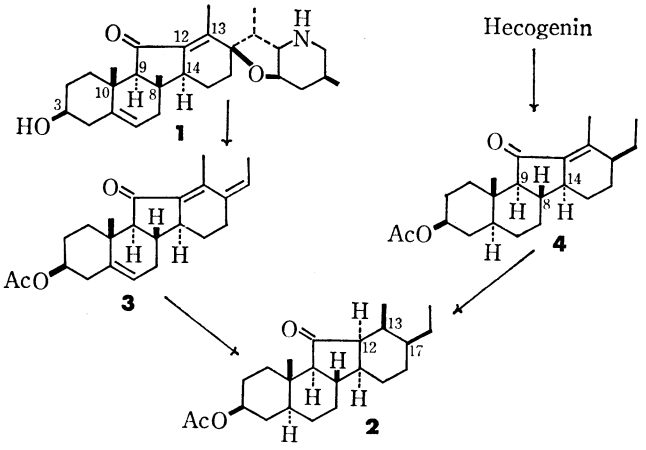
The synthesis of C/D *trans*- and *cis*-fused C-nor-D-homo-5α-pregnan-3β-ol 3-acetates (**13a** and **32**) from jervine (**1**) is described. The configurations of both the compounds and the synthetic intermediates were determined on the basis of chemical and spectral evidence.

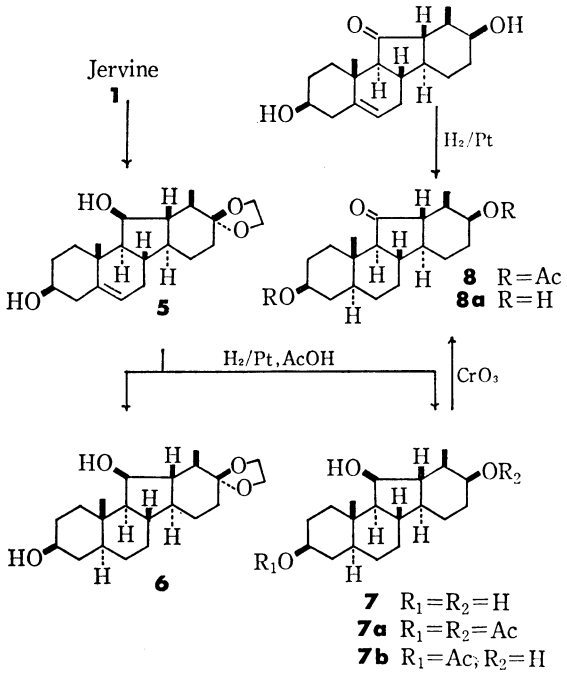
During the past decade synthetic studies of C-nor-D-homosteroid hormones have been reported by several groups.[3-7] In the present paper we describe the transformation of jervine (**1**) into etiojervane analogs of 5α-pregnan-3β-ol, which include both C/D *cis*- and *trans*-fused ring systems. In connection with the study on the synthesis and NMR spectra of (22S, 23R, 25S)-12α(not 12β)- and Δ^{12}-jervanines,[8] the results of the present work are useful for discussion[9] on conformations of the rings in etiojervanes.

In 1953, Fried and Klingsberg[10] isolated 17-ethyletiojervan-3β-ol-11-one 3-acetate (**2**) in 33% yield from the hydrogenation product of the corresponding $\Delta^{5,12,17(20)}$-triene derivative (**3**), obtained from jervine (**1**) by one-step fragmentation. Later, Mitsuhashi and Shimizu[5a] prepared the compound (**2**) in 80% yield by the same reaction of 17β-ethyletiojerv-12-en-3β-ol-11-one 3-acetate (**4**), which had been derived from hecogenin, and correlated both the alkaloid and sapogenin, elucidating the configurations of C_3, C_8, C_9, C_{10} and C_{14} in jervine (**1**). However, the spatial arrangement at C_{12} and C_{13} of the compound (**2**), a key intermediate for the correlation, has not been determined yet. The present work was undertaken with an aim to clarify these configurations.



Scheme 1.

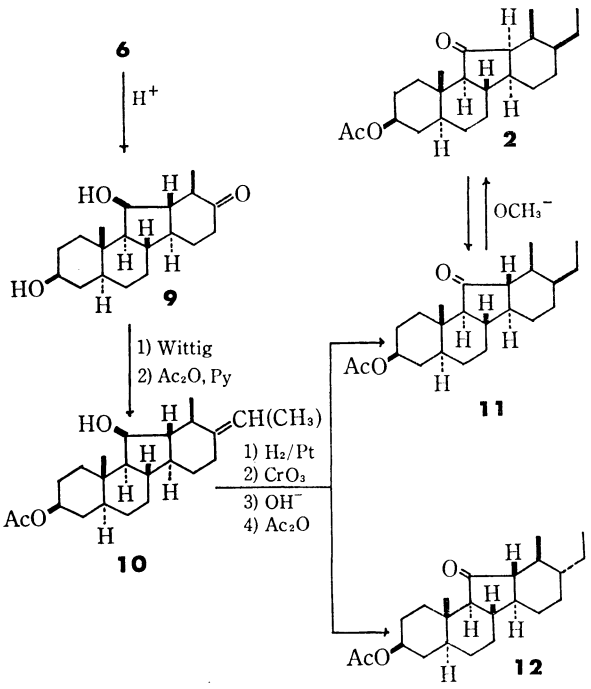
Hydrogenation of 12β-etiojerv-5-ene-3β,11β-diol-17-one 17-ethylene acetal[3b] (**5**), prepared from **3** by a four-stage process, over platinum in acetic acid afforded its 5α,6-dihydro derivative (**6**), mp 192—193 °C, in 88% yield along with triol (**7**), mp 235—236 °C (5%). Compound (**7**), with a molecular formula of $C_{19}H_{32}O_3$, is considered to be a hydrogenolysis product at C_{17}. On partial acetylation of compound (**7**) with acetic anhydride and pyridine afforded 3,17-diacetate (**7a**), mp 142—143 °C, which was oxidized with Jones' reagent to give 11-ketone (**8**), mp 120—121 °C. The ketone (**8**) was identified as 5α,12β-etiojervane-3β,17β-diol-11-one 3,17-diacetate by derivation from the corresponding 5,6-dehydro compound[11] with a well-defined configuration, indicating that triol **7** could be formulated as 3β,11β,17β-triol. In view of the fact that no hydrogenolysis product was isolated by the same treatment of the corresponding 11-deoxy (compound **15**) and 11-oxo derivatives,[9] the formation of **7** would reveal specific participation of the 11-hydroxy group to the catalytic reaction.



Scheme 2.

Treatment of 17-acetal **6** with acid produced 17-ketone (**9**), mp 188—190 °C, in 85% yield, whose NMR spectrum (19-CH_3, δ 1.04) and ORD curve (Cotton effect, $a=-115°$) were consistent with the assigned configurations. The Witting reaction of **9** with ethylidenetriphenylphosphorane[12] proceeded smoothly and, after acetylation, gave the 17-ethylidene derivative (**10**), mp 156—157 °C, in a good yield (crude 82% and pure 41%). Compound **10**, when hydrogenated over platinum and then oxidized with chromium(VI) oxide, was transformed into a mixture of 17-epimeric 11-ketones (**11** and **12**), which showed a single spot differing from that of compound **2** on various solvent

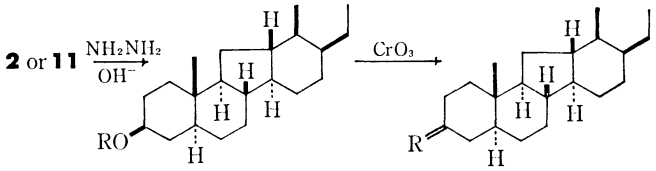
systems on TLC and resisted further purification. However, treatment of the mixture with sodium methoxide in refluxing methanol effected epimerization at the carbon atom(s) adjacent to the 11-oxo group and, on acetylation and subsequent purification by preparative TLC, led to isolation of the relevant compound (**2**) in 15% yield. Judging from chemical shifts of the 19-methyl protons of the mixture (**11** and **12**, δ 0.84) and the epimerized product (**2**, δ 0.90), this isomerization took place with configurational inversion only at C_{12}.[13] The transformation from compound **5** into the mixture (**11** and **12**) involves no epimerization at C_{12} and C_{13} (all compounds, 12βH and 13αH). The present result, combined with the Mitsuhashi work,[5a] confirms the compound in question to be represented correctly by formula **2** (12αH, 13αH and 17αH).



Scheme 3.

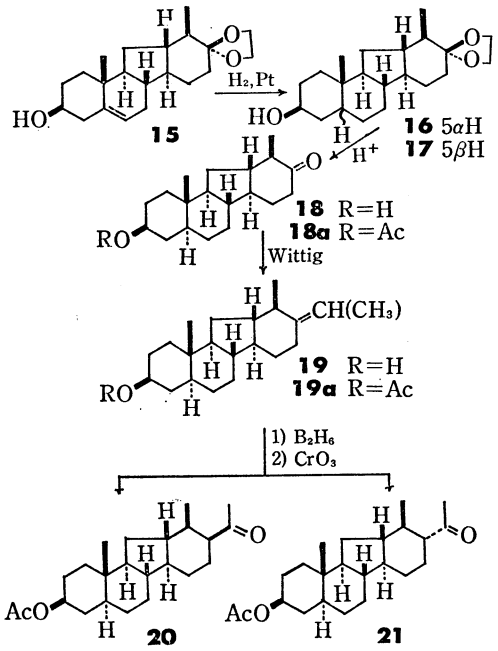
The afore-mentioned result suggests that a 12β-epimer of **2** with a 17β-ethyl group must be contained in the mixture. In fact, treatment of **2** with alkali in refluxing methanol followed by acetylation resulted in formation of a nearly 1 : 1 equilibrium mixture of **2** and the 12β-epimer, from which the latter (**11**), mp 121—123 °C, was isolated in 35% yield (crude 46%) by preparative TLC, showing practically the same IR spectrum as that of the mixture. In accordance with the assigned configurations, these 12-epimeric 11-ketones (**2** and **11**) exhibited negative Cotton effects with amplitudes of −82° and −170°, respectively, in the ORD curves.[14] On the other hand, the relevant hydrogenation mixture of **11** and **12** was treated with the base and then acetylated repeatedly, when most of one (**11**) of the two 12α-epimers was epimerized to the 12β-epimer (**2**), the other (**12**) being left as the main component of the mixture. This treatment led to isolation of compound **12** in 14% yield (crude 40%), mp 109—109.5 °C, suggesting that the mixture in question would contain almost equal amounts of 17-epimers (**11** and **12**). It is to be noted that, while the hydrogenation of double bonds at C_{12}—C_{13}, C_{13}—C_{17}, and C_{16}—C_{17} proceeded with the *cis*-addition mainly from the rear side, as illustrated by those of **4** and other compounds,[14] the hydrogen addition to a double bond at C_{17}–C_{20} took place from both sides.

The Wolff-Kishner reduction of 11-ketone **2** by a modification of the Huang-Minlon[15] or the Barton procedure[16] effected removal of the 11-oxo group, giving 3β-alcohol (**13**), mp 124—125 °C, as the sole isolable product in a moderate yield. Compound **13** was also obtained from 12-epimeric 11-ketone **11** in almost the same yield by the same treatment. This compound was readily acetylated to 3β-acetate (**13a**), mp 94.5—95 °C, or oxidized to 3-ketone (**14**), mp 119—121 °C, in good yield, the latter being further transformed into the ethylene acetal (**14a**), mp 98—100 °C. The following experiments were undertaken with a view to clarify the configuration at C_{12} of this compound (**13**).



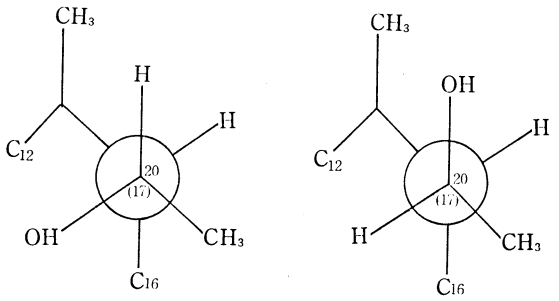
Hydrogenation of 12β-etiojerv-5-en-3β-ol-17-one 17-ethylene acetal[4d] (**15**) over platinum gave its 5α,6-dihydro derivative (**16**), mp 177—179 °C, in 80% yield, along with its 5β-isomer (**17**), mp 107—109 °C. The major product (**16**) on acid hydrolysis formed 17-ketone (**18**), mp 179—180 °C, in 90% yield, which was readily derived into 3β-acetate (**18a**), mp 134.5—135 °C. The assigned configurations (5αH, 12βH and 13αH) at C_5, C_{12} and C_{13} of these 17-ketones were confirmed by the NMR spectra (19-methyl protons, **18**, δ 0.75 and **18a**, 0.78) and the ORD curves (Cotton effect, both **18** and **18a**, $a=-105°$). Compound **18** was then submitted to the Wittig reaction[12] to give an oily mixture of the 17-ethylidene derivatives (**19**) in 97% yield, which exhibited two sharp singlets with relative intensity of 4 to 3 due to the 19-methyl protons at δ 0.73 and 0.76 in the NMR spectrum. However, the mixture (**19**) and also its hydrogenation product, 17-ethyletiojervan-3β-ols, again resisted further purification, showing a single spot on TLC. Thus the mixture **19**, after being converted into 3-acetates (**19a**), amorphous, in 79% yield, was submitted to hydroboration[17] and subsequent oxidation with sodium dichromate in sulfuric acid,[18] giving a 4 : 3 mixture of 17β- and 17α-acetyletiojervan-3β-ol 3-acetates (**20**), mp 189—191 °C, and (**21**), mp 110.5—111 °C, which were isolated in 28 and 18% yields, respectively, along with the unreacted starting material (**19a**) (9%). The configurations at C_{17} of these compounds were assigned on the basis that the former (**20**) (17β(axial)-acetyl] was epimerized quantitatively with base to the latter (**21**)

[17α(equatorial)-acetyl].

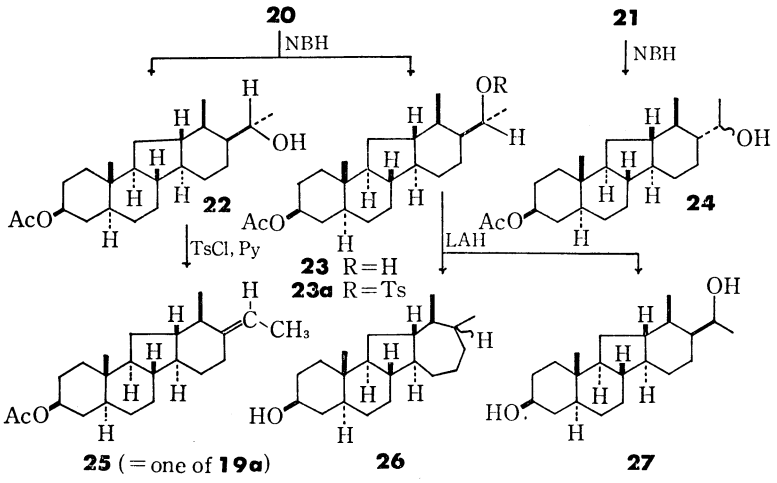


Scheme 4.

Reduction of 20-ketone (**20**) with sodium borohydride (NBH) in ethanol produced nearly equal amounts of 20α-(*S*)- and 20β-(*R*)-alcohols (**22**), mp 150—151 °C, and (**23**), mp 117—118 °C, which were readily isolated by preparative TLC. The configurational assignment to C_{20} of these epimeric alcohols was deduced from chemical shifts of the respective 18-methyl protons (**22**, δ 0.94 and **23**, 1.04); in each of these compounds the respective 21-methyl groups would be located at the most remote position from the D-ring as shown in **22A** and **23A**, and hence the 21-hydroxy group in **23** would be disposed 1,3-diaxial to the 18-methyl and deshield the 18-methyl protons more seriously in **23** than those in **22** in the NMR spectra. On the other hand, reduction of the isomeric 20-ketone (**21**) with sodium borohydride under comparable conditions gave an inseparable mixture of the corresponding 20-alcohols (**24**), mp 115—118 °C, in a moderate yield. The R_f values of these alcohols (**24**) on TLC clearly differed from those of alcohols **22** and **23**, indicating that the afore-mentioned hydride reduction took place without any configurational change at C_{17}.



Attempted removal of the 20-hydroxy groups in compounds **22** and **23** did not proceed as expected. 20α-(*S*)-Alcohol (**22**), when treated with *p*-toluenesulfonyl chloride in pyridine, formed no tosylate but produced olefin (**25**), mp 92—92.5 °C, with a molecular formula of $C_{23}H_{36}O_2$ in 94% yield. The structure [one of 17-ethylideneetiojervanes (**19a**)] and configuration were assigned on the basis of the spectral data [Mass, *m/e* 344; NMR, δ 0.77 (3H, s, 19-C<u>H</u>$_3$), 1.66 (3H, d J= 6 Hz, 21-C<u>H</u>$_3$), and 5.15 (1H, q J=6 Hz, <u>H</u> at C_{20})] and the conformation (**22A**) of the starting alcohol (**22**). Naturally, the NMR spectrum of **25** closely resembled that of **19a**. On the other hand, 20β-(*R*)-alcohol (**23**) was converted under the same conditions as **22** into the corresponding tosylate (**23a**), amorphous, showing a single spot on TLC. Treatment of **23a** with lithium aluminium hydride gave two products (**26**), amorphous, and (**27**), mp 190—191 °C, which were isolated in 24 and 37% yields, respectively, by preparative TLC. The latter (**27**) was derived by simple hydrolysis of **23** and hence identified as 3,20-glycol, resulting only from hydrogenolysis of the O–S bond. The former (**26**) displayed three methyl proton signals, one singlet (19-C<u>H</u>$_3$) and two doublets (both J=

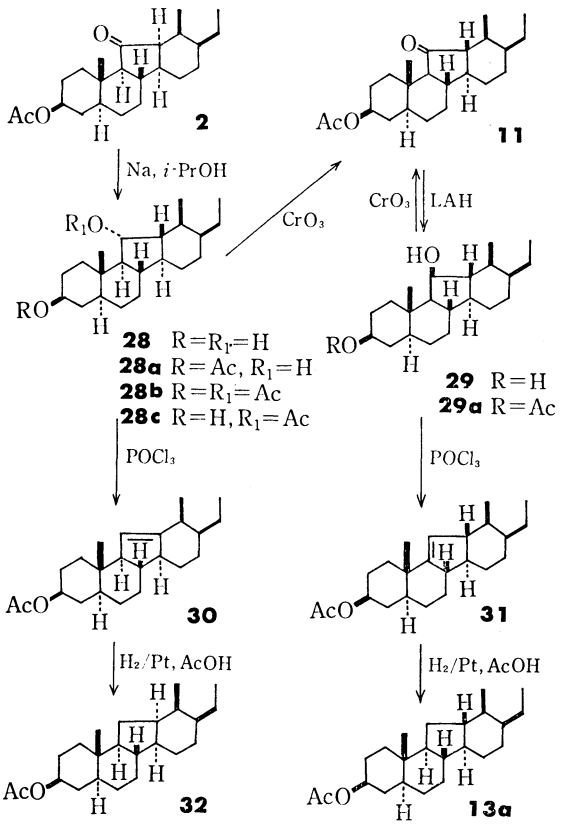


Scheme 5.

6 Hz) at δ 0.75, 0.97 and 1.19 in the NMR spectrum. These spectral data, as combined with consideration of the conformation (**23A**) of the starting alcohol, led to tentative assignment of formula **26** to the amorphous product.

The configuration at C_{12} of compound **13** was finally elucidated as follows. Reduction of 5α,12α-etiojervan-3β-ol-11-one 3-acetate (**2**) with sodium in isopropyl alcohol afforded 3β,11α-alcohol (**28**), mp 158—161 °C, in a good yield, whose configuration at C_{11} was consistent with the NMR spectrum: δ 0.775 (3H, s, 19-CH_3) and 4.00 (1H, br W_H=12 Hz). Treatment of **28** with acetic anhydride and pyridine gave a four-component mixture, from which the corresponding 3-acetate (**28a**), mp 128—129 °C, was isolated as the main product by preparative TLC in a moderate yield (pure 35%, and crude 65%). This compound (**28a**), when oxidized with chromium(VI) oxide, gave 5α,12β-etiojervan-3β-ol-11-one 3-acetate (**11**) in a good yield. Reduction of the 11-ketone (**11**) with lithium aluminium hydride in refluxing dioxane led to formation of the corresponding 3β,11β-alcohol (**29**), mp 186—188 °C, showing the following NMR spectrum: δ 1.02 (3H, s, 19-CH_3) and 4.06 (1H, do d J=6 and 8 Hz). This alcohol (**29**) underwent monoacetylation to give 3-acetate (**29a**), mp 151—152 °C, which was reconverted by oxidation into 12β*H*-11-ketone (**11**). The results indicate that 11-alcohols **28** and **29** are epimeric to each other only at C_{11} and the reduction of 11-ketone (**2**) to 11α-alcohol (**28**) is accompanied by configurational inversion at C_{12} (12αH to 12βH). The hydride reduction of 12α*H*-11-ketone (**2**) under the same conditions as that of 12β*H*-11-ketone (**11**) resulted only in hydrolysis of the 3-acetoxy group owing to severe steric hindrance due to β-oriented methyl and ethyl groups at C_{13} and C_{17}, respectively, leading to the recovery of the starting ketone after acetylation.

Treatment of 12α*H*-11α-alcohol (**28a**) with phosphoryl chloride in pyridine gave olefin (**30**), oil, in 90% yield. The same treatment of 12β*H*-11β-alcohol (**29a**) also produced olefin (**31**), oil, in quantitative yield, which was evidently different from olefin **30**. The structure of these olefins was assigned as shown in formulas **30** and **31**, respectively, on the basis of chemical shifts of the respective 19-methyl protons (**30**, δ 0.77 and **31**, 0.92) as well as the reaction mode. The chemical shift difference (0.15 ppm) in question between olefins was in good accord with that (0.175 ppm) in the corresponding normal steroid olefins,[19] and the formation of these olefins was interpreted by assuming that the dehydration proceeds in an E2-type *trans*-elimination manner. Hydrogenation of the latter olefin (**31**), 12β*H*-$\Delta^{9(11)}$-olefin, over platinum in acetic acid led to formation of the compound (**13a**) in question, mp 92—94 °C, establishing all the configurations of **13a** (5αH, 12βH, 13αH and 17αH). The same reaction of another olefin (**30**), 9α*H*-Δ^{11}-olefin, produced an isomeric compound (**32**), amorphous, formulated as 5α,12α-etiojervan-3β-ol 3-acetate. These compounds (**13a** and **32**) are regarded as C/D *trans*- and *cis*-etiojervane analogs of 5α-pregnan-3β-ol 3-acetate.



Scheme 6.

Experimental

All the melting points are uncorrected. The homogeneity of each compound was always checked by TLC on silica gel (Wakogel B-5) using various solvent systems, and the spots were developed with ceric sulfate in dil sulfuric acid and/or iodine. The optical rotations, ORD curves and IR spectra were measured in chloroform, dioxane and Nujol, respectively, unless otherwise stated. The NMR spectra were obtained in deuteriochloroform at 60 and/or 100 MHz, and the chemical shifts were given in δ-values, TMS being used as an internal reference. The abbreviations "s, d, t, q, br, m and do" in the NMR spectra denote "singlet, doublet, triplet, quartet, broad, multiplet and double," respectively.

17β-Ethyl-5α,12α-etiojervan-3β-ol-11-one 3-Acetate (2). a) A solution of 17-ethyletiojerv-5,12,17(20)-trien-3β-ol-17-one 3-acetate[10] (**3**, 8.33 g), mp 183—185 °C, in acetic acid (AcOH, 700 ml) was hydrogenated over Adams platinum (Pt, 5.76 g as $PtO_2 \cdot H_2O$) at room temperature (temp) for 16 h, when 2060 ml of hydrogen (3.5 mol) had been consumed. After removal of the catalyst by filtration and the solvent *in vacuo* by azeotropization with benzene, the residue was dissolved in methanol, and the methanol solution was concentrated to 70 ml and cooled to yield a crystalline substance, which was collected by filtration. Recrystallization from methanol afforded **2** (3.02 g), mp 115.5—116.5 °C (lit,[10] 114—116 °C); $[\alpha]_D$ −15.8° (lit,[10] −8.6°); ORD, $[\Phi]^{trough}_{334}$ −4520°, $[\Phi]^{trough}_{323}$ −2180°, $[\Phi]^{peak}_{293}$ +3680°, a=−82°; IR, ν_{max} 1730, 1260 and 1025 cm^{-1}; NMR, δ 0.72 (3H, d J=7 Hz, 18-CH_3), 0.90 (3H, s, 19-CH_3), 2.01 (3H, s, OCO-CH_3) and 4.65 (1H, br, H at C_3). This compound proved to be identical with a sample[5a], mp 118.2—118.9 °C and $[\alpha]_D$ −15.5°, obtained from hecogenin by direct comparison (IR, mixed mp and TLC). The mother liquors obtained on the concentration and recrystallization consisted of a

multicomponent mixture and resisted further purification.

b) A solution of **10** (156 mg), in AcOH (10 ml) was hydrogenated over Adams Pt (204 mg) at room temp, and 1.1 mol of hydrogen was consumed for 45 min. The reaction mixture gave an amorphous substance (142 mg) after usual work up; NMR, δ 0.84 (3H, t J=6 Hz, 21-C$\underline{H}_3$), 0.97 (3H, d J=6.5 Hz, 18-C$\underline{H}_3$), 1.06 (3H, s, 19-C$\underline{H}_3$), 2.01 (3H, s, OCOC$\underline{H}_3$), 4.01 (1H, br W_H=15.5 Hz, $\underline{H}$ at C_{11}) and 4.67 (1H, br, $\underline{H}$ at C_3). This was mixed with a complex prepared from chromium(VI) oxide (CrO_3, 215 mg) and pyridine (Py, 2 ml) under cooling and stirred at room temp overnight. The mixture was poured into water and extracted with ether, and the ether solution was washed with 1 M hydrochloric acid, 5% aqueous sodium hydrogencarbonate and saturated brine, dried and evaporated to leave a crystalline mixture (140 mg) of **11** and **12**, which showed a single spot on TLC.

The mixture was treated with 1 M sodium methoxide in refluxing methanol (15 ml) under nitrogen for 2 h. The solution was evaporated *in vacuo* and shaken with chloroform and water, and the chloroform solution was washed, dried and evaporated to leave amorphous residue (132 mg), which was acetylated with acetic anhydride (Ac_2O, 1 ml) and Py, (1.3 ml) at room temp overnight. The reaction mixture gave amorphous residue (143 mg) after usual work up, which showed two spots and was separated by preparative TLC (7 plates) with a 3 : 2 mixture of benzene and chloroform. The less mobile fraction gave a crystalline substance (18 mg), which on trituration with methanol had mp 114—117 °C. The more mobile fraction gave an amorphous material (84 mg), showing the same spot as the starting mixture, which was again treated in the same manner as the aforementioned mixture to give the crystalline substance (10 mg) besides the main amorphous material (73 mg). The crystalline substances were combined and recrystallized from methanol to yield **2** (9 mg), mp 118—119 °C, which was identical with an authentic sample (TLC, IR, NMR and optical rotation). The main amorphous material (73 mg) was treated twice in the same manner as described above and after usual work-up, gave a new crystalline substance (56.5 mg) with the same R_f value as the more mobile part. The substance was triturated with methanol to yield **12** (20 mg), mp 106—107 °C, and was recrystallized repeatedly from methanol to give an analytical sample, mp 109—109.5 °C; $[\alpha]_D$ −94.6°; ORD, $[\Phi]_{334}^{trough}$ −11350°, $[\Phi]_{323}^{trough}$ −6370°, $[\Phi]_{315}$=0°, $[\Phi]_{291}^{peak}$ −10520°, a=−219°; IR, ν_{max} 1732, 1234 and 1022 cm^{-1}; NMR, δ 0.85 (3H, s, 19-C$\underline{H}_3$). Found: C, 76.53; H, 10.04%. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07%.

*5α,12β-Etiojervane-3β,11β-diol-17-one 17-Ethylene Acetal (**6**) and 5α,12β-Etiojervane-3β,11β,17β-triol (**7**).* A solution of etiojerv-5-ene-3β,11β-diol-17-one 17-ethylene acetal[3b] (**5**, 2.50 g), mp 173—174 °C, in AcOH (50 ml) was hydrogenated over the Adams Pt (0.80 g) at room temp for 1 h, when 445 ml of hydrogen had been taken up. After removal of the catalyst and solvent, the residue was dissolved in chloroform, and the chloroform solution was washed with 5% aqueous sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate and evaporated to leave an amorphous substance (3.08 g), which crystallized on trituration with acetone and was collected by filtration to yield **6** (1.36 g), mp 182—184 °C. The filtrate, showing two spots, was separated by preparative TLC (30 plates) over silica gel (Wakogel B-5, 10 g per plate) with ether as solvent. More mobile fractions, eluted with acetone, gave amorphous residue (0.60 g), which crystallized as needles on trituration with acetone to give **6** (0.35 g), mp 183—188 °C. Two recrystallizations from acetone gave an analytical sample, mp 192—193 °C; $[\alpha]_D$ +39.4°; IR, ν_{max} 3490, 3340, 1108 and 1031 cm^{-1}; NMR, δ 0.98 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 1.03 (3H, s, 19-C$\underline{H}_3$), 1.50 and 2.01 (each 1H, s, $\underline{OH}$) and 3.85 (4H, s, $OC_2\underline{H}_4O$). Found: C, 71.88; H, 9.81%. Calcd for $C_{21}H_{34}O$: C, 71.96; H, 9.78%.

Less mobile fractions, eluted with chloroform, gave crystalline triol (**7**, 0.64 g), which on recrystallization from acetone had mp 231—234 °C and amounted to 0.11 g. This was recrystallized from acetone for analysis: mp 235—236 °C; $[\alpha]_D$ +63.3° (MeOH); IR, ν_{max} 3340, 1715 (acetone ?) and 1044 cm^{-1}. Found: C, 73.76; H, 10.47%. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46%.

*5α,12β-Etiojervane-3β,17β-diol-11-one 3,17-Diacetate (**8**).*

a) A solution of etiojerv-5-ene-3β,17β-diol-11-one[11] (107 mg) in AcOH (4 ml) was hydrogenated over Adams Pt (59 mg) at room temp for 1 h, when 1.27 mol of hydrogen had been consumed. After removal of the catalyst by filtration and the solvent *in vacuo* by evaporation, the residue was diluted with water and the solution was extracted with chloroform. The chloroform extracts were washed with 5% aqueous sodium hydrogencarbonate and water, dried, and evaporated to leave an amorphous residue (111 mg), which showed three spots and was separated by preparative TLC (8 plates) with ether. The most mobile part gave an amorphous substance (10 mg), which would be 5β,12β-etiojervane-3β,17β-diol-11-one from its NMR data, but was not further examined: δ 0.97 (3H, s, 19-C$\underline{H}_3$), 1.26 (3H, d J=4 Hz, 18-C$\underline{H}_3$), 3.77 (1H, br s W_H=8 Hz, $\underline{H}$ at C_{17}) and 4.07 (1H, br s W_H=9 Hz, $\underline{H}$ at C_3).

The middle part gave a crystalline substance (66 mg), which on trituration with acetone–isopropyl ether gave **8a** (61 mg), mp 179.5—180.5 °C. Recrystallization from the same solvent mixture afforded an analytical sample, mp 180.5—181 °C; $[\alpha]_D$ −44.2° (MeOH); IR, ν_{max} 3290, 1727 and 1028 cm^{-1}; NMR, δ 0.83 (3H, s, 19-C$\underline{H}_3$), 1.25 (3H, d J=5.5 Hz, 18-C$\underline{H}_3$), 3.59 (1H, br W_H=24 Hz, $\underline{H}$ at C_3) and 3.76 (1H, br s W_H=8 Hz, $\underline{H}$ at C_{17}). Found: C, 74.48; H, 9.91%. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87%. The least mobile part gave a crystalline substance (11 mg). The NMR spectrum indicated the compound to be etiojerva-3β,11β,17β-triol-11-one, but this was not further examined: NMR, δ 1.02 (3H, s, 19-C$\underline{H}_3$), 1.24 (3H, br s W_H=5 Hz, 18-C$\underline{H}_3$), 1.56 (s, disappeared on addition of D_2O, $\underline{OH}$), 6.43 (1H, br W_H=27 Hz, $\underline{H}$ at C_3), 3.81 (1H, br s W_H=8 Hz, $\underline{H}$ at C_{17}) and 4.08 (1H, do d J=6 and 10 Hz, $\underline{H}$ at C_{11}).

Compound **8a** (45 mg) was acetylated with Ac_2O (1 ml) and Py (1 ml) at room temp for 22 h. The reaction mixture gave amorphous residue (61 mg) after usual work up, which was crystallized from dil methanol to yield a crystalline substance (**8**), mp 123—125 °C; IR, ν_{max} 1743—1724, 1251, 1234 and 1024 cm^{-1}; NMR, δ 0.86 (3H, s, 19-C$\underline{H}_3$), 1.14 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 1.99 and 2.04 (each 3H, s, 2OCOC$\underline{H}_3$), 5.42 (1H, br W_H=24 Hz, $\underline{H}$ at C_3) and 4.94 (1H, br s W_H=7.5 Hz, $\underline{H}$ at C_{17}).

b) Compound **7** (72 mg) was acetylated with Ac_2O (1 ml) and Py (1 ml) at room temp for 3 h. The reaction mixture was worked up as usual to give an amorphous residue (91.5 mg), showing two spots, which was separated by preparative TLC (2 plates) over silica gel using a 1 : 1 mixture of ether and benzene. More mobile fractions, eluted with acetone, gave an amorphous residue (45 mg), which crystallized on trituration with isopropyl ether to give 3,17-diacetate **7a** (12 mg), mp 138—139 °C. Recrystallization from isopropyl ether gave an analytical sample, mp 142—143 °C; $[\alpha]_D$ +64.8°; Mass, m/e 332 (M^+-CH_3COOH), 314, 299, 272 and 254; IR, ν_{max} 3515, 1729, 1715, 1254, 1241 and 1025

cm^{-1}; NMR, δ 0.99 (3H, d J=5 Hz, 18-C$\underline{H}_3$), 1.07 (3H, s, 19-C$\underline{H}_3$), 1.99 and 2.02 (each 3H, s, 2OCOC$\underline{H}_3$), 4.10 (1H, do d J=8 and 5.5 Hz, $\underline{H}$ at C_{11}), 4.70 (1H, br, $\underline{H}$ at C_3) and 5.00 (1H, br s W_H=6Hz, $\underline{H}$ at C_{17}). Found: C, 69.51; H, 9.55%. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24%.

Less mobile fractions, eluted with acetone, gave a crystalline residue (42 mg), which on trituration with acetone–isopropyl ether afforded triol 3-monoacetate (**7b**, 24 mg), mp, 172.5—173 °C. Recrystallization from the same solvent mixture gave an analytical sample: mp 173—173.5 °C; $[\alpha]_D$+35.6°; Mass, *m/e* 332 (M^+-H_2O), 314 and 272; IR, ν_{max} 3465, 3305, 1734, 1243, 1026 and 1018 cm^{-1}; NMR, δ 1.06 (3H, s, 19-C$\underline{H}_3$), 1.09 (3H, d J=7 Hz, 18-C$\underline{H}_3$), 2.02 (3H, s, OCOC$\underline{H}_3$), 3.81 (1H, br s W_H=6 Hz, $\underline{H}$ at C_{17}), 4.08 (1H, do d J=8.5 and 5 Hz, $\underline{H}$ at C_{11}) and 4.71 (1H, br W_H=24 Hz, $\underline{H}$ at C_3). Found: C, 71.82; H, 9.71%. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78%.

A solution of **7a** (40 mg) in acetone (4 ml) was treated with Jones' reagent (0.2 ml) in an ice-bath under stirring for 1 h. After addition of ethanol and evaporation of the solvent *in vacuo*, the resulting residue was diluted with water and extracted with chloroform. The chloroform solution was washed with 5% aqueous sodium hydrogencarbonate and water, dried and evaporated to give an amorphous residue (41 mg), which showed a single spot on TLC. Trituration with dil methanol afforded a crystalline substance (**8**, 19 mg), mp 120—121 °C, which was identical with an authentic sample.

*5α,12β-Etiojervane-3β,11β-diol-17-one (**9**).* Compound **6** (1.314 g) was dissolved in a solution of acetone (130 ml) and water (13 ml) containing *p*-toluenesulfonic acid (PTS, 146 mg), and refluxed for 3 h under stirring. After evaporation of the solvents below 25 °C the residue was made alkaline with 5% aqueous sodium hydrogencarbonate and extracted with chloroform repeatedly. The chloroform solution was washed with water, dried and evaporated to leave a crystalline material (1.497 g), which on recrystallization from acetone–isopropyl ether gave **9** (977 mg), mp 187—189 °C. Two recrystallizations from the same solvent mixture afforded an analytical sample, mp 188—190 °C; $[\alpha]_D$ +11.2° (MeOH); ORD, $[\Phi]_{318}^{trough}$ −4440°, $[\Phi]_{310}^{trough}$ −4080°, $[\Phi]_{274}^{peak}$ +7090°, a=−115°; IR, ν_{max} 3410, 1701 and 1037 cm^{-1}; NMR, δ 1.04 (3H, s, 19-C$\underline{H}_3$), 1.12 (3H, d J=7 Hz, 18-C$\underline{H}_3$), 3.55 (1H, br, $\underline{H}$ at C_3) and 4.12 (1H, br W_H=15 Hz, $\underline{H}$ at C_{11}). Found: C, 74.56; H, 9.76%. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H. 9.87%.

*17-Ethylidene-5α,12β-etiojervane-3β,11β-diol 3-Acetate (**10**).* A suspended mixture of sodium hydride (Wako, 309 mg, *ca.* 50% in oil) in pentane (10 ml) was stirred for 2 min and then decanted, and the procedure was repeated five times to remove the oil. After removal of the pentane *in vacuo* the residual hydride was mixed with dimethyl sulfoxide (DMSO, 5 ml), which had been dried over calcium hydride and distilled, in a stream of nitrogen, stirred at room temp for 15 min and then at 70—73 °C for 50 min, and cooled, when the mixture became homogeneous and gray. To the solution was added dropwise a solution of ethyltriphenylphosphonium bromide (2.232 g, 6 mmol) in dry DMSO (12 ml) at room temp during 3 min under nitrogen, and the solution was stirred at room temp for 15 min. To the resulting dark red solution was added a solution of **9** (464 mg, 1.5 mmol) in dry tetrahydrofuran (THF, 5.5 ml) at room temp during 5 min under nitrogen. The whole mixture was further stirred at room temp for 15 min and then at 50—51 °C (bath temp) for 22 h. The reaction mixture was poured into ice-water and after being salted out, extracted with ether repeatedly. The ether solution was washed with saturated brine, dried and evaporated to leave oily residue (2.165 g). This was treated with Ac_2O (5 ml) and Py (10 ml) at room temp for 3 h and then worked up as usual to give an amorphous substance (1.908 g), showing two spots, which was separated by preparative TLC (25 plates) with benzene. The minor fraction amounted to 75 mg but was not further examined.

The main, less mobile fraction gave a crystalline substance (380 mg), which on recrystallization from acetone afforded **10** (191 mg), mp 152—154 °C. This was recrystallized twice from isopropyl ether for analysis: mp 156—157 °C; $[\alpha]_D$ +53.3°; IR ν_{max} 3505, 1713, 1267 and 1031 cm^{-1}; NMR, δ 1.04 (3H, s, 19-C$\underline{H}_3$), 1.19 (3H, d J=5.5 Hz, 18-C$\underline{H}_3$), 1.61 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 2.01 (3H, s, OCOC$\underline{H}_3$), 4.10 (1H, br W_H=14.5 Hz, $\underline{H}$ at C_{11}), 4.64 (1H, br, $\underline{H}$ at C_3) and 5.17 (1H, q J=6 Hz, $\underline{H}$ at C_{20}). Found: C, 76.52; H, 10.08%. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07%.

*17β-Ethyl-5α,12β-etiojervan-3β-ol-11-one 3-Acetate (**11**).* a) Compound **2** (730 mg) was dissolved in methanol (48 ml) containing 5% potassium hydroxide and refluxed for 1 h under nitrogen. The solution was diluted with water under stirring to yield an amorphous substance (650 mg), which was collected, dried and treated with Ac_2O (4 ml) and Py (7 ml) at room temp overnight. After removal of the solvents by azeotropization with benzene, the residue crystallized on trituration with methanol. This crystalline material, showing two spots on TLC (chloroform : benzene=1 : 1), was dissolved in benzene and chromatographed on a mixture of silicic acid (22 g) and celite (1.5 g). Fractions eluted with benzene gave crystals (245 mg), which showed a single spot on TLC. Recrystallization from methanol afforded an analytical sample of **11**, mp 121—123 °C; $[\alpha]_D$ −66.8°; ORD, $[\Phi]_{334}^{trough}$ −9930°, $[\Phi]_{323}^{trough}$ −5810°, $[\Phi]_{293}^{peak}$ +7120°, a=−170°; IR, ν_{max} 1730, 1245 and 1025 cm^{-1}; NMR, δ 0.84 (3H, s, 19-C$\underline{H}_3$), 0.94 (3H?, t J=7 Hz, 21-C$\underline{H}_3$?), 1.16 (3H?, d J=6.5 Hz, 18-C$\underline{H}_3$), 2.02 (3H, s, OCOC$\underline{H}_3$) and 4.65 (1H, br, $\underline{H}$ at C_3). Found: C, 76.78; H, 10.32%. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07%.

b) A solution of compound **28a** (34 mg) in acetone (3.5 ml) cooled in an ice-bath was treated with Jones' reagent (0.05 ml) for 1 h under stirring. After addition of ethanol to decompose excess of chromium(VI) oxide (CrO_3), the solution was evaporated *in vacuo* below 40 °C, and then shaken with water and chloroform. The chloroform solution was worked up as usual to give a crystalline substance (35 mg), which on recrystallization from methanol afforded **11** (24 mg), mp 120—121 °C. This was identical with an authentic sample obtained by epimerization of **2**.

Equilibrium Measurements. Compound **2** (51 mg) in methanol (1 ml) was mixed with methanol (4 ml) containing 5% potassium hydroxide and allowed to stand at room temp for 60 h. After removal of methanol *in vacuo* the residue was shaken with chloroform and water. The chloroform solution gave a mixture (46 mg) of 12-epimeric alcohols, which was acetylated with Ac_2O (0.24 ml) and Py (0.48 ml) at room temp overnight. The reaction mixture was mixed with water (100 ml) under stirring to give an amorphous substance, which was collected by filtration and dried thoroughly. The resulting mixture (44 mg) of **2** and **11** had an optical rotation of $[\alpha]_D$ −43.2°.

Compound **11** (51 mg) was treated in the same manner as **2** produced a mixture of **2** and **11**, which showed an optical rotation of $[\alpha]_D$ −44.3°. The specific rotations in both experiments were practically the same, indicating that the equilibrium mixture consisted of 45% of the former (**2**) and 55% of the latter (**11**).

*17β-Ethyl-5α,12β-etiojervan-3β-ol (**13**) and Its 3-Acetate (**13a**).* a) Freshly-distilled diethylene glycol (DEG, 75 ml) containing sodium (2.0 g) was heated to 180 °C, and anhydrous hydrazine[20] (40 ml) was added to the solution, and refluxed for a while and cooled. After addition of compound **2** (3.52 g) the mixture was refluxed (at *ca.* 145 °C) for 16 h, cooled and the condenser was removed. The solution was heated to 180 °C to distill off excess of the hydrazine, and a new condenser was then set up. The solution was again refluxed at the temp for 24 h, cooled and mixed with water (450 ml), giving an amorphous powder (3.08 g), which was collected, dried and crystallized from methanol. Recrystallization from methanol afforded **13** (1.72 g), mp 124—125 °C; $[\alpha]_D$ + 75.9°, IR, no absorption near 1700 cm^{-1}; NMR, δ 0.74 (3H, s, 19-C$\underline{H}_3$), 0.84 (3H?, d J=6 Hz, 18-C$\underline{H}_3$) and 3.64 (1H, br, $\underline{H}$ at C_3). Found: C, 82.68; H, 11.45%. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.33%.

Compound **13** (52 mg) was treated with Ac_2O (0.7 ml) and Py (1 ml) at room temp overnight. After usual work up the residue (57 mg) afforded **13a** (29 mg), 94.5—95 °C, on trituration with acetone and subsequent recrystallization from acetone; $[\alpha]_D^{14}$ + 55.3°; IR, ν_{max} 1742 and 1244 cm^{-1}; NMR, δ 0.76 (3H, s, 19-C$\underline{H}_3$), 0.83 (3H, d J=6.5 Hz, 18-C$\underline{H}_3$), 0.85 (3H, t J=6.5 Hz, 21-C$\underline{H}_3$), 2.03 (3H, s, OCOC$\underline{H}_3$) and 4.72 (1H, br, $\underline{H}$ at C_3). Found: C, 79.98; H, 11.13%. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05%.

b) The Wolff-Kishner reduction of compound **11** (240 mg) was carried out in the same way as mentioned above and produced crude **13** (221 mg), having mp 108—120 °C. Recrystallization from methanol afforded **13** (93 mg), mp 120—122 °C, in pure state, which was identical with that prepared from **2**.

*17β-Ethyl-5α,12β-etiojervan-3-one (**14**) and Its Ethylene Acetal (**14a**).* To a pasty complex prepared from Py (15 ml) and CrO_3 (1.5 g) was added **13** (1.50 g) dissolved in Py (15 ml), and the mixture was stirred at room temp for 15h. After removal of the solvent the mixture was extracted with chloroform, and the chloroform solution was washed with 1 M hydrochloric acid, 10% aqueous sodium hydroxide and water, dried and then evaporated to leave an oily substance, which crystallized on trituration with methanol and recrystallized from the same solvent to yield **14** (1.16 g), mp 118—119 °C. This sample was recrystallized from methanol for analysis: mp 119—121 °C; $[\alpha]_D$ +113.5°; IR, ν_{max} 1707 cm^{-1}; NMR, δ 0.85 (3H, d J=6 Hz, 18-C$\underline{H}_3$) and 0.94 (3H, s, 19-C$\underline{H}_3$). Found: C, 83.51; H, 11.20%. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33%.

A solution of **14** (352 mg) in benzene (60 ml) containing PTS (18 mg) and ethylene glycol (1.75 ml) was refluxed for 8 h under a Dean-Stark apparatus and then cooled, when the solution was separated into two layers. The upper layer was separated, washed with 5% aqueous sodium hydrogencarbonate (60 ml) and water (60 ml), dried and evaporated *in vacuo* to leave a crystalline residue. Recrystallization from acetone gave **14a** (247 mg), mp 98—100 °C; $[\alpha]_D$ +63.5°; IR, ν_{max} 1110, 1080 and 1066 cm^{-1}; NMR, δ 0.77 (3H, s, 19-C$\underline{H}_3$), 0.85 (3H?, d J=7 Hz, 18-C$\underline{H}_3$) and 3.93 (4H, s, OC$_2\underline{H}_4$O). Found: C, 79.96; H, 11.02%. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05%.

*5α,12β-Etiojervan-3β-ol-17-one 17-Ethylene Acetal (**16**) and Its 5β-Isomer (**17**).* A solution of 12β-etiojerv-5-en-3β-ol-17-one 17-ethylene acetal[4d] (**15**, 777 mg), mp 175—177 °C, in AcOH (20 ml) was hydrogenated over Adams Pt (150 mg) at room temp and 95 ml of hydrogen was consumed for 30 min. The reaction mixture was worked up as usual to give an amorphous substance (860 mg), which crystallized on trituration with isopropyl ether and was collected by filtration. This crystalline substance (**16**, 612 mg), mp 177—179 °C, was recrystallized twice from isopropyl ether for analysis: mp 177—179 °C; $[\alpha]_D$ +50.4°; IR, ν_{max} 3445, 1110, 1077 and 1043 cm^{-1}; NMR, δ 0.74 (3H, s, 19-C$\underline{H}_3$), 0.83 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 3.55 (1H, br, $\underline{H}$ at C_3) and 3.87 (4H, s, OC$_2\underline{H}_4$O). Found: C, 75.21; H, 10.15%. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25%.

The filtrate, obtained on crystallization of **16**, was evaporated and then separated into three parts by preparative TLC (10 plates) with a 1 : 2 mixture of ether and benzene. The middle part (77 mg) showed the same IR spectrum and R_f value as **16**. The most mobile part (46 mg) crystallized on trituration with isopropyl ether, had mp 107—109 °C and amounted to 9 mg. The NMR and IR spectra indicated this compound to be a 5β-isomer of **16**; $[\alpha]_D$ +43.5°; IR, ν_{max} 3340, 1086, 1042 and 1031 cm^{-1}; NMR, δ 0.82 (3H, d J=5 Hz, 18-C$\underline{H}_3$), 0.89 (3H, s, 19-C$\underline{H}_3$), 3.91 (4H, s, OC$_2\underline{H}_4$O) and 4.06 (1H, br W_H=8.5 Hz, $\underline{H}$ at C_3). Found: C, 75.28; H, 10.40%. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25%

*5α,12β-Etiojervan-3β-ol-17-one (**18**) and Its 3-Acetate (**18a**).* Compound **16** (560 mg) was dissolved in acetone (50 ml) and water (5 ml) containing PTS (53 mg) and refluxed for 3 h. After removal of most of the solvents the residue was made alkaline with 5% aqueous sidium hydrogencarbonate and extracted with chloroform repeatedly. The resulting solution was washed with water, dried and evaporated to leave a crystalline residue, which was recrystallized from acetone-isopropyl ether (1 : 1) to yield **18** (439 mg), mp 176—179 °C. Recrystallization from the same solvent mixture afforded an analytical sample: mp 179—180 °C; $[\alpha]_D$ +5.0°; ORD, $[\Phi]_{318}^{trough}$ −4300°, $[\Phi]_{310}^{trough}$ −3500°, $[\Phi]_{273}^{peak}$ +6200°, a=−105°; IR, ν_{max} 3500, 3430, 1691 and 1035 cm^{-1}; NMR, δ 0.75 (3H, s, 19-C$\underline{H}_3$), 0.97 (3H, d J=6.5 Hz, 18-C$\underline{H}_3$) and 3.52 (1H, br, $\underline{H}$ at C_3). Found: C, 78.39; H, 10.34%. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41%.

Compound **18** (206 mg) was treated with Ac_2O (1 ml) and Py (2 ml) at room temp for 5 h, and the mixture was mixed with water under cooling and extracted with ether repeatedly. The ether solution gave a crystalline residue, which was recrystallized from isopropyl ether to yield **18a** (207 mg), mp 132—134 °C. This was recrystallized from the solvent for analysis: mp 134.5—135 °C; $[\alpha]_D$ −1.84°; ORD, $[\Phi]_{318}^{trough}$ −4900°, $[\Phi]_{309}^{trough}$ −4200°; $[\Phi]_{274}^{peak}$ +5600°, a=−105°; IR, ν_{max} 1736, 1702, 1244 and 1024 cm^{-1}; NMR, δ 0.78 (3H, s, 19-C$\underline{H}_3$), 0.99 (3H, d J=6.5 Hz, 18-C$\underline{H}_3$), 1.99 (3H, s, OCOC$\underline{H}_3$) and 4.68 (1H, br, $\underline{H}$ at C_3). Found: C, 75.92; H, 9.66%. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70%.

*17-Ethylidene-5α,12β-etiojervan-3β-ol (**19**) and Its 3-Acetate (**19a**).* The Wittig reaction of **18** was conducted in practically the same manner as that of **9**. To a red-brown solution, prepared from sodium hydride (313 mg, *ca.* 50% in oil) and ethyltriphenylphosphonium bromide (2.137 g, 5.76 mmol) in DMSO (14 ml), was added **18** (412 mg, 1.42 mmol) in THF (5.5 ml) at room temp during 2 min under stirring in a stream of nitrogen, and the mixture was stirred at room temp for 20 min and then at 50 °C (bath temp) for 22 h under nitrogen. The reaction mixture gave an amorphous residue (1.983 g) after usual work up, which was submitted to column chromatography over alumina (Merck, acidic 25 g, 20.5 cm in length and 1.6 cm in diameter), using hexane as solvent, to remove triphenylphosphine oxide. Fractions eluted with hexane-benzene (1 : 2, 150 ml), benzene (600 ml), benzene-ether (1 : 1. 800 ml) and ether (750 ml) were collected, evaporated and purified by preparative TLC (21 plates), using a 1 : 2 mixture of ether and

benzene. The main fraction was extracted with acetone and, after evaporation, dissolved in chloroform. The chloroform solution was worked up as usual to leave an oily mixture (**19**, 413 mg); IR, ($CHCl_3$), ν_{max} 3420 and 1027 cm^{-1}; NMR, δ 0.73 and 0.76 (total 3H, each s, intensity ratio 4 : 3, 19-C$\underline{H}_3$), 0.95 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 1.60 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 3.56 (1H, br, $\underline{H}$ at C_3) and 5.15 (1H, q J=6 Hz, $\underline{H}$ at C_{20}).

The mixture (**19**, 410 mg) was treated with Ac_2O (2 ml) and Py (4 ml) at room temp for 12 h; it afforded the acetates (**19a**, 385 mg), amorphous, showing only a single spot on TLC; IR (film), ν_{max} 1738, 1241 and 1026 cm^{-1}; NMR, δ 0.74 and 0.77 (total 3H, each s, intensity ratio 4 : 3 19-C$\underline{H}_3$), 0.97 (3H, d J=6.5 Hz, 18-C$\underline{H}_3$), 1.58 (3H, d J=7.5 Hz, 21-C$\underline{H}_3$), 2.00 (3H, s, OCOC$\underline{H}_3$), 4.67 (1H, br, $\underline{H}$ at C_3) and 5.15 (1H, q J=7.5 Hz, $\underline{H}$ at C_{20}).

Hydrogenation of ***19***. A solution of **19** (315 mg) in AcOH (14 ml) was hydrogenated over Adams Pt (109 mg) at room temp for 40 min, when 25 ml (1 mol) of hydrogen had been consumed. After usual work up the reaction mixture gave a gelatinous substance, which was purified by preparative TLC (18 plates) with a 1 : 2 mixture of ether and benzene. The main fraction gave an oily substance (294 mg), showing a single spot, which exhibited an NMR spectrum superimposable over that of **13** and crystallized partially on standing in hexane. The crystalline material thus obtained amounted to 21 mg, had mp 83—88 °C (*cf.*, **13**, mp 124—125 °C) and showed an IR spectrum almost the same as that of **13**. The hydrogenation product would be a mixture of **13** and its 17-epimer but resisted further purification.

*17β-Acetyl-5α,12β-etiojervan-3β-ol 3-Acetate (**20**) and Its 17α-Isomer (**21**).* a) Diborane was generated by addition of boron trifluoride etherate (4 ml) in diglyme (22 ml) to excess of sodium borohydride (NBH) in diglyme, and was passed through a solution of **19a** (1.258 g) in ether (65 ml) at room temp during 25 min under stirring in a stream of nitrogen, and the resulting solution was stirred at room temp for 45 min and then heated at 70—80°C for 1 h. To the solution was added water (10 ml) and then an aqueous solution (25 ml) containing sodium dichromate (5.0 g as dihydrate) and conc sulfuric acid (3.7 ml) during 10 min under stirring and cooling with an ice-bath, and the whole mixture (two layers) was further stirred at room temp for 18 h. The aqueous layer was shaken with ether, and the ether and diglyme solutions were combined, washed with 5% aqueous sodium hydrogencarbonate repeatedly and then with saturated brine, dried and evaporated to leave amorphous residue (1.241 g), showing absorption maxima at 3435, 1735 and 1717 cm^{-1} in the IR spectrum (neat), wihch gave four spots on TLC and was separated by column chromatography with silica gel (Mallinckrodt, 26 g) with benzene.

The first fraction (115 mg) showing the largest R_f value proved to be the unreacted starting material (**19a**). The second fraction yielded crystalline substances (**20**, 269 mg), mp 189—190.5 °C. The third fraction yielded oily substances (226 mg). The fourth (389 mg) with the least R_f value was again dissolved in ether (6 ml), oxidized with the acidic chromate solution (6 ml) for 14 h and separated by preparative TLC (20 plates) with benzene. Each fraction was detected with iodine, eluted with acetone and, after evaporation, dissolved in chloroform and the chloroform solution was washed with 5% aqueous sodium hydrogencarbonate and water, treated with active carbon to remove iodine, dried and evaporated. The first fraction yielded crystalline substances (**20**, 80 mg), but the second fraction, which would be boron adducts (241 mg), was not examined further. The crystalline substances were combined and recrystallized from methanol to yield an analytical sample of **20**, mp 189—191 °C; $[\alpha]_D$ +36.8°; ORD, $[\Phi]^{peak}_{309}$ +2700°; $[\Phi]_{289}$=0°, $[\Phi]^{trough}_{252}$ −2560°, a=+52.6°; Mass, *m/e* 360 (M^+); IR, ν_{max} 1729, 1709, 1253 and 1021 cm^{-1}; NMR, δ 0.77 (3H, s, 19-C$\underline{H}_3$), 0.93 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 1.98 (3H, s, OCOC$\underline{H}_3$), 2.09 (3H, s, 21-C$\underline{H}_3$), 2.83 (1H, br W_H=11 Hz, $\underline{H}$ at C_{17}) and 4.70 (1H, br, $\underline{H}$ at C_3). Found: C, 76.64; H, 10.10%. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07%.

The oily substances (the third fraction, 226 mg) were triturated with aqueous methanol to yield the crystalline substances (**21**, 136 mg), mp 92—110 °C. Recrystallization from the same solvent afforded an analytical sample, mp 110.5—111 °C; $[\alpha]_D$ +24.3°; ORD, $[\Phi]^{trough}_{322}$ −2110°; $[\Phi]_{302}$=0°, $[\Phi]^{peak}_{255}$ +6050°; a=−81.6°; Mass *m/e* 360 (M^+); IR ($CHCl_3$), ν_{max} 1722, 1258 and 1027 cm^{-1}; NMR, δ 0.76 (3H, s, 19-C$\underline{H}_3$), 0.81 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 1.99 (3H, s, OCOC$\underline{H}_3$), 2.09 (3H, s, 21-C$\underline{H}_3$) and 4.68 (1H, br, $\underline{H}$ at C_3). Found: C, 76.85; H, 10.03%. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07%.

b) A solution of **20** (25 mg) was refluxed with 1 M sodium methoxide in methanol (10 ml) for 25 h under nitrogen. After removal of the solvent *in vacuo* the residue was mixed with water and extracted with chloroform. The chloroform solution was washed with water, dried and evaporated to leave a crystalline substance (27 mg), which was treated with Ac_2O (0.5 ml) and Py (0.5 ml) at room temp for 16 h. The reaction mixture gave **21** (13 mg), mp 110.5—111 °C, after being worked up as usual, which was identical with the afore-mentioned sample **21** [IR ($CHCl_3$) and TLC]. The starting material (**20**) could not be detected by TLC.

*17β-Ethyl-5α,12β-etiojervane-3β,20α-diol 3-Acetate (**22**) and Its 20β-Isomer (**23**).* A solution of **20** (212 mg) in ethanol (30 ml) was treated with NBH (622 mg) at room temp for 16 h under stirring. After dropwise addition of AcOH (2.4 ml) under cooling with ice-bath during 15 min, the solution was evaporated below 30 °C *in vacuo*, and the residue was mixed with water and extracted with chloroform repeatedly. The chloroform solution gave amorphous material (232 mg), which was separated by preparative TLC (10 plates) with a 1 : 10 mixture of ether and benzene. The most mobile part (81 mg) crystallized on trituration with acetone-isopropyl ether to give **22** (77 mg), mp 149.5—150 °C. This was recrystallized from the same solvent mixture for analysis: mp 150—151 °C; $[\alpha]_D$ +48.7°; IR, ν_{max} 3520, 1725, 1267 and 1028 cm^{-1}; NMR, δ 0.76 (3H, s, 19-C$\underline{H}_3$), 0.94 (3H, d J=5 Hz, 18-C$\underline{H}_3$), 1.22 (3H, d J=6.5 Hz, 21-C$\underline{H}_3$), 2.01 (3H, s, OCOC$\underline{H}_3$), 4.07 (1H, br m W_H=10 Hz, $\underline{H}$ at C_{20}) and 4.67 (1H, br, $\underline{H}$ at C_3). Found: C, 76.17; H, 10.37%. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57%.

The middle part (96 mg) crystallized on trituration with hexane to give **23** (73 mg), mp 117—118 °C. Recrystallization from hexane afforded an analytical sample: mp 117—118 °C; $[\alpha]_D$ +44.8°; IR ν_{max} 3530, 1726, 1260 and 1031 cm^{-1}: NMR, δ 0.78 (3H, s, 19-C$\underline{H}_3$), 1.04 (3H, d J=5 Hz, 18-C$\underline{H}_3$), 1.21 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 2.02 (3H, s, OCOC$\underline{H}_3$), 3.99 (1H, br m, W_H=16 Hz, $\underline{H}$ at C_{20}) and 4.70 (1H, br, $\underline{H}$ at C_3). Found: C, 76.43; H, 10.63%. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57%.

The least mobile part gave a crystalline substance (42 mg) which would be a mixture of 3-alcohols but was not further examined.

*17α-Ethyl-5α,12β-etiojervane-3β,20ξ-diol 3-Acetate (**24**).* A solution of **21** (62 mg) in ethanol (10 ml) was treated with NBH (209 mg) at room temp and the reduction was practically complete after 3 h (*cf.*, the same reduction of **22**).

The reaction mixture was worked up as mentioned above to leave an amorphous residue (61 mg), which was purified by preparative TLC (3 plates) with a 10 : 1 mixture of benzene and ether. The crystalline, main fraction (39 mg), which showed a single spot differing from those of **22** and **23**, was recrystallized from isopropyl ether-hexane to give **24** (13 mg), mp 115—118 °C; $[\alpha]_D$ +21.2°; IR, ν_{max} 3410, 1733, 1710 (shoulder), 1245 and 1040 cm^{-1}; NMR, δ 0.78 (3H, s, 19-C$\underline{H}_3$), 0.91 (3H?, d J=5 Hz, 18-C$\underline{H}_3$), 1.10 (3H?, t J=6 Hz, 21-C$\underline{H}_3$), 2.13 (3H, s, OCOC$\underline{H}_3$), 4.07 (1H, br m W_H=15 Hz, $\underline{H}$ at C_{20}) and 4.65 (1H, br, $\underline{H}$ at C_3). Found; C, 76.10; H, 10.41%. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57%.

Treatment of **22** *with* p-*Toluenesulfonyl Chloride.* To a solution of **22** (74 mg) in Py (1.2 ml) was added *p*-toluenesulfonyl chloride (168 mg) and the mixture was stirred at room temp for 42 h. Water was poured onto the mixture and the resulting suspension was extracted with ether. The extracts were worked up as usual to give a crystalline substance (76 mg), showing a single spot on TLC, which was triturated with methanol to give **25** (66 mg), mp 92—92.5 °C. This was recrystallized from methanol for analysis: mp 92—92.5 °C; $[\alpha]_D$ +55.4°; Mass, *m/e* 344 (M^+); IR, ν_{max} 1738, 1657 (w), 1237 and 1024 cm^{-1}; NMR, δ 0.77 (3H, s, 19-C$\underline{H}_3$), 0.99 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 1.66 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 2.00 (3H, s, OCOC$\underline{H}_3$), 4.70 (1H, br W_H=24 Hz, $\underline{H}$ at C_3) and 5.15 (1H, q J=6 Hz, $\underline{H}$ at C_{20}). Found: C, 79.05; H, 10.26%. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53%.

*Reaction of 20-Tosylate (***23a***) of* **23** *with Lithium Aluminium Hydride (LAH).* A solution of **23** (67 mg) in Py (1 ml) was treated with *p*-toluenesulfonyl chloride (158 mg) at room temp for 42 h under stirring. The reaction mixture was worked up in the same manner as **22** and afforded oily tosylate (**23a**, 96 mg), which gave a single spot on TLC and showed absorption maxima at 1724, 1600, 1492, 1380, 1257, 1176, 1027 and 900 cm^{-1} in the IR spectrum ($CHCl_3$); NMR, δ 0.77 (3H, s, 19-C$\underline{H}_3$), 0.88 (3H, d J=7 Hz, 18-C$\underline{H}_3$), 1.31 (3H, d J=7 Hz, 21-C$\underline{H}_3$), 2.00 (3H, s, OCOC$\underline{H}_3$), 2.43 (3H, s, $C\underline{H}_3C_6H_4$) and 4.80 (2H, br, 2$\underline{H}$ at C_3 and C_{20}). This tosylate, without further purification, was refluxed with LAH (160 mg) in THF (15 ml) for 24 h and gave oily residue (75 mg) after usual work up, which showed two spots on TLC and was separated by preparative TLC (7 plates) with a 1 : 2 mixture of ether and benzene. The more mobile part (17 mg) gave an oily substance (**26**); NMR, δ 0.75 (3H, s, 19-C$\underline{H}_3$), 0.97 and 1.19 (each 3H d J=6 Hz, 2C$\underline{H}_3$ at C_{13} and C_{17a} or *vice versa*) and 3.68 (1H, br, $\underline{H}$ at C_3). The less mobile part (25 mg) crystallized on trituration with acetone-isopropyl ether to give **27** (8 mg), mp 182—185 °C. This was recrystallized from the same solvent mixture for analysis: mp 190—191 °C; $[\alpha]_D$ +46° (MeOH); IR, ν_{max} 3400, 3340, 1042 and 1030 cm^{-1}; NMR, δ 0.75 (3H, s, 19-C$\underline{H}_3$), 1.02 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 1.19 (3H, d J=6 Hz, 21-C$\underline{H}_3$), 3.65 (1H, br, $\underline{H}$ at C_3) and 4.00 (1H, br m W_H=17 Hz, $\underline{H}$ at C_{20}).

*17β-Ethyl-5α,12β-etiojervane-3β,11α-diol (***28***) and Its Acetates (***28a—28c***).* To a refluxing solution of **2** (241 mg) in isopropyl alcohol (40 ml) were added sodium pellets (1.6 g) in small portions during 1 h, and the mixture was further refluxed for 1 h.[21] After being cooled the mixture was diluted with water (20 ml) and evaporated below 42 °C *in vacuo*. The residue was mixed with water and extracted with chloroform repeatedly. The chloroform solution gave oily substance (263 mg), which crystallized on trituration with acetone-isopropyl ether to yield **28** (160 mg), mp 145—146.5 °C. Recrystallization from acetone afforded an analytical sample: mp 158—161 °C; $[\alpha]_D$ +0.42°; IR, ν_{max} 3355, 3295 and 1041 cm^{-1}; NMR, δ 0.775 (3H, s, 19-C$\underline{H}_3$), 0.89 (3H?, t J=6 Hz, 21-C$\underline{H}_3$?), 0.98 (3H, J=6 Hz, 18-C$\underline{H}_3$), 3.65 (1H, br, $\underline{H}$ at C_3) and 4.00 (1H, br W_H=12 Hz, $\underline{H}$ at C_{11}). Found: C, 78.57; H, 11.30%. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32%.

Compound **28** (112 mg) was acetylated with Ac_2O (0.4 ml) and Py (1.2 ml) at 17 °C for 2 h. The product (133 mg) was separated into 4 fractions (oil 35 mg, amorphous 72 mg, oil 12 mg, and crystalline 22 mg) by preparative TLC (7 plates) with a 1 : 5 mixture of ether and benzene. The last fraction afforded the unreacted material (**28**, 12 mg), which had mp 176—177 °C and 158—160 °C on recrystallization from acetone-isopropyl ether and acetone, respectively. The first and third fractions proved to be 3,11-diacetate (**28b**) and 11-acetate (**28c**), respectively, on the basis of the IR and NMR spectra: **28b**; oil, IR ($CHCl_3$), ν_{max} 1726, 1255 and 1027 cm^{-1}; NMR δ 0.84 (3H, d J=5 Hz, 18-C$\underline{H}_3$), 0.885 (3H, s, 19-C$\underline{H}_3$), 1.99 (6H, s, 2OCOC$\underline{H}_3$), 4.70 (1H, br, $\underline{H}$ at C_3) and 5.24 (1H, br W_H=12 Hz, $\underline{H}$ at C_{11}): **28c**; oil, IR ($CHCl_3$), ν_{max} 3600, 3400, 1727, 1253 and 1031 cm^{-1}; NMR, δ 0.84 (3H, d J=5 Hz, 18-C$\underline{H}_3$), 0.875 (3H, s, 19-C$\underline{H}_3$), 1.98 (3H, s, OCOC$\underline{H}_3$), 3.65 (1H, br, $\underline{H}$ at C_3) and 5.28 (1H, br W_H=13 Hz, $\underline{H}$ at C_{11}).

The second, main fraction crystallized on trituration with isopropyl ether to give **28a**, which on recrystallization from the same solvent afforded a pure sample (40 mg), mp 128—129 °C; $[\alpha]_D$ +42.0°; IR, ν_{max} 3570, 1724, 1255 and 1031 cm^{-1}; NMR, δ 0.79 (3H, s, 19-C$\underline{H}_3$), 0.98 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 2.00 (3H, s, OCOC$\underline{H}_3$), 3.98 (1H, br W_H=11 Hz, $\underline{H}$ at C_{11}) and 4.68 (1H, br, $\underline{H}$ at C_3). Found: C, 76.16; H, 10.47%. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57%.

Attempted Hydride Reduction of **2**. a) A solution of **2** (51 mg) in dry THF (10 ml) was refluxed with NBH (30 mg) for 11.5 h and cooled. After addition of acetone (4 ml) the mixture was evaporated *in vacuo* and the residue was mixed with water and extracted with chloroform. The chloroform solution was washed with water, dried and evaporated to leave an amorphous substance, which crystallized on trituration with methanol, had mp 112—114 °C, and amounted to 32 mg. This was identified as the starting material **2** (IR, mixed mp and TLC).

b) A solution of **2** (51 mg) in THF (15 ml) was refluxed with LAH (260 mg) for 2.5 h under stirring. After addition of ice-water the mixture was acidified with 2 M hydrochloric acid (15 ml) and extracted with chloroform. The chloroform solution gave an oily substance (54 mg), which showed absorption maxima at 3615, 3440, 1728, 1031 and 1016 cm^{-1} in the IR spectrum. Treatment of **2** with the same reagent under more vigorous conditions (reflux in dry dioxane for 13 h) gave practically the same result.

*17β-Ethyl-5α,12β-etiojervane-3β,11β-diol (***29***) and Its 3-Acetate (***29a***).* A solution **11** (263 mg) in dioxane (20 ml) was refluxed with LAH (513 mg) for 45 h under stirring. After decomposition of excess reagent with methanol and water, the resulting precipitate was removed by filtration and washed with methanol. The filtrate and washings were combined and concentrated to dryness under reduced pressure. The residue was dissolved in chloroform and worked up as usual to give a crystalline substance (250 mg), which on trituration with acetone afforded **29** (220 mg), mp 185—186 °C. This was recrystallized from acetone for analysis: mp 186—188 °C; $[\alpha]_D$ +52°; IR, ν_{max} 3330, 1077, 1043 and 1033 cm^{-1}; NMR, δ 1.02 (3H, s, 19-C$\underline{H}_3$), 3.60 (1H, br, $\underline{H}$ at C_3) and 4.06 (1H, do d J=6 and 8 Hz, $\underline{H}$ at C_{11}). Found: C, 78.75; H, 11.22%. Calcd for $C_{21}H_{36}O_2$: C,

78.69; H, 11.32%.

Compound **29** (207 mg) was acetylated with Ac_2O (1 ml) and Py (2 ml) at 18 °C for 3 h. The product (235 mg) was triturated with acetone–isopropyl ether to yield **29a** (115 mg), mp 149—151 °C. This was recrystallized from the same solvent mixture for analysis: mp 151—152 °C; $[\alpha]_D$ +44°; IR, ν_{max} 3490, 1713, 1260 and 1033 cm^{-1}; NMR δ 1.04 (3H, s, 19-C$\underline{H}_3$), 2.01 (3H, s, OCOC$\underline{H}_3$) and 4.07 (1H, do d J=6 and 8 Hz, $\underline{H}$ at C_{11}). Found: C, 75.92; H, 10.30%. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57%.

*17β-Ethyl-5α-etiojerv-11-en-3β-ol Acetate (**30**).* To a solution of **28a** (101 mg) in freshly distilled Py (1 ml) was added freshly distilled phosphoryl chloride (0.1 ml) at 0 °C under stirring. A white salt was immediately precipitated. After being stirred at room temp for 1 h, the mixture was poured onto ice–water (30 ml). The resulting suspension was extracted with chloroform repeatedly. The extracts were washed with 1 M hydrochloric acid, 5% aqueous sodium hydrogencarbonate and water, dried, and evaporated to leave oily residue (111 mg), which showed a single spot on TLC and was chromatographed on silica gel (5 g) impregnated with 10% silver nitrate with benzene to afford pure oily substrance (**30**, 85 mg). Mass, *m/e* 344 (M^+), 315 ($M^+-C_2H_5$) and 255 ($M^+-C_2H_5-$AcOH); IR ($CHCl_3$), ν_{max} 1725, 1257 and 1022 cm^{-1}; NMR, δ 0.77 (3H, s, 19-C$\underline{H}_3$), 0.88 (3H, t J=7 Hz, 21-C$\underline{H}_3$), 1.02 (3H, d J=6 Hz, 18-C$\underline{H}_3$ 2.04 (3H, s, OCOC$\underline{H}_3$), 4.72 (1H, br, $\underline{H}$ at C_3) and 5.33 (1H, br s W_H=6 Hz, $\underline{H}$ at C_{11}).

A solution of **30** (6 mg) in AcOH (1 ml) was allowed to stand at room temp for 1 h. The mixture was diluted with water and extracted with chloroform. The extract was worked up as usual to give oily substance (6 mg), which was identical with the starting material substance (NMR and TLC).

*17β-Ethyl-5α,12β-etiojerv-9(11)-en-3β-ol Acetate (**31**).* To a solution of **29a** (192 mg) in freshly-distilled Py (2 ml) was added freshly-distilled phosphoryl chloride (0.3 ml) at 0 °C under stirring. The mixture was stirred at room temp for 1 h and poured onto ice–water (30 ml). After usual work up, the mixture afforded oily residue (235 mg), which was purified by column chromatography on silica gel (5 g) with benzene to give pure oily substance (**31**, 188 mg); Mass, *m/e* 344 (M^+), 329 (M^+-CH_3), 315 ($M^+-C_2H_5$), 284 (M^+ −AcOH), 269 (M^+-AcOH$-CH_3$) and 255 (M^+-AcOH $-C_2H_5$); IR ($CHCl_3$), ν_{max} 1725, 1253 and 1024 cm^{-1}; NMR, δ 0.87 (3H, t J=8 Hz, 21-C$\underline{H}_3$), 0.92 (3H, s, 19-C$\underline{H}_3$), 0.98 (3H, d J=6.5 Hz, 18-C$\underline{H}_3$), 2.03 (3H, s, OCOC$\underline{H}_3$), 4.71 (1H, br, $\underline{H}$ at C_3) and 4.61 (1H, br s W_H= 6 Hz, $\underline{H}$ at C_{11}).

A solution of **31** (11 mg) in AcOH (1 ml) was stirred at room temp for 2 h. The mixture was worked up as usual to afford an oily residue (11 mg), which was identical with the starting material (NMR and TLC).

*17β-Ethyl-5α,12α-etiojervan-3β-ol Acetate (**32**).* A solution of compound **30** (76 mg) in AcOH (3.5 ml) was hydrogenated over Adams Pt (151 mg) at room temp for 55 min, when 5.9 ml of hydrogen (1.11 mol) had been consumed. The product (77 mg), oil, showed a single spot on TLC: $[\alpha]_D$ +0.5°; Mass, *m/e* 286 (M^+-AcOH, base); IR ($CHCl_3$), ν_{max} 1728, 1256 and 1025 cm^{-1}; NMR, δ 0.81 (3H, s, 19-C$\underline{H}_3$), 2.01 (3H, s, OCOC$\underline{H}_3$) and 4.73 (1H, br, $\underline{H}$ at C_3).

*17β-Ethyl-5α,12β-etiojervan-3β-ol Acetate (**13a**).* A solution of compound **31** (171 mg) in AcOH (4 ml) was hydrogenated over Adams Pt (118 mg) at room temp for 35 min, when 8.8 ml of hydrogen (0.74 mol) had been consumed. The catalyst (101 mg) was further added to the reaction mixture and hydrogenation was continued for 30 min, when 24.4 ml of hydrogen had been taken up. The product (164 mg) crystallized on trituration with methanol, had mp 74—75 °C, and amounted to 125 mg. It was recrystallized twice from aqueous methanol and then from acetone to give a pure material, mp 92—94 °C, which was identical with compound **13a** in all respects.

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