CHEMISTRY LETTERS, pp. 975-978, 1976. Published by the Chemical Society of Japan

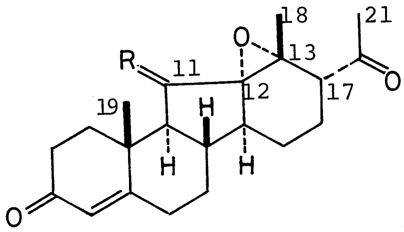
# REACTIONS OF 11-OXYGENATED 17α-ACETYL-12α,13α-EPOXYETIOJERVANES WITH BORON TRIFLUORIDE ETHERATE[1)]

Akio MURAI, Hiroshi SASAMORI, and Tadashi MASAMUNE
Department of Chemistry, Faculty of Science, Hokkaido University,
Sapporo 060

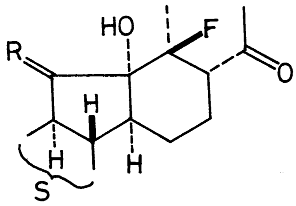
Treatment of 11α-hydroxy-, 11α-acetoxy-, and 11-oxo-17α-acetyl-12α,13α-epoxyetiojervanes (**1**, **1a**, and **11**) with boron trifluoride etherate gave mixtures of several compounds, respectively, including interesting rearranged products, e.g., compounds (**12** and **13**) with bicyclo[3.3.1]nonane-2,9-dione and hydrooxepin moieties.

A number of papers have been reported of the cleavage of epoxy rings, accompanying the ring skeletal rearrangement in the field of steroid and other related compounds.[2)] However, only one example[3)] has been known as for the transformation of a C-nor-D-homosteroid (etiojervane) into a normal steroid. In connection with studies aimed at the synthesis of biologically active normal steroids from etiojervanes, we examined epoxy ring cleavage reactions of the titled compounds with boron trifluoride etherate. In the present paper we describe the reaction result involving formation of interesting rearranged products.

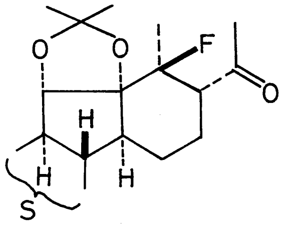
Brief treatment (30 sec) of 17α-acetyl-12α,13α-epoxyetiojerv-4-en-3-on-11α-ol[4)] (**1**) with the acid in benzene at room temperature afforded a multi-component mixture, from which four compounds (**2** ∿ **5**) were isolated after chromatography in 20, 10, 10 and 11% yields, respectively. The major product (**2**), $C_{21}H_{29}O_4F$,[5)] mp 153-155°C and $[\alpha]_D$ +38°,[5)] exhibited the following spectra: Mass, m/e 364 ($M^+$), 346, 326, and 301 ( $M^+$-HF-$COCH_3$ ); UV,[5)] $\lambda_{max}$ 239 nm (ε 10,000); IR,[5)] $\nu_{max}$ (Nujol) 3440 (br), 1703, 1660, and 1610 $cm^{-1}$; NMR,[5)] δ 1.26, 1.50, and 2.37 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 3.34 (1H, br $W_H$ = 18 Hz, $\underline{H}$ at $C_{17}$), and 4.02 (1H, d J = 8 Hz, $\underline{H}$ at $C_{11}$). Compound **2**, when acetylated with acetic anhydride and also oxidized with the Jones reagent, was converted into the corresponding monoacetate (**2a**), mp 143-145°C and $[\alpha]_D$ +75°, $\nu_{max}$ 1737 and 1243 $cm^{-1}$, and ketone (**6**), mp 190.5-191.5°C and $[\alpha]_D$ +182°, $\nu_{max}$ 1753 $cm^{-1}$, δ 1.21 and 1.47 (each 3H, s, 19- and 18-$C\underline{H}_3$), in 95 and 85% yields, respectively. Moreover, compound **2** readily formed its acetonide (**7**), oil, $\delta_{max}$ 1384 and 1373 $cm^{-1}$, and also consumed one mole of periodic acid to give lactol (**8**), mp 128-130°C, $\nu_{max}$ 3570 and 3440 $cm^{-1}$, δ 5.40 (1H, d J = 8 Hz, $\underline{H}$ at $C_{11}$), and no absorption near δ 9.0. All these results indicate that the compound is represented by structure **2** with a cis-glycol partial formula. Interestingly, compound **2**, when treated with weak base ($K_2CO_3$) in aqueous methanol at room temperature, was not regenerated into the starting epoxide (**1**) but underwent dehydrofluorination to yield $\Delta^{13(17)}$-20-ketone (**9**), mp 173-174°C, quantitatively; $\lambda_{max}$ 245 nm (ε 17,000); δ 1.20 and 1.87 (each 3H, s, 19- and 18-$CH_3$). The latter (9) was further transformed by treatment with strong base (KOH) at room temperature into a rearranged 13α-pregnane derivative (10), $C_{21}H_{28}O_4$, mp 164-166°C and $[\alpha]_D$ +64°; m/e 344 ($M^+$), 326, and 301; $\lambda_{max}$ 237 nm (ε 10,000); $\nu_{max}$ 3600, 3440, 1714, 1665, and 1614 $cm^{-1}$; δ 1.25, 1.37, and 1.60 (each 3H, s, 19-, 18-, and 21-$CH_3$[6])), and 4.33 (1H, s, H at $C_{12}$).



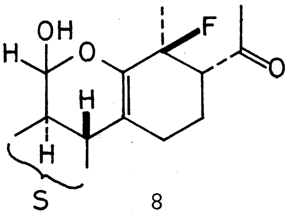
1 R=β-H, α-OH
1a R=β-H, α-OAc
11 R=O
14 R=$H_2$



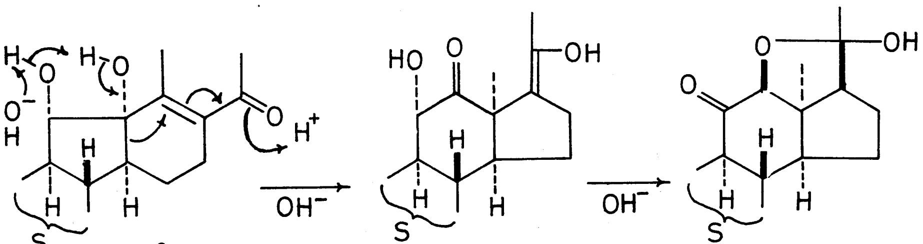
2 R=β-H, α-OH
2a R=β-H, α-OAc
6 R=O



7

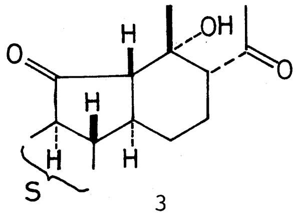


8

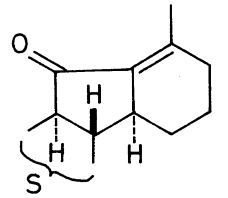


9 10

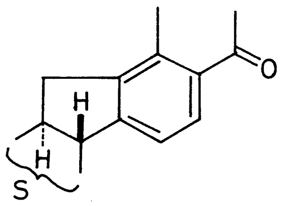
Structure 3, 4, and 5 were deduced for three minor products (3 ∿ 5), mp 175-176.5°C, 112-115°C, and 143-145°C, and $[\alpha]_D$ +26°, +148°, and +97°, from the spectral data: 3, m/e 344 ($M^+$), 326, and 301; $\lambda_{max}$ (MeOH) 236 nm (ε 14,000); $\nu_{max}$ (Nujol) 3480, 1732, 1692, 1675, and 1610 $cm^{-1}$; δ 1.20, 1.58, and 2.25 [each 3H, s, 19- ($\delta_{cal}$ 1.21 for 12βH and 1.26 for 12αH)[7]), 18-, and 21-$CH_3$]: 4, m/e 284 ($M^+$) and 269; $\lambda_{max}$ 247 nm (ε 13,000); $\nu_{max}$ 1708, 1668, and 1639 $cm^{-1}$; δ 1.24 and 2.15 (each 3H, 19- and 18-$CH_3$); 5, m/e 308 ($M^+$), 293, and 265; $\lambda_{max}$ 295 and 239 nm (ε 3700 and 13,000); $\nu_{max}$ (Nujol) no OH, 1665 (br), and 1615 $cm^{-1}$; δ 1.32, 2.42, and 2.56 (each 3H, s, 19-, 18-, and 21-$CH_3$), 7.04 and 7.56 (each 1H, ABq J = 8 Hz, 2H at $C_{15}$ and $C_{16}$).



3



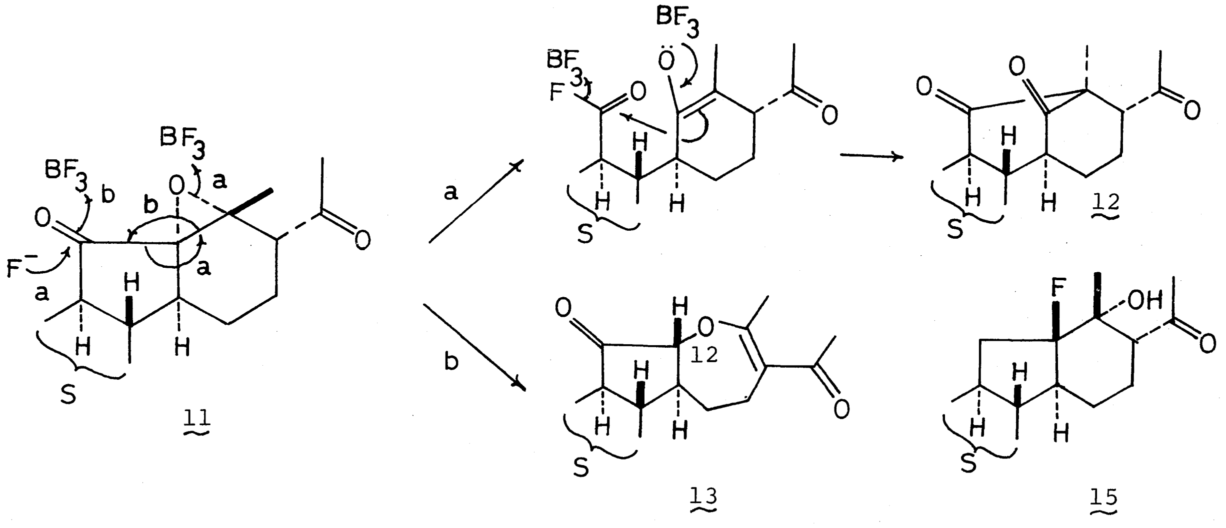
4



5

Treatment (15 min) of 11α-acetoxy-12α,13α-epoxide$^{4)}$ (1a) with the Lewis acid gave 11α-acetoxy-fluorohydrin (2a), as a sole isolable product, in a 60% yield with the unreacted starting epoxide (1a) (10%).

Prolonged treatment (140 min) of 11-oxo-12α,13α-epoxide$^{4)}$ (11) with the acid produced a complex mixture, from which 11-oxo-fluorohydrin (6) and two new compounds (12 and 13) were isolated in 25, 20, and 20% yields, respectively. Compound 12, mp 227-228°C, $[\alpha]_D$ +95°, had the same molecular formula $C_{21}H_{26}O_4$ as the starting epoxide (11). The spectra, m/e 342 ($M^+$) and 299; $\lambda_{max}$ 234 nm (ε 14,000); $\nu_{max}$ 1716 (s), 1667, and 1619 $cm^{-1}$; δ 2.19 (3H, s, 21-C$\underline{H}_3$), indicated that the 17-acetyl and $\Delta^4$-3-carbonyl groups remained unchanged. In view of the absence of a hydroxy group (no absorption near 3400 $cm^{-1}$), the remaining two oxygen atoms must exist as two carbonyl groups [$\nu_{max}$ 1742 and 1716 (s) $cm^{-1}$]. Moreover, the Mass spectrum displayed the presence of a readily removable carbonyl group at m/e 271 ($M^+$-$CH_3CO$ -CO). The NMR spectrum also exhibited two three-proton singlets (19- and 18-C$\underline{H}_3$) at δ 1.07 and 1.48 as well as two broad one-proton peaks ($W_H$ = 20 and 8 Hz) at δ 3.18 and 3.54, the latter two being attributable to protons on the carbon atoms ($C_{17}$ and $C_{14}$ or <u>vice</u> <u>versa</u>) adjacent to carbonyl groups. All these spectral data revealed the presence of a bicyclo[3.3.1]nonane-2,9-dione moiety$^{8)}$ and hence the compound is represented most favorably by formula 12.



11

12

13

15

Compound 13, mp 198-200°C and $[\alpha]_D$ +160.5°, also had the same molecular formula $C_{21}H_{26}O_4$ as the starting epoxide (11). The UV spectrum [$\lambda_{max}$ 245 nm (ε 14,000)] indicated that an α,β-unsaturated carbonyl or an analogous group was newly formed. The IR spectrum also revealed the presence of two carbonyl groups, other than the $\Delta^4$-3-carbonyl group ($\nu_{max}$ 1674 and 1618 $cm^{-1}$), at higher wave numbers ($\nu_{max}$ 1750 and 1714 $cm^{-1}$) as compared with those of 11- and 20-carbonyl groups of usual 17-acetyl-11-oxoetiojervanes ($\nu_{max}$ <u>ca</u>. 1735 and 1705 $cm^{-1}$). These absorptions, as coupled with that due to a vinyl ether grouping 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 three-proton (19-$C\underline{H}_3$) and six-proton singlets (18- and 21-$C\underline{H}_3$) at δ 1.23 and 2.10 in the NMR spectrum. The relevant low field peak (δ 5.42) could be assigned to a proton on the carbon atom ($C_{12}$) flanked by a carbonyl group and an oxygen atom. These spectra indicated the presence of a partial structure $O{=}C(C_{11})\text{-}\overset{|}{C}H\text{-}O\text{-}C(CH_3){=}\overset{|}{C}\text{-}C({=}O)CH_3(C_{21})$, and hence led to assignment of formula 13 to the compound.

While we have analogous precedents[9)] regarding the novel rearrangement, involving C-C bond cleavage of the epoxy ring, of 11-oxo-12α,13α-epoxide (11) into hydrooxepin (13), the transformation of compound 11 with an α,β-epoxy-carbonyl group into compound 12 with a bicyclo[3.3.1]nonane-2,9-dione moiety is most noteworthy and would probably be the first example as for such rearrangements. 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 accordance with this, 11-unsubstituted 12α,13α-epoxide (14) on treatment (30 sec) with the acid gave acetophenone (5) and 12β-fluoro-13α-alcohol (15), mp 157-159°C and $[\alpha]_D$ +83°, in 60 and 12% yields. The latter (15), evidently resulting from attack of a fluoride anion to $C_{12}$, showed the following spectra and underwent no dehydrofluorination under the basic conditions described above: $[\Phi]^{\text{peak}}_{304}$ +4750°, $[\Phi]^{\text{trough}}_{280}$ -4250°, a = +90° (dioxane); m/e 348 ($M^+$), 333, 328, and 310; $\lambda_{max}$ 237 nm (ε 10,000); $\nu_{max}$ 3460, 1696, 1657, and 1616 $cm^{-1}$; δ 1.17, 1.25, and 2.26 (each 3H, s, 19-, 18-, and 21-$C\underline{H}_3$), 2.89 (1H, br $W_H$ = 18 Hz, $\underline{H}$ at $C_{17}$), and 5.75 (1H, s, $\underline{H}$ at $C_4$).

## REFERENCES and FOOTNOTES

1 Part XXVII of "C-Nor-D-homosteroids and Related Alkaloids" and Part II of "12,13-Epoxy-C-nor-D-homosteroids"; the preceding Part, Ref. 4.

2 D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms", Elsevier Publ. Co., New York (1968), p. 353; D. Baldwin, J. R. Hanson, and A. M. Holtom, J. Chem. Soc. Perkin I, 1973, 2687, and Refs cited therein.

3 J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, Tetrahedron, 21, 2489 (1965).

4 A. Murai, H. Sasamori, and T. Masamune, Bull. Chem. Soc. Jpn, in press.

5 All new compounds gave elementary analyses in good accord with the assigned structures. Optical rotations, UV, IR, and NMR spectra were measured in chloroform, ethanol, chloroform, and deuterochloroform, respectively. The abbreviations "s, d, and br" and "br and s" in the NMR and IR spectra denote "singlet, doublet, and broad" and "broad and strong", respectively.

6 *Cf.*, M. Biollaz, J. Schmidlin, and J. Kalvoda, Helv. Chim. Acta, 58, 1433 (1975).

7 T. Masamune, A. Murai, K. Nishizakura, T. Orito, S. Numata, and H. Sasamori, Bull. Chem. Soc. Jpn, 49, 1622 (1976).

8 *Cf.*, P. W. Hickmott and J. R. Hargreaves, Tetrahedron, 23, 3151 (1967); D. Y. Curtin and R. R. Fraser, J. Am. Chem. Soc., 81, 662 (1959).

9 J. M. Coxon, R. P. Garland, M. P. Hartshorn, and G. A. Lane, Chem. Commun., 1968, 1506; Tetrahedron, 26, 1533 (1970); M. Niwa, M. Iguchi, and S. Yamamura, Tetrahedron Lett., 1975, 3661.

(Received June 18, 1976)