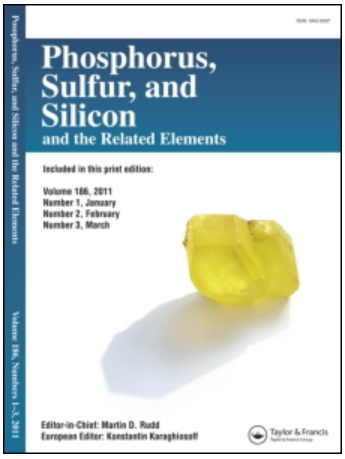

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STEREOSTRUCTURE OF ISOMERIC (±)-1-THIOFLAVANONE 1-OXIDES

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The synthesis, separation and stereochemistry of 1-epimeric (±)-1-thioflavanone 1-oxide isomers with equatorial phenyl group are described. The higher melting isomer **(2a)** has a 1,2-*cis*-, the lower melting one **(2b)** a 1,2-*trans* configuration. ^{1}H NMR and mass spectral data for both isomers and X-ray diffraction analysis of **2a** are also presented.

Keywords: Stereoisomerism; Sulfoxides; Thiopyrans; X-Ray crystallography

INTRODUCTION

A plethora of methods suitable for the transformation of sulfides into sulfoxides has recently been reviewed[1]. Most of the methods can not avoid the formation of sulfones as by-products of overoxidation, moreover, frequently formation and epimerization[2] of chiral sulfoxides make more difficult to obtain homogeneous products.

By the usual methods of preparation even after purification by column chromatography thioflavanone 1-oxides **(2)** have been obtained and characterized (e.g. by NMR spectroscopy)[3,4] as a mixture of isomers. Formation of the isomers in ~1:1 ratio has been observed in solution[5] when dimethyldioxirane was used as the oxidant (^{1}H NMR).

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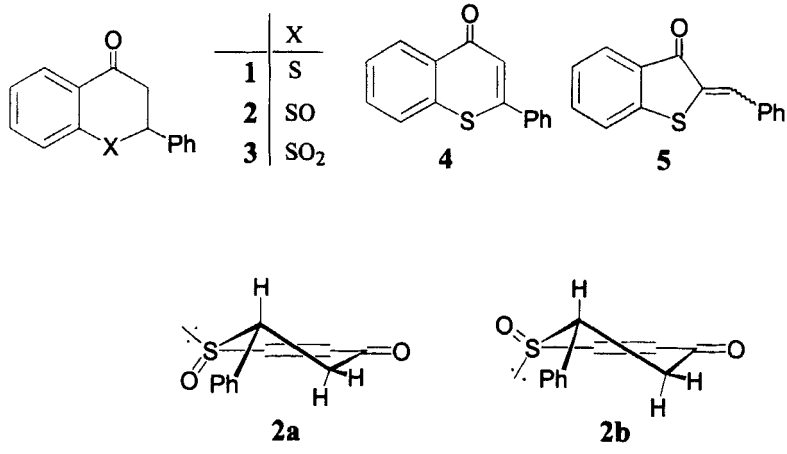
RESULTS AND DISCUSSION

Homogeneous thioflavanone 1-oxide has been prepared in crystalline form with m.p. about 150°C by using monoperoxyphthalic acid[6] or $NaIO_4$[7] as the oxidant in yields of 45% and 59%, respectively. On the basis of a syn-axial effect[8] reflected in the ^1H NMR spectrum this product has been suggested to have a 1,2-*cis* stereostructure with *axial* S-O group and transformed[9] by treatment with KOH/EtOH, previously described[10] for an analogous transformation of thiochromanone 1-oxides, into thioflavone (**4**). We found crude sulfoxide **2** (with correct C, H, and S analysis data) to be homogeneous by TLC. However, the moderate yield of the product with constant m.p. 149 – 150 °C indicated the formation of isomers. Actually when **1** was treated with $NaIO_4$ as described earlier[6], the $CHCl_3$ solution of the processed reaction mixture contained a higher amount of the higher melting isomer (in ratio of 2:1, by ^1H NMR)(Scheme 1).



SCHEME 1

In order to make careful search into the spectral properties and stereostructure of thioflavanone 1-oxide we aimed at the isolation of both isomers indistinguishable by TLC. By systematic crystallization of the crude (TLC homogeneous) sulfoxide **2** from benzene with addition of heptane or hexane (see Experimental) beside the product with m.p. 149–150 °C also

the more soluble isomer with constant m.p. 120 – 121 °C was isolated in pure (^{1}H NMR) form.

The chemical reactivity (e.g. transformation with elimination of the elements of water into thioflavone **4** by treatment with KOH/EtOH) of both isomers was found to be practically identical. Similarly the IR spectra did not exhibit any significant difference. Therefore careful ^{1}H NMR measurements were performed for $CDCl_3$ solutions of pure **2** isomers (see Table I) before getting acquainted with the earlier unpublished data[9] of the until then known[6] sulfoxide.

TABLE I ^{1}H NMR data of compounds **1** – **3**

Compound	*Solvent*	δ *[ppm]*			*J [Hz]*			*Ref.*
		2-H_a	*3-H_a*	*3-H_e*	*$2_a,3_a$*	*$2_a,3_e$*	*$3_a,3_e$*	
1	$CDCl_3$	4.74	3.36	3.22	12.3	3.9	16.4	
2a	$CDCl_3$	4.50	4.16	3.04	12.6	2.6	17.4	
2b	$CDCl_3$	4.55	3.30	3.45	11.7	3.9	18.2	
3	$CDCl_3$	4.90	4.05	3.45	12.5	3.1	17.5	
1	$CDCl_3$	4.73	3.33*	3.21†	12.1	3.9	16.5	[11]
1	[D_6]DMSO	4.95	3.44	3.09	12.4	3.6	16.4	[9]
2a	[D_6]DMSO	5.11	4.02	3.03	12.3	2.6	17.2	[9]
3	[D_6]DMSO	5.73	4.21	3.32	12.4	3.3	18.0	[9]

* – Erroneously assigned as 3-H_e. [11]
† – Erroneously assigned as 3-H_a. [11]

The high $J_{2\text{-H},3\text{-H}}$ coupling constants (12.6 Hz and 11.7 Hz, respectively) of the ^{1}H NMR spectra for the isomers revealed (see Table I) that both sulfoxides have the same conformation with an equatorial phenyl group, consequently the two **2** isomers must be 1-epimeric sulfoxides. The considerable downfield shift ($\Delta\delta$ = 0.80 ppm, in $CDCl_3$) of the 3-H_a signal of the higher melting **2** isomer (as compared to the chemical shift of the same hydrogen of **1**) due to the deshielding effect caused by the anisotropy of the S-O moiety ("syn-axial effect"[8]), moreover the greater ($\Delta\delta$ = 0.14 ppm) chemical shift difference of 3-H_a of the higher melting **2** isomer

when measured in $CDCl_3$ and $[D_6]$DMSO, respectively, in comparison to the $\Delta\delta = 0.01$ ppm difference for 3-H_e suggested the higher melting isomer to be 1,2-*cis* sulfoxide (**2a**) and the recently isolated lower melting one to be the 1,2-*trans* epimer (**2b**) with an equatorial S-O moiety.

The above stereochemical assignation was unequivocally proved by the single crystal X-ray diffraction analysis of the more appropriately crystallizing higher melting isomer (**2a**). Crystals suitable for X-ray diffraction could be grown from samples recrystallized from benzene/heptane and a colorless crystal with approximate dimensions of 0.3 mm × 0.3 mm × 0.2 mm was chosen for the measurement. Data were collected at 293(1) K on an Enraf Nonius MACH3 diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å) and ω-2θ motion. **2a,** $C_{15}H_{12}O_2S$, crystallizes in the monoclinic system, space group $P2_1/c$ with a = 9.851(2) Å, b=12.595(3) Å, c = 10.325(3) Å, $\beta = 97.43°$, V = 1270.2(5) $Å^3$ and Z = 4. For $\theta_{max} = 29.97°$, 2671 reflections were measured of wich 1989 were independent, 1431 with $I > 2\sigma(I)$ and an intensity decay of 3% was observed. The structure was solved using the SIR-97 software[16] and refined on F^2 using SHELX-97[17] and the WINGX-97 system[18] with R(F) = 0.034 and $wR(F^2) = 0.1012$ for 1988 reflections and 163 parameters, treatment of H atoms was mixed. ORTEP plot of **2a** at the 50% probability level is shown in Figure 1.

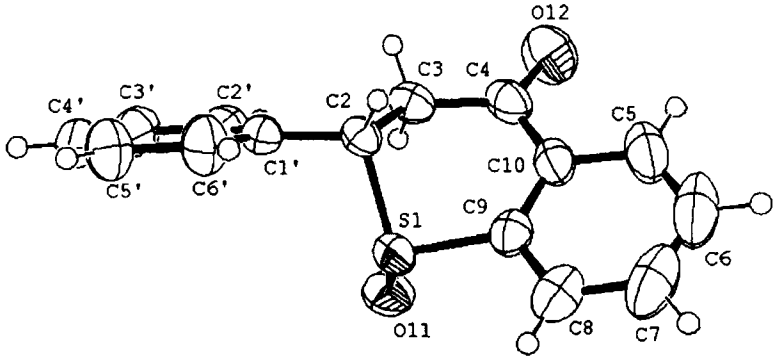


FIGURE 1 ORTEP drawing of compound **2a** with 50% of the thermal ellipsoids

Also the EI mass spectrometric investigations of the **2** isomers are in accordance with the above conclusions. The fragmentation pattern was

found to be analogous for both isomers. The relative intensities of the initial fragments were, however, dissimilar namely the $m/z = 237$ [$M^+ - 1 - H_2O$] fragment was formed more readily from the higher melting isomer (see Table II). The pattern of subsequent fragmentation of both isomers (especially that of **2a**) resembled the fragmentation of thioaurone (**5**) and not that of the isomeric thioflavone (**4**). Thus the greater tendency of **2a** to form the initial particles $m/z = 239$, 238, and 237 (see Table II) suggests the fragmentation to start with the transient formation of the thiiranium ion species postulated earlier[12–15] for the ring-contraction transformation of 1-thiobenzopyrans to give benzothiophen derivatives (e.g. thioaurone **5**) in heterolytic or photochemical reactions.

TABLE II Initial fragments of the EI mass spectra of compounds **2a**, **2b**, **3**, **4**, and **5**

Compound	*m/z (%)*
2a	256(3) [$M^{+\cdot}$], 239(15) [$M^{+\cdot}$- $OH^{\cdot}$], 238(55) [$M^{+\cdot}$- H_2O], 237(100) [$M^{+\cdot}$- 1-H_2O]
2b	256(6) [$M^{+\cdot}$], 239(7) [$M^{+\cdot}$- $OH^{\cdot}$], 238(23) [$M^{+\cdot}$- H_2O], 237(35) [$M^{+\cdot}$- 1- H_2O]
3	272(5) [$M^{+\cdot}$], 208(35) [$M^{+\cdot}$-SO_2]
4	238(100) [$M^{+\cdot}$], 210(89) [$M^{+\cdot}$- CO]
5	238(49) [$M^{+\cdot}$], 237(100) [$M^{+\cdot}$-1], 208(5)

EXPERIMENTAL SECTION

General

Melting point (uncorrected): Kofler block. Solutions were concentrated under reduced pressure in a rotary evaporator (< 40 °C, bath). TLC: Kiesegel 60 F_{254} (Merck, Alurolle), $CHCl_3$/EtOAc (95:5) and $CHCl_3/Et_2O$ (9:1). IR (KBr discs): Perkin-Elmer 16 PC-FT. 200-MHz ^1H NMR: Bruker WP 200 SY, $CDCl_3$ as solvent, TMS as internal standard. MS: VG-7035, GC/MS/DS (ion current 0.1 mA, direct insertion technique, 70 and 20 eV).

Preparation of thioflavanone 1-oxides (2a and 2b)

Thioflavanone (**1**) was oxidized by treatment with $NaIO_4$ in hot aq. MeOH as described earlier[7] to give TLC-homogeneous crude **2**. Systematic

repeated recrystallizations from benzene with addition of heptane afforded the less soluble pure **2a**, m.p. 150–151°C, lit.: 149–150°C (from PhH/heptane)[7], 148 – 151°C (from PhH/petroleum ether)[6] and the more soluble isomer **2b**, m.p. 120–121°C (from PhH at room temperature with addition of hexane).

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