Thioureidoquinazolin-4(3*H*)-ones

1. Acid-induced recyclization of 3-(*N'*,*N'*-dialkylthioureido)quinazolin-4(3*H*)-ones into 1,3,4-thiadiazoles

G. G. Rusu,[a,b] N. A. Barba,[a] and M. Z. Krimer†[b]*

[a]*Moldova State University, 60 ul. A. Mateevici, MD-2009 Chisinau, Moldova. Fax: +7 (042 2) 24 0655*

[b]*Institute of Chemistry of the Moldova Academy of Sciences, 3 ul. Academy, MD-2028 Chisinau, Moldova. Fax: +7 (042 2) 73 9775*

3-(*N'*,*N'*-Dialkylthioureido)quinazolin-4(3*H*)-ones prepared by the reaction of 3-aminoquinazolin-4(3*H*)-one with thiuram disulfides undergo the previously unknown acid-induced recyclization to give the corresponding 5-(2-aminophenyl)-2-dialkylamino-1,3,4-thiadiazoles. The structures of the products obtained were confirmed by IR and ^{1}H and ^{13}C NMR data. A plausible mechanism of the recyclization is discussed.

Key words: 3-aminoquinazolin-4(3*H*)-one, 5-(2-aminophenyl)-2-dialkylamino-1,3,4-thiadiazoles, acid-induced recyclization, thiuram disulfides, trisubstituted thioureas.

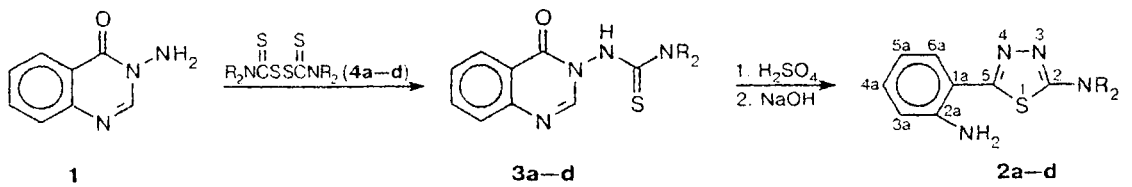
Among 3-aminoquinazolin-4(3*H*)-ones, only 1,3-disubstituted thioureas, exhibiting fungicidal,[1] anticonvulsant,[2] antiparkinsonian,[3] and antiinflammatory[4] properties, are well studied, while the corresponding trisubstituted derivatives have not been described. Although the method for the synthesis of trisubstituted thioureas by reacting primary amines with thiuram disulfides has long been known,[5] similar reactions involving 3-aminoquinazolin-4(3*H*)-ones have not been carried out. In addition, recent studies have shown that trisubstituted aryl- and heterylthioureas easily decompose by inorganic acids to give isothiocyanates,[6,7] which is an alternative to the method of synthesizing isothiocyanates by thiophosgenation of aryl- and heterylamines. For this reason, the goal of the present work was to synthesize trisubstituted quinazolinylthioureas with potential physiological activity and study their reactions with strong acids.

In the present communication, a two-step transformation of 3-aminoquinazolin-4(3*H*)-one (**1**) into 5-(2-aminophenyl)-2-dialkylamino-1,3,4-thiadiazoles (**2a—d**) *via* a previously unknown acid-induced recyclization of 3-(*N'*,*N'*-dialkylthioureido)quinazolin-4(3*H*)-ones (**3a—d**) is described (Scheme 1).

Thioureas **3a—d** were obtained in good yields by the reaction of equimolar amounts of compound **1** and the corresponding thiuram disulfides **4a—d** in DMF at 95—100 °C (the modified Nair method).[5] It turned out that the reaction course and the yield of the final product are virtually independent of the starting thiuram structure, which allows new trisubstituted thioureas with a quinazolinone fragment to be obtained easily in the same way. The structures of thioureas **3a—d** were confirmed by data of elemental analysis and ^{1}H NMR and IR spectroscopy (Table 1). The IR spectra of these compounds show absorption bands from CO (ν ~1680 cm^{-1}) and N—H stretching vibrations (ν ~3250 cm^{-1}). This suggests a cyclic structure of the reaction products rather than the betaine one formed in the reaction of thioanalogs **1** with CS_2 in the presence of an alkali.[8] The ^{1}H NMR spectra of thioureidoquinazolinones **3a—d** contain a low-field signal from the

† Deceased.

Scheme 1



1 **3a—d** **2a—d**

R = Me (**a**), Et (**b**), R_2N — morpholino (**c**), R_2N — piperidino (**d**)

Published in *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 10, pp. 1785—1788, October, 2000.

N—H proton of the thiourea fragment (δ ~ 10.7) and a distinct singlet from the HC(2) proton of the quinazolinone fragment at δ 7.9.

While studying the reactions of compounds **3a—d** with different inorganic acids (HCl (gas), H_3PO_4, and H_2SO_4), we obtained unusual results. Indeed, compounds **3a—d** react with HCl and H_3PO_4 to give normal salts that are stable even at 130 °C, whereas heating with conc. H_2SO_4 in dioxane at 90—95 °C causes their recyclization into thiadiazoles **2a—d**. In the reaction with H_2SO_4, as with HCl and H_3PO_4, quinazolinones **3a—d** initially produce salts in the form of voluminous

Table 1. Main physicochemical characteristics of thiadiazoles **2a—d** and quinazolinones **3a—d**

Compound	Yield (%)	M. p./°C	Found / Calculated (%)			Molecular formula	IR, ν/cm^{-1}	^{1}H NMR, δ (*J*/Hz)	^{13}C NMR, δ
			C	H	N				
2a	97	203—205	54.50 54.52	5.53 5.49	25.04 25.43	$C_{10}H_{12}N_4S$	3400, 3320 (NH_2)	7.35—6.60 (m, 4 H, CH arom.); 6.80 (s, 2 H, NH_2); 3.10 (s, 6 H, $N(CH_3)_2$)	169.05 (C(2)); 159.36 (C(5)); 111.825 (C(1a)); 146.235 (C(2a)); 115.855 (C(3a)); 129.80 (C(4a)); 115.59 (C(5a)); 129.69 (C(6a)); 41.09 ($N(CH_3)_2$)
2b	98	115—116	57.90 58.04	6.30 6.49	22.40 22.56	$C_{12}H_{16}N_4S$	3410, 3325 (NH_2)	7.25—6.55 (m, 4 H, CH arom.); 6.80 (s, 2 H, NH_2); 3.45 (q, 4 H, CH_2, J = 7.2); 1.20 (t, 6 H, CH_3, J = 7.2)	167.43 (C(2)); 158.68 (C(5)); 112.075 (C(1a)); 146.43 (C(2a)); 116.02 (C(3a)); 129.89 (C(4a)); 115.74 (C(5a)); 129.89 (C(6a)); 46.78 and 12.57 (NEt_2)
2c	73	132—133	55.09 54.94	5.43 5.38	21.25 21.36	$C_{12}H_{14}N_4OS$	3400, 3312 (NH_2)	7.25—6.55 (m, 4 H, CH arom.); 6.80 (s, 2 H, NH_2); 3.75 and 3.45 (2 t, 8 H, CH_2)	169.55 (C(2)); 160.17 (C(5)); 111.34 (C(1a)); 146.31 (C(2a)); 115.86 (C(3a)); 130.08 (C(4a)); 115.54 (C(5a)); 129.77 (C(6a)); 65.19 and 49.37 (morpholino)
2d	92	217—218	60.04 59.97	6.29 6.19	21.42 21.52	$C_{13}H_{16}N_4S$	3415, 3335 (NH_2)	7.25—6.60 (m, 4 H, CH arom.); 6.80 (s, 2 H, NH_2); 3.46 (s, 4 H, CH_2); 1.60 (s, 6 H, CH_2)	169.27 (C(2)); 159.56 (C(5)); 111.66 (C(1a)); 146.33 (C(2a)); 115.855 (C(3a)); 129.89 (C(4a)); 115.54 (C(5a)); 128.29 (C(6a)); 50.59, 24.57, and 23.41 (piperidino)
3a	88	210—211	53.04 53.21	4.62 4.87	22.59 22.56	$C_{11}H_{12}N_4OS$	3250 (—NH), 1685 (C=O), 1322 (C=S)	10.7 (s, 1 H, NH); 7.9 (s, 1 H, CH—C(2)); 8.2—7.5 (m, 4 H, CH arom.); 3.5 (s, 6 H, $N(CH_3)_2$)	
3b	74.2	168—170	56.37 56.50	5.75 5.84	20.20 20.27	$C_{13}H_{16}N_4OS$	3250 (—NH), 1680 (C=O), 1325 (C=S)	10.75 (s, 1 H, NH); 7.9 (s, 1 H, CH—C(2)); 8.2—7.5 (m, 4 H, CH arom.); 3.8 (q, 4 H, CH_2, J = 7.2); 1.3 (t, 6 H, CH_3, J = 7.2)	
3c	85.5	226—228	53.66 53.78	4.80 4.86	19.37 19.30	$C_{13}H_{14}N_4O_2S$	3240 (—NH), 1690 (C=O), 1320 (C=S)	10.8 (s, 1 H, NH); 7.9 (s, 1 H, CH—C(2)); 8.2—7.5 (m, 4 H, CH arom.); 4.0 and 3.75 (2 t, 8 H, CH_2)	
3d	86	215—216	58.14 58.31	5.40 5.59	19.29 19.43	$C_{14}H_{16}N_4OS$	3240 (—NH), 1685 (C=O), 1320 (C=S)	10.6 (s, 1 H, NH); 7.9 (s, 1 H, CH); 8.2—7.5 (m, 4 H, CH arom.); 3.95 (s, 4 H, CH_2); 1.75 (s, 6 H, CH_2)	

precipitates. With an increase in temperature, the precipitates dissolve, and thiadiazolium salts **2a—d** crystallize on cooling. Apparently, a proton first adds to the N(1) atom of quinazolinone to give salt **A** (Scheme 2). In the presence of an excess of H_2SO_4 at high temperature there is an equilibrium between salt **A** and open form **B**. Intermediate **B** is nothing but 1-benzoylthiosemicarbazide, whose acid-catalyzed cyclization proceeds according to the known mechanism[9] (in our case, *via* intermediate salts **C**, **D**, **E**, and **F**). Form **F** changes to salt **2**, probably, as a result of intramolecular elimination—addition of a water molecule (intermediate **G**) and tautomerization (intermediate **H**) followed by decarbonylation. The mechanism proposed implies that the molar ratio of H_2SO_4 to **3a—d** should be at least 2 : 1 for recyclization to occur. A search for optimum reaction conditions showed that a threefold excess of the acid is really needed.

The structures of thiadiazoles **2a—d** were confirmed by data of elemental analysis, ^1H and ^{13}C NMR spectroscopy, and IR spectroscopy (see Table 1). Their IR spectra, unlike those of quinazolinones **3a—d**, contain no absorption bands from CO stretching vibrations, but show $\nu_{as}(NH_2)$ and $\nu_s(NH_2)$ bands.

The ^1H NMR spectra of thiadiazoles **2a—d** show signals from the NH_2 protons at δ 6.80. Such a downfield shift is due to the deshielding effect of an electron-withdrawing *ortho*-substituent (thiadiazolyl) and to the presence of an intramolecular hydrogen bond linking the $-NH_2$ group with the N(4) atom of the thiadiazole ring (the occurrence of this H bond was proved by X-ray diffraction analysis[10] of crystal **2a**). Our results are in full agreement with the data of ^1H NMR study of substituted anilines.[11,12] ^1H NMR spectra of thiadiazoles **2a—d** contain signals from the $-NR_2$ protons. Signals from the protons of the N-bound methyl and methylene groups are shifted upfield by *ca.* 0.4—0.5 ppm as compared to those for quinazolinones **3a—d**. This indicates, by analogy with the corresponding aromatic derivatives,[13] that the deshielding effect of the thiocarbamoyl group is higher than that of the heterocycle.

In the ^{13}C NMR spectra of compounds **2a—d**, the number of resonance signals is equal to the number of nonequivalent C atoms, and the chemical shifts of the atoms correspond to their nearest environment and hybridization state[13] (see Table 1).

Thus, it was established that heating in the presence of conc. H_2SO_4 causes opening of the quinazolinone ring in 3-(*N'*,*N'*-dialkylthioureido)quinazolin-4(3*H*)-ones **3a—d**, which undergo unusual recyclization to give unknown 5-(2-aminophenyl)-2-dialkylamino-1,3,4-thiadiazoles **2a—d**.

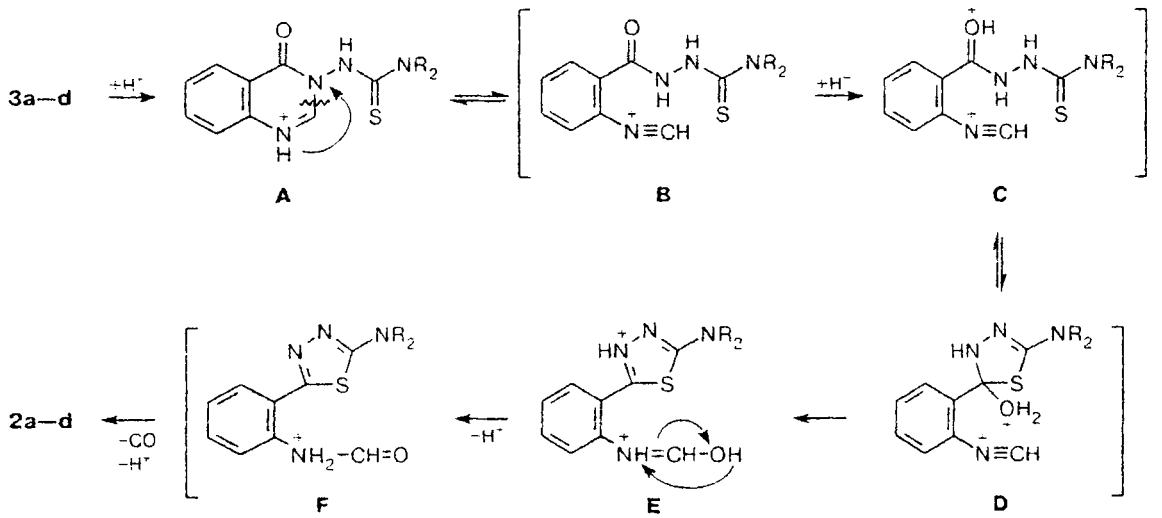
Experimental

Melting points were determined on a Boetius stage microscope. IR spectra were recorded on a Specord 75 IR instrument (suspensions in Vaseline oil). ^1H and ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer (399.95 and 100.58 MHz, respectively) in DMSO-d_6. The course of the reaction was monitored by TLC on Silufol UV-254 plates in hexane—acetone (5 : 1).

The starting 3-aminoquinazolin-4(3*H*)-one (**1**) was prepared according to the known procedure.[14] Thiuram disulfides **4a,b** were commercial chemicals (reagent purity). Thiuram disulfides **4c,d** were synthesized as described in Ref. 15.

3-(*N'*,*N'*-Dialkylthioureido)quinazolin-4(3*H*)-one (3a). A mixture of compound **1** (1.61 g, 0.01 mol) and disulfide **4a** (2.40 g, 0.01 mol) in 10 mL of DMF was heated in a boiling water bath for 3 h. On cooling, the reaction mixture was poured into 40 mL of 2% NaOH. The sulfur that formed was filtered off, and the filtrate was acidified with conc. AcOH (2.5 mL). The resulting precipitate **3a** was filtered off, washed repeatedly

Scheme 2



on the filter with cold water, and dried *in vacuo* at 70 °C. The product was recrystallized from ethanol.

Analogously, compounds **3b—d** were synthesized. Their physicochemical characteristics are given in Table 1.

5-(2-Aminophenyl)-2-dialkylamino-1,3,4-thiadiazole (2a). Sulfuric acid (ρ = 1.84 g cm^{-3}) (2.94 g, 0.03 mol) was added dropwise with vigorous stirring to a suspension of compound **3a** (2.48 g, 0.01 mol) in 15 mL of dry 1,4-dioxane. The thickened reaction mixture was slowly heated with stirring to 95—100 °C to give a homogeneous solution, kept at this temperature for 1 h, and cooled to 10 °C. The thiadiazolium sulfate that formed was filtered off. Then the sulfate was dissolved in 15 mL of water and treated with a concentrated solution of NaOH. The precipitate of **2a** was filtered off, washed with cold water, and dried *in vacuo* at 50 °C. The crude product was purified as follows. A batch of 1 g was dissolved in 20 mL of benzene, and the solution was filtered through a layer of Al_2O_3. Two thirds of the solvent was removed, and the product was precipitated by adding hexane (5—7 mL).

Analogously, the corresponding thiadiazoles **2b—d** were obtained from compounds **3b—d**. The physicochemical characteristics of compounds **2a—d** are presented in Table 1.

References

1. Eur. Pat. 572,782; *Chem. Abstr.*, 1994, **121**, 255816.
2. H. El-Feky Said, *Pharmazie*, 1993, **48**, No. 12, 894.
3. V. K. Pandey, *Curr. Sci.*, 1986, **55**, 243.
4. S. Kumar Atul Singh, A. K. Saxena, and K. Shanker, *Ind. J. Chem., Sect. B*, 1988, **27**, No. 5, 443.
5. J. G. Nair, *J. Ind. Chem. Soc.*, 1965, **42 B**, No. 6, 359.
6. Lyu Van Boi, Ph. D. (Chem.) Thesis, Moldova State University, Chisinau, 1991, 135 pp. (in Russian).
7. G. G. Rusu, Ya. E. Gutsu, and N. A. Barba, *Zh. Org. Khim.*, 1995, **31**, 1721 [*Russ. J. Org. Chem.*, 1995, **31** (Engl. Transl.)].
8. P. B. Tabukdar, S. K. Sengupta, and A. K. Datta, *Ind. J. Chem., Sect. B*, 1977, **15 B**, N 12, 1110.
9. *Heterocyclic Compounds*, Ed. R. C. Elderfield, New York, 1961, **7**, 541 pp.
10. S. T. Malinovskii, G. G. Rusu, N. A. Barba, M. Z. Krimer, and Ya. Lipkovski, *Kristallografiya*, 2000, No. 2 [*Crystallogr. Repts.*, 2000 (Engl. Transl.)].
11. L. K. Dyall, *Aust. J. Chem.*, 1964, **17**, 419.
12. T. Yanemoto, W. F. Reynolds, H. M. Hutton, and T. Schaefer, *Canad. J. Chem.*, 1965, **43**, 2668.
13. C. Pretsch and S. Seibl, *Tables of Spectral Data for Structure Determination of Organic Compounds, 2nd Ed.*, Springer Verlag, Berlin—Heidelberg—New York—London—Paris—Tokyo—Hong Kong, 1989.
14. P. S. N. Reddy and P. P. Reddy, *Ind. J. Chem., Sect. B*, 1988, **27 B**, No. 8, 763.
15. US Pat 3,147,308; *Chem. Abstr.*, 1964, **61**, 14539e.

Received July 19, 1999;
in revised form June 21, 2000