Tetrahedron Vol 25. pp 4551 to 4567. Pergamon Press 1969 Printed in Great Britain

THE SYNTHESIS OF ETIOJERVANE ANALOGS OF TESTOSTERONE AND ESTRONE*

T. MASAMUNE and K. ORITO

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Japan

(*Received in Japan* 26 *April* 1969; *Received in the UK for publication* 10 *June* 1969)

Abstract—The synthesis is described of C-nor-D-homotestosterone acetate (X) and C-nor-D-homoestrone (XXVIII), from jervine (I), each of which possesses the testosterone and estrone configuration, respectively, at each of the ring junctions. Beckmann rearrangement of the 3-acetate (IIIa) of 17α-acetyletiojerv-5-en-3β-ol 20-oxime (III), an intermediate in the synthesis of C-nor-D-homo-17-epiprogesterone, gave rise to acetamide 3-acetate (IVa), which after hydrolysis was submitted to Ruschig reaction to yield ketoalcohol (VI). Hydrogenation of 3-acetate (VIa) of VI in the presence of Pt under neutral conditions resulted in a good yield of 17β-alcohol (VIIIa), which on hydrolysis followed by Oppenauer oxidation and acetylation was converted into X in an over-all yield of 4·5% from I. On the other hand, acetamide 3-alcohol (IV) was oxidized under Oppenauer conditions and then dehydrogenated with DDQ to give dienone (XXV). Treatment of XXV according to Dreiden's procedure effected aromatization of the A-ring to yield phenol amide (XXVIa), which was transformed, via the same type of reaction sequence as that from IVa to VIa, into XXVIII in an over-all yield of 1·5% from I. Spectral and chemical evidence are adduced for configurational assignment to both the compounds and all the synthetic intermediates.

THE synthesis of modified steroid hormones has received considerable attention in the search of analogs with enhanced or more specific physiological properties. During the past few years etiojervane† analogs of cortisone,[1] progesterone,[3, 4a] testosterone,[4b, 5] estrone[4c] and others[5, 6] have been prepared. In this paper we describe a new synthesis of C-nor-D-homotestosterone and C-nor-D-homoestrone by a pathway which has been applied to C-nor-D-homo-17-epiprogesterone.[3]

In the previous paper[3] on the synthesis of the etiojervane analog of progesterone, we reported on the transformation of jervine (I), one of the most readily available veratrum alkaloids, into 22,27-iminojerv-5-ene-3β,23β-diol (II) in 40% yield (5 steps), which was then degraded to 17-acetyletiojerv-5-en-3β-ol 20-oxime (III). In a continuing study the degradation was improved to 88% from 60% yield[3] (4 steps) by careful treatment of each step (Experimental). Compound II was, therefore, selected as a starting material for our present synthesis. On the other hand, it has recently been reported[7] that the previous configurational assignment (12α<u>H</u>, 17α<u>H</u>) to the compound should be revised as shown by III (12β<u>H</u>, 17β<u>H</u>). Thus we also describe the details on the revision in the present paper, in which all the compounds are represented by revised formulae.

20-Oxime 3-acetate (IIIa), m.p. 232–234°, prepared by treatment of oxime III with acetic acid and hydrogen chloride, was submitted to Beckmann rearrangement ($POCl_3$ and Py)[5] to yield acetamide 3-acetate (IVa), m.p. 295·5–296°. The strong

* Part XV of *C-Nor-D-homosteroids and Related Alkaloids*: Part (XIV) IV, Ref. 15.

† For the designations "etiojervane and jervane," see Refs 1 and 2.

absorption at 1642 cm^{-1} in the IR spectrum confirmed the presence of an amido group in IVa and the broad signal with half-width of 18 c/s at τ 6·50 assignable to the 17-proton in the NMR spectrum indicated the acetylamino group to be equatorial.[8] This amide on hydrolysis gave 17-amino-3-alcohol (V), m.p. 211·5–213°, in 73% yield from III (3 steps). Attempted one-step transformations of the acetamido (N_2O_4 and AcONa in CCl_4 or AcOH–Ac_2O)[9] or of the amino group ($NaNO_2$ and AcOH, reflux)[10] to an OH failed; in most of the cases the starting compounds (5,6-dihydro derivate of IVa, or (V) were unaffected, and under more vigorous conditions only tarry substances were formed. Compound V was then degraded, by Ruschig reaction,[11] to 17-keto-3-alcohol (VI), m.p. 167–168°; that is, V, when treated with N-chlorosuccinimide (NCS), was converted into the chloroamine, which underwent dehydrochlorination with sodium ethoxide followed by hydrolysis with acid to give VI, in 61% yield (3 steps). An alternate approach to 17-ketone VI starting from 20-oxime III proceeded via the corresponding 20-ketone[3] (XII, described later), but proved to be unsuccessful; attempted degradation of the latter with n-butyl nitrite and sodium ethoxide to the oxime of VI led to recovery of the starting material or formation of tarry substance.[12]

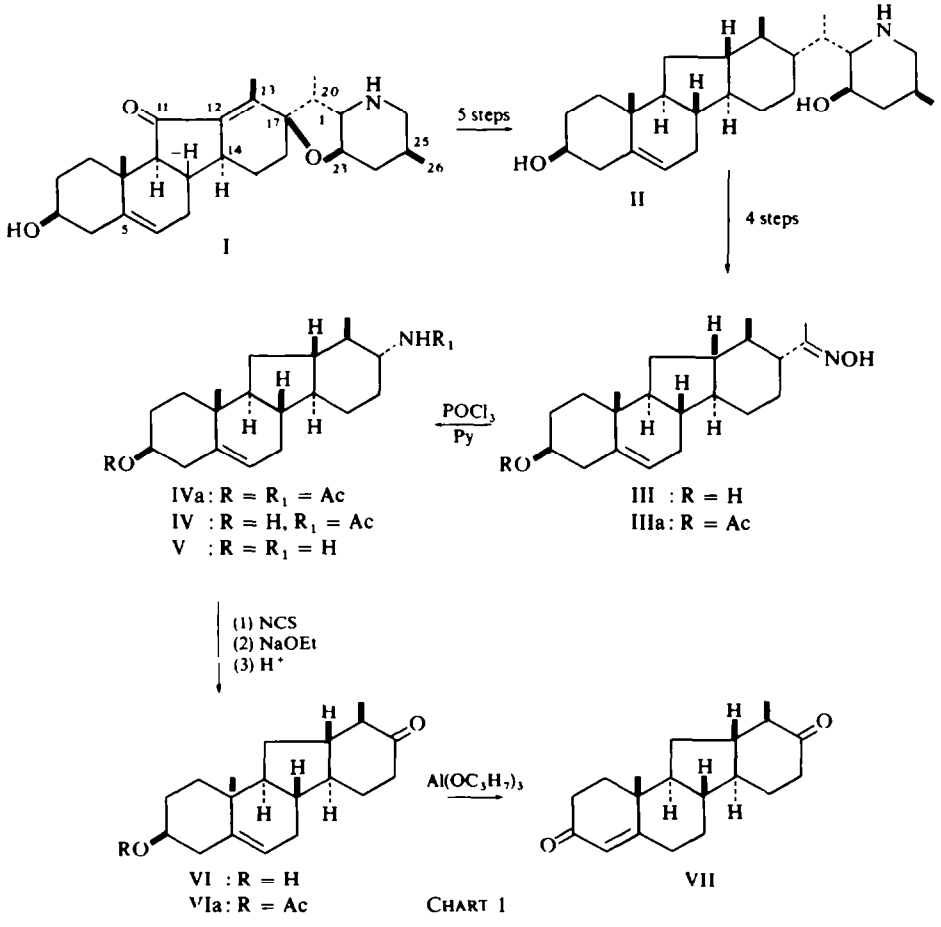


CHART 1

The ketone VI was readily converted into the 3-acetate (VIa), m.p. 136–137°, and also into the Δ^4-3-ketone (VII), m.p. 182–183°, in almost quantitative yields. The two ketones VI and VIa exhibited negative Cotton effects with amplitudes of $-111°$ and $-108°$ in the ORD curves. These values were consistent with the stereostructure of C/D *trans*-fused linkage (12β<u>H</u>) and α-hydrogen configuration at C_{13}, as already discussed by Kupchan[4b] and us,[1a] but would not necessarily exclude the alternative with α-hydrogens at C_{12} and C_{13} as pointed out by Johns[5] (12α-etiojervan-3β-ol-17-one, $a = -94°$). However, in view of the stability of VI to alkali (recovered unchanged after treatment with KOH in refluxing MeOH in an almost quantitative yield), the former configuration (12β<u>H</u>, 13α<u>H</u>) would be preferable to the latter (12α<u>H</u>, 13α<u>H</u>), and this will be supported later.

Hydrogenation of 17-keto-3-acetate VIa in the presence of platinum in absolute ethanol effected only reduction of the 17-ketonic group and produced, as a main product, a 4:3 mixture of 17β-alcohol (VIIIa), m.p. 163·5–164·5°, and 17α-alcohol (IXa), m.p. 171–172°. The configurational assignment to these alcohols was deduced from the R_f values on TLC as well as the NMR spectra; the 17-proton at τ 6·28 in VIIIa exhibited half-width of 7 c/s (equatorial), while the corresponding at τ 6·94 in IXa that of 14 c/s (axial).[13] These alcohols were hydrolysed with alkali to yield the respective 3-deacetyl derivatives, 3β,17β-glycol (VIII), m.p. 187–188°, and 3β,17α-glycol (IX), m.p. 182·5–183·5°, in yields of 50 and 33%, respectively, from VIa (2 steps). Similarly, ketoalcohol VI was hydrogenated under the same conditions as keto-acetate VIa. This reduction, however, proved to be less practical owing to difficult separation of the alcohols formed; VIII and IX were isolated in pure state in 32 and 24% yields only after careful preparative TLC. On the other hand, reduction of VI with sodium borohydride led to formation of the undesired alcohol IX as a major product.

3β,17β-Glycol VIII was submitted to Oppenauer oxidation and then acetylated to give etiojerv-4-en-17β-ol-3-one 17-acetate (X), m.p. 135·5–136·5°, in 60% yield (2 steps) along with a small amount of VII (16%). In accordance with the structure, X displayed absorption maxima at 1663 and 1616 cm^{-1} due to the Δ^4-3-keto group in the IR spectrum and also the broad signal with half-width of 7 c/s assignable to the 17-proton at τ 4·99 in the NMR spectrum. The isomeric alcohol IX was likewise treated and afforded both a 17-epimer (XI), m.p. 188–188·5°, of X and Δ^4-3,17-dione VII in 50 and 16% yields, respectively. The absorption due to the 17-proton of XI appeared at τ 5·50 with half-width of 15 c/s. On the basis of the afore-mentioned spectral data,[13] compound X must possess the testosterone configuration at each of the asymmetric centers and is, therefore, regarded as C-nor-D-homotestosterone acetate. In fact, these acetates X and XI and ketone VII were identical, in all respects, with the respective authentic specimens prepared by the procedure of Kupchan and Levine,[4b] whose configurations have been established (12β<u>H</u>, 13α<u>H</u>). It is noteworthy that, although our synthesis involves 20 steps, its over-all yield (4·5%) from jervine is commendably good.

The series of transformations described in the previous sections established the configuration of C_{12} (βH) and also probably of C_{13} (αH) in oxime III. However, there remained the possibility of epimerization at C_{13} during formation of 17-ketone VI from III, because VI was obtained by acid hydrolysis of its precursor, 17-imine. In order to confirm the stereochemistry of C_{13} as well as C_{17} (in II to IV), the following

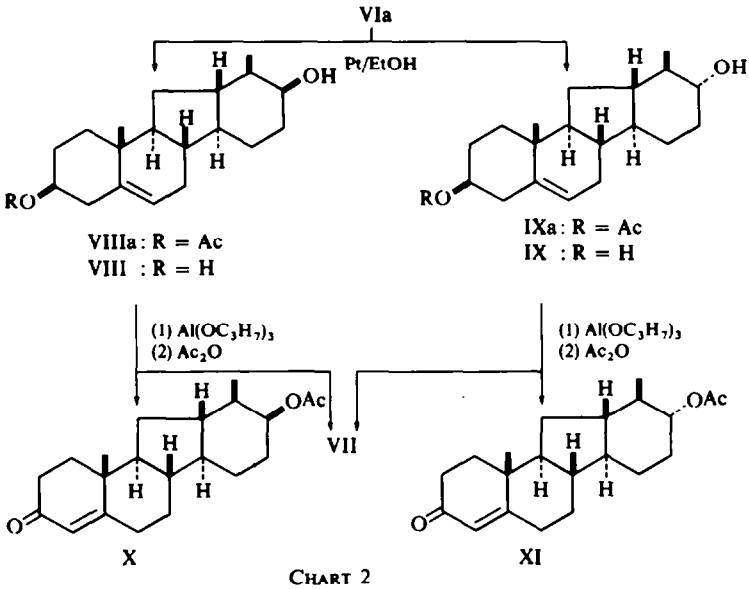


CHART 2

experiments were undertaken; oxime III was hydrolysed very smoothly and quantitatively to methyl ketone (XII), m.p. 127–128°, under mild conditions using Pines *et al.* method[14] (treatment with $NaHSO_3$ followed by acidification).* Compound XII remained unchanged after reflux with alkali in methanol, indicative of the stable and, accordingly, equatorial disposition (βH) of the 17-substituent. Hydrogenation of XII over platinum in acetic acid afforded two products, the 5α,6-dihydro derivative (XIII), m.p. 147–148°, and its 5β-isomer (XIV), oil, in 67 and 22% yields, respectively. The C_5 configurations of XIII and XIV were assigned on the basis of the different R_f values and the NMR spectra; the protons at C_{19} and C_3 in the former appeared at τ 9·24 as a singlet and at τ 6·37 as a broad peak (half-width 15 c/s), respectively, while those in the latter at τ 9·09 and 5·92 (half-width 7 c/s).[13,16] Oxidation of the major product XIII with perbenzoic acid followed by saponification gave rise to 3,17-glycol (XV), m.p. 169–170°, in 16% yield, 50% of the starting material being recovered unchanged. This compound XV was identified as etiojervane-3β-17α-diol, because XV was identical with a product obtained by hydrogenation of 3β,17α-glycol IX under the same conditions. In view of the well-known stereochemistry of Beckmann rearrangement[17] and Baeyer-Villiger reaction,[18] the above reaction sequence indicates that oxime III as well as II must be represented by formulas III and II, respectively. In addition, the etiojervane analog of progesterone, which was previously prepared by Oppenauer oxidation of XII and then assigned the 12αH, 13αH and 17βH configurations,[3] should also be formulated as C-nor-D-homo-17-epiprogesterone, since the analog was stable to alkali.[3]

* Acid hydrolysis of III under reflux in aqueous AcOH containing pyruvic acid afforded only the crude methyl ketone XII in a low yield and involved the possibility of epimerization at C_{17}.[3] It was found that the ease of hydrolysis depends on the stereochemistry of C/D ring juncture as well as a 17-substituent; e.g., only acidification of the solution at room temp effected the conversion of 20-oxime of a 17β-acetyl-12α-etiojervane analog into the corresponding methyl ketone. Cf., ref. 15.

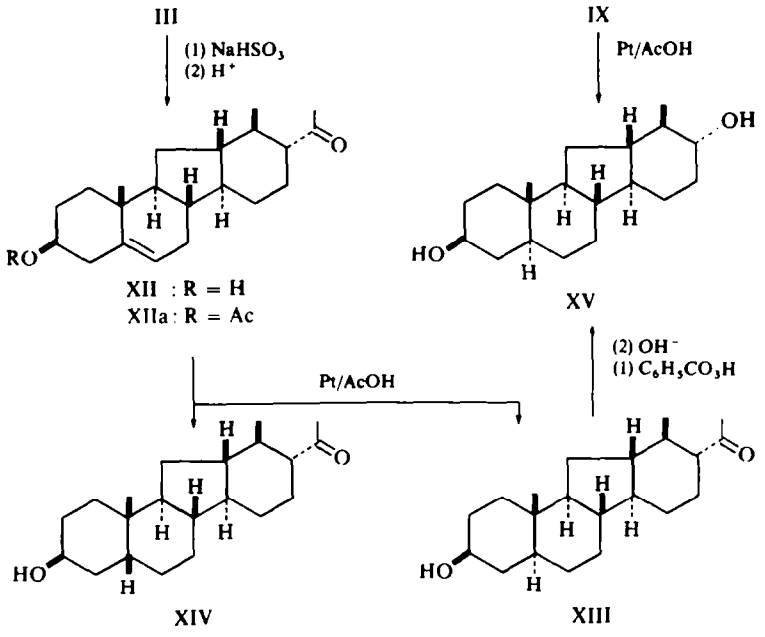


CHART 3

The revision of configurations (12β<u>H</u>, 13α<u>H</u>, 17β<u>H</u>) of compounds II and III described in the preceding section led us to have a doubt to the assigned structure[3,19] (12α<u>H</u>, 13α<u>H</u>, 17α<u>H</u>) to the N-acetyl-11-oxo derivative (XVIa) of II, which had been unaffected under rather strongly alkaline conditions and transformed to II by Wolff-Kishner reduction.[3] However, the inertness to alkali does not necessarily imply that no epimerization takes place at the relevant carbon (C_{12}) adjacent to C_{11} during the reaction. Thus it became desirable to correlate XVIa with a compound with known configurations through a series of reactions involving no epimerization at C_{12}.

Reduction of N-acetyl-11-ketone XVIa with sodium borohydride afforded 11β-alcohol (XVIIa), m.p. 243–244°, in 93% yield, which underwent partial acetylation to give its 3-O,23-O-diacetyl derivative (XVIIb), m.p. 224·5–225·5°. On treatment with chromic anhydride in pyridine, XVIIb was reconverted into the 11-ketone, m.p. 211–212°, in 88% yield from XVIIa, which was identical with 3,23-diacetate (XVIb) of XVIa, proving the retention of C_{12} configuration during the above hydride reduction. Compound XVIIa was hydrolyzed, by reflux with alkali in ethylene glycol containing hydrazine, to the corresponding amine (XVII), m.p. 240–241°, in 95% yield. This amine was degraded according to the procedure of Johnson *et al.*[20] XVII was transformed to the N-chloro derivative with NCS, which on treatment with sodium methoxide and then with acid yielded aldehyde (XVIII), m.p. 198–202°, whose structure was assigned on the spectral data; ν_{max} 2730 and 1713 cm^{-1}, and τ 0·38 (1H, broad singlet, CHO) and 8·93 (3H, doublet J = 5 c/s, 21-Me). The aldehyde was further degraded, with n-butyl nitrite and sodium methoxide, to 20-oxime (XIX), m.p. 167–168°, which was smoothly hydrolysed under the same conditions as III to yield 20-ketone (XX), m.p. 180–181°, in an overall yield of 69% from XVII (5 steps).

Undoubtedly, this ketone XX is an 11β-hydroxy derivative of 20-ketone XII, and the chemical shifts of the 19-, 18- and 21-methyl protons (τ 8·75, 9·03 and 7·86), as compared with those (τ 9·01, 9·17 and 7·87) of XII, are in good accord with the structure.[16,21]

The acetyl side chain at C_{17} of XX was transformed into the hydroxyl group in the same manner as its 11-deoxy compound XII; hydrogenation of XX over platinum in acetic acid afforded, as a single product, its 5α,6-dihydro derivative (XXI), m.p. 173–174°, in 90% yield. The C_5 configuration was based on the NMR spectrum; the 19-Me protons appeared at τ 8·96,[16,21] and the 3-proton at τ 6·37 as a broad signal with half-width of 15 c/s. This hydrogenation, in contrast with that of XII, is of interest, since the presence of the 11β-OH group has resulted in the almost exclusive α-attack of hydrogen to C_5. This compound XXI was successively oxidized with perbenzoic acid, hydrolysed with alkali and again oxidized with chromic anhydride, producing triketone (XXII), m.p. 174–175·5°, in 10% yield from XXI (3 steps), 53% of the starting material XXI being recovered unchanged. The compound XXII was identified as etiojervane-3,11,17-trione (12βH), because it was readily derived from

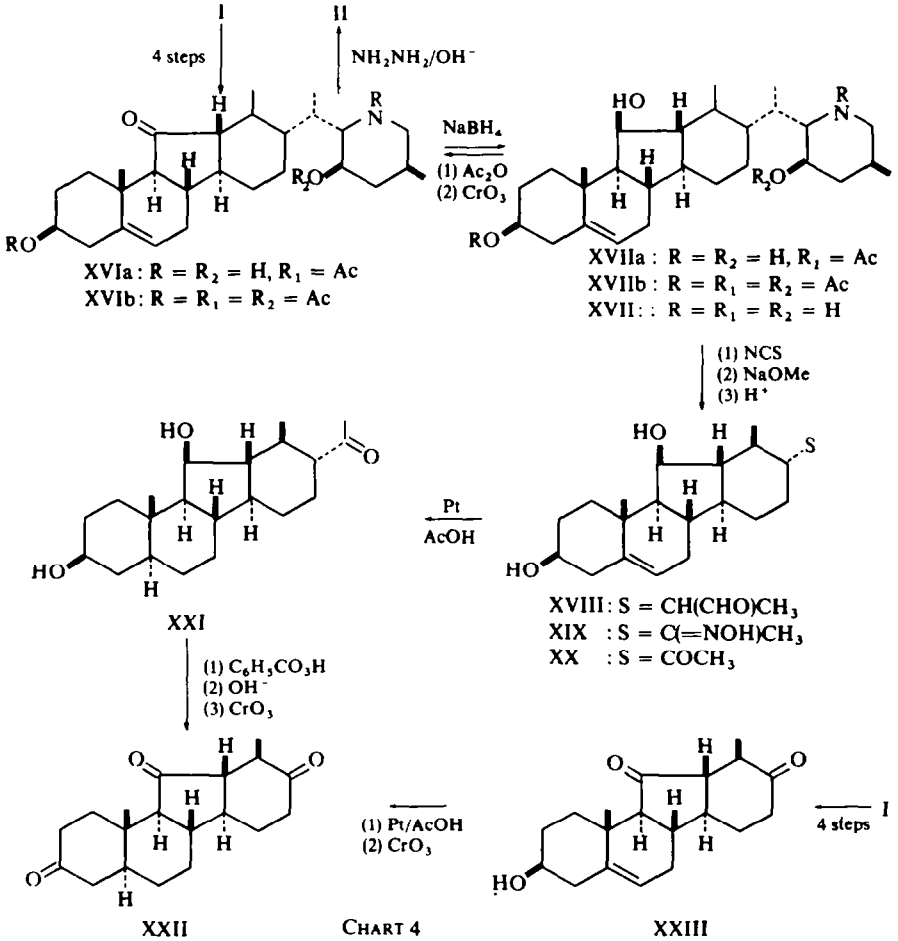


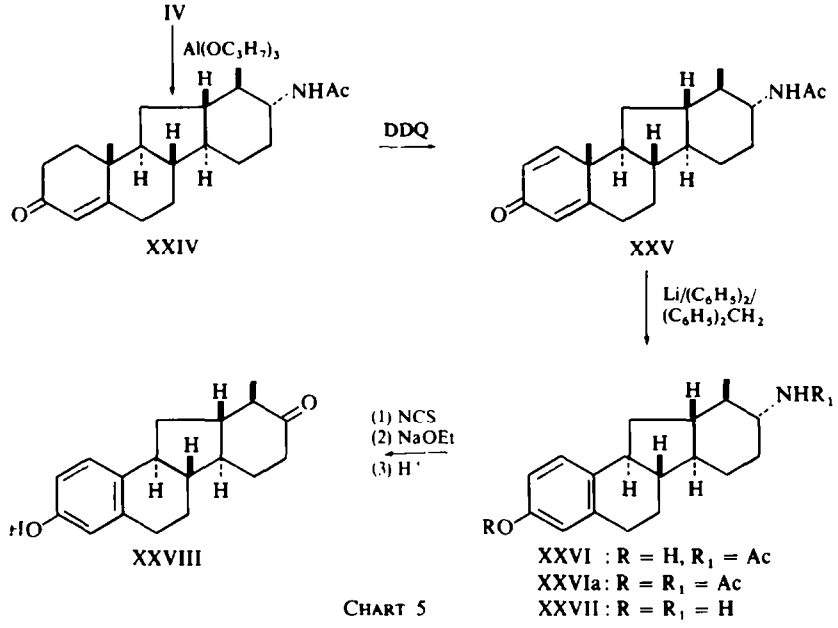
CHART 4

etiojerv-5-en-3β-ol-11,17-dione[4b, 22] (XXIII) with the established configuration (12β<u>H</u>, 13α<u>H</u>)[1a, 4a] via hydrogenation (Pt, AcOH) followed by oxidation (CrO_3) in 65% yield.* These findings have confirmed that compound XVI in question possesses the β<u>H</u> configuration at C_{12} (C/D *trans*-fused linkage) as represented by formula XVI.

We have now completed the stereochemistry of etiojervanes and iminojervanes related to C-nor-D-homotestosterone, and will proceed further with the synthesis of C-nor-D-homoestrone. The most important step for the synthesis is aromatization of ring A. As an approach aimed at a good yield of formation of compounds with aromatic ring A, the 19-Me oxygenation by irradiation[23, 24] were undertaken for several 11-oxo- and 11β-hydroxy-imonojervane derivatives including XVIa and XVIIb. Furthermore, XVIa and XVIIa were transformed into the respective 1,4-dien-3-oxo derivatives, and the aromatization for the compounds were also attempted under various conditions.[25, 26] However, all these attempts gave no good results. The aromatization via these routes are now under examination and the details will be reported later.

The successful route to C-nor-D-homoestrone started from amide 3-acetate IVa. This amide was hydrolysed, under mild conditions, to amide 3-alcohol (IV), m.p. 284–285°, which on Oppenauer oxidation gave Δ^4-3-ketone (XXIV), m.p. 238–240°, in 86% yield from IVa (2 steps). Treatment of XXIV with DDQ in dioxan[27] effected the dehydrogenation at C_1 and C_2, producing 1,4-dien-3-one (XXV), m.p. 212–213°, in 73% yield. In accordance with the assigned structure, the UV and IR spectra showed an absorption maximum at 244 mμ (ε 16,800) and those at 1660 and 1616 cm^{-1}. The NMR spectrum displayed three peaks at τ 3·18, 3·87 and 3·81, which appeared as a doublet (J = 10 c/s), a double doublet (J = 10 and 2 c/s) and a doublet (J = 2 c/s) and were attributed to the protons at C_1, C_2 and C_4, respectively. Further treatment of the cross-conjugated ketone XXV by Dreiden's procedure[26] resulted in aromatization of the ring A to yield phenol 17-amide (XXVI), which without isolation was transformed into the phenol 3-acetate 17-amide (XXVIa), m.p. 250–252°, in 28% yield from XXV (2 steps). All the spectral data confirmed the presence of the aromatic ring A in XXVIa; λ_{max} 278 and 271 mμ (ε 1100 and 1100), ν_{max} 1770, 1635 and 1574 cm^{-1}, and τ 7·73 (aromatic OAc) and three-proton signals below τ 3·4 (Experimental). This amide phenol acetate XXVIa on reflux with alkali in diethylene glycol containing hydrazine as an antioxidant was saponified to 17-amino-3-phenol (XXVII), the IR spectrum of which suggested that it would exist as betaine, ammonium phenolate. Compound XXVII was then subjected to the same degradation as 17-amine V and produced phenol 17-ketone (XXVIII), m.p. 260–261°, in 24% yield from XXVIa (4 steps). The transformation from IV to XXVIII involves no epimerization at C_{12} and C_{13}. Hence compound XXVIII possesses the estrone configuration at each of the asymmetric centers and is, therefore, regarded as C-nor-D-homoestrone. Indeed, it was identical with Kupchan's sample[4c] in all respects. The present synthesis consists of 19 steps and the over-all yield from jervine is 1·5%. Improved syntheses of XXVIII as well as C-nor-D-homoequilenin are now in progress.

* Compound XXII had been obtained by Kupchan and Levine by Oppenauer oxidation of XXIII and subsequent hydrogenation (Pd, EtOAc); Ref. 4b. Our sample of XXII, prepared from XXIII only under acidic or neutral conditions, was naturally identical with an authentic specimen prepared by their method.



XXVI : R = H, R_1 = Ac
XXVIa: R = R_1 = Ac
XXVII : R = R_1 = H

CHART 5

EXPERIMENTAL

All the m.ps were uncorrected. The homogenity of each compound was always checked by TLC on silica gel (Wakogel B-5) using various solvent systems, and the spots were developed with cerric sulfate in dil H_2SO_4 and/or I_2. The optical rotations, ORD curves, UV and IR spectra were measured in $CHCl_3$, dioxan, 99% EtOH and Nujol, respectively, unless otherwise stated. The NMR spectra were obtained in $CDCl_3$ at 60 and/or 100 Mc and the chemical shifts were given in τ-values, TMS being used as an internal reference. The abbreviations "s, d, q, br and m" in the NMR spectra denote "singlet, doublet, quartet, broad and multiplet," respectively.

17α-Acetyletiojerv-5-en-3β-ol 20-oxime (III) *and its 3-acetate* (IIIa)

To a soln of II[3] (1·00 g), m.p. 221–223°, in dry THF (40 ml) NCS (480 mg) was added at room temp, and the mixture was stirred at 35° (bath temp) for 70 min. Upon cooling and addition of water, the crude chloroamine ppt was collected by filtration, dried over P_2O_5 and amounted to 1·126 g. To the chloroamine in anhyd MeOH (120 ml) was added a NaOMe soln at 0°, prepared by addition of Na (2·76 g) into MeOH (120 ml). The soln was stirred at room temp for 1·5 hr and then concentrated to 60 ml below 35° under reduced press. To the residual soln water (200 ml) was added dropwise and then carefully 6N HCl (25 ml) at 0°. The resulting mixture was continuously stirred at room temp, the white crystals (crude aldehydes) which separated, were collected, washed and dried over P_2O_5.

The aldehyde mixture (755 mg) was dissolved in anhyd MeOH (35 ml) containing n-butyl nitrite (2·4 ml) at 0° and then mixed with a NaOMe soln prepared from Na (1·41 g) and MeOH (35 ml) at 0°. The whole soln was allowed to stand at the same temp for 6 hr, then neutralized with conc HCl and concentrated to 10 ml below 35° under reduced press. On addition of water (200 ml) and stirring, crystals (737 mg) separated and were collected, washed with water and dried. Recrystallization from MeOH gave III, needles (580 mg), m.p. 197–198·5°, as the 1st crop, and that (126 mg), m.p. 194–197°, as the 2nd one; $[\alpha]_D^{23}$ −27·6° (95% MeOH); IR, ν_{max} 3340, 1680 and 1060 cm^{-1}. (Found: C, 76·14; H, 10·17; N, 4·15. Calc. for $C_{21}H_{33}O_2N$: C, 76·09; H, 10·03; N, 4·23%).

Into an AcOH soln (60 ml) containing III (740 mg) N_2 was passed for 5 min and next HCl gas for 7 min at room temp. The soln, which was saturated with HCl, was allowed to stand at room temp for 15 hr and then diluted with benzene (100 ml). After removal of the solvents, the crystalline residue (832 mg), m.p. 199–202°, was dissolved in $CHCl_3$ (30 ml) and passed rapidly through a column filled with silica gel (Merck,

5 g). The $CHCl_3$ soln afforded crude IIIa on removal of the solvent, which crystallized on trituration with acetone. Recrystallization from acetone gave IIIa (632 mg), m.p. 229–231°, in a pure state as the 1st crop and crude IIIa (129 mg), m.p. 210–216°, as the 2nd. Two recrystallizations from acetone-$CHCl_3$ gave an analytical sample, m.p. 232–234°; $[\alpha]_D^{23}$ −42·4°; IR, ν_{max} 3240, 1729, 1250 and 1032 cm^{-1}; NMR, τ 9·19 (3H, d J = 5·5 c/s, 18-Me), 9·01 (3H, s, 19-Me); 8·19 (3H, s, 21-Me), 7·97 (3H, s, OAc), 5·42 (1H, br, 3-H), and 4·63 (1H, br, 6-H). (Found: C, 74·05, H, 9·43; N, 3·82. $C_{23}H_{35}O_2N$ requires: C, 73·95; H, 9·45; N, 3·75%).

17α-Acetylaminoetiojerv-5-en-3β-ol (IV) *and its 3-acetate* (IVa)

To IIIa (500 mg) in pyridine (Py, 6 ml) $POCl_3$ (3·5 ml) in Py (8 ml) was added at 0° with stirring. The soln was kept at 0° for 3 hr and, after careful addition of conc HCl (4 ml) with cooling in an ice-bath, was diluted with water and extracted with EtOAc (3 × 40 ml). The EtOAc soln was washed with 2N HCl (2 × 30 ml) and then with sat NaCl aq (2 × 30 ml), dried over Na_2SO_4 and evaporated to dryness to give crystalline residue (533 mg). This was dissolved in $CHCl_3$ (20 ml) and passed rapidly through a column of silica gel (Merck, 3 g). The column was washed with $CHCl_3$ (500 ml), and the washings were combined with the 1st $CHCl_3$ soln. On removal of the solvent the combined soln gave a crystalline material, which on recrystallization from $CHCl_3$-acetone gave IVa (357 mg), m.p. 291–283°. An additional amount (68 mg) of IVa having m.p. 284–287° was obtained from the mother liquor. Two recrystallizations of the 1st crop from MeOH gave an analytical sample, m.p. 295·5–296°; $[\alpha]_D^{20}$ −58·0°; IR, ν_{max} 3280, 1732, 1642, 1553, 1247 and 1041 cm^{-1}; NMR, τ 9·05 (3H, br s, 18-Me), 9·01 (3H, s, 19-Me), 8·05 and 7·99 (each 3H, s, OAc and NAc or *vice versa*), and 6·50 (1H, br W_H = 18 c/s, 17-H), 5·40 (1H, br, 3-H). (Found: C, 73·75; H, 9·49; N, 3·74. $C_{23}H_{35}O_3N$ requires: C, 73·95; H, 9·45; N, 3·75%).

The amide acetate IVa, (2·0 g) was hydrolysed by heating in MeOH (70 ml) containing 5% KOH at 40° for 20 min. After cooling, the soln was diluted with water (200 ml) and extracted with $CHCl_3$ (3 × 100 ml). The $CHCl_3$ soln was washed with water (2 × 100 ml), dried and evaporated to give a crystalline residue. Recrystallization from MeOH afforded IV (1·744 g), m.p. 284–287°. Two recrystallizations from the same solvent gave an analytical sample, m.p. 284–285°; $[\alpha]_D^{25}$ −43·0° (99% EtOH); IR, ν_{max} 3280, 3070, 1642 and 1556 cm^{-1}. (Found: C, 75·95; H, 10·11; N, 4·31. $C_{21}H_{33}O_2N$ requires: C, 76·09; H, 10·03; N, 4·23%).

17α-Aminoetiojerv-5-en-3β-ol (V)

Na (2·5 g) was dissolved in freshly distilled diethylene glycol (DEG, 100 ml) by heating. To the cooled soln anhydrous NH_2NH_2 (6 ml) and then amide IVa (1·5 g) was added and the whole soln was refluxed for 24 hr and cooled. After addition of water (100 ml), the soln was extracted with $CHCl_3$ (3 × 50 ml), and the $CHCl_3$ soln was washed with water (2 × 50 ml), dried and evaporated to give an oily residue (1·2 g), which was crystallized from MeOH–acetone. Recrystallization from the same solvent mixture gave V, needles (955 mg), m.p. 209–211°. A crude sample of V (151 mg) having m.p. 198–204° was obtained from the mother liquor. Two recrystallizations from MeOH–acetone gave an analytical sample, m.p. 211·5–213°; $[\alpha]_D^{20}$ −86·6°; IR, ν_{max} 3360 and 1670 cm^{-1}. (Found: C, 79·08; H, 10·65; N, 4·70. $C_{19}H_{31}ON$ requires: C, 78·84; H, 10·80; N, 4·84%).

Etiojerv-5-en-3β-ol-17-one (VI) *and its 3-acetate* (VIa)

To V (800 mg) dissolved in a mixture of $CHCl_3$ (20 ml) and CCl_4 (20 ml) NCS (1·080 g) was added. After stirring at room temp for 30 min, the mixture was washed with water (5 × 30 ml), dried over Na_2SO_4 and evaporated to dryness below 30° by azeotropization with abs EtOH (5 ml), leaving a crystalline residue (970 mg).

The chloroamine thus obtained was refluxed in abs EtOH (50 ml) containing Na (1·73 g) for 1·5 hr and, after being cooled, the soln was mixed with water (100 ml) and extracted with $CHCl_3$ (3 × 30 ml). The $CHCl_3$ soln was washed with water (2 × 20 ml), dried and evaporated under reduced press to give an oil. The oily residue was dissolved in a soln of MeOH (40 ml) and 6N H_2SO_4 (20 ml), and allowed to stand at room temp for 20 hr. The reaction mixture was diluted with water (70 ml) and extracted with ether (5 × 30 ml). The ether extracts were washed with water (2 × 30 ml), dried and, after removal of the solvent, gave a crystalline residue (394 mg).

On the other hand, the aqueous layer was washed once with $CHCl_3$ (20 ml) to remove coloured substance (12 mg), basified with dil NaOH aq and then extracted with $CHCl_3$ (2 × 20 ml). The $CHCl_3$ soln gave an oil, after being washed, dried and evaporated. This oily substance (410 mg) consisted mainly of the starting amine and, therefore, was again treated with NCS (550 mg) in $CHCl_3$ (10 ml) and CCl_4 (10 ml)

in the same way as described above and afforded the chloroamine (475 mg). This was further refluxed in abs EtOH (30 ml) containing Na (1·03 g) for 1·5 hr and then worked up as above, leaving an oily substance (455 mg), which was dissolved in MeOH (30 ml) and 6N H_2SO_4 (15 ml) and allowed to stand at room temp for 19 hr. The mixture, after addition of water (50 ml), was extracted with ether (5 × 30 ml), and the ether extracts gave an oil (266 mg) after being washed with water, dried and distilled. The aqueous layer was worked up as above and gave an oil (40 mg) from the $CHCl_3$ extracts after basification, from which the starting amine (27 mg) having m.p. 208–211° was recovered unchanged on crystallization from MeOH, and an unidentified oil (25 mg) from $CHCl_3$ extracts before basification.

The crystalline (394 mg) and oily residue (266 mg) from the ether extracts was dissolved in $CHCl_3$ (5 ml) and purified by chromatography on silicic acid (Mallinckrodt, 15 g). Elution with $CHCl_3$ yielded a semi-crystalline substance (533 mg) showing R_f of 0·75 on TLC (Wakogel B-5, a 5:1 mixture of $CHCl_3$ and acetone). Crystallization from ether produced VI (365 mg), m.p. 164–166°, as the 1st crop and a slightly crude sample (122 mg) of VI, m.p. 162–165°, as the 2nd one. Recrystallization from aqueous MeOH gave an analytical sample, m.p. 167–168°; $[\alpha]_D^{20}$ −83·0°; IR, ν_{max} 3470 and 1693 cm^{-1}; NMR, τ 9·03 (3H, s, 19-Me), 8·97 (3H, d J = 6 c/s, 18-Me), 6·45 (1H, br, 3-H), and 4·62 (1H, br, 6-H); ORD (MeOH, 23·5°), $[\phi]_{308}^{trough}$ −6930°, $[\phi]_{274}^{peak}$ +4200°, a = −111°. (Found: C, 79·23; H, 9·64. $C_{19}H_{28}O_2$ requires: C, 79·12; H, 9·79%).

The ketone VI (48 mg) was refluxed in a mixture of MeOH (4 ml) and water (1 ml) containing 5% KOH for 1 hr under a stream of N_2. After addition of water (30 ml), the mixture was extracted with CH_2Cl_2 (2 × 10 ml), and the CH_2Cl_2 extracts gave a solid (48 mg) after being worked up as usual. Recrystallization from ether afforded a crystalline compound (41 mg), m.p. 166–167°, which was identical with the starting ketone (IR, NMR and mixed m.p.).

The ketone VI (60 mg) was treated with Ac_2O (1 ml) and Py (2 ml) at room temp for 24 hr. The soln was poured into ice-water (70 ml) and stirred for 30 min to give white ppts, which were extracted with CH_2Cl_2 (30 ml), washed with water (2 × 10 ml) and dried. The CH_2Cl_2 soln gave VIa (63 mg), m.p. 136–137°, on removal of the solvent and recrystallization from ether. Recrystallization from MeOH gave an analytical sample, m.p. 136–137°; $[\alpha]_D^{23}$ −94·0°; IR, ν_{max} 1730, 1706, 1247 and 1028 cm^{-1}; NMR, τ 9·02 (3H, s, 19-Me), 8·97 (3H, d J = 6 c/s, 18-Me), 8·02 (3H, s, OAc), 5·50 (1H, br, 3-H), and 4·65 (1H, br, 6-H); ORD (MeOH, 24·5°), $[\phi]_{308}^{trough}$ −6700°, $[\phi]_{273}^{peak}$ +4100°, a = −108°. (Found: C, 76·25; H, 9·13. $C_{21}H_{30}O_3$ requires: C, 76·32; H, 9·15%).

Etiojerv-4-ene-3,17-dione (VII)

A soln of VI (30 mg) in toluene (50 ml, redistilled) and cyclohexanone (5 ml, redistilled) was heated to distil off about 40 ml of toluene to dry the system. To the cooled, stirred soln was added aluminum isopropoxide (100 mg), and the mixture was refluxed for 2 hr. After being cooled it was distilled with steam until most of the solvents had been removed, and the residue extracted with ether (4 × 50 ml). The ether soln yielded a crystalline substance after being washed with water (2 × 50 ml), dried and evaporated, which on recrystallization from ether gave VII (25 mg), m.p. 182–183°; $[\alpha]_D^{23}$ +118·0°; IR, ν_{max} 1704, 1663 and 1616 cm^{-1}; NMR, τ 8·98 (3H, d J = 6 c/s, 18-Me), 8·86 (3H, s, 19-Me), and 4·23 (1H, s, 4-H). This compound was identical with an authentic specimen[4b] in all respects.

Reduction of VI *and* VIa

(a) Acetate VIa (144 mg) in EtOH (16 ml) was hydrogenated over prereduced Adams Pt (74 mg as $PtO_2 \cdot H_2O$) at room temp (17°) for 30 min, when 5·6 ml of H_2 (1·03 mol) had been absorbed. After removal of the catalyst and addition of water (40 ml), the mixture was extracted with ether (3 × 20 ml), and the ether soln was washed with water (20 ml), dried over Na_2SO_4 and evaporated to leave an oil (136 mg), which was separated by preparative TLC, using 8 plates; each made of 10 g of silica gel (Wakogel B-5) with an area of 20 cm by 20 cm. The oil was developed with a 7:3 mixture of benzene and EtOAc and extracted with a 5:1 mixture of ether and acetone.

The most mobile fraction (R_f 0·56), after work up as usual, gave a crystalline substance (80 mg) showing one spot. Recrystallization of 40 mg of the substance from ether afforded VIIIa (29 mg), needles, m.p. 163·5–164·5°; $[\alpha]_D^{23}$ −23·6°; IR, ν_{max} 3500, 1712, 1265, 1250, 1040 and 1030 cm^{-1}; NMR, τ 9·09 (3H, d J = 6 c/s, 18-Me), 9·02 (3H, s, 19-Me), 8·05 (3H, s, OAc), 6·28 (1H, br W_H = 7 c/s, 17-H), 5·55 (1H, br, 3-H), and 4·63 (1H, br, 6-H). (Found: C, 75·94; H, 9·68. $C_{21}H_{32}O_3$ requires: C, 75·86; H, 9·70%).

The remaining crystalline residue (40 mg) was hydrolysed by heating in MeOH (10 ml) containing 5% KOH at 50° for 15 min. After cooling, the soln was diluted with water (20 ml) and extracted with $CHCl_3$

(2 × 15 ml). The $CHCl_3$ soln was washed with water (15 ml), dried and evaporated to leave an oil (36 mg). Crystallization from acetone–ether gave VIII (31 mg), m.p. 187–188°. Recrystallization from acetone gave an analytical sample, m.p. 187–188°; $[\alpha]_D^{18}$ −40·1°; IR, ν_{max} 3360, 3320 and 1055 cm^{-1}. (Found: C, 78·60; H, 10·41. $C_{19}H_{30}O_2$ requires: C, 78·57; H, 10·14%).

The middle fraction (R_f 0·46) gave a crystalline substance (61 mg) showing one spot. Crystallization of 30 mg of the substance from ether gave IXa (21 mg), plates, m.p. 171–172°. Recrystallization from ether–*n*-hexane gave an analytical sample, m.p. 171–172°; $[\alpha]_D^{18}$ −74·9°; IR, ν_{max} 3350, 1734, 1246, 1038 and 1014 cm^{-1}; NMR, τ 9·06 (3H, d J = 6 c/s, 18-Me), 9·01 (3H, s, 19-Me), 8·01 (3H, s, OAc), 6·94 (1H, br W_H = 14 c/s, 17-H), 5·52 (1H, br, 3-H), and 4·61 (1H, br, 6-H). (Found: C, 76·05; H, 9·69. $C_{21}H_{32}O_3$ requires: C, 75·86; H, 9·70%).

Hydrolysis of the remaining crystalline residue (31 mg) was carried out in the manner described for the crude material of VIIIa and gave IX (22 mg), m.p. 181–182°, after crystallization from acetone. Recrystallization from acetone gave an analytical sample, m.p. 182·5–183·5°; $[\alpha]_D^{18}$ −71·8°; IR, ν_{max} 3470, 3430, 1050, 1014 and 1000 cm^{-1}. (Found: C, 78·65; H, 10·42. $C_{19}H_{30}O_2$ requires: C, 78·57; H, 10·41%).

Two fractions showing R_f of 0·33 and 0·30 were combined and gave oil (2 mg), which was identified as a 4:3 mixture of VIII and IX from the R_f values on TLC.

(b) Hydrogenation of VI (50 mg) was carried out in the presence of Pt (16 mg) at 13·5° in EtOH (8 ml) and ceased after 40 min, when 4·1 ml of H_2 (1·03 mol) had been consumed. After work up as usual, 53 mg of oil was obtained, which showed 2 spots with R_f of 0·57 and 0·52 (Wakogel B-5, a 1:1 mixture of EtOAc and benzene). Crystallization and recrystallization from EtOAc gave VIII (11 mg), m.p. 186–188°. The mother liquors were combined, evaporated to dryness and purified cautiously by preparative TLC (5 plates, a 3:7 mixture of EtOAc and benzene). Each fraction was collected by cutting and extracted with acetone and, after removal of the solvent, reextracted with CH_2Cl_2. A fraction showing higher R_f value (0·57) left oily residue (13 mg), which was crystallized from ether–MeOH to give VIII (7 mg), m.p. 186–188°. The afore-mentioned samples of VIII (11 + 7 = 18 mg) were combined and recrystallized from acetone to give VIII (17 mg), m.p. 187–188° in a pure state. On the other hand, a fraction showing lower R_f value (0·52) left an oily residue (19 mg), which on crystallization from ether–MeOH gave IX (14 mg), m.p. 180–181°. Recrystallization from acetone afforded IX (12 mg), m.p. 182·5–183·5°, in a pure state.

(c) 17-Ketone VI (45 mg) in anhyd MeOH (3 ml) was treated with $NaBH_4$ (25 mg) at 0° for 1 hr under stirring. After addition of AcOH, the mixture was diluted with water, basified with 5% Na_2CO_3 aq, and extracted with ether (2 × 10 ml). The ether soln was washed with water (2 × 10 ml), dried, and evaporated to dryness to leave an oily residue (46 mg), which was shown to be a 1:6 mixture of VIII and IX by TLC and submitted to purification by preparative TLC as in the case of (b). A fraction showing R_f of 0·57 gave an oil (6 mg), from which VIII, m.p. 187–188° was obtained on crystallization from acetone. A fraction with R_f 0·52 left an oil (38 mg), which was crystallized from MeOH–ether to give IX (27 mg), m.p. 180–181°. Recrystallization from acetone gave IX (18 mg), m.p. 182–183°, in a pure state.

Etiojerv-4-en-17β-ol-3-one 17-acetate (C-nor-D-homotestosterone acetate, X)

A soln of VIII (30 mg) in freshly-distilled toluene (50 ml) and cyclohexanone (5 ml) was heated to distil off about 40 ml toluene to dry the system. After addition of aluminum isopropoxide (60 mg), the mixture was refluxed under stirring for 50 min. After cooling, it was diluted with water (10 ml) and distilled with steam, and the residue extracted with ether (5 × 40 ml). The ether soln was washed with water (2 × 50 ml), dried and evaporated to leave an oil (31 mg).

The oil, after drying, was treated with Ac_2O (0·5 ml) and Py (1 ml) at room temp for 15 hr. The soln was evaporated by azeotropization with benzene and the residue dissolved in ether (20 ml), washed with water (2 × 10 ml), dried and, after removal of the solvent, purified by preparative TLC (5 plates, a 4:1 mixture of benzene and ether). Each fraction was collected by cutting, extracted with acetone and, after evaporation, was dissolved in ether and dried.

The most mobile fraction (R_f 0·8) gave an oil (4 mg), which was treated with 5% KOH in MeOH (2 ml) at 50° for 20 min. The MeOH soln was diluted with water, extracted with $CHCl_2$ (2 × 10 ml), and the CH_2Cl_2 soln was washed with water (30 ml), dried and evaporated to give crystalline material. Recrystallization from ether afforded the starting compound (2 mg), m.p. 187–188°, which was identified by IR, TLC and mixed m.p.

The middle fraction (R_f 0·6) left a crystalline residue (18 mg) after being worked up as usual. Recrystallization from ether gave X (15 mg), m.p. 135·5–136·5°, which was identical with an authentic specimen[4b] prepared by Kupchan and Levine; $[\alpha]_D^{23}$ +188°; IR, ν_{max} ($CHCl_3$) 1728, 1663 and 1616 cm^{-1}; NMR, τ

9·11 (3H, d J = 5 c/s, 18-Me), 8·85 (3H, s, 19-Me), 7·93 (3H, s, OAc), 4·99 (1H, br W_H = 7 c/s, 17-H), and 4·25 (1H, s, 4-H).

The least mobile fraction (R_f 0·4) left a crystalline residue (8 mg), which on recrystallization from ether–acetone gave VII (5 mg), m.p. 181–182°. This was identified by TLC, IR and mixed m.p.

Etiojerv-4-en-17α-ol-3-one 17-acetate (XI)

Compound IX (25 mg) dissolved in toluene (50 ml) and cyclohexanone (5 ml) was oxidized with aluminum isopropoxide (50 mg) as for VIII and, after work up, gave an oily substance (25 mg). This oil was acetylated with Ac_2O (5 ml) and Py (1 ml) at room temp for 15 hr and gave an oil (25 mg), which was purified by preparative TLC (3 plates, a 4:1 mixture of benzene and ether).

A fraction with R_f value 0·8 left an oil (3 mg), which was hydrolysed as described and gave the starting material IX (1·2 mg), m.p. 180–181°, after being worked up and then recrystallized from MeOH–ether.

A fraction with R_f value of 0·4 left a crystalline residue (6 mg), which on recrystallization from ether–acetone gave VII (4 mg), m.p. 181–182°.

A main fraction (R_f 0·6) gave an oil (15 mg) after work up, which crystallized on trituration with ether. Recrystallization from the same solvent gave XI (13 mg), m.p. 188–188·5°, which was identified by direct comparison with a sample[46] donated by Kupchan and Levine; $[\alpha]_D^{23}$ +92·0°; IR, ν_{max} 1727, 1663 and 1615 cm^{-1}; NMR, τ 9·10 (3H, d J = 6 c/s, 18-Me), 8·86 (3H, 2, 19-Me), 7·93 (3H, s, OAc), 5·50 (1H, br W_H = 15 c/s, 17-H), and 4·24 (1H, s, 4-H).

17α-*Acetyletiojerv-5-en-3β-ol* (XII) *and its 3-acetate* (XIIa)

(a) Oxime III (400 mg) was refluxed with $NaHSO_3$ (560 mg) in EtOH (27 ml) and water (18 ml) for 10 hr.[14] After removal of the solvents, 1N HCl (16 ml) and $CHCl_3$ (24 ml) were added, and the mixture shaken for 1·5 hr. After separation of the $CHCl_3$ layer, the aqueous soln was again shaken with $CHCl_3$ (2 × 10 ml). All the $CHCl_3$ solns were combined, washed with water (2 × 20 ml), dried and evaporated to leave a residue (376 mg), m.p. 120–123°, which on trituration with MeOH–ether crystallized, yielding 344 mg, m.p. 125–127°. Recrystallization from MeOH–ether gave an analytical sample, m.p. 127–128°; $[\alpha]_D^{23}$ −50·6°; IR, ν_{max} 3470 and 1700 cm^{-1}; NMR, τ 9·16 (3H, d J = 5·5 c/s, 18-Me), 9·02 (3H, s, 19-Me), 7·87 (3H, s, 21-Me), 6·46 (1H, br, 3-H), and 4·66 (1H, br, 6-H). (Found: C, 79·63; H, 10·20. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·20%).

Compound XII (70 mg) was treated with 5% KOH in refluxing MeOH (6 ml) in N_2 for 1 hr. The cooled soln was poured into water (20 ml) and extracted with $CHCl_3$ (2 × 10 ml). The $CHCl_3$ soln was washed with water (2 × 10 ml), dried and evaporated leaving crystalline residue (71 mg). Recrystallization from MeOH–ether gave crystals (13 mg), m.p. 127–128° and (48 mg) having m.p. 125–127°, which were identical with the starting ketone XII in all respects.

Methyl ketone XII (350 mg) was acetylated with Ac_2O (4 ml) and Py (4 ml) at room temp for 20 hr. After removal of the solvents by azeotropization with benzene, the residue was dissolved in ether (30 ml), and the ether soln was washed with sat NaCl aq (2 × 15 ml), dried and evaporated leaving a solid (383 mg). Recrystallizations from ether–hexane and then ether–benzene gave 3-acetate XIIa (292 mg), m.p. 120–121°; $[\alpha]_D^{23}$ −63·0°; IR, ν_{max} 1735, 1710, 1257 and 1030 cm^{-1}; NMR, τ 9·17 (3H, d J = 6 c/s, 18-Me), 9·01 (3H, s, 19-Me), 7·98 (3H, s, OAc), 7·87 (3H, s, 21-Me), and 4·63 (1H, br, 6-H). (Found: C, 77·23; H, 9·66. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·56%).

(b) Oxime III (100 mg) was refluxed with conc HCl (2 ml) in EtOH (20 ml) for 3 days, and gave an oil (97 mg) after work up, which was separated into 2 fractions by preparative TLC (4 plates, a 5:1 mixture of $CHCl_3$ and acetone). One fraction (R_f 0·75) gave a crystalline substance (47 mg), which on recrystallization from MeOH–ether afforded XII (34 mg), m.p. 127–129°. Another (R_f 0·50) gave an oil (42 mg), which had the same R_f value as the starting material III but was not further examined.

(c) For the hydrolysis of III in a soln containing pyruvic acid, see Ref. 3.

17α-*Acetyletiojervan-3β-ol* (XIII) *and its 5β-epimer* (XIV)

Compound XII (300 mg) in AcOH (10 ml) was hydrogenated over prereduced Adams Pt (137 mg) at 22°, and after 30 min 23·7 ml of H_2 (1·03 mol) was consumed. After filtration of the catalyst and removal of the AcOH by azeotropization with benzene, the residue was dissolved in $CHCl_3$ (20 ml). The $CHCl_3$ soln was washed with 5% Na_2CO_3 aq (10 ml) and then with water (2 × 10 ml), dried and evaporated leaving an oil (297 mg). This oil was further separated by preparative TLC (13 plates, a 10:3 mixture of benzene and ether). Each fraction was extracted with acetone, and the acetone extracts, after evaporation, were dissolved in $CHCl_3$ (20 or 30 ml).

A more mobile fraction (R_f 0·58) gave XIV (66 mg), oil, which resisted crystallization; IR, ν_{max} 3430 and 1710 cm^{-1}; NMR, τ 9·17 (3H, d J = 5·5 c/s, 18-Me), 9·09 (3H, s, 19-Me), 7·87 (3H, s, 21-Me), and 5·92 (1H, br W_H = 7 c/s, 3-H). (Found: C, 79·15; H, 10·98. $C_{21}H_{34}O_2$ requires: C, 79·23; H, 10·76%).

A less mobile fraction (R_f 0·47) left a solid (220 mg) after work up, which was crystallized from ether–n-hexane to give XIII (202 mg), m.p. 146–148°. Recrystallization from the same solvent mixture afforded an analytical sample, needles, m.p. 147–148°; $[\alpha]_D^{23}$ +50·5°; IR, ν_{max} 3525 and 1707 cm^{-1}; NMR, τ 9·24 (3H, s, 19-Me), 9·16 (3H, d J = 6 c/s, 18-Me), 7·88 (3H, s, 21-Me), and 6·37 (1H, br W_H = 15 c/s, 3-H). (Found: C, 79·19; H, 10·76. $C_{21}H_{34}O_2$ requires: C, 79·23; H, 10·80%).

Etiojervane-3β,17α-diol (XV)

(a) *From* XIII. Compound XIII (150 mg) was treated with 105 mg (1·5 equiv) perbenzoic acid (activity 93%, checked by titration with 0·1N $Na_2S_2O_3$aq) in $CHCl_3$ (4 ml) at room temp (20°) for 5 days in the dark. An additional amount (70 mg, 1 equiv) of perbenzoic acid was added and the whole soln left at 30° for another 4 days. After shaking with 0·1N $Na_2S_2O_3$ (35 ml), the soln was washed with 5% Na_2CO_3aq (20 ml) and then with water (2 × 20 ml), dried and evaporated to leave an oil (150 mg). The oil was further treated with 5% KOH in MeOH (10 ml) at room temp for 12 hr, diluted with water (25 ml) and extracted with $CHCl_3$ (2 × 10 ml). The $CHCl_3$ soln was washed with water (2 × 20 ml), dried and evaporated to leave an oil (109 mg). This oil was divided into 2 fractions by preparative TLC (5 plates, a 5:2 mixture of benzene and ether). A more mobile fraction (R_f 0·5) left a solid (81 mg), which was crystallized from ether–n-hexane to yield the starting material (XIII, 75 mg), m.p. 147–148°. A less mobile fraction (R_f 0·3) left a solid (27 mg) showing one spot. Recrystallization from acetone–ether gave XV (20 mg), m.p. 169–170°; $[\alpha]_D^{20}$ +49·8°; IR, ν_{max} 3410 cm^{-1}; NMR, τ 9·24 (3H, s, 19-Me) and 9·02 (3H, d J = 5 c/s, 18-Me). (Found: C, 77·88; H, 10·94. $C_{19}H_{32}O_2$ requires: C, 78·03; H, 11·03%).

(b) *From* IX. Compound IX (32 mg) in AcOH (7 ml) was hydrogenated over prereduced Adams Pt (30 mg as $PtO_2 \cdot H_2O$) at room temp (20°) and 2·75 ml of H_2 (1·04 mol) was absorbed after 25 min. After work up, 37 mg of an oil was obtained, which crystallized on trituration with acetone–ether. Fractional recrystallizations from acetone–ether gave XV (11 mg), m.p. 167·5–168·5°, which was identical with an authentic sample derived from XIII. Further recrystallization from the same solvent gave XV, m.p. 169–170°, in a pure state.

22,27-*Iminojerv-5-ene-3β,11β,23β-triol* (XVII), *and its* N-*acetyl* (XVIIa) *and* 3-O,23-O,N-*triacetyl derivatives* (XVIIb)

Compound XVIa[3] (5·0 g) dissolved in dioxan (100 ml) was mixed with $NaBH_4$ and refluxed for 48 hr, until the spot of XVIa had disappeared on TLC. After dropwise addition of AcOH (10 ml) and water (40 ml) under ice-cooling to decompose the excess of $NaBH_4$, the mixture was diluted with water (100 ml), basified with dil NaOHaq, and extracted with $CHCl_3$ (5 × 50 ml). The $CHCl_3$ soln was washed with water (2 × 100 ml), dried and evaporated to leave an oily residue (5·3 g), which was crystallized from EtOH–acetone to give XVIIa (4·65 g), m.p. 241–244°. Recrystallization from EtOH–acetone afforded an analytical sample, m.p. 243–244° (reported m.p., 239–240°, cf. Ref 7); $[\alpha]_D^{23}$ −51·9°; IR, ν_{max} 3525, 3395, 1608, 1049 and 1025 cm^{-1}; NMR, τ 8·755 (3H, s, 19-Me). (Found: C, 73·45; H, 10·05; N, 3·00. $C_{29}H_{47}O_4N$ requires: C, 73·53; H, 10·00; N, 2·96%).

To XVIIa (4·5 g), which had been dissolved in hot ethylene glycol (100 ml) and cooled, ethylene glycol (150 ml) containing KOH (15 g) and 85% $NH_2NH_2 \cdot H_2O$ (4 ml) was added. The soln was refluxed for 20 hr, cooled, poured into ice–water and stirred for 1 hr; the ppts formed after being washed with water and dried, were heated with anhyd MeOH (200 ml). After filtration of insoluble material, the filtrate (MeOH soln) was concentrated to give a crystalline substance (3·90 g); the 1st crop (3·2 g) had m.p. 240–241° and the 2nd (0·7 g) m.p. 239–241°. Recrystallization from MeOH afforded an analytical sample, m.p. 240–241°; $[\alpha]_D^{23}$ −58·8° (99% EtOH); IR, ν_{max} 3430, 3260, 1089, 1060 and 1045 cm^{-1}. (Found: C, 75·16; H, 10·49; N, 3·45. $C_{27}H_{45}O_3N$ requires: C, 75·13; H, 10·51; N, 3·25%).

Compound XVIIa (200 mg) was treated with Ac_2O (1 ml) and Py (2 ml) at room temp for 24 hr and poured into ice–water (200 ml). The resulting ppts were stirred for 2 hr, collected by filtration and, after being washed with water and dried, dissolved in ether (30 ml). The ether soln was washed with water (2 × 15 ml), dried and evaporated to leave an oil (264 mg), which was purified by preparative TLC (7 plates, ether). A main fraction (R_f 0·4) left an oil (244 mg), which was crystallized from ether to give XVIIb

(214 mg), m.p. 224–225·5°. Recrystallization from ether afforded an analytical sample, m.p. 224·5–225·5°; $[\alpha]_D^{23}$ −34·8°; IR, ν_{max} 3480, 1735, 1644, 1245, 1030, and 1022 cm^{-1}; NMR, τ 8·74 (3H, s, 19-Me). (Found: C, 71·39; H, 9·17; N, 2·45. $C_{33}H_{51}O_6N$ requires: C, 71·06; H, 9·22; N, 2·51%). Other fractions (R_f 0·5, tri-O-acetyl derivatives ? and R_f 0·2, 3-O-acetyl derivative ?) were very small.

3-O,23-O,N-*Triacetyl*-22,27-*iminojerv*-5-*ene*-3β,23β-*diol*-11-*one* (XVIb)

(a) Amide XVIa[3] (1·0 g) was acetylated with Ac_2O (10 ml) and Py (20 ml) at room temp for 20 hr. After work up the residual oil (1·23 g) was crystallized from acetone–ether to yield XVIb (1·08 g), m.p. 210–211°. Recrystallization from the same solvent mixture afforded an analytical sample, m.p. 211–212°; $[\alpha]_D^{22}$ −88·5°; IR, ν_{max} 1733, 1647, 1242, 1038 and 1026 cm^{-1}; NMR, τ 8·97 (3H, s, 19-Me). (Found: C, 71·44; H, 8·93; N, 2·69. $C_{33}H_{49}O_6N$ requires: C, 71·32; H, 8·89; N, 2·52%).

(b) Compound XVIIb (50 mg) was treated with CrO_3 (76 mg) in Py (2 ml) at room temp for 24 hr under stirring. After addition of water (20 ml) the mixture was extracted with $CHCl_3$ (2 × 10 ml), and the $CHCl_3$ soln was washed with 2N HCl (3 × 10 ml) and then with water (2 × 10 ml), dried and evaporated to leave an oil (52 mg). Crystallization from acetone–ether gave XVIb (46 mg), m.p. 209–211°, which on recrystallization from the same solvent mixture had m.p. 211–212° and was identical with a sample prepared from XVIa.

17α-*Acetyletiojerv*-5-*ene*-3β,11β-*diol* 20-*oxime* (XIX)

To a soln of amine XVII (3·0 g) in dioxan (200 ml) and MeOH (20 ml) NCS (1·5 g) was added, and the mixture was stirred at 35° for 60 min. Upon dropwise addition of water (1·2 l.) under ice-cooling, the crude chloroamine ppt, was collected and washed with water (1 l.), dried over P_2O_5 under reduced pressure yielding 3·23 g. To the chloroamine dissolved in a mixture of dioxan (50 ml) and anhyd MeOH (70 ml) and cooled at 0° 2N NaOMe in MeOH (40 ml) was added dropwise under stirring. The soln was allowed to stand at 35° (bath temp) for 2 hr and then concentrated to 100 ml under reduced press. To the concentrate water (500 ml) and then 6N HCl (16 ml) was added slowly during 2 hr under stirring and ice-cooling, and the mixture was stirred at room temp for 12 hr. During stirring crystals separated out, and these were collected, washed with water and dried over P_2O_5. The resulting crystals (aldehyde XVIII) had m.p. 184–190° and amounted to 1·83 g. Recrystallization from acetone gave a purer sample of XVIII, m.p. 198–202°; $[\alpha]_D^{23}$ −37·7°; IR, ν_{max} 3570, 3290, 2730, 1713, and 1060 cm^{-1}; NMR, τ 9·025 (3H, d J = 7 c/s, 18-Me), 8·93 (3H, d J = 5 c/s, 21-Me), 8·75 (3H, s, 19-Me), 4·75 (1H, br, 6-H), and 0·38 (1H, s, CHO). (Found: C, 76·41; H, 9·98. $C_{22}H_{34}O_3$ requires: C, 76·26; H, 9·89%).

To the crude aldehyde (1·0 g) dissolved in MeOH (30 ml) and cooled at 0°, n-BuONO (3 ml) and 2N NaOMe in MeOH (30 ml) were added, and the soln was allowed to stand at 5° for 5·5 hr. To the soln cooled in an ice-bath, water (50 ml) was added slowly for 30 min and then 6N HCl (11 ml) under stirring, when crude the oxime (XIX) crystallized out. This was collected, washed with water, dried and dissolved in $CHCl_3$ (100 ml). The $CHCl_3$ soln was washed with sat NaCl aq (2 × 50 ml), dried and evaporated to leave an oil (1·092 g), which crystallized on trituration with MeOH. Recrystallization from MeOH gave XIX (626 mg), m.p. 167–168°, and an additional amount of XIX (215 mg), m.p. 165–167°, was obtained on recrystallization of the mother liquor from aqueous MeOH. Recrystallization from MeOH gave an analytical sample, m.p. 167–168°; $[\alpha]_D^{23}$ −29·3°; IR, ν_{max} 3390, 1649, 1054 and 1021 cm^{-1}. (Found: C, 72·46; H, 9·51; N, 3·90. $C_{21}H_{33}O_3N$ requires: C, 72·58; H, 9·57; N, 4·03%).

17α-*Acetyletiojerv*-5-*ene*-3β,11β-diol (XX)

The oxime XIX (500 mg) was refluxed with $NaHSO_3$ (500 mg) in EtOH (25 ml) and water (20 ml) for 10 hr. After removal of EtOH under reduced press the residue was shaken with 1N HCl (30 ml) and $CHCl_3$ (40 ml) for 1·5 hr. After separation of the $CHCl_3$ layer the aqueous soln was shaken with $CHCl_3$ (2 × 10 ml), and all the $CHCl_3$ solns were combined, washed with sat NaCl aq (2 × 30 ml), dried and evaporated to leave a crystalline residue (487 mg), which was crystallized from acetone–ether. Recrystallization from acetone–ether gave XX (331 mg), m.p. 180–181°, and concentration of the mother liquor afforded an additional amount of XX (118 mg), m.p. 180–181°. Recrystallization of the 1st crop from the same solvent mixture gave an analytical sample, m.p. 180–181°; $[\alpha]_D^{23}$ −75·5°; IR, ν_{max} 3475, 3440, 3305, 1701 and 1056 cm^{-1}; NMR, τ 9·03 (3H, d J = 6 c/s, 18-Me), 8·75 (3H, s, 19-Me), 7·86 (3H, s, 21-Me), and 4·76 (1H, br, 6-H). (Found: C, 75·68; H, 9·93. $C_{21}H_{32}O_3$ requires: C, 75·86; H, 9·70%).

17α-*Acetyletiojervane*-3β,11β-*diol* (XXI)

Compound XX (300 mg) in AcOH (10 ml) was hydrogenated over prereduced Adams Pt (150 mg) at

room temp (20°) and absorbed 23·1 ml of H_2 (1·05 mol) in 25 min. After work up an oil (323 mg) was obtained and crystallized from MeOH to yield XXI (272 mg), m.p. 172–173°. Recrystallization from MeOH afforded an analytical sample, m.p. 173–174°; $[\alpha]_D^{23}$ +32·2°; IR, ν_{max} 3510, 3460, 1704, 1080, 1039 and 1029 cm^{-1}; NMR, τ 9·05 (3H, d J = 6 c/s, 18-Me), 8·96 (3H, s, 19-Me), 7·87 (3H, s, 21-Me), 6·37 (1H, br W_H = 15 c/s, 3-H), and 5·84 (1H, br W_H = 10 c/s, 11-H). (Found: C, 75·45; H, 10·40. $C_{21}H_{34}O_3$ requires: C, 75·40; H, 10·25%).

Etiojervane-3,11,17-*trione* (XXII)

(a) Compound XXI (200 mg) in $CHCl_3$ (2 ml) was treated with 135 mg (1·5 equiv) perbenzoic acid (activity 93%) in $CHCl_3$ (2 ml) at 27° for 8 days. Additional perbenzoic acid (90 mg) in $CHCl_3$ (1 ml) was added and the soln was kept for another 3 days. The $CHCl_3$ soln was washed with 5% Na_2CO_3 aq (20 ml), washed with water (2 × 20 ml), dried and evaporated to leave an oil (257 mg). The oil was hydrolysed with 5% KOH in MeOH (10 ml) at room temp for 12 hr. After work up, the soln gave an oily substance, which was separated into 2 fractions by preparative TLC (7 plates, a 7:2 mixture of $CHCl_3$ and acetone). A more mobile fraction (R_f 0·50) gave crystals (107 mg), m.p. 172–173°, which were identified as the starting material XXI. A less mobile fraction left an oil (25 mg), which was further oxidized with CrO_3 (66 mg) in Py at room temp for 20 hr under stirring. The soln was diluted with water (15 ml) and extracted with $CHCl_3$ (2 × 10 ml). The $CHCl_3$ soln was washed with 2N HCl (2 × 10 ml) and water (2 × 10 ml), dried and evaporated to leave an oil (23 mg), which on trituration with $CHCl_3$–ether crystallized, had m.p. 172–175° and amounted to 17 mg. Recrystallization from $CHCl_3$–n-hexane gave XXII, m.p. 174–175·5°, in pure state, which was identical with an authentic sample prepared according to the literature;[4b] $[\alpha]_D^{23}$ −72°; IR, ν_{max} 1737 and 1710 cm^{-1}.

(b) Compound XXIII[22] (50 mg) in AcOH (5 ml) was hydrogenated over prereduced Adams Pt (25 mg) at 12° and absorbed 8·1 ml H_2 (2·08 mol) in 45 min. After work up, the mixture gave an oil (47 mg), which without further purification was oxidized with CrO_3 (100 mg) in Py (2 ml) at room temp for 25 hr under stirring. The mixture was diluted with water (10 ml) and extracted with CH_2Cl_2 (2 × 10 ml). The CH_2Cl_2 soln was washed with 2N HCl (3 × 10 ml) and then with water (3 × 10 ml), dried and evaporated to dryness to leave an oil (41 mg). The oil was crystallized from ether–$CHCl_3$ to give crystals (32 mg), m.p. 174–176°, which were identical with a sample of XXII derived from XXI. Recrystallization from n-hexane–$CHCl_3$ afforded XXII (20 mg), m.p. 175–176°, in pure state.

17α-*Acetylaminoetiojerv*-4-*en*-3-*one* (XXIV)

To a mixture of dry toluene (300 ml) and cyclohexanone (50 ml, redistilled) amide IV (1·682 g) was added and some toluene (200 ml) was distilled off to dry the system. Aluminum isopropoxide (1·5 g) was added to the mixture and refluxed for 3 hr under stirring. When cooled, the mixture was filtered to remove the resulting ppt, which was then washed with MeOH. The filtrate and the MeOH washings were combined, diluted with water (50 ml), stirred for 30 min and distilled with steam to remove most of the solvents. The residue was extracted with $CHCl_3$ (3 × 70 ml), and the $CHCl_3$ soln was washed with water (2 × 100 ml), dried and distilled off to give a crystalline product (1·688 g), which was crystallized from $CHCl_3$–acetone to yield XXIV (1·346 g), m.p. 233–236°. Concentration of the mother liquor gave an additional amount (0·137 g) of XXIV, m.p. 230–235°. A sample was recrystallized twice for analysis: m.p. 238–240°; $[\alpha]_D^{23}$ +141°; UV, λ_{max} 240 mμ (ε 16,200); IR, ν_{max} 3300, 3070, 1670, 1662, 1616, and 1552 cm^{-1}; NMR, 9·06 (3H, br s, 18-Me), 8·86 (3H, s, 19-Me), 8·01 (3H, s, NAc), 6·46 (1H, br, 17-H), 4·39 (1H, br d, J = 9 /s, NH), and 4·27 (1H, s, 4-H). (Found: C, 76·59; H, 9·38; N, 4·34. $C_{21}H_{31}O_2N$ requires: C, 76·55; H, 9·48; N, 4·25%).

17α-*Acetylaminoetiojerv*-1,4-*dien*-3-*one* (XXV)

To a soln of XXIV (640 mg) in anhyd dioxan (10 ml) DDQ (670 mg, 1·5 mol) was added. After gently refluxing for 8 hr under stirring, the mixture was mixed with $CHCl_3$ (30 ml) and cooled to room temp. The hydroquinone ppt which formed was washed with $CHCl_3$ (30 ml). The filtrate and the $CHCl_3$ washings were combined, washed with 2N NaOH aq (2 × 30 ml) and then water (3 × 30 ml), dried over anhyd Na_2SO_4 and evaporated to dryness. The residual oil was dissolved in $CHCl_3$ (5 ml) and chromatographed on standard alumina (Merck, 5 g). Elution with $CHCl_3$ (500 ml) afforded an oil (520 mg), which crystallized on trituration with acetone. Recrystallization from acetone gave XXV (465 mg), m.p. 210–213°. A sample was recrystallized twice from acetone for analysis: m.p. 212–213°; $[\alpha]_D^{23}$ +77·0°; UV, λ_{max} 244 mμ (ε 16,800); IR, ν_{max} ($CHCl_3$) 3440, 1657, 1621, 1600, and 1512 cm^{-1}, and (Nujol) 3480, 3360, 3270, 3090, 1660, 1649, 1616, 1589, 1573, and 1543 cm^{-1}; NMR, τ 9·02 (3H, br, s 18-Me), 8·81 (3H, s, 19-Me), 6·50

(1H, br W_H = 15 c/s, 17-H), 4·10 (1H, br d J = 8 c/s, NH), 3·87 (1H, double d J = 10 and 2 c/s, 2-H), 3·81 (1H, d J = 2 c/s, 4-H), and 3·18 (1H, d J = 10 c/s, 1-H). (Found: C, 76·80; H, 8·68; N, 4·27. $C_{21}H_{29}O_2N$ requires: C, 77·02; H, 8·93; N, 4·28%).

17α-*Acetylaminoetiojerv*-1,3,5(10)-*trien*-3-*ol* (XXVI) *and its* 3-*acetate* (XXVIa)

A mixture of biphenyl (300 mg), Li (70 mg) and anhyd THF (5 ml) was refluxed for 30 min under vigorous stirring, when the soln became dark bluish green. To the refluxing mixture a soln of XXV (312 mg) and diphenylmethane (0·2 ml) in anhyd THF (5 ml) was added dropwise over 10 min. The mixture was refluxed for an additional 1 hr and then cooled. After decomposing the excess Li with NH_4Cl (200 mg), the mixture was acidified with 2N HCl (20 ml) and extracted with $CHCl_3$ (3 × 50 ml). The $CHCl_3$ soln was washed with sat NaCl aq (2 × 20 ml) and then water, dried and evaporated to leave an oil, which was purified by preparative TLC (13 plates, a 5:1 mixture of $CHCl_3$ and acetone). Fractions showing R_f of 0·25 were collected and extracted with MeOH. The MeOH soln was evaporated and the residue treated with $CHCl_3$ (20 ml) containing 20% MeOH to remove insoluble material (SiO_2) by filtration. The filtrate on removal of the solvents gave crude, semi-crystalline phenol XXVI (130 mg); ν_{max} 3280, 3090, 1627, 1560, and 1502 cm^{-1}. This XXVI resisted further crystallization and was submitted to acetylation. Material XXVI (130 mg) was heated with Ac_2O (5 ml) and Py (5 ml) at 70° for 1·5 hr. After removal of the solvents by azeotropization with benzene, the residue was dissolved in $CHCl_3$ (20 ml). The $CHCl_3$ soln was washed with water (3 × 10 ml), dried and evaporated to give oil (129 mg), which was crystallized from acetone to yield XXVIa (98 mg), m.p. 247–250°. Two recrystallizations from MeOH–acetone afforded an analytical sample, m.p. 250–252°; $[\alpha]_D^{23}$ +55·2°; UV, λ_{max} 278 and 271 mμ (ε 1100 and 1100); IR, ν_{max} 3230, 3080, 1770, 1635, 1574, and 1494 cm^{-1}; NMR, τ 8·98 (3H, br s, 18-Me), 8·02 (3H, s, NAc), 7·73 (3H, s, OAc), 6·50 (1H, br W_H = 18 c/s, 17-H), 4·50 (1H, br d J = 10 c/s, NH), 3·24 (1H, double d J = 9 and 2·5 c/s, 2-H), 3·23 (1H, double d J = 2·5 and 1 c/s, 4-H), and 2·97 (1H, double d J = 9 and 1 c/s, 1-H). (Found: C, 74·37; H, 8·13; N, 4·00. $C_{22}H_{29}O_3N$ requires: C, 74·33; H, 8·22; N, 3·94%).

17α-*Aminoetiojerv*-1,3,5(10)-*trien*-3-*ol* (XXVII) *and etiojerv*-1,3,5(10)-*trien*-3-*ol*-17-*one* (*C-nor-D-homoestrone*, XXVIII)

To freshly distilled diethylene glycol (10 ml) containing a few drops of anhyd NH_2NH_2 Na (0·25 g) was added, and the mixture was heated to dissolve the Na and then cooled. To the soln anhyd NH_2NH_2 (1 ml) and XXVIa (150 mg) were added, and the whole was refluxed for 24 hr. After being cooled, the soln was poured into ice-water (100 ml) under stirring, neutralized with 1N HCl (about 10 ml) and then kept at room temp for 1 hr. The resulting ppt was collected by filtration, washed with water and dried over P_2O_5 under reduced press to give crude sample of XXVII (92 mg), which showed a broad absorption near 3000 cm^{-1} and also absorption maxima at 1612, 1580, 1528 and 1503 cm^{-1} in the IR spectrum (Nujol).

The crude phenol XXVII (90 mg) in MeOH (2 ml) and THF (3 ml) was treated with NCS (92 mg) at 35° for 1 hr. The mixture was diluted with water (100 ml) under stirring and cooling, kept for 10 min and then filtered. The ppt was dried over P_2O_5 in the dark under reduced press. The chloroamine (87 mg) thus obtained was refluxed with 1·5N NaOEt in abs EtOH (5 ml) for 2 hr. To the cooled soln a mixture of MeOH (5 ml) and 8N H_2SO_4 (5 ml) was added slowly under stirring. The mixture was allowed to stand at room temp for 24 hr, diluted with water (50 ml) and shaken with hot benzene (3 × 30 ml). The benzene soln was washed with sat NaCl aq (2 × 20 ml), dried over anhyd Na_2SO_4 and evaporated to dryness to give a crystalline product (38 mg). Recrystallization from MeOH–benzene afforded XXVIII (28 mg), m.p. 258–260°, which was identical with Kupchan's C-nor-D-homoestrone. Further recrystallization from MeOH–benzene gave XXVIII in a pure state, m.p. 260–261°; IR, ν_{max} 3390, 1694, 1622, 1583, and 1503 cm^{-1}.

Acknowledgement—The authors wish to express their thanks to Dr. M. W. Klohs, Riker Laboratories, for generously providing them with a large amount of crude jervine and to Prof. S. M. Kupchan, University of Wisconsin, for kind donation of the samples of XI and XXVIII. They are also indebted to Mr. S. Shimokawa, Hokkaido University, for measurement of the NMR spectra.

REFERENCES

[1] [a] T. Masamune, A. Murai and S. Numata, *Tetrahedron* **25**, 3145 (1969); [b] S. M. Kupchan, T. Masamune and G. W. A. Milne, *J. Org. Chem.* **29**, 755 (1964).

[2] F. C. Chang and R. C. Ebersole, *Tetrahedron Letters* 3521 (1968).

[3] T. Masamune, K. Orito and A. Murai, *Bull. Chem. Soc. Japan* **39**, 2503 (1966).
[4] [a] S. M. Kupchan and M. J. Abu El-Haj, *J. Org. Chem.* **33**, 647 (1968); [b] S. M. Kupchan and S. D. Levine, *J. Am. Chem. Soc.* **86**, 701 (1964); [c] S. M. Kupchan, A. W. By and M. S. Flom, *J. Org. Chem.* **33**, 911 (1968).
[5] W. F. Johns and I. Laos, *Ibid.* **30**, 123 (1965), and Refs cited there.
[6] H. Mitsuhashi and K. Kawahara, *Tetrahedron* **21**, 1215 (1965), and Refs cited there.
[7] T. Masamune, K. Orito and A. Murai, *Tetrahedron Letters* 251 (1969).
[8] Cf. J. Tadanier and W. Cole, *J. Org. Chem.* **27**, 4624 (1962).
[9] Cf. E. W. White, *J. Am. Chem. Soc.* **77**, 6008, 6011, 6014 (1955); Y. Sato and H. G. Latham, Jr., *J. Org. Chem.* **22**, 981 (1957); R. Stevenson, *Ibid.* **28**, 188 (1963).
[10] Cf. M. Bockmühl, G. Ehrhart, H. Ruschig, and W. Aumüller, *Brit. Pat.* 501, 421 (1939); *Chem. Abstr.* **33**, 6340 (1939).
[11] Cf. G. Ehrhart, H. Ruschig and W. Aumüller, *Angew. Chem.* **52**, 363 (1939).
[12] Cf. M. G. Ettlinger and L. F. Fieser, *J. Biol. Chem.* **164**, 451 (1946).
[13] N. S. Bhacca and D. H. Williams, *Application of NMR Spectroscopy in Organic Chemistry* p. 79. Holden-Day, San Francisco (1964).
[14] S. H. Pines, J. M. Chemerda and M. A. Kozlowski, *J. Org. Chem.* **31**, 3446 (1966).
[15] H. Suginome, N. Sato and T. Masamune, *Tetrahedron Letters* in press.
[16] T. Masamune, N. Sato, K. Kobayashi, I. Yamazaki and Y. Mori, *Tetrahedron* **23**, 1591 (1967).
[17] P. de Mayo, *Molecular Rearrangements* p. 491. Interscience, New York (1963).
[18] Ref. 17, p. 579.
[19] O. Wintersteiner and M. Moore, *Tetrahedron* **20**, 1947 (1964); **21**, 779 (1965).
[20] R. W. Franck and W. S. Johnson, *Tetrahedron Letters* 545 (1963); R. W. Franck, G. P. Rizzi and W. S. Johnson, *Steroids* **4**, 463 (1964).
[21] T. Masamune, A. Murai, H. Ono, K. Orito and H. Suginome, *Tetrahedron Letters* 255 (1969), footnote 9.
[22] J. Fried and A. Klingsberg, *J. Am. Chem. Soc.* **75**, 4929 (1953).
[23] Cf. H. Wehrli, M. S. Heller, K. Schaffner and O. Jeger, *Helv. Chim. Acta* **44**, 2162 (1961); M. S. Heller, H. Wehrli, K. Schaffner and O. Jeger, *Ibid.* **45**, 1261 (1962); J. Iriarte, K. Schaffner and O. Jeger, *Ibid.* **46**, 1599 (1963); J. Fried and J. W. Brown, *Tetrahedron Letters* 1677 (1966).
[24] Cf. H. Suginome, I. Yamazaki, H. Ono and T. Masamune, *Ibid.* 5259 (1968); H. Suginome, N. Sato and T. Masamune, *Bull. Chem. Soc. Japan* **42**, 215 (1969).
[25] Cf. K. Tsuda, S. Nozoe and Y. Okada, *J. Org. Chem.* **28**, 78 (1963).
[26] H. L. Dryden, G. M. Webber and J. J. Wieczorek, *J. Am. Chem. Soc.* **86**, 742 (1964).
[27] Cf. R. Owyang, *Steroid Reactions* (Edited by C. Djerassi) p. 227. Holden-Day, San Francisco (1963).