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# EPOXIDATION OF 7-DOUBLE BOND OF CHOLESTA-5,7-DIEN-3β-OL BY PERMANGANATE

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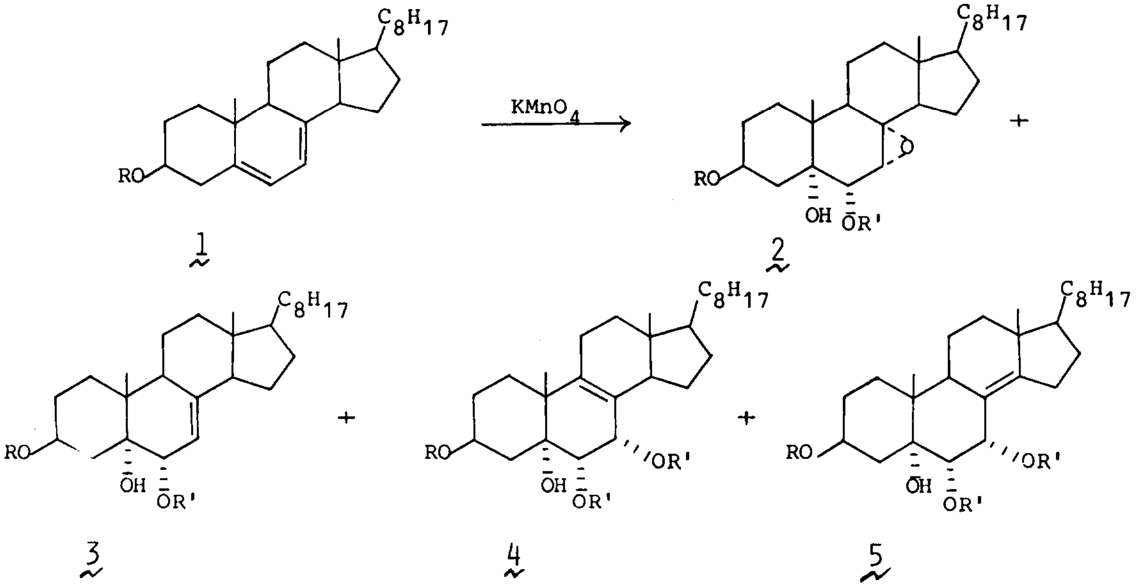
Abstract: The 5,7-diene system of ring B unsaturated steroids is transformed by neutral or alkaline permanganate mainly into a 5α,6α-dihydroxy-7α,8α-epoxide and minor amounts of more polar compounds.

In a recent paper[1] it was reported that 3β-acetoxy-5α,6α,7α,8β-tetrahydroxycholestane (mp 196°C, $[\alpha]_D^{24}$ 9°, obtained by hydroxylation with potassium permanganate of 3β-acetoxycholesta-5,7-diene 1b) was transformed by methanolic-aqueous KOH into 7α,8α-epoxy-3β,5α,6α-trihydroxycholestane (2a), and by Pb(OAc)$_4$ into 3β-acetoxy-5-oxo-7-formyl-7α,8α-epoxy-5,6-secocholestane.

To our knowledge oxirane formation from an 1,2-trans-diol in aqueous basic medium or by action of Pb(OAc)$_4$ is unprecedented. On the contrary, the epoxy compounds obtained in these reactions are in line with the presence of an oxide ring in the starting material, to which the structure 2b should be attributed.

Our investigations on neutral or alkaline permanganate oxidation of cholesta-5,7-dien-3β-ol (1a) demonstrate[2] that the oxidation product (80% Y) is mainly constituted (ca. 75%) by epoxy triol 2a; mp 172-173°C, $[\alpha]_D^{23}$ 4.5° (lit.[1] mp 171-172°C, $[\alpha]_D^{24}$ 12.5°) and by minor amounts (ca. 15%) of 3β,5α,6α-trihydroxycholest-7-ene (3a) (mp 231-232°C, $[\alpha]_D^{23}$ 26.4°; $^1$HNMR: δ 0.55 (s, 3H, 18-H, calcd[3] 0.534), 0.98 (s, 3H, 19-H, calcd[3] 0.955), 3.9-4 (m, 2H, 3α-H and 6β-H), 5.0 (m, 1H, 7-H, $\frac{W}{2}$ ca. 8 Hz)) and of two more polar tetrols, 3β,5α,6α,7α-tetrahydroxycholest-8(14)-ene (4a) (ca. 3%) (mp 246-247°C, $[\alpha]_D^{23}$ -37°) and 3β,5α,6α,7α-tetrahydroxycholest-8-ene (5a) (ca. 7%) (mp 211-212°C, $[\alpha]_D^{23}$ 6°). 4a and 5a were inseparable on TLC and were transformed into the corresponding separable 3β,6α, 7α-triacetates: 4c (mp 194-195°C, $[\alpha]_D^{23}$ 15°, $^1$HNMR: δ 0.82 (s, 3H, 18-H, calcd[3] 0.824), 0.88 (s, 3H, 19-H, calcd[3] 0.881), 2.00, 2.06, 2.09 (3 x s, 9H, 3β,6α,7α-$OCOCH_3$), 3.2 (m, 1H, 5α-OH), 4.94 (bd, 1H, 6β-H, J 4 Hz), 5.0 (m, 1H, 3α-H, $\frac{W}{2}$ ca. 25 Hz), 5.96 (bd, 1H, 7β-H, J 4 Hz)) and 5c (mp 157-158°C, $[\alpha]_D^{23}$ 24°, $^1$HNMR: δ 0.61 (s, 3H, 18-H), 1.24 (s, 3H, 19-H), 2.00, 2.02, 2.06 (3 x s, 9H, 3β,6α,7α-$OCOCH_3$), 2.6 (m, 1H, 5α-OH), 5.05 (m, 1H, 3β-H, $\frac{W}{2}$ ca. 25 Hz), 5.32 (bd, 1H, 7β-H, $\frac{W}{2}$ ca. 8 Hz), 5.52 (bd, 1H, 6β-H, $\frac{W}{2}$ ca. 8 Hz)). 4c and 5c yielded by saponification 4a and 5a.



a; R = R' = H

b; R = Ac, R' = H

c; R = R' = Ac

In order to prove that the acetylation of 3β-hydroxy group of 1a cannot modify the reactivity of the 5,7-diene system, we tried the oxidation of 1b by neutral and alkaline permanganate. In both instances direct crystallization of the oxidation mixture gave 2b (80% Y), mp 195-196°C, $[\alpha]_D^{23}$ 5°, (compare with the constants given for the supposed 3β-acetoxy-5α,6α,7α,8β-tetrahydroxycholestane[1]), $C_{29}H_{48}O_5\cdot\frac{1}{2}H_2O$;[8] $\frac{m}{e}$ 476 ($M^+$); IR ($CS_2$) 3560, 3420, 3025, (Chf) 1730, 1620, 1250 cm$^{-1}$; $^1$HNMR: δ 1.98 (s, 3H, 3β-$OCOCH_3$), 2.84 (d, 1H, 6α-OH, J 11 Hz), 3.59 (bd, 1H, 7β-H, $\frac{W}{2}$ ca. 6 Hz), 3.69 (dd, 1H, 6β-H, J 11 Hz, $\frac{W}{2}$ ca. 6 Hz), 4.15 (m, 1H, OH), 5.0 ppm (m, 1H, 3α-H, $\frac{W}{2}$ ca. 25 Hz). After exchange with $^2H_2O$ both signals at 2.84 and 4.15 disappeared and the dd at δ 3.69 collapsed to a bs, $\frac{W}{2}$ ca. 6 Hz. In addition two singlets were present at δ 0.72 and 1.02 ppm for C-18 and C-19 protons. The presence of the 7α,8α-epoxide bridge causes radical changes in molecular geometry and hence Zürcher additivity rules[3] are no longer applicable to check the proposed structure.[4] Acetylation of **2b** gave the diacetate **2c**; mp 190-191°C; $[\alpha]_D^{23}$ 21°; IR ($CS_2$) 3460, 1740, 1250; $^1$HNMR: δ 0.76 and 1.10 (2 x s, 6H, C-18H and C-19H), 2.00, 2.20 (2 x s, 6H, 6α- and 3β-$OCOCH_3$), 3.6 (bd, 1H, 7β-H, $\frac{W}{2}$ ca. 4 Hz), 4.5 (m, 1H, OH), 5.00 (m, 1H, 3α-H, $\frac{W}{2}$ ca. 25 Hz), 5.18 ppm (bd, 1H, 6β-H, $\frac{W}{2}$ ca. 4 Hz). Saponification of **2b** and **2c** gave **2a**.

TLC analysis of mother liquors from **2b** revealed the presence of small amounts of **2b** and of three more polar compounds, which could not be completely resolved by PLC. Better separation was achieved after acetylation. **2c**, **3c**, **4c**, and **5c** were obtained, thus showing that the action of permanganate on **1b** gives the same set of products as on **1a**.

Our results demonstrate that the main oxidation products of the 5,7-diene steroids **1a** and **1b** are the epoxy compounds **2a** and **2b**, respectively. Small amounts of more polar compounds of type **3**, **4**, and **5** are also formed. Tetrahydroxylation of 5,7-diene system was not observed.

Actually **2b** corresponds in constants (mp and optical rotation) to the supposed tetrahydroxylation product[1] to which the structure **2b** should be attributed. Additional evidence for this assumption is that **2b** gave the reported seco-epoxy aldehyde by treatment with $Pb(OAc)_4$ and **2a** by saponification.

This is the first successful trapping and isolation of an epoxide as product from permanganate oxidation of a steroidal diene. A pertinent precedent is the formation in fair yields of <u>all</u>-<u>cis</u> epoxydiols in the permanganate oxidation of cyclopentadiene and 1,3-cyclohexadiene.[7] In the latter reaction tetrols are minor companions of epoxydiols and it was proposed that the last compounds or reactive intermediates related to them are intermediates in the formation of tetrahydroxylation compounds. In the present case it is reasonable to suppose that the small amounts of unsaturated triols of type **4** and **5** derive from a clevage of 7α,8α-epoxide followed by elimination of elements of water.

Permanganate oxidation of steroidal 5,7-dienes to yield epoxy-diols appears general in scope and useful in planning synthesis in steroid field.

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## References and Notes

1. W. J. Rodewald and Z. Bończa-Tomaszewski, Tetrahedron Letters, 169 (1979).
2. The oxidation was performed as described by M. Fieser et al. for ergosterol.[5] The reaction mixture was centrifuged and the ppt resuspended in acetone for the recovery of oxidation products. In some experiments $MgSO_4$ was added as buffer and similar results were obtained. In the case of ergosterol the same set of products was obtained.[6]
3. N. S. Baccha and D. H. Williams, 'Applications of NMR Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, p. 13, 1964; W. Arnold, W. Meister, and G. Englert, Helv. Chim. Acta, **57**, 1559 (1974).
4. The calculated[3] chemical shifts of the C-18 and C-19 protons of the supposed pentol monoacetate are at $\delta$ 0.823 and 1.148 ppm, respectively. Deviations from the observed values are too large to support this structure.
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6. M. Anastasia, A. Fiecchi, and A. Scala, J. Org. Chem., submitted for the pubblication.
7. H. Z. Sable, K. A. Powell, H. Katchian, C. B. Niewoehner, and S. B. Kadlec, Tetrahedron, **26**, 1509 (1970).
8. This compound was obtained only as a hemihydrate as demonstrated by the elemental analysis. Satisfactory elemental analyses were obtained for all fully characterized compounds.

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