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PREPARATION OF 5α-CHOLESTANE-2α,5-syn- AND -anti-EPISULFOXIDES AND THE CONFIGURATION OF THE SULFINYL OXYGENS

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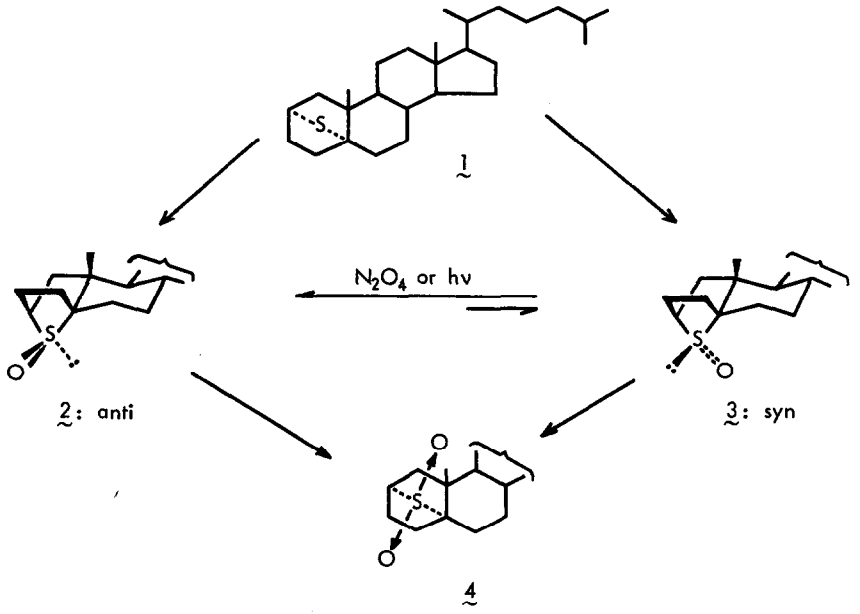
Although extensive studies on sulfoxides diastereoisomeric at the sulfur atom have disclosed their chemical and physico-chemical properties (1, 2), little is known about the properties of the oxides of sulfur-bridged compounds (3). We now wish to report a stereoselective preparation of 5α-cholestane-2α,5-syn- and -anti-episulfoxides, comprising the 7-thiabicyclo[2.2.1]heptyl 7-oxide system, and an observation that the sulfinyl oxygen exchange reaction requires unusually drastic conditions.

Oxidation of 5α-cholestan-2α,5-episulfide (1) (4) with 1 mole of m-chloroperbenzoic acid in CH_2Cl_2 gave two sulfoxide isomers; 2 (mp 132.5-133.5°, $[\alpha]_D$ +98°, ν_{max}^{Nujol} 1062, 1051, 1030 cm^{-1})



and 3 (mp 160-162°, $[\alpha]_D$ -38°, ν_{max}^{Nujol} 1052, 1030 cm^{-1}) in 81.1% and 1.3% yield, respectively. In contrast, 3 was predominantly obtained in 91.7% yield together with 1.6% of 2 by t-butyl hypochlorite oxidation of 1 in THF-MeOH at -78°. That 2 and 3 are diastereoisomeric was confirmed by their oxidation with excess m-chloroperbenzoic acid leading to the identical sulfone (4), mp 204.5-205.5°, $[\alpha]_D$ +61°, $\nu_{max}^{CCl_4}$ 1300, 1146, 1116 cm^{-1}. The results of the oxidation of 1 with various reagents are shown in TABLE I.

Table I. The Results of the Oxidation of 5α-Cholestan-2α,5-episulfide (1) with Various Oxidizing Agents as Determined by GLC

Reagent	Product and yield (%) Total yield	anti (2)	syn (3)	Remarks
m-Cl·C_6H_4·CO_3H	82.4	98.5	1.5	CH_2Cl_2, 25°, 1 hr
H_2O_2	56.9	97.7	2.3	30.3% of recovered 1 acetone, 25°, 20 hr
CrO_3	82.2	97.7	2.3	pyridine, 25°, 48 hr
$NaIO_4$	56.5	98.6	1.4	28.6% of recovered 1 dioxane-H_2O, 25°, 20 hr
t-BuO_2H	85.7	97.1	2.9	benzene, 50°, 50 hr
N_2O_4	31.2	91.6	8.4	ether, 0°, 30 min
PhIO	46.8	94.7	5.3	benzene, 75°, 2 hr
t-BuOCl	93.3	1.6	98.4	THF-MeOH, -78°, 1 hr

The configurations of the sulfinyl oxygens in 2 and 3 were assigned by consideration of their chromatographic behavior, selectivity in oxidation with peroxy reagents, and NMR data. It is known that the isomer with the more sterically accessible sulfinyl oxygen has the higher retention time in chromatography (1).

Of the two sulfoxides, 2 is less mobile on TLC and GLC, and hence was assigned as the anti-sulfoxide. Distribution of isomeric sulfoxides formed on the oxidation of a sulfide with peroxy reagents generally depends upon an accessibility of the electrophiles to the reaction site ("steric approach control"). The selective formation of 2 in the oxidation of 1 with the reagents is in keeping with the

above assignment. In the NMR spectra determined by 100 Mc spin-decoupling experiment, the 1α-proton of 3 resonates at 2.82 ppm, lower by 0.97 ppm than that of the parent sulfide (1.85 ppm), whereas the corresponding proton of 2 shows a small upfield shift (0.08 ppm). Since the downfield shift observed in 3 is obviously caused by the proximity of the proton and the sulfinyl oxygen and the upfield shift in 2 is due to the magnetic anisotropy of the sulfur-oxygen bond, 3 should be the syn-sulfoxide and 2 the anti-isomer, consistent with the above assignment.

The relative thermodynamic stabilities of the two sulfoxide isomers were studied. Unexpectedly, both 2 and 3 were found to be stable in HCl-dioxane and even in conc H_2SO_4, and were also stable at 250° in contrast to sulfoxides generally reported (1, 2). Furthermore, on treatment with dinitrogen tetroxide under normal conditions no change was observed, but very long treatment of the each pure isomer with the reagent (1 month) at 0° furnished identical equilibrium mixtures, consisting of 2 (92%) and 3 (8%). This ratio, corresponding to $\Delta G = 1.34$ kcal/mole for the reaction, syn $\rightleftharpoons$ anti, indicates that the anti sulfoxide is more stable than the syn isomer. Model examination also reveals that there exists in the syn sulfoxide a severe nonbonded repulsion between the sulfinyl oxygen and the 7α- or 9α-hydrogen, and the distance between them is indeed within their van der Waals radii (2.7 Å).

Hammond et al. (5) reported a failure in non-sensitized photoisomerization of dialkyl sulfoxides, we could, however, observe the photoinduced-isomerization of 2 and 3 as shown in TABLE II.

Table II. Photoinduced Isomerization

Substrate	Irradiation time (hr)	Recovery (%)	anti (2) (%)	syn (3) (%)
anti (2)	8	72.8	90.4	9.6
	14	64.7	90.3	9.7
syn (3)	17	55.4	77.3	22.7
	35	29.7	76.4	23.6

When 2 was irradiated by monochromatic light (λ_{max} 277 mμ) in ether under N_2 at room temperature for 8 hr, a mixture consisting of 2 (90%) and 3 (10%) was obtained. Further irradiation did not change the isomer ratio but caused a gradual decomposition of the substrate. On the other hand, irradiation of 3 under the same conditions for 17 hr gave the isomers 2 and 3 in the ratio of 77 : 23, a ratio not obtained from 2, even on prolonged irradiation.

These findings suggest that the bridge-top sulfoxides in the strained system resist not only an acid catalyzed oxygen exchange reaction (2) but also a thermal pyramidal inversion (6). The mechanism of the photoinduced isomerization observed is ambiguous at present, but at least it seems not to involve pyramydal inversion from the fact that mixtures of the same isomer ratio could not be obtained starting from the either isomer.

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