12,13-Epoxy-*C*-nor-*D*-homosteroids. IV.[1] The Reaction of 11-Oxygenated 17α-Acetyl-12α,13α-epoxyetiojervanes with Boron Trifluoride Etherate[2]

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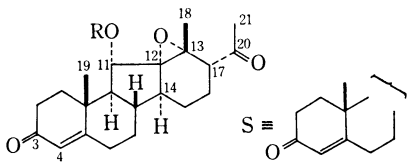
(Received July 10, 1976)

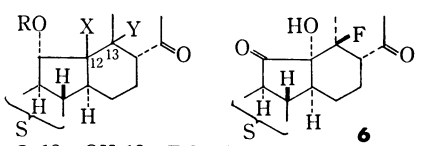
The titled compounds were treated with boron trifluoride etherate in benzene at room temperature. 11α-Hydroxy-12α,13α-epoxide (**1**) underwent rapid cleavage of the epoxy ring at both C_{13} and C_{12} to give 11α-hydroxy-13β-fluoro-12α-alcohol (**2**), 13α-hydroxy-12βH-11-ketone (**3**), 17-deacetyl-Δ^{12}-11-ketone (**4**), and an acetophenone derivative (**5**) in comparative yields. The same acid treatment of 11α-acetoxy-12α,13α-epoxide (**1a**) yielded 11α-acetoxy-13β-fluoro-12α-alcohol (**2a**) as a single isolable product, while that of 11-unsubstituted 12α,13α-epoxide (**16**) afforded 12β-fluoro-13α-alcohol (**17**) besides **5**, a major product. Evidently, compounds **2a** and **17** are products formed by the epoxy ring opening at C_{13} and C_{12}, respectively. Interestingly, compounds **2** and **2a**, when treated with bases, produced a rearranged 13α-pregnane derivative (**12**) *via* 11α,12α-dihydroxy-$\Delta^{13(17)}$-20-ketone (**10**), in good yields. On the other hand, the epoxy cleavage of 11-oxo-12α,13α-epoxide (**13**) led to predominant formation of rearranged products, bicyclo[3.3.1]nonane-2,9-dione and hydrooxepin derivatives (**14** and **15**). It is emphasized that the epoxy cleavage reactions proceeded more slowly and took place at C_{13} rather than at C_{12} with increase of electronegativity of the 11-substituents.

In the previous paper[3] we reported the synthesis and stereochemistry of 17α-acetyl-12,13-epoxyetiojervanes. As a continuing study aimed at the preparation of biologically active normal steroids from jervine, we have examined reactions of several 11-oxygenated 17α-acetyl-12α,13α-epoxyetiojervanes with boron trifluoride etherate, keeping in mind the Coxon and coworkers' result, a low yield of formation of hecogenin acetate by the acid treatment of the corresponding 12α,13α-epoxy-*C*-nor-*D*-homospirostan.[4] Contrary to the expectation, the reactions have not led to the desirable rearrangement but have resulted in formation of many compounds including interesting rearranged products such as bicyclo[3.3.1]nonane-2,9-dione and hydrooxepin derivatives.[5]

Treatment of 17α-acetyl-12α,13α-epoxyetiojerv-4-en-11α-ol-3-one (**1**), the most readily available 12,13-epoxides, with boron trifluoride etherate in benzene at room temperature for 30 s afforded a multi-component mixture, from which four compounds (**2**—**5**) were isolated after careful chromatography in 20, 10, 10, and 11% yields, respectively. The major product (**2**), mp 153—155 °C, was assigned structure **2** on the following evidence. The mass [*m/e* 364 (M^+), 346, 345, 344, 326 (M^+-HF-H_2O), and 301 ($M^+-HF-COCH_3$)] and NMR spectra [δ 2.37 (3H, s, 21-C$\underline{H}_3$), 3.34 (2H, br W_H=28 Hz, $\underline{H}$ at C_{17} and O$\underline{H}$) and 5.96 (1H, s, O$\underline{H}$)] revealed the presence of one fluorine atom, one acetyl (at C_{17}) and two hydroxyl groups. These spectra, as coupled with the UV [λ_{max} 239 nm (ε 10000)] and IR spectral data (ν_{max} 1703 cm^{-1}), indicated that the A ring and 17-side chain remained unchanged. The NMR spectrum also exhibited two three-proton singlets due to the 19- and 18-methyl protons at δ 1.26 and 1.50, a one-proton singlet ($\underline{H}$ at C_4) at δ 5.76 and also one doublet (J=8 Hz) due to a proton on the carbon atom (at C_{11}) bearing the hydroxyl group at δ 4.02. Compound **2**, when acetylated with acetic anhydride at room temperature and also oxidized with the Jones reagent, was converted into the corresponding monoacetate and hydroxy ketone (**2a** and **6**), mp 140—142 and 188—190 °C, in 95 and 85% yields, respectively. The latter (**6**) displayed a strong absorption maximum at 1753 cm^{-1} in the IR spectrum, proving that the secondary hydroxyl group in question existed in a five-membered C ring. These facts were consistent with the assigned formula (**2**) and also with an alternate formula (**2'**). Compound **2** was then treated with periodic acid in aqueous dioxane at room temperature for 18 h, when one mole of the acid had been consumed. The resulting single product, mp 128—130 °C, isolated in a 75% yield, was formulated as lactol (**7**) rather than keto aldehyde (**8**) on the spectral data (Exp). Moreover, compound **2** readily formed the corresponding acetonide (**9**), oil, by treatment with acetone and acid ($HClO_4$) at room temperature in a quantitative yield. All these results indicate that the compound is represented by structure **2** with a *cis*-glycol partial formula, excluding the alternate structure (**2'**), and also establish the previously assigned 12α,13α-epoxy configuration to the starting epoxide (**1**).

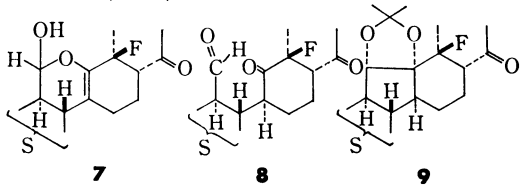


1 R=H
1a R=Ac



6

2 12α-OH,13β-F,R=H
2a 12α-OH,13β-F,R=Ac
2' 12β-OH,13α-F

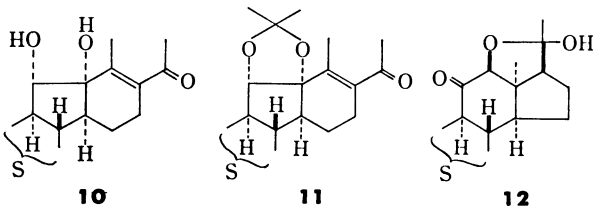


7 **8** **9**

The configuration of the fluorine atom at C_{13} was deduced from analogous examples[4,6] as well as consideration of the 11-carbonyl frequency of hydroxy ketone (**6**) as discussed below. The relevant absorption maximum was observed at a higher wave number (ν_{max} 1753 cm^{-1}) than that (ν_{max} *ca.* 1735 cm^{-1}) of usual 11-oxo-12α-etiojervanes without any substituent at C_{12}. The Dreiding model indicates that the D ring of **6** would probably adopt a half-chair or a twist-boat (bowsprit and flagpole at C_{14} and C_{17}) conformation with both the 17α-acetyl and 13β-fluoro substituents pseudo-equatorial. If the D ring assumes another twist-boat form (bowsprit-flagpole at C_{13} and C_{15}), the pseudo-equatorial 17α-acetyl group would readily form hydrogen-bonding with the 12α-hydroxyl group and show the absorption maximum at a lower wave number than at the observed (ν_{max} 1715 cm^{-1}). With either one of the afore-mentioned conformations with the fluorine atom pseudo-equatorial, the carbon-fluorine and 11-carbonyl bonds were located to be 1,3-diaxial-like and hence the carbonyl absorption would be susceptible to hypsochromic effect owing to the nearby dipole (C–F bond). Furthermore the 12α-hydroxyl group was disposed almost perpendicular to the 11-carbonyl bond and would exert no influence on the frequency in question. This presumption is reasonable and supports the above β-assignment to the fluorine atom. Here we emphasize that fluorohydrin (**2**) would result from a nucleophilic attack of a fluoride anion, probably contained in the reagent,[6b] to the epoxy ring at C_{13}.

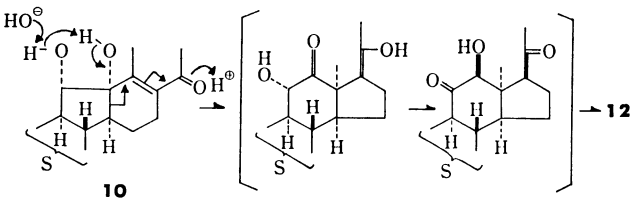
11α-Hydroxy-fluorohydrin (**2**) was then treated with potassium carbonate in aqueous methanol at room temperature for 1 h. Contrary to the expectation that the starting epoxide (**1**) would be regenerated, compound **2** underwent dehydrofluorination to give $\Delta^{13(17)}$-20-ketone (**10**), mp 173—174 °C, in a quantitative yield, which on treatment with acetone and acid ($HClO_4$) formed the corresponding acetonide (**11**), oil, in a good yield. The latter (**11**) was also obtained by treatment of acetonide **9** with potassium carbonate under the same conditions as mentioned above. In accordance with the assigned structures, compound **10** exhibited an absorption maximum at 245 nm (ε 17000) and two three-proton singlets due to the 19- and 18-methyl protons at δ 1.20 and 1.87 in the UV and NMR spectra, and compound **11** showed absorption maxima at 1383 and 1372 cm^{-1} and two three-proton singlets due to the acetonide methyl protons at δ 1.50 and 1.56 in the IR and NMR spectra. However, prolonged treatment of fluorohydrin **2** or the α,β-unsaturated ketone (**10**) with the base (K_2CO_3) afforded a new compound (**12**), mp 164—166 °C, in low yields (7—28%) along with the unsaturated ketone (**10**). This new nompound could be obtained from the starting fluorohydrin (**2**), $\Delta^{13(17)}$-20-ketone (**10**) and also 11-acetoxy-fluorohydrin (**2a**) by treatment with potassium hydroxide in ethanol at room temperature for *ca.* 2 h in quantitative yields.

Compound **12** had the same molecular formula $C_{21}H_{28}O_4$ as the α,β-unsaturated ketone (**10**). The mass spectrum suggested the presence of hydroxyl and acetyl groups at *m/e* 344 (M^+), 326 (M^+-H_2O), 311,



10 **11** **12**

and 301 (base, M^+-COCH_3). However, the NMR spectrum exhibited three three-proton singlets at δ 1.25, 1.37, and 1.60, the former two singlets being assignable to the 19- and probably 18-methyl protons but the last (δ 1.60) being not attributed to the acetyl methyl protons. This singlet would be ascribed to methyl protons of a partial formula CH_3–(C)(OH)–O–,[7] in which (C) denotes a quarternary carbon. The IR spectrum displayed three absorption maxima at 1714, 1665, and 1614 cm^{-1} in the double bond region and also due to (a) hydroxyl group(s) at 3600 and 3440 cm^{-1}. The above two absorptions (1665 and 1614 cm^{-1}) revealed the existence of the Δ^4-3-carbonyl system, which was supported by the UV [λ_{max} 237 nm (ε 10000)] and NMR spectra [δ 5.69 (1H, s, H at C_4)]. Hence, the remaining oxygen atom would have to constitute a carbonyl group (ν_{max} 1714 cm^{-1}) on a straight chain or a six-membered ring. Moreover, a one-proton singlet was observed at a low field (δ 4.33), which was ascribed to a proton on the carbon atom flanked by a carbonyl group and an oxygen atom. These facts, combined with the chemical shift (δ 1.25 or 1.37) of the 19-methyl protons, indicate that the compound is represented most favorably by the 13α-pregnane formula (**12**) with an oxo group at C_{11} and a hemi-acetal group formed by the 12-hydroxyl and 17-acetyl groups. Presumably, formation of the 13α-pregnane (**12**) (Scheme 1) would take place *via* (i) intramolecular Michael addition of a carbanion at C_{14}, generated by cleavage of the bond at C_{12}–C_{14}, into a partially positive β-carbon at C_{13} of the α,β-unsaturated carbonyl system ($\Delta^{13(17)}$-20-one) and (ii) subsequent tautomerization at C_{11} and C_{12} as well as epimerization at C_{17} of the resulting 13α-pregnane derivative (iii) followed by conversion into the hemi-acetal structure.

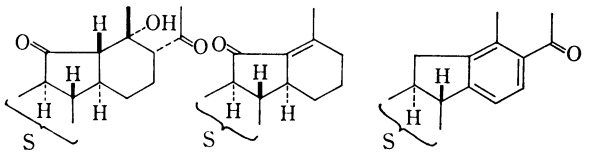


10 → **12**

Scheme 1. Pathway for formation of 13α-pregnane (**12**).

The second product (**3**) mp 175.0—176.5 °C, had the same molecular formula $C_{21}H_{28}O_4$ as the starting epoxide (**1**) and was formulated as structure **3**. In good accord with the structure, the IR spectrum revealed the presence of five-membered carbonyl and hydroxyl groups at 1732 and 3480 cm^{-1}, and the NMR spectrum showed two three-proton singlets at δ 1.20 and 1.58, which could be attributed to the 19- and 18-methyl protons. These chemical shifts indicate that the hydroxyl group is attached to the carbon at C_{13},

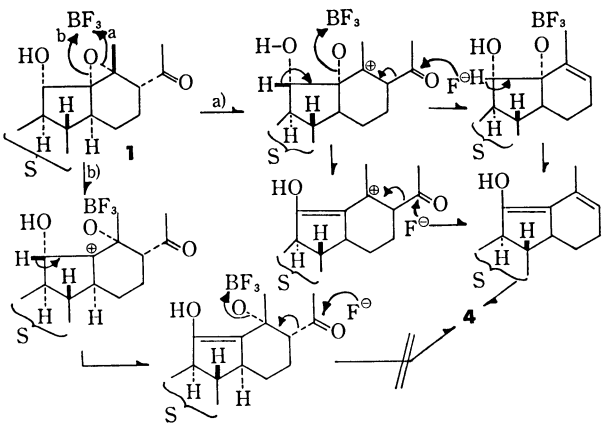
and also that the C and D rings are *trans*-fused (12βH) (19-CH_3, δ_{obsd} 1.20; δ_{calc} 1.21 for 12βH, and 1.26 for 12αH).[8] In view of the fact that the corresponding 12-epimer (12αH) was not isolated, compound **3** would probably be formed by cleavage of the epoxide ring at C_{12} with concomitant hydride shift of the β-oriented hydrogen at C_{11} to the carbon atom at C_{12}.



3 **4** **5**

The third product (**4**), mp 112—115 °C, had a molecular formula of $C_{19}H_{24}O_2$, indicative of elimination of a $C_2H_4O_2$ (CH_3CO+OH) moiety from the starting epoxide (**1**) and was assigned formula **4**. Removal of the 17-acetyl group was revealed by the absence of a three-proton singlet near δ 2.3 in the NMR spectrum. The UV and IR specta [λ_{max} 247 nm (ε 13000), and ν_{max} 1708 and 1639 cm^{-1}] showed the presence of a new α,β-unsaturated carbonyl group (Δ^{12}-11-one) besides the Δ^4-3-carbonyl system (ν_{max} 1668 and 1639 cm^{-1}). This was confirmed by appearance of two three-proton singlets due to 19- and 18-methyl protons at δ 1.24 and 2.15 as well as a one-proton singlet (H at C_4) at δ 5.77 in the NMR spectrum. This compound (**4**) was also produced by treatment of hydroxy ketone (**3**) with base (KOH) in refluxing methanol though in a low yield. The transformation of hydroxy ketone (**3**) into Δ^{12}-11-ketone (**4**) evidently takes place by retro-aldol reaction, initiated by attack of hydroxide ion to the acetyl carbonyl group, and subsequent migration of the resulting double bond (at C_{13}–C_{17}). On the other hand, the α,β-unsaturated ketone (**4**) was *not* obtained by the boron trifluoride treatment (including work-up) of hydroxy ketone (**3**) under the same conditions as those for formation of the compround (**4**) from epoxide **1**. Probably, formation of compound **4** would be formed by initial cleavage of the epoxy ring at C_{13} followed by degradation of the resulting cationic glycol *via* several pathways as shown in Scheme 2.

The fourth product (**5**), mp 143—145 °C, was assigned reasonably a substituted acetophenone structure



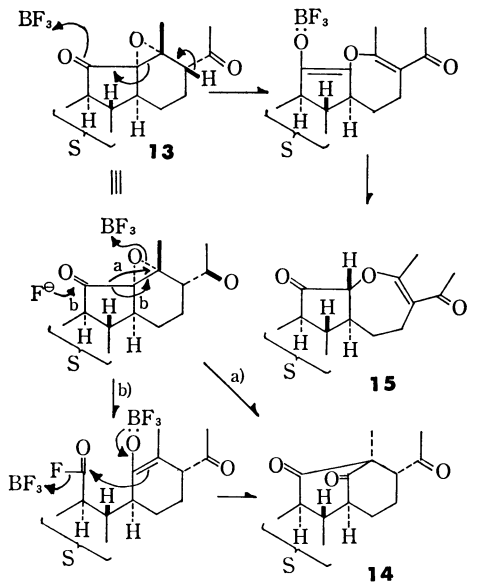
Scheme 2. Pathway for formation of Δ^{12}-11-ketone (**4**).

(**5**) on the basis of the spectral data (Exp). We only mention that the chemical shift (δ 1.32) of 19-methyl protons was in good accord with that of the corresponding veratramine derivatives.[9]

11α-Acetoxy-12α,13α-epoxide (**1a**), 11-acetate of 11α-alcohol **1**, was similarly treated with boron trifluoride etherate in benzene at room temperature. The reaction proceeded slowly and afforded fluorohydrin, as an only isolable product in a 60% yield, after 15 min, when the starting epoxide (**1a**) was recovered unchanged in a 10% yield. The sole product, mp 143—145 °C, was identified as 11-acetate (**2a**) of the 11α-hydroxy-fluorohydrin (**2**) as described before. It should be noted that no product, considered to be formed by initial cleavage of the epoxy ring at C_{12}, was isolated, when the starting epoxide passed from 11α-alcohol (**1**) to 11α-acetate (**1a**).

11-Oxo-12α,13α-epoxide (**13**) was then treated with excess of the Lewis acid under almost the same conditions as mentioned above. The epoxide cleavage proceeded only slowly and, after 140 min, gave a complex mixture, from which three compounds (**6**, **14**, and **15**) were isolated by column chromatogrphy in 25, 20, and 20% yields, respectively. The first product, mp 190.5—191.5 °C, was identified as 11-oxo-fluorohydrin (**6**). The second product (**14**), mp 227—228 °C, had the same molecular formula $C_{21}H_{26}O_4$ as the starting epoxide (**13**). The mass [*m/e* 342 (M^+) and 299(M^+-COCH_3)], UV [λ_{max} 234 nm (ε 14000)], IR [ν_{max} 1667 and 1619 cm^{-1}], and NMR spectra [δ 2.19 (3H, s, 21-$C\underline{H}_3$) and 5.72 (1H, s, H at C_4)] indicated that the 17-acetyl and Δ^4-3-carbonyl groups were left unchanged. In view of the absence of a hydroxyl group (no absorption near 3400 cm^{-1}), the remaining two oxygen atoms would have to exist as two carbonyl groups, which were observed as two absorption bands at 1742 and 1716 cm^{-1}, the latter being overlapping with that of the acetyl carbonyl group. The mass spectrum [*m/e* 271 (M^+-CH_3CO-CO)] suggested that one of the two carbonyl groups would be readily removable. The NMR spectrum also exhibited two three-proton singlets due to the 19- and 18-methyl protons at relatively low fields (δ 1.07 and 1.48) as well as a broad one-proton signal (W_H=8 Hz) at δ 3.54 besides that (20 Hz) due to the 17β-proton at δ 3.18. The signal (δ 3.54) would be attributed to a proton on the carbon atom (C_{14}) adjacent to the carbonyl group. All these spectral data revealed the presence of a bicyclo[3.3.1]nonane-2,9-dione[10] moiety and hence the compound was formulated most favorably as structure **14**.

The third product, mp 198—200 °C, also had the same molecular formula $C_{21}H_{26}O_4$ as the starting epoxide (**13**) and was assigned formual **15** on the basis of the following spectral data. The UV spectrum [λ_{max} 245 nm (ε 14000)] showed that an α,β-unsaturated carbonyl or an analogous system was newly formed besides the original Δ^4-3-carbonyl group [δ 5.78 (1H, s, H at C_4)]. The mass spectrum, unlike those of other 17-acetyletiojervanes, displayed a fragmentation peak caused by removal of a CH_2CO moiety at *m/e* 300 instead of that (M^+-CH_3CO) at *m/e* 299, but the NMR spectrum still exhibited a six-proton

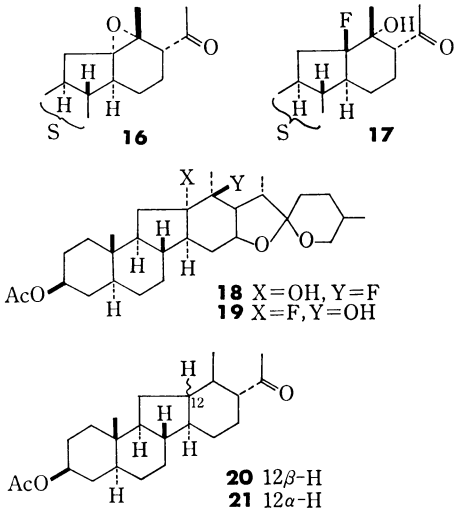


Scheme 3. Pathway for formation of compounds **14** and **15**.

singlet at δ 2.10, which was assignable to the 18-methyl and acetyl-methyl protons. The IR spectrum revealed the presence of two carbonyl groups, besides the Δ^4-3-carbonyl group (ν_{max} 1674 and 1618 cm^{-1}), at higher wave numbers (ν_{max} 1750 and 1714 cm^{-1}) as compared with those of five-membered carbonyl and 17-acetyl groups of usual 17-acetyl-11-oxoetiojervanes (ν_{max} *ca.*, 1735 and 1705 cm^{-1}). These carbonyl absorptions, coupled with an absorption due to a vinyl ether at 1044 cm^{-1}, were ascribed to α-alkoxy five-membered carbonyl and vinylogous ester carbonyl groups, respectively. Moreover, a broad one-proton doublet (J =10 Hz) was observed at δ 5.42 along with a 19-methyl proton singlet at δ 1.23. The relevant low field peak could be assigned to a proton on the carbon atom flanked by a carbonyl group and an oxygen atom. These results indicated the existence of a partial formula O=C(at C_{11})–CH–O–C(CH_3)=C–C(=O)CH_3, which led to assignment of formula **15** to the compound.

The formation of these two compounds (**14** and **15**) was rationalized as described in Scheme 3.[11] While we have analogous precedents[12] regarding the novel elimination-rearrangement involving the C–C bond cleavage of an epoxide ring of the 11-oxo-12,13-epoxide (**13**) to give the seven-membered ether ring compound (**15**), the transformation of epoxide **13** into compound **14**, a rearrangement of α,β-epoxy-carbonyl system into a bicyclo[3.3.1]nonane-2,9-dione system under acidic conditions, is most noteworthy and would probably be the first example as for such rearrangements. It should be emphasized that all these products again resulted from cleavage of the epoxide ring at C_{13}, apart from that whether the respective reactions are concerted or step-wise.

The same treatment of 11-unsubstituted 12α,13α-epoxide (**16**) only for 30 s produced two compounds (**5** and **17**) in 60 and 12% yields, the starting epoxide (**16**) being not detected on TLC. The major product, mp 141—143 °C, was identified as acetophenone (**5**), and would be formed by cleavage of the epoxide ring at C_{13} and/or C_{12} followed by dehydration and dehydrogenation. The minor product (**17**) had a molecular formula of $C_{21}H_{29}O_3F$ and was assigned 12β-fluoro-13α-hydroxy structure (**17**) on the basis of the following facts. (i) The molecular formula and spectral data indicated product **17** to be a fluorohydrin formed by simple cleavage of the epoxy ring. (ii) The product (**17**) underwent no dehydrofluorination, the starting material being recovered unchanged, under the same basic (K_2CO_3) conditions as those under which 13β-fluoro-12α-alcohols (**2** and **2a**) were readily converted into $\Delta^{13(17)}$-20-ketone (**10**). (iii) 13β-Fluoro-12α-hydroxy-etiojervanes and *C*-nor-*D*-homospirostan[4] (**2**, **2a**, **6**, and **18**) exhibited signals due to the 18-methyl protons at δ 1.50, 1.58, 1.47, and 1.58, respectively, which 12α-fluoro-13β-hydroxy-*C*-nor-*D*-homospirostan[4] (**19**) and the product in question displayed the corresponding signals at higher fields, δ 1.27 and 1.29. Moreover, compounds **2**, **2a**, and **6** showed signals due to the protons at C_{17} near δ 3.30 (W_H= 24—20 Hz), δ 3.34, 3.30, and 3.27, respectively, while compound **17** displayed the 17-proton at δ 2.89 (W_H= 18 Hz). All these facts revealed that the substituent at C_{13} in product **17** was not a fluorine atom but a hydroxyl group, and hence the product (**17**) is represented favorably by structure **17**. This structure was also supported by the ORD curves; **17**, a=+90°; 17α-acetyl-12β-etiojervan-3β-ol 3-acetate[13] and its 12α-epimer[14] (**20** and **21**), a=+53° and +34°.[15] Compound **17** evidently resulted from the epoxide ring cleavage at C_{12}. In summary, we again emphasize that the epoxide opening reactions proceeded more slowly and took place at C_{13} rather than at C_{12} with increase of electronegativity of the 11-substituents.



Experimental

All the melting points were uncorrected. The homogenity of each compound was always checked by TLC on silica gel (Wakogel B-5) with various solvent systems, and the spots were developed with cerium(IV) sulfate in dil sulfuric acid and/or iodine. The optical rotations, UV, and IR spectra

were measured in chloroform, ethanol, and chloroform, respectively, unless otherwise stated. The NMR spectra were obtained in deuterochloroform at 100 MHz, and the chemical shifts were given in δ-values, TMS being used as an internal reference. The abbreviations "s, d, and br" in the NMR spectra denote "singlet, doublet, and broad", respectively.

*Treatment of 17α-Acetyl-12α,13α-epoxy-11α-hydroxyetiojerv-4-en-3-one (**1**) with Boron Trifluoride Etherate (BF_3).* A solution of **1** (900 mg) in anhydrous benzene (93 ml) was stirred with BF_3 (2 ml), freshly distilled over calcium hydride, at room temperature (temp.) for 30 s. The solution was mixed with ether (50 ml), washed with 5% aqueous sodium hydrogencarbonate ($NaHCO_3$) and water, dried over anhydrous sodium sulfate, and evaporated to leave amorphous residue (877 mg), which was chromatographed over silica gel (Merck 70—230 mesh, 26 g) with mixtures of benzene and ether. Benzene–ether (5 : 1) eluates gave etiojerva-4,12-diene-3,11-dione (**4**, 74 mg), mp 112—115 °C (from hexane–methanol) and $[\alpha]_D$ +97°; MS, *m/e* 284 (M^+) and 269; UV, IR, and NMR, in the text. Found: C, 79.98; H, 8.58%. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51%.

Benzene–ether (3 : 1) eluates gave 17-acetyletiojerva-4,12,14,16-tetraen-3-one (**5**, 92 mg), mp 143—145 °C (from hexane–acetone) and $[\alpha]_D$ +148°; MS, *m/e* 308 (M^+), 293, and 265; UV, λ_{max} 295 nm (ε 4000) and 239 (13000); IR (Nujol), ν_{max} no OH, 1680—1650 (broad), and 1615 cm^{-1}; NMR, δ 1.32, 2.42, and 2.56 (each 3H, s, 19-, 18-, and 21-C<u>H</u>$_3$), and 5.85 (1H, s, <u>H</u> at C_4), 7.04 and 7.56 (each 1H, ABq J=8 Hz, 2<u>H</u> at C_{15} and C_{16}). Found: C, 81.55; H, 7.73%. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84%.

Benzene–ether (2 : 1) eluates afforded 17α-acetyl-13α-hydroxy-12β-etiojerv-4-ene-3,11-dione (**3**, 90 mg), mp 175.0—176.5 °C (from isopropyl ether–acetone) and $[\alpha]_D$ +26°; MS, *m/e* 344 (M^+), 326, and 301; UV (MeOH), λ_{max} 236 nm (ε 14,000); IR (Nujol), ν_{max} 3480, 1732, 1692, 1675, and 1610 cm^{-1}; NMR, δ 1.20, 1.58, and 2.25 (each 3H, s, 19-, 18-, and 21-C<u>H</u>$_3$), 4.01 (1H, s, O<u>H</u>), and 5.78 (1H, s, <u>H</u> at C_4). Found: C, 73.06; H, 8.27%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

Benzene–ether (1 : 1) eluates afforded 17α-acetyl-11α,12α-dihydroxy-13β-fluoro-13-epietiojerv-4-en-3-one (**2**, 180 mg), mp 153—155 °C (from ether) and $[\alpha]_D$ +38°; MS and UV (MeOH), in the text; IR (Nujol), ν_{max} 3400—3480 (broad), 1703, 1660, and 1610 cm^{-1}; NMR, in the text. Found: C, 69.53; H, 8.15%. Calcd for $C_{21}H_{29}O_4F$: C, 69.20; H, 8.02%.

Compound **3** (15 mg) was refluxed in methanol containing 5% potassium hydroxide. After being cooled, the mixture was made neutral with 10% aqueous acetic acid, evaporated and shaken with water and chloroform. The chloroform solution was washed with water, dried and evaporated to leave amorphous residue (13 mg), which was separated by preparative TLC over silica gel (Wakogel B-5F, one plate with 20×20 cm^2) with a 3 : 1 mixture of benzene and ether to yield **4** (4 mg), mp 112—114 °C. This was identical with the afore-mentioned sample in IR, NMR, and TLC.

*Treatment of 17α-Acetyl-12α,13α-epoxy-11α-hydroxyetiojerv-4-en-3-one 11-Acetate (**1a**) with BF_3.* A solution of **1a** (196 mg) in anhydrous benzene (18 ml) was stirred with BF_3 (0.4 ml) at room temp for 15 min. The reaction mixture was worked up as described above to leave amorphous residue (206 mg), showing one major and one minor spot, which was separated by chromatography over silica gel (7 g). The major fraction, eluted with benzene–ether (3 : 1) afforded 11-acetoxy-fluorohydrin (**2a**, 103 mg), mp 143—145 °C (from isopropyl ether–acetone) and $[\alpha]_D$ +75°; MS, *m/e* 406 (M^+), 388, 386, 346, 326, and 283; UV, λ_{max} 238 nm (ε 10000); IR, ν_{max} 3420, 1737, 1717, 1663, 1614, and 1243 cm^{-1}; NMR, δ 1.24, 1.58, 2.32, and 2.12 (each 3H, s, 19-, 18-, 21-C<u>H</u>$_3$, and OCOC<u>H</u>$_3$), 3.30 and 5.42 (each 1H, br W_H=24 and 12 Hz, 2<u>H</u> at C_{17} and C_{11}), 5.56 and 5.75 (each 1H, s, O<u>H</u> and <u>H</u> at C_4). The minor fraction, eluted with benzene–ether (1 : 1), gave acetate (20 mg), mp 198—200 °C (from ether), which was identified as the starting epoxide (**1a**) (IR, NMR, TLC, and mixed mp).

*Treatment of 17α-Acetyl-12α,13α-epoxyetiojerv-4-en-3,11-dione (**13**) with BF_3.* Compound **13** (180 mg) in benzene (20 ml) was treated with BF_3 (0.28 ml) at room temp for 140 min. The reaction mixture was worked up as mentioned above to leave amorphous residue (182 mg), which was separated into three fractions by preparative TLC over silica gel (Wakogel B-5F, 9 plates) with a 3 : 1 mixture of benzene and ether. A most mobile fraction gave a crystalline substance, which was recrystallized from isopropyl ether–acetone to yield a bicyclo[3.3.1]nonane-2,9-dione derivative (**14**, 35 mg), mp 227—228 °C and $[\alpha]_D$ +95°; MS, IR (Nujol), and NMR, in the text. Found: C, 73.26; H, 7.66%. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66%.

A middle fraction afforded 11-oxo-fluorohydrin (**6**, 47 mg), mp 190.5—191.5 °C (from isopropyl ether–acetone) and $[\alpha]_D$ +182°; MS, *m/e* 362 (M^+), 342, 319, and 299; UV, λ_{max} 234 nm (ε 12,000); IR, ν_{max} 3380, 1753, 1699, 1644, and 1615 cm^{-1}; NMR, δ 1.21, 1.47, and 2.33 (each 3H, s, 19-, 18-, and 21-C<u>H</u>$_3$), 3.24 (1H, br W_H=20 Hz, <u>H</u> at C_{17}), 5.72 and 5.77 (each 1H, s, O<u>H</u> and <u>H</u> at C_4). Found: C, 69.38; H, 7.58%. Calcd for $C_{21}H_{27}O_4F$: C, 69.62; H, 7.51%.

A least mobile fraction gave an oxepin derivative (**15**, 35 mg), mp 198—200 °C (from isopropyl ether) and $[\alpha]_D$ +160.5°; MS, *m/e* 342 (M^+), 300 ($M^+ - CH_2CO$), 282, and 267; UV, IR (Nujol), and NMR, in the text. Found: C, 73.36; H, 7.69%. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66%.

*Treatment of 17α-Acetyl-12α,13α-epoxyetiojerv-4-en-3-one (**16**) with BF_3.* Compound **16** (500 mg) in benzene (50 ml) was stirred with BF_3 (0.72 ml) at room temp for 30 s. The reaction mixture was worked up as usual to leave an amorphous material, which was separated into two fractions by chromatography over silica gel (Merck 70—230 mesh, 30 g) with benzene–ether mixtures. Eluates with benzene–ether (5 : 1) gave a crystalline substance (284 mg), mp 141—143 °C (from hexane–acetone), which was identical with acetophenone (**5**) in IR, NMR, TLC, and mixed mp. Eluates with benzene–ether (3 : 1) afforded 17α-acetyl-12β-fluoro-13α-hydroxyetiojerv-4-en-3-one (**17**, 66 mg), mp 157—159 °C (from ether) and $[\alpha]_D$ +83°; ORD, $[\Phi]_{306}^{peak}$ +4750°, $[\Phi]_{282}^{trough}$ −4250°, a=+90°; MS, *m/e* 348 (M^+), 333, 328, and 310; UV, λ_{max} 237 nm (ε 10000); IR, ν_{max} 3460, 1696, 1657, and 1616 cm^{-1}; NMR, δ 1.17, 1.25, and 2.26 (each 3H, s, 19-, 18-, and 21-C<u>H</u>$_3$), 2.89 (1H, br W_H= 18 Hz, <u>H</u> at C_{17}), 4.32 and 5.75 (each 1H, s, O<u>H</u> and <u>H</u> at C_4). Found: C, 72.19; H, 8.54%. Calcd for $C_{21}H_{29}O_3F$: C, 72.38; H, 8.39%.

*Oxidation of Fluorohydrin **2**.* (i) A solution of **2** (20 mg) in dry acetone (3 ml) was stirred with the Jones reagent (0.2 ml) for 2 h under cooling with ice. After addition of ethanol to decompose excess of the reagent, the solution was evaporated and shaken with water and chloroform. The chloroform solution was worked up as usual to leave a crystalline substance, showing a single spot, which was recrystallized from isopropyl ether–acetone to give 11-oxo-fluorohydrin (**6**, 16 mg), mp 188—190 °C, which was identical with the above-mentioned sample in IR, NMR, TLC, and mixed mp.

(ii) A solution of **2** (20 mg) in dioxane (1.5 ml) was stirred with periodic acid (50 mg as $HIO_4 \cdot 2H_2O$) in water (0.5 ml) at room temp for 18 h. The solution was diluted with water, extracted with chloroform, and the chloroform solution, after being worked up as usual, gave a crystalline material, showing a single spot. This was recrystallized from ether to give lactol (**7**, 14 mg), mp 128—130 °C; MS, *m/e* 362 (M^+), 347, and 342; IR, ν_{max} 3570, 3440, 1715, 1665, and 1615 cm^{-1}; NMR, δ 1.24, 1.33, and 2.26 (each 3H, s, 19-, 18-, and 21-C$\underline{H}_3$), 3.70 (1H, s, O$\underline{H}$), 5.40 (1H, d J=8 Hz, $\underline{H}$ at C_{11}), and 5.73 (1H, s, $\underline{H}$ at C_4), and no absorption near δ 1.0.

*11-Acetate (**2a**) and 11,12-Acetonide (**9**) of Fluorohydrin **2**.* (i) Compound **2** (15 mg) was treated with acetic anhydride (0.15 ml) and pyridine (0.3 ml) at room temp for 24 h under stirring. The reaction mixture was worked up as usual to give **2a** (17 mg), mp 140—142 °C (from isopropyl ether-acetone), which was identical with the sample obtained from **1a** (IR, NMR, and mixed mp).

(ii) A solution of **2** (10 mg) in acetone (2 ml) was stirred with 60% aqueous perchloric acid (0.1 ml) for 1.5 h. The solution was made alkaline with 5% aqueous $NaHCO_3$, evaporated and extracted with chloroform. The chloroform solution, after being worked up as usual, gave acetonide (**9**), oil, showing a single spot on TLC; MS, *m/e* 405 (M^++1), 389, and 384; IR, ν_{max} 1715, 1664, 1614, 1384, and 1373 cm^{-1}; NMR, δ 1.23, 1.40, 1.53, and 2.26 (3H, 6H, 3H, and 3H, each s, 19-, 18-, and 21-C$\underline{H}_3$, and acetonide 2C$\underline{H}_3$ or *vice versa*), 4.71 (1H, br W_H=12 Hz, $\underline{H}$ at C_{11}), and 5.76 (1H, s, $\underline{H}$ at C_4).

*Alkali Treatment of 11-Hydroxy-fluorohydrin (**2**), Its 11-Acetate (**2a**), and Its 11,12-Acetonide (**9**).* (i) Compound **2a** (18 mg) was stirred with potassium carbonate (200 mg) in a mixture of methanol (6 ml) and water (2 ml) at room temp for 2 h under nitrogen. The reaction mixture, after being worked up as usual, left amorphous residue (17.5 mg), showing two spots, which was separated into two fractions by preparative TLC over silica gel (Wakogel B-5F, one plate). A less polar fraction gave a crystalline substance, which on recrystallization from hexane-acetone afforded $\Delta^{13(17)}$-20-ketone (**10**, 10 mg), mp 173—174 °C and $[\alpha]_D$ −26°; MS, *m/e* 344 (M^+), 326, 311, and 301; UV, in the text; IR, ν_{max} 3620, 3440, 1680 (shoulder), 1662, and 1613 cm^{-1}; NMR, δ 1.20, 1.87, and 2.29 (each 3H, s, 19-, 18-, and 21-C$\underline{H}_3$), 3.32 (2H, br, s, 2O$\underline{H}$), 3.61 (1H, br W_H=15 Hz, $\underline{H}$ at C_{11}), and 5.78 (1H, s, $\underline{H}$ at C_4). Found: C, 72.89; H, 8.12%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%. A more polar fraction was identified as 13α-pregnane (**12**, 1 mg), by comparison with the sample described later (MS and TLC).

When compound **2a** (12.8 mg) was treated with the base under the same conditions for 1 h as mentioned above, the product (10 mg), mp 170—172 °C, showed a single spot and was identified as **10**.

Compound **10** (7.3 mg) was stirred with acetone (2 ml) containing perchloric acid (60%, 0.1 ml) at room temp for 1 h. The mixture was worked up as usual to leave oily residue, showing a single spot, which was purified by preparative TLC to yield acetonide (**11**, 8.0 mg), oil and $[\alpha]_D$ −43°; MS, *m/e* 384 (M^+), 369, and 326; UV, λ_{max} 241 nm (ε 16000); IR, ν_{max} no OH, 1664, 1615, 1383, and 1372 cm^{-1}; NMR, δ 1.16, 1.50, 1.56, 1.86 and 2.30 (each 3H, 19-, 18-, and 21-C$\underline{H}_3$, acetonide 2C$\underline{H}_3$, or *vice versa*), 4.18 (1H, d J= 8 Hz, $\underline{H}$ at C_{11}), and 5.80 (1H, s, $\underline{H}$ at C_4). This acetonide (**11**, 16 mg) was obtained by treatment of **9** (17 mg) with potassium carbonate.

(ii) A solution of **2a** (20 mg) in ethanol (5 ml) containing 5% potassium hydroxide was stirred at room temp for 100 min. The solution was made neutral with 10% aqueous acetic acid under cooling, evaporated below 40 °C, and shaken with water and chloroform. The chloroform solution was worked up as usual to leave an oily material, showing a single spot, which was purified by preparative TLC to give a 13α-pregnane derivative (**12**, 13 mg), mp 164—166 °C (isopropyl ether-acetone) and $[\alpha]_D$ +64°; MS, UV, IR, and NMR, in the text; NMR (C_5D_5N), δ 1.30, 1.58, and 1.74 (each 3H, s, 19-, 18-, and 21-C$\underline{H}_3$), 4.50 and 5.76 (each 1H, s, 2$\underline{H}$ at C_{12} and C_4).[16]

Found: C, 73.08; H, 8.12%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

Treatment of **2** (5.3 mg) and **10** (4.7 mg) with potassium hydroxide under almost the same conditions as mentioned above afforded **12** (5.0 and 4.7 mg, respectively), and that of **10** (9.7 mg) with potassium carbonate also gave **12** (2.7 mg) along with the starting material (**10**, 4.7 mg) after preparative TLC.

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