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α-EPITHIOKETOSTEROIDS: CONFORMATION AND REACTIVITY

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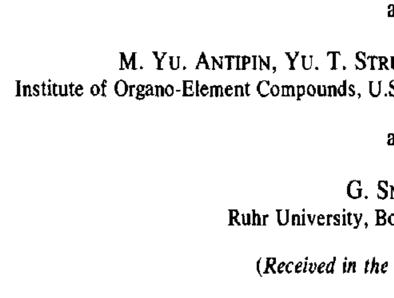
Abstract—In order to correlate reactivity with geometry, the conformational analysis of 16,17α-epithiopregnenolone has been carried out using X-ray analysis, low-temperature circular dichroism and quantum chemical calculation. Lack of conformational homogeneity of the acetyl side-chain is revealed; however the conformational equilibrium is restricted to the conformers with relative trans-orientation of epithio- and keto-groups.

It was observed that nucleophilic ring-opening of 16,17α - epithio - 20 - oxosteroids **1**[1,2] markedly differs from that of 16,17α - epoxy(epimino) - analogues.[3] The distinctions are both in reactivity, increasing in the following sequence: oxirane **2** > NH-aziridine **3** > NAc-aziridine **4** ⩾ thiirane **1**, and in the general direction of the reactions. Compared with oxirane **2**, thiirane **1** is much more inert in ring-opening reactions and commonly the reactions of **1** are completed with a desulphurisation. Only two cases are known,[1,2] in which thiirane **1** reacts with attack of reagent (thiolacetic acid, benzyl mercaptan), leading to a regio- and stereoselective trans- ringe-scission at the secondary atom C-16. In most reactions of oxirane **2** such scission is predominant[3] but not exclusive; cleavage at tertiary centre, in particular with thiolacetic acid,[4] was also observed.



A ground-state conformation of the molecule are expected to be responsible, equally with other factors, for the three-membered ring-opening reactions.[3,5] It, therefore, was of interest to evaluate the preferable geometry of thiirane **1**. To this end we investigated, using X-ray crystallography (more detailed data of X-ray analysis for thiirane **1** were published in Ref. 6) and low-temperature CD techniques the conformation of **1** in solid state and in solution. In addition, we carried out quantum chemical calculation of relative energies for different rotational isomers around the C-17–C-20 axis.

The general view of 3-acetoxy 16,17α - epithio - pregn - 5 - en - 3β - ol - 20 - on **1** in crystalline state with the interatomic distances is shown in Fig. 1. The bond distances shown in Fig. 1 are within the range of values normally found in other 5-pregnene molecules. 5-Membered ring D in this structure, as well as in 16,17α - epoxy - 20 - oxosteroid **2**[7] has C-14 α-envelope conformation (C-14 below the plane of the other D-ring atoms, which are coplanar to within 0.009 Å). The angle between C-13–C-15-bond and C-13, C-15–C-17 plane is equal to 38°. The sulfur atom is situated below the plane C-13C-17C-16C-15 atoms at-1, 567(2) Å, and the angle between that plane and three membered cycle plane is 68°. These data confirm the thiirane **1** structure and completely eliminate the literature contradictions on this matter.[8–10]

It is known that 16,17α-substituted 20 - oxo - pregnanes have preferred orientation of the 17β-acetyl side-chain as illustrated in Fig. 2, conformer A.[11,12] The situation , however, changes in a case of the compounds with three-membered cycle vicinity to the 20-carbonyl function. So, an unusual 17β-acetyl group conformation with trans-orientation 20-carbonyl group and three-membered ring relatively C-17–C-20-bond has been observed in 16,17α-epoxy-[3,7,13] and 16,17α-methylene substituted[13,14] structures. Preferred orientation of 17β-acetyl chain for 16,17α - epimino - 20 - oxosteroids **3**, **4** depends considerably on the substitution at nitrogen atom, being cis- in NH-aziridine **3** (Fig. 2, conformer D) and gauche (conformer A) in N-acetylaziridine **4**. We have found that side-chain conformation of thiirane **1** in solid agrees qualitatively with the conformation of oxirane **2**, assigned on the basis of X-ray analysis.[7] But the exact orientation of the side-chain in **1** is somewhat

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different from that observed in **2** and the torsion angles for these structures differ to the considerable extent. So, in crystalline state 20-carbonyl group of thiirane **1** is asymmetrically trans-oriented to the heterocycle (torsional angle C-21–C-20–C-17–C-16 = 13.6°) (Fig. 2, conformer B), whereas in oxirane **2** keto-group is symmetrically situated (conformer C).

The energies of thiirane **1** in different side-chain conformations were estimated by the CNDO/2 molecular orbital calculations based upon the observed atomic coordinates.[6] Only a fragment of the steroid ring D was considered in the calculation. One of the strengths of this method is its ability to provide reasonable charge distribution in molecule. In Fig. 3 are presented the energy differences (ΔE) resulting from a complete rotation of 17β-acetyl group around C-17–C-20-bond (15° stepwise of increments). According to the data the nearly symmetrical trans-conformer C has a minimum energy value. All the rest minimum energy values are occurred near the side-chain conformations in which torsional angle θ C-21–C-20–C-17–C-16 increases from $+30°$ to $+90°$. But, as can be seen from Fig. 3, the energy increase due to the rotation of 17β-acetyl group in opposite direction up to preferred in crystalline state conformer **B** ($\theta = +13.6°$) proceeds more rapidly. These results mean that the solid-state conformation of thiirane **1** is not energetically preferred (this discrepancy could result from the influence in the crystal of the intermolecular and packing forces that perturb and side-chain conformation[15]) and it may well be deviated considerably from that in solution. Therefore we have investigated the conformational equilibrium of thiirane **1** by variable-temperature CD

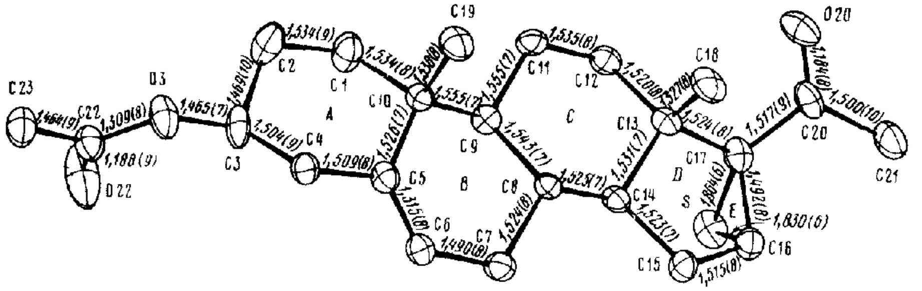

Fig. 1. General view of 3 - acetoxy - 16,17α - epithio - pregn - 5 - en - 3β - ol - 20 - on **1** in crystalline state; interatomic distances are shown in Å.

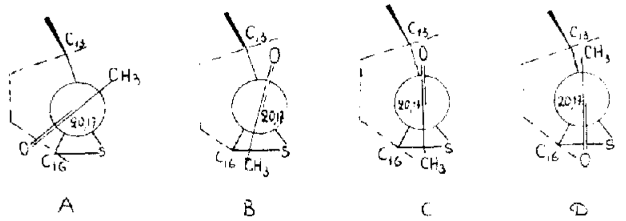

Fig. 2. Partial structures showing projections of ring D and the 17β-acetyl group conformations as viewed from C-20 to C-17.

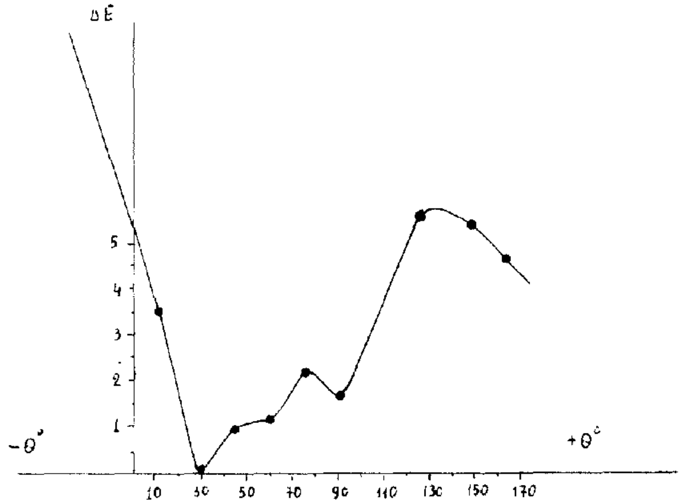

Fig. 3. Plot of the values of ΔE against θ; for the conformer, in which C-16–C-17 bond and 20-keto group are anticoplanar, $\theta = 0°$; for conformer **B** $\theta = 13°$; for conformer **C** $\theta = 30°$, etc.

method. Preliminary analysis of CD-spectra for **1** was carried out without employment of low-temperature techniques and the conclusions about preferred conformation were rather uncertain.[13] This investigation is of special interest because chiroptical and other chemical and physicochemical properties of α,β-epithioketones, not only in the steroid field, have not been investigated at present time.

In Table are listed the data of CD spectra obtained in EPA (ether, i-pentane, ethanol = 5:5:2) at +20°, −190°. A bathochromic shift is observed both for $n \rightarrow \sigma^*_{c\text{-}s}$ and for $n \rightarrow \pi^*_{c=o}$ transitions compared with standard magnitudes for these chromophores.[11,12,16] It indicates that epithio- and carbonyl group in thiirane **1** form a conjugative system. Of interest is that observed negative $n \rightarrow \sigma^*_{C\text{-}S}$ Cotton effect at 275 nm does not quite good keep in limit of the symmetry rules proposed for thiiranes.[11,16] This suggests that the charge distribution in α,β-epithioketone **1** is much more complicated than in an usual thiirane without an adjacent carbonyl function.

It was shown[13,17] the signs of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ Cotton effects of the α,β-epoxyketones follow the "reverse octant rule" and its signs depend on which octant 3-membered ring appear in and are nearly not affected by the remainder of the molecule.

However, the empirical correlations concerning of a contribution of the thiirane cycle adjacent to keto-group to $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ Cotton effect are still unknown. The data below show that epithioketone **1** follow a "normal octant rule".[11] The molecular (Dreiding) models and octant projection of **1** in the light of "normal octant rule" for carbonyl chromophore indicates that in energy preferred conformation C the episulfide ring falls into a positive octant; therefore a positive Cotton effect would be predicted for $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition of the C-20 = 0 group of thiirane **1**. According to octant projections the decreasing of the positive rotational strength would be predicted for all other conformers with next energy minimum ($\theta = +30° + 60°$) and the side-chain rotation up to $\theta = +90°$ would give rise to the conformer with negative Cotton effect (Fig. 4). This is in accord with the experimental observations: an augmentation of the positive $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ Cotton effects is observed upon decreasing temperature (Table 1). This result is expected since the population of the more stable conformer C (Fig. 2) with positive rotational strength would be increased at low temperature. A positive maximum of the CD band of the $n \rightarrow \pi^*$-transition at low temperature increases very strongly, ($J^{+20}_{-190} = -44$) suggesting that thiirane **1** is a conformationally mobile system and the preferred conformation C is not strictly fixed. The constancy of $n \rightarrow \pi^*$ maximum and an absence of new CD maxima in the region allows us to conclude that all the conformations are similar and all of them are located mainly near preferred s-trans conformer C. The equal interest is the strong increasing of the negative $n \rightarrow \sigma_{C\text{-}S}$ Cotton effect at low temperature ($J^{+20}_{-190} = -49$). Such observation might reasonably account for the changes in electronic interactions of epithio- and keto-group upon changing of their geometrical orientation.

Table 1.

t°	$\pi \rightarrow \pi^*_{c=o}$ ΔE (λ_{max}, nm)	$n \rightarrow \sigma^*_{c\text{-}s}$ ΔE (λ_{max}, nm)	$n \rightarrow \pi^*_{c=o}$ ΔE (λ_{max}, nm)
+20	+14.25(220)	−3.87(275)	+5.70(312)
−190	+16.44(218)	−7.59(274)	+10.27(312)

The above spectroscopical examination, the X-ray analyiss data and quantum chemical calculation for thiirane **1** show the lack of conformational homogeneity of 17β-side chain, but the conformational equilibrium is restricted by the conformers with relative trans-orientation of epithio- and keto-groups. The nature of the electronic interactions in α,β-epoxy (epimino, cyclopropyl) ketones has been described as a type of hyperconjugation which results from orbital overlap of the bend bonds of the small ring with the p-orbitals of the attached carbonyl group.[18,19]. For α,β-epithioketones such investigations have not been carried out. Following Walsh's prediction of special geometric requirement for such interaction[20] it has been shown that for maximum conjugative interaction p-orbital of the carbonyl group should lie parallel and symmetrically to the plane of the three-membered ring.[18,19] Such geometrical position is achieved in s-trans conformation of compounds **1**–**5**. We conclude therefore that one of the factors stabilizing the thiirane **1** in trans-conformation is a conjugation of episulphide cycle and carbonyl group.

Using CNDO/2 method we made an attempt to understand the electron density changes in thiirane **1** compared with oxirane **2**. The charge distribution in energy preferred ground station conformations and the interatomic distances determined by X-ray analysis for the molecules **1** and **2** are represented in Fig. 5. The first observation made from the comparative analysis of compounds **1** and **2** (Fig. 5) is that the charge distributions at C-16, C-17 and heteroatom in thiirane **1** differ essentially from that in oxirane **2**: an electrophility both of C-17 and C-16 centres in thiirane is very low and the oxygen atom of

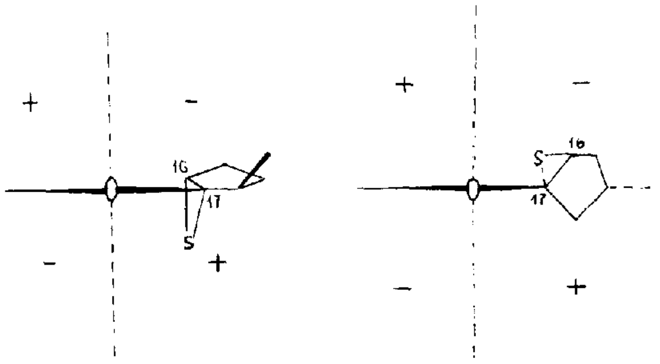

Fig. 4. Octant projections of thiirane **1** in conformation C (left) and in conformation, in which torsional angle $\theta = +90°$ (right).

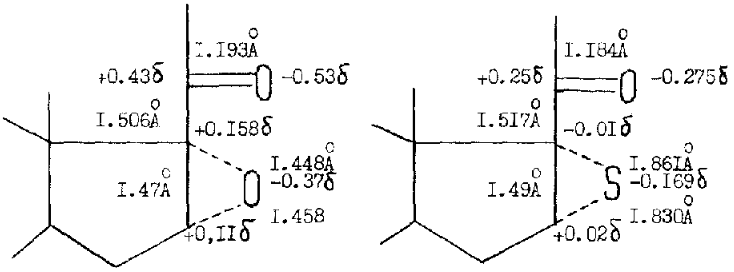

Fig. 5. The charge distribution in energy preferred ground state conformations of ring D fragment for **1** and **2**, estimated by the CNDO/2 molecular orbital calculations; interatomic distances (Å) determined by X-ray analysis

heterocycle bears the larger negative charge than the sulphur atom. The second observation is a high polarization of carbonyl group in oxirane **2** and a decrease of its polarization in thiirane **1**. Worth noting is the unequal C–S bond distances in thiirane. The first difference may be reasonably accounted for the low electronegativity of sulphur compared with oxygen.[21] It seems possible to suggest, as it has been done for more simple system ($-S-CH_2-CO-$)[22–24] that the decrease of the carbonyl group polarization in thiirane **1** is due to some transfer of carbonyl density from carbonyl group to a vacant orbital on the sulphur atom. Then, the low electrophility of C-17-center in thiirane **1** is due not only by smaller electronegativity of sulphur but also by delocalization of the p-electrons of the C-20=O bond into the episulphide cycle, i.e. opposite direction to oxirane **2**.

These results thus seem to provide a very satisfactory interpretation to the differences in the nucleophilic ring opening reactions undergone by thiirane **1** and oxirane **2**. The observed conformational and electronic distinctions between **1** and **2** we may expect to lead to a different chemical behavior of these compounds. Indeed, the low reactivity of thiirane **1** is surely depends on the poor electrophilicity of attacked centres and owing to it the thiirane **1** in contrast to oxirane **2** reacts with great difficulty with nucleophilic reagents at the secondary C-16-atom and does not react at all at tertiary C-17-atom. The side-chain mobility in thiirane **1** may explain the easy sulphur elimination in a conformation in which the coplanarity of carbonyl group and C-17–S bond is achieved. Moreover, the bond C-17–S is longer and so presumably weaker than in usual thiirane. As a result the opening reactions of thiirane **1** are usually completed by desulphurisation.

EXPERIMENTAL

Crystals suitable for X-ray analysis of thiirane **I** with m.p. 181° were obtained by crystallisation from dioxane. The crystals are orthorhombic, at 20°C a = 12.658(2), b = 25.585(4), c = 6.3940(9) Å, V = 2070.7(9) Å^3, d(calc.) = 1.25 g/cm^{-3}, Z = 4, space group $P2_12_12_1$. The unit cell parameters and intensities of 1911 independent reflections were measured (ω-scan. method, θ max $\leq$ 57°) on an automatic 4-circle diffractomer (Hilger and Watts) equipped with graphite monochromator using CuK_α-radiation. The structure was solved by direct method using MULTAN programme and refined in the full-matrix anisotropic least-squares with 1677 reflections having $F^2 > 2\sigma$. All hydrogen atoms were included in the refinement with the fixed coordinates and isotropic thermal parameters ($B_{iso} = 4.0$ Å^2). The absolute configuration was determined taking into account the anomalous scattering by S and O-atoms. The final R-values are R = 0.0624 and R = 0.0787 (for the inverted model R = 0.0692 and $R_G = 0.0864$). All calculations were carried out with EXTL-system on Nova-1200 and Eclipse S/200 computers.

All CD spectra were recorded with the Dichrograph III (Jobin Yvon) in EPA at +20° to −190°C in cells of thickness 0.01–1.00 cm and concentration of about 0.2–1 mg/g.

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