Stereochemistry of the C and D Rings of C-Nor-D-homosteroids. IV.[1] The Relative Stabilities and NMR Spectra of 17-Substituted C/D *trans*- and *cis*-Fused Etiojervanes[2]

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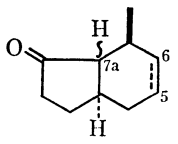
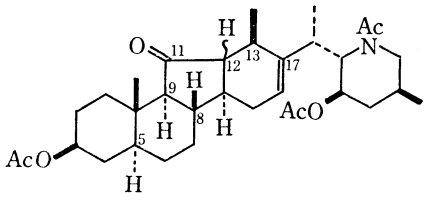
(1) The relative stabilities between 17-substituted C/D *trans*- and *cis*-fused 11-oxoetiojervanes were investigated by treatment of both or either one of these 12-epimeric compounds under equilibrating conditions. The equilibrium ratios thus obtained were estimated qualitatively in terms of the configuration and bulkiness of substituent(s) at C_{17}. (2) The chemical shifts of 19- and 18-methyl protons in a number of etiojervanes were examined collectively. The "principle of additivity" holds satisfactorily for the 19-methyl protons of all etiojervanes, with two exceptional cases, irrespective of the configuration at C_{12} and also for the 18-methyl protons of 12β-etiojervanes. However, the principle is not applicable for the latter protons of 12α-etiojervanes, suggesting that the D ring would take different conformations depending on the 17-substituents.

The Relative Stabilities. The relative stabilities of *trans*- and *cis*-hydrindanone systems have been investigated extensively and found to depend delicately upon structural change.[3] This variety has been illustrated by simple[4] and complex hydrindanone systems[5] as well as normal (D ring) and modified (A and B rings) steroidal ketone.[3,6,7] Qualitative, sometimes temporizing, explanations have been given for these results, but no general understanding appears to be available. Recently, a few of attempts to rationalize the observed relative stabilities by calculational methods have been reported and applied successfully to a variety of these compounds.[8,9] Nevertheless, it is still desirable to accumulate experimental results concerning the stabilities of hydrindanone systems incorporated into large and complex natural products.[10] For example, House and Rasmusson have reported that the *trans*-fused isomer (**1**) of 7-methyl-3a,4,7,7a-tetrahydro-1-indanone is greatly stable as compared with the *cis*-fused isomer (**2**),[11] while the situation has become completely opposite with the corresponding etiojervane analogs with a bulky substituent (S) at C_{17} (**3** and **4**).[12] This fact, as combined with the previously observed results, has led us to have interest in more detailed examination of the relative stabilities of the titled compounds. Recently, we reported the summarized result concerning this stability relationship as a preliminary communication.[13] We describe herein the details and also, in connection with this, discuss the NMR spectra of C/D *trans*- and *cis*-fused etiojervanes.



1 Δ^5, 7aβH
2 Δ^5, 7aαH
20 no Δ^5, 7aβH
21 no Δ^5, 7aαH

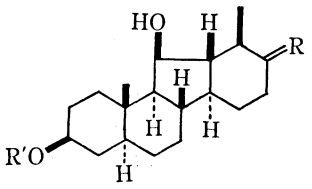


3 12βH
4 12αH

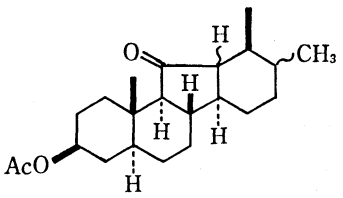
Prior to the epimerization studies, several 17-substituted etiojervanes were newly prepared, and syntheses of two representative compounds, 17-methyl- and 17-hydroxy-17-isopropyl-11-oxoetiojervanes, are described below. 5α,12β-Etiojervane-3β,11β-diol-17-one[14] (**5**) underwent the Wittig reaction[15] and subsequent acetylation to give the 17-methylene derivative (**6**), mp 172—173 °C, in 67% yield. Hydrogenation over Adams platinum produced a mixture of the 17β- and 17α-methyl compounds (**7** and **8**) in 84% yield, which was oxidized with chromic anhydride to mixture of the corresponding 11-oxo derivatives (**9** and **10**). While each of these mixtures showed a single spot on various TLC and resisted further purification, the mixture of compounds **9** and **10**, on treatment with sodium methoxide in refluxing methanol and subsequent acetylation, gave a product, which consisted mainly of the unreacted starting material but showed two spots clearly on TLC. Repeated epimerizations followed by acetylation effected isolation of a 12α-epimer (**11**), mp 163.5—164 °C, in 16% yield. Conversely, the same treatment of the 12α-epimer (**11**) produced the 12β-epimer (**9**), mp 140—141 °C, in good yield. As expected, these 12-epimeric 11-ketones (**9** and **11**) displayed negative Cotton effects with amplitudes of −157° and −77° in the ORD curves[12a] and signals due to the 19-methyl protons at δ 0.86 and 0.90 in the NMR spectra. The β-configuration of 17-methyl groups in both compounds was deduced from the fact that the epimerization of compound **9** to **11** took place, as discussed later.

17-Hydroxy-17-isopropyl-11-oxoetiojervanes were prepared from 12β-etiojerv-5-en-3β-ol-11,17-dione 17-ethylene acetal[16] (**12**). Hydrogenation of **12** over platinum in acetic acid produced the 5α,6-dihydro derivative (**13**), mp 172—174 °C, in 97% yield, which on hydrolysis with acid gave 11,17-diketone (**14**), mp 159—162 °C, in good yield. Treatment of **14** with

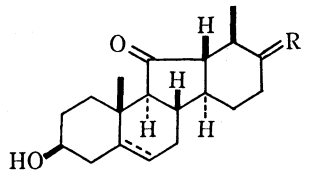
isopropylmagnesium bromide in ether produced a complex mixture, from which four compounds (**15**—**18**), having mp 180—182 °C, 168—170 °C, 136—138 °C and 193—195 °C, could be isolated by repeated preparative TLC in 16, 19, 1.5 and 4% yields (crude 40, 41, 3 and 5.5%), respectively. Contrary to the expectation, two major products (**15** and **16**) were formulated as 3β,11β,17β-triol and 3β,11β-diol-17-one, respectively, on the basis of the spectral data, indicating that reduction of the sterically hindered 11-carbonyl group occurred as a main reaction. While the former **15** revealed no absorption maximum in the carbonyl region, the latter **16** exhibited the maxima at 3400 and 1700 cm^{-1} and also a negative Cotton effect (a= −88°).[16,17] On the other hand, two minor products (**17** and **18**) were expected 17-isopropyl adducts. In accordance with the assigned structures, both the compounds (**17** and **18**) showed absorption maxima at 1732 and 1733 cm^{-1} in the IR spectra and also negative Cotton effects (a= −151° and −157°) in the ORD curves. Moreover, the configurations of two substituents at C_{17} were assigned as shown in the formulas (**17** and **18**) by epimerization experiments in the same manner as that compound **9**.



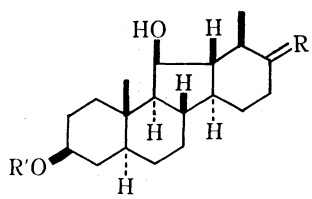
5 R=O R′=H
6 R=CH_2 R′=Ac
7 R=-CH_3, ···H R′=Ac
8 R=-H, ···CH_3 R′=Ac



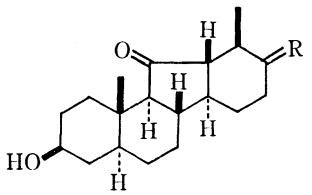
9 12βH, 17βCH_3
10 12βH, 17αCH_3
11 12αH, 17βCH_3



12 Δ^5, R=OC_2H_4O
13 5αH, R=OC_2H_4O
14 5αH, R=O

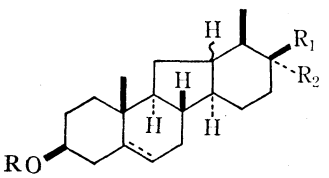


15 R=-H, ···OH, R′=H
15a R=-H, ···OH, R′=Ac
16 R=O, R′=H



17 R=-C_3H_7, ···H
18 R=-H, ···C_3H_7

Equilibration studies were carried out by treatment of both or either one of C/D *trans*- and *cis*-fused 17-substituted 11-oxo-etiojervanes (**19** in Table 1) with 1 M sodium methoxide in refluxing methanol for several hours, and the summarized result, including the reported ones, is listed in Table 1.



19 A=12βH
B=12αH

As shown in Table 1, 17-unsubstituted 12β-etiojervanes (IA and IIA in Table 1), regarded as reference compounds, were not epimerized completely, and the corresponding 12α-epimers (IB and IIB) could not be detected even by repeated TLC. Conversely, compounds IB and IIB were transformed quantitatively into IA and IIA, respectively. In view of the small equilibrium ratio (3 : 1) between *trans*- and *cis*-methylhydrindanones[11] (**20** and **21**), the present result would be rationalized by assuming that the five-membered C ring in etiojervanes **19** is fused in a *trans*-manner with the B ring and would therefore take a half-chair form rather than an envelope form. This conformation would lead to remarkable stabilization of *trans*-fused isomers (IA), as compared with *trans*-methylhydrindanone (**20**), and would also explain well the result that 12β-etiojervanes [IIIA (=**13**), IVA (=**12**) and VA[17]] with the same two substituents were much more stable than the corresponding 12α-epimers. Naturally, 12β-etiojervanes (VIA—IXA) with only one α-oriented (equatorial) substituent, apart from that (XA) with a bulky substituent,[12] were extremely favored under the equilibrating conditions over the respective 12α-epimers.

On the other hand, 17β-substituted 12β-etiojervanes (XIA—XIVA) would be destabilized by the axially disposed substituents, as compared with the refernce compounds (IA and IIA). This destabilization would increase in passing from the small[18] (OH, XIA), medium (CH_3, XIIA=**9** and C_2H_5, XIIIA) to the large(S, XIVA) substituent, leading to decrease of the

Table 1. Equilibration of 17-substituted 11-oxo-12β- and 12α-etiojervanes compounds (**19**)[a] and equlibrium ratio[b]

No.	C_5	R	R_1 (β)	R_2 (α)	12βH (A)	Ratio[b]	12αH (B)
I	5αH	Ac	H	H	(1)	⇐⇒	(1)
II	Δ^5	Ac	H	H	(1)	⇐⇒	(1)
III	5αH	H	OC_2H_4O		**13** (16)	—//→	
IV	Δ^5	H	OC_2H_4O		**12** (16)	—//→	
V	Δ^5	Ac	$CHCH_3$		(17)	←—	(18)
VI	5αH	Ac	H	OH	(1)	⇐⇒	(1)
VII	5βH	Ac	H	OH	(1)	⇐⇒	(1)
VIII	Δ^5	H	H	OH	(1)	—//→	
IX	5αH	Ac	H	C_2H_5	(14)	—//→	
X	5αH	Ac	H	S	(12)	13 : 1	(12)
XI	Δ^5	H	OH	H	(1)	40 : 1	Exp
XII	5αH	Ac	CH_3	H	**9**	6 : 1	**11**
XIII	5αH	Ac	C_2H_5	H	(14)	11 : 9	(14)
XIV	5αH	Ac	S	H		←//—	(12)
XV	Δ^5	H	OH	C_2H	(19)	—//→	
XVI	Δ^5	H	C_2H	OH	(19)	—//→	
XVII	Δ^5	Ac	OH	C_2H_5	(19)	—//→	
XVIII	Δ^5	Ac	C_2H_5	OH	(19)	11 : 1	Exp
XIX	5αH	H	OH	C_3H_7	**18**	—//→	
XX	5αH	H	C_3H_7	OH	**17**	3 : 1	Exp

a) The symbols "A and B" refer to the configuration of C_{12}, and the numbers on parentheses to the references in which the compounds are cited. The symbols "**13** (=IIIA) and Exp" denote "compound **13** described in the text and compounds characterized in Experimental part in this paper." The formulas "$CHCH_3$, C_2H, C_3H_7 and S" mean "ethylidene, ethinyl, isopropyl groups, and a 17-substituent of **3** and **4**," respectively. b) The equilibrium ratio was obtained by measuring the amounts of isolated products.

ratio (12βH : 12αH) in question. The observed result was indeed in good accord with this presumption. Fortunately, a 12α-isomer (XIB), mp 237—239 °C, of XIA could be isolated by repeated epimerizations, showing a negative Cotton effect with amplitude of −69°. It is to be noted that the equilibrium ratio between XIIIA and XIIIB with a 17β-ethyl group was found to be about 1 : 1, suggesting that the energy difference between the reference compounds (IA and IB or IIA and IIB) would nearly equal the conformational energy (1.8 kcal)[18] of an ethyl group.

The afore-mentioned results indicated that the relative stabilities between 12-epimeric etiojervanes (XV—XX) with two substituents at C_{17} would depend on the relative bulkiness of β- and α-substituents. 12β-Etiojervanes (XVA and XVIA)[19] with two similar or those (XVIIA[19] and XIXA) with larger α-oriented substituents must be much more stable than the corresponding 12α-epimers. Indeed it was the case. On the other hand, the relative stabilities between 12-epimeric etiojervanes (XVIII and XX) with larger β-substituents must become comparable, and the unstable epimers might be isolable. The observed results were completely in accordance with this expectation, and 17β-ethyl-17α-hydroxy- and 17β-isopropyl-17α-hydroxy-12α-etiojervanes (XVIIIB and XXB), mp 149—150 °C and amorphous, could be isolated from the epimerization mixtures of the respective 12β-epimers (XVIIIA[19] and XXA (=**17**)].

In summary, the relevant stabilities depend upon the configuration and bulkiness of substituents at C_{17} and the equilibrium ratios are estimated roughly on the basis of these factors. This rationalization not only holds for both reactants and products, as mentioned in this paper, but also is applicable to reaction intermediates, as reported in the previous papers.[20,21] Moreover, the result suggests that both the C and D rings would probably take a somewhat fixed conformation at least in 12β-etiojervanes, and this conformational rigidity will be supported by the NMR spectra described in the following sections.

The NMR Spectra. During synthetic studies on C-nor-D-homo-steroid hormones, we have synthesized a number of etiojervanes. In view of the close similarities of structure within these etiojervanes, an intercomparison of the NMR spectra of a series of these compounds would be valuable in confirming certain stereochemical points as well as promoting the structure determination of new derivatives. In the previous papers on the NMR spectra of 22,27-imino-17,23-oxidojervanes [(22S,23R,25S)jervanines][22] and etiojerva-12,14,16-trienes with an aromatic D ring,[23] we have reported that the effects of many different substituents on the chemical shifts of 19-methyl protons are additive. However, these data have been confined to the correlation of the chemical shifts with changes of substituents only at C_3, C_4, C_5 and C_{11}. Moreover, it has not been reported whether or not the "principle of additivity" is applicable to the chemical shifts of 18-methyl protons. Hence we examined collectively the NMR spectra of a series of stereochemically well-established 17-substituted 12β- and 12α-etiojervanes, paying special attention to the influence due to the difference of C/D ring junctures and the

Table 2. The contribution ($\Delta\delta$) of functional groups to the chemical shift of the 19-methyl protons of etiojervanes

Groups	A (12βH, Δ^{11}, Δ^{12})				B (12αH)			
	T (5αH, Δ^4, Δ^5)		C (5βH)		T (5αH, Δ^4, Δ^5)		C (5βH)	
Reference shifts[a]	0.74	(176)[b]	0.87	(7)[b]	0.79	(116)[b]	0.92	(13)[b]
Functional groups	$\Delta\delta$[c]		$\Delta\delta$[c]		$\Delta\delta$[c]		$\Delta\delta$[c]	
Δ^1, 3=O					0.23	(4)		
Δ^1, 3=O, Δ^4	0.43	(2)	—		0.43	(2)	—	
2α-Br					0.08	(3)		
2α-Cl					0.07	(1)		
3β-OH	0.02	(58)	0.02	(3)	0.02	(25)	0.02	(2)
3β-OAc	0.03	(90)	0.03	(3)	0.03	(51)	0.03	(3)
3-OCH_2CH_2O-	0.03	(10)			0.03	(3)	0.04	(1)
3=O	0.21	(1)	0.09	(1)	0.21	(16)	0.09	(3)
3=O, Δ^4	0.40	(22)	—		0.40	(18)	—	
3=O, Δ^4, Δ^6			—		0.34	(3)	—	
4α-Br					0.04	(1)		
Δ^5	0.21	(92)	—		0.21	(12)	—	
6α-SAc					0.00	(4)		
Δ^8					0.17	(1)		
Δ^8, 11=O					0.28	(4)	0.40	(2)
$\Delta^{9(11)}$	0.15	(1)						
Δ^{11}	0.00	(2)			—		—	
Δ^{11}, $\Delta^{13(17)}$	0.02	(1)			—		—	
11β-OH	0.29	(30)			0.27	(6)		
11β-OAc	0.20	(3)						
11α-OH	0.02	(2)						
11α-OAc	0.12	(3)						
11=O	0.07	(52)	0.08	(4)	0.07	(27)	0.08	(9)
11=O, Δ^{12}	0.07	(10)	0.08	(1)	—		—	
11=O, Δ_{12}, $\Delta^{17(20)}$	0.12	(4)			—		—	
11=O, Δ^{12}, 17=O	0.12	(3)			—		—	
11β-ONO					−0.05	(1)		
11β,17β-O-					0.16	(2)	0.16	(2)
Δ^{12}	0.00	(14)			—		—	
13α,17α-O-					0.05	(1)		
13β,17β-O-					−0.02	(1)		
$\Delta^{13(17)}$	0.08	(1)			−0.10	(22)	−0.10	(5)
Δ^{16}	0.00	(8)	0.00	(1)	0.00	(4)	0.00	(1)
16β-OR					0.00	(3)		
16=O					0.06	(3)		
$\Delta^{17(20)}$	−0.01	(7)			0.01	(1)		
17=O	0.00	(16)			−0.10	(10)		
17β-C≡CH[d]	0.07	(2)						

a) The shifts refer to the assigned chemical shifts for 19-methyl protons of hypothetical compounds without any substituent. Solvent, $CDCl_3$. b) The figures in the parentheses refer to numbers of examples. c) The negative sign denotes shielding effect. d) The $\Delta\delta$ values of a number of 17-substituents, 0.00.

contribution of substituents at C_{17}. The result follows as.

19-Methyl Protons: In order to examine both additivity and magnitude of the shielding effects, all the compounds were first classified into two groups, A and B. The group A includes compounds having a C/D *trans*-fused ring (12βH) and those having an unsaturated carbon atom at C_{12} (Δ^{11} or Δ^{12}), and the group B compounds possessing a C/D *cis*-linkage (12αH). Each group was further divided into two groups, T (5αH, Δ^4 and Δ^5) and C (5βH), according to the mode of A/B ring juncture, as usually done in the normal steroid series. While reference compounds of the respective groups, 5- and 12-epimeric etiojervanes without any substituent, are not known, 5α,12β- and 5α,12α-etiojervan-3β-ols (**22** and **23**) and their acetates[1] (**22a** and **23a**) have recently been prepared and, moreover, a number of pairs of etiojervanes differing only by the configuration at C_5 have also been reported. In view of the well-known deshielding effects (0.02 and 0.03 ppm) of 3β-hydroxy and 3β-acetoxy groups for the chemical shift of 19-methyl protons,[22,23] the reference chemical

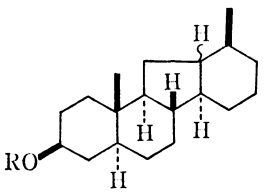
Table 3. The chemical shift of the 18-methyl protons of 12β-etiojervanes. substituents and chemical shifts (δ)[a]

C_{17}		C_{11}					
β	α	H_2	(44)[b]	O	(36)[b]	β-OH	(18)[b]
H	H	0.84±0.01	(2)	1.18±0.02	(3)	1.01±0.02	(2)
OH	H	0.95±0.04	(3)	1.29±0.04	(3)	1.09	(1)
H	OH	0.96±0.02	(2)	1.30±0.03	(5)		
OAc	H	0.89	(1)	1.17±0.03	(2)	0.99	(1)
H	OAc	0.90	(1)	1.20±0.02	(3)		
Ac	H	0.93[c]	(1)				
H	Ac	0.83±0.02	(6)				
CH_3	H			1.14	(1)	1.01	(1)
C_2H_5	H	0.84±0.01	(5)	1.16	(1)		
H	OTs			1.16	(1)		
H	NHAc	0.96±0.02	(3)				
H	$C(=NOH)CH_3$	0.81	(1)				
H	$C_4H_9O_3$[d]					1.02	(1)
H	$CH(CHO)CH_3$					0.975	(1)
H	$C_5H_9O_2$[e]					1.14±0.01	(2)
H	$COCH_2OAc$					0.95	(1)
OCH_2CH_2O		0.85±0.03	(5)	1.18±0.02	(2)	1.01±0.03	(3)
=O		1.00±0.03	(6)	1.34±0.02	(4)	1.14±0.02	(3)
$=CH_2$						1.15	(1)
$=CH(CH_3)$		0.97±0.02	(3)	1.32	(1)	1.18	(1)
Ac	OH			1.31	(1)		
OH	Ac			1.26	(1)		
$COCH_2OAc$	OAc			1.28	(1)		
C≡CH	OH			1.44	(1)		
OH	C≡CH			1.46	(1)		
$CH=CH_2$	OH			1.22	(1)		
OH	$CH=CH_2$			1.17	(1)		
C_2H_5	OH			1.23	(1)		
OH	C_2H_5			1.22	(1)		
Others[f]							

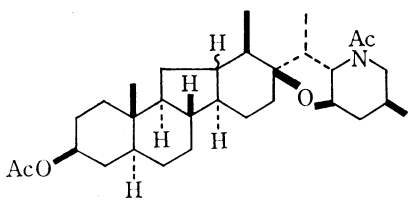
a) Solvent, $CDCl_3$. b) The figures in the parentheses refer to number of examples. c) The calculated δ-value, 0.89. d) $C_4H_9O_3$=CH(OH)$COOC_2H_5$. e) $C_5H_9O_2$=acetonide of a -CH(OH)CH_2OH group. f) 11=H_2, 17β-CH(OH)CH_3 0.93±0.02 (3) and 1.03±0.01 (3); 11=H_2, 17β-CH(OTs)CH_3 0.88 (1); $\Delta^{9(11)}$, 17β-C_2H_5 0.98 (1); Δ^{11}, 17β-C_2H_5 1.02 (1); 11β-OAc, 17α-CH(OH)CH_3 0.90 (1) and 0.84 (1); 11β-OAc, 17α-Ac 0.87 (1); 11α-OH, 17β-C_2H_5 0.98 (2); 11α-OAc, 17β-C_2H_5 0.84 (2).

shifts in the respective groups were assigned as shown in Table 2. The contributions of various functional groups were obtained by pairing compounds which differed only by the single group in question and by taking the average of difference of the chemical shifts. The calculated values, having available the reference shifts and the contributions listed in Table 2, were in good agreement, usually within 0.02 ppm (the deviation of 30 examples among 430 compounds examined, 0.03 ppm) except two exceptional cases, with the observed chemical shifts, indicating that the shielding effects are really active.

On the results given in Table 2, some comments are presented in the following. (1) The reference 19-methyl protons (δ 0.74 and 0.87) of the C/D *trans*-fused groups (A-T and A-C) appear at lower field than the corresponding protons (δ 0.71 and 0.83) in the iminooxidojervane series,[22] but still at higher field than those (δ 0.792 and 0.925) in the normal steroid series.[24] However, the difference (0.13 ppm) between their



22 12β-H, R=H **23** 12α-H, R=H
22a 12β-H, R=Ac **23a** 12α-H, R=Ac



24 12β-H
25 12α-H

chemical shifts is equal to those (0.12 and 0.133 ppm) in the latter two series. (2) The 19-methyl protons of compounds in the C/D *trans*-fused groups (A-T and A-C) were observed at about 0.05 ppm high fields as compared with those in the corresponding C/D *cis*-fused groups (B-T and B-C). This chemical shift difference is represented by the reference shifts of two paired groups in Table 2: A-T and B-T, δ 0.74 and 0.79; A-C and B-C, δ 0.87 and 0.92. This difference is also almost the same as that (0.07 ppm) between diacetyl-5α,6,12β,13-tetrahydrojervine (**24**) and its 12α-epimer[12a] (**25**), a sole compound known as 12α-iminooxidojervane, supporting the 12α-configuration of the latter (**25**). (3) Each functional group in the A, B and C rings of compounds included in the C/D *trans*-fused groups (A-T and A-C) provides almost the same deshielding effect as the same group in the iminooxidojervane system, and it would not be necessary to repeat the previous discussions on the contribution of these groups. However, it is emphasized that this result, as coupled with the afore-mentioned reference shifts, implies that the chemical shifts of 19-methyl protons in the iminooxidojervane series can be estimated from Table 2, by assuming the contribution of 17-substituents of iminooxidojervane to be −0.04 ppm (up-field shift). (4) Each functional group in the C/D *cis*-fused groups (B-T and B-C) displays the contribution similar to the same group in the C/D *trans*-fused (A-T and A-C), as far as the functional groups in question exist in the A, B, and C rings. This indicates that the steric relation of these groups to the 19-methyl group hardly suffers change in passing from the *trans*-fused C/D linkage to the *cis*-fused, though the C-ring is expected to undergo distortion owing to the different C/D ring junctures. (5) Most of the functional groups in the saturated D ring exert no influence on the chemical shifts of 19-methyl portons. This has been demonstrated by a number of substituents at C_{17} in the C/D *trans*-fused as well as *cis*-fused compounds. Only exceptional functions are a 17β-ethinyl group in the group A-T and two 13,17-epoxy in that B-T. The deshielding effect of the former 17β-ethinyl group would be explained well by assuming that the substituent is oriented axial on the D ring with a slightly deformed chair conformation, though no reasonable interpretation is given for the effect of the two groups owing to obscure conformations of the D ring. (6) Several unsaturated functional groups (Δ^{12}, $\Delta^{13(17)}$, $\Delta^{17(20)}$ and 17=O) in the D ring of compounds with an unsaturated carbon atom at C_{12} provide deshielding effects, which would result from deformation of the C and D rings. On the other hand, unsaturated groups in the D ring in the C/D *cis*-fused groups (B-T and B-C), specially a double bond at C_{13}–C_{17} and a 17-carbonyl group, make important contributions to the relevant chemical shifts. According to a molecular model, the D ring in these compounds is disposed on the upper side of the molecule and the carbon atom at C_{17} approaches the 19-methyl group. These shielding effects would therefore be understood well as a result of the magnetic anisotropy of suchlike unsaturated groups. (7) Two exceptional cases for which the "additivity rule" does not hold were observed for a few of isojervine derivatives. This abnormality had already been discussed in the previous paper.[25]

Table 4. The chemical shift of the 18-methyl protons of 12α-etiojervanes

Substituents and chemical shifts (δ)[a]					
C_{17}		C_{11}			
β	α	H_2	(59)[b]	O	(15)[b]
H	H	0.80±0.01	(2)	0.92±0.01	(2)
OH	H	1.04±0.02	(7)		
H	OH	1.03±0.04	(9)	0.89±0.01	(2)
OAc	H	0.91±0.02	(6)	0.93	(1)
H	OAc	0.92±0.01	(10)	0.92	(1)
Ac	H	0.82±0.02	(3)		
H	Ac	0.83±0.02	(3)		
CH_3	H			0.88	(1)
C_2H_5	H			0.72	(1)
H	OTs			0.80±0.01	(2)
=O		1.00±0.02	(7)		
$=CH(CH_3)$				0.95	(1)
$COCH_2OAc$	OH			0.83	(1)
C_2H_5	OH			0.71	(1)
Others[c]					

a) Solvent, $CDCl_3$. b) The figures in the parentheses refer to numbers of examples. c) 11=H_2, 11β,17β-oxido 0.95±0.01 (4); 11=H_2, 17β-CH(OH)CH_3 0.87 (1); 11=H_2, 17α-CH(OH)CH_3 0.92 (1) and 0.90 (1); 11=H_2, 17β-CH(OAc)CH_3, 0.79 (1); 11=H_2, 17α-CH(OAc)CH_3 0.87 (1) and 0.83 (1); 11=H_2, 17β-CH(OH)CH_3, 17α-OH 0.92 (1); 11=H_2, 17β-CH(ONO)CH_3, 17α-OH 0.79 (1); 11=O, Δ^{16} 0.92 (2); 11=O, 17β-CH(OH)CH_2OAc, 17α-OH 0.82 (1); 11=O, 17β-CH(OAc)CH_2OAc, 17α-OH 1.03 (1).

18-Methyl Protons: In Tables 3 and 4 are summarized the chemical shifts of 18-methyl protons of a number of 12β- and 12α-etiojervanes with a β-methyl group at C_{13} (not with an unsaturated carbon atom at C_{13}). The signals due to the 18-methyl protons were distinguished without difficulty in most of the spectra, but the chemical shifts were given not so exactly as those due to the sharp 19-methyl protons, because the protons usually appeared as relatively indistinctly resolved doublets or overlapping signals above the background of methylene and methine protons. This inaccuracy was observed in many cases when the substituents at C_{17} were complex and, specially, the "S" group containing secondary methyl groups, and these undiscernible chemical shift data were not included in Tables 3 and 4. The present data seem at first to be confined to the correlation of the chemical shifts only with changes of substituents in the C and D rings. However, it must be emphasized that various functional groups in the A and B rings exert no important influence on the relevant chemical shifts, as far as the B and C rings are fused in a *trans*-manner (8βH and 9αH).

On the basis of the data summarized in Table 3, we examined the contributions of substituents at C_{11} and C_{17} for the 18-methyl protons of 12β-etiojervanes in the same manner as those for the 19-methyl protons, and found that the "additivity rule" holds roughly

Table 5. The contribution ($\Delta\delta$) of functional groups to the chemical shift of the 18-methyl protons of 12α-etiojervanes

Reference chemical shift[a] Functional groups at C_{11}		$\Delta\delta$[b]	δ 0.84 Functional groups at C_{17}		$\Delta\delta$[b]
$=H_2$	0.00	(44)	$=H_2$	0.00	(7)
=O	0.33	(36)	=O	0.16	(13)
β-OH	0.15	(19)	$=CH(CH_3)$	0.16	(5)
α-OH	0.16	(2)	$=CH_2$	0.16	(1)
β-OAc	−0.05	(3)	$-OCH_2CH_2O-$	0.01	(10)
α-OAc	−0.02	(2)	β-OH	0.11	(12)
Δ^{11}	0.20	(2)	α-OH	0.12	(12)
$\Delta^{9(11)}$	0.16	(1)	β-OAc	0.02	(4)
			α-OAc	0.05	(5)
			β-Ac	0.04	(2)
			α-Ac	0.00	(10)
			β-CH_3	0.00	(2)
			β- and α-C_2H_5[c]	−0.02	(13+1)
			β- and α-$COCH_2OAc$[c]	−0.04	(1+1)
			β- and α-$CH=CH_2$[c]	0.03	(1+1)
			β- and α-C≡CH[c]	0.18	(1+1)
			α-OTs	−0.01	(1)
			α-NHAc	0.12	(3)
			α-C(=NOH)CH_3	−0.03	(1)

a) The chemical shift of 18-methyl protons of compounds without any substituent in the C and D rings. Solvent, $CDCl_3$. b) The figures in the parentheses refer to numbers of examples. The negative sign denotes shielding effect. c) The contributions due to these 17α-substituents were assumed to be the same as those due to the corresponding 17β-substituents.

for the relevant shifts; namely, the observed chemical shifts are in good agreement (within 0.04 ppm) with the calculated values, assuming the chemical shift (δ 0.84) of compounds containing no substituents in the C and D rings to be the reference shift and having available the contributions of functional groups at C_{11} and C_{17} listed in Table 5. The following points are noted from Table 5. (1) In contrast to the contributions for the 19-methyl protons, 11β-hydroxy and acetoxy groups exhibited almost the same deshielding and shielding effects ($\Delta\delta$ 0.15 and −0.05 ppm) for the 18-methyl protons as the corresponding 11α-groups ($\Delta\delta$ 0.16 and −0.05 ppm). These effects are nearly equal to those in the iminooxidojervane series.[22] To the contrary, the deshielding effect ($\Delta\delta$ 0.33 ppm) of the carbonyl group at C_{11} is remarkably large as compared with that ($\Delta\delta$ 0.02 ppm) in the iminooxidojervane series,[22] indicating that the methyl group is oriented equatorial in the D ring with a fixed, slightly deformed chair form and hence located in the plane of the trigonal carbon atom in question. (2) The chemical shifts of 18-methyl protons depend largely on the β- and/or α-substituent(s) and extend from δ 0.84 to 1.46. Interestingly, the relevant signals of two compounds having the same substituents at C_{11} and/or C_{17} but differing only in the configuration at C_{17}, apart from the functional groups in the A and B rings, were found in almost the same fields except in the case of 17-acetyl-12α-etiojervanes (see Table 3). It follows that a substituent at C_{17}, whether the configuration is β or α, provides almost the same contribution (see Table 5). (3) The deshielding effects ($\Delta\delta$ in Table 5) of several 17-substituents (=O, β- and α-OH, and β- and α-OAc) are roughly the same as those ($\Delta\delta$ 0.22, 0.15, 0.21?, 0.00 and 0.05) of the corresponding substituents at C_1 in 5β-androstane series,[26] but completely different from those in 5α-androstane series.[26] This similarity in the deshielding effect between the first two series would support the afore-mentioned conformation in respect to the D ring.

The following comments are given for the chemical shifts of 18-methyl protons of 12α-etiojervanes in Table 4. (1) Contrary to the previous results, the "additivity rule" does *not* hold for the chemical shifts in question. This was exemplified clearly by the variety of shelding effects of a 11-carbonyl group ($\Delta\delta$ −0.14—+0.12 ppm), indicating that the D ring would not take a fixed conformation in the C/D *cis*-fused etiojervanes. (2) The 18-methyl protons in 12α-etiojervanes having no substituents at C_{11} were observed in higher or lower fields than those in the corresponding 12β-etiojervanes. These up- and down-field shifts ($\Delta\delta$ −0.04—+0.09 ppm) naturally depend on the functional groups at C_{17} as well as on the conformations of D ring and are therefore too difficult to be estimated. However, it is noteworthy that several β-oriented substituents (OH, OAc and Ac) at C_{17} exhibit essentially the same contributions ($\Delta\delta$ 0.24, 0.11 and 0.02 ppm) as the corresponding α-oriented, although this does not always imply that the 18-methyl group would have the similar steric relation for the respective 17β- and 17α-grops. (3) The 18-methyl protons in 11-oxo-12α-etiojervanes appeared at remarkably high field ($\Delta\delta$ −0.26—−0.52 ppm) as compared with those in the corresponding 12β-etiojervanes. This large up-field shift evidently results from the conformational change of the D ring

in passing from C/D *trans*-fused compounds to *cis*-fused; the D ring would assume a twist boat or more probably a half-chair conformation, and the β-methyl group at C_{13} would become equatorial in either of the conformations and hence located on the upper side of the C ring and in the conical region extending above the plane of the trigonal carbon atom of a 11-carbonyl group.

Experimental

All the melting points were uncorrected. The homogeneity of each compound was always checked by TLC on silica gel (Wakogel B-5) with 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, m, br, and do" in the NMR spectra denote "singlet, doublet, triplet, multiplet, broad, and double," respectively.

*17-Methylidene-5α,12β-etiojervane-3β,11β-diol 3-Acetate (**6**).* A suspended mixture of sodium hydride (Wako, 510 mg, *ca.* 50% in oil) in pentane (20 ml) was stirred for a while and then decanted under a stream of nitrogen. This procedure was repeated several times to remove the oil. After removal of the pentane *in vacuo* the residual hydride was mixed with fresh dimethylsulfoxide (DMSO, 6 ml), which had been dried over calcium hydride and distilled twice under nitrogen, stirred at 62—72 °C for 1 h and cooled, when the mixture became homogeneous and gray. To the solution was added dropwise a solution of dry methyltriphenylphosphonium bromide (2.863 g) in DMSO (10 ml) at room temperature (temp), and the whole solution was stirred at room temp for 20 min. To the resulting yellow, gel-like mixture was added a solution of 5α,12β-etiojervane-3β,11β-diol-17-one (**5**, 610 mg) in tetrahydrofuran (THF, 10.5 ml) at room temp under nitrogen during 10 min. The whole mixture was stirred at 50 °C (bath temp) for 22 h, cooled and poured into ice-water and, after being salted out, extracted with ether repeatedly. The ether solution was washed with saturated brine, dried over sodium sulfate and evaporated to leave oily residue (2.667 g). The residue was treated with acetic anhydride (Ac_2O, 5.5 ml) and pyridine (Py, 10 ml) at room temp for 3 h, poured onto crushed ice, salted out, and extracted with ether repeatedly. The ether extracts were washed with 2M hydrochloric acid, 5% aqueous sodium bicarbonate and saturated brine, dried and evaporated to give amorphous substance (2.164 g). A suspended mixture of the substance in hexane containing a trace of benzene was passed through an alumina column (Merck, acidic) with a 5 : 1 mixture of hexane and benzene to remove resin, and the whole eluate was then purified by preparative TLC over silica gel (Wakogel, 32 plates) with benzene to give crystalline substance (511 mg), showing a single spot, as a main fraction. This was triturated with acetone-isopropyl ether, collected by filtration to give **6** (409 mg), mp 171.5—172 °C. This was recrystallized twice from the same solvent mixture for analysis: mp 172—173 °C; $[\alpha]_D$ +40.9°; IR, ν_{max} 3600, 3080, 1724, 1640, 1262, 1024, and 891 cm^{-1}; NMR, δ 1.04 (3H, s, 19-C$\underline{H}_3$), 1.15 (3H, d J=6 Hz, 18-C$\underline{H}_3$), 1.97 (3H, s, OCOC$\underline{H}_3$), 4.15 (1H, br W_H=16 Hz, $\underline{H}$ at C_{11}), and 4.65 (3H, br m, 2$\underline{H}$ at C_{20} and $\underline{H}$ at C_3). Found: C, 76.28; H, 9.97%. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89%.

*Hydrogenation of **6**.* A solution of **6** (354 mg) in acetic acid (14 ml) was hydrogenated over pre-reduced Adams platinum (232 mg as $PtO_2 \cdot H_2O$) for 1 h, when 1.02 mol of hydrogen had been consumed. After removal of the catalyst, the solution was evaporated *in vacuo* below 40 °C and then treated with benzene (azeotropization) to give crystalline residue, which was dissolved in chloroform. The chloroform solution, after being worked up as usual, gave crystalline residue (355 mg), which on trituration with acetone afforded a mixture (295 mg) of 17β- and 17α-methyl-5α,12β-etiojervane-3β,11β-diol 3-acetates (**7** and **8**), mp 184—187 °C, showing a single spot. This was recrystallized from acetone-isopropyl ether and had mp 189—190 °C; $[\alpha]_D$+36.1°; IR, ν_{max} 3480, 1704, 1263, and 1031 cm^{-1}; NMR, δ 0.84 (3H, d J=7 Hz, 17-C$\underline{H}_3$), 1.01 (3H, d J=5.5 Hz, 18-C$\underline{H}_3$), 1.04 (3H, s, 19-C$\underline{H}_3$), 1.98 (3H, s, OCOC$\underline{H}_3$), 4.07 (1H, do d J=5 and 8 Hz, $\underline{H}$ at C_{11}), and 4.68 (1H, br m W_H=23 Hz, $\underline{H}$ at C_3). Found: C, 75.86; H, 10.52%. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41%.

*Oxidation of a Mixture of **7** and **8**.* A solution of a mixture of **7** and **8** (the preceding section, 248 mg) in Py (3 ml) was added chromic anhydride (CrO_3, 344 mg) under stirring during 30 min, and the whole mixture was further stirred at room temp for 14 h. The mixture was poured into ice-water (50 ml), extracted with ether (4×50 ml), and the ether solution was washed with 1M hydrochloric acid (3×20 ml), 5% aqueous sodium bicarbonate (2×20 ml) and saturated brine, dried and evaporated to leave crystalline residue (263 mg), showing a single spot. This was triturated with methanol-isopropyl ether to give a mixture of 17β- and 17α-methyl-5α,12β-etiojervan-3β-ol-11-one (**9** and **10**); the first crop (145 mg), mp 137—138 °C, the second (50 mg), mp 134—135 °C, and the third (11 mg), mp 130—131 °C. These were collected and recrystallized from methanol to give a mixture having mp 138.5—139 °C; $[\alpha]_D$ −74.1°; ORD, $[\Phi]_{334}^{trough}$ −9940°, $[\Phi]_{322}^{trough}$ −5510°, $[\Phi]_{293}^{peak}$ +8320°, a=−182.6°: IR, ν_{max} 1732, 1727, 1241, and 1027 cm^{-1}; NMR, δ 0.81 (3H, d J=6 Hz, 17-C$\underline{H}_3$), 0.87 (3H, s, 19-C$\underline{H}_3$), 1.14 (3H, d J=5.5 Hz, 18-C$\underline{H}_3$), 2.01 (3H, s, OCOC$\underline{H}_3$), and 4.68 (1H, br W_H=23 Hz, $\underline{H}$ at C_3). Found: C, 76.26; H, 9.90%. Found: C, 76.26; H, 9.89%.

*17β-Methyl-5α,12α-etiojervan-3β-ol-11-one 3-Acetate (**11**).* A solution of the mixture of **9** and **10** (the preceding section, 186 mg) was treated with 1M sodium methoxide in refluxing methanol (20 ml) for 2 h under nitrogen. After being cooled, the solution was evaporated, poured into water (30 ml) and extracted with chloroform repeatedly. The chloroform solution was worked up as usual to give crystalline residue (188 mg), which was treated with Ac_2O (1 ml) and Py (2 ml) at room temp for 3 h. The product (196 mg), showing two spots on TLC, was separated by preparative TLC with a 2 : 3 mixture of chloroform and benzene into two fractions; the starting crystalline mixture (168 mg) with larger R_f value and a new crystalline substance (17 mg) with smaller R_f. These treatments (epimerization, acetylation and subsequent purification by TLC) were repeated three times for the recovered starting mixture and led to isolation of 56 mg of the new material with 125 mg of the recovered, unchanged material. The latter had mp 127—129 °C on recrystallization from methanol-isopropyl ether and amounted to 116 mg. The former was recrystallized from isopropyl ether to give **11** (31 mg), mp 163—164 °C. This was recrystallized from the same solvent for analysis: mp 163.5—164 °C; $[\alpha]_D$ −18.2°; ORD, $[\Phi]_{334}^{trough}$ −4350°, $[\Phi]_{323}^{trough}$ −2210°, $[\Phi]_{292}^{peak}$ +3350°, a=−77°; IR, ν_{max} 1726, 1239, 1036, and 1027 cm^{-1}; NMR, δ 0.74 (3H, d J=7 Hz, 17-

CH_3), 0.88 (3H, d J=5 Hz, 18-C$\underline{H}_3$), 0.90 (3H, s, 19-C$\underline{H}_3$), 1.99 (3H, s, OCOC$\underline{H}_3$), and 4.69 (1H, br W_H=23 Hz, $\underline{H}$ at C_3). Found: C, 76.32; H, 9.92%. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89%.

*17β-Methyl-5α,12β-etiojervan-3β-ol-11-one 3-Acetate (**9**).* A solution of compound **11** (46 mg) was refluxed with 1M sodium methoxide in methanol (7 ml) for 2 h under nitrogen, cooled and then evaporated to leave oily residue. The residue was mixed with water (30 ml) and extracted with chloroform. The chloroform extracts gave a crystalline mixture (36.5 mg), which was treated with Ac_2O (0.5 ml) and Py (0.5 ml) at room temp for 3 h and then worked up as usual to give a crystalline acetate mixture (37 mg), showing two spots. This was separated by preparative TLC over silica gel (3 plates) with a 3 : 2 mixture of benzene and chloroform into two fractions; one (29 mg) with larger R_f value and the other (5 mg) with smaller R_f. The latter had mp 155—158 °C on trituration with isopropyl ether, amounted to 2.5 mg, and was identified as the starting material (**11**). The former was recrystallized from isopropyl ether–methanol to give **9** (21 mg), mp 138.5—139 °C. This was recrystallized from the same solvent mixture for analysis: mp 140—141 °C; $[\alpha]_D$ −80.2°; ORD, $[\Phi]_{334}^{trough}$ −8150°, $[\Phi]_{324}^{trough}$ −4450°, $[\Phi]_{292}^{peak}$ −7600°, a=−156.5°; IR, ν_{max} 1732, 1727, 1241, and 1027 cm^{-1}; NMR, δ 0.81 (3H, d J=5.5 Hz, 17-C$\underline{H}_3$), 0.86 (3H, s, 19-C$\underline{H}_3$), 1.14 (3H, d J=5.5 Hz, 18-C$\underline{H}_3$), 2.02 (3H, s, OCOC$\underline{H}_3$), and 4.67 (1H, br W_H=28 Hz, $\underline{H}$ at C_3). Found: C, 76.13; H, 9.95%. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89%.

*5α,12β-Etiojervan-3β-ol-11,17-dione 17-Ethylene Acetal (**13**).* A solution of 12β-etiojerv-5-en-3β-ol-11,17-dione 17-ethylene acetal (**12**, 3.56 g) in acetic acid (220 mg) was hydrogenated over Adams platinum (1.78 g) at room temp for 1.5 h, when 340 ml (1.21 mol) of hydrogen had been consumed. The reaction mixture was worked up as usual to give oily residue, which crystallized on trituration with isopropyl ether, had mp 162—164 °C and amounted to 3.33 g. This was recrystallized from isopropyl ether and then from acetone–isopropyl ether to give **13**, mp 172—174 °C; $[\alpha]_D$ −47°; ORD, $[\Phi]_{334}^{trough}$ −7310°, $[\Phi]_{278}^{peak}$ +6960°, a=−143°, IR, ν_{max} 3480, 3350, 1731, 1099, 1077, 1064, and 1030 cm^{-1}; NMR δ 0.83 (3H, s, 19-C$\underline{H}_3$), 1.16 (3H, d J=6.5 Hz, 18-C$\underline{H}_3$), 3.65 (1H, br, $\underline{H}$ at C_3), and 3.91 (4H, s, OC$\underline{H}_2$C$\underline{H}_2$O). Found: C, 71.91; H, 9.21%. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26%.

*5α,12β-Etiojervan-3β-ol-11,17-dione (**14**).* A solution of compound **13** (756 mg) in acetone (62 ml) and water (10 ml) was refluxed with *p*-toluenesulfonic acid (150 mg) for 4 hr. The solution was made neutral with 5% aqueous sodium bicarbonate, evaporated and extracted with chloroform. The chloroform solution was worked up as usual to give oily residue, which crystallized on trituration with acetone, had mp 159—162 °C, and amounted to 516 mg. This was recrystallized from acetone–isopropyl ether to give **14**, mp 169—172 °C; $[\alpha]_D$ −81°; ORD, $[\Phi]_{334}^{trough}$ −9980°, $[\Phi]_{332}^{trough}$ −8070°, $[\Phi]_{280}^{peak}$ +11430°, a=−214.1°; Mass, *m/e* 304 (M^+); IR, ν_{max} 3470, 1732, 1712, 1694, and 1033 cm^{-1}; NMR, δ 0.83 (3H, s, 19-C$\underline{H}_3$), 1.29 (3H, d J=6.5 Hz, 18-C$\underline{H}_3$), and 3.51 (1H, br, $\underline{H}$ at C_3).

*Reaction of **14** with Isopropylmagnesium Bromide.* To a mixture of dried magnesium ribbons (10.0 g) in dry ether (450 ml) was added dropwise isopropyl bromide (57.6 g) during 40 min, and the mixture was further stirred at room temp for 40 min. To the cooled, suspended mixture was added compound **13** (1.10 g) in ether containing a small amount of THF under stirring, and the whole mixture was refluxed for 4.5 h under nitrogen. After addition of saturated aqueous ammonium chloride (80 ml), the ether layer was separated and the aqueous layer was extracted with ether repeatedly. The ether solutions were combined and then worked up as usual to give oily residue (1.18 g), which was separated by preparative TLC over silica gel (45 plates) with a 1 : 1 mixture of benzene and ethyl acetate into four fractions, named fractions A—D in the order of R_f value. Fraction D (448 mg), the least mobile fraction showing a single spot, was crystallized on trituration with acetone–isopropyl ether and then recrystallized from the same solvent mixture to give 5α,12β-etiojervane-3β,11β,17α-triol (**15**, 189 mg), mp 180—182 °C; IR, ν_{max} 3380, 1098, 1058, 1023, and 970 cm^{-1}. This was converted into the diacetyl derivative (**15a**), amorphous; $[\alpha]_D$ 0.0°; Mass, *m/e* 332 (M^+−60), 314, 272, and 254; NMR, δ 1.04 (3H?, d J=6 Hz, 18-C$\underline{H}_3$), 1.06 (3H, s, 19-C$\underline{H}_3$), 2.00 and 2.03 (total 6H, each s, 2O-COC$\underline{H}_3$), 4.17 (1H, br W_H=15 Hz, $\underline{H}$ at C_{11}), and 4.65 (2H, br m, 2$\underline{H}$ at C_3 and C_{17}). Fraction C (455 mg), showing a single spot, crystallized on trituration with acetone–isopropyl ether and was then recrystallized from the same solvent mixture to yield **16** (204 mg), mp 168—170 °C; $[\alpha]_D$ −4.0°; ORD, $[\Phi]_{318}^{trough}$ −3300°, $[\Phi]_{276}^{peak}$ +5510°, a=−88°; Mass, m/e 306 (M^+); IR, ν_{max} 3560, 3440, 1700, 1100, 1053, and 864 cm^{-1}; NMR, δ 1.06 (3H, s, 19-C$\underline{H}_3$), 1.14 (3H?, d J=6.5 Hz, 18-C$\underline{H}_3$), 3.58 (1H, br W_H=24 Hz, $\underline{H}$ at C_3), and 4.18 (1H, br W_H=13 Hz, $\underline{H}$ at C_{11}). Fraction A (29 mg), the most mobile fraction, was identified as the starting material (IR and TLC). Fraction B (335 mg) were further separated by repeated preparative TLC over silica gel (18 plates), 8 : 1, 4 : 1 and 2 : 1 mixtures of benzene and ether being used successively as solvents, into several fractions. One (55 mg) of the two major fractions crystallized on trituration with acetone–isopropyl ether and was recrystallized from the same solvent mixture to give **17** (26 mg), mp 136—138 °C; $[\alpha]_D$ −11.7°; ORD, $[\Phi]_{327}^{trough}$ −9590°, $[\Phi]_{287}^{peak}$ +5500°, a=−151°; Mass, *m/e* 348 (M^+); IR, ν_{max} 3460, 1732, 1042, and 972 cm^{-1}; NMR, δ 0.83 (3H, s, 19-C$\underline{H}_3$), 0.92 [6H?, d J=6.5 Hz, CH(C$\underline{H}_3$)$_2$], 1.21 (3H?, d J=7 Hz, 18-C$\underline{H}_3$), and 3.65 (1H, br m, $\underline{H}$ at C_3). The other (127 mg) of the two major fractions was crystallized and recrystallized from acetone–isopropyl ether to yield **18** (60 mg), mp 193—195 °C; $[\alpha]_D$ −5.6°; ORD, $[\Phi]_{332}^{trough}$ −8330°, $[\Phi]_{290}^{peak}$ +7370°, a=−157°; Mass *m/e* 348 (M^+); IR, ν_{max} 3570, 1733, 1050, and 988 cm^{-1}; NMR, δ 0.84 (3H, s, 19-C$\underline{H}_3$), 0.93 [6H, d J=6 Hz, CH(C$\underline{H}_3$)$_2$], 1.23 (3H?, d J=6.5 Hz, 18-C$\underline{H}_3$), and 3.58 (1H, br m, $\underline{H}$ at C_3).

Equilibration Experiments. The studies were carried out for all the compounds listed in Table 1. Each reactant was treated with 1M sodium methoxide in methanol under reflux for several hours, and the product, after acetylation when necessary, was separated by preparative TLC, as had been illustrated in the sections of the preparation of compounds **9** and **11**. The equlibrium ratio was determined by measuring the amounts of isolated products and the result is summarized in Table 1. Each epimerzation experiment is not described here, and only new compounds, obtained during these studies, are characterized in the following.

12β-Etiojerv-5-ene-3β,17α-diol-11-one. Mp 212.5—213 °C (from acetone); $[\alpha]_D$ −158.2° (CH_3OH); ORD, $[\Phi]_{333}^{trough}$ −10990°, $[\Phi]_{321}^{trough}$ −7360°, $[\Phi]_{291}^{peak}$ +5710°, a=−167°; Found: C, 75.00; H, 9.31%. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27%.

12α-Etiojerv-5-ene-3β,17β-diol-11-one (XIB). Mp 237—239 °C (from methanol). The 3,17-diacetate. Mp 140—141 °C (from methanol); ORD, $[\Phi]_{333}^{trough}$ −3750°, $[\Phi]_{322}^{trough}$ −5520°, $[\Phi]_{294}^{peak}$ +1290°, a=−68.1°; IR, ν_{max} 1732, 1241, and 1056 cm^{-1}; NMR, δ 0.93 (3H, d J=7 Hz, 18-C$\underline{H}_3$),

1.12 (3H?, s, 19-C$\underline{H}_3$), 2.06 (6H, s, 2OCOC$\underline{H}_3$), and 4.83 (2H, br W_H=21 Hz, 2$\underline{H}$ at C_3 and C_{17}), and 5.50 (1H, br s, $\underline{H}$ at C_6).

17β-Ethyl-12α-etiojervane-3β,17α-diol-11-one 3-Acetate (XVIIIB) Mp 149—150 °C (from acetone-isopropyl ether); $[\alpha]_D$ −60°; ORD, $[\Phi]_{332}^{trough}$ −5290°, $[\Phi]_{291}^{peak}$ +1840°, a=−71.3°; IR, ν_{max} 3546, 1725, 1258, and 1032 cm^{-1}; NMR, δ 0.71 (3H, d J=7.5 Hz, 18-C$\underline{H}_3$), 0.91 (3H, t J=7 Hz, 21-C$\underline{H}_3$), 1.11 (3H?, s, 19-C$\underline{H}_3$), 2.02 (3H, s, OCOC$\underline{H}_3$), 4.58 (1H, br m, $\underline{H}$ at C_3), and 5.42 (1H, br s, $\underline{H}$ at C_6). Found: C, 73.71; H, 9.29%. Calcd for $C_{23}H_{34}O_4$; C, 73.76; H, 9.15%.

17β-Isopropyl-5α,12α-etiojervane-3β,17α-diol-11-one (XXB). Amorphous, $[\alpha]_D$ −5.6°; ORD, $[\Phi]_{334}^{trough}$ −2330°, $[\Phi]_{296}^{peak}$ +4640°, a=−69.7°; IR ($CHCl_3$), ν_{max} 3500, 1730, and 1043 cm^{-1}; Mass, *m/e* 348 (M^+); NMR, δ 0.80 (3H, d J= 7 Hz, 18-C$\underline{H}_3$), 0.89 (3H?, s, 19-C$\underline{H}_3$), and 3.54 (1H, br m, $\underline{H}$ at C_3).

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