Thioureas from 3-aminoquinazolin-4(3*H*)-one
2.* Unusual alkaline recyclization of 3-(*N*′,*N*′,*S*-trialkylisothioureido)quinazolin-4(3*H*)-ones into new 1,3,4-oxadiazoles

G. G. Rusu

Institute of Chemistry of the Moldova Academy of Sciences,
3 ul. Academy, MD-2028 Chisinau, Moldova.
Fax: +7 (373) 73 9775. E-mail: ghenadie@hotmail.com

3-(*N*′,*N*′,*S*-trialkylisothioureido)quinazolin-4(3*H*)-ones obtained by the reactions of 3-(*N*′,*N*′-dialkylthioureido)quinazolin-4(3*H*)-ones with alkyl halides undergo unusual recyclization into 5-(2-aminophenyl)-2-dialkylamino-1,3,4-oxadiazoles under the action of aqueous solutions of alkali, hydrazine, and primary aliphatic amines. A plausible mechanism of the recyclization was proposed.

Key words: 5-(2-aminophenyl)-2-dialkylamino-1,3,4-oxadiazoles, isothioureas, thioureidoquinazolin-4(3*H*)-ones, alkaline recyclization.

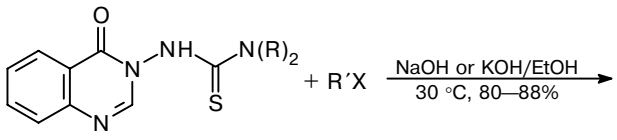
In the previous communication,[1] we described for the first time the synthesis and acid recyclization of 3-(*N*′,*N*′-dialkylthioureido)quinazolin-4(3*H*)-ones (**1**) into 5-(2-aminophenyl)-2-dialkylamino-1,3,4-thiadiazoles, which are convenient intermediates for the construction of new heterocyclic systems. Insofar as compounds **1** undergo recyclization only in the presence of such a strong acid as conc. H_2SO_4, it was assumed that the possible reaction mechanism includes (at a certain step) the protonation of the carbonyl O atom of the quinazolinone fragment of the molecule. Based on this assumption, one can expect that the replacement of the S atom by the O atom in quinazolinones **1** will afford on recyclization the corresponding 5-(2-aminophenyl)-2-dialkylamino-1,3,4-oxadiazoles (**2**).

Oxygen-containing analogs of quinazolinones **1** can be prepared by the reaction of 3-aminoquinazolin-4(3*H*)-one with *N*,*N*-dialkylcarbamoyl chloride,[2] by desulfurization of **1** under the action of PbO and HgO[3,4] or dimethyl sulfoxide in the presence of electrophilic catalysts,[5] or by alkaline hydrolysis of the corresponding alkylthio derivatives.[6] The last method was used in the present work.

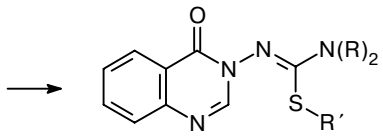
Quinazolinones **1** were alkylated in ethanol in the presence of an equimolar amount of alkali, with a slight excess (up to 5%) of alkyl halide owing to its volatility (Scheme 1).

It turned out that the yield of the final product does not depend on the nature of an alkali (NaOH or KOH), but decreases in the presence of organic bases (Et_3N, pyridine, or *N*,*N*-dimethylaniline) or with an increase in the reaction temperature, because of partial resinification of the reaction mixture.

Scheme 1



1a—d



3a—h

1: NR_2 = NMe_2 (**a**), NEt_2 (**b**), morpholino (**c**), piperidino (**d**);
3: R′ = Me (**a—d**), All (**e—h**), NR_2 = NMe_2 (**a,e**), NEt_2 (**b,f**), morpholino (**c,g**), piperidino (**d,h**)

The structures of isothioureas **3a—h** were confirmed by data from elemental analysis and ^1H NMR and IR spectroscopy (Tables 1, 2). The IR spectra of these compounds contain no ν(NH) absorption band at ~3250 cm^{-1} characteristic of those of the starting thioureas, while the band corresponding to the carbonyl group is unexpectedly shifted toward the low-frequency region by ~10—15 cm^{-1}.

Because the disappearance of the intramolecular hydrogen bond during the transformation of compounds **1** into **3** should be accompanied by an increase in ν(C=O),

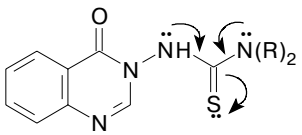
* For Part 1, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 262—265, February, 2001.

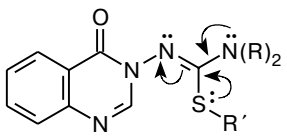
Table 1. Main parameters of quinazolinones **3a—h** and oxadiazoles **2a—d**

Compound	Yield (%)	M. p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
2a	78	163—165	58.52 58.82	5.72 5.88	27.64 27.45	$C_{10}H_{12}N_4O$
2b	75	112—114	61.88 62.07	6.63 6.90	23.87 24.14	$C_{12}H_{16}N_4O$
2c	65	147—149	58.20 58.54	5.35 5.69	22.50 22.58	$C_{12}H_{14}N_4O_2$
2d	80	166—168	63.66 63.93	6.28 6.56	23.13 22.95	$C_{13}H_{16}N_4O$
3a	81	103—105	54.33 54.96	5.22 5.34	21.41 21.37	$C_{12}H_{14}N_4OS$
3b	76	78—80	57.50 57.93	6.11 6.21	19.02 19.31	$C_{14}H_{18}N_4OS$
3c	93	128—130	55.13 55.26	5.20 5.26	18.57 18.42	$C_{14}H_{16}N_4O_2S$
3d	85	117—119	59.39 59.60	5.47 5.96	18.50 18.54	$C_{15}H_{18}N_4OS$
3e	89	112—113	58.20 58.33	5.45 5.55	19.51 19.44	$C_{14}H_{16}N_4OS$
3f	85	57—59	60.44 60.76	6.18 6.33	17.53 17.72	$C_{16}H_{20}N_4OS$
3g	83	85—87	57.90 58.18	5.29 5.45	16.88 16.97	$C_{16}H_{18}N_4O_2S$
3h	77	88—89	62.07 62.19	5.95 6.10	17.14 17.07	$C_{17}H_{20}N_4OS$

the observed shift can be attributed only to some changes in the electronic effects. Probably, the electron density on the N(3) atom in isothioureas **3** is higher than in thioureas **1**, owing to the +M effect of the S and N atoms of the dialkylamino group:



1a—d



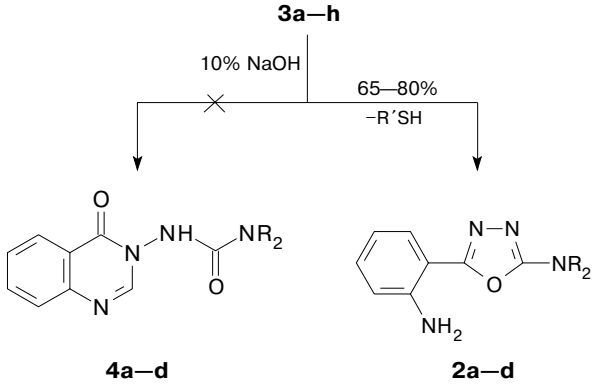
3a—h

It is an increase in the electron density on the O atom of compounds **3** that leads to the aforesaid shift of the CO absorption band, which correlates with the literature data.[7]

The ^{1}H NMR spectra of compounds **3a—h** show signals from the protons of the —N(R)$_2$ and —SR′ of the isothiourea fragment and do not contain a low-field signal from the NH proton. The quinazolinone fragment is characterized by a singlet from the proton at the C(2) atom at δ 7.9—8.0 (see Table 2).

Hydrolysis of compounds **3** with 10% NaOH resulted in the evolution of R′SH, which was identified from a specific unpleasant odor and from blackening of a strip of filter paper wetted with a solution of an Hg^{2+} salt. In the case of compounds **3e—h**, prop-2-enethiol was additionally identified by comparing its physical constants with the literature data.[8] However, the expected 3-(*N*′,*N*′-dialkylureido)quinazolin-4(3*H*)-ones (**4a—d**) were not formed. Instead, 5-(2-aminophenyl)-2-dialkylamino-1,3,4-oxadiazoles (**2a—d**) as products of alkaline recyclization of the quinazolinone fragment of isothioureas **3a—h** were isolated from the reaction mixture in good yields (Scheme 2).

Scheme 2



2: R = Me (**a**), Et (**b**), NR$_2$ — morpholino (**c**), NR$_2$ — piperidino (**d**)

The structures of oxadiazoles **2a—d** were proved by comparing their IR and ^{1}H NMR spectra with those of the corresponding 5-(2-aminophenyl)-2-dialkylamino-1,3,4-thiadiazoles,[1] as well as using data from elemental analysis (see Table 1) and mass spectrometry (*m*/*z* value of the molecular ion peak) (see Table 2). The IR spectra of compounds **2a—d** do not contain the absorption band at ~1670 cm^{-1} corresponding to the carbonyl group, but show ν_{as} and ν_s bands at ~3300—3400 cm^{-1} characteristic of primary amines. The ^{1}H NMR spectra of these compounds exhibit neither a singlet from the proton at the C(2) atom of the quinazolinone fragment nor signal from the SR′ protons. Instead, a signal (sometimes broadened) from the protons of the primary amino group appears at δ ~6.5.

While considering a plausible pathway for the transformation of isothioureas **3** into oxadiazoles **2**, we assumed that a nucleophile (OH$^-$) can attack either the C atom of the isothiourea fragment or the electron-deficient C(2) atom of the quinazolinone. In the former case, compound **2** has to be formed through an intermediate quinazolinone **4**. If this is the case, then the reaction with a primary amine or hydrazine instead of

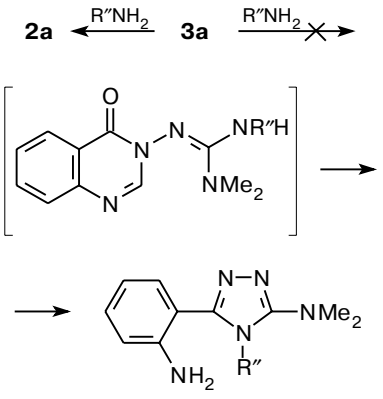
Table 2. Spectral parameters of quinazolinones **3a**—**h** and oxadiazoles **2a**—**d**

Compound	IR, ν/cm^{-1}	^1H NMR (δ, J/Hz)
2a	3408, 3315 (NH_2)	3.10 (s, 6 H, NMe_2); 6.45 (s, 2 H, NH_2); 7.55—6.55 (m, 4 H, CH arom.)
2b	3410, 3320 (NH_2)	1.20 (t, 6 H, 2 Me, J = 7.2); 3.50 (q, 4 H, 2 CH_2, J = 7.2); 6.45 (s, 2 H, NH_2); 7.55—6.60 (m, 4 H, CH arom.)
2c	3400, 3310 (NH_2)	3.70, 3.50 (both t, 8 H, 4 CH_2 morph.); 6.40 (br.s, 2 H, NH_2); 7.55—6.605 (m, 4 H, CH arom.)
2d	3416, 3312 (NH_2)	1.70 (s, 6 H, 3 CH_2 piper.); 3.50 (t, 4 H, CH_2NCH_2); 6.40 (br.s, 2 H, NH_2); 7.55—6.70 (m, 4 H, CH arom.)
3a	1608 (C=N) 1670 (C=O)	2.23 (s, 3 H, SMe); 3.25 (s, 6 H, NMe_2); 7.95 (s, 1 H, CH); 8.2—7.4 (m, 4 H, CH arom.)
3b	1616 (C=N) 1664 (C=O)	1.30 (t, 6 H, 2 Me, J = 7.0); 2.25 (s, 3 H, SMe); 3.70 (q, 4 H, 2 CH_2, J = 7.0); 7.95 (s, 1 H, CH); 8.2—7.4 (m, 4 H, CH arom.)
3c	1620 (C=N) 1664 (C=O)	2.25 (s, 3 H, SMe); 3.80, 3.55 (both t, 8 H, 4 CH_2 morph.); 7.95 (s, 1 H, CH); 8.2—7.4 (m, 4 H, CH arom.)
3d	1614 (C=N) 1665 (C=O)	1.70 (s, 6 H, 3 CH_2 piper.); 2.25 (s, 3 H, SMe); 3.70 (t, 4 H, CH_2NCH_2); 8.05 (s, 1 H, CH); 8.2—7.4 (m, 4 H, CH arom.)
3e	1600 (C=N) 1665 (C=O)	3.25 (s, 6 H, NMe_2); 3.32 (d, 2 H, SCH_2, J = 6.60); 5.10 (m, 2 H, CH_2=); 5.65 (m, 1 H, CH=); 7.90 (s, 1 H, CH); 8.2—7.4 (m, 4 H, CH arom.)
3f	1616 (C=N) 1660 (C=O)	1.30 (t, 6 H, 2 Me, J = 7.0); 3.30 (d, 2 H, SCH_2, J = 6.60); 3.70 (q, 4 H, 2 CH_2, J = 7.0); 5.10 (m, 2 H, CH_2=); 5.65 (m, 1 H, CH=); 8.0 (s, 1 H, CH); 8.2—7.4 (m, 4 H, CH arom.)
3g	1620 (C=N) 1662 (C=O)	3.80, 3.55 (both t, 8 H, 4 CH_2 morph.); 3.30 (d, 2 H, SCH_2, J = 6.60); 5.10 (m, 2 H, CH_2=); 5.70 (m, 1 H, CH=); 8.0 (s, 1 H, CH); 8.2—7.5 (m, 4 H, CH arom.)
3h	1625 (C=N) 1665 (C=O)	1.70 (s, 6 H, 3 CH_2 piper.); 3.35 (d, 2 H, SCH_2, J = 6.60); 3.73 (t, 4 H, CH_2NCH_2); 5.10 (m, 2 H, CH_2=); 5.70 (m, 1 H, CH=); 8.0 (s, 1 H, CH); 8.2—7.5 (m, 4 H, CH arom.)

Note. MS, m/z (I_{rel} (%)): **2a** — 204 $[M]^+$ (100); **2b** — 232 $[M]^+$ (100); **2c** — 246 $[M]^+$ (100); **2d** — 244 $[M]^+$ (100).

alkali should give the corresponding intermediate guanidines, which are supposed to undergo cyclization into 1,2,4-triazoles (**5**), by analogy with the cyclization of 1-acylguanidines.[9] However, heating of isothiourea **3a** with 100% hydrazine hydrate, allylamine, butylamine, and ethanolamine, as well as with their 10% aqueous solutions unexpectedly yielded the same product, namely, oxadiazole **2a** (Scheme 3).

Scheme 3



5

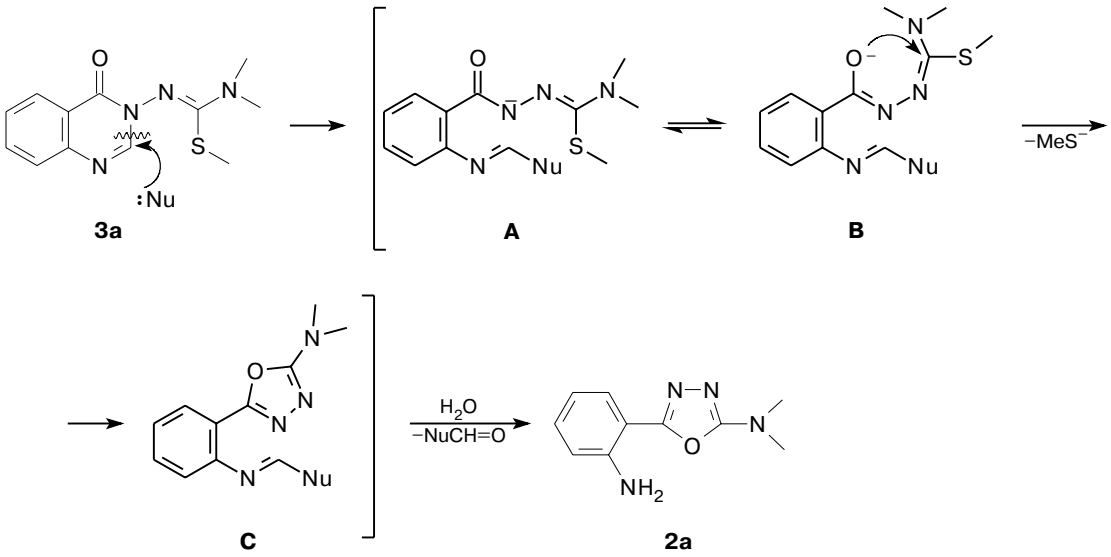
Such a reaction pathway can be due to a nucleophile attack on the C(2) atom of the quinazolinone. This also elucidates why the structure of the final product is independent of the nature of the nucleophile, and the recyclization of compounds **3** may be roughly illustrated in the case of **3a** (Scheme 4).

The opening of the quinazolinone ring seems to give intermediates **A** and **B**, which are the deprotonated forms of S-alkyl derivatives of 1-aroylthiosemicarbazide. When heated, they release alkanethiolate to undergo cyclization into 1,3,4-oxadiazole derivatives.[10]

Hence, it was found that 3-(*N′*,*N′*-dialkylthioureido)quinazolin-4(3*H*)-ones (**1**) can be converted to 5-(2-aminophenyl)-2-dialkylamino-1,3,4-oxadiazoles (**2**) by recyclization of the corresponding isothioureido derivatives **3** under the action of aqueous solutions of alkalis, hydrazine, and some primary aliphatic amines.

We also plan to synthesize 3-(*N′*,*N′*-dialkylureido)quinazolin-4(3*H*)-ones (**4**) by oxidative desulfur-

Scheme 4



ization of thioureas **1a**—**d** and study their transformations in the presence of acids and bases.

Experimental

The melting points were determined on a Boetius microscope stage. IR spectra were recorded on a Specord 75IR instrument (suspensions in Vaseline oil). ^{1}H NMR spectra were recorded on a Varian XL-400 spectrometer (399.95 MHz) in DMSO-d_6. Mass spectra recorded on a Finnigan MAT.INCOS-50 instrument (ionizing voltage 70 eV). The course of the reaction was monitored by TLC on Silufol UV-254 plates in a hexane—acetone mixture (5 : 1).

The starting 3-(*N*′,*N*′-dialkylthioureido)quinazolin-4(3*H*)-ones were prepared as described in Ref. 1. Commercial alkyl halides (reagent grade) were distilled before use.

3-(*N*′,*N*′,*S*-Trimethylisothioureido)quinazolin-4(3*H*)-one (3a). A mixture of compound **1a** (2.48 g, 0.01 mol) and NaOH or KOH (0.01 mol) was dissolved in 25 mL of ethanol. Then, methyl iodide (1.50 g, 0.0105 mol) in 2 mL of ethanol was added with stirring at room temperature. The reaction mixture was kept at 30—35 °C for 1 h and then at 60 °C for 0.5 h. The ethanol was removed on a rotary evaporator at a reduced pressure. Benzene (25 mL) was added to the residue, and the benzene solution was washed three times with water, dried over anhydrous Na_2SO_4, and filtered through a thin layer of Al_2O_3. After the removal of the solvent, the residue was crystallized from hexane to give compound **3a** (2.13 g, 81%), m.p. 103—105 °C.

Compounds **3b**—**h** were synthesized in a similar manner. The yields, melting points, and spectral parameters of the reaction products are presented in Tables 1 and 2.

5-(2-Aminophenyl)-2-dimethylamino-1,3,4-oxadiazole (2a). ***A.*** A mixture of isothiourea **3a** (1.31 g, 0.005 mol; 2.88 g in the case of **3e**) and a 10% aqueous solution of alkali (hydrazine, allylamine, butylamine, or ethanolamine) (10 mL) was refluxed for 30—45 min until alkanethiol ceased to evolve (a filter paper wetted with a solution of an Hg^{2+} salt no longer turned black). The resulting oily substance solidified into a white voluminous precipitate. After cooling, the precipitate was filtered off, washed on the filter with water to a neutral reaction, dried, and recrystallized from ethanol to give compound **2a** (1.59 g, 78%), m.p. 163—165 °C.

Analogously, compounds **2b**—**d** were synthesized. The yields, melting points, and spectral parameters of the oxadiazoles **2a**—**d** obtained are presented in Tables 1 and 2.

B. A mixture of compound **3a** (1.31 g, 0.005 mol) and 100% hydrazine hydrate (allylamine, butylamine, or ethanolamine) (5 mL) was heated on a boiling water bath for 1 h. After cooling, water (20 mL) was added. The precipitate that formed was filtered off, washed several times with water on the filter, and dried to give virtually pure compound **2a** (1.50 g, 73.5%), m.p. 162—163 °C.

The author is grateful to L. D. Konyushkin, a senior research worker of the N. D. Zelinsky Institute of Organic Chemistry, for his assistance in recording ^{1}H NMR and mass spectra.

References

1. G. G. Rusu, N. A. Barba, and M. Z. Krimer, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 1785 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 1763].
2. S. L. Johnson and H. M. Giron, *J. Org. Chem.*, 1972, **37**, 1383.
3. H. Kessler and D. Leibfritz, *Tetrahedron Lett.*, 1970, 1595.
4. H. Z. Lecher and C. Gubernator, *J. Am. Chem. Soc.*, 1953, **75**, 1087.
5. M. Mikolajczuk and J. Luczak, *Chem. Ind.* (*London*), 1972, 76.
6. H. Ohta and M. Ohta, *J. Chem. Soc. Jpn, Pure Chem. Sect.*, 1957, **78**, 700.
7. *Infrared Absorption Spectroscopy*, Ed. K. Nakanisi, San-Francisco—Tokyo, 1962.
8. *Spravochnik khimika* [*Chemist's Handbook*], Khimiya, Moscow—Leningrad, 1964, vol. 2, p. 914 (in Russian).
9. *Heterocyclic Compounds*, Ed. R. C. Elderfield, New York, 1961, vol. 7, 541 pp.
10. J. Hoggarth, *J. Chem. Soc.*, 1949, 1918.

Received April 25, 2000;
in revised form September 4, 2000