

OZONATION OF 3 β -ACETOXY-5 α -CHLORO-CHOLESTANE IN SOLUTION.
X-RAY STUDY OF 3 β -ACETOXY-5 α -CHLORO-14-CHOLESTENE-OZONIDE.

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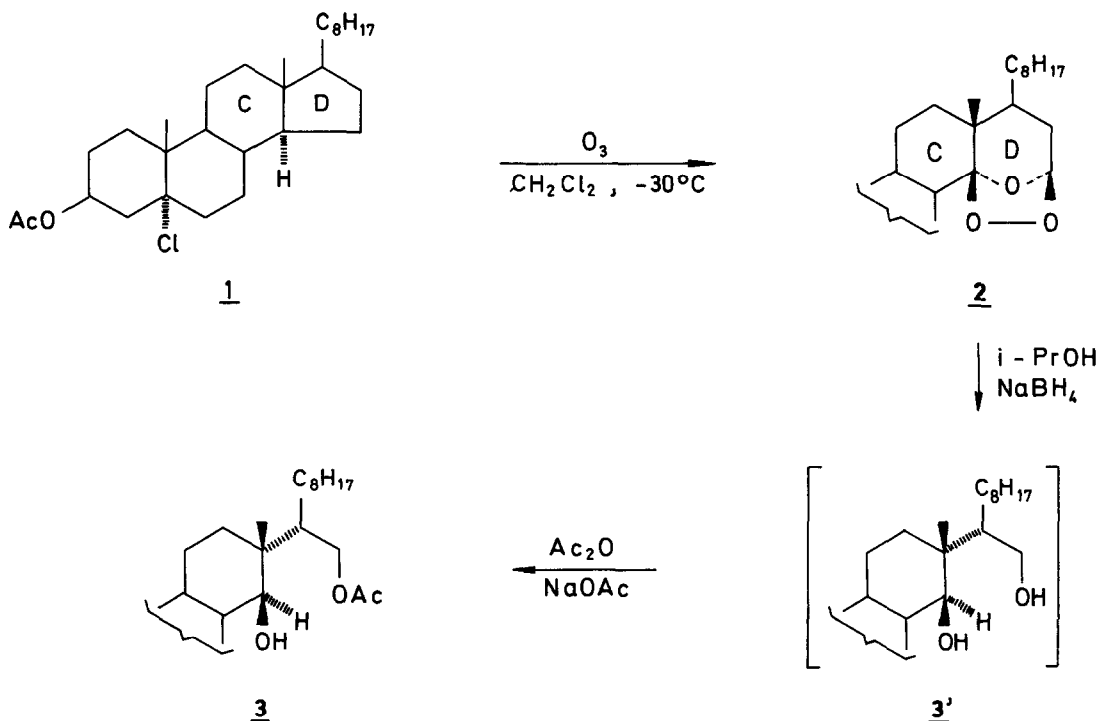
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Summary: *A selected saturated steroid derivative has been subjected to ozonation in solution. As the main reaction product 14,15-ozonide has been isolated in crystalline form whose structure has been unambiguously confirmed by the X-ray diffraction method.*

Wife and co-workers¹ reported recently on selective oxidation of steroids by using so called "dry ozonation" procedure. Starting from 5 α -cholestanyl-3 β -acetate they obtained two isomeric C(14)-C(15) ozonides as the main oxidation products, whose structures were deduced on the basis of corresponding spectroscopic data (mainly by chemical ionization mass spectrometry and ¹H-n.m.r. spectroscopy).

Independently and simultaneously, we have started our investigations on the ozonation reaction of 3 β -acetoxy-5 α -chloro-cholestane (1)². However, differently from all other authors¹, we performed ozonation of the selected steroid in a solution, in order to prove or disprove the necessity of using silica in such oxidation procedures. In a representative experiment 3 β -acetoxy-5 α -chloro-cholestane (5 g) in CH₂Cl₂ (100 cm³) was treated with ozone for 4 hrs at - 30 \pm 2°C. The excess of O₃ was then removed by a stream of air, the reaction mixture was allowed to warm to room temperature and fractionated by column chromatography on silica gel, whereupon the 14,15-ozonide 2³ (450 mg) was isolated as the main oxidation product⁴ (2,5 g of the starting compound 1 was recovered).

The ozonide 2 was further chemically transformed under fragmentation-reduction conditions (by heating it in iso-propanol with NaBH₄), according to the reaction scheme 1. After partial acetylation of the intermediately formed diol 3', the structure of the 3,15-diacetate 3 was determined on the basis of its IR- and M-spectra, as well as the corresponding elemental microanalysis⁵ (we suppose that the newly created hydroxyl group at C(14) is sterically hindered, so that it is not acetylated under the usual acetylation conditions).



Scheme 1.

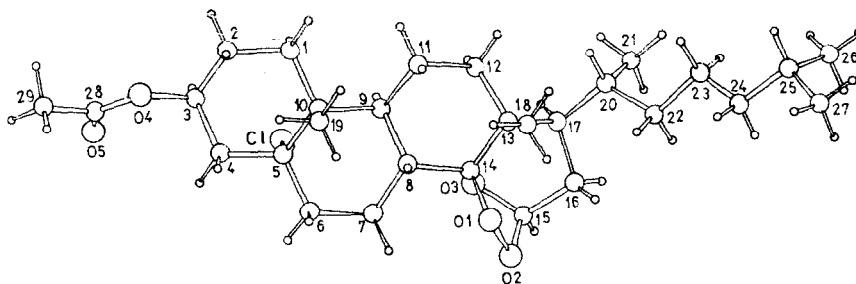
The unusual stability of the well-crystallizing ozonide 2 enabled us, for the first time, to substantiate its structure by X-ray diffraction.

The crystal structure of 2 was solved in the orthorhombic space group $P2_1^2 2_1 2_1$ by direct methods using the MULTAN program⁶ and refined to a final $R = 0.049$ for 2335 independent computer diffractometer data⁷. The revealed molecular geometry⁸ depicted in two projections (Figure 1) shows that the novel five-membered hetero-ring is almost perpendicular to the best plane of rings A, B and C. The latter rings exhibit the usual chair conformations, while ring D enlarged by an additional O atom, forming an ether bridge between C(14) and C(15), assumes an intermediate shape between the four canonical forms⁹ B (boat), E (envelope), S (screw-boat) and T (twist-boat). According to the *puckering parameters*¹⁰ $Q = 0.822(6) \text{ \AA}$, $\theta = 81.5(4)^\circ$ and $\phi = 107.9(4)^\circ$ the nearest form is B. In the novel five-membered hetero ring possessing an envelope form

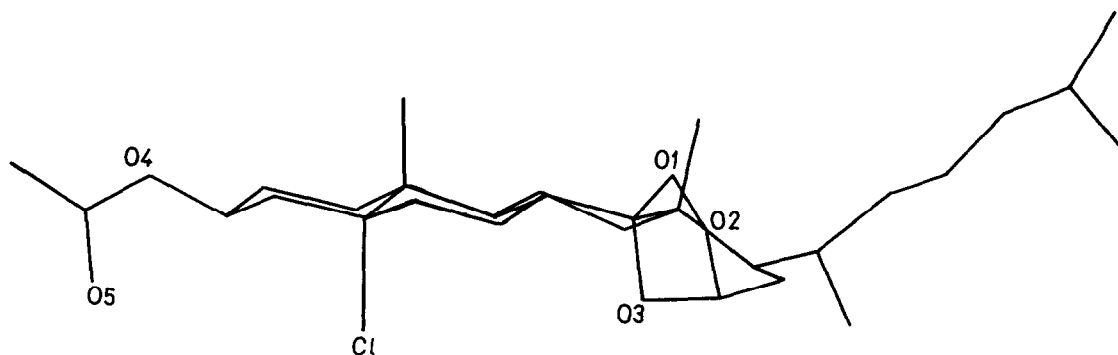
with C(15) on the flap ($Q = 0.484(6) \text{ \AA}$, $\phi = 67.8(7)^\circ$), while the corresponding lowest *asymmetry factor*¹¹ $fC_s(C15) = 3.6 \times 10^{-2} \text{ \AA}$ the C-O distances vary between 1.400(6) and 1.474(5) \AA . Both C(14) and C(15) bear one shorter and one longer C-O bond, while the length of the O-O peroxy bridge (1.464(4) \AA) indicates a real single bond¹². The lowest endocyclic bond angle ($99.7(5)^\circ$) appears at O(2). The long linear 1,5-dimethyl-*n*-hexyl chain bond β -equato-

rially to C(17) is protruding from the mean plane of the steroid skeleton with a dihedral angle about 35° .

The ozonide 2 has the absolute configuration corresponding to the thermodynamically more stable isomer (a similar observation was already made by Wife¹). Finally, we want to stress the fact that our results absolutely disprove the generally accepted belief that saturated steroids are inert toward ozone in solution.



a)



b)

Figure 1. a) A perspective view of the molecule with atomic numbering. The bare numbers are for carbon unless indicated otherwise.

b) A view of the molecule parallel to the least squares plane of the atoms from C(1)-C(17).

References and Notes

1. R.L. Wife, D. Kyle, L.J. Mulheirn and H.C. Volger, *J.Chem.Soc., Chem. Commun.*, 1982, 306 (as well as references cited therein).
2. As a representative saturated steroid system we have chosen the 5 α -chloro-cholestane-derivative 1, owing to a possibility of subsequent selective Δ -4 or Δ -5 bond regeneration. In addition, we wanted to examine a possible influence of 5 α -chloro-atom on the course of ozonation reaction.
3. m.p.135 $^{\circ}$ C; IR(KBr): 2940, 1735, 1240-1030 cm^{-1} ; $^1\text{H-NMR}(\text{CDCl}_3)$: δ = 0.85 (s,3H), 0.95(s,3H), 1.0(d,6H), 1.12(d,3H), 2.05(s,3H), 5.2-5.6(m,1H), 5.9 (d,J=6.5 Hz, 1H); mass spectrum: 510.5(M^+), 460.5($\text{M}-\text{H}_2\text{O}-\text{O}_2$) $^+$; satisfactory microanalysis for $\text{C}_{29}\text{H}_{47}\text{O}_5\text{Cl}$.
4. Besides the ozonide 2, we isolated other three more polar products, whose structures are yet under investigation.
5. m.p.85 $^{\circ}$ C; IR(KBr): 3620-3300, 2950, 1740, 1250, 1030 cm^{-1} ; mass spectrum: 504(M^+-HCl); satisfactory microanalysis for $\text{C}_{31}\text{H}_{53}\text{O}_5\text{Cl}$.
6. G. Germain, P. Main and M.M. Woolfson, *Acta Cryst.* A27, 368 (1971).
7. Intensities were collected on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated MoK_α -radiation ($\lambda = 0.71073 \text{ \AA}$). The lattice parameters $a = 7.936(4)$, $b = 16.669(2)$, $c = 21.568(3) \text{ \AA}$ ($Z = 4$) were determined and refined by diffractometry.
8. A listing of positional parameters for non-hydrogen and hydrogen atoms together with anisotropic vibrational parameters for non-hydrogen atoms of 2 may be obtained from the Cambridge Data Centre Univ. Lab., Lensfield Road, Cambridge, England (see: *Tetrahedron Lett.* 3081 (1978)).
9. J.C.A. Boeyens, *J.Cryst.Mol.Struct.* 8, 317 (1978).
10. D. Cremer and J.A. Pople, *J.Am.Chem.Soc.* 97, 1354 (1975).
11. A. Kálmán, M. Czugler and K. Simon, in *Molecular Structure and Biological Activity*, eds: J.F. Griffin and W.L. Duax, pp. 367-376, New York: Elsevier Biomedical (1982).
12. L. Pauling, *The Nature of Chemical Bond*, 3rd. ed. Ithaca: Cornell Univ. Press (1960).

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