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Quinoxaline-2,3-Dithiol in Reactions with Propargyl Bromide and 1,3-Dibromopropyne

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Abstract—Propargyl bromide with quinoxaline-2,3-dithiol in DMSO in the presence of K_2CO_3 affords 2,3-bis-(2-propynylsulfanyl)quinoxaline in good yield whereas in absolute methanol in the presence of sodium methoxide at 20°C a 1:2 mixture of 2,3-bis(2-propynylsulfanyl)quinoxaline and 3-(2-propynylsulfanyl)-2(1*H*)-quinoxalinethione is formed. Individual 3-(2-propynylsulfanyl)-2(1*H*)-quinoxalinethione was obtained by crystallization of this mixture from ether. The reaction of 1,3-dibromopropyne with quinoxaline-2,3-dithiol in ethanol in the presence of NaOH at heating results in 2-bromomethylidene-1,4-(3*H*)-dithiino[2,3-*b*]quinoxaline in 77% yield. Performing this reaction in methanol in the presence of sodium methoxide during long heating (16 h) led to 2,3-bis[(3-bromo-2-propynyl)sulfanyl]quinoxaline in 72% yield.

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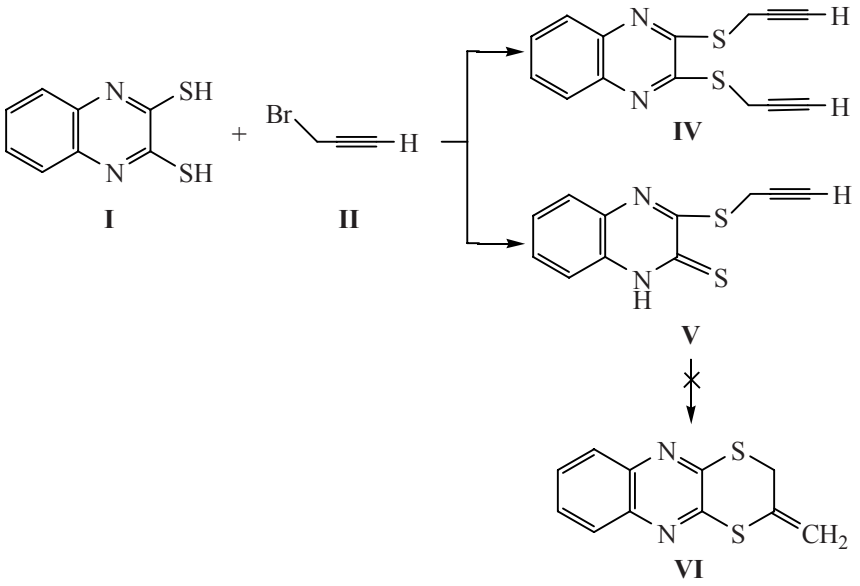
The reaction of some dinucleophiles with acetylenic compounds may lead to formation of cyclic products as a result of double addition to the triple bond [1–4]. Quinoxaline-2,3-dithiol (**I**) is known to be an effective ligand for complex formation with salts of palladium [5], copper [6, 7], mercury [8], nickel [9, 10], manganese [11], titanium [12], molybdenum [13], tin and lead [14]. Among chemical substances containing the quinoxaline cycle in the molecule a lot of biologically active compounds possessing antimicrobial [15–17], anti-inflammatory [18], analgetic [19], anticonvulsant [20] activity are known.

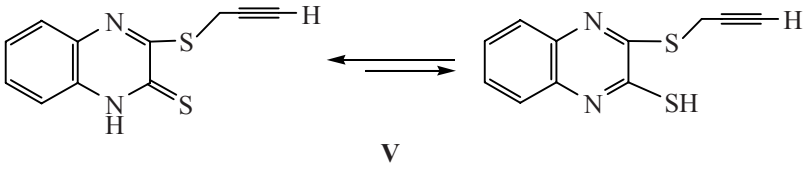
Until now, the reactions of quinoxaline-2,3-dithiol (**I**) with acetylenic compounds remain poorly studied. Earlier, we have described the synthesis of 2-acylmethyl- and 2-acylmethylene-1,3-dithiolo[4,5-*b*]quinoxalines by the reaction of quinoxaline-2,3-dithiol (**I**) with substituted acetylenic ketones and 1-bromo-2-acylacetylenes in DMSO in the presence of K_2CO_3 [21]. By the reaction of quinoxaline-2,3-dithiol (**I**) with methylpropiolate in DMSO at 80–90°C 2,3-di-(methoxycarbonylvinylthio)quinoxaline (37% yield) and 2-methoxycarbonylmethyl-1,3-dithiolo[2,3-*b*]quinoxaline (34% yield) were obtained [22].

In the present work, the reactions of quinoxaline-2,3-dithiol (**I**) with propargyl bromide (**II**) and 1,3-dibromopropyne (**III**) are investigated aiming at synthesis of ethynylsubstituted quinoxaline-2,3-dithiols as promising biologically active compounds. We have found that dithiol **I** reacts with two-fold excess of propargyl bromide **II** in absolute methanol in the presence of sodium methoxide at 20°C to give 2,3-bis (2-propynylsulfanyl)quinoxaline (**IV**) in 84% yield. When performing this reaction in DMSO in the presence of K_2CO_3 at heating (65–70°C) the yield of compound **IV** is reduced to 58%. It was established that the reaction of equimolar amounts of quinoxaline-2,3-dithiol and propargyl bromide in absolute methanol in the presence of sodium methoxide at 20°C results in the formation of the mixture of the two products, compound **IV** and 3-(2-propynylsulfanyl)-2 (1*H*)-quinoxalinethione (**V**) in the ratio of 1:2.

The ratio of compounds **IV** and **V** in the isolated product was determined from the integral intensities of the methylene group protons in the ^{1}H NMR spectra. Individual compound **V** was obtained after treatment of the mixture of compounds **IV** and **V** with ether at gentle heating and separation of the insoluble in ether compound **V**. It should be noted that compound **V** can exist in tautomeric equilibrium thione-amine $\leftrightharpoons$ thiol-imine. In the two-dimensional NMR spectra ^{15}N–^{1}H

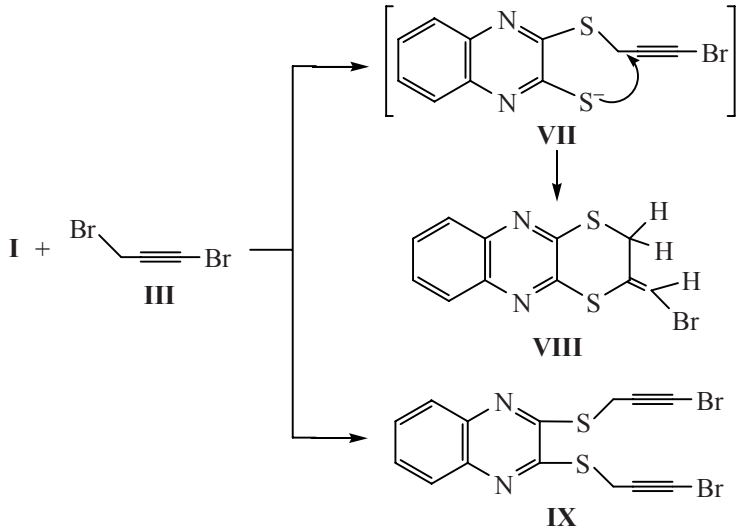


(HMBC-gp) two types of signals are observed, one of which refers to the nitrogen atom of the pyridine type N=C– (–74.1 ppm) and the second one to the amide type NH– (–233.7 ppm). This allows us to conclude that compound **V** in solution exists mainly in the thione-amine form.



We assumed that the treatment of compound **V** with sodium ethoxide in ethanol at heating (75–78°C, 8 h) would allow to obtain the cyclic compound, 2-vinyl-1,4(3*H*)-dithiino[2,3-*b*]quinoxaline (**VI**). However, we failed to obtain it.

The reaction of equimolar amounts of dithiol **I** with 1,3-dibromopropyne (**III**) in absolute ethanol in the presence of NaOH at 70–75°C gave 2[(*Z*)-bromomethylidene]-3*H*-1,4-dithiino[2,3-*b*]quinoxaline (**VIII**) as the sole product in 63% yield.



The reaction proceeds stereoselectively via the intermediate formation of sulfide **VII** which after nucleophilic trans-addition of the thiolate anion to the activated acetylenic bond gives the cyclic product of the *Z*-configuration **VIII**. In the 2D NMR spectrum $\{^1H–^1H\}$ (NOESY) a cross peak between the CH_2 group protons at 2.6 ppm and the =CHBr proton at 6.91 ppm is observed, that corresponds to the *Z*-isomer of compound **VIII**. In the reaction of dithiol **I** with excess of 1,3-dibromopropyne **III** in absolute methanol in the presence of sodium methoxide upon prolonged heating (60°C) 2,3-bis[(3-bromo-2-propynyl)-sulfanyl]quinoxaline (**IX**) is formed in 72% yield.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra of the synthesized compounds were recorded on a Specord IR-75 instrument in KBr pellets. ^1H, ^{13}C and ^{15}N NMR spectra of the studied compounds were registered on Bruker DPX 400 and Bruker AV 400 spectrometers (400.13, 100.61 and 40.56 MHz, respectively) in DMSO-d_6 at 27°C. The values of ^1H, ^{13}C chemical shifts are measured relative to TMS. To assign the signals and establish the structure of the compounds the heteronuclear two-dimensional NMR procedures $^1H–^{13}C$ HSQC (Heteronuclear Single Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Correlation) and homonuclear procedure NOESY $^1H–^1H$ were used. The ^{15}N NMR spectra were registered by the use of the $^1H–^{15}N$ HMBC technique with $MeNO_2$ as an external standard.

2,3-Bis(2-propynylsulfanyl)quinoxaline IV. To the solution of sodium methoxide prepared by dissolving of 0.24 g of sodium metal in 15 ml of absolute methanol the solution of 0.97 g of quinoxaline-2,3-dithiol **I** in 15 ml of absolute methanol, 1.2 g propargyl bromide **II** were added and stirred at 20°C for 2 h. The reaction mixture was cooled to 0°C, the precipitate formed filtered off, washed on filter with cold water and dried in vacuum. Yield 1.13 g (84%), mp 109–110°C. IR spectrum, ν, cm^{-1}: 595 (C–S), 1475 (CH_2), 1590, 1610 (C=N, C=C), 2120, (C≡C), 2935 (CH_2), 3315 (≡CH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.32 d (2H, 2≡CH, $^4J_{HH}$ 2.2), 4.22 d (4H, $2CH_2$, $^4J_{HH}$ 2.2), 7.72–7.94 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 18.46 (CH_2), 74.05 (≡CH), 79.61 (CH_2–*C*≡), 127.42-139.36 (C_6H_4), 151.94 (N=C–S). ^{15}N NMR spectrum, δ, ppm: –75.3. Found, %: C 62.20; H 3.78; N 10.55; S 23.48. $C_{14}H_{10}N_2S_2$. Calculated, %: C 62.22; H 3.70; N 10.37; S 23.70.

When the reaction of 0.97 g of dithiol **I** with 1.2 g of propargyl bromide **II** was performed in 25 ml of DMSO in the presence of K_2CO_3 upon heating (65–70°C) during 3 h the yield of compound **IV** was 0.79 g (59%), mp 109–110°C.

2,3-Bis(2-propynylsulfanyl)quinoxaline (IV) and 3-(2-propynylsulfanyl)-2(1*H*)quinoxalinethione (V). To the solution of 0.97 g of dithiol **I** in 15 mol of absolute methanol the solution of 0.3 g of propargyl bromide **II** in 10 ml of absolute methanol was added and then, slowly and with stirring, the solution of sodium methoxide prepared from 0.24 g of sodium metal and 15 ml of absolute methanol). The reaction mixture was stirred at 20°C for 5 h, cooled to 0°C, the precipitate formed filtered off, washed on filter with water and dried in vacuum to afford 0.88 g of the reaction product. Based on the integral intensities of the methylene group protons in the ^1H NMR spectrum of the reaction mixture it was established that it contains compounds **IV** and **V** in the ratio of 1:2. In the IR spectrum of this mixture the absorption band of the C=S bond at 1244 cm^{-1} of compound **V** is presented.

3-(2-Propynylsulfanyl)-2(1*H*)quinoxalinethione (V). 0.74 g of the mixture of diadduct **IV** and compound **V** in the ratio of 1:2 was placed in 25 ml of ether and stirred at slight heating for 15 min. The insoluble in ether precipitate was filtered off and dried in vacuum to afford 0.46 g of compound **V**, mp 205–206°C. IR spectrum, ν, cm^{-1}: 592 (C–S), 1246 (C=S), 1470 (CH_2), 1593, 1615 (C=N, C=C), 2105 (C≡C), 2954 (CH_2), 3265 (NH), 3310 (≡CH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.14 t (1H, ≡CH, $^4J_{HH}$ 2.3), 3.96 d (2H, CH_2, $^4J_{HH}$ 2.3), 7.29–7.70 m (4H, C_6H_4, $^3J_{HH}$ 7.9), 12.64 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 17.09 (CH_2), 73.32 (≡CH), 79.81 (CH_2, –*C*≡), 115.74–152.72 (C_6H_4, N=C–S–CH_2), 158.56 (C=S). ^{15}N NMR spectrum, δ, ppm: –74.1 (N=C–S), -233.7 (NH). Found, % : C 57.05; H 3.52; N 12.22; S 27.77. $C_{11}H_8N_2S_2$. Calculated, % : C 56.90; H 3.45; N 12.07; S 27.59.

2-[(*Z*)-Bromomethylidene]-1,4-dithiino[2,3-*b*]quinoxaline (VIII). To the solution of 0.97 g of quinoxaline-2,3-dithiol **I** in 20 ml of absolute ethanol the solution of 0.99 g of 1,3-dibromopropyne **III** in 10 ml of absolute ethanol was added, then slowly upon stirring 0.2 g of dry NaOH was added, heated to 75°C and stirred for 2 h. The reaction mixture was cooled to 0°C, the precipitated crystals filtered off, washed on filter with cold water and dried in vacuum. Yield 0.98 g

(63%), light-brown crystals with mp 279–281°C (from methanol). IR spectrum, ν, cm^{-1}: 595 (C–S), 1480 (CH_2), 1590, 1660 (C=N, C=C), 2910 (CH_2). ^1H NMR spectrum, δ, ppm: 4.26 s (2H, CH_2), 6.91 s (1H, =CHBr), 7.77–7.92 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 19.95 (CH_2), 110.32 (=CHBr), 130.26-139.49 (C_6H_4), 136.34 (*C*≡CHBr), 151.06 (N=C–S), 151.91 (N=C–S–CH_2). ^{15}N NMR spectrum, δ, ppm: –66.4. Found, %: C 42.65; H 2.47; Br 25.68; N 9.42; S 20.69. $C_{11}H_7BrN_2S_2$. Calculated, % : C 42.44; H 2.25; Br 25.72; N 9.00; S 20.58.

When the reaction of equimolar amounts of dithiol **I** with 1,3-dibromopropyne **III** was performed in absolute methanol in the presence of sodium methoxide for 2 h the yield of compound **VIII** was 55%, in DMSO 53%, in DMF 44%.

2,3-Bis[(3-bromo-2-propynyl)sulfanyl]quinoxaline (IX). To the solution of 0.97 g of quinoxaline-2,3-dithiol **I** in 20 ml of absolute methanol the solution of sodium methoxide prepared from 0.23 g of sodium metal in 15 ml of absolute methanol was added slowly in small portions upon stirring. After all the solution of sodium methoxide was added the solution of 1.98 g of 1,3-dibromopropyne **III** in 20 ml of absolute methanol was added, the reaction mixture heated to 40–45°C, stirred for 16 h, cooled to 0°C, the precipitate formed filtered off, washed on filter with cold water and dried in vacuum. Yield 1.55 g (72%), mp 210–212°C. IR spectrum, ν, cm^{-1}: 605 (C–S), 1460 (CH_2), 1590, 1625 (C=N, C=C), 2230 (C≡C). ^1H NMR spectrum, δ, ppm: 4.29 s (4H, $2CH_2$), 7.93–7.95 m (4H, C_6H_4). ^{13}C NMR spectrum, δ, ppm: 19.90 (CH_2), 44.74 (≡CBr), 76.02 (CH_2–*C*≡), 127.57–139.31 (C_6H_4), 151.67 (N=C–S). ^{15}N NMR spectrum, δ, ppm: –74.9. Found, % : C 39.44; H 2.05; Br 37.20; N 6.68; S15.16. $C_{14}H_8Br_2N_2S_2$. Calculated, % : C 39.25; H 1.87; Br 37.38; N 6.54; S 14.95.

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