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Acid Catalyzed Rearrangement of 16β,17β-Epoxydigitoxigenin 3-Acetate. The Formation of Spiro Compound and Tetraenolide

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On treatment with boron trifluoride etherate, 16β,17β-epoxydigitoxigenin 3-acetate undergoes unusual rearrangement leading to novel spiro compound and tetraenolide, whose 3-hydroxy derivative is one of the aglycon of neriumosides.

In the course of studies on the chemical transformation of gitoxin,1,2) we have previously shown the photochemical transformation of a cardenolide derivative, 16β,17β-epoxydigitoxigenin 3-acetate (**1**),3) which was prepared from gitoxin.

We report here the acid-catalyzed rearrangement of epoxide **1**. The acid-catalyzed 1,2-migration of the carbonyl group in α,β-epoxy carbonyl compounds has been studied intensively.4) Whereas, the acid-catalyzed rearrangement of α,β-unsaturated γ,δ-epoxy ester, ketones, and nitrile are known in the ionone series, e.g. **2a**,5) **2b**,6) and **2c**.7) From these studies, it has been shown that the

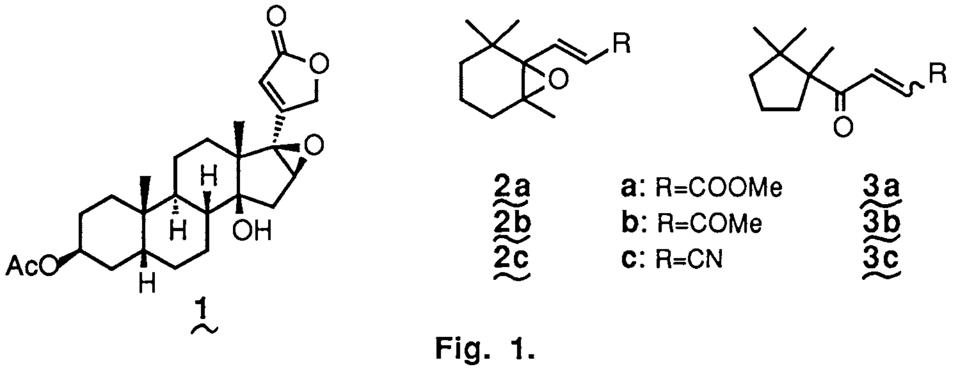
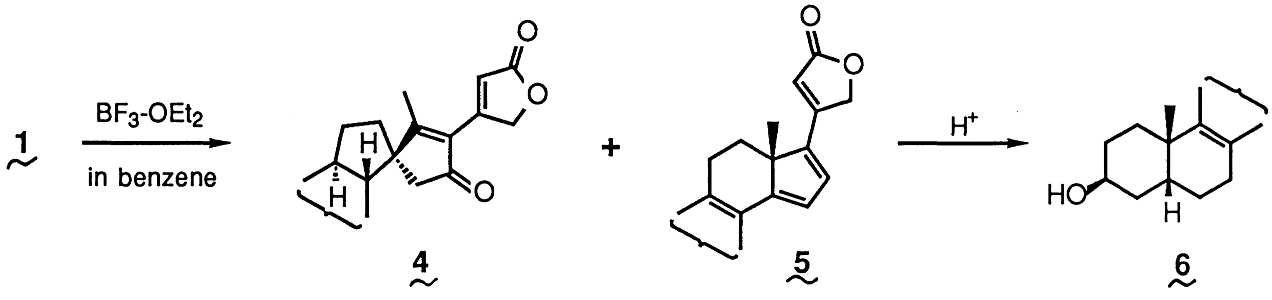


Fig. 1.

BF_3-OEt_2 catalyzed reaction of 2a-c undergoes 1,2-migration of methylene group in the γ-position leading to cyclopentane derivatives 3a-c. It was interesting to study the influence of cardenolide skeleton on cleavage of the oxirane and on rearrangement in 1.

A 0.012 M solution of the epoxide 1 in dry benzene was stirred in the presence of 1.3 equiv. BF_3-OEt_2 under argon at room temperature. After work-up, chromatography (SiO_2) gave the spiro compound 4 (20%) and the tetraenolide 5 (45%).



Scheme 1.

The structure of 4 was deduced from the spectral data[8)] and determined by X-ray crystallographic analysis.[9)]

The mass spectrum of the tetraenolide 5 showed a molecular peak at m/z 394 indicating the molecular formula $C_{25}H_{30}O_4$ which was also evidenced by the elemental analysis. The UV maximum of 5 at 389 nm (ε=21000) and three doublets and five singlets in the ^{13}C-NMR spectrum indicated the presence of the tetraene moiety.[10)] Further evidence for the structure of 5 was obtained from hydrolysis of the 3-acetyl group with 10% HCl leading to the known 3β-hydroxy-5β-carda-8,14,16,20(22)-tetraenolide (6) (82%).[11)] The compound 6 is one of the aglycon of neriumosides, which are isolated from the fresh root bark of *Nerium odorum*.

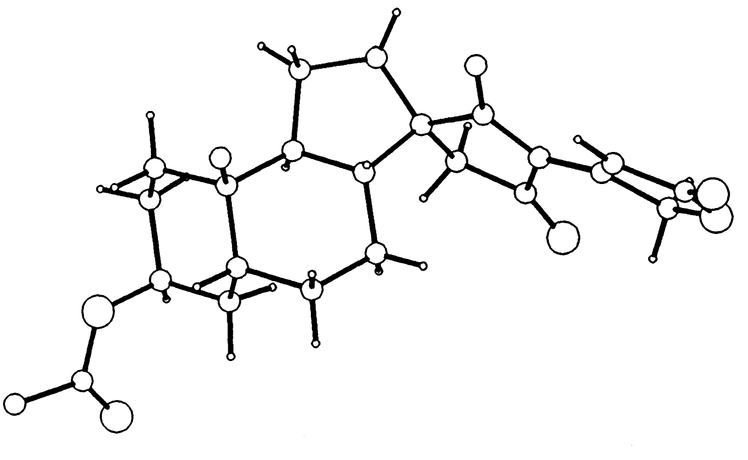
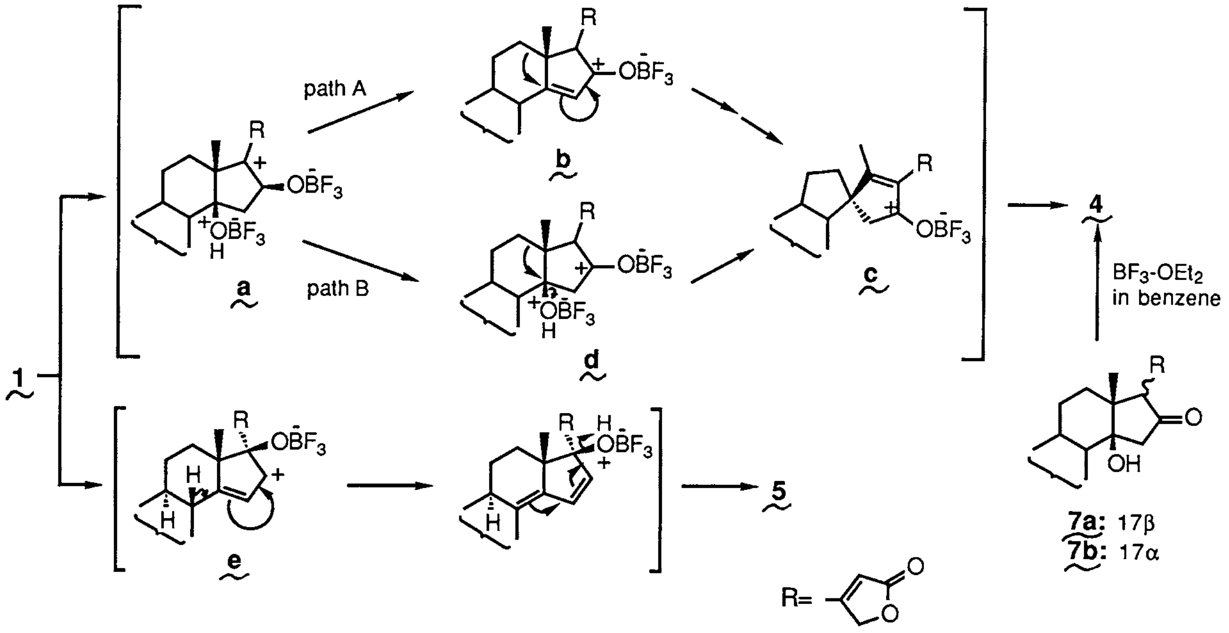


Fig. 2. Molecular stucture for 4.

The formation of the spirane 4 can be explained in terms of two possible routes as shown in Scheme 2. The unusual C(γ),O-bond cleavage of the oxirane of **1** may lead to the intermediate **a**, which subsequently undergoes dehydration[12] and 1,2-H shift to give **b**, followed by C-12,C-13 bond migration[13] to the spirane **4** (path A). In the alternative route (path B) **4** is formed via the intermediate **d**, which undergoes bond migration[14] leading to **4**. The formation of **4** was also observed on treatment of the ketone **7a**[2] and the α-epimer **7b**[2] with BF_3-OEt_2 in 27% and 66% yields, respectively. On the other hand, **1** undergoes dehydration and the normal C(γ),O-bond cleavage of the oxirane[5—7] to **e**, followed by elimination leading to the tetraenolide **5**.



Scheme 2.

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8) Spectral data for **4**: IR ($CHCl_3$) 1748, 1707, and 1622 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.00, 2.05, and 2.22 (9H, 3s), 2.17 and 2.59 (2H, each d, J=18.6 Hz), 5.06-5.09 (1H, m), 5.25 and 5.31 (2H, each dd, J_1=18.3 and J_2=1.8 Hz), and 6.28 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 14.9, 21.4, and 22.6 (3q), 20.4, 22.9, 25.1, 26.7, 30.5, 31.8, 35.9, 45.2, and 72.9 (9t), 36.1, 41.0, 46.7, 70.1, and 116.7 (5d), and 35.3, 56.5, 130.8, 156.1, 170.5, 173.7, 184.1, and 204.2 (8s).

9) Crystal data for **4**: $C_{25}H_{32}O_5$, Mr=412.53, orthorhombic, space group p212121, a=9.543(2), b=31.376(9), c=7.338(1) Å, V=2197.2(8) $Å^3$, Z=4, Dx=1.247 Mg/m^3, l(Mo-Ka)=0.71069 Å, m(Mo-Ka)=0.0924 mm^{-1}, F(000)=888, room temperature. Final R=0.077 for 1717 unique observed reflections.

10) Spectral data for **5**: IR ($CHCl_3$) 1740, 1612, and 1596 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.12, 1.24, and 2.06 (9H, 3s), 4.92-5.00 (1H, m), 5.06 (2H, s), 5.82 (1H, s), and 6.16 and 6.77 (2H, each d, J=2.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 20.7, 21.5, and 27.4 (3q), 22.8, 23.9, 24.0, 27.4, 30.5, 31.5, 32.7, and 71.2 (8t), 38.4, 70.2, 108.5, 119.3, and 135.3 (5d), and 37.6, 51.2, 124.5, 142.5, 143.7, 156.3, 165.8, 170.7, and 175.0 (9s).

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13) The analogous C-12,C-13 bond migration to C-14 was observed on treatment of 3β-acetoxycholest-14-ene with BF_3-OEt_2.15)

14) The analogous bond migration was observed on treatment of 3β,6β-diacetoxy-9β-cholestan-5α-ol with sulfuric acid in acetic anhydride-acetic acid (C-1,C-10 bond)16) and 14β-hydroxy-15-oxo- and 15α-acetoxy-14β-hydroxy-etianic acid derivatives with thionyl chloride (C-12,C-13 bond).17)

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