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CYANOACETYLENE AND ITS DERIVATIVES. 30*. REACTIONS OF 2,3-DIMERCAPTOQUINOXALINE WITH 3-PHENYL-2-PROPYNONITRILE AND 4-ALKYL-4-HYDROXY-2-ALKYNONITRILES

L. V. Andriyankova, S. A. Zhivet'ev, A. G. Mal'kina, M. A. Andriyankov, A. V. Afonin, and B. A. Trofimov

The reaction of 2,3-dimercaptoquinoxaline with 3-phenyl-2-propynonitrile (~10 mass % KOH, 20-25°C, 5 h, dioxane) gave the S,S-diadduct (as with unsubstituted acetylene). 2,3-Dimercaptoquinoxaline reacted with 4-alkyl-4-hydroxy-2-alkynonitriles to give 2-cyanomethyl-2-(1-hydroxy-1-alkyl)-1,3-dioxolano[4,5-b]quinoxalines or 3-cyanomethylene-8-imino-2,2,6,6-tetramethyl-1,7-dioxa-4-thiaspiro-[4.4]nonane.

Keywords: 4-alkyl-4-hydroxy-2-alkynonitriles, 2-cyanomethyl-2-(1-hydroxy-1-alkyl)-1,3-dithiolano-[4,5-*b*]quinoxaline, 2,3-di(vinylthio)quinoxaline, 2,3-dimercaptoquinoxaline, 2,3-di(2-cyanoethenyl-1-phenyl)thio]quinoxaline, 3-cyanomethylene-8-imino-2,2,6,6-tetramethyl-1,7-dioxa-4-thiaspiro[4.4]nonane, 3-phenyl-2-propynonitrile, heterocyclization.

The reactivity of substituted cyanoacetylenes in reactions with sulfur-containing heterocycles has been well studied in papers [2-8] and in reviews [9, 10]. New polyfunctional heterocycles have been obtained as result of these studies: 1,3-thiazinoazoles [2], 1,4-oxathianyl-2-thiobenzoxazoles [3], 1,3-oxazolidinobenzimidazoles [4], pyrimidyl-2-thio-1,4-dioxane or -1,4-oxathiane [5], 1,3-oxathiolane- and 1,4-oxathiane-2-thioquinolines [6], diquinolyl-5-thio-2-propenonitrile [7], and 3-(quinolyl-8-thio)-2-alkenonitriles [8]. There is no mention of the reaction of 2,3-dimercaptoquinoxaline with acetylene and its cyano derivatives in the literature. Meanwhile this reaction may open a simple route to new families of functionalized heterocyclic compounds, with the prospect of creating medicinals.

The current work is concerned with a study of the features and regularities of the nucleophilic addition of 2,3-dimercaptoquinoxaline to substituted cyanoacetylenes with the purpose of obtaining potentially biologically active heterocyclic compounds.

The reaction of 2,3-dimercaptoquinoxaline with acetylene was carried out first for comparison. 2,3-Dimercaptoquinoxaline added to acetylene in aqueous dioxane (KOH or $Cd(OAc)_2 \cdot 3H_2O$, 14 atm, 200-205°C) to give 2,3-di(vinylthio)quinoxaline (**1**) in a yield which depended on the catalyst. In the presence of KOH the yield was 54%, while in the presence of $Cd(OAc)_2 \cdot 3H_2O$ it was 21%.

* For paper 29 see [1].

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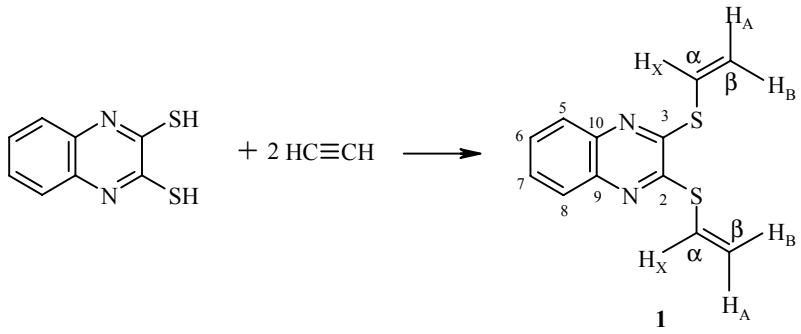
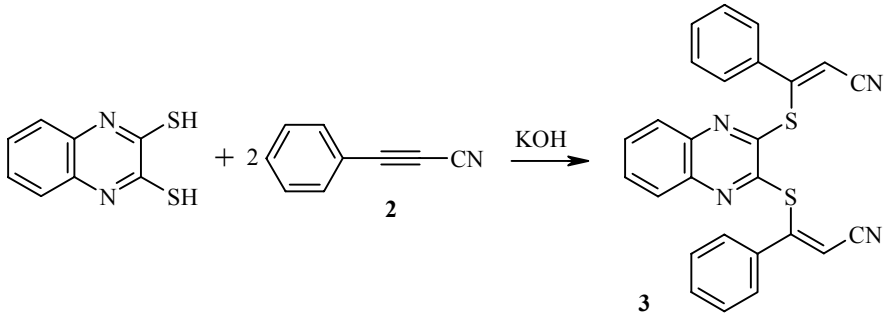


1

Compound **1** is a yellow crystalline substance, soluble in most organic solvents. Absorption bands at 3060, 1580, 940, 590, and 580 cm^{-1}, characterizing vibrations of the S–CH=CH_2 group, appear in its IR spectrum. The ^1H and ^{13}C NMR spectra also confirm the structure of divinyl compound **1** (see Experimental).

The nucleophilic addition of 2,3-dimercaptoquinoxaline to 3-phenyl-2-propynonitrile (**2**), as expected, occurred under considerably milder conditions (room temperature) than for unsubstituted acetylene to give 2,3-di[(1-phenyl-2-cyanoethenyl)thio]quinoxaline (**3**) (Table 1).



2 **3**

The yield of the diadduct **3** is considerably influenced by the solvent. For example, 2,3-dimercaptoquinoxaline does not react with acetylene **2** in dioxane, whereas in water compound **3** is formed in 20% yield. The maximum yield (80%) of diadduct **3** was obtained with a 1:2 ratio of 2,3-dimercaptoquinoxaline to acetylene **2** in 4:1 water–dioxane at room temperature in the presence of KOH (10 mass %). Boiling the reaction mixture led to decrease in yield of diadduct **3** to 60%. The IR, ^1H and ^{13}C NMR spectra of diadduct **3** agreed completely with its structure (Table 2).

TABLE 1. Characteristics of Compounds **3**, **5a**, **5b**, and **7**

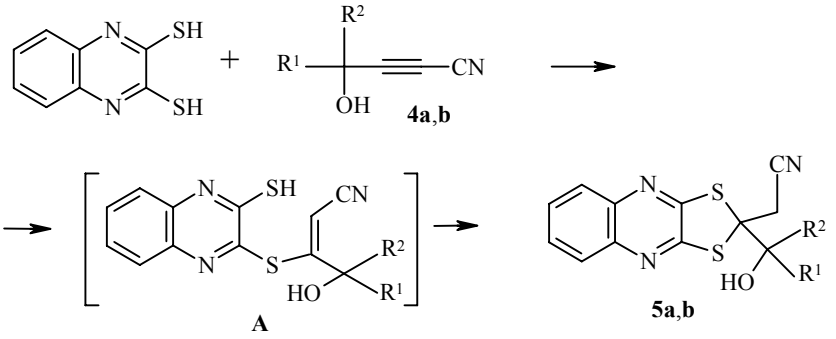
Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	N	S		
3	$C_{26}H_{16}N_4S_2$	69.56 / 69.62	3.45 / 3.60	11.96 / 12.49	14.29 / 14.30	180-183	80
5a	$C_{14}H_{13}N_3OS_2$	55.10 / 55.42	4.35 / 4.32	13.79 / 13.85	21.10 / 21.14	187-189	70
5b	$C_{17}H_{17}N_3OS_2$	59.09 / 59.45	5.20 / 4.99	12.11 / 12.23	18.35 / 18.67	191-193	71
7	$C_{16}H_{10}N_4O_2S_2$	54.58 / 54.22	2.65 / 2.84	15.60 / 15.81	17.74 / 18.08	> 300 (dec.)	11

* Compound **3** was reprecipitated from chloroform in hexane, compounds **5a** and **5b** from acetone in hexane.

The reaction of 2,3-dimercaptoquinoxaline with 4-hydroxy-4-methyl-2-pentynonitrile (**4a**) and 3-(1-cyclohexyl-1-hydroxy)-2-propynonitrile (**4b**) did not occur in the same way. In these case the direction of the reaction depends considerably on the ratio of the reagents and the solvent. With equimolar ratio of 2,3-dimercaptoquinoxaline and acetylenes **4a** and **4b** the reaction did not stop at the addition stage: further cyclization occurs to give 2-cyanomethyl-2-(1-hydroxy-1-methylethyl)-1,3-dithiolano[4,5-*b*]quinoxaline (**5a**) and 2-cyanomethyl-2-(1-cyclohexyl-1-hydroxy)-1,3-dithiolano[4,5-*b*]quinoxaline (**5b**).

The reaction was carried out under mild conditions without a catalyst (DMSO, 20-25°C, 1 h). Use of a basic catalyst (LiOH) or disodium salt of 2,3-dimercaptoquinoxaline in the reaction under similar conditions led to 2- to 3-fold decrease in the yield of compounds **5a,b** and a simultaneous increase in the amount of resinous products.

Apparently the formation of compounds **5a,b** includes the intermediate monoadduct **A**, in which the polarization of the double bond and location of the free mercapto group are suitable for intramolecular cyclization.



4, **5 a** $R^1 = R^2 = Me$; **b** $R^1 – R^2 = (CH_2)_5$

The IR spectra of compounds **5a,b** include absorption band in the region of 2250 cm^{-1}, characteristic of cyano group attached to a saturated radical (Table 2). Singlets for the CH_3, CH_2, and OH groups and characteristic multiplet for the cyclohexyl group and signal of aromatic protons are present in their ^1H NMR spectra. The ^{13}C NMR spectra confirm their individuality (Table 2).

The direction of the reaction changed markedly when twofold excess of acetylene **4a** was used. 8-Imino-2,2,6,6-tetramethyl-3-cyanomethylene-1,7-dioxa-4-thiaspiro[4.4]nonane (**6a**) was unexpectedly formed when disodium salt of 2,3-dimercaptoquinoxaline reacted with acetylene **4a** in water. 2,2'-Dioxodi(quinoxalin-3-yl)disulfide (**7**) (11% yield) was also isolated from the reaction mixture.

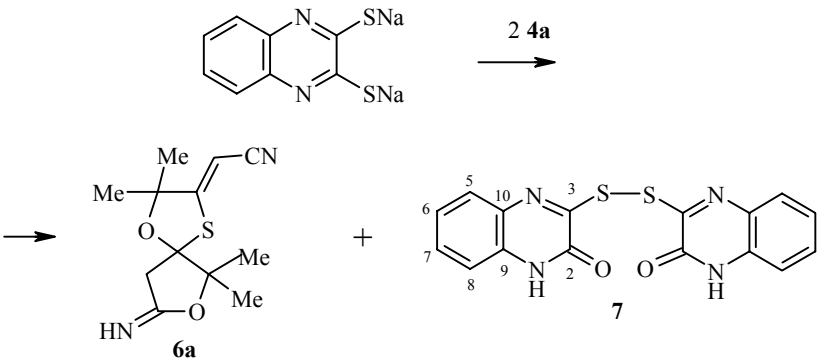


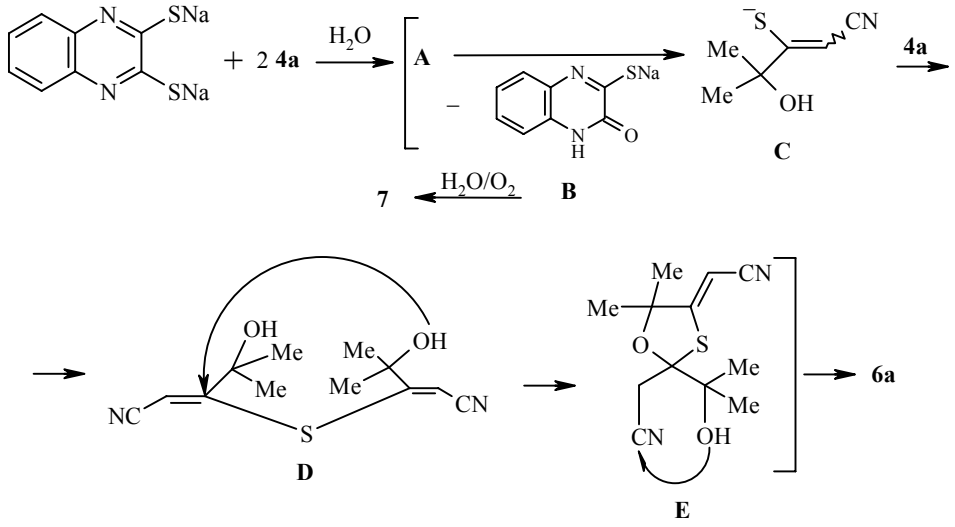
TABLE 2. Spectroscopic Characteristics of the Synthesized Compounds **3**, **5a,b**, and **7**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm*			^{13}C NMR spectrum, δ, ppm
		Alk	OH, s	Ar	
3	3030, 2210, 1580, 1560, 1440, 1330, 1250, 1230, 1170, 1130, 1100, 990, 760, 750, 690, 660, 590	—	—	7.27-7.63 (14H, m)	104.10 (=CH); 116.04 (CN); 127.75, 127.93, 128.08, 128.81, 140.49 (Ph); 136.64 (C–Ph); 130.08, 130.89, 151.00, 155.51 (Ar)
5a	3460, 2980, 2940, 2250, 1650, 1620, 1550, 1520, 1460, 1450, 1420, 1360, 1340, 1260, 1170, 1110, 1030, 960, 900, 800, 750, 660, 610, 590, 560	1.59 (6H, s, $2CH_3$); 3.68 (2H, s, CH_2CN)	5.13	7.62 (2H, m, H-6, H-7); 7.81 (2H, m, H-5, H-8)	26.27, 28.62 (CH_3); 31.57 (CH_2); 69.56 (C–OH); 75.79 (S–C–S); 117.38 (CN); 127.84-159.26 (Ar)
5b	3350, 2950, 2940, 2850, 2250, 1600, 1550, 1520, 1480, 1440, 1360, 1340, 1310, 1260, 1250, 1210, 1170, 1150, 1130, 1100, 1080, 1020, 970, 930, 900, 870, 840, 770, 670, 600, 590, 520	1.65 (10H, m, 5 CH_2); 3.67 (2H, s, CH_2CN)	4.75	7.60 (2H, m, H-6, H-7); 7.80 (2H, m, H-5, H-8)	22.46, 25.78 (cyclohexyl); 31.54 (CH_2); 71.29 (C–OH); 77.62 (S–C–S); 118.04 (CN); 128.51-159.95 (Ar)
7	3420, 1740, 1660, 1600, 1580, 1530, 1420, 1380, 1350, 1320, 1250, 1150, 1120, 1040, 1020, 970, 750, 650, 620, 580, 450	—	—	7.34 (2H, s, 2NH); 7.63 (2H, m, H-6, H-7); 7.78, 7.96 (4H, m, H-5, H-8)	116.67 (C-5); 127.99 (C-6); 128.16 (C-7); 130.04 (C-8); 151.15 (C-2); 155.62 (C-3); 126.79 (C-9); 144.47 (C-10)

* Compound **3**: δ 6.08 ppm (2H, s, =CH).

The spirocycle **6a** was formed also by interaction of 2,3-dimercaptoquinoxaline with acetylene **4a** in the presence of base (2 mol of MOH, M = Li, Na, K), i.e., without preliminary preparation of the salt. In similar conditions the spirocycle **6a** was isolated in 64-66% yield. With a greater than twofold excess of acetylene **4a** the yield of the spirocycle **6a** was reduced to 30-40%. When the reaction mixture was boiled its yield was halved. Use of dioxane, ether, triethylamine, or ethanol instead of water led to a mixture of products which was difficult to separate. The same thing occurred when 2,3-dimercaptoquinoxaline reacted with acetylene **4b**.

The sequence of reactions leading to the spirocycle **6a** evidently begins with formation of the normal adduct **A**, which is hydrolyzed at the thioimide bond (N)–C–S with the separation of the salt **B** (oxidation of which gives disulfide **7**). The formed intermediate **C** is added to second molecule of acetylene **4a** to give adduct **D** in which one of the hydroxy groups adds across the molecule to a double bond to give intermediate **E**, further cyclization of which gives the final product – spirocycle **6a**. Spirocycle **6a** had been prepared previously from acetylene **4a** and sodium sulfide [9, 11].



The IR, ^{1}H and ^{13}C NMR spectra corresponded completely to the structural formula of spirocycle **6a** and to the data cited elsewhere [11]. The structure of disulfide **7** was confirmed by IR, ^{1}H and ^{13}C NMR spectra (Table 2).

In conclusion interaction of 2,3-dimercaptoquinoxaline with acetylene and compound **2** gives only S,S-diadducts **1** and **3**. The direction of the reaction with the hydroxyalkylcyanoacetylenes **4** depends on the solvent and the ratio of the starting materials: either 1,3-dithiolanoquinoxalines **5** or the spirocyle **6** are formed.

EXPERIMENTAL

IR spectra of KBr tablets were recorded on a Specord IR-75 spectrometer. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ (**1, 3, 6a**), acetone-d_6 (**5a,b)**, and DMSO-d_6 (**7**) solutions with HMDS as internal standard were recorded with a Bruker DPX-400 (400 MHz) apparatus.

2-3-Dimercaptoquinoxaline and acetylene were commercial products of chemically pure quality. 3-Phenyl-2-propynonitrile (**2**) and hydroxyalkylcyanoacetylenes (**4a,b**) were prepared by known methods [12,13]. Column and thin-layer chromatography were carried out on Silpearl silica gel (eluent chloroform–benzene–ethanol 20:4:1). Physicochemical constants of the compounds obtained are given in Tables 1 and 2.

2,3-Di(vinylthio)quinoxaline (1). 2,3-Dimercaptoquinoxaline (5.82 g, 30 mmol), KOH (2.30 g, 41 mmol), dioxane (100 ml), and water (5 ml) were placed in a 0.25 l autoclave. The mixture was then saturated with acetylene at 14 atm. The reaction mixture was kept for 1 h at 200-205°C. Dioxane was distilled from the cooled mixture and the viscous residue was distilled in vacuum at 175-185°C (2 mm Hg) to give the yellow crystalline compound **1** (4.00 g, 54%); mp 96-98°C (ethanol). IR spectrum, ν, cm^{-1}: 3060, 1580, 1550, 1520, 1470, 1370, 1340, 1260, 1250, 1170, 1160, 1140, 1100, 1030, 1000, 940, 880, 760, 750, 720, 590, 580. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 5.65 (2H, d, $2H_A$); 5.72 (2H, d, $2H_B$); 7.42 (2H, q, $2H_X$) ($^3J_{AX}$ = 10.1, $^3J_{BX}$ = 17.7); 7.58 (2H, m, H-6, H-7); 7.90 (2H, m, H-5, H-8). ^{13}C NMR spectrum, δ, ppm: 117.78 (2C-β); 126.33, 127.75, 128.65 (2C-α, C-5, C-8, C-6, C-7); 140.11 (C-9, C-10); 151.73 (C-2, C-3). Found, %: C 58.25; H 4.03; N 11.12; S 26.00. $C_{12}H_{10}N_2S_2$. Calculated, %: C 58.51; H 4.09; N 11.37; S 26.03.

In similar conditions in the presence of $Cd(OAc)_2 \cdot 3H_2O$ (3.9 g, 14 mmol) instead of KOH, compound **1** was obtained in 21% yield (1.56 g).

2,3-Di[(2-cyanoethenyl-1-phenyl)thio]quinoxaline (3). Solution of compound **2** (0.25 g, 2 mmol) in dioxane (3 ml) was added dropwise to 2,3-dimercaptoquinoxaline (0.19 g, 1 mmol) and KOH (0.04 g, 0.7 mmol) in water (12 ml). The mixture was stirred for 5 h at 20-25°C, the precipitate was filtered off, washed with water, and dried in vacuum to give compound **3** (0.35 g).

When the reaction mixture was boiled with other conditions the same, 0.26 g (60%) of compound **3** were obtained.

2-Cyanomethyl-2-(1-hydroxy-1-methylethyl)-1,3-dithiolano[4,5-*b*]quinoxaline (5a). 2,3-Dimercapto-quinoxaline (0.19 g, 1 mmol) and acetylene **4a** (0.11 g, 1 mmol) in DMSO (5 ml) were stirred for 1 h at 20-25°C. The mixture was poured onto ice, the precipitate formed was filtered off, washed with water, and dried in vacuum to give compound **5a** (0.21 g).

2-Cyanomethyl-2-(1-cyclohexyl-1-hydroxy)-1,3-dithiolano[4,5-*b*]quinoxaline (5b) was prepared analogously from 2,3-dimercaptoquinoxaline (0.19 g, 1 mmol) and acetylene **4b** (0.15 g, 1 mmol). Compound **5b** (0.24 g) was isolated.

3-Cyanomethylene-8-imino-2,2,6,6-tetramethyl-1,7-dioxa-4-thiospiro[4.4]nonane (6a). A. Disodium salt of 2,3-dimercaptoquinoxaline (0.24 g, 1 mmol) and acetylene **4a** (0.22 g, 2 mmol) in water (10 ml) were stirred for 1 h at 20-25°C. Water was evaporated from the reaction mixture and the crystalline residue was washed several times with acetone. The acetone solution was passed through small (4-5 cm) layer of Al_2O_3 (to remove NaOH). Acetone was evaporated and compound **6a** (0.37 g, 74%) was isolated by column chromatography. Mp 65-67% (reprecipitated from chloroform in hexane) (lit. mp 64-65°C [11]).

The precipitate which did not dissolve in acetone was dissolved in water (pH~10) and 10% aqueous HCl was added to pH~1. The precipitate which formed was filtered off, washed with water, and dried in vacuum to give 2,2'-dioxodi(quinoxalin-3-yl)disulfide (**7**) (0.04 g).

B. Compounds **6a** (0.32 g, 64%) and **7** (0.02 g) were obtained analogously from 2,3-dimercaptoquinoxaline (0.19 g, 1 mmol), acetylene **4a** (0.22 g, 2 mmol), and NaOH (0.08 g, 2 mmol) in water (10 ml).

C. Compounds **6a** (0.33 g, 66%) and **7** (0.03 g) were obtained analogously from 2,3-dimercaptoquinoxaline (0.19 g, 1 mmol), acetylene **4a** (0.22g, 2 mmol), and KOH (0.11 g, 2 mmol) in water (10 ml).

D. Compounds **6a** (0.33 g, 66%) and **7** (0.03 g) were obtained analogously from 2,3-dimercaptoquinoxaline (0.19 g, 1 mmol), acetylene **4a** (0.22 g, 2 mmol), and LiOH (0.05 g, 2 mmol) in water (10 ml).

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