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SYNTHESIS, PROPERTIES, AND MASS-SPECTROMETRIC FRAGMENTATION OF 2-THIO DERIVATIVES OF 3-ARYLQUINAZOLIN-4-ONES

Yu. A. Azev[1], B. V. Golomolzin[1], T. Dyulcks[2], N. A. Klyuev[3], and Yu. G. Yatluk[1]

We have studied the reactions of alkylation, oxidation, and hydrolysis of 3-aryl-2-thioxoquinazolin-4-ones. Alkylation in an alkaline medium occurs exclusively at the sulfur atom. Oxidation by hydrogen peroxide leads to formation of 3-arylquinazoline-2,4-diones. The latter are also obtained in base or acid hydrolysis of the synthesized S-alkyl derivatives. When 3-aryl-2-thioxoquinazolin-4-ones are reacted with iodine, we obtain the disulfides, while the reaction with chlorine in hydrochloric acid leads to 2-chloroquinazolin-4-ones. Studying the mass spectrometric behavior of the compounds obtained made it possible to observe in the gas phase ring–chain isomerization of the heterocyclic ring, and also S–N migration of the propargyl radical in molecular ions of the S-propargyl derivatives.

Keywords: 3-aryl-2-thioxoquinazolin-4-ones, alkylation, hydrolysis, mass-spectrometric fragmentation, oxidation, skeletal rearrangements, thermolysis.

The quinazoline ring is an essential part of many natural alkaloids [1]. Among quinazoline derivatives we find compounds with diverse biological activity (hypotonic, antiallergic, antibacterial, anthelmintic) [2]. Recently there has been an active search for antagonists of folic and isofolic acids, which are cell mitosis inhibitors [3, 4]. The antitumor [2] and radioprotective [5, 6] properties of quinazoline derivatives have been studied. It was shown earlier [6] that the radioprotective activity of 2-aminoalkylthio derivatives of 3-phenylquinazolin-4-one can be optimized by changing the alkyl chain in the position 2, and the duration of this effect probably depends on the aryl group in the position 3. It has been hypothesized that the N-arylquinazoline moiety facilitates penetration of the substance into the cell and that the aminothiol formed after hydrolytic decomposition of the molecule exerts a radioprotective effect.

The aim of this work was to study new synthesis routes, chemical conversions, and mass-spectrometric characteristics of derivatives of aryl-2-thioxoquinazolin-4-ones.

We synthesized the starting 3-aryl-2-thioxoquinazolin-4-ones **1a-d** by condensation of anthranilic acid with arylthioureas according to the method in [7]. The presence of a 2-thioxo group within their molecules results in more opportunities for functionalization of the arylquinazolones. Thus as a result of oxidation of 3-(4-methyl-phenyl)-2-thioxoquinazolin-4-one (**1b**) by hydrogen peroxide in alkaline medium, we obtained 3-(4-methyl-phenyl)quinazoline-2,4-dione (**2b**) (Scheme 1), the structure of which has been confirmed by an alternate synthesis from anthranilic acid and phenyl isocyanate [5]. At the same time, when alkaline solutions of the thiones **1a,c,d** were treated with a solution of iodine in 10% KI according to the method described in [8], the disulfides **3a,c,d** were obtained.

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[1]Ural State Technical University, Ekaterinburg 620002, Russia; e-mail: azural@dialup.utk.ru. [2]Bremen University, Germany D28334; e-mail: duelcks@chemie.uni-bremen.de. [3]Institute of Ecology and Evolution Problems, Russian Academy of Sciences, Moscow 117071. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 440-446, March, 2007. Original article submitted September 7, 2005; revised September 18, 2006.

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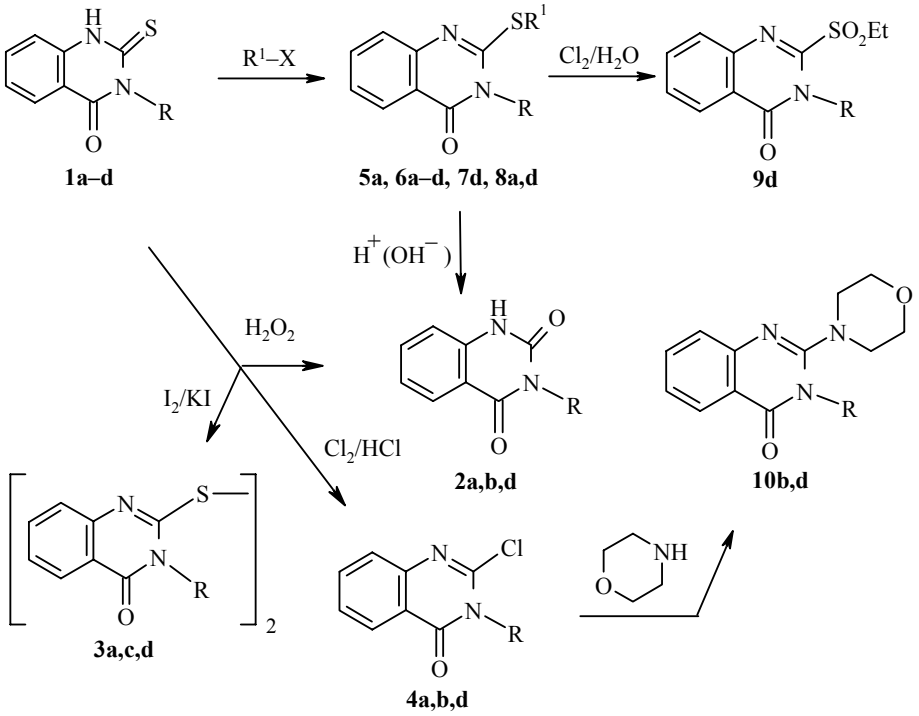
We know that methods involving chlorination of the corresponding thiones in aqueous medium are used for synthesis of sulfonyl chlorides [9]. In studying oxidation of a suspension of the compounds **1a,b,d** by chlorine in a 10% HCl solution, we found a simple route for synthesis of 3-aryl-2-chloroquinazolin-4-ones **4a,b,d**. The reaction probably occurs through a step of formation of the corresponding intermediate sulfonyl chloride, which is converted to the 2-chloro derivative **4** (Scheme 1), analogously to the mechanisms described in [9, 10].

Scheme 1



a R = Ph, **b** R = 4-MeC_6H_4, **c** R = 4-$MeOC_6H_4$, **d** R = 4-ClC_6H_4; **5** $R^1 = CH_2CH_2NEt_2$;

6 $R^1 = CH_2C{\equiv}CH$; **7** R^1 = Et, **8** R = CH_2CH_2OH; X = Cl, Br, I

2-Alkylthio derivatives **5-8** were obtained as a result of the reaction of thiones **1** with alkyl halides in alkaline solution at room temperature, while 3-(4-chlorophenyl)-2-ethylsulfonylquinazolin-4-one (**9d**) was formed when quinazolone **7d** is oxidized by chlorine in water.

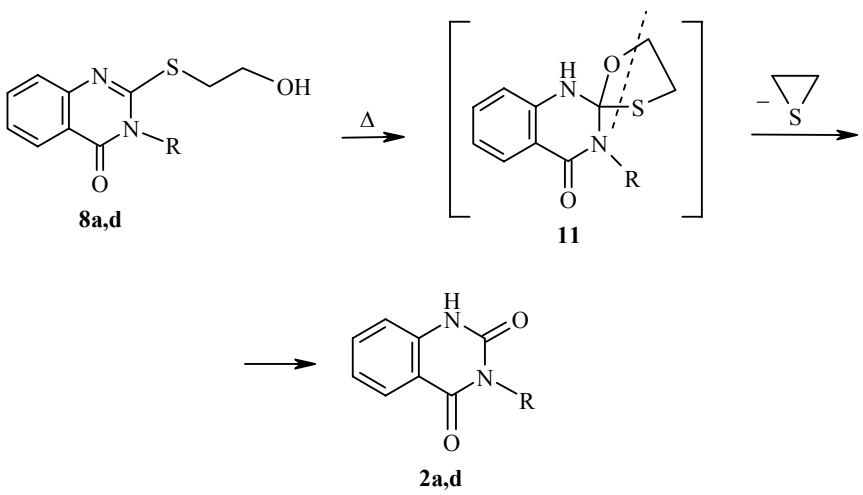
The alkylthio derivatives **6a,b** are hydrolyzed when heated in 15% solutions of HCl or NaOH, yielding the known 3-arylquinazoline-2,4-diones **2a,b**, which confirms the structure of the former as the S-alkyl rather than the N-alkyl derivatives.

We found that when compounds **8a,d** are heated at a temperature of 175-180°C for 30 min, 3-arylquinazolinediones **2a,d** are formed in 30% yield. Such a conversion can be the result of intramolecular nucleophilic attack on the terminal OH group of the alkyl substituent at the $C_{(2)}$ atom of the quinazoline ring with formation of the cyclic intermediate **11**, which then is cleaved according to Scheme 2.

The chloro derivatives **4** obtained in this work can be a convenient starting material for synthesis of diverse 2-substituted 3-arylquinazolin-4-ones. Thus as a result of brief heating of chloro derivatives **4b,d** with morpholine in ethanol, the morpholino derivatives **10b,d** are formed in 35-40% yield.

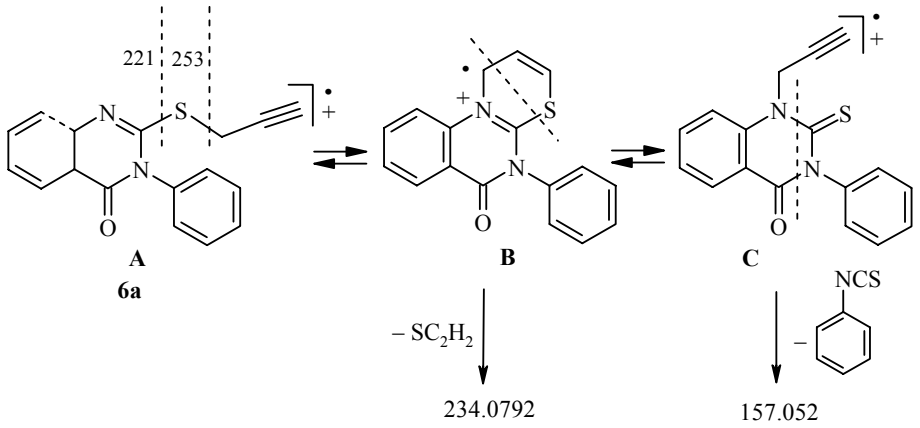
In studying the mass spectra of the propargyl derivatives of **6**, we observed unusual fragmentation of the molecular ion. In the mass spectra of these compounds, regardless of the structure of the aryl substituent, we observe an intense peak with *m*/*z* 157. By high-resolution mass spectrometry, it was established that cleavage of aryl isothiocyanate [ArNCS] from molecule **6** always leads to formation of a fragment having the composition $C_{10}H_7NO$ (found: *m*/*z* 157.052; calculated: *m*/*z* 157.0527, δ 0.3 ppm). Furthermore, determination of the metastable ions (DADI method) showed that ions with *m*/*z* 263, 253, 234, 221, and 157 are formed directly from the molecular ion **6a**.

Scheme 2



The proposed structure for **6a** as the alkylthio derivative **A** (see Scheme 3) is supported by the presence of the following ions in the mass spectrum: *m*/*z* 253 $[M–C_3H_3]^+$, *m*/*z* 221 $[M–SCH_2CCH]^+$, and *m*/*z* 194 $[(M–SCH_2CCHHCN]^+$. At the same time, the appearance of the ions *m*/*z* 157 $[M–SCN–C_6H_4R]^+$ ($C_{10}H_7NO$ with δ 0.3 ppm) and $[M–SC_2H_2]^+$ (234.0792, for $C_{15}H_{10}N_2O$: 234.0793, δ 0.3 ppm) can be explained only as the result of partial rearrangement of the molecular ion. In this case, detachment of the SC_2H_4 fragment is possible from the cyclic structure **B**, while detachment of the fragment $SCN–C_6H_4R$ calls for retro Diels–Alder cleavage

Scheme 3



of the isomeric form of the molecular ion **C**. The thione form **C** also explains formation of the ion $[M–CHO]^+$ (*m*/*z* 263), since it has a distorted *boat* conformation. Formation of such an isomer can be analogous to high-temperature rearrangement of allyl ethers of phenols or enols to form isomeric C-allyl derivatives (O–Alk → C–Alk), known as the Claisen rearrangement. Similar high-temperature rearrangements have been described for heterocyclic derivatives [11]. However, we must note that the mass spectrometric rearrangement S–Alk → N–Alk of the propargyl derivatives which we observed is not a high-temperature process, since the ratio of the intensities of the molecular ion and the ion with *m*/*z* 157 $[M–SCNArR]^+$ is practically constant over a broad temperature range.

The examples given for mass spectrometric fragmentation confirm that migration of the alkyl group from the S atom to the $N_{(1)}$ atom of quinazoline is possible for the S-propargyl derivatives, capable of forming a six-center complex.

In conclusion, we should emphasize that in this work we have tested different synthetic routes for novel 3-arylquinazolines. The compounds obtained are of independent interest, and can also be studied as carriers for different biologically active groups. We have observed novel chemical (thermal) transformations of quinazolines which may be of metabolic interest. As a result of studying mass spectrometric fragmentation of 2-thio derivatives of 3-arylquinazolone, we have observed mass spectrometric skeletal rearrangements for 2-thiopropargyl derivatives of 3-arylquinazolones.

TABLE 1 Derivatives of 3-N-Arylquinazol-4-one

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{28}H_{18}N_4O_2S_2$	66.2 / 66.4	3.8 / 3.6	9.9 / 11.1	250-251	30
3c	$C_{30}H_{22}N_4O_4S_2$	63.3 / 63.6	4.0 / 3.9	9.5 / 9.9	260-261	30
3d	$C_{28}H_{16}Cl_2N_4O_2S_2$	58.2 / 58.4	2.6 / 2.8	9.5 / 9.7	262-263	25
4a	$C_{14}H_9ClN_2O$	65.4 / 65.5	3.5 / 3.5	10.7 / 10.9	112-113	20
4b	$C_{15}H_{11}ClN_2O$	66.5 / 66.5	4.0 / 4.1	10.0 / 10.3	125-126	25
4d	$C_{14}H_8Cl_2N_2O$	57.5 / 57.8	2.6 / 2.8	9.6 / 9.6	149-150	45
5a	$C_{20}H_{23}N_3OS$	67.9 / 68.0	6.6 / 6.7	11.6 / 11.9	77-78	45
6a	$C_{17}H_{12}N_2OS$	69.7 / 69.8	4.0 / 4.1	9.6 / 9.6	184-185	50
6b	$C_{18}H_{14}N_2OS$	70.5 / 70.6	4.5 / 4.6	9.0 / 9.1	157-159	45
6c	$C_{18}H_{14}N_2O_2S$	66.9 / 67.1	4.6 / 4.4	9.4 / 9.7	193-194	45
6d	$C_{17}H_{11}ClN_2OS$	62.2 / 62.5	3.4 / 3.4	8.5 / 8.6	195-196	55
7d	$C_{16}H_{13}ClN_2OS$	60.5 / 60.7	3.9 / 4.1	8.6 / 8.8	157-158	40
8a	$C_{16}H_{14}N_2O_2S$	64.1 / 64.4	4.8 / 4.7	9.3 / 9.4	98-99	40
8d	$C_{16}H_{13}ClN_2O_2$	57.6 / 57.7	3.9 / 3.9	8.2 / 8.4	161-162	40
9d	$C_{16}H_{13}ClN_2O_3S$	54.9 / 55.1	3.8 / 3.8	8.2 / 8.0	185-186	45
10b	$C_{19}H_{19}N_3O_2$	70.8 / 71.0	6.1 / 6.0	13.0 / 13.1	133-134	30
10d	$C_{18}H_{16}ClN_3O_2$	63.0 / 63.2	4.6 / 4.7	12.1 / 12.3	140-141	35

EXPERIMENTAL

The mass spectra were taken on a double-focusing Finnigan MAT 8200 mass spectrometer using a direct injection system with ionization energy 70 eV.

Oxidation of 3-(4-Methylphenyl)-2-thioxoquinazolin-4-one (1) by Hydrogen Peroxide. A 30% aqueous solution of H_2O_2 (22 ml) was slowly added to a solution of compound **1b** (10.8 g, 40 mmol) (obtained according to [7]) in a 10% aqueous solution of KOH (70 ml), with heating up to 70°C and stirring; the mixture was boiled for 15 min and then cooled down, and then concentrated HCl was added down to pH 1. The precipitate of **2b** formed was filtered out and recrystallized from butanol. Yield 45%; mp 258°C (mp 258°C [3, 5, 8]).

Bis(2-quinazolyl) Disulfide 3a. A solution of iodine (2.5 g, 10 mmol) in a 10% aqueous solution of KI (75 ml) was added to a solution of of compound **1a (**10 mmol) in a 5% aqueous solution of KOH (25 ml) at 20°C. The precipitate formed of the disulfide **3a** was filtered out and recrystallized from ethanol.

Disulfides 3c,d were obtained similarly.

Alkylation of 3-Aryl-2-thioxoquinazolin-4-ones. Compound **1** (10 mmol) was dissolved in a 5% NaOH solution (50 ml) and filtered. A solution of the corresponding alkyl halide ($ClCH_2CH_2NEt_2$, $BrCH_2CCH$, IEt, or $ClCH_2CH_2OH$) in water (10 ml) was added to the filtrate. The reaction mass was stirred at room temperature for 1 h 30 min to 2 h. The precipitate formed of products **5-8** was filtered out and recrystallized from aqueous ethanol (see Table 1). Mass spectrum, *m*/*z* (I_{rel}, %): **6a** - 292 $[M]^+$ (58), 291 (98), 263 (5), 253 (19), 234 (17), 221 (19), 157 (100); **6b** – 306 $[M]^+$ (64), 305 (98), 273 (8), 248 (18), 235 (19), 224 (7), 157 (100); **6c** – 322 $[M]^+$ (87), 321 (91), 283 (11), 251 (16), 180 (6), 157 (100); **6d** – 326 $[M]^+$ (45), 325 (65), 291 (12), 255 (17), 252 (9), 192 (8), 157 (100).

3-(4-Chlorophenyl)-2-ethylsulfonylquinazolin-4-one (9d). Gaseous chlorine was passed through a suspension of ethylthioquinazolone **7d** (1.0 mmol) in water (10 ml) at 5-7°C for 25-30 min. The precipitate of the sulfone was filtered out, washed with ethanol, and recrystallized from aqueous ethanol.

Hydrolysis of 2-Alkylthio Derivatives of 3-Arylquinazol-4-ones. A. A solution of the alkylthio derivative **6a** (146 mg, 0.5 mmol) was boiled in of 15% aqueous HCl (10 ml) for 1 h. The reaction mass was cooled down, and the precipitate was filtered out and recrystallized from ethanol. Yield of quinazolinedione **2a**, 70 mg (30%); mp 272°C (mp 272°C [3, 8]).

B. A solution of compound **6b** (153 mg, 0.5 mmol) in a 15% alcoholic NaOH solution (3 ml) was boiled for 1 h; the reaction mass was filtered, the mother liquor was diluted with water 1:5, the precipitate formed of compound **2b** was filtered out and reprecipitated from ethanol by water. Yield 50 mg (20%); mp 258°C (mp 258°C [3, 5, 8]).

Thermolysis of 2-(2-Hydroxyethylthio)-3-phenylquinazol-4-one (8a). Compound **8a** (1.0 mmol) was heated at 175-180°C for 1 h. The quinazolinedione **2a** formed was extracted from the solid mass with butanol. The solution was cooled down and the precipitate was filtered out. Yield 70 mg (15%); mp 272°C (mp 272°C [3, 5, 8]).

Thermolysis of compound **8d** was carried out similarly. Yield of compound **8d** 25%; mp 295°C (mp 295°C [3, 5, 8]).

2-Chloro-3-phenylquinazolin-4-one (4a). Gaseous chlorine was passed through a suspension of compound **1a** (1.0 mmol) in 10% HCl (10 ml) at 5-10°C for 45-50 min. The precipitate of compound **4** was filtered out and recrystallized from ethanol.

2-Chloro derivatives 4b,d were obtained similarly (see Table 1).

3-(4-Methylphenyl)-2-(N-morpholyl)quinazolin-4-one (10b). A solution of chloro derivative **4b** (0.05 mmol) and morpholine (3.0 mmol) in ethanol (2 ml) was boiled for 1 h. The reaction mass was cooled down; the precipitate was filtered out and washed with water.

Compound 10d was obtained similarly (see Table 1).

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