

Synthesis and Single Crystal X-Ray Structure of Bis[4-oxo-3-(2-ethoxycarbonylphenyl)-3,4-dihydroquinazolin-2-yl]disulfide

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Z. Naturforsch. **2009**, *64b*, 1065 – 1069; received May 22, 2009

Diethyl 2,2'-thiocarbonyl-bis(azanediyl)dibenzoate was synthesized from the reaction of ethyl anthranilate with thiophosgene. Its treatment with sodium ethoxide in ethanol at room temperature gave ethyl 2-(4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4*H*)-yl) benzoate, whereas in the presence of ethyl nitroacetate and under the same reaction conditions, the corresponding bis(quinazolin)disulfide was formed. Its structure was confirmed by IR, ¹H and ¹³C NMR spectroscopy elemental analysis and single crystal X-ray structure determination.

Key words: Thiophosgene, Ethyl Anthranilate, Ethyl Nitroacetate, Disulfide, Single Crystal X-Ray Structure

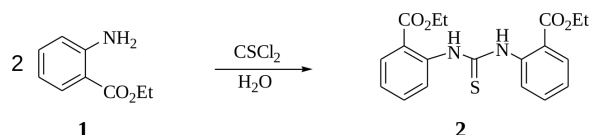
Introduction

The reaction of *o*-substituted arylamines with thiophosgene to form isothiocyanates is well known [1, 2]. However, the direct generation of *N,N'*-disubstituted thioureas by using this reaction is not so well-known. Herein, we report the preparation of diethyl 2,2'-thiocarbonyl-bis(azanediyl)dibenzoate (**2**) and its treatment with sodium ethoxide in ethanol at r. t. leading to ethyl 2-(4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4*H*)-yl) benzoate (**3**), which may possess biological activity and provide an incentive for further exploration of this class of compounds as potential drug precursors [3–9]. Finally, we treated the *N,N'*-disubstituted thiourea **2** with ethyl nitroacetate in the presence of sodium ethoxide in ethanol at r. t. to form bis[4-oxo-3-(2-ethoxycarbonylphenyl)-3,4-dihydroquinazolin-2-yl]disulfide (**4**).

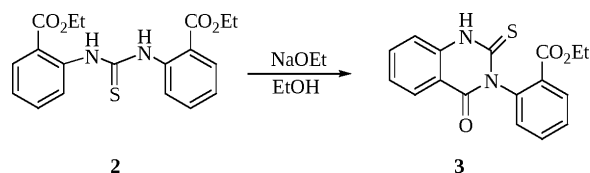
Results and Discussion

The *N,N'*-disubstituted thiourea **2** was prepared from the reaction of ethyl anthranilate (**1**) with thiophosgene [1, 2] (Scheme 1).

Treatment of the *N,N'*-disubstituted thiourea **2** with sodium ethoxide in ethanol at r. t. afforded the corresponding quinazoline derivative **3** in 89 % yield (Scheme 2).



Scheme 1.



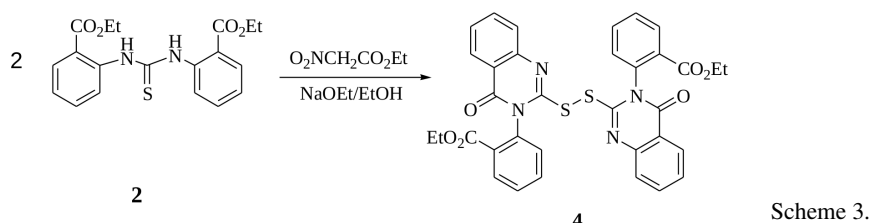
Scheme 2.

We observed that treatment of the thiourea **2** with ethyl nitroacetate and sodium ethoxide in ethanol under the same reaction conditions gave, surprisingly, the corresponding disulfide **4** in moderate yield (46 %, Scheme 3).

The structure of compound **4** was confirmed by IR, ¹H and ¹³C NMR spectroscopy, elemental analysis and X-ray single crystal structure determination.

Description of the crystal structure of **4**

The crystals of **4** are built up from molecules, the geometry of which reveals a pseudo (non-crystallographic) two-fold axis running through the center

Table 1. Crystal data and structure refinement details for **4**.

Empirical formula	C ₃₄ H ₂₆ N ₄ O ₆ S ₂
Formula weight, g mol ⁻¹	650.71
Crystal system, space group	monoclinic, <i>P</i> ₂ ₁ / <i>n</i>
<i>a</i> , Å	12.483(4)
<i>b</i> , Å	18.819(5)
<i>c</i> , Å	13.853(4)
β , deg	110.77(3)
<i>V</i> , Å ³	3042.8(15)
<i>Z</i>	4
<i>D</i> _{calc} , g cm ⁻³	1.420
μ , mm ⁻¹	0.229
<i>F</i> (000), e	1352
Crystal size, mm	0.24 × 0.13 × 0.08
Crystal color and form	colorless block
Data collection method	ω scans
Radiation type; wavelength λ , Å	MoK α ; 0.71073
<i>T</i> , K	100(2)
θ range, deg	2.68–25.50
<i>h</i> , <i>k</i> , <i>l</i> ranges	–15 ≤ <i>h</i> ≤ 15, –20 ≤ <i>k</i> ≤ 22, –16 ≤ <i>l</i> ≤ 14
Measured / independent refl.	24906 / 5655
Observed refl. [<i>I</i> > 2 σ (<i>I</i>)]	3251
Refinement on	<i>F</i> ²
Data / parameters	5655 / 429
<i>R</i> 1 / <i>wR</i> 2 [<i>F</i> _o ² ≥ 2 σ (<i>F</i> _o ²)] ^a	0.069 / 0.157
<i>R</i> 1 / <i>wR</i> 2 (all data) ^a	0.118 / 0.189
Weighting parameter <i>a</i> / <i>b</i>	0.0980 / 0.0
GoF = <i>S</i> ^b	1.017
$\Delta\rho_{\max}$ / $\Delta\rho_{\min}$, e Å ⁻³	0.64 / –0.36

^a $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$, $wR2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (aP)^2 + bP]^{-1}$, where $P = (\text{Max}(F_o^2, 0) + 2F_c^2) / 3$;
^b $\text{GoF} = [\sum w(F_o^2 - F_c^2)^2 / (n_{\text{obs}} - n_{\text{param}})]^{1/2}$.

of the S–S bond (Fig. 1). The S–S bond length of 2.023(2) Å is close to the average value observed in organic disulfides [10]. The summary of the experimental details is given in Table 1.

The value of the torsion angle C(11)–S(1)–S(2)–C(12) amounts to 91.9(2)°, which is very close to the average found in compounds of similar structure [10]. The values of the torsion angles S–S–C–N (Table 2) indicate that the S–S bond lies in the plane of the respective quinazolin-4-one ring. Thus, according to the Shefter classification [11], molecule **4** exists in a so-called equatorial conformation. At the same time, the two quinazolin-4-one moieties are almost perpendicu-

Table 2. Selected interatomic distances (Å), valence and torsion angles (deg) in **4**.

S(1)–S(2)	2.023(2)	N(12)–C(92)	1.414(5)
S(1)–C(11)	1.798(4)	N(21)–C(11)	1.286(5)
S(2)–C(12)	1.790(4)	N(21)–C(31)	1.411(5)
N(11)–C(11)	1.375(5)	N(22)–C(12)	1.280(5)
N(11)–C(13)	1.446(5)	N(22)–C(32)	1.398(5)
N(11)–C(91)	1.410(5)	C(81)–C(91)	1.458(5)
N(12)–C(12)	1.390(5)	C(82)–C(92)	1.460(6)
N(12)–C(14)	1.455(5)		
C(11)–S(1)–S(2)	101.4(2)	C(12)–S(2)–S(1)	100.9(2)
C(11)–S(1)–S(2)–C(12)		91.9(2)	
C(13)–N(11)–C(11)–S(1)		11.5(4)	
S(2)–S(1)–C(11)–N(21)		2.1(3)	
C(14)–N(12)–C(12)–S(2)		9.9(4)	
S(1)–S(2)–C(12)–N(22)		5.3(3)	
C(91)–N(11)–C(13)–C(23)		90.3(4)	
C(83)–O(23)–C(73)–C(63)		170.7(4)	
C(92)–N(12)–C(14)–C(24)		98.9(4)	
C(84)–O(24)–C(74)–C(64)		–179.8(4)	
C(53)–C(63)–C(73)–O(13)		18.7(6)	
C(73)–O(23)–C(83)–C(93)		–158.8(8)	
C(54)–C(64)–C(74)–O(14)		15.6(6)	
C(74)–O(24)–C(84)–C(94)		–166.7(5)	

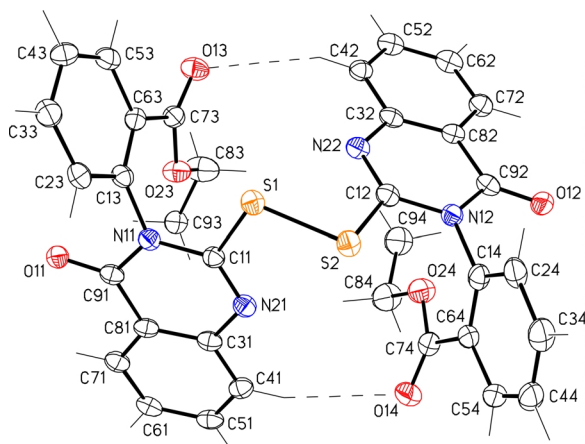


Fig. 1. The molecular structure of compound **4** showing the atom numbering scheme. Only one position (with higher occupation factor) for each of the disordered methyl groups is shown. The intramolecular C–H...O contacts forming two *S*(13) motifs are shown with dashed lines. Displacement ellipsoids are drawn at the 30% probability level.

D—H...A	D—H (Å)	H...A (Å)	D...A (Å)	D—H...A (deg)
C(41)—H(41)...O(14)	0.95	2.63	3.552(6)	164
C(51)—H(51)...O(11) ⁱ	0.95	2.53	3.281(5)	136
C(42)—H(42)...O(13)	0.95	2.66	3.540(5)	154
C(33)—H(33)...O(12) ⁱⁱ	0.95	2.63	3.462(5)	146
C(83)—H(83B)...O(14) ⁱⁱⁱ	0.99	2.71	3.501(7)	137

Table 3. Geometry of proposed hydrogen bonds for **4** (Å, deg).

Symmetry codes: (i) $x - 1/2, -y + 3/2, z - 1/2$; (ii) $x, y, z + 1$; (iii) $x + 1/2, -y + 3/2, z + 1/2$.

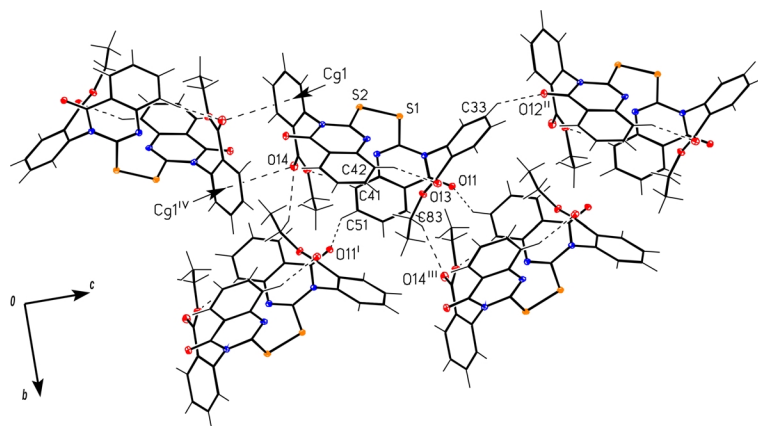


Fig. 2. The arrangement of the molecules in the crystal lattice of **4** (viewed down the *a* axis). Intermolecular C—H...O and C=O... π contacts are shown with dashed lines. Symmetry codes are given in Table 3.

lar to each other, with the dihedral angle between the least-squares planes defined by the condensed rings amounting to $87.5(1)^\circ$. The quinazolin-4-one rings are also almost perpendicular to the respective, directly bonded, phenyl rings.

The overall conformation of the molecule **4** is stabilized by two intramolecular C—H...O contacts (Table 3) linking the two halves of the molecule and resulting in two *S*(13) motifs, as shown in Fig. 1. Atom O(14) is additionally involved in a weak intermolecular C—H...O interaction, as well as in a close centrosymmetric C=O... π contact [C(74)=O(14)...Cg(1)^{iv}; symmetry code (*iv*): $-x, -y + 1, -z$; Cg(1) is the centroid of the phenyl C(14)–C(64) ring; geometrical parameters: O...Cg 3.784(4) Å, perpendicular O...Cg 3.698 Å, C...Cg 3.865(4) Å, C=O...Cg angle $84.7(2)^\circ$]. Two other carbonyl oxygen atoms, O(11) and O(12), act as acceptors of yet another set of intermolecular hydrogen contacts (Table 3). All that gives rise to a three-dimensional architecture of the crystal lattice of compound **4**, shown in Fig. 2.

Conclusions

In summary, we have synthesized a new derivative of 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline **3** and the related bis(quinazoline)-disulfide **4** under two convenient reaction conditions. The single crystal X-ray analysis of compound **4** reveals that the S—S bond lies

in the planes of the quinazolin-4-one rings, but with almost perpendicular mutual orientation of these two ring planes.

Experimental Section

General procedures

Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perrin and Armarego [12]. ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were carried out on a Bruker 300 spectrometer in CDCl_3 with tetramethylsilane as internal standard. Infrared spectra were recorded on a Thermo Nicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells, measured as Nujol mulls or films. Melting points were determined on a Philip Harris C4954718 apparatus and are uncorrected. Elemental analysis was performed on a Carlo Erba 1106 C, H, N analyzer.

Diethyl 2,2'-thiocarbonyl-bis(azanediyl)dibenzoate (**2**)

In a 250 mL round-bottomed flask were placed water (50 mL) and thiophosgene (2.53 g, 1.75 mL, 22 mmol). To the vigorously stirred reaction mixture was added slowly ethyl anthranilate (**1**) (3.63 g, 22 mmol, diluted in ethyl acetate), during about half an hour. The dark-brown oil was separated, washed with 10 % hydrochloric acid (2 mL), and placed in a two-necked flask for steam distillation. Product **2** passed over with water as a pale-yellow oil. The product was extracted with dichloromethane (30 mL) and dried

over sodium sulfate. Removal of the solvent gave a yellow oil which was recrystallized from *n*-hexane to give **2** as pale-yellow crystals (not suitable for an X-ray experiment). Yield: 1.23 g (30 %); m. p. 86–87 °C. – ^1H NMR (CDCl_3): δ (ppm) = 1.39 (t, J = 7.2 Hz, 6H), 4.36 (q, J = 6.9 Hz, 4H), 7.18 (td, J_1 = 8.7 Hz, J_2 = 1.5 Hz, 2H, Ar), 7.57 (td, J_1 = 8.7 Hz, J_2 = 1.5 Hz, 2H, Ar), 8.05 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 2H, Ar), 8.50 (bd, J = 8.4 Hz, 2H, Ar), 11.05 (s, exchanged by D_2O addition, 2H, NH). – ^{13}C NMR (CDCl_3): δ (ppm) = 14.17, 61.59, 118.64, 123.10, 123.73, 131.08, 133.30, 140.51, 167.49, 178.82. – FT IR: ν = 3236, 2976, 1685, 1605, 1580, 1509, 1447, 1364, 1301, 1251, 1168, 1089, 1004, 927, 765, 730 cm^{-1} . – Anal. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$: calcd. C 62.27, H 5.41, N 7.52; found C 62.38, H 5.50, N 7.45.

Ethyl 2-(4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-yl)benzoate (3)

In a 25 mL round-bottomed flask, absolute ethanol (10 mL) was reacted with sodium (0.015 g, 0.65 mmol), and after cooling to r. t. compound **2** (0.12 g, 0.322 mmol) was added. The reaction mixture was stirred at r. t. for 15 min. Then the mixture was acidified with 10 % acetic acid (2 mL), and the white precipitate was collected by vacuum filtration. The white solid was recrystallized from absolute ethanol to give the desired product **3** as white needles. Yield: 93 mg (89 %); m. p. 183–185 °C. – ^1H NMR (CDCl_3): δ (ppm) = 1.14 (t, J = 6.9 Hz, 3H), 4.19 (q, J = 6.9 Hz, 2H), 7.15 (d, 8.1 Hz, 1H), 7.34 (d, J = 9.3 Hz, 2H), 7.60 (td, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.64 (td, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.74 (td, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 10.89 (s, exchanged by D_2O addition, 1H, NH). – ^{13}C NMR (CDCl_3): δ (ppm) = 13.85, 61.26, 114.94, 116.45, 125.05, 127.78, 128.72, 129.32, 130.29, 132.17, 133.75, 135.69, 138.91, 138.97, 160.26, 164.29, 176.44. – FT IR: ν = 3245, 3136, 2976, 1717, 1665, 1620, 1529, 1487, 1406, 1263, 1199, 757 cm^{-1} . – Anal. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: calcd. C 62.56, H 4.32, N 8.58; found C 62.67, H 4.40, N 8.45.

Bis[4-oxo-3-(2-ethoxycarbonylphenyl)-3,4-dihydroquinazolin-2-yl]disulfide (4)

In a 25 mL round-bottomed flask, absolute ethanol (3 mL) was reacted with sodium (0.092 g, 4 mmol), and after cooling to r. t. ethyl nitroacetate (0.665 g, 5 mmol) was added. The reaction mixture was stirred at r. t. for 15 min. Compound **2** (1.86 g, 5 mmol) was added, and the stirring was continued for further 24 h, during which a yellowish-white precipitate was formed. The precipitate was extracted with chloroform

and dried over sodium sulfate. Removal of the solvent gave **4** as pale-yellow needles. Yield: 0.41 g, (46 %); m. p. 189–192 °C. – ^1H NMR (CDCl_3): δ (ppm) = 1.14 (t, J = 6.9 Hz, 6H), 4.18 (q, J = 6.9 Hz, 2H), 4.20 (q, J = 6.9 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H, Ar), 7.32 (d, J = 7.8 Hz, 2H, Ar), 7.35 (t, J = 6.9 Hz, 2H, Ar), 7.61 (td, J_1 = 7.5 Hz, J_2 = 0.9 Hz, 2H, Ar), 7.64 (td, J_1 = 9.6 Hz, J_2 = 1.5 Hz, 2H, Ar), 7.75 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2H, Ar), 8.18 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2H, Ar), 8.28 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2H, Ar). – ^{13}C NMR (CDCl_3): δ (ppm) = 13.85, 61.29, 115.07, 116.45, 125.07, 127.83, 128.68, 129.34, 130.34, 132.19, 133.77, 135.69, 138.97, 139.00, 160.35, 164.32, 176.38. – FT IR: ν = 3218, 3173, 3072, 3035, 2976, 1719, 1663, 1620, 1525, 1487, 1451, 1406, 1365, 1199, 1127, 1078, 1039, 988, 890, 800, 756, 715 cm^{-1} . – Anal. for $\text{C}_{34}\text{H}_{26}\text{N}_4\text{O}_6\text{S}_2$: calcd. C 62.76, H 4.03, N 8.61; found C 62.84, H 4.11, N 8.50.

Crystal structure determination of 4

The crystallographic measurement for crystal **4** was performed on a κ -geometry Kuma KM4CCD automated four-circle diffractometer with graphite-monochromatized MoK_α radiation. The data were collected at 100(2) K using the Oxford Cryosystems cooler. The data were corrected for Lorentz and polarization effects. A summary of the conditions for the data collection and the structure refinement parameters are given in Table 1. Data collection, cell refinement, and data reduction and analysis were carried out with the KM4CCD software CRYSLIS CCD and CRYSLIS RED, respectively [13]. The structure was solved by Direct Methods using SHELXS-97 [14] and refined by full-matrix least-squares techniques using SHELXL-97 [14] with anisotropic displacement parameters for non-H atoms, except for disordered low-occupied methyl C930 and C940 atoms. Both ethyl groups are disordered and were refined with methylene C atoms in the same positions and with the same anisotropic displacement parameters (constraints were applied with EXYZ and EADP instructions). Methyl C atoms were refined in two distinct positions. The ethyl groups were refined with s. o. f. = 0.76(3)/0.24(3) for C83/C830–C93/C930 and 0.71(2)/0.29(2) for C84/C840–C94/C940. Most of the H atoms were found in difference Fourier maps, and in the final refinement cycles all hydrogens were treated as riding atoms, with C–H distances of 0.95–0.99 Å, and with U_{iso} values of 1.5 $U_{\text{eq}}(\text{C})$ for CH_3 groups, and 1.2 $U_{\text{eq}}(\text{C})$ for CH_2 and CH groups. All figures were made using the program XP [15].

CCDC 731854 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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