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TRANSFORMATION OF STEROIDAL 5α,8α-PEROXIDES TO THE 14-MEMBERED RING CONTAINING 5,10;8,9-DISECO-STEROID DERIVATIVES

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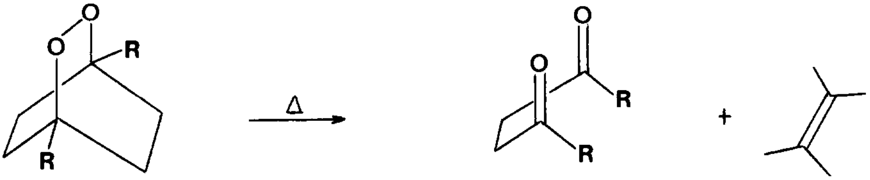
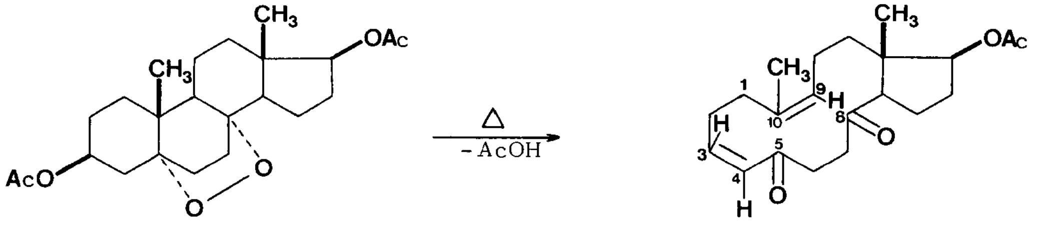
Abstract: *Thermal decomposition of steroidal 5α,8α-peroxides (such as* **1** *) resulted in bisfragmentation of the C(5)-C(10) and C(8)-C(9) bonds, and elimination of acetic acid, to produce a new type of bicyclic compounds, namely 5,10;8,9-diseco-steroid derivatives (such as* **2** *). Some chemical transformations of product* **2** *are described.*

Although there are several efficient methods for cleavage of the steroidal C(5)-C(10)[1] and C(8)-C(9)[2] bond, these methods cannot effectively induce fragmentation of both these bonds in the same molecule.[3] We therefore anticipated another approach, namely if a reaction of the cycloreversion type, such as the known thermal decomposition of saturated [2.2.2]-endoperoxides[4] (Scheme 1), were applied to steroidal 5α,8α-peroxides, it could result in the desired C(5)-C(10) and C(8)-C(9) bisfragmentation and formation of hitherto unknown bicyclic systems (derived from steroids) containing a 14-membered ring (fused to ring D) instead of the three fused 6-membered rings A, B and C. Actually, in the present study, this was proven to be the case.



SCHEME 1

When 5α,8α-peroxy-androstane-3β,17β-diol diacetate 1[5] (prepared by singlet oxygenation of 3β,17β-diacetoxy-androsta-5,7-diene[6], followed by diimide reduction[4]) was thermolyzed in boiling acetic acid under nitrogen for 28 hrs, it underwent the expected decomposition and, in addition, acetic acid elimination, to produce (in about 20% yield) the diseco derivative 2, as a single 3(4)*E*,9(10)*E*-stereoisomer (Scheme 2).[7] This product was isolated from the reaction mixture and purified by column chromatography on silica gel[8].



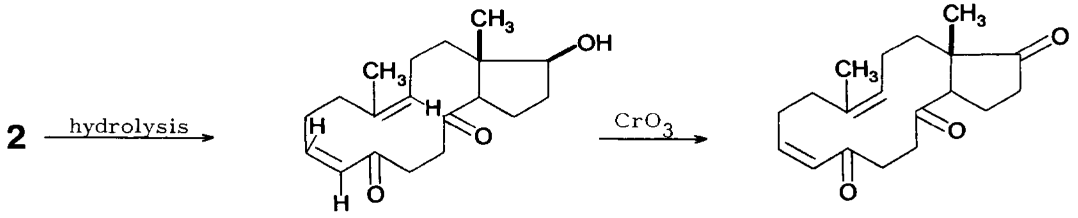
1

2 (E,E)

SCHEME 2

The stereochemistry of the Δ^3-double bond in compound 2 was determined on the basis of ^{1}H-NMR spectral data, the coupling constant, *J*=17 Hz, between the olefinic C(3) and C(4) protons being taken as evidence of their mutual *E* relationship. On the other hand, the *E* configuration at the Δ^9-double bond was deduced from the reasonable assumption that the thermal decomposition of the 5α,8α-peroxide 1 proceeded as a concerted symmetry allowed $-\left[{}_{\pi}2_{s}+{}_{\pi}2_{s}+{}_{\pi}2_{s}\right]-$ -process.

Acid hydrolysis of the diseco-compound 2 afforded the 17β-hydroxy derivative 3 (in 67.5% yield), which, upon subsequent oxidation (with Killiani acid), gave the corresponding 17-ketone 4 (in 87.7% yield) (Scheme 3).

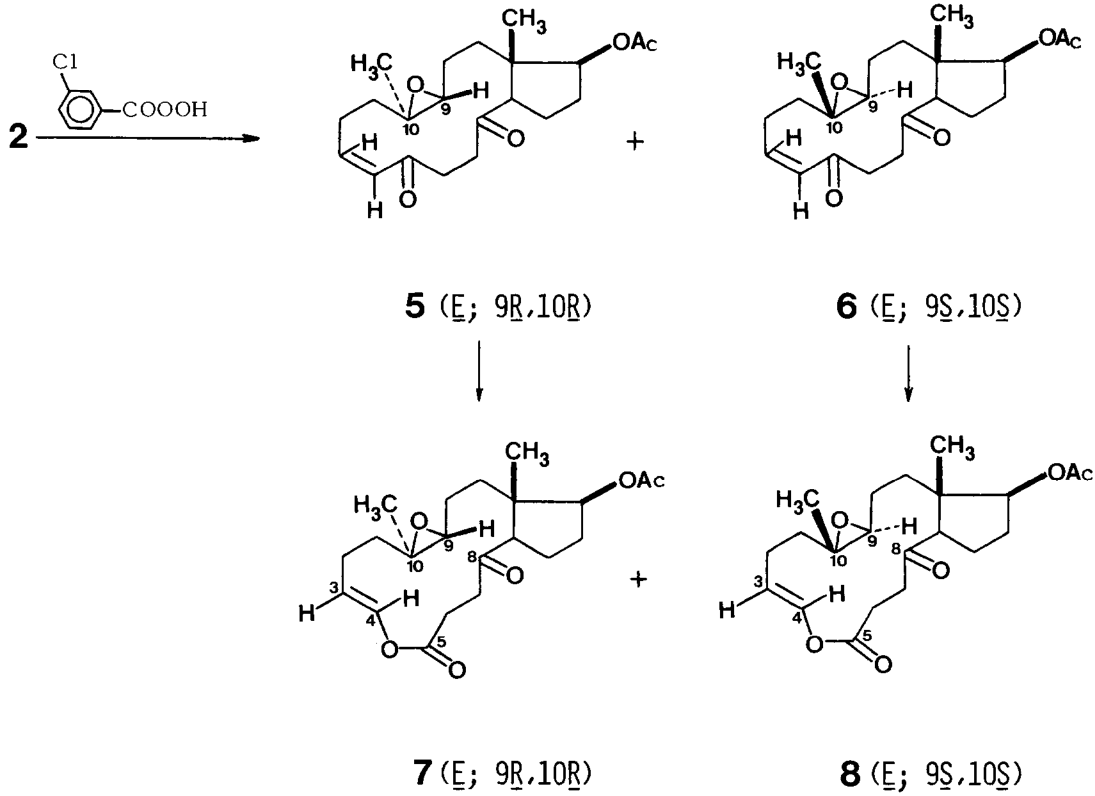


3

4

SCHEME 3

Treatment of the diseco diketone **2** with 3 molar equivalents of *m*-chloroperbenzoic acid in the presence of $NaHCO_3$ in dichloromethane-ether (1:1) solution at room temperature resulted, first, in non-stereospecific epoxidation of the Δ^9-double bond with formation of the stereoisomeric (9*R*,10*R*)- and (9*S*,10*S*)-epoxides (**5** and **6**), which subsequently underwent the Baeyer-Villiger oxidation to give, as final products, the corresponding 15-membered cyclic (9*R*,10*R*)- and (9*S*,10*S*)-epoxy-enol-lactones (**7** and **8**), in a ratio of about 1:1.2 (the total yield of both stereoisomers being 67.2%) (Scheme 4).[7] In some experiments epoxide **5** was isolated and quantitatively converted (with *m*-chloroperbenzoic acid, as described above) to the epoxy-enol-lactone **7**.



5 (E; 9R,10R)

6 (E; 9S,10S)

7 (E; 9R,10R)

8 (E; 9S,10S)

SCHEME 4

Since the usual physical methods (^1H-NMR, ^{13}C-NMR and IR spectroscopy) have shown to be inadequate for a complete configurational assignment at C(9) and C(10) in products **5** - **8**, the ***trans***-(9*S*,10*S*)-configuration of the epoxide ring in the epoxy-enol-lactone **8** was established by X-ray analysis (which also revealed the *E* configuration at the Δ^3-double bond). In this way, indirectly, the proposed *E*,*E* stereochemistry at the two double bonds of the 14-membered ring in the diseco compound **2** was unequivocally confirmed.

Similar bisfragmentation of the C(5)-C(10) and C(8)-C(9) bonds has been accomplished also in some other steroid series (such as cholestane and 17-keto-androstane), indicating that thermal decomposition of steroidal 5α,8α-peroxides represents a general method for the formation of 5,10;8,9-diseco structures of type **2**. The preparation of such bicyclic systems and their further transformations (*e.g.* to **7** and **8**) seem to be of particular interest because of the possibility to correlate steroids with some other naturally occurring products containing a 14-membered ring (for example cembrenoids,[9] some derivatives of which, isolated from marine organisms, possess significant cytotoxic and antineoplastic activity) or a substituted 5-membered ring, which also can exert important physiological activity.

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4. M. Balci, *Chem. Rev.*, 81, 91 (1981), and references therein.

5. All new compounds (**1** - **8**) were fully characterized by elemental analysis and spectral data.

6. W. G. Dauben and D. S. Fullerton, *J. Org. Chem.*, 36, 3277 (1971).

7. The numbering in the diseco compounds **2** - **8**, for the sake of clarity, is that used in steroid systems.

8. *Compound* **2** ($C_{21}H_{30}O_4$), oil: MS - *m/z* 346 (M^+); ^{1}H-NMR (360 MHz, $CDCl_3$), selected data: δ(ppm) 0.86 (s, H_3C-18), 1.56 (s, H_3C-19), 2.05 (s, AcO-17), 4.88 (t, H-17), 5.19 (t, H-9), 5.93 (d, H-4, *J*=17 Hz), 6.57 (dxt, H-3, *J*=17 and 8 Hz); ^{13}C-NMR (20.1 MHz, $CDCl_3$), selected data: δ(ppm) 148.1 (C-3), 129.8 (C-4), 200.7 (C-5), 208.2 (C-8), 128.2 (C-9), 133.0 (C-10).

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