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# PREPARATION AND REACTIONS OF HYDROXY CYCLIC SULFITES

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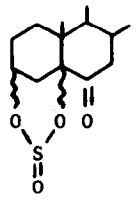
In the preceding paper[1] it was demonstrated that the cyclic sulfites derived from 3β,5β-dihydroxy- and 3α,5α-dihydroxy-cholestan-6-one and the 7α-bromo derivative of the former exist with the heterocyclic rings in boat conformations and the S=O axial or equatorial, depending upon the compound or its mode of preparation. We describe here the reductions of the non-brominated oxo cyclic sulfites and the reactions of the reduction products with base.

Treatment of the oxo sulfite mixture (~ 9% 1a and 91% 1b,[1] obtained from 3β,5-dihydroxy-5β-cholestan-6-one by reaction with thionyl chloride-pyridine at 1°) with lithium aluminum tri-t-butoxy hydride (LATBH) in dry tetrahydrofuran for 45 min gave two isomeric hydroxy sulfites, A and B,[2] in yields of 6% and 57%, respectively. The assignment of structures was made as follows: saponification of both A and B (and their acetate derivatives) with methanolic potassium hydroxide solution gave the 3β,5β,6β-triol 4,[3] indicating β configurations for the oxygen substituents at C-3, C-5, and C-6 in the sulfites. Compound A exhibited nmr and ir spectra consistent with structure 2a (heterocyclic ring as a boat) while the nmr spectrum of B showed a 3α-hydrogen signal (248 Hz) upfield relative to the absorption (276 Hz) of the 6α-hydrogen (see Table I). The C-6 oxygen is therefore esterified as part of the heterocyclic ring, the hydroxy group is at C-3, and B must be a product of rearrangement (3a) which occurred during the reduction, presumably from 1b. The mechanism of the rearrangement is being investigated.

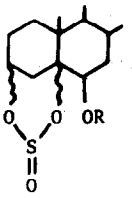
Two configurations at sulfur are possible in the five-membered sulfite ring (as in 3a)[4] just as in the 6-membered sulfites. Verification of the structural and configurational assignment to isomer B was obtained by reduction of 3β-acetoxy-5-hydroxy-5β-cholestan-6-one to the corresponding 6β-hydroxy steroid[3] and treatment of this material with thionyl chloride-pyridine at 1°. Chromatographic separation yielded two isomeric sulfites, one of which (3b) was identical to the acetate of B. The other (which gave the triol 4 upon saponification) showed 19-H absorption (75 Hz) in its nmr spectrum at a markedly lower field than 3b (19-H

at 57 Hz) and is therefore assigned structure 5 in which the S=O is directed toward the C-19 methyl group.



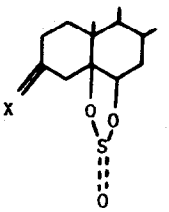
3β,5β Series
1a, S=O axial
1b, S=O equatorial

3α,5α Series
1c, S=O axial



3β,5β Series
2a, S=O axial, R=H
2b, S=O axial, R=Ac

3α,5α Series
2c, S=O axial, R=H
2d, S=O axial, R=Ac



3a, X = 

3b, X = 

3c, X=O

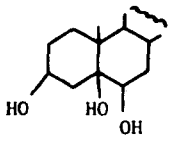
TABLE I[+]

PHYSICAL CONSTANTS OF CYCLIC SULFITES

| Compound | Physical Data [mp; $[\alpha]_D$; $\bar{\nu}$ max (S=O); nmr (Hz)] |
|---|---|
| 2a | 178.5-180°; -8°; 1196 $cm^{-1}$; 19-H (69), 4β-H (195, d of d, J = 15 and 4), 6α-H (232, d of d with superimposed center legs, J = 3 and 3), 3α-H (284, $W_{1/2}$ = 8) |
| 2b | oil; -47°; 1196 $cm^{-1}$; 19-H (66), 4β-H (202, d of d, J = 15 and 4), 3α-H (282, $W_{1/2}$ = 8), 6α-H (305, $W_{1/2}$ = 6) |
| 2c | 171-173°; +39°; 1181 $cm^{-1}$; 19-H (72), 4α-H (198, d of d, J = 15 and 3), 6α-H (232, $W_{1/2}$ = 4), 3β-H (283, $W_{1/2}$ = 7) |
| 2d | 144-145°; +35°; 1199 $cm^{-1}$; 19-H (70), 4α-H (195, d of d, J = 15 and 4), 3β-H (281, $W_{1/2}$ = 8), 6α-H (299, $W_{1/2}$ = 4) |
| 3a | 116-120° (after drying in vacuo); ±0°; 1217 $cm^{-1}$; 19-H (54.5), 3α-H (248, $W_{1/2}$ = 8), 6α-H (276, d of d unresolved, J ~ 3 and 3) |
| 3b | 133-134.5°; +5°; 1218 $cm^{-1}$; 19-H (57), 6α-H (270, d of d unresolved, $W_{1/2}$ = 6), 3α-H (303, $W_{1/2}$ = 8) |
| 3c | 129-131° dec; +15°; 1218 $cm^{-1}$; 19-H (62), 6α-H (279, $W_{1/2}$ = 6) |
| 5 | 85°*; -11°; ~1235 $cm^{-1}$ (under acetoxy C-O stretch); 19-H (75), 6α-H (245, d, J = 5), 3α-H (299, $W_{1/2}$ = 8) |

[+]Optical rotations in $CHCl_3$; ir spectra in $CCl_4$; nmr spectra in $CDCl_3$ at 60 MHz with TMS standard.
*Contains solvent (EtOH) of crystallization.

Oxidation of 3a with chromic oxide reagent[5] gave the oxo sulfite 3c (64% yield). The latter underwent thermal decomposition to give 5α-cholestan-3,6-dione (78%) in a manner typical of 1,2-cyclic sulfites.[6] The dione was also obtained when 3a was treated with methanolic potassium hydroxide. Isolated as an intermediate in this reaction was 6β-hydroxy-cholest-4-en-6-one which could be converted to the dione under the reaction conditions.[7a]

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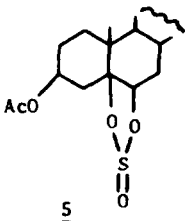


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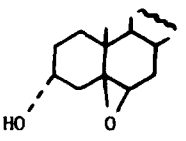


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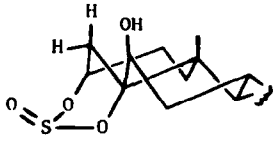
In contrast to the behavior of 1b toward LATBH, its 3α,5α diastereomer 1c underwent reduction with no rearrangement, yielding the 6β-hydroxy sulfite 2c. Rearrangement to a 5,6-sulfite is undoubtedly precluded in this instance by the trans diaxial relationship of the substituents at C-5 and C-6. When 2c was boiled with methanolic potassium hydroxide, the corresponding triol was not obtained; the oxide 6[7b] was formed in 79% yield, presumably by the generation of an oxyanion at C-6 which then affected an intramolecular displacement of the sulfite oxygen at C-5. Inspection of models (see 2c perspective view) shows that attack at the sulfur atom is partially inhibited by the steroid A ring, thereby favoring oxyanion formation. An alternate mechanism may involve attack at sulfur leading to a dipolar intermediate which collapses to oxide 6.[8]




2c, perspective view

We are extending these studies to other cyclic sulfites in order to test the generality, if any, of ring rearrangements as reported here in the reduction of 1b.

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(*) To whom inquiries should be addressed.

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(2) Satisfactory elementary analyses were obtained for all new compounds reported here.

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