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Article

Synthesis, Molecular Structure and Crystal Packing Peculiarities of Some 5-Arylidene-3-Phenylrhodanine Derivatives

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Abstract

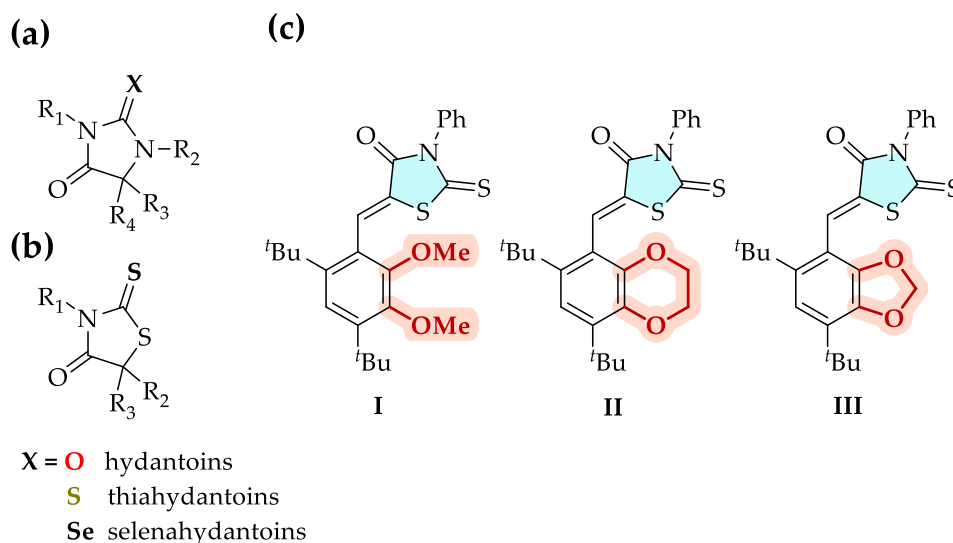
We report the synthesis and single-crystal X-ray structures of three novel (Z)-5-arylidene-3-phenylrhodanine derivatives, differing in the substituents on the benzylidene fragment (two methoxy groups (compound **I**), a dioxine ring (compound **II**), or a dioxole ring (compound **III**)). Despite the overall similarity of the molecules, their supramolecular architectures were found out to be strikingly different. In both compounds **I** and **II**, short S...S chalcogen bonds together with forced C-H...O hydrogen bonds generate dimeric motifs, whereas **III** lacks S...S interactions and instead features an $n \rightarrow \pi^*$ contact from the rhodanine carbonyl oxygen to the benzodioxole ring, as well as C-H...S bifurcate hydrogen bond. The results of intermolecular interactions in those structures are checked *via* Hirshfield surface analysis. The fine modulation of the arylidene substituent can switch the primary intermolecular synthon from chalcogen bonding to $n \rightarrow \pi^*$ interactions, offering new possibilities for crystal engineering of rhodanine-based materials.

Keywords: rhodanines; 5-arylidene-rhodanines; π -stacking; hydrogen bonds; crystal packing; X-ray diffraction

1. Introduction

Rhodanines, also known as 2-thio-4-oxothiazolidines, are a common class of heterocyclic compound whose structure and properties have been extensively studied using X-ray diffraction (XRD). This method enables the precise determination of molecules' three-dimensional structures, the nature of crystal packing and intermolecular interactions. This information is important for understanding their biochemical activity and industrial applications [1]. Analysis of the X-ray diffraction of various rhodanine derivatives shows that they predominantly crystallize in the monoclinic system, although other lattice types are also present [2,3]. A notable feature is that a unit cell may contain multiple independent molecules, suggesting complex packing [4]. Rhodanines are much more than just «hydantoins with sulfur». Replacing nitrogen and oxygen atoms with sulfur can radically alter the electronic structure, resulting in greater polarizability and different reactivity. Both classes are «workhorses» of medicinal chemistry due to their different biological activity profiles, and they are often compared as bioisosteres to determine which scaffold is best suited to a specific task (e.g. whether higher lipophilicity or specific binding to the metal in the enzyme's active site is required). From an X-ray structural analysis perspective, the similarities and differences between rhodanines and hydantoins are evident. Hydantoins have a flat ring and characteristic bond lengths of approximately 1.21–1.23 Å [2] for their two carbonyl groups (C=O). In thiols, the C=S bond is significantly longer than the C=O bond. The S–C bond length is 1.7525(12) Å, and for different

derivatives it ranges from 1.632 to 1.650 Å [5,6]. This is much longer than a typical C=O double bond (approximately 1.22 Å).



Scheme 1. General structural formula for 5,5-disubstituted hydantoins (a), 5,5-disubstituted rhodanines (b) and compounds I-III investigated in this work (c).

From the crystal chemistry perspective, rhodanine arises as an interesting structural fragment, which, most commonly [7–9], forms hydrogen bonds with carbonyl oxygen atom as an acceptor.

The first investigations of molecular structure and hydrogen bonding analysis in condensed matter of rhodanine were performed by van der Helm *et al.* in 1962 [10] with unit cell dimensions reported earlier by Merritt and Lessor in 1955 [11]. There, a dimeric homosynthon around an inversion axis is discussed, which is formed by strong N-H...O hydrogen bonds. This motif is, in fact, one of the main kinds of intermolecular interactions found in rhodanines unsubstituted at a nitrogen atom. In this work, we pply investigate a change in crystal packing of rhodanines when a different kind of substitute gets introduced. A phenyl ring as such a candidate was chosen for its ability of forming $\pi\cdots\pi$ and various types of C-H... π interactions [12], which would, in theory, give rise to a new type of synthons formed by rhodanine entity.

2. Materials and Methods

General Information

All used solvents have been distilled and purified by standard protocols before use. Column chromatography was performed using 60 Å silica gel (Merck), thin-layer chromatography – with ALUGRAM Xtra SLI G/UV₂₅₄ plates (Macherey-Nagel). All melting point temperatures were determined using OptiMelt MPA 100 in dynamic mode (1 °C min⁻¹, 0.1 °C resolution). NMR spectra were recorded using Bruker Avance 400, Bruker AV 600 and Agilent 400 MR spectrometers at room temperature with determination of chemical shifts relative to the residual solvent signals. IR-spectra were recorded using Thermo Scientific Nicolet iS5 Fourier spectrometer using attenuated total reflection (ATR) sampling (32 scans, 4 cm⁻¹ resolution). HPMS spectra registration was conducted using G3 QToF and AB SciexTripleTOF 5600+ quadrupole time-of-flight mass-spectrometers using electro- and photospray-ionization, respectfully.

Single-Crystal X-Ray Analysis (SC-XRD)

Experimental data sets for **I** and **II** were collected on a STOE STADI VARI PILATUS diffractometer by means of φ -scans using focusing-mirror collimated Cu-K α radiation (λ = 1.5406 Å)

at room temperature. Initial indexing, refinement of unit cell parameters and integration of reflections were performed using the X-Area 1.67 (STOE & Cie GmbH) [14–16]. Absorption corrections based on measurements of equivalent reflections were applied using LANA [17].

Experimental data set for **III** was collected on a Bruker D8 Venture diffractometer by means of φ - and ω -scans using graphite monochromatized Mo-K α radiation ($\lambda = 0.71073$ Å, Incoatec I μ S 3.0) at 150 K. Initial indexing, refinement of unit cell parameters and integration of reflections were performed using the Bruker APEX3 software package [18,19]. Absorption corrections based on measurements of equivalent reflections were applied using SADABS program [20].

All structures were solved by direct methods [21] and refined by full-matrix least squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. All hydrogen atoms in phenyl ring in both **I** and **II** were refined using a riding model with $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$, and hydrogen atoms in *tert*-butyl groups in were refined as a rotating group. All atoms in **III** and H(12) in **I** were refined with both positional and thermal parameters.

All calculations and refinements were performed using the SHELXTL software package [21,22]. The illustrations were obtained using the XP program.

General Synthetic Protocol for Compounds I-III.

In a round-bottom flask, equipped with a magnetic stirrer and a reflux condenser, a solution of 4,6-di-*tert*-butyl-disubstituted benzaldehyde (1 eq.) and 3-phenyl-2-thioxothiazolidin-4-one (1 eq.) in ethanol (3-5 ml) was prepared. After the addition of piperidine (1 eq.), the reaction mixture was refluxed for 4 minutes, after which glacial acetic acid was added (1 ml). The mixture was left refluxing for a total of 24 h. The total reaction conversion was determined by means of thin-layer chromatography. After the mixture was cooled to room temperature, it was treated with saturated ammonium chloride solution. The resulted precipitate was filtered out, washed several times with water and dried on air. The purification of product was made by column chromatography (using the same eluent as in thin-layer chromatography, *vide infra* for each compound).

(Z)-5-(4,6-di-*tert*-butyl-2,3-Dimethoxybenzylidene)-3-Phenyl-2-Thioxothiazolidin-4-One

0.395 mmol of each reagent - aldehyde, thioxothiazolidine and piperidine - was used. An ethyl acetate / petroleum ether (1:10 *v/v*) was chosen as an eluent. Yield 0.08 g (50%) as yellow powder. M.p. 199 – 200°C. ^1H NMR (400 MHz, DMSO- d_6 , ppm) δ 1.36 (s, 18H, ^iBu), 3.63 (s, 3H, -OMe), 3.88 (s, 3H, -OMe), 7.18 (s, 1H, arom.), 7.44-7.46 (m, 2H, arom.), 7.52-7.58 (m, 3H, arom.), 8.14 (s, 1H, CH). ^{13}C NMR (101 MHz, DMSO- d_6 , ppm) δ 30.13 (^iBu), 31.30 (^iBu), 35.28, 35.88, 60.31 (-OMe), 120.02, 124.76, 127.17, 128.86 (2C), 129.29 (2C), 129.49, 131.25, 135.16, 143.77 (2C), 150.47, 151.13, 166.41, 195.78. IR (cm $^{-1}$) ν 527, 547, 611, 625, 651, 691, 707, 747, 799, 818, 839, 881, 916, 930, 974, 1016, 1036, 1073, 1151, 1171, 1236 (^iBu), 1298, 1355, 1386, 1396, 1474, 1496, 1579, 1713, 2868 (-OMe), 2963, 2961. HRMS (ESI/TOF-MS, *m/z*, [M+H] $^+$): calculated for $\text{C}_{26}\text{H}_{31}\text{NO}_3\text{S}_2$ 470.1818, found 470.1815.

(Z)-5-((6,8-di-*tert*-butyl-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methylene)-3-Phenyl-2-Thioxothiazolidin-4-One

0.540 mmol of each reagent - aldehyde, thioxothiazolidine and piperidine - was used. An ethyl acetate / petroleum ether (1:5 *v/v*) was chosen as an eluent. Yield 0.13 g (52%) as yellow powder. M.p. 196 – 197°C. ^1H NMR (400 MHz, DMSO- d_6 , ppm) δ 1.35 (d, $J = 3.1$ Hz, 18H, ^iBu), 4.34 (d, $J = 24.7$ Hz, 4H, 2-CH $_2$), 6.95 (s, 1H, CH), 7.42-7.45 (m, 2H, arom.), 7.49 – 7.57 (m, 3H, arom.), 8.08 (s, 1H, CH). ^{13}C NMR (101 MHz, DMSO- d_6 , ppm) δ 29.29 (^iBu), 31.36 (^iBu), 35.02, 35.57, 62.93 (-CH $_2$ -), 64.04 (-CH $_2$ -), 116.24, 118.31, 126.45, 128.80 (2C), 129.23 (2C), 129.39, 131.31, 135.18, 138.69, 140.44, 141.00, 141.11, 166.56, 195.21 (C=O). IR (cm $^{-1}$) ν 552, 567, 611, 624, 638, 691, 698, 731, 748, 771, 819, 838, 872, 892, 947, 955, 1012, 1043, 1085, 1104, 1158, 1173, 1235 (^iBu), 1283, 1301, 1353, 1413, 1479, 1591, 1710, 2868 (-OCH $_2$ -), 2943, 2976. HRMS (ESI/TOF-MS, *m/z*, [M+H] $^+$): calculated for $\text{C}_{26}\text{H}_{29}\text{NO}_3\text{S}_2$ 468.1662, found 468.1663.

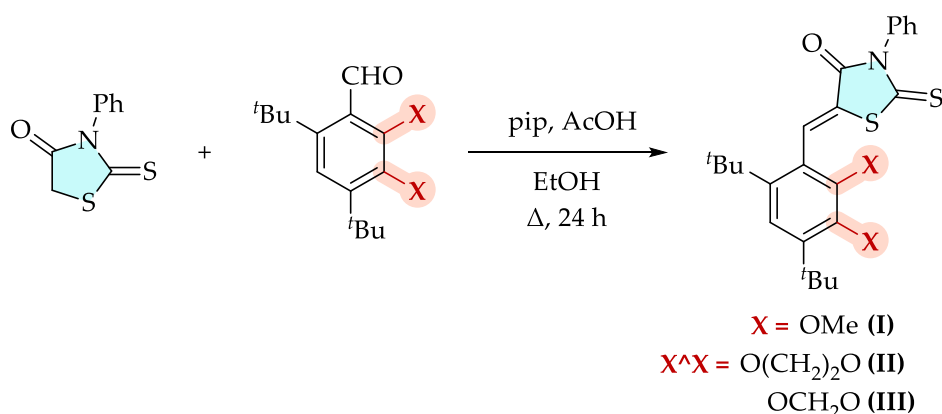
(Z)-5-((5,7-di-tert-butylbenzo[d][1,3]dioxol-4-yl)methylene)-3-Phenyl-2-Thioxothiazolidin-4-One

0.150 mmol of each reagent - aldehyde, thioxothiazolidine and piperidine - was used. An ethyl acetate / petroleum ether (1:5 *v/v*) was chosen as an eluent. Yield 0.14 g (54%) as yellow powder. M.p. 204 – 205°C. ¹HNMR (400 MHz, DMSO-*d*₆, ppm) δ 1.34 (s, 9H, ^tBu), 1.36 (s, 9H, ^tBu), 6.13 (s, 2H, CH₂), 6.90 (s, 1H, arom.), 7.46 – 7.57 (*m*, 5H, arom), 8.05 (s, 1H, CH). ¹³CNMR (101 MHz, DMSO-*d*₆, ppm) δ 29.05 (^tBu), 31.34 (^tBu), 33.94, 35.84, 100.84, 112.11, 116.93, 126.63, 128.82 (2C), 129.20, 129.26 (2C), 129.47, 132.50, 135.15, 141.90, 142.73, 145.45, 166.40, 194.70 (C=O). IR (cm⁻¹) ν 536, 564, 603, 622, 693, 732, 740, 759, 819, 841, 870, 898, 950, 971, 1023, 1087, 1147, 1173, 1236 (^tBu), 1352, 1365, 1412, 1465, 1495, 1594, 1724, 2868 (-OCH₂-), 2956. HRMS (ESI/TOF-MS, *m/z*, [M+H]⁺): calculated for C₂₅H₂₇NO₃S₂ 454.1505, found 454.1504.

3. Results and Discussion

3.1. Synthesis of 5-Arylidenerhodanines I-III

5-Arylidenerhodanines **I-III** containing ether moieties in 2- and 3-positions of the benzene ring of arylidene substituent were synthesized by means of condensation of 5-unsubstituted rhodanine with corresponding ether-substituted benzaldehydes (Scheme 2). The Knoevenagel reaction [23] of *N*-phenylrhodanine with 2,3-disubstituted 3,6-di-*tert*-butyl-benzaldehydes proceed smoothly in refluxing ethanol with piperidine as a base, affording the arylidene derivatives with moderate yields from 50 to 54%. It is noteworthy that this reaction is remarkably tolerant even to bulky *tert*-butyl groups placed in used benzaldehyde derivatives. Using ¹H and ¹³C NMR spectroscopy (*vide supra*) it is shown that only *Z*-isomer is formed during the reaction, with no traces of the *E*-isomer detectable.



Scheme 2. Synthesis of 5-arylidenerhodanines **I-III**.

3.2. Single-Crystal X-Ray Diffraction

The arylidene rhodanines **I**, **II** and **III** crystallize in space groups *P*2₁/*c*, *P*-1 and *Pbcn*, respectively, with one molecule (*Z*-isomer) without any solvate ones in the asymmetric unit. In all of the three crystal structures (**Figures 1-3**), the interatomic distances, proper to both tabular ones and the ones found in similar compounds, are observed (see Supplementary Information) In particular, the C=C distances are equal to 1.342(3), 1.331(3) and 1.3513(19) Å (in **I**, **II** and **III**, respectively) and are close to proper double bond lengths. The torsion angle between rhodanine and phenyl rings attached to a nitrogen atom in the above compounds vary from 70.27(18)° (in **III**) to 80.6(2)° (in **I**). The molecular volumes, derived from CIF files with atomic coordinates standard uncertainties, do not differ much and are equal to 393.37 ± 0.58 (**I**), 374.86 ± 0.55 (**II**) and 374.87 ± 0.55 Å³ (**III**), respectively; in the first case, a slight increase of molecular volume is due to presence of two free methoxy groups and the absence of any cyclic group, compared to the other two structures.

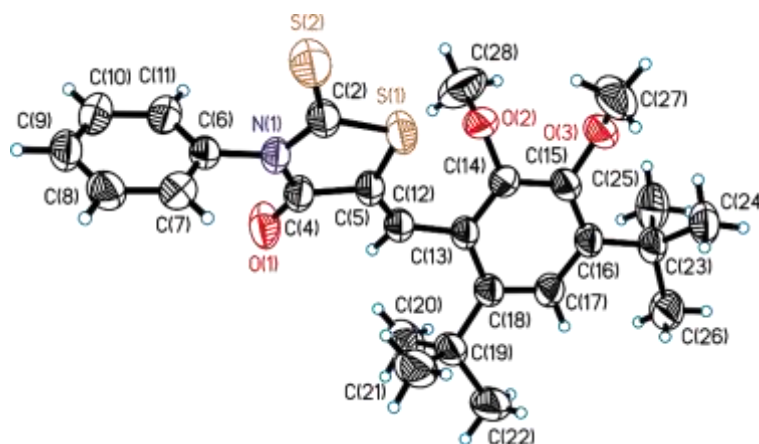


Figure 1. Molecular structures of compound **I**. Hydrogen atoms' labelling has been omitted for simplicity. Thermal ellipsoids are shown at 50% probability.

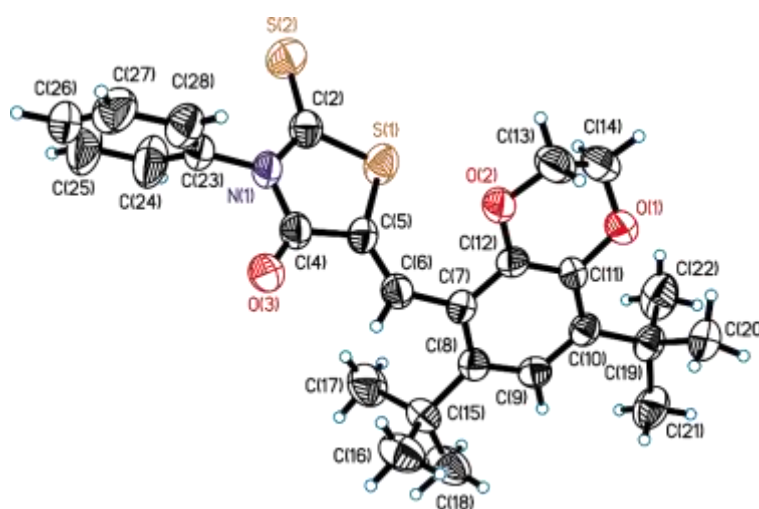


Figure 2. Molecular structures of compound **II**. Hydrogen atoms' labelling has been omitted for simplicity. Thermal ellipsoids are shown at 50% probability.

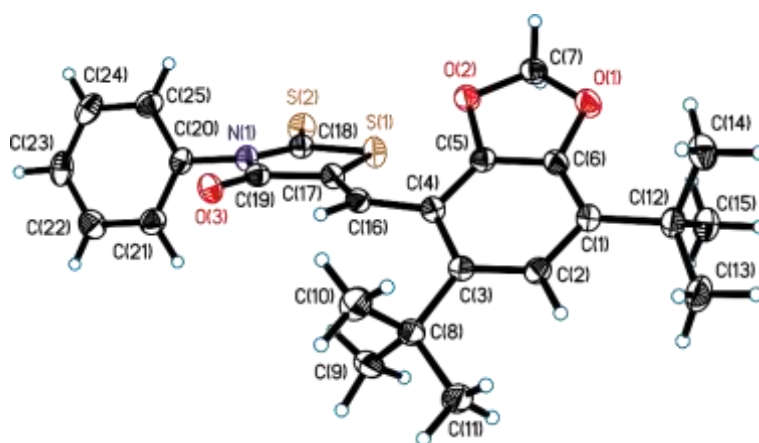


Figure 3. Molecular structures of compound **III**. Hydrogen atoms' labelling has been omitted for simplicity. Thermal ellipsoids are shown at 50% probability.

The substituted arylidene rhodanines structurally differ only in substituents at phenyl ring connected by a heterocycle by a C=C-bond: that is, the two methoxy groups in **I**, the dioxine ring in **II** and the dioxole one in **III**. Nevertheless, the crystal packing of all three structures is drastically different, as each one of them crystallizes in a different space group.

The crystal packing in above-mentioned structures reveals distinct supramolecular motifs, which include weak forced C-H...O hydrogen bonds between *tert*-butyl groups and a rhodanine carbonyl oxygen, as well as short S...S-bonds, which can be classified as a stronger, i.e. structure-forming interactions. The latter short contacts can be classified as chalcogen bonds [24–27]. These interactions form a cyclic dimer around an inversion centre, which, in turn, further reinforces the layered packing. Both the distance and the angle in this type of interaction correlates with those found in Cambridge Structural Database (CSD, version 5.43, **Figure 7**), especially for atomic separations. Apart from chalcogen bond dimers in **I** and **II**, no short intermolecular contacts were observed (**Figures 4–5**).

In the structure **III**, however, a somewhat acidic hydrogen in benzodioxole ring is introduced, so that the chalcogen bond dimeric synthon is omitted altogether and instead is changed to a layered chain of bifurcate C-H...S hydrogen bonds (**Figure 6**). This drastic change indicates an importance of an acidic hydrogen in arylidene fragment in terms of crystal packing. It is noteworthy that in the case of *all* the molecules under consideration, a change in substituents of the phenyl ring mostly leads to a difference in the space groups of crystals **I–III**.

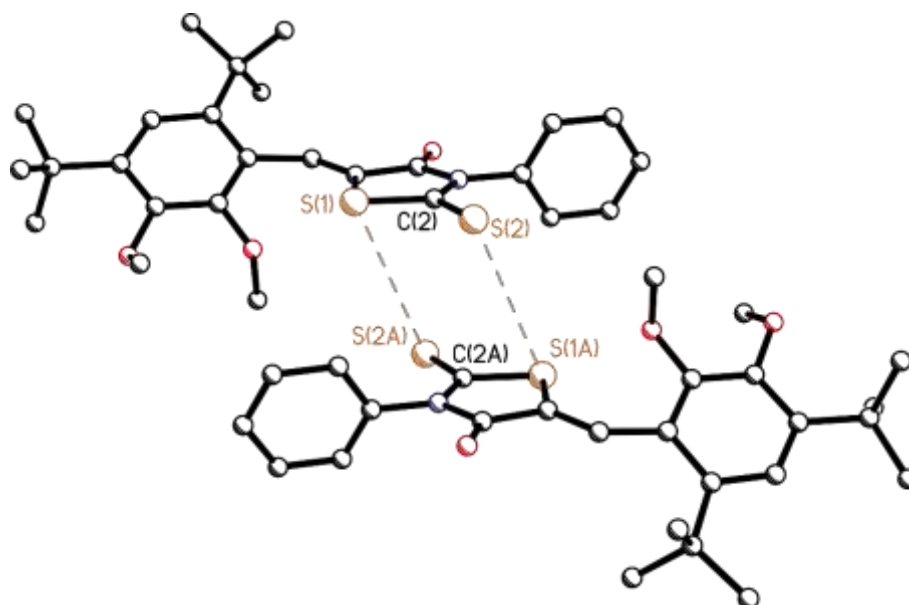


Figure 4. Chalcogen bonding in a dimeric homosynthon for **I**. The S(1)...S(2A) distance is 4.0827(9) Å and C(2A)-S(2A)...S(1) angle is equal to 95.09(8)°. Symmetry code for an equivalent molecular entity: 1-x, 1-y, 1-z.

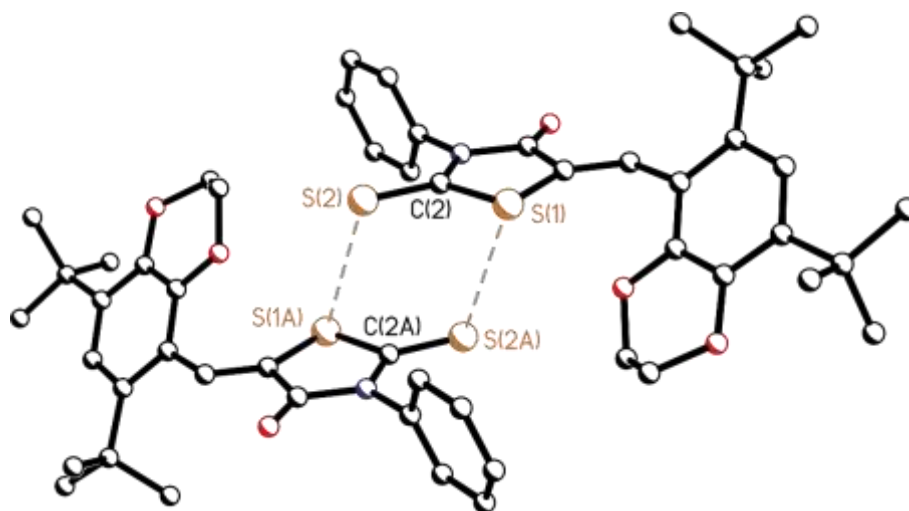


Figure 5. Chalcogen bonding in a dimeric homosynthon for **II**. The S(1)···S(2A) distance is 3.804(1) Å and C(2A)-S(2A)···S(1) angle is equal to 101.9(1)°. Symmetry code for an equivalent molecular entity: 1-x, 1-y, -z.

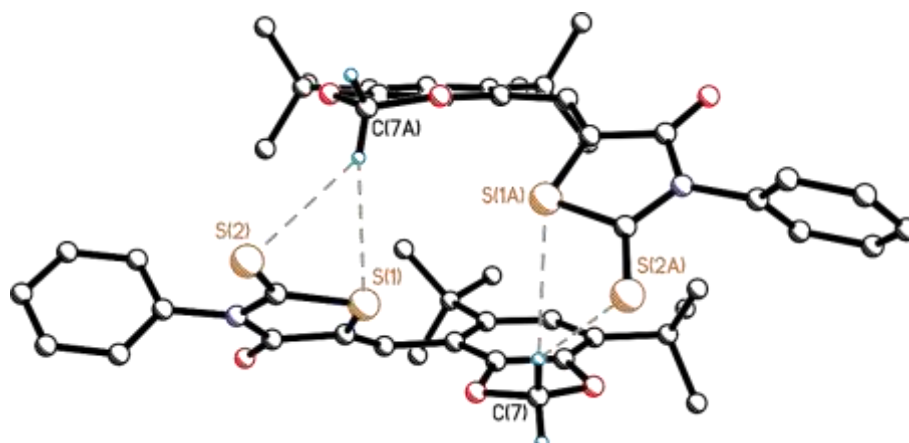


Figure 6. Hydrogen bonding in a heterosynthon forming infinite chains in **III**. The C(7)-H···S(1A) distance is 3.04(2) Å, the C(7)-H···S(2A) distance is 2.89(2) Å, the C(7)-H···S angles are equal to 142.0(14) and 143.3(14) to S(1A) and S(2A), respectively. Symmetry code for an equivalent molecular entity: 1-x, +y, 1/2-z.

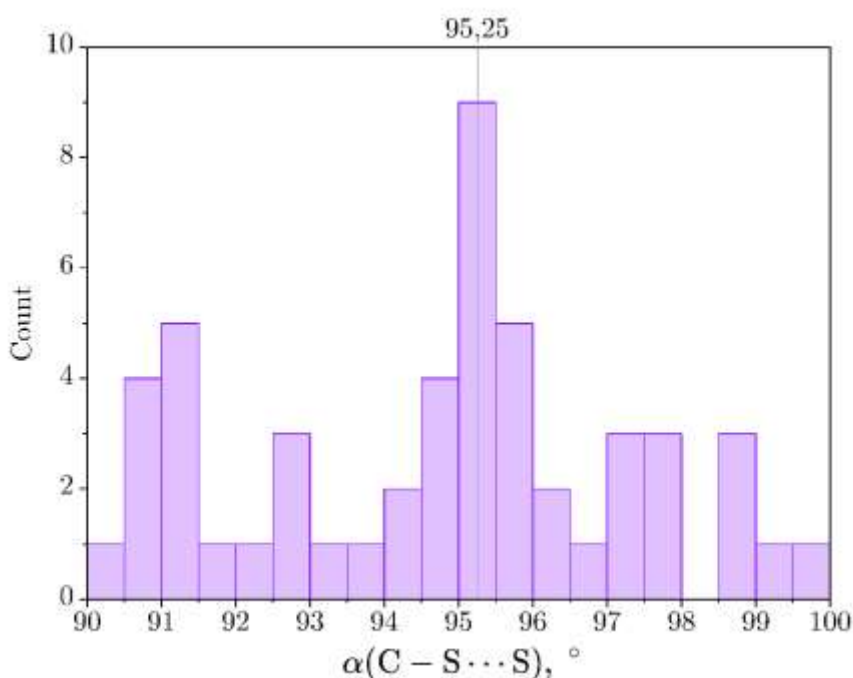


Figure 7. Distribution of C-S···S angles in the structures containing a rhodanine fragment from 90 to 100° (CSDConQuest, version 5.43, November 2023, total of 50 entries).

3.3. Hirshfeld Surface Analysis

To visualize and explore the intermolecular interactions in more detail, a Hirshfeld surface analysis was conducted using *Crystal Explorer* 17.5 [28]. In the resulted surfaces, generated over d_{norm} , the distances equal to, less and greater than the sum of van der Waals radii, are showed in white, red and blue, respectively (see Supplementary Information). According to the two-dimensional fingerprint plots, the most contribution in forming the intermolecular interactions is given from H···H, H···O/O···H, C···C, as well as H···C/ C···H-contacts. However, it is worth noting that the H···H

contacts have to be considered as forced ones and in no way contribute to the stabilization of the crystal packing. Hirshfield fingerprint plots regularly show a significant overestimation of the proportion of contacts of this type, which was recently shown by Vener, Churakov *et al.* [29].

In structure **III**, some strong, directional intermolecular contacts are observed *via* Hirshfield surface, which are at most absent in structures **I** and **II**. A more detailed analysis showed that those contacts can be classified as $n\cdots\pi^*$ ones and are formed between the rhodanine carbonyl oxygen atom and the π^* -orbital of a benzodioxole ring (**Figure 8**). Examples of such type of interaction have been previously appeared in literature [30,31].

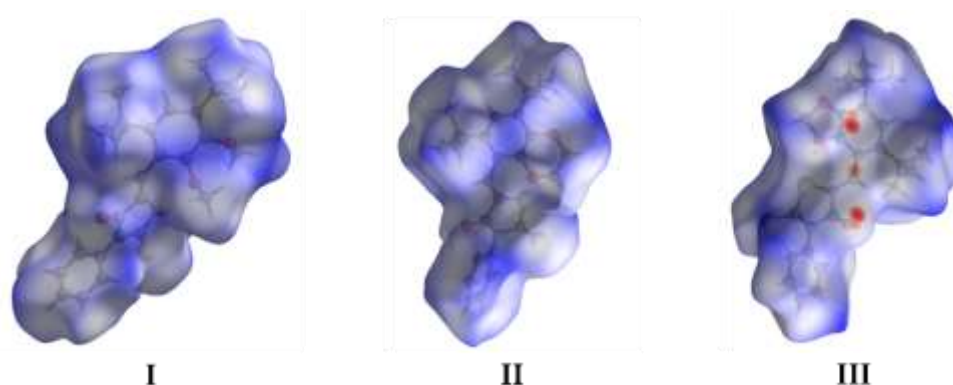


Figure 7. View of the three-dimensional Hirshfeld surface plotted over d_{norm} for compounds **I–III**.

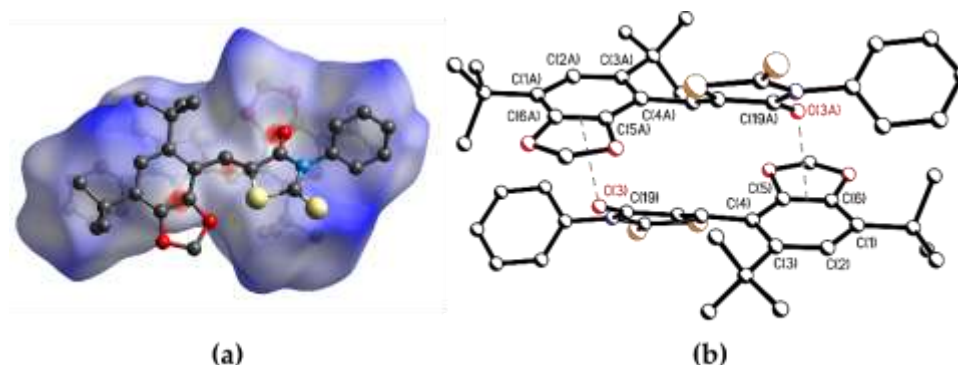


Figure 8. The most pronounced intermolecular interactions in **III** according to Hirshfeld surface analysis **(a)** and their correlation with the $n\cdots\pi^*$ type contact (indicated by a gray dotted line) in the dimeric synthon **(b)**. The distance between O(3) and bond center between atoms C(5) and C(6) is 2.9955(15) Å and the C(19)–O(3) $\cdots$ Cent angle is equal to 130.85(9)°.

4. Conclusions

Three new (*Z*)-5-arylidene-3-phenylrhodanine derivatives **I–III** were synthesized *via* Knoevenagel condensation and characterized by single-crystal X-ray diffraction. Despite their similar molecular structures, the compounds crystallize in three different space groups, demonstrating a remarkable sensitivity of crystal packing to minor substituent changes on the benzylidene ring. The supramolecular architectures are governed by a competitive interplay of weak directional interactions: in **I** and **II**, short S $\cdots$ S chalcogen bonds form cyclic dimeric homosynths, whereas in **III** these are replaced by a layered network of bifurcated C–H $\cdots$ S hydrogen bonds and an $n\cdots\pi^*$ contact involving the rhodanine carbonyl oxygen and the benzodioxole ring. Although the Hirshfeld surface analysis highlights H $\cdots$ H contacts as a major part in intermolecular interactions, the observed chalcogen bonding and $n\cdots\pi^*$ interactions are the primary structure-directing forces. These findings provide new insights into the crystal engineering of rhodanine-based materials, showing that the

balance between those types of interactions can be tuned by rational choice of the arylidene substituent in rhodanine.

Author Contributions: Conceptualization, A.V.F., D.R.C. and I.A.Y.; methodology, X.B. and A.V.F.; investigation, D.R.C. and A.D.M.; writing—original draft preparation, D.R.C.; writing—review and editing, X.B., D.R.C., A.D.M., I.A.Y., A.V.T. and A.V.F.; visualization, D.R.C. and A.D.M.; supervision, I.A.Y., A.V.F. and E.K.B. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement: All crystal structure data and full refinement details are published in Cambridge Crystallographic Data Center (CCDC) with respective deposition numbers: 2421110 (I), 2421015 (II), 2409952 (III). The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Conflicts of Interest: The authors declare no conflicts of interest.

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