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The Synthesis of an Etiojervane Analog of Corticosterone.[1]

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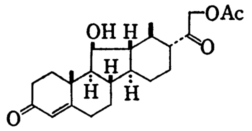
The synthesis of C-nor-D-homo-17-epicorticosterone 21-acetate (**1**) from jervine (**3**), which possesses the corticosterone configuration at each of the ring junctions, is described. Etiojerv-5-ene-3β,11β-diol-17-one (**4**), obtained by a seven-step process from **3**, was subjected to the Darzens reaction and afforded glycidic ester (**7**), which was converted by treatment with boron trifluoride into olefin (**9**). Catalytic hydrogenation followed by reduction with lithium aluminum hydride gave rise to tetraol (**15**), which was isolated as the acetonide (**16**). After Oppenauer oxidation of **16**, acid hydrolysis and subsequent partial acetylation, the resulting monoacetate (**19**) was oxidized with dicyclohexylcarbodiimide in dimethylsulfoxide to give compound **1**. Spectral and chemical evidence are presented for configurational assignment to both the compound and the synthetic intermediates.

Interest continues in the search for analogs with enhanced or more specific pharmacological properties in the synthesis of modified steroid hormones. During the last few years etiojervane analogs of cortisone,[2] progesterone,[3,4a] testosterone,[4b,5,6] estrone,[4c,5,7] and others[8-11] have been prepared. We describe herewith the synthesis of C-nor-D-homo-17-epicorticosterone 21-acetate (**1**), which possesses the corticosterone configuration at each ring junction and differs from the corresponding aldosterone (**2**) only in the function at C_{18} and the configuration at C_{17}.



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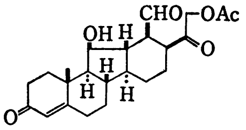

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The readily available veratrum alkaloid jervine (**3**) was converted by a seven-step process into etiojerv-5-ene-3β,11β-diol-17-one[2] (**4**) *via* trienone[4b,12] (**5**) in an over-all yield of 13.5%. Compound **4** was selected as the starting material for the following reasons. (1) A synthetic route[3,13] *via* hydration of the 17,20-double bond of **5** followed by selective oxidation at C_{20} to the 17-*acetyl group* would be impractical, in view of the instability of a closely related compound, 17α-acetyletiojerva-5,12-dien-3β-ol[14] (**6**), owing to the facile oxidative cleavage. (2) Dihydrojervine derivatives with *trans*-fused C/D linkage and open ring E, obtained by the double Birch reductions of **3**[3,15,16] or by acetolysis of 12,13-dihydrojervine and subsequent hydrogenation,[16,17] led to formation of the corresponding 17α-*acetyl* (*not* 17β) derivatives by the fragmentation of ring E.[18,19] However, selective introduction of a hydroxyl or an acetoxyl group

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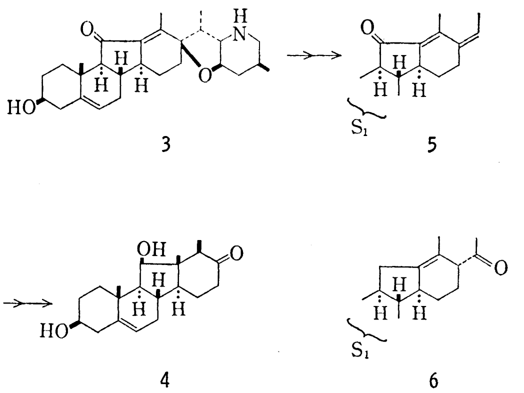
into C_{21} in a final stage of the synthesis would be difficult.



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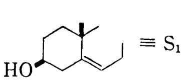
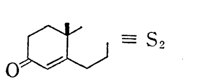
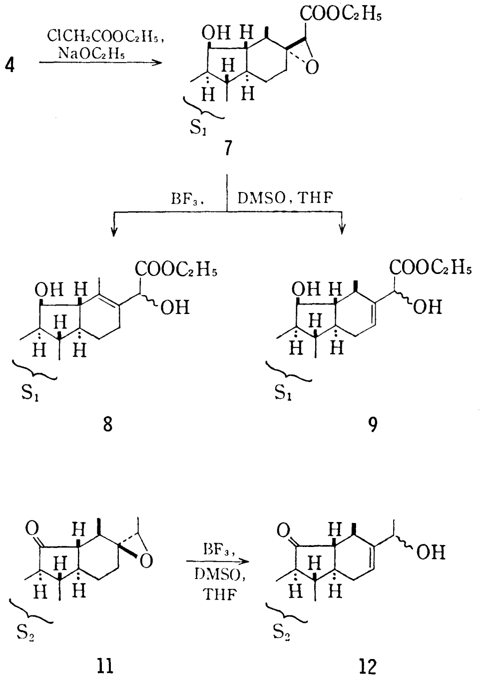




Alkylation at C_{17}, the most important step, was carried out under various conditions. The Wittig reaction of **4** with carbethoxymethylenetriphenylphosphorane[2] and the Darzens reaction under the conditions used for steroidal 3-ketones[20] were attempted for preparing compounds with 17-substituents convertible to the side chain of corticosterone, but proved to be unsuccessful, most of the starting compound **4** being recovered unchanged. However, treatment of **4** by a modified procedure of the latter reaction, using ethyl chloroacetate (8 mol) and sodium ethoxide (5 mol) in dimethyl sulfoxide (DMSO) at room temperature, resulted in formation of glycidic ester (**7**), mp 176—178°C, in 36% yield after chromatographic separation, along with an almost equal amount of the unreacted compound **4**. Compound **7** displayed a peak at *m/e* 390 due to the molecular ion and absorptions at 1747 cm^{-1} and at τ 8.84 (triplet) and 5.75 (quartet) due to the carbethoxy group in the mass, IR, and NMR spectra, respectively, which were consistent with the structure. The configuration of the side chain at C_{17} was assigned β (α-epoxide) on the analogy of the Grignard reactions in unhindered ketones[21] and, especially, of the ethynylation of C-nor-D-homocortisone synthesis (17β-ethynyl 40% and 17α-ethynyl 5%).[2]

Glycidic ester **7**, on treatment with boron trifluoride etherate in a refluxing solution of tetrahydrofuran (THF) and DMSO, afforded a 1 : 2 mixture of two allyl alcohols. The mixture was subjected to separation by preparative thin layer chromatography (tlc) to give **8**, mp 150—151°C, and **9**, mp 152—153°C, in 23 and 40% yields, respectively. The former showed a signal (singlet) due to the methyl protons attached to the 13,17-double bond at τ 8.07, and the latter one ($W_{\rm H}$=12 Hz) due to the new olefinic proton at τ 4.11 in the NMR spectrum. The presence of a double bond at C_{12}–C_{13} of **8** was excluded, because the 18-methyl protons of etiojerv-12-en-11β-ol derivatives appeared at a higher field over τ 8.20.[14]

Kupchan and El-Haj[4a] obtained etiojerva-4,16-dien-20-ol-3,11-dione (**10**) as the only isolable product by treatment of a compound with an epoxy function at C_{17} and C_{20} (**11**) under almost the same conditions. They assigned the β-configuration to the relevant epoxy group on the basis of this reaction result, which was rationalized by a concerted cleavage of the diaxially oriented C_{17}–O and C_{16}–H bonds.[22] In view of the stereochemical peculiarity in C and D rings of etiojervanes, the rationalization leading to the preferential elimination of proton from the less hindered carbon C_{16} would not be unreasonable. Contrary to expectation, the present result differed from theirs in the formation of two olefins **8** and **9**. This would be explicable on the premise of a two-step elimination mechanism; cleavage of the presumed α-epoxy group at C_{17} followed by removal of one of the protons on two adjacent carbons C_{13} and C_{16}. It would be improbable that the reaction proceeded with a concerted mechanism, whereby compounds with two *trans*-fused five-membered rings should result from contraction of the D ring.[23] It is to be noted that compound **8** is the first etiojervane derivative with both the 13,17-double bond and *trans*-fused C/D linkage (12βH, 14αH).



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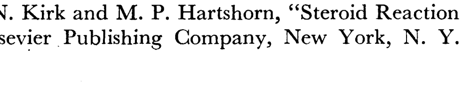

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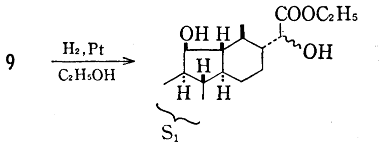
Hydrogenation of olefin **9** over platinum in ethanol took place selectively, giving the 16,17-dihydro derivative (**12**), mp 177—179°C, in 81% yield. A signal at τ 4.11 due to the proton at C_{16} of **9** disappeared in the NMR spectrum of **12**. On the other hand, compound **8** with the tetra-substituted double bond remained unchanged by the same treatment. The side chain configuration at C_{17} of **12** was tentatively assigned to α on the basis that (1) hydrogenation of an iminojervane derivative (**13**) with the double bond at C_{16} and C_{17} as well as the *trans*-fused C/D linkage produced a compound (**14**) with the 17α-side chain, resulting from attack of hydrogen from the upper (β) side,[16] and (2) adsorption of the double bond in question on the catalyst would possibly occur at the same side as the fixed 11-hydroxy group rather than the rotatable 20-hydroxyl.[24]



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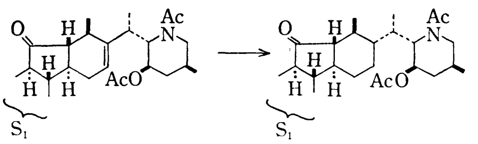
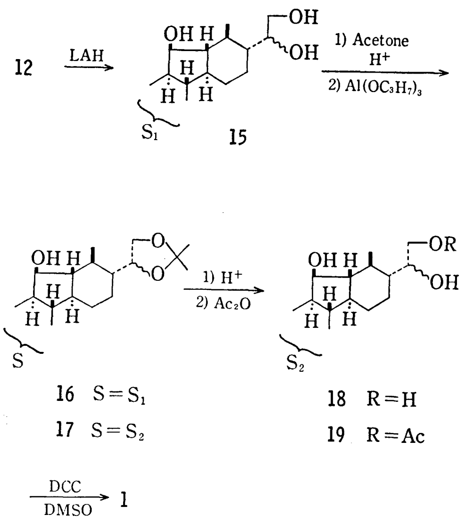


13 3-Acetate

14 3-Acetate

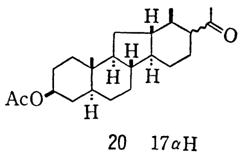
Reduction of ester **12** with lithium aluminum hydride (LAH) gave rise to etiojerv-5-ene-3β,11β,20ξ,-21-tetrol (**15**) as crystalline state, which was scarcely soluble in the usual organic solvents, and without further purification, converted by treatment with acetone and *p*-toluenesulfonic acid (PTS) into the acetonide (**16**), mp 217—220°C in 47% yield from **12**. The mass (*m/e* 390, M^+), IR (ν_{max} 1068 and 1052 cm^{-1}) and NMR spectra (τ 8.62, 6H, singlet) were in good accord with the structure. The Oppenauer oxidation[13] of acetonide **16** proceeded without any change of the 11β-hydroxy group and afforded an αβ-unsaturated ketone (**17**), mp 160—162°C, in 85% yield, which showed strong absorption maxima at 1650 and 1610 cm^{-1} in the IR spectrum.

Acetonide **17** was then subjected to hydrolysis with acid to give triol (**18**), which was also hardly soluble in the usual organic solvents and used for the next reaction without further purification. Treatment of **18** with acetic anhydride (1.3 mol) in dioxane effected partial acetylation at C_{21}, giving monoacetate (**19**), oil, after separation by preparative tlc. Selective oxidation of the 20-hydroxyl to the oxo function by the usual procedures, using anhydrous chromic acid in acetic acid or in pyridine or Jones' reagent,[25] failed owing to the susceptibility of the 11β-hydroxyl group to oxidation. However, oxidation was achieved by treatment of **19** with dicyclohexylcarbodiimide (DCC), trifluoroacetic acid and pyridine in DMSO at room temperature.[26] The resulting product (**1**) mp 209—211°C, isolated in 30% yield from **17** by preparative tlc, was analyzed for $C_{23}H_{32}O_5$, which was supported by the mass spectrum (*m/e* 388, M^+). In accordance with the assigned structure, the compound exhibited absorption maxima at 3420, 1748, 1728, 1665, and 1610 cm^{-1} due to the hydroxyl and carbonyl functions in the IR spectrum, and two singlets at τ 8.60 and 7.88 (19-CH_3 and $OCOCH_3$), a doublet with *J* of 6 Hz at τ 9.05 (18–CH_3), a multiplet and a singlet at τ 5.35 and 4.38 (H at C_{11} and C_4) in the NMR spectrum. The CD and ORD curves of **1** clearly exhibited a positive Cotton effect, as compared with those of acetonide **17** (Fig. 1). Analogous with the fact that two epimeric, well established etiojervanes (**20** and **21**) with the 17β- and 17α-acetyl group displayed negative and positive Cotton effects ($a = -91°$ and $+61°$), respectively.[14] The positive Cotton effect due to the 20-oxo function of **1** indicated the 17-substituent to be α-oriented, supporting the hydrogenation result of **9**. Accordingly, compound **1** is regarded as C-nor-D-homo-17-epicorticosterone 21-acetate. Since functionalization of the 18-methyl group of related compounds has been achieved,[27] compound **1** or the synthetic intermediates would be useful for the synthesis of etiojervane analogs of aldosterone. The present synthesis involves 16 steps and the over-all yield from jervine **3** is 0.3%. Improved syntheses of **1** and **2** are now in progress.



16 S=S₁
17 S=S₂

18 R=H
19 R=Ac



20 17αH
21 17βH

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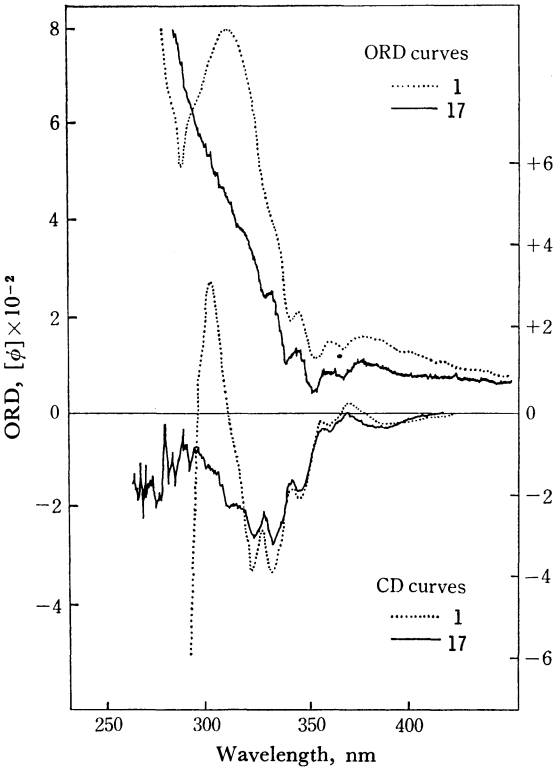

Fig. 1. The ORD and CD curves of 20-oxo and 20-hyoxy-ethiojervanes **1** and **17**.

Experimental

The melting points were measured in open capillaries and uncorrected. Homogeneity of each compound was always checked by TLC on silica gel (Wakogel B-5) and/or alumina (Merck G). The optical rotations and IR spectra were taken in methanol and in Nujol unless otherwise stated. The NMR spectra were measured in deuterochloroform at 60 and/or 100 MHz, tetramethylsilane being used as an internal reference, unless otherwise sated. The abbreviations s, d, t, q, br, and m in the NMR spectra denote singlet, doublet, tripelt, quartet, broad, and multiplet, respectively.

*17β-Carbethoxymethylen-17α,20ξ-expoxyetiojerv5-ene-3β,11β-diol- (**7**).* To a solution of etiojerv-5-ene-3β,11β-diol-17-one[2] (**4**, 9.14 g), 194—195°C, in DMSO (400 m*l*), freshly distilled at bp 95°C/35 mmHg over sodium hydride, were added ethyl chloroacetate (13.5 m*l*) and sodium ethoxide (11.7 g) under cooling, and the mixture was stirred at room temperature for 48 hr in a sealed tube. The mixture was shaken with water (400 m*l*) and chloroform (200 m*l*). After separation of the chloroform layer, the aqueous solution was extracted with chloroform (3×100 m*l*). All the chloroform solutions were combined, washed with an aqueous sodium chloride solution and water, dried over anhydrous sodium sulfate, and evaporated to leave brown oil. The oil (14.35 g) was chromatographed over alumina (Merck, neutral 250 g), using benzene, benzene-ether, ether, and acetone as eluents. Fractions eluted with benzene-ether and ether amounted to 9.66 g after removal of the solvents and, on trituration with acetone-ether, yielded crystalline material (**7**, 3.07 g), which was collected by filtration and showed a single spot. The filtrate was evaporated off to leave amorphous residue (4.68 g), which was again chromatographed over silica gel (Merck, 70—325 mesh, 181 g), using the same solvents as mentioned above. Eluates with benzene-ether contained **7** (checked by tlc) and crystallized partially on trituration with ether or ether-acetone. The crystalline substance (**7**, 1.11 g), collected by filtration, was combined with the afore-mentioned and recrystallized from ether-acetone for analysis to give **7** (3.80 g), mp 176—178°C; $[\alpha]_D$ −58.9°; mass, *m/e* 390 (M^+); IR, ν_{max} 3470 and 1747 cm^{-1}; NMR, τ 9.11 (3H, d, J=7 Hz, 18-CH_3), 8.84 (3H, t, J=7 Hz, COOCH$_2$CH_3), 8.76 (3H, s, 19-CH_3), 6.50 (1H, m, *H* at C$_3$), 5.75 (2H, q, J=7 Hz, COOCH_2CH$_3$), 5.70 (1H, m, *H* at C$_{11}$), 4.77 (1H, br s, *H* at C$_6$), and 4.43 (1H, s, *H* at C$_{20}$).

Found: C, 70.45; H, 8.73%. Calcd for $C_{23}H_{34}O_5$: C, 70.45; H, 8.78%.

Examination of the mother liquors obtained on removal of **7** by tlc indicated the presence of an almost equal amount of **4**.

*17-Carbethoxymethylenetiojerva-5,13(17)-diene-3β,11β,20-ξ-triol (**8**) and 17-carbethoxymethylenetiojerva-5,16-diene-3β,11β,20ξ-triol (**9**).* A solution of **7** (500 mg) in dry THF (25 m*l*) and DMSO (25 m*l*) was refluxed with boron trifluoride etherate (0.5 m*l*) for 5 hr and for another 3 hr after addition of the same fluoride (0.5 m*l*). After being cooled, the solution was mixed with water (150 m*l*) and then extracted with chloroform (50, 25, and 25 m*l*). The chloroform solutions were dried and evaporated under reduced pressure to leave amorphous residue (506 mg). This was separated into 2 parts by preparative tlc using ether and 18 plates; each plate was made of silica gel (Wakogel B-5, 10 g) with an area 20×20 cm^2. A less mobile fraction showing a single spot was extracted with acetone–methanol and gave amorphous substance (140 mg) after removal of the solvent, which crystallized on trituration with acetone–ether to yield **8** (115 mg), mp 149—150°C. This was recrystallized from the same solvent for analysis; mp 150—151°C; $[\alpha]_D$ −146.9°; IR, ν_{max} 3370, 3270 (shoulder), 1749 and 1295 cm^{-1}; NMR, τ 8.65 (3H, s, 19-CH_3), 8.65 (3H, t, J=7 Hz, COOCH$_2$-CH_3), 8.07 (3H, s, 18-CH_3), 6.50 (1H, m, *H* at C$_3$), 5.75 (2H, q, J=7 Hz, COOCH_2CH$_3$), 5.70 (1H, m, *H* at C$_{11}$), 4.94 (1H, s, *H* at C$_{20}$), and 4.72 (1H, br s, *H* at C$_6$).

Found: C, 70.54; H, 8.72%. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78%.

The more mobile fraction (288 mg) showing a single spot crystallized on trituration with acetone–ether to give **9** (199 mg), mp 147—149°C. This was recrystallized from the same solvent for analysis; mp 152—153°C; $[\alpha]_D$ −145.3°; IR, ν_{max} 3520, 3390, 3210, 1723, and 1285 cm^{-1}; NMR, τ 8.82 (3H, d, J=6 Hz, 18-CH_3), 8.72 (3H, s, 19-CH_3), 8.72 (3H, t J=7 Hz, COOCH$_2$CH_3), 6.50 (1H, m, *H* at C$_3$), 5.75 (2H, q, J=7 Hz, COOCH_2CH$_3$), 5.70 (1H, m, *H* at C$_{11}$), 5.36 (1H, s, *H* at C$_{20}$), 4.75 (1H, br s, *H* at C$_6$), and 4.11 (1H, br s W_H=12 Hz, *H* at C$_{16}$).

Found: C, 70.66; H, 9.07%. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78%.

*17α-Carbethoxymethylenetiojerv-5-ene-3β,11β,20ξ-triol (**12**).* Compound **9** (1.70 g) was hydrogenated over prereduced Adams platinum (800 mg as PtO·H$_2$O) in ethanol (125 m*l*) at room temperature for 2 days, when 100 m*l* of hydrogen (1 mol) had been absorbed. The reaction was continued for 3.5 days. After removal of the catalyst and the solvent, the residue was dissolved in chloroform. The solution was washed with an aqueous sodium chloride solution and water, dried and evaporated to leave amorphous residue (1.97 g), which crystallized on trituration with acetone-ether to give **12** (1.49 g), mp 167—170°C, showing a single spot. This was recrystallized from the same solvent for analysis; mp 177—179°C; $[\alpha]_D$ −53.5°; IR, ν_{max} 3470, 1717 and 1240 cm^{-1}; NMR, τ 8.98 (3H, d, J=6Hz, 18-CH_3), 8.77 (3H, s, 19-CH_3), 8.72 (3H, t, J=7 Hz, COOCH$_2$CH_3), 6.50 (1H, m, *H* at C_3), 5.76 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 5.72 (2H, m, *H* at C_{11} and C_{20}), and 4.75 (1H, br s, H at C_6).

Found: C, 70.21; H. 9.43%. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24%.

*17α-Ethyletiojerv-5-ene-3β,11β,20ξ,21-tetrol 20,21-Acetonide (**16**).* To a suspension of LAH (500 mg) in dry THF (40 m*l*) was added compound **12** (500 mg) in dry THF (35 m*l*) under stirring during 50 min, and the mixture was stirred at room temperature for 1 hr. To the cooled mixture were added dropwise methanol (2 m*l*) and water (20 m*l*) under stirring to decompose excess of the LAH, and then 1 N hydrochloric acid to dissolve the resulting aluminum hydroxide. The mixture was extracted with ethyl acetate (3×20 m*l*), and the solution was washed with water. The aqueous washings were again extracted with ethyl acetate (20 m*l*). All the acetate solutions were combined, evaporated and dried over phosphorus pentoxide under reduced pressure to leave crystalline material (crude tetrol **15**, 427 mg), which was used for the next reaction without further purification.

A solution of the crude tetrol **15** in acetone (40 m*l*), freshly distilled over potassium carbonate after reflux with potassium permanganate, was stirred with PTS (400 mg) at room temperature for 10 min, when the spot of **15** had disappeared. After 40 min, the solution was mixed with an aqueous, saturated sodium bicarbonate solution and extracted with chloroform (3×40 m*l*). The chloroform solution was washed with water, dried and evaporated to leave amorphous residue (513 mg), which showed 2 spots on tlc and was separated by preparative tlc (ether and 13 plates). The more mobile, main fraction gave amorphous substance which was crystallized and recrystallized from acetone-ether to give **16** (237 mg), mp 217—220°C; $[\alpha]_D$ −49.2°; mass, *m/e* 390 (M^+); IR, ν_{max} 3430, 1068, and 1052 cm^{-1}; NMR, τ 8.85 (3H, d, *J*=5 Hz, 18-CH_3), 8.75 (3H, s, 19-CH_3). 8.62 (6H, s, CH_3CCH_3), 6.50 (1H, m, *H* at C_3), 6.00 (3H, m, *H* at C_{20} and C_{21}), 5.70 (1H, m, *H* at C_{11}), and 4.75 (1*H*, br s, *H* at C_6).

Found: C, 73.87; H, 9.74%. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81.

*17α-Ethyletiojerv-4-ene-11β,20ξ,21-triol-3-one 20,21-Acetonide (**17**).* A solution of compound **16** (200 mg) in toluene (55 m*l*) containing cyclohexanone (5 m*l*) was heated under stirring until 28 m*l* of the toluene was removed. After addition of aluminum isopropoxide (480 mg), the whole mixture was refluxed for 3.7 hr and cooled. After addition of acetone (8 m*l*) and water (8 m*l*), the mixture was stirred at room temperature overnight and filtered. The filtrate was subjected to steam distillation to give oily residue which was extracted with chloroform repeatedly. The extracts yielded amorphous substance (225 mg) which crystallized on trituration with ether to give **17** (168 mg), mp 156—158°C. This was recrystallized from acetone-ether for analysis; mp 160—162°C; $[\alpha]_D$ +100.0°; IR, ν_{max} 3410, 1650, 1610, 1075, and 1060 cm^{-1}; NMR, τ 8.87 (3H, d, *J*=5 Hz, 18-CH_3), 8.64 (6H, s, CH_3CCH_3), 8.59 (3H, s, 19-CH_3), 6.05 (4H, m, *H* at C_{11}, C_{20}, and C_{21}), and 4.28 (1H, s, *H* at C_4).

Found: C, 74.10; H, 9.26%. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34%.

*17α-Ethyletiojerv-4-ene-11β,21-diol-20-one 21-Acetate (C-Nor-D-homo-17-epicorticosterone 21-Acetate, **1**).* A solution of compound **17** (100 mg) in methanol (8 ml) containing concentrated hydrochloric acid (4 drops) was stirred at room temperature for 1.5 hr. After removal of the methanol below 40°C, the residue was extracted with chloroform, and the chloroform solution was evaporated and dried over phosphorus pentoxide under reduced pressure to leave resinous substance (crude **18**, 93 mg).

The resin was dissolved in pyridine (0.2 m*l*) and treated with acetic anhydride (36 m*l*) in dioxane (0.4 m*l*) at room temperature for 15 hr. The mixture was poured into ice-water (70 m*l*) and extracted with chloroform repeatedly. The chloroform solution was washed with 1 N hydrochloric acid and water, dried and evaporated to leave oily residue (126 mg) which was separated by preparative tlc (ether and 3 plates). The main fraction afforded oil (crude **19**, 60 mg) which was used for the next reaction without further purification.

A solution of the oil (50 mg) in a 1 : 3 mixture of dry DMSO and benzene (0.64 m*l*) was treated with DCC (80 mg, 3 equiv) and 0.5 M trifluoroacetic acid and 1 M pyridine in DMSO (0.13 m*l*) at room temperature for 3.5 hr in a sealed tube. On addition of ether, precipitates separated out and were removed by filtration. The ether filtrate was washed with water, dried and evpaorated to leave amorphous residue (66 mg) which was separated into 3 parts by preparative TLC (ether and 1 plate). The main fraction gave crystalline material (**1**, 20 mg), mp 208—211°C, on removal of the solvent. This was recrystallized from acetone-ether for analysis; mp 209—211°C; CD and ORD (Fig. 1); mass, *m/e* 388 (M^+); IR, ν_{max} 3420, 1748, 1728, 1665, and 1610 cm^{-1}; NMR, τ 9.05 (3H, d, *J*=6 Hz, 18-CH_3), 8.60 (3H, s, 19-CH_3), 7.88 (3H, s, $OCOCH_3$), 5.80 (1H, m, *H* at C_{11}), 5.35 (2H, s, *H* at C_{21}), and 4.38 (1H, s, *H* at C_4).

Found: C, 70.88; H, 8.43%. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30%.

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