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THE EFFECT OF THE NATURE OF THE SUBSTITUENT ON THE STRUCTURE OF A 1,3,4-OXATHIAZOL-2-ONE RING

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A series of 5-aryl(thienyl) substituted 1,3,4-oxathiazol-2-ones has been synthesized. The molecular structures of 5-(4-nitrophenyl)-, 5-(5-ethylthieno[2,3-b]thiophen-2-yl)-, 5-(5-ethyl-2-ethylsulfanylthiophen-3-yl)-, and 5-(5-methylsulfonylthiophen-2-yl)-1,3,4-oxathiazol-2-ones have been investigated by X-ray analysis. The thiophene and oxathiazolone fragments are coplanar. The geometric parameters of the oxathiazolone ring are discussed. Electron acceptor substituents in the para position of the benzene ring and in the 5 position of the thiophene ring have the greatest effect on the system conjugation in the oxathiazolone ring.

Keywords: 5-aryl(thienyl)-1,3,4-oxathiazol-2-ones, geometry of the oxathiazol-2-one ring, X-ray structural analysis.

Derivatives of 1,3,4-oxathiazol-2-one (OTA) have been successfully used as physiologically active compounds, e.g. as fungicides [1, 2] and PAL (phenylalanine ammonia lyase inhibitors type) [3], as well as starting compounds in the synthesis of various five membered heterocycles which contain a C=N–S fragment (isothiazolines, thiadiazoles) [4-7]. The process of preparing these is based on the thermal decarboxylation of an oxathiazolone ring to form unstable nitrile sulfides which readily undergo 1,3-dipolar cycloaddition *in situ* with the corresponding dipolarophiles [4]. Since the course of the reaction depends specifically on the stability of the π-electron system of the OTA [4, 6] one of the current problems relates to a study of the structure and effect of the nature of the substituent at position 5 on its stabilization. This can be achieved as is reported by creating a high degree of delocalization of electron density in the OTA ring, e.g. *via* introduction of aromatic substituents conjugated to the oxathiazolone ring.

Previously there have been reported only one representative of the aromatic series – 5-phenyl-OTA (**1a**) [8] and one of the heterocyclic series – 5-(2-methylsulfonyl-5-methylthiophen-3-yl)-OTA [9]. In our work we discuss the effect of several benzene and thiophene series substituents on the geometry and shift of electron density in the oxathiazolone ring with the use of X-ray structural analysis. We have synthesized the previously known 5-(4-nitrophenyl)-OTA (**1b**) by method [2] and a series of novel 5-thienyl substituted OTA **2a-h**: 5-(5-methylthiophen-2-yl)-OTA **2a**, 5-(5-ethylthieno[2,3-b]thiophen-2-yl)-OTA (**2b**), 5-(5-ethyl-2-ethylsulfanyl-thiophen-3-yl)-OTA (**2c**), 5-(5-methylsulfonylthiophen-2-yl)-OTA (**2d**), 5-(benzo[b]thiophen-3-yl)-OTA (**2e**), 5-(2-ethylsulfonylthiophen-3-yl)-OTA (**2f**), 5-(5-methylsulfanylthiophen-2-yl)-OTA (**2g**), and 5-(2-ethylsulfanyl-thiophen-3-yl)-OTA (**2h**) by method [5].

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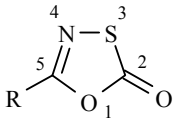
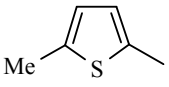
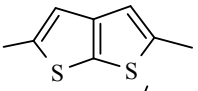
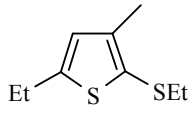
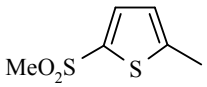
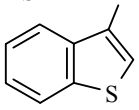
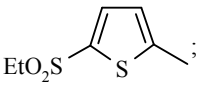
The compounds prepared were characterized by elemental analysis data and by IR (Table 1), mass, and ^{1}H and ^{13}C NMR spectroscopy (Table 2).

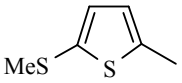
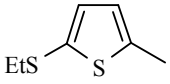


1a,b, 2a–h

1 a R = Ph, **b** R = 4-O_2NPh;

2 a R =  ; **b** R =  ; **c** R =  ;

d R =  ; **e** R =  ; **f** R =  ;

g R =  ; **h** R = 

For compounds **1b** and **2b-d** the molecular structure was determined using X-ray structural analysis and a comparative analysis of the geometric parameters (bond lengths) of the thiazolone rings was carried out.

In the studies [10, 11] it was shown that saturated hydrocarbon substituents do not affect the geometric parameters of the OTA ring. Hence the structure of the OTA ring in 5-adamantyl-OTA is virtually the same in the crystal phase as in unsubstituted OTA or its methyl derivative in the gaseous phase [12, 13]. Hence the geometric parameters of 5-adamantyl-OTA (Ad-OTA) [10] were taken as a standard for comparison of bond lengths in compounds **1a,b** and **2b-d**. The corresponding data for these compounds is given in Table 3.

TABLE 1. Characteristics for Compounds **2a-h**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	IR spectrum ($CHCl_3$), ν, cm^{-1}	Yield, %
		C	H	S			
2a	$C_7H_5NO_2S_2$	42.08 / 42.19	2.61 / 2.52	32.30 / 32.71	97-98	1760 (C=O)	72
2b	$C_{10}H_7NO_2S_3$	44.72 / 44.58	2.81 / 2.62	35.60 / 35.71	104-105	1748 (C=O)	60
2c	$C_{10}H_{11}NO_2S_3$	44.05 / 43.94	4.20 / 4.06	35.37 / 35.18	59-61	1750-1775 (C=O)	67
2d	$C_7H_5NO_4S_3$	32.05 / 31.93	2.15 / 1.91	36.70 / 36.53	167-170	1770 (C=O), 1155, 1335 (SO_2)	79
2e	$C_{10}H_5NO_2S_2$	51.12 / 51.04	2.31 / 2.14	27.04 / 27.25	133-134	1748-1770 (C=O)	61
2f	$C_8H_7NO_4S_3$	34.92 / 34.65	2.70 / 2.54	34.53 / 34.68	98-99	1765-1785 (C=O) 1145-1330 (SO_2)	84
2g	$C_7H_5NO_2S_3$	36.13 / 36.35	2.39 / 2.60	41.70 / 41.58	72-73	1758-1770 (C=O)	75
2h	$C_8H_7NO_2S_3$	39.06 / 39.17	3.05 / 2.88	38.82 / 39.21	103-105*[2]	1750-1770 (C=O)	71

* Solvents: EtOH (compounds **2a-c,e,f**), $CHCl_3$ (compound **2d**), or MeOH (compound **2g**).

*[2] Column chromatographed on *L* grade silica gel (100-160 mesh), eluent CCl_4.

TABLE 2. Spectroscopic Characteristics for Compounds **2a-h**

Compound	^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz)	^{13}C NMR spectrum (DMSO-d_6), δ, ppm	Mass spectrum, *m/z*, *I* (%)
2a	2.58 (3H, s, CH_3); 6.98, 7.50 (2H, two d, *J* = 3.5, H-4,3)	—	199 $[M]^+$ (100), 155 (60), 123 (30), 124 (30)
2b	1.39 (3H, t, *J* = 7.25, $C\underline{H_3}CH_2$); 2.95 (2H, q, *J* = 7.25, $C\underline{H_2}CH_3$); 6.97 (1H, s, H-4); 7.70 (1H, s, H-3)	—	269 $[M]^+$ (100), 225 (60), 193 (40)
2c	1.31 (3H, t, *J* = 7.0, $C\underline{H_3}CH_2$); 1.44 (3H, t, *J* = 7.0, $C\underline{H_3}CH_2S$); 2.70 (2H, q, *J* = 7.0, $C\underline{H_2}CH_3$); 3.07 (2H, q, *J* =7.0, $CH_3C\underline{H_2}S$); 7.08 (1H, s, H-4)	13.68 (q, $\underline{C}H_3CH_2S$); 15.23 (q, $\underline{C}H_3CH_2$); 23.25 (t, $S\underline{C}H_2CH_3$); 30.40 (t, $\underline{C}H_2CH_3$); 122.27 (s, C-3); 123.64 (d, C-3); 142.36 (s, C-2); 145.70 (s, C-5); 153.93 (s, C=N); 173.52 (s, C=O)	273 $[M]^+$ (26), 212 (38), 201 (39), 200 (45), 199 (98)
2d	3.24 (3H, s, $C\underline{H_3}SO_2$); 7.68, 7.72 (2H, two d, *J* = 3.5, H-3,4)	44.84 (q, CH_3SO_2); 128.60 (s, C-2); 131.47 (d, C-4); 133.71 (d, C-3); 146.30 (s, C-5); 51.39 (s, C=N); 172.84 (s, C=O)	263 $[M]^+$ (78), 219 (32), 205 (15), 191 (100), 190 (74)
2e	7.51 (2H, m, H-5,6); 7.92, 8.69 (2H, two d, *J* = 8.2, H-4',7'); 8.25 (1H, s, H-2)	—	235 $[M]^+$ (30), 191 (100), 159 (70), 133 (30)
2f	1.20 (3H, t, *J* = 7.0, $C\underline{H_3}CH_2$); 3.73 (2H, q, *J* = 7.0, $C\underline{H_2}CH_3$); 7.69, 8.20 (2H, two d, *J* = 4.5, H-4,5)	7.37 (q, $\underline{C}H_3CH_2$); 50.17 (t, CH_2SO_2); 128.22 (s, C-2); 130.56 (d, C-4); 137.74 (d, C-5); 141.88 (s, C-3); 151.15 (s, C=N); 163.58 (s, C=O)	277 $[M]^+$ (34), 205 (13), 203 (100), 175 (78), 153 (8), 110 (31)
2g	2.60 (3H, s, SCH_3); 6.79, 7.54 (2H, two d, *J* = 3.5, H-3,4)	18.99 (q, CH_3S); 126.16 (s, C-2); 127.60 (d, C-4); 132.24 (d, C-3); 146.69 (s, C-5); 173.26 (s, C= N)	231 $[M]^+$ (66), 206 (39), 187 (45), 155 (42), 151 (99)
2h	1.45 (3H, t, *J* = 7.0, $C\underline{H_3}CH_2$); 3.11 (2H, q, *J* = 7.0, $C\underline{H_2}CH_3$); 7.22, 7.41 (2H, two d, *J* = 4.5, H-4,5)	13.80 (q, $\underline{C}H_3CH_2$); 30.40 (t, CH_2S); 122.5 (s, C-2); 123.6 (d, C-4); 127.9 (d, C-5); 145.7 (s, C-3); 153.9 (s, C=N); 173.4 (s, C=O)	245 $[M]^+$ (33), 219 (101), 184 (21), 171 (83)

TABLE 3. Bond Lengths (*r*) in the OTA Ring in Compounds Ad-OTA, **1a,b,** and **2b-d**

Bond	*r*, Å					
	Ad-OTA	**1a**	**1b**	**2b**	**2c**	**2d**
O(1)–C(2)	1.392	1.384	1.416	1.421	1.400	1.376
O(1)–C(5)	1.377	1.379	1.383	1.464	1.423	1.373
C(2)–S(3)	1.750	1.752	1.713	1.802	1.733	1.736
S(3)–N(4)	1.687	1.680	1.734	1.735	1.710	1.705
N(4)–C(5)	1.272	1.268	1.292	1.286	1.254	1.280
C(2)–O(2)	1.188	1.185	1.215	1.119	1.178	1.233
C(5)–C(R)	1.491	1.460	1.440	1.434	1.445	1.414

As found in [8] the crystalline structure of compound **1a** consists of two crystallographically independent molecules, the geometric parameters of which agree within the experimental error limits, hence their mean values are given in Table 3. Molecule **1a** is planar. Attention was turned to the averaged endocyclic C–O bonds in the OTA ring and compared with the analogous bonds in the Ad-OTA molecule. The C(5)–R bond is shortened due to the change in hybridization of the carbon atom of the R substituent from sp^3 to sp^2. The remaining bond lengths in the **1a** molecule are virtually identical those in Ad-OTA.

The **1b** molecule is also planar according to X-ray analysis (Fig. 1) but the distribution of electron density in the OTA ring differs from that in molecule **1a**. The endocyclic C–O bonds are asymmetric, the difference in bond lengths (0.033 Å) being even greater than in the Ad-OTA molecule. The C(5)=N(4), S(3)–N(4), and C(2)=O(2) bonds are markedly longer that the corresponding bonds in molecule **1a** but, by contrast, the S(3)–C(2) and C(5)–C(R) are shorter. This points to the formation of two fragment with conjugated bonds in the molecule; the first fragment being R–C(5)=N(4)–and the second –S(3)–C(2)=O(2). A similar conclusion regarding the shift of electron density in the OTA ring in the presence of electronegative groups was made in [14] from an analysis of the ^{15}N and ^{13}C chemical shifts of a series of para substituted 5-phenyl-1,3,4-oxathiazol-2-ones.

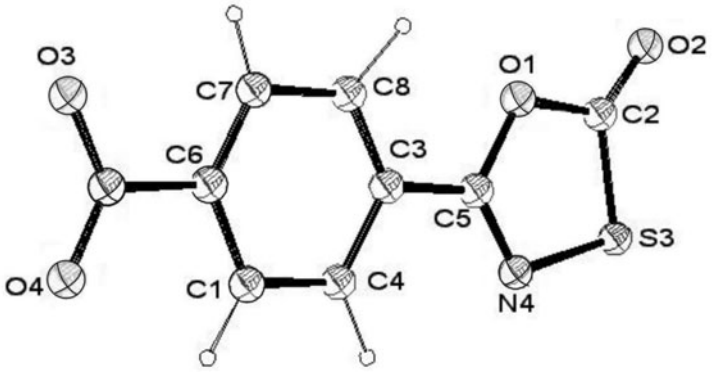


Fig. 1. Molecular structure of compound **1b**.

It was of interest to study in this scheme the effect of a thiophene substituent on the geometric parameters of the thiazolone ring. The most simple methyl derivative 5-(5-methylthiophen-2-yl)-OTA (**2a**) proved unstable to X-ray radiation.

The X-ray analysis showed that, in the crystal structure of **2b**, the thienothiophene system is statistically twisted relative to the OTA ring by 180º to give *cis*- and *trans*- forms (Fig. 2) with a population density of 2:1. The molecules of both forms are planar. Attention was turned to the marked difference in the bond lengths of the S(3)–C(2) and C(5)–O(1) bonds (see Table 3) when compared with the analogous bonds in the Ad-OTA and **1a,b** molecules, i.e. evidence for separation of the R–C(5)=N(4)–S(3)–and –O(1)–C(2)=O(2) fragments. It is apparent that the 1,3-dipolar addition reaction can occur under milder conditions in this case.

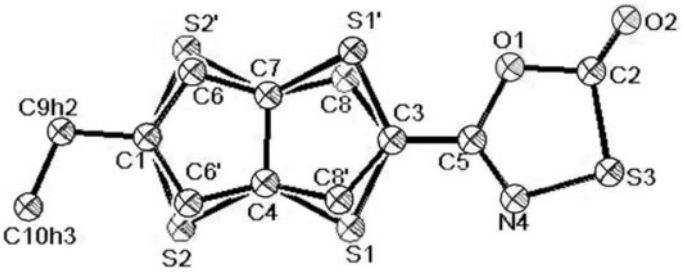


Fig. 2. Molecular structure of compound **2b**.

The **2c** molecule, including the carbon atoms of the ethyl groups, is also planar (Fig. 3). A difference is preserved (0.023 Å) in the O(1)–C(2) and O(1)–C(5) bond lengths. The O(1)–C(5), S(3)–N(4), S(3)–C(2) and the N(4)=C(5) and C(2)=O(2) bonds are clearly localized as single and double bonds respectively. This points to little delocalization of electron density in the OTA ring.

The **2d** molecule (Fig. 4) is planar with the exception of the sulfonyl group which is orientated asymmetrically with respect to the thiophene ring (T) to form a dihedral angle T/C(6)S(1)C(7) of 71.85º. Atoms O(3) and O(4) deviate from the T plane by 0.089 and 0.887 Å respectively. It was found that virtually the same orientation of the sulfonyl group relative to the thiophene ring plane had been seen previously in the molecule 5-(5-methyl-2-methylsulfonylthiophen-3-yl)-OTA [9]. The S(3)–N(4) and O(2)=C(2) bonds are lengthened and the S(3)–C(2) bond shortened when compared with the analogous bonds in Ad-OTA and **1a**. The endocyclic C–O bonds are virtually identical such that the electron density delocalizes over the whole OTA ring. The C(5)–C(R) bond is markedly shorter than an ordinary C_{sp2}–C_{sp2} bond which points to the formation of a single conjugated system for the oxathiazolone and thiophene rings.

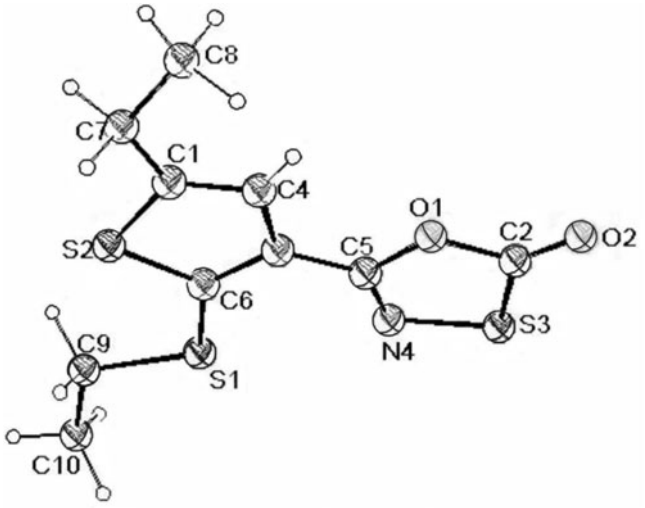


Fig. 3. Molecular structure of compound **2c**.

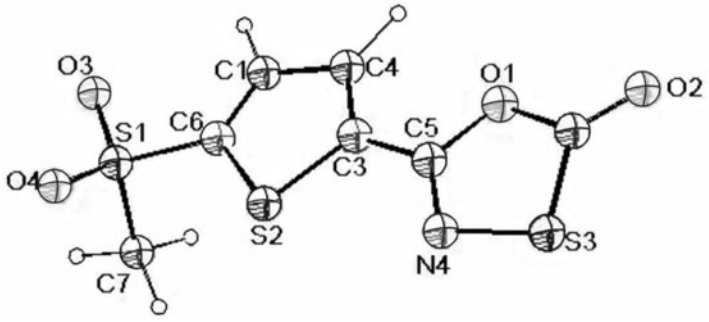


Fig. 4. Molecular structure of compound **2d**.

The investigation carried out has shown that the 5-aryl(thienyl) substituted 1,3,4-oxathiazol-2-one molecules have a planar structure in the crystal, which is favourable for their conjugation. Benzene and thiophene series substituents having electron acceptor NO_2 or SO_2R groups (compounds **1b** and **2d**) have a marked effect on the electron density delocalization pattern in the oxathiazole ring allowing the formation of a high degree of delocalization of the π electronic system including aryl (thienyl) substituents.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-275 instrument. ^{1}H NMR spectra were obtained on a Bruker WM-250 (250 MHz) and ^{13}C NMR spectra on a Bruker AM-300 instrument (75 MHz) using TMS as internal standard. Mass spectra were taken on a Varian MAT CH-6 spectrometer and a Varian MAT 311A with

ionization intensity 70 eV and direct introduction of the substance into the ion source. TLC was carried out on Silufol UV-254 plates with ethyl acetate–hexane as eluent and column chromatography on L (100-160 mesh) silica gel.

X-ray structural study of 1b, 2b-d. Unit cell parameters and sets of experimental reflections with $I > 2\sigma(I)$ were obtained on an RED-4 four circle diffractometer (λCuKα radiation, graphite monochromator, $\theta/2\theta$ scanning, $\theta < 60^{\circ}$) at 293K. The structures were solved by a direct method and refined using least squares analysis in the anisotropic approximation for non hydrogen atoms. The coordinates of the H atoms were basically revealed in electron density difference synthesis (the missing H atoms in the methyl groups were calculated geometrically) and refined isotropically using least squares analysis. All of the calculations were carried out using the AREN program package on an IBM PC/AT personal computer [15]. The atomic coordinates and geometric parameters have been placed in the Cambridge structural database (CCDC 736680 and 736683).

Crystals of 1b as transparent, colorless plates were grown from an ethyl acetate solution and are monoclinic. Unit cell parameters: a = 7.814(1), b = 16.307(1), c = 7.504(8) Å, β = 67.72(50)º, V = 884.93(6) Å^3, d_{calc} = 1.692 g/cm^3. Space group $P2_1/n$, Z = 4, 762 independent reflections were used in the calculation. Difference factor R = 0.065.

Crystals of 2b as light-yellow scales were grown from ethyl alcohol solution and are rhombic. Unit cell parameters: a = 8.704(1), b = 18.810(1), c = 6.891(3) Å, V = 1128.30(2) Å^3, d_{calc} = 1.595 g/cm^3. Space group $Pna2_1$, Z = 4, 655 independent reflections were used in the calculation. The structure could be solved only by varying the nature of the atoms and population densities. The final difference factor R = 0.103

Crystals of 2c as flat, light plates were grown from ethyl alcohol solution and are monoclinic. Unit cell parameters: a = 17.625(2), b = 16.578(2), c = 4.101(1) Å, β = 96.10(5)º, V = 1191.46(4) Å^3, d_{calc} = 1.533 g/cm^3. Space group $P2_1/a$, Z = 4, 930 independent reflections were used in the calculation. Difference factor R = 0.072.

Crystals of 2d were prepared as colorless, elongated prisms from chloroform solution and are monoclinic. Unit cell parameters: a = 15.423(2), b = 11.375(2), c = 5.751(1) Å, β = 89.89(3)º, V = 1008.93(2) Å^3, d_{calc} = 1.743 g/cm^3. Space group $P2_1/n$, Z = 4, 951 independent reflections were used in the calculation. Difference factor R = 0.078.

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