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# OXIDATIVE CYCLOCONDENSATION OF CYCLIC THIO(SELENO)UREAS. 4*. ELECTRONIC EFFECTS OF THE SUBSTITUENTS AND THE MEDIUM

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*We have studied the electronic effect of substituents, steric factors, the medium, and the nature of the oxidizing agent on oxidative cyclocondensation of 2-thioxo-4-quinazolone and its substituted derivatives. We have found that electron-donor substituents promote the reaction while electron-acceptor substituents inhibit the reaction.*

**Keywords:** 8H,15H-1,2,4-thiadiazolo[3,2-*b*:5,4-*b*']diquinazoline-8,15-dione, 2-thioxo-4-quinazolone, quinazoline-2,4-dione, oxidative cyclocondensation, electronic substituent effects.

A rather large number of methods are known for obtaining 1,2,4-thia(seleno)diazoles from aliphatic thio(seleno)amides [2-5], thioureas [6-9], thiocyanates and their derivatives [10, 11], amidines, amidoximes and amidinothioureas [12-14], isothioureas [15], thiobiurets and thioguanidines [2, 16], thiatriazoles, dithiazoles, oxazarines and heterocumulenes [17-21]. The simplest and most accessible method has proven to be the one based on oxidation of thioamides and thioureas. Synthesis from amidino derivatives can be considered as an intermediate step in obtaining them from thioureas and thioamides. The mechanism for the formation of 1,2,4-thia(seleno)diazoles from thioamides and thioureas has not yet been studied in detail. The effect of various factors on the course of the reaction also has not been studied (electronic effects of substituents, steric factors, temperature, the nature of the solvent, the oxidizing agent, etc.). These reactions have not been generally studied for cyclic thioureas. As far as 1,2,4-selenodiazoles are concerned, only their synthesis from selenobenzamides [22, 23] and amidines [11] has been described. Only a few derivatives in this class of compounds have been synthesized.

Cyclic thio(seleno)ureas are a huge class of heterocyclic compounds. Pyrimidinones (the cyclic analogs of thio(seleno)ureas) condensed with benzene, thiophene, and pyridine rings are of considerable interest for theoretical organic chemistry, in connection with their existence in various tautomeric forms.

A large number of derivatives of these compounds have been synthesized so far. They include substances having pesticidal and also other types of physiological activity.

* For Communication 3, see [1].

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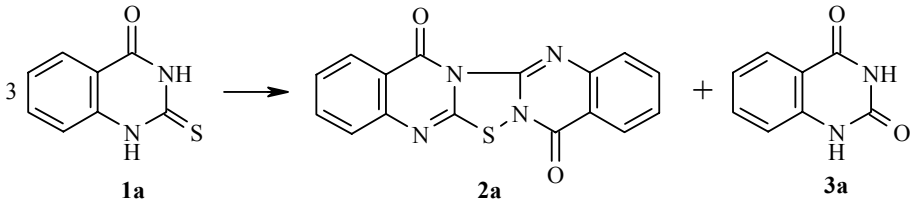
Most preparations in this series are used in agriculture and medicine. Despite the huge amount of data accumulated and the appearance of new information from studying their reactivity, no literature data are available on the reactions of oxidative cyclocondensation of cyclic thioureas and their analogs.

However, synthesis of polynuclear condensed derivatives of 1,2,4-thia(seleno)diazoles based on simple cyclic thio(seleno)ureas is of great theoretical and practical interest. So it is important to study our recently discovered novel reaction of symmetric and asymmetric oxidative cyclocondensation of cyclic thio(seleno)ureas [24] and to search for biologically active compounds among condensed 1,2,4-thiadiazoles.

Earlier while studying the synthesis and reactivity of heterocyclic systems containing various hetero atoms in the exocyclic position (2-oxo-, -thioxo, -selenoxo-, aminopyrimidines, thieno[2,3-*d*]pyrimidines, quinazolines and their substituted derivatives), we observed that 2-thioxo-4-quinazolone (**1a**) in DMSO in the presence of $P_2O_5$ forms 8H,15H-1,2,4-thiadiazolo[3,2-*b*:5,4-*b*']diquinazoline-8,15-dione (**2a**) [24], i.e., undergo oxidative cyclocondensation.




With the aim of studying the effect of the nature of the oxidizing agent and the solvent, in the reaction of oxidative cyclocondensation we used other solvents and different oxidizing agents besides DMSO and $P_2O_5$. Carrying out the reaction in dry DMSO in the presence of $P_2O_5$ for 1 h leads to formation of compound **2a** in 30% yield (Table 1). Increasing the reaction time up to 10 h increases the product yield up to 60%, but along with that we observe formation of 2-oxo-4-quinazolone (quinazoline-2,4-dione) (**3a**): the oxidation product of the starting compound **1a** (8%).

TABLE 1. Effect of the Nature of the Solvent and the Condensing Agent on Oxidative Cyclocondensation of 2-Thioxo-4-quinazolone

| Reaction conditions | | Yield, % | |
|---|---|---|---|
| Solvent + oxidizing agent | Time, h | **2a** | **3a** |
| DMSO | | 0 | 0 |
| DMSO + $P_2O_5$ | 1 | 30 | 0 |
| DMSO + $P_2O_5$ | 2 | 50 | 0 |
| DMSO + $P_2O_5$ | 4 | 55 | Traces |
| DMSO + $P_2O_5$ | 6 | 58 | 5 |
| DMSO + $P_2O_5$ | 10 | 60 | 8 |
| DMF + $P_2O_5$ | 2 | 0 | 0 |
| DMF + $P_2O_5$ | 6 | 0 | 0 |
| Dioxane + $P_2O_5$ | 2 | 0 | 0 |
| Dioxane + $P_2O_5$ | 6 | 0 | 0 |
| DMSO + $H_2SO_4$ | 1 | 20 | 0 |
| DMSO + $H_2SO_4$ | 2 | 66 | 7 |
| DMSO + $H_2SO_4$ | 6 | 70 | 10 |
| DMF + $H_2SO_4$ | 6 | 0 | 50 |
| Dioxane + $H_2SO_4$ | 6 | 0 | Traces |
| Abs. methanol. + $I_2$ | 5 min | 45 | 0 |
| Abs. methanol. + $I_2$ | 10 min | 50 | 0 |
| Abs. methanol. + $I_2$ | 20 min | 58 | 0 |

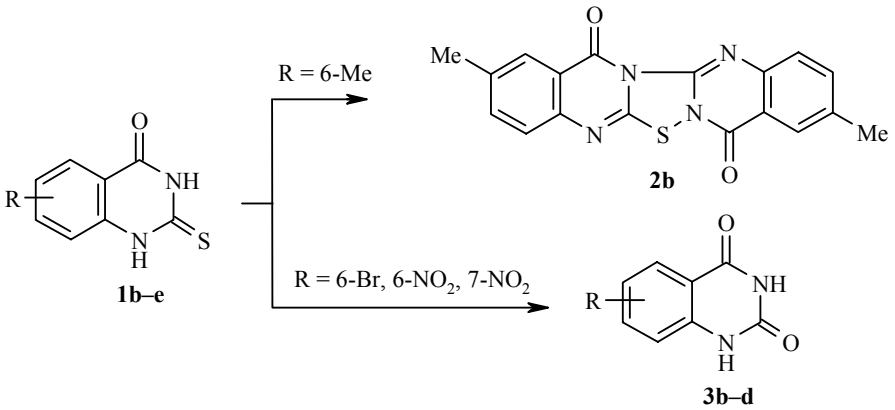
The reactions do not occur in DMF, dioxane, or in alcohol in the absence or in the presence of $P_2O_5$. Cyclocondensation does not occur in these solvents even in the presence of concentrated $H_2SO_4$. In DMSO, when we replace $P_2O_5$ by concentrated sulfuric acid, the reaction of cyclocondensation does occur. Under these conditions, the content of secondary product **3a** increases a little (10%). When we increase the reaction time (6 h) in this solvent in the presence of $H_2SO_4$, the amount of quinazolinedione **3a** increases even more. In absolute methanol, in the presence of iodine the reaction proceeds very rapidly, and after 5-20 min the product of oxidative cyclocondensation **2a** is formed (45-58% yield); in this case, we do not observe formation of compound **3a**. An increase in the reaction time did not substantially affect the product yield. Thus the results obtained show that in order to carry out oxidative cyclocondensation, we need the presence of a solvent/oxidizing agent of the DMSO type [25], dehydrating agents, and in absolute methanol we need the presence of molecular iodine as an oxidizing agent. In order to carry out cyclocondensation, we need the presence of acids, the role of which involves catalysis of the oxidation process.

With the aim of studying the effect of temperature on the course of this reaction, we carried it out at temperatures of 0°C, 25°C, 80°C, 140°C in DMSO in the presence of concentrated $H_2SO_4$ or $P_2O_5$. We might hypothesize that if the reaction is carried out in the presence of sulfuric acid, along with the increase in yield of product **2**, the yield of quinazolinedione **3a** would sharply increase due to acid hydrolysis of the starting compound. However, the experiments showed that the content of compound **3** did not appreciably increase (Table 2).

When the reaction is carried out in the presence of $P_2O_5$, the product yields are lower than when using sulfuric acid, but formation of product **3a** is less than in the second case. On the whole, raising the temperature leads to an increase in the yield of reaction product, and accordingly the conversion of the starting compound to the product increases.

The yield of reaction products sharply increases as the temperature is raised from 0 to 25°C. Further increase in the reaction temperature up to 140°C smoothly increases the product yield. The results obtained suggest that it is advisable to carry out oxidative cyclocondensation at room temperature, since in this case, there are no secondary compounds and the target product is easily isolated from the reaction mixture.

With the aim of studying the electronic effects of substituents on the aromatic ring of 2-thioxo-4-quinazoline and to expand the range of application of the reaction, we studied oxidative cyclocondensation of 6-methyl-, 6-bromo-, 6-nitro-, and 7-nitro-2-thioxo-4-quinazolones **1b-e** in DMSO in the presence of concentrated $H_2SO_4$ at room temperature. 6-Methyl-2-thioxo-4-quinazolone (**1b**) under these conditions undergoes oxidative cyclocondensation, and the corresponding thiadiazolodiquinazolinedione **2b** is readily formed in 75% yield. Under analogous condition, thioxo-4-quinazolones **1c-e** do not react. Instead of the expected products, the corresponding 6-bromo-, 6-nitro-, and 7-nitroquinazoline-2,4-diones **3b-d** are formed.




**1b** R = 6-Me, **1c**, **3b** R = 6-Br, **1d**, **3c** R = 6-$NO_2$, **1e, 3d** R = 7-$NO_2$

TABLE 2. Dependence of Yield of Product **2** on Temperature and Solvent*

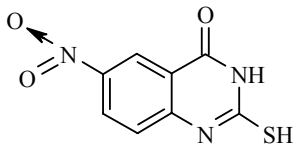
| T, °C | Conversion of starting compound, % | Yield, % | | T, °C | Conversion of starting compound, % | Yield, % | |
|---|---|---|---|---|---|---|---|
| | | **2a** | **3a** | | | **2a** | **3a** |
| DMSO + $P_2O_5$*[2] | | | | DMSO + $H_2SO_4$*[2] | | | |
| 0 | 10 | 10 | 0 | 0 | 30 | 30 | 0 |
| 25 | 56 | 55 | 0 | 25 | 76 | 68 | 8 |
| 80 | 66 | 65 | traces | 80 | 90 | 81 | 9 |
| 140 | 77 | 74 | 3 | 140 | 100 | 90 | 10 |

* Reaction time: 4 h.

*[2] Solvent + oxidizing agent.

Formation of the cyclocondensation products from compounds **1c-e** was not observed even when the temperature was raised (140°C) and the reaction time was increased (10 h).

The data obtained allow us to conclude that electron-acceptor substituents or substituents with a *-I* effect hinder the occurrence of the reaction, while electron-donor substituents favor oxidative cyclocondensation. Such an effect from electron-acceptor substituents is probably connected with their strong negative inductive and mesomeric effects, i.e., in this case delocalization of electron density on the sulfur atom occurs through the conjugation chain, passing through the pyrimidine and benzene rings. As a result, the C–S bond is polarized to a greater degree than in 2-thioxo-4-quinazoline itself. This facilitates breaking of this bond when treated with an oxidizing agent, as in the case of compound **1c**.



Thus the course of the reaction of oxidative cyclocondensation of 2-thioxo-4-quinazoline derivatives is affected substantially by the electronic effect of the substituents. When an electron-donor substituent is introduced at the 6 position of the aromatic ring, the reaction proceeds readily and the oxidative cyclocondensation product is obtained in good yield. Introducing electron-acceptor substituents enhances the oxidation and hydrolysis processes, and leads to formation of quinazoline-2,4-dione derivatives **3b-d**.

## EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer in KBr disks and on an IK-29 in alcoholic solution; the UV spectra were taken on a Hitachi EPS-ST spectrometer (ethyl alcohol as the solvent). The mass spectra were taken on an MKh-1303, MKh-1321, and MKh-1310 spectrometer; the $^1$H NMR spectra were taken on a JNM-4H-100 (100 MHz) and a Tesla BS-567A, internal standards TMS, HMDS (0.05 ppm). The $R_f$ values were determined on Silufol UV-254. The visualizing agents were iodine vapor, UV light, $KMnO_4$+$H_2SO_4$+$H_2O$ (0.5 g + 2 ml + 48 ml). The solvents were purified and dried according to the procedure in [26].

**2-Thioxo-4-quinazolone (1a)** was synthesized by the procedure in [27].

**6-Methyl-2-thioxo-4-quinazolone (1b).** Ammonium thiocyanate (1.65 g, 20 mmol) and conc. HCl (1.2 ml) were added to a solution of 5-methylanthranilic acid (3 g, 20 mmol) in *o*-xylene. The mixture was boiled for 6 h and then cooled down. The precipitate was filtered out, washed with water, and dried. The

crystals obtained were dissolved in a 2 N NaOH solution (100 ml), then this was neutralized with dilute acetic acid. The precipitate was filtered out, washed with water, and dried. Yield 3 g (80%); mp 288-290°C, $R_f$ 0.61 (acetone–benzene, 1:4). IR spectrum, ν, $cm^{-1}$: 1680 (C=O), 3110, 3310 (NH). Mass spectrum, *m*/*z* (*I*, %): 192 $[M]^+$ (100), 177 $[M–CH_3]^+$ (30), 164 $[M^1–CO]^+$ (70), 149 $[M–HNCO]^+$ (45), 133 $[M–HNCS]^+$ (40). $^1H$ NMR spectrum ($CF_3COOH$), δ, ppm: 6.90-8.70 (3H, m, arom. protons); 2.12 (3H, s, $C_{(6)}–CH_3$). The data correspond to the data given in [28].

**6-Bromo-2-thioxo-4-quinazolone (1c).** Sodium thiocyanate (2.85 g, 35 mmol) and conc. HCl (2 ml) were added to a solution of 5-bromoanthranilic acid (7.6 g, 35 mmol) in *o*-xylene. The mixture was boiled for 6 h and then cooled. The precipitate was filtered out, washed with water, and dried. The crystals obtained were dissolved in a 2 N NaOH solution (150 ml), and then this solution was neutralized with dilute acetic acid. The precipitate was filtered out, washed with water, and dried. Yield 3 g (30%); mp 323-325°C, $R_f$ 0.74 (acetone–benzene, 1:9). The data correspond to the data given in [28].

**2-Chloro-6-nitro-4-quinazolone.** 2,4-Dichloro-6-nitroquinazoline (2.07 g, 10 mmol) was dissolved in $POCl_3$ (10 ml) and a few drops of triethylamine were added. The reaction mixture was boiled for 2 h at the boiling point of phosphorus oxychloride. After this, the excess of the latter was distilled off and the precipitate formed was washed with distilled water. A 10% NaOH solution (20 ml) was added to the residue, and the mixture was boiled for 1 h. The solution was acidified with 10% HCl. The precipitate was filtered out and recrystallized from alcohol. 2-Chloro-6-nitro-4-quinazolone (1.45 g, 74%) was obtained; mp 243-244°C (alcohol). Mass spectrum, *m*/*z* (*I*, %):* 225/227 $[M]^+$ (100), 197/199 $[M–CO]^+$ (75), 189 $[M–Cl]^+$ (55). The data correspond to the data given in [29].

**6-Nitro-2-thioxo-4-quinazolone (1d).** Potassium hydrogen sulfide (1.8 g, 25 mmol) was added to a solution of 2-chloro-6-nitro-4-quinazolone (4.5 g, 20 mmol) in aqueous alcohol (1:3) (100 ml). The mixture was heated in a water bath at 85-90°C for 4 h and then cooled and diluted with water. The precipitate was filtered out, washed with water, dried, and recrystallized from alcohol. Yield 1.78 g (40%) of a substance with mp 267-268°C, $R_f$ 0.7 (methanol–chloroform, 1:5). IR spectrum, ν, $cm^{-1}$: 1350 (NO), 1685 (CO), 3190, 3330 (NH). Mass spectrum, *m*/*z* (*I*, %): 223 $[M]^+$ (100), 195 $[M–CO]^+$ (70), 144 $[M–HNCS]^+$ (30). $^1H$ NMR spectrum ($CF_3COOH$), δ, ppm: 7.10-8.70 (3H, m, arom. protons).

**7-Nitro-2-thioxo-4-quinazolone (1e).** A mixture of 4-nitroanthranilic acid (2 g, 10 mmol) and ammonium thiocyanate (1.1 g, 15 mmol) was melted at 200-220°C for 20 min. The mixture was cooled and dissolved in 2 N NaOH; the undissolved precipitate was filtered out. The mother liquor was neutralized and the precipitate was filtered out, washed with water, and dried. Yield of product 0.25 g (10%); mp 250-252°C (alcohol), $R_f$ 0.6 (acetone–benzene, 2:5). IR spectrum, ν, $cm^{-1}$: 1350 (NO), 1680 (CO), 3190, 3325 (NH). Mass spectrum, *m*/*z* (*I*, %): 223 $[M]^+$ (100), 195 $[M–CO]^+$ (55), 144 $[M–HNCS]^+$ (45). $^1H$ NMR spectrum ($CF_3COOH$), δ, ppm: 7.20-8.85 (3H, m, arom. protons). The data correspond to the data given in [29].

**8H,15H-1,2,4-Thiadiazolo[3,2-*b*:5,4-*b*']diquinazoline-8,15-dione (2a).** For methods A, B, see [24]. C. Iodine (2.54 g, 15 mmol) was added to a solution of 2-thioxo-4-quinazolone (1.78 g, 10 mmol) in absolute methanol (30 ml) while boiling. The reaction mixture was boiled for 15 min, cooled down, and diluted with water. The aqueous solution was boiled until the dark-brown color disappeared. The solution was cooled down and the precipitate was filtered out, washed with water, recrystallized from DMF, and dried. Yield of product 58%. The physicochemical and spectral data for the product obtained were identical to the data in [24].

**2,10-Dimethyl-8H,15H-1,2,4-thiadiazolo[3,2-*b*:5,4-*b*']diquinazoline-8,15-dione (2b).** Conc. $H_2SO_4$ (2 ml) was added with stirring to a solution of compound **1b** (1.90 g, 10 mmol) in DMSO (10 ml). The mixture was stirred for 4 h. The precipitate was filtered out, washed with water and then with DMF, and dried. Yield of product 75%; mp 267-268°C, $R_f$ 0.46 (acetone–benzene, 2:3). IR spectrum, ν, $cm^{-1}$: 1685 (CO) (as a broadened band). Mass spectrum, *m*/*z* (*I*, %): 348 $[M]^+$ (100), 320 $[M–CO]^+$ (82), 290 (46), 275 $[M]^+$ (100). Found, %: C 68.40; H 3.72; N 17.59. $C_{18}H_{12}N_4O_2S$. Calculated, %: C 68.35; H 3.79; N 17.72.

* The values of *m*/*z* are given for ions with the isotope $^{35}Cl$.

**2-Oxoquinazolones 3b-d** were obtained similarly by oxidative cyclocondensation of 6-bromo-, 6-nitro-, 7-nitro-2-thioxo-4-quinazolones **1b-e**. The properties of compounds **3b-d** correspond to those described in [29].

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