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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Structure of the Reaction Product of Anthranilic Acid Hydrazide with Carbon Disulfide in Alkaline Medium

V. N. Britsun, A. N. Esipenko, A. A. Kudryavtsev, and M. O. Lozinskii

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 5, Kiev, 02094 Ukraine
e-mail: ioch@bpci.kiev.ua

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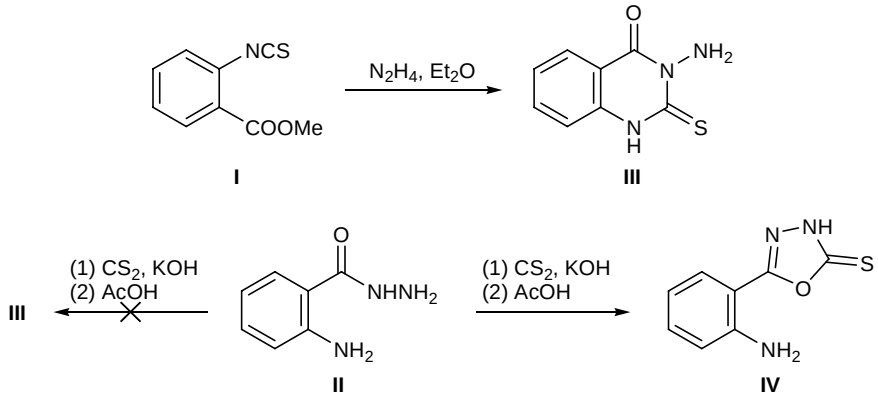
Abstract—The reaction of anthranilic acid hydrazide with carbon disulfide in alkaline medium yields 5-(2-aminophenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione rather than 3-amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one. The structure of the product was proved by spectral methods and chemical transformations.

3-Amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one possesses several reaction centers, and it can be used in the synthesis of various fused heterocycles [1–3]. A number of procedures for the preparation of 3-amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one have been reported [4–10]; among these, those proposed in [8, 10] may be regarded as preparative, taking into account accessibility of the initial compounds, simplicity of the experimental procedure, and product yield. However, the chemical shifts of protons in the ^{1}H NMR spectra and IR frequencies of functional groups, given in the above publications, are different. The melting points are also different: 188–190°C [8] and 227–230°C [10]. It is known that heating of hydrazides with carbon disulfide in the presence of bases is a classical method for the synthesis of 1,3,4-oxadiazoles [11]. According to patent [12], the reaction of anthranilic acid hydrazide with potassium *O*-ethyl dithiocarbonate in butanol gives 78% of 5-(2-aminophenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione with mp 185–186°C.

The goal of the present work was to unambiguously determine the structure of products formed by condensation of methyl 2-isothiocyanatobenzoate (**I**) with hydrazine in diethyl ether and by reaction of anthranilic acid hydrazide (**II**) with carbon disulfide and potassium hydroxide in ethanol. The reactions were carried out following the procedures described in [8, 10] (Scheme 1), and the products were characterized by the ^{1}H and ^{13}C NMR and IR spectra and elemental analyses.

The reaction of isothiocyanate **I** with hydrazine gave a product whose analytical sample had mp 255–257°C. In the reaction of anthranilic acid hydrazide (**II**) with carbon disulfide in the presence of KOH in ethanol we isolated a compound with mp 203–205°C.

Scheme 1.



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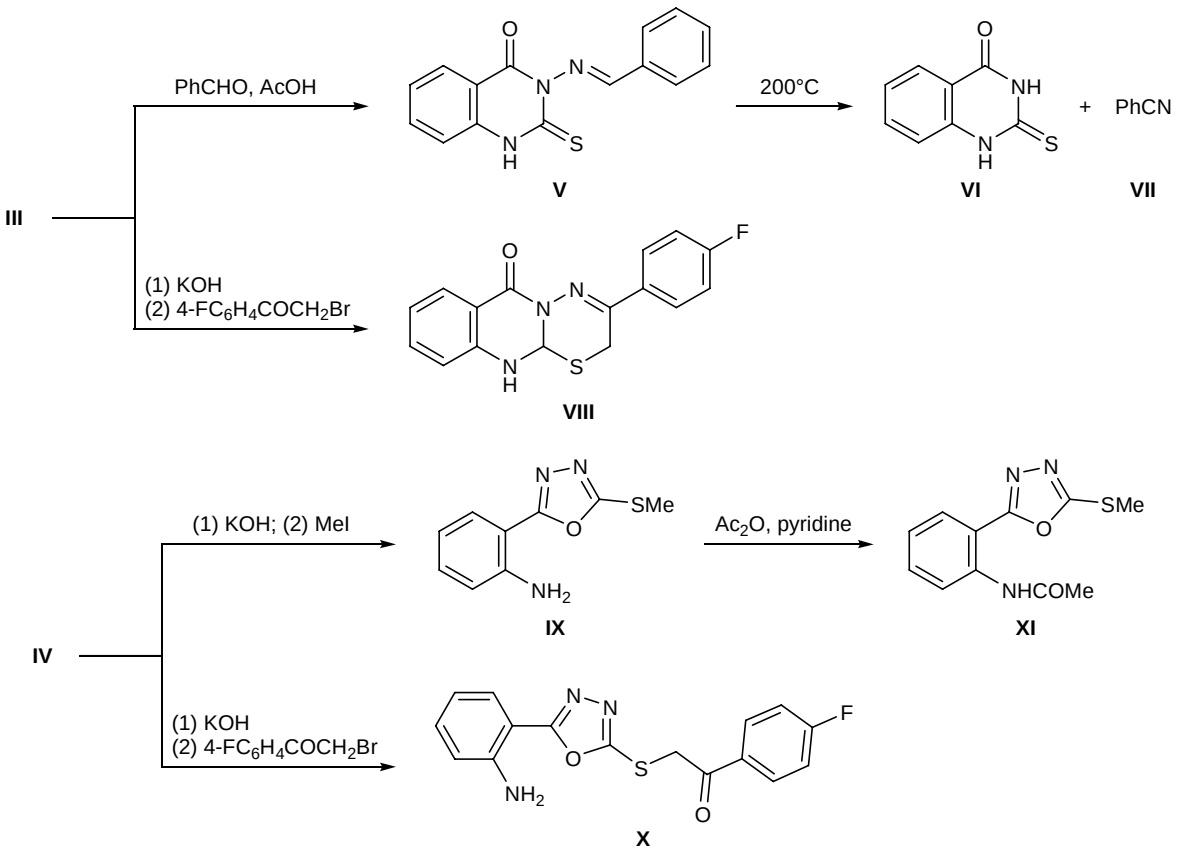
Scheme 2.



According to the data of elemental analysis, both products had the composition $C_8H_7N_3OS$, but their mixture showed depression of the melting point. Therefore, these are different compounds. Their ^{1}H NMR spectra were similar in the signal positions and intensities. The spectra contained signals which may be assigned to NH_2 (δ 6.38–6.40 ppm), NH–CS (δ 12.50–13.50 ppm), and four aromatic protons. The ^{13}C NMR spectra revealed the presence of eight carbon atoms in molecules of both compounds and the presence of a donor substituent in the benzene ring of the product obtained from anthranilic acid hydrazide (**II**) and carbon disulfide (δ_C 103.3 ppm). In the IR spectra of both compounds we observed absorption bands belonging to stretching vibrations of NH(NH_2) and C=N groups (3300 and 1640–1650 cm^{-1}, respectively); however, the IR spectrum of the product obtained by reaction of isothiocyanate **I** with hydrazine contained a band at 1695 cm^{-1}, which was unambiguously identified as carbonyl absorption. Thus the analytical and spectral (^{1}H and ^{13}C NMR and IR) data lead us to presume that the reaction of compound **I** with hydrazine gives 3-amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one (**III**) and that hydrazide **II** reacts with carbon disulfide to afford 5-(2-aminophenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (**IV**) (Scheme 1).

In order to finally confirm the structure of compounds **III** and **IV**, they were brought into some transformations as shown in Scheme 2. Quinazolin-4-one **III** reacted with benzaldehyde to afford 3-(benzylideneamino)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one (**V**). On heating to 200°C, Schiff base **V** decomposed to give 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one (**VI**) and benzonitrile (**VII**). By reaction of quinazolin-4-one **III** with 4-fluorophenacyl bromide we obtained 3-(4-fluorophenyl)-2*H*,6*H*-[1,3,4]thiadiazino-[2,3-*b*]quinazolin-6-one (**VIII**). This result can be regarded as a rigorous proof for location of the amino and thioxo group in initial quinazolin-4-one **III** in positions *2* and *3*, respectively.

Alkylation of 1,3,4-oxadiazole-2-thione **IV** with methyl iodide and 4-fluorophenacyl bromide in alkaline medium lead to formation of 5-(2-aminophenyl)-2-methylsulfanyl-1,3,4-oxadiazole (**IX**) and 5-(2-aminophenyl)-2-(4-fluorophenacylsulfanyl)-1,3,4-oxadiazole (**X**). Compound **IX** failed to react with benzaldehyde, presumably because of steric hindrances created by the

amino group and oxadiazole ring in the *ortho* positions of the benzene ring. On the other hand, the alklylation of **IV** with acetic anhydride readily occurred to give 5-(2-acetylaminophenyl)-2-methylsulfanyl-1,3,4-oxadiazole (**XI**).

Thus we have revised the assignment given in [8] and unambiguously proved by ^{1}H and ^{13}C NMR and IR spectroscopy and chemical transformations that the reaction of anthranilic acid hydrazide with carbon disulfide in alkaline medium yields 5-(2-aminophenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione rather than 3-amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one.

EXPERIMENTAL

The NMR spectra were recorded from solutions in DMSO-d_6 on a Varian-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using tetramethylsilane as internal reference. The IR spectra were measured in KBr on a UR-20 spectrometer.

3-Amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one (III) was synthesized according to the procedure described in [10] by reaction of methyl 2-isothiocyanatobenzoate (**I**) with hydrazine in diethyl ether. Yield 83%, mp 255–257°C (from DMSO); published data [10]: mp 227–230°C. IR spectrum, ν, cm^{-1}: 1410, 1440, 1495, 1570, 1650 (C=N), 1695 (C=O), 3200, 3300. ^{1}H NMR spectrum, δ, ppm: 6.40 s (2H, NH_2), 7.23 m (1H, H_{arom}), 7.34 d (1H, H_{arom}, J = 8.4 Hz), 7.62 d.d (1H, H_{arom}, J_1 = 8.4, J_2 = 0.8 Hz), 7.91 d (1H, H_{arom}, J = 7.2 Hz), 12.50 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 115.8 (C^{4a}), 119.1 (C^8), 123.1 (C^6), 126.2 (C^7), 133.8 (C^5), 141.9 (C^{8a}), 155.9 (C^4), 169.5 (C^2). Found, %: C 50.01; H 3.58; N 21.54; S 16.73. $C_8H_7N_3OS$. Calculated, %: C 49.73; H 3.65; N 21.75; S 16.59.

5-(2-Aminophenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (IV) was synthesized according to the procedure described in [8] by reaction of anthranilic acid hydrazide with carbon disulfide and potassium hydroxide in ethanol. Yield 69%, mp 199–201°C (from ethanol); published data [12]: mp 185–186°C. IR spectrum, ν, cm^{-1}: 1460, 1500, 1580, 1640 (C=N), 3000, 3100, 3300. ^{1}H NMR spectrum, δ, ppm: 6.38 s (2H, NH_2), 6.68 m (1H, H_{arom}), 6.89 d (1H, H_{arom}, J = 8.7 Hz), 7.28 d.d (1H, H_{arom}, J_1 = 8.7, J_2 = 1.3 Hz), 7.54 d (1H, H_{arom}, J = 7.2 Hz), 13.50 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 103.3 (C^2), 115.7 (C^5), 116.0 (C^3), 127.3 (C^4), 132.5 (C^6), 147.3 (C^1), 160.9 (C^5, oxadiazole), 175.9 (C^2, oxadiazole). Found, %: C 49.58; H 3.79; N 22.03; S 16.52. $C_8H_7N_3OS$. Calculated, %: C 49.73; H 3.65; N 21.75; S 16.59.

3-Benzylideneamino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one (V). A solution of 10 mmol of quinazolin-4-one **III** and 15 mmol of benzaldehyde in 15 ml of acetic acid was heated for 4 h. The mixture was cooled, and the precipitate was filtered off, washed with diethyl ether (5 ml), and dried. Yield 2.10 g (75%), mp 272–274°C. IR spectrum, ν, cm^{-1}: 1420, 1500, 1550, 1630 (C=N), 1690 (C=O), 3260. ^{1}H NMR spectrum, δ, ppm: 7.32–7.40 m (2H, H_{arom}), 7.59 m (3H, H_{arom}), 7.74 m (1H, H_{arom}), 7.95–8.01 m (4H, H_{arom}), 8.67 s (1H, N=CH), 13.09 s (1H, NH). Found, %: C 63.98; H 4.19; N 15.03. $C_{15}H_{11}N_3OS$. Calculated, %: C 64.04; H 3.94; N 14.94.

Thermal decomposition of 3-benzylideneamino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one (V). Compound **V**, 10 mmol, was heated for 30 min at 180°C, cooled, and treated with diethyl ether (2× 5 ml). The precipitate of 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one (**VI**) was filtered off and dried. Yield 1.48 g (83%), mp 299–302°C; published data [13]: mp 304–305°C. IR spectrum, ν, cm^{-1}: 1440, 1480, 1580, 1640 (C=N), 1720 (C=O), 3150. ^{1}H NMR spectrum, δ, ppm: 7.32 m (2H, H_{arom}), 7.73 d.d (1H, H_{arom}, J_1 = 8.1, J_2 = 0.6 Hz), 7.92 d (1H, H_{arom}, J = 7.8 Hz), 12.48 s (1H, N^3H), 12.71 s (1H, N^1H). Found, %: C 54.15; H 3.20; N 16.00. $C_8H_6N_2OS$. Calculated, %: C 53.92; H 3.39; N 15.72. The ether solution was evaporated, and benzonitrile (**VII**) was distilled under reduced pressure (water-jet pump). Yield 0.66 g (64%), bp 185–188°C; published data [14]: bp 191°C. Found, %: C 81.76; H 5.16; N 13.40. C_7H_5N. Calculated, %: C 81.53; H 4.89; N 13.58.

3-(4-Fluorophenyl)-2*H*,6*H*-[1,3,4]thiadiazino-[2,3-*b*]quinazolin-6-one (VIII). A solution of 10 mmol of 4-fluorophenacyl bromide in 5 ml of ethanol was added to a solution of 10 mmol of quinazolin-4-one **III** and 10 mmol of KOH in 20 ml of ethanol, and the mixture was heated for 30 min under reflux. The mixture was cooled and diluted with 50 ml of water, and the precipitate of compound **VIII** was filtered off. Yield 2.11 g (68%), mp 215–218°C (from nitromethane). IR spectrum, ν, cm^{-1}: 1480, 1530, 1570, 1620 (C=N), 1700 (C=O), 3100. ^{1}H NMR spectrum, δ, ppm: 4.33 s (2H, CH_2), 7.37 m (2H, H_{arom}), 7.55 m (2H, H_{arom}), 7.80 m (1H, H_{arom}), 8.14 m (3H, H_{arom}). Found, %: C 62.01; H 3.19; N 13.33. $C_{16}H_{10}FN_3OS$. Calculated, %: C 61.73; H 3.24; N 13.50.

5-(2-Aminophenyl)-2-methylsulfanyl-1,3,4-oxadiazole (IX) and 5-(2-aminophenyl)-2-(4-fluorophenacylsulfanyl)-1,3,4-oxadiazole (X). A solution of 10 mmol of methyl iodide or 4-fluorophenacyl bromide in 5 ml of ethanol was added to a solution of 10 mmol of 1,3,4-oxadiazole-2-thione **IV** and 10 mmol of KOH in 20 ml of ethanol, and the mixture was heated for 30 min under reflux. The mixture was cooled and diluted with 50 ml of water, and the precipitate of compound **IX** or **X** was filtered off.

Compound **IX**. Yield 1.74 g (84%), mp 94–96°C (from 2-propanol). IR spectrum, ν, cm^{-1}: 1460, 1490, 1505, 1550, 1630 (C=N), 3350, 3450. ^{1}H NMR spectrum, δ, ppm: 2.76 s (3H, SCH_3), 6.64 m (1H, H_{arom}), 6.88 d (1H, H_{arom}, J = 7.8 Hz), 7.23 d.d (1H, H_{arom}, J_1 = 6.6, J_2 = 1.1 Hz), 7.59 d (1H, H_{arom}, J = 6.6 Hz). Found, %: C 52.02; H 4.62; N 19.99. $C_9H_9N_3OS$. Calculated, %: C 52.16; H 4.38; N 20.28.

Compound **X**. Yield 2.60 g (79%), mp 173–175°C (from nitromethane). IR spectrum, ν, cm^{-1}: 1500, 1560, 1610, 1640 (C=N), 1690 (C=O), 3350, 3450. ^{1}H NMR spectrum, δ, ppm: 5.09 s (2H, SCH_2), 6.41 s (2H, NH_2), 6.61 m (1H, H_{arom}), 6.87 m (1H, H_{arom}), 7.20 m (1H, H_{arom}), 7.53 m (2H, H_{arom}), 7.56 m (1H, H_{arom}), 8.16 m (2H, H_{arom}). Found, %: C 58.51; H 3.82; N 13.02. $C_{16}H_{12}FN_3O_2S$. Calculated, %: C 58.35; H 3.67; N 12.76.

5-(2-Acetaminophenyl)-2-methylsulfanyl-1,3,4-oxadiazole (XI). A solution of 5 mmol of compound **IX** in a mixture of 2 ml of acetic anhydride and 0.7 ml of pyridine was heated to 110°C, kept for 5 min at that temperature, and cooled, and the precipitate was filtered off. Yield 0.86 g (69%), mp 145–147°C. IR spectrum, ν, cm^{-1}: 1450, 1490, 1550, 1610, 1630 (C=N), 1710 (C=O), 3300. ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, CH_3C=O), 2.79 s (3H, SCH_3), 7.24 m (1H, H_{arom}), 7.54 m (1H, H_{arom}), 7.84 d (1H, H_{arom}, J = 6.9 Hz), 8.39 d (1H, H_{arom}, J = 8.1 Hz), 10.46 s (1H, NH). Found, %: C 52.88; H 4.32; N 17.01. $C_{11}H_{11}N_3O_2S$. Calculated, %: C 53.00; H 4.45; N 16.86.

REFERENCES

1. Gakhar, H.K., Baveja, P., and Kumar, N., *Indian J. Chem., Sect. B*, 1982, vol. 21, no. 1, p. 64.
2. Gakhar, H.K., Sharma, A., and Gupta, S.B., *Indian J. Chem., Sect. B*, 1982, vol. 21, no. 5, p. 456.
3. Santagati, M., Modica, M., Scolaro, L., and Santagati, A., *J. Chem. Res., Synop*., 1999, no. 2, p. 86; *Chem. Abstr*., 1999, vol. 130, no. 267409y.
4. Modi, S.K., Gakhar, H.K., and Narang, K.S., *Indian J. Chem*., 1970, vol. 8, no. 5, p. 389.
5. Gakhar, H.K., Gupta, S.K., and Kumar, N., *Indian J. Chem., Sect. B*, 1981, vol. 20, no. 1, p. 14.
6. Pathak, U.S., Devani, M.V., Shishoo, C.J., and Kulkarni, R.R., *Indian J. Chem., Sect. B*, 1986, vol. 25, no. 5, p. 489.
7. Rusu, G.G., Koval', D., Gutsu, Ya.E., and Barba, N.A., *Khim. Geterotsikl. Soedin*., 1995, no. 7, p. 1000.
8. Liu, K.Ch. and Hu, M.K., *Arch. Pharm*., 1987, vol. 320, no. 2, p. 166; *Chem. Abstr*., 1987, vol. 107, no. 198229a.
9. Liu, K.Ch., Hu, M.K., and Lin, G.O., *Chung-hun Yao Hsueh Tsa Chih*., 1990, vol. 42, no. 1, p. 83; *Chem. Abstr*., 1991, vol. 114, no. 23910h.
10. Cherbuliez, E., Wilhalm, B., Jaccard, S., and Rabinovitz, J., *Helv. Chim. Acta*, 1967, vol. 50, no. 8, p. 2563.
11. *Five- and Six-Membered Compounds with Nitrogen and Oxygen (Excluding Oxazoles)*, Wiley, R.H., Ed., New York: Intersci., 1962, p. 273.
12. Koenig, A.V. and Kabbe, H.J., FRG Patent Appl. no. 1930263, 1971; *Chem. Abstr*., 1971, vol. 74, no. 105695m.
13. Howard, J.Ch. and Klein, G., *J. Org. Chem*., 1962, vol. 27, p. 3701.
14. *Beilsteins Handbuch der organischen Chemie*, 1926, vol. 9, p. 275.