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REACTIONS OF 2-ALLYLTHIOBENZIMIDAZOLE, -OXAZOLE, -THIAZOLE, AND THE ISOMERIC THIONES WITH DICHLOROCARBENE

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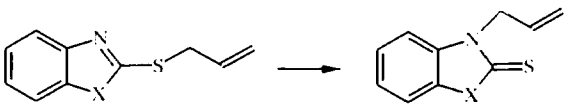
The reactions of 2-allylthiobenzimidazole, -oxazole, and -thiazole, and the thiones formed from them on heating, with dichlorocarbene have been investigated under phase transfer catalysis conditions.

Keywords: benzoxazole, benzimidazole, benzothiazole, dichlorocarbene, thiones, rearrangement.

Derivatives of benzimidazoles and their oxygen and sulfur analogs possess a wide spectrum of biological activity [1-5]. The problems of synthesis and rearrangement of alkylthio- and allylthio-substituted benzothiazoles, -oxazoles, and -imidazoles have been highlighted in [6-8].

It was established in [7] that allyl sulfides are converted on heating into thiones isomeric with them.

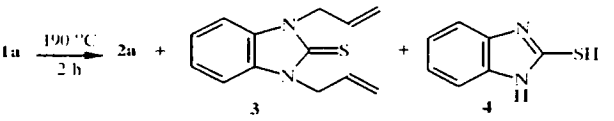
A study of the thermal conversions of allyl sulfides **1a-c** showed that, as discovered by the authors of the work mentioned, the sole products obtained on heating 2-allylbenzoxazole **1b** and 2-allylthiobenzothiazole **1c** to 200°C were the isomeric thiones **2b,c** in yield up to 60%. Their formation is the result of a coordinated 3,3-sigmatropic shift.



1a–c **2a–c**

a X = NH, b X = O, c X = S

The isomeric conversions of 2-allylthiobenzimidazole **1a** are somewhat different. On heating it for 2 h at 190°C a mixture is formed containing N-allylbenzimidazoline-2-thione (**2a**), N,N'-diallylbenzimidazoline-2-thione (**3**), and 2-mercaptobenzimidazole (**4**):



1a 190°C, 2 h **2a** + **3** + **4**

The complex composition of the reaction products is caused by the fact that disproportionation occurs together with the 3,3-sigmatropic rearrangement of the initial sulfide **1a** into the isomeric thione **2a**. This may be caused by sigmatropic shift by an uncoordinated mechanism with an intermolecular transfer of the allyl group, and

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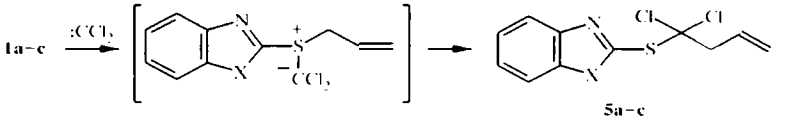
also by the presence in sulfide **1a** of a reactive hydrogen atom on a nitrogen atom which is replaced by the allyl group in the course of the reaction. A similar transallylation process was observed in the rearrangement of allyl thienyl sulfides [9].

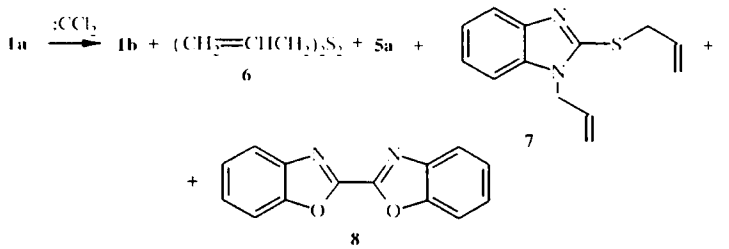
The presence of the allylthio group in the molecules of sulfides **1a-c** affords the possibility of further chemical modification of these compounds by reaction with electrophilic reagents. Dichlorocarbene was used as reagent, the generation of which in a two-phase system is a convenient synthetic method for introducing chlorine-containing fragments into organic molecule.

The reaction of each allylthio derivative **1a-c** with dichlorocarbene has its own special features. All three sulfides form substances corresponding to the addition of the :CCl_2 fragment to the initial molecule. Since introduction at the C–S bond occurs when allyl sulfides react with :CCl_2, the following scheme of formation of dichlorosulfides **5a-c** may be proposed. The scheme includes the initial formation of an ylide with subsequent 2,3-sigmatropic rearrangement:



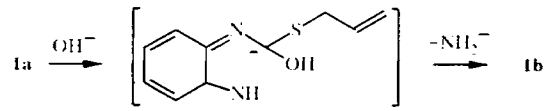
The yields of the dichlorosulfides did not exceed 2%. The mass spectra of sulfides **5a-c** are characterized by the presence of peaks for M, M+2, and M+4 ions in a ratio of 100 : 66 : 10, which corresponds to the presence of two chlorine atoms in their molecules. The presence of ion peaks of mass M-35 and M-71 in the spectra also indicates that the :CCl_2 fragment is included into their molecules.

The reaction of sulfide **1a** with dichlorocarbene occurs in several directions: a) introduction of dichlorocarbene at the C–S bond as a result of the initial formation of S-ylide, with a subsequent 1,3-sigmatropic rearrangement into 2-(1,1-dichloro-3-butenylthio)benzimidazole (**5a**); b) substitution of the imidazole ring NH group by oxygen with the formation of 2-allylthiobenzoxazole (**1b**) and its disproportionation into diallyl disulfide **6** and 2,2'-bisbenzoxazole (**8**); c) allylation at the nitrogen atom with the formation of 1-allyl-2-allylthiobenzimidazole (**7**):

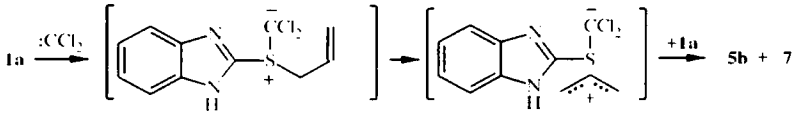


Compounds **5**, **7**, and **8** were obtained as a mixture separable with difficulty in a ratio 3 : 1 : 4, consequently conclusions on the compound probable structures were drawn on the basis of chromato-mass spectrometric data. The mass spectra of each of these three compounds were characterized by the presence of intense molecular ion peaks, but the presence of peaks for fragment ions formed a basis for proposing such structures.

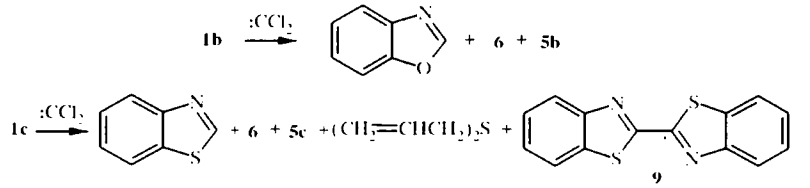
The formation of 2-allylthiobenzoxazole (**1b**) is of particular interest. This may be represented as the result of fission of the imidazole ring in the alkaline medium and replacement of the NH fragment by hydroxy group with subsequent cyclization:



The appearance of diallyl disulfide **6** and 2,2'-bisbenzoxazole **8** in the reaction mixture is related to the disproportionation of sulfide **1a**, which may occur through the intermediate formation of radical particles. The formation of sulfide **7** is the result of intermolecular transfer of allyl group during the 2,3-sigmatropic rearrangement of the intermediate ylide:

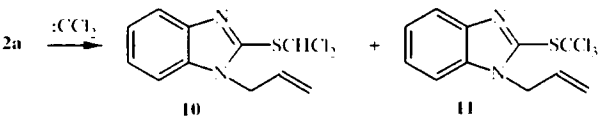


The reaction of sulfide **1b** with dichlorocarbene leads to the formation of mixture of benzoxazole (37%) and diallyl disulfide **6** (21%). The reaction of sulfide **1c** gave diallyl sulfide (15%) and benzothiazole dimer (**9**) (<1%), in addition to benzothiazole (24%) and diallyl disulfide (15%).

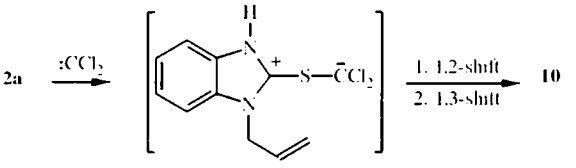


Such a composition for the reaction products from sulfides **1b,c** in this reaction indicates the possibility of nucleophilic fission of the C=S bond in alkaline medium with subsequent disproportionation of the radical particles, which is confirmed by the presence of dimer **9** in the reaction mixture.

The reaction of thiones **2a-c** with dichlorocarbene depends on the presence of second heteroatom in the azole fragment. No visible changes of the initial compound were observed for thione **2b** even after 40 h heating at 45-50°C. Only by chromato-mass spectrometry the presence of 1% of a compound with molecular weight 273 was discovered in the reaction mixture. This corresponds to the addition of one molecule of dichlorocarbene to thione **2b**. In the case of thione **2a** sulfides **10** and **11**, containing dichloromethyl and trichloromethyl groups, were formed by addition of dichlorocarbene at the C=S group:

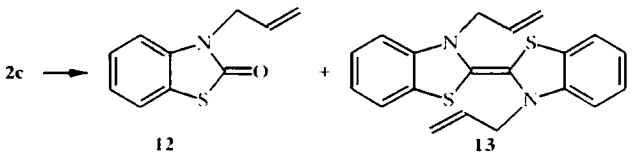


The formation of sulfide **10** may be represented as the result of the initial formation of ylide and two subsequent 1,2- and 1,3-hydride shifts in it:



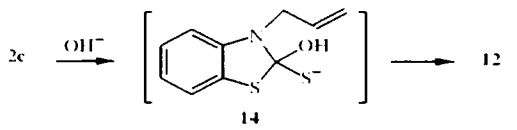
The significant loosening of the C=S bond formed by the overlap of 2*p*-orbitals of the carbon atom and 3*p*-orbitals of the sulfur atom point in favor of this scheme. Thione **2a** acts as a nucleophilic agent in this reaction and dichlorocarbene acts as an electrophile. The appearance of trichloromethyl derivative **11** may be the result of nucleophilic attack by the CCl_3^- anion on the thione group of thione **2a**.

Reaction of thione **2c** with dichlorocarbene forms N-allylbenzothiazolone **12** and 2,2'-bis(3-allylbenzothiazolinylidene) **13**:



12 13

The formation of thiazolone **12** is the result of nucleophilic attack of hydroxyl ion on the C=S bond with subsequent elimination of SH anion, which is a characteristic of the conversion of thiones in the presence of nucleophiles [10]:



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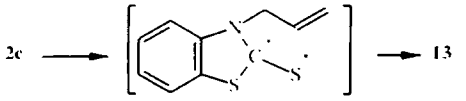
The formation of dimer **13** is caused by disproportionation of the radical intermediate formed from thione **2c** on heating in the presence of alkali, as occurs for dialkylthiones [10]:



EXPERIMENTAL

Chromato-mass spectrometric analysis was carried out on a Hewlett-Packard HP 5972 instrument in electron capture mode with an ionizing energy of 70 eV using an HP Ultra 1 capillary column (l = 17.5 m, d = 0.17 mm) in isothermic mode at 70°C, and with temperature programming from 70°C to 300°C (rate of heating 16°C/min), carrier gas was helium. The IR spectra were taken on an UR 20 instrument in Nujol. The ^{1}H and ^{13}C NMR spectra were recorded on Varian VXR 400 and DPX 300 spectrometers using 25% solutions of samples in $CDCl_3$. Internal standard was TMS. The precision of determining chemical shifts was 0.01 ppm, and coupling constants 0.5 Hz. Silufol UV 254 plates were used for TLC analysis, and columns of Merck silica gel 60 (0.063-0.200 mm) were used for separation of reaction products.

2-Allylthiobenzimid(oxa,thio)azoles (1a-c) were obtained by a modified procedure [7]. The melting points and spectral characteristics (^{1}H, ^{13}C NMR) of compounds **1a-c** were identical to the literature data [11-13].

Thermal Rearrangement of 2-Allylthiobenzimid(oxa,thio)azoles (1a-c) was carried out by heating at 200°C in ampoules, loaded with 1-4 g of substance and previously purged with inert gas. After cooling, the solid residue was dissolved in CCl_4 (for **1a**) or benzene (for **1b,c**) and the reaction products were separated by chromatography on silica gel. The time of heating and the eluents for chromatography were selected separately for each compound.

Thermal Rearrangement of Compound 1a. The reaction mixture was heated for 2 h, eluent CCl_4–hexane–ether, 43 : 47 : 10. Three compounds were separated: 3-allylbenzimidazoline-2-thione (**2a**) (1 g, 25%), 1,3-diallylbenzimidazoline-2-thione (**3**) (0.8 g, 16%), and 2-mercaptobenzimidazole (**4**) (1 g, 28%).

3-Allylbenzimidazoline-2-thione (2a). White crystalline substance; mp 110-112°C. IR spectrum: 1370-1480 cm^{-1} (C=S). Mass spectrum, m/z (I_{rel}, %): 190 (M^+, 64), 175 (100), 157 (27), 149 (11), 130 (11), 122 (21), 77 (9), 39 (13). The ^{1}H NMR spectrum was identical with that reported in the literature [8, 11]. ^{13}C NMR spectrum: 132.66; 130.84; 130.51; 123.42; 123.42; 122.89; 118.27; 110.11; 109.68 (C_{4a}–C_{8a} and –CH=CH_2); 168.27 (C=S); 46.50 ppm (NCH_2). Found, %: C 63.55; H 5.61; N 14.31; S 14.69. $C_{10}H_{10}N_2S$. Calculated, %: C 63.12; H 5.30; N 14.73; S 16.85.

1,3-Diallylbenzimidazoline-2-thione (3). Mp 73-75°C. IR spectrum: 1370 cm^{-1} (C=S). Mass spectrum, *m/z* (I_{rel}, %): 230 (M^+, 53), 215 (100), 197 (8), 174 (16), 130 (15), 103 (10), 51 (10), 39 (15). ^1H NMR spectrum: 5.03 (4H, dt, J = 5.44, 1.65 Hz, NCH_2); 5.19 (2H, ddd, J = 17.14, 1.61 Hz, $=CH_{trans}$, H_{cis}); 5.26 (2H, ddd, J = 10.31, 1.37 Hz, $=CH_{trans}$, H_{cis}); 5.46 (2H, m, J = 17.14, 10.31, 5.44 Hz, CH); 7.16-7.24 ppm (4H, m, H_{arom}). ^{13}C NMR spectrum: 131.91; 131.07; 122.94; 118.08; 109.49 (C_{14}–C_{15} and $-CH=CH_2$); 169.64 (C=S); 47.25 ppm (CH_2). Found, %: C 68.51; H 6.57; N 11.14; S 13.93. $C_{13}H_{14}N_2S$. Calculated, %: C 67.79; H 6.13; N 12.17; S 13.92.

3-Allylbenzoxazoline-2-thione (2b). The reaction mixture was heated for 6 h, eluent hexane–benzene, 1 : 3. Thione (0.6 g, 60%) was obtained; mp 90-92°C. ^1H NMR spectrum was identical with that reported in literature [7]. IR spectrum: 1390 cm^{-1} (C=S). Mass spectrum, *m/z* (I_{rel}, %): 191 (M^+, 69), 176 (100), 122 (73), 77 (14), 63 (17), 41 (16), 39 (23).

3-Allylbenzothiazoline-2-thione (2c). The reaction mixture was heated for 4 h, eluent hexane–benzene, 1 : 3. Thione (0.6 g, 60%) was obtained. The melting point and spectral characteristics (IR, ^1H and ^{13}C NMR) were identical with the literature data [14]. Mass spectrum, *m/z* (I_{rel}, %): 207 (M^+, 33), 192 (100), 174 (12), 108 (17), 69 (9), 39 (12).

Reactions of Sulfides 1a-c and Thiones 2a-c with Dichlorocarbene. Mixture of sulfide (or thione) (0.01 mol) and TBAB in $CHCl_3$ (10 ml) was stirred at room temperature for 10 min, 50% NaOH solution (0.02 mol) was added, and the mixture stirred at 45-55°C (duration of stirring was different for each sulfide and thione). A check on the reaction progress was carried out by TLC after each hour. Water (25 ml) was added at the end of the reaction, the organic layer was separated, and the aqueous layer extracted with ether. The organic layer and the ether extract were washed separately with 0.1 N HCl solution (3 × 25 ml), and with 10% $NaHCO_3$ solution to neutral reaction, then dried over $MgSO_4$. The solvent was distilled off, the residues combined, and the reaction products isolated by chromatography on silica gel.

Reaction of Sulfide 1a with Dichlorocarbene. The reaction mixture was stirred for 18 h, eluent hexane–benzene, 1 : 3. 2-Allylthiobenzoxazole **1b** (0.1 g, 5%), diallyl disulfide **6** (0.7 g, 37%), and 4 : 1 : 3 mixture (0.9 g) of 1-allyl-2-allylthiobenzimidazole (**7**), 2,2'-bisbenzoxazole (**8**), and 2-(1,1-dichloro-3-butenylthio)-benzimidazole (**5a**) (according to data of chromato-mass spectrometry) was obtained.

2-(1,1-Dichloro-3-butenylthio)benzimidazole (5a). Mass spectrum, *m/z* (I_{rel}, %): 272 (M^+, 41), 237 (63), 201 (25), 189 (100), 161 (72), 134 (43), 130 (53), 102 (20), 90 (32), 63 (15), 41 (23).

1-Allyl-2-allylthiobenzimidazole (7). Mass spectrum, *m/z* (I_{rel}, %): 230 (M^+, 40), 215 (100), 189 (20), 175 (15), 156 (31), 130 (35), 90 (15), 77 (15), 39 (25).

2,2'-Bisbenzoxazole (8). Mass spectrum, *m/z* (I_{rel}, %): 236 (M^+, 42), 221 (100), 169 (18), 160 (9), 137 (42), 111 (14), 102 (27), 75 (23), 51 (9), 39 (36).

Reaction of Sulfide 1b with Dichlorocarbene. The reaction mixture was stirred for 25 h, eluent hexane–benzene, 1 : 3. Benzoxazole (0.7 g, 37%) and diallyl disulfide (0.4 g, 21%) were obtained.

2-(1,1-Dichloro-3-butenylthio)benzoxazole (5). Mass spectrum, *m/z* (I_{rel}, %): 271 (M^+, 18), 236 (100), 204 (30), 151 (45), 121 (9), 85 (30), 63 (16), 50 (22).

Benzoxazole. Mass spectrum, *m/z* (I_{rel}, %): 119 (M^+, 100), 91 (59), 63 (52), 62 (18), 52 (7).

Reaction of Sulfide 1c with Dichlorocarbene. The reaction mixture was stirred for 25 h, eluent hexane–benzene, 2 : 1. Diallyl disulfide **6** (0.5 g, 24%), diallyl sulfide (0.3 g, 15%), and benzothiazole (0.5 g, 24%) containing 2,2'-bisbenzothiazole **9** (2 %) according to data of chromato-mass spectrometry were obtained.

2-(1,1-Dichloro-3-butenylthio)benzothiazole (5c). Mass spectrum, *m/z* (I_{rel}, %): 289 (M^+, 20), 254 (21), 218 (11), 192 (88), 167 (100), 136 (12), 122 (20), 108 (47), 87 (39), 51 (30).

2,2'-Bisbenzothiazole (9). Mass spectrum, *m/z* (I_{rel}, %): 268 (M^+, 100), 149 (20), 134 (8), 108 (17), 82 (9), 69 (17).

Reaction of Thione 2a with Dichlorocarbene. The reaction mixture was stirred for 20 h, eluent CCl_4–hexane–ether, 43 : 47 : 10. 1-Allyl-2-dichloromethylthiobenzimidazole (**10**) (0.25 g, 25%) and 1-allyl-2-trichloromethylthiobenzimidazole (**11**) (0.62 g, 60%) were obtained.

1-Allyl-2-dichloromethylthiobenzimidazole (10). Mass spectrum, *m/z* (I_{rel}, %): 276 (M+4$^+$, 8), 274 (M+2$^+$, 40), 272 (M^+, 64), 257 (100), 237 (35), 201 (28), 189 (16), 161 (95), 134 (49), 129 (16), 90 (25), 75 (19), 63 (11), 41 (40). ^1H NMR spectrum: 7.41 (4H, m, H_{arom}); 5.86 (1H, m, –CH–); 5.30; 5.25 (2H, m, $=CH_2$); 4.93 ppm (2H, m, $-CH_2$).

1-Allyl-2-trichloromethylthiobenzimidazole (11). Mass spectrum, *m/z* (I_{rel}, %): 310 (M+4$^+$, 4), 308 (M+2$^+$, 13), 306 (M$^+$, 12), 271 (7), 189 (100), 156 (16), 130 (21), 77 (15), 41 (55). ^{1}H NMR spectrum: 7.41 (4H, m, H_{arom}); 5.26 (1H, ddt, J = 10.37, 1.63, 0.74 Hz, $=CH_{2trans}$); 5.25 (1H, m, –CH=); 5.12 (2H, m, $–CH_2–$); 5.07 ppm (1H, ddt, J = 17.10, 1.78, 0.72 Hz, $=CH_{2cis}$). ^{13}C NMR spectrum: 156.27 ($C_{(1)}$), 143.60 ($C_{(8)}$), 138.47 ($C_{(4)}$), 131.72 (–CH=), 125.13, 123.48, 121.51, 118.17, 111.26 ($C_{(6)}$), ($C_{(7)}$), ($C_{(8)}$), ($C_{(9)}$), (=CH_2); 47.58 ppm (–CH_2). Found, %: C 44.80; H 3.10; Cl 30.28; N 8.88; S 8.72. $C_{11}H_9Cl_3N_2S$. Calculated, %: C 43.13; H 2.94; Cl 34.31; N 9.15; S 10.45.

Reaction of Thione 2b with Dichlorocarbene. The reaction mixture was stirred for 40 h. A check on the reaction using TLC in various solvent systems showed no other reaction products. According to chromato-mass spectroscopy the reaction product of thione **2b** with dichlorocarbene, *viz.* dichlorosulfide **5b** (less than 1%), was found in the reaction mixture.

Reaction of Thione 2c with Dichlorocarbene. The reaction mixture was stirred for 5 h, eluent hexane–benzene, 1 : 3. N-Allylbenzothiazolone (**12**) (0.6 g, 29%) and 2,2'-bis(3-allylbenzothiazolinylidene (**13**) (0.2 g, 10%) were obtained.

N-Allylbenzothiazolone (12). IR spectrum: 1680 cm^{-1} (C=O). Mass spectrum, *m/z* (I_{rel}, %): 191 (M$^+$, 100), 176 (6), 162 (49), 150 (48), 148 (27), 136 (37), 122 (24), 106 (24), 95 (13), 78 (16), 69 (32), 63 (13), 41 (65), 39 (72). ^{1}H NMR spectrum: 7.00-7.37 (4H, m, H_{arom}); 5.88 (1H, m, –CH=); 5.24 (2H, m, $=CH_2$); 4.58 ppm (2H, dt, J = 5.22, 1.66 Hz, $–CH_2–$). ^{13}C NMR spectrum: 169.69 ($C_{(2)}$), 136.88 ($C_{(4)}$), 130.62 (–CH=), 128.26 ($C_{(5)}$), 126.21 ($C_{(6)}$), 123.09 ($C_{(8)}$), 122.51 ($C_{(7)}$), 117.95 (=CH_2), 111.04 ($C_{(9)}$), 44.77 ppm (–CH_2–). Found, %: C 62.74; H 4.68; N 7.30; S 17.12. $C_{10}H_9NOS$. Calculated, %: C 62.80; H 4.74; N 7.33; S 16.77.

2,2'-Bis(3-allylbenzothiazolinylidene) (13). Mass spectrum, *m/z* (I_{rel}, %): 350 (M$^+$, 1), 309 (100), 268 (49), 174 (8), 108 (13), 69 (9), 41 (47), 39 (25). ^{1}H NMR spectrum: 3.39 (2H, ddd, J = 13.42, 5.25, 1.50 Hz, $–NCH_2$); 3.86 (AB); 5.14 (2H, dddd, J = 10.33, 10.02, 1.64, 1.34 Hz, $=CH_2$); 5.26 (2H, dddd, J = 17.7, 16.35, 1.64, 1.34 Hz, $=CH_2$); 5.77 (1H, m, J = 17.17, 10.39, 5.25 Hz, –CH=); 5.99 (1H, m, J = 17.38, 10.02, 5.62 Hz, –CH=); H_{arom} 6.39 (1H, dd, J = 7.02 Hz); 6.48 (1H, td, J = 7.58, 1.25 Hz); 6.72 (1H, td, J = 7.49, 1.06 Hz); 7.04 (1H, dd, J = 7.53, 1.29 Hz); 7.36 (1H, td, J = 7.72, 1.14 Hz); 7.46 (1H, td, J = 7.23, 1.26 Hz); 7.82 (1H, dd, J = 7.37, 1.63 Hz); 7.98 ppm (1H, dd, J = 8.19, 1.60 Hz). ^{13}C NMR spectrum: 146.18 (C=C), 145.83 ($C_{(4,4')}$), 134-107 (C_{arom}, –CH=, =CH_2), 47.29 ppm (–CH_2). Found, %: C 68.37; H 5.08. $C_{20}H_{18}N_2S_2$. Calculated, %: C 68.57; H 5.14.

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