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Synthesis of trans-1,2-bis(2-R-amino-1,3,4--thiadiazol-5-yl)ethene and trans-1,2-bis[3-(4--substituted-Δ^2-1,2,4-triazoline-5-thione)]ethene

Synteza trans-1,2-bis(2-R-amino-1,3,4-tiadiazol-5-yl)etenu
i trans-1,2-bis[3-(4-podstawionych-Δ^2-1,2,4-triazolino-5-tionu)]etenu

INTRODUCTION

Depending on the nature of substituents the derivatives of 1,2,4-triazole and 1,3,4-thiadiazole can show various pharmacological activity. There are known drugs containing the 1,2,4-triazole group e.g. Triazolam [1], Alprazolam [2], Etizolam [3], Furacrylin [4] and drugs containing 1,3,4-thiadiazole`group e.g. Acetazolamide [5], Benzolamide [6], Methazolamide [7], Furidazine [8]. Derivatives of the 1,2,4-triazole and 1,3,4-thiadiazole could be prepared in the cyclization of acyl derivatives of thiosemicarbazide. The reactions were carried out in acidic media. Cyclization of alkaline medium leads to 1,2,4-triazole system [9–14] and in the acidic medium 1,3,4-thiadiazole were obtained [13,14].

In the previous papers [15–18] it was stated that the reaction of cyclization was affected not only by *pH* of the medium but also by the substituents in thiosemicarbazide derivatives.

Cyclization of thiosemicarbazide derivatives containing the substituents of acidic nature led with good yield to 1,3,4-thiadiazole and with lower yield to 1,2,4-triazole system [15,16].Cyclization of thiosemicarbazide derivatives con-

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taining the substituents of alkaline nature wither in alkaline or in acidic media led to 1,2,4-triazole system with good yield [15,17,18].

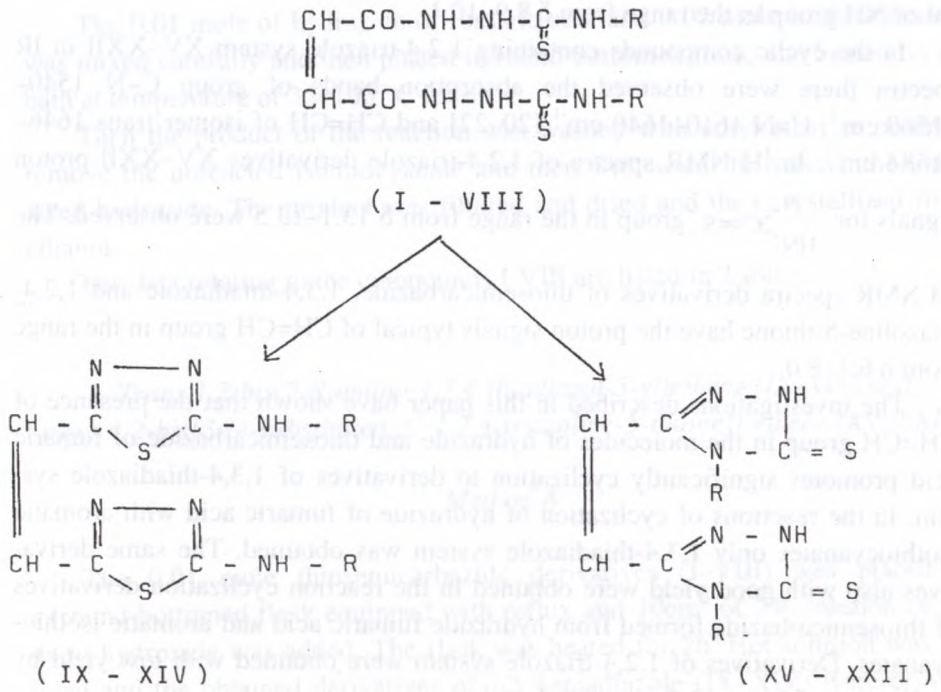
It has been found that the direct cyclization of hydrazides acids with isothiocyanates to 1,2,4-triazole and 1,3,4-thiadiazole system is possible as well. This fact has been unknown in literature up to now. The direction of these reactions depended on the substituents in acyl group of hydrazides acids. The obtaining of 1,2,4-triazole and 1,3,4-thiadiazole derivatives was possible from hydrazides acids too. The conditions of reaction of hydrazides acids with isothiocyanates were established experimentally. Derivatives of 1,2,4-triazole and 1,3,4-thiadiazole were obtaining not in each case. In this paper there are shown the results of studies on the reaction of cyclization of fumaroil thiosemicarbazide derivatives in alkaline and acidic media and possibility of cyclization of hydrazide fumaric acid with isothiocyanates.

INVESTIGATIONS, RESULTS AND DISCUSSION

Thiosemicarbazide derivatives were obtained in the reaction of the hydrazide of fumaric acid with isothiocyanates. The reactions were carried out by heating substrates in the alloy for 10h at the temperature of 100°C. The reactions of cyclization of thiosemicarbazide derivatives in alkaline media run according to the scheme 1.

Cyclization of thiosemicarbazide derivatives obtained from hydrazide of fumaric acid and aromatic isothiocyanates (I–VI) in this medium led to formation of the mixture containing derivatives of 1,3,4-thiadiazole (high yield 65–70 %) and 1,2,4-triazoline-5-thione (low yield 16–25 %). The cyclization of the same thiosemicarbazide derivatives in acidic medium led only to formation of 1,3,4-thiadiazole (yield 30–42 %). Cyclization of thiosemicarbazide derivatives obtained from hydrazide of fumaric acid and ethyl and ethoxycarbonylmethyl isothiocyanates (VII, VIII) in alkaline medium led only to formation of derivatives of 1,2,4-triazole system. During cyclization of thiosemicarbazide derivatives with ethoxycarbonylmethyl group, hydrolysis of ester group took place as well. The same compounds were obtained also in the reaction of cyclization performed in acidic medium. The derivatives of 1,3,4-thiadiazole (IX–XIV) were obtained also by the heating of hydrazide of fumaric acid with aromatic isothiocyanates in alloy for 10h at the temperature of 140°C and in N,N-dimethylacetamide at boiling point. The structure of obtained products in

the paper was confirmed by elemental analysis as well as by IR and ^{1}H NMR spectra.



R = C_6H_5 , p-$OCH_3C_6H_4$, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, p-BrC_6H_4 , C_2H_5 (VII, XXI) , $CH_2COOC_2H_5$ (VIII) , CH_2COOH (XXII)

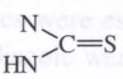
In IR spectra of thiosemicarbazide derivatives I–VIII the characteristic absorption bands were observed: 1668–1685 cm^{-1} corresponding to CH=CH group of isomer trans, 1670–1720 cm^{-1} corresponding to C=O group and 3180–3360 cm^{-1} corresponding to NH group.

^{1}H NMR spectra of thiosemicarbazide derivatives I–VIII have 3 protons signals, typical of NH group in the range from δ 8.0–10.0.

In the IR spectra with 1,3,4-thiadiazole IX–XIV there were observed the absorption bands for NH group 3200–3300 cm^{-1}, absorption bands for CH=CH

group of isomer trans 1614–1680 cm^{-1} and absorption bands for C–S–C group of thiadiazole 710–750 cm^{-1} [19].

In ^1H NMR spectra of this compounds IX-XIV have the proton signals typical of NH group in the range from δ 8.9–10.1.

In the cyclic compounds containing 1,2,4-triazole system XV–XXII in IR spectra there were observed the absorption bands of group C–N 1540–1560 cm^{-1}, C=N 1610–1640 cm^{-1} [20–22] and CH=CH of isomer trans 1646–1684 cm^{-1}. In ^1H NMR spectra of 1,2,4-triazole derivatives XV–XXII proton signals for  group in the range from δ 13.1–13.5 were observed. The ^1H NMR spectra derivatives of thiosemicarbazide, 1,3,4-thiadiazole and 1,2,4-triazoline-5-thione have the proton signals typical of CH=CH group in the range from δ 6.1–8.0.

The investigations described in this paper have shown that the presence of CH=CH group in the molecules of hydrazide and thiosemicarbazide of fumaric acid promotes significantly cyclization to derivatives of 1,3,4-thiadiazole system. In the reactions of cyclization of hydrazide of fumaric acid with aromatic isothiocyanates only 1,3,4-thiadiazole system was obtained. The same derivatives also with good yield were obtained in the reaction cyclization derivatives of thiosemicarbazide formed from hydrazide fumaric acid and aromatic isothiocyanates. Derivatives of 1,2,4-triazole system were obtained with low yield by cyclization of fumaroil thiosemicarbazides.

The results of these investigations confirm our earlier suppositions relating to the effect of substituents present in molecules of thiosemicarbazide derivatives on the course of cyclization of acyl thiosemicarbazide derivatives to 1,3,4-thiadiazole and 1,2,4-triazole system.

EXPERIMENTAL

Melting points were determined in Fischer-Johns block and presented without any corrections. IR spectra were recorded in KBr Perkin Elmer FT 1725 X spectrophotometer. The ^1H NMR spectra were recorded on Tesla BS-567 A spectrometer (100Hz) in DMSO-d_6 with TMS as internal standard.

1. Fumaroil thiosemicarbazides (I–VIII)

The 0.01 mole of hydrazide of fumaric acid and 0.02 mole isothiocyanates was mixed carefully and then placed in round-bottomed flask, and heated on oil bath at temperature of 35–100 °C for 8h.

Then the product of the reaction was washed with ethyl ether in order to remove the unreacted isothiocyanate and then with water to remove the unreacted hydrazide. The product was filtered and dried and then crystallized from ethanol.

The data relating to the compounds I-VIII are listed in Table 1.

2. Trans 1,2-bis(2-R-amino-1,3,4-thiadiazol-5-yl)ethene (IX–XIV) and trans 1,2-bis[3-(4-substituted-Δ^2-1,2,4-triazoline-5-thione)] ethene (XV–XXII)

Method A

The 0.01 mole thiosemicarbazide derivatives (I–VIII) was placed in a (round-bottomed flask equipped with reflux and 10cm^3 of 2% solution of sodium hydroxide was added. The flask was heated for 2h. Hot solution was filtered and the obtained derivatives of 1,3,4-thiadiazole (IX–XIV) were crystallized from ethanol. The data relating to these compounds are listed in Table 2.

After the cooling the filtrate was neutralized with diluted hydrochloric acid. The precipitated compound was filtered and crystallized from ethanol. The data related to the 1,2,4-triazoline-5-thione derivatives (XV–XXII) are listed in Table 3.

Method B (IX–XIV)

The mixture of 0.01 mole of hydrazide of fumaric acid and 0.02 mole of isothiocyanate was heated in a round-bottomed flask on oil bath for 10h at the temperature of 140°C. The product of reaction was washed with ethyl ether to remove the unreacted isothiocyanate and then with water to remove the unreacted hydrazide. The residue solid was crystallized from ethanol. The same products as in the method A were obtained.

Method C (IX–XIV)

The 0.01 mole of hydrazide of fumaric acid and 0.02 mole of isothiocyanate in 10cm^3 of the N,N-dimethylacetamide was heated in a round-bottomed flask at boiling point for 10h. After cooling the solution 40cm^3 of water was added. Precipitated compound was filtered, washed carefully with the ethyl ether and water, dried and crystallized from ethanol.

The same products as in the method A and B were obtained.

Method D (IX–XIV)

The 0.01 mole of thiosemicarbazide derivatives (I–VI) and 10cm^3 3N HCl was refluxed for 2h. The mixture was kept for 24h at the room temperature. The precipitated product was filtered, dried and crystallized from ethanol. Mixed melting points have not shown any variations. IR and ^{1}H NMR spectra the compounds by the method A,B,C,D are identical.

3. Trans 1,2-bis[3-(4-substituted-Δ^2-1,2,4-triazoline-5-thione)]ethene

Method B (XXI, XXII)

The 0,01 mole of thiosemicarbazide derivatives (VII, VIII) and 10cm^3 3N HCl was refluxed for 2h. The mixture was kept for 24h at the room temperature. The precipitated product was filtered, dried and crystallized from ethanol. The same products as in the method A were obtained. Yield of reactions: 14–15 %.

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STRESZCZENIE

Reakcje pochodnych tiosemikarbazydowych kwasu fumarowego w środowisku zasadowym prowadziły do otrzymania pochodnych 1,3,4-tiadiazolu i 1,2,4-triazolino-5-tionu. Cyklizacja pochodnych tiosemikarbazydowych kwasu fumarowego, otrzymanych z izotiocyjanianów aromatycznych w środowisku kwasowym, prowadziła tylko do pochodnych 1,3,4-tiadiazolu. Te same pochodne 1,3,4-tiadiazolu otrzymano również przez ogrzewanie hydrazydu kwasu fumarowego z izotiocyjanianami aromatycznymi w stopie lub w N,N-dimetyloacetamidzie.

Przeprowadzone badania wskazują, że obecność grupy CH=CH w cząsteczce hydrazydu lub tiosemikarbazydu kwasu fumarowego sprzyja cyklizacji, w wyniku której otrzymujemy pochodne 1,3,4-tiadiazolu. Pochodne 1,2,4-triazolu zostały otrzymane z małą wydajnością przez cyklizację pochodnych tiosemikarbazydowych kwasu fumarowego.

Table 1. Physical and chemical data for compound I–VIII

No	R	Formula molecular weight	Yield, [%]	M.p., [°C]	Analysis Calculated/Found %C	%H	%N	IR (cm^{-1}) KBr	^1H NMR, δ (ppm) DMSO-d_6
1	2	3	4	5	6	7	8	9	10
I	C_6H_5	$C_{18}H_{18}N_6S_2O_2$ 414.492	92	216–217	52.16 52.68	4.38 4.71	20.29 21.02	3230 NH 3030 CH arom. 2970, 1450 CH aliph. 1680 C=O 1679 CH=CH trans 1540, 1350 C=S	6.89–6.95(m,2H,CH=CH) 7.19–7.61(m,10H,arom) 9.78, 9.82, 9.86(3s,6H,6NH)
II	*p*-$OCH_3C_6H_4$	$C_{20}H_{22}N_6S_2O_4$ 474.544	91	198–200	50.62 50.28	4.67 4.73	17.71 17.43	3210 NH 3000 CH arom. 2940, 1440 CH aliph. 1680 C=O 1675 CH=CH trans 1540, 1340 C=S	2.54(s,6H,2CH_3) 6.86–6.97(m,2H,CH=CH) 7.30–7.42(m,8H,arom) 9.54, 9.63, 9.71(3s,6H,6NH)
III	2-$CH_3C_6H_4$	$C_{20}H_{22}N_6S_2O_2$ 442.544	89	152–154	54.28 54.89	5.01 5.02	18.99 18.43	3260 NH 3020 CH arom. 2960, 1460 CH aliph. 1684 CH=CH trans 1670 C=O 1540, 1340 C=S	2.46(s,6H,2CH_3) 7.10–7.11(m,2H,CH=CH) 7.19–7.34(m,8H,arom) 9.48, 9.60, 9.70(3s,6H,6NH)
IV	3-$CH_3C_6H_4$	$C_{20}H_{22}N_6S_2O_2$ 442.544	90	210–212	54.28 54.41	5.01 5.11	18.99 19.02	3180 NH 3020 CH arom. 2970, 1480 CH aliph. 1680 C=O 1668 CH=CH trans 1540, 1340 C=S	2.54(s,6H,2CH_3) 6.72–6.79(m,2H,CH=CH) 7.18–7.46(m,8H,arom) 9.79, 9.83, 9.89(3s,6H,6NH)

Table 1. – continued

1	2	3	4	5	6	7	8	9	10
V	4-$CH_3C_6H_4$	$C_{20}H_{22}N_6S_2O_2$ 442.544	91	180–182	54.28 54.02	5.01 5.27	18.99 18.71	3190 NH 3030 CH arom. 2940, 1480 CH aliph. 1684 CH=CH trans 1680 C=O 1540, 1320 C=S	2.53(s,6H,2CH_3) 6.96–7.16(m,2H,CH=CH) 7.18–7.48(m,8H,arom) 9.76, 9.86, 9.90(3s,6H,6NH)
VI	*p*-BrC_6H_4	$C_{18}H_{16}N_6S_2O_2Br_2$ 572.308	88	210–212	37.78 37.59	2.82 2.71	14.69 14.89	3190 NH 3000 CH arom. 2940, 1490 CH aliph. 1684 CH=CH trans 1680 C=O 1540, 1340 C=S	7.26–7.52(m,2H,CH=CH) 7.52–7.61(m,8H,arom) 9.78, 9.80, 9.97(3s,6H,6NH)
VII	C_2H_5	$C_{10}H_{18}N_6S_2O_2$ 318.412	75	187–188	37.72 37.28	5.69 5.94	26.40 26.20	3270 NH 2980, 1440 CH aliph. 1690 C=O 1685 CH=CH trans 1530, 1370 C=S	0.98–1.13(t,6H,2CH_3) 3.34–3.53(q,4H,2CH_2) 6.78–7.14(m,2H,CH=CH) 9:13, 9.20, 9.23(3s,6H,6NH)
VIII	$CH_2COOC_2H_5$	$C_{14}H_{22}N_6S_2O_6$ 434.482	87	184–186	38.70 38.42	5.10 5.07	19.35 19.42	3360 NH 2990, 1440 CH aliph. 1720 C=O 1670 CH=CH trans 1540, 1380 C=S	1.13–1.27(t,6H,2CH_3) 3.35–3.90(q,4H,2CH_2) 4.13(s,4H,2CH_2) 6.05–6.29(m,2H,CH=CH) 7.90, 7.96, 7.99(3s,6H,6NH)

Table 2. Physical and chemical data for compound IX–XIV

No	R	Formula molecular weight	Yield, [%] Method				M.p., [°C]	Analysis Calculated/Found			IR (cm^{-1}) KBr	^1H NMR, δ (ppm) DMSO-d_6
			A	B	C	D		%C	%H	%N		
1	2	3	4	5	6	7	8	9	10	11	12	13
IX	C_6H_5	$C_{18}H_{14}N_6S_2$ 378.460	70	56	47	42	234–236	57.12 57.30	3.64 3.52	22.16 22.38	3230 NH 3030 CH arom. 1667 CH=CH trans 750 C–S–C	6.86–6.94(m,2H,CH=CH) 7.24–7.64(m,10H,arom.) 9.88(s,2H,2NH)
X	*p*-$OCH_3C_6H_4$	$C_{20}H_{18}N_6S_2O_2$ 438.512	69	48	37	34	229–230	54.77 54.69	4.14 4.21	19.18 18.94	3210 NH 3120 CH arom. 2950, 1440 CH aliph. 1614 CH=CH trans 1240 C–O–C 720 C–S–C	2.53(s,6H,2CH_3) 6.84–6.93(m,2H,CH=CH) 7.36–7.51(m,8H,arom.) 9.57(s,2H,2NH)
XI	2-$CH_3C_6H_4$	$C_{20}H_{18}N_6S_2$ 406.512	67	54	42	40	192–194	59.09 59.18	4.46 4.36	20.77 20.60	3300 NH 2970 CH arom. 2950, 1440 CH aliph. 1614 CH=CH trans 720 C–S–C	2.49(s,6H,2CH_3) 6.84–7.09(m,2H,CH=CH) 7.15–7.94(m,8H,arom.) 8.85(s,2H,2NH)

Table 2. – continued

1	2	3	4	5	6	7	8	9	10	11	12	13
XII	3-$CH_3C_6H_4$	$C_{20}H_{18}N_6S_2$ 406.512	68	49	41	39	204–206	59.09 59.21	4.46 4.29	20.77 20.82	3200 NH 3140 CH arom. 2980, 1480 CH aliph. 1623 CH=CH trans 730 C–S–C	2.48(s,6H,2CH_3) 6.72–6.79(m,2H,CH=CH) 7.14–7.44(m,8H,arom.) 9.77(s,2H,2NH)
XIII	4-$CH_3C_6H_4$	$C_{20}H_{18}N_6S_2$ 406.512	69	40	38	37	232–234	59.09 58.98	4.46 4.34	20.77 20.70	3230 NH 3120 CH arom. 2960, 1487 CH aliph. 1680 CH=CH trans 720 C–S–C	2.46(s,6H,2CH_3) 6.15–6.18(m,2H,CH=CH) 7.14–7.36(m,8H,arom.) 9.65(s,2H,2NH)
XIV	*p*-BrC_6H_4	$C_{18}H_{12}N_6S_2Br_2$ 536.276	65	45	34	30	258–260	40.31 40.25	2.25 2.10	15.67 15.70	3170 NH 3030 CH arom. 1614 CH=CH trans 710 C–S–C	6.64–6.70(m,2H,CH=CH) 7.40–7.70(m,8H,arom.) 10.10(s,2H,2NH)

Table 3. Physical and chemical data for compound XV–XXII

No	R	Formula molecular weight	Yield, [%]	M.p., [°C]	Analysis Calculated/Found %C	%H	%N	IR (cm^{-1}) KBr	^1H NMR, δ (ppm) DMSO-d_6
1	2	3	4	5	6	7	8	9	10
XV	C_6H_5	$C_{18}H_{14}N_6S_2$ 378.460	25	176–178	57.12 57.42	3.64 3.30	22.16 22.49	3120 CH arom. 16809 CH=CH trans 1610 C=N 1540 C–N	6.83–6.97(m,2H,CH=CH) 7.15–7.64(m,10H,arom) 13.30(s,2H,2 NH–C=S)
XVI	*p*-$OCH_3C_6H_4$	$C_{20}H_{18}N_6S_2O_2$ 438.512	20	210–212	54.77 54.75	4.14 4.69	19.18 18.96	3100 CH arom. 2950, 1460 CH aliph. 1678 CH=CH trans 1610 C=N 1540 C–N 1250 C–O–C	2.45(s,6H,2CH_3) 6.65–6.90(m,2H,CH=CH) 7.00–7.21(m,8H,arom) 13.10(s,2H,2 NH–C=S)
XVII	2-$CH_3C_6H_4$	$C_{20}H_{18}N_6S_2$ 406.512	18	198–200	59.09 58.96	4.46 4.20	20.77 20.52	3030 CH arom. 2970, 1460 CH aliph. 1665 CH=CH trans 1610 C=N 1560 C–N	2.51(s,6H,2CH_3) 6.90–7.12(m,2H,CH=CH) 7.17–7.71(m,8H,arom) 13.54(s,2H,2 NH–C=S)
XVIII	3-$CH_3C_6H_4$	$C_{20}H_{18}N_6S_2$ 406.512	17	240–242	59.09 58.78	4.46 4.98	20.77 20.54	3100 CH arom. 2950, 1470 CH aliph. 1680 CH=CH trans 1610 C=N 1550 C–N	2.40(s,6H,2CH_3) 6.76–6.92(m,2H,CH=CH) 7.10–7.46(m,8H,arom) 13.26(s,2H,2 NH–C=S)

Table 3. – continued

1	2	3	4	5	6	7	8	9	10
XIX	4-$CH_3C_6H_4$	$C_{20}H_{18}N_6S_2$ 406.512	19	207–209	59.09 59.62	4.46 4.38	20.77 20.72	3120 CH arom. 2920, 1420 CH aliph. 1684 CH=CH trans 1610 C=N 1540 C–N	2.53(s,6H,2CH_3) 6.90–7.01(m,2H,CH=CH) 7.12–7.42(m,8H,arom) 13.24(s,2H,2 NH–C=S)
XX	*p*-BrC_6H_4	$C_{18}H_{12}N_6S_2Br_2$ 536.288	18	214–216	40.31 40.24	2.25 2.53	15.67 15.76	3090 CH arom. 1678 CH=CH trans 1610 C=N 1540 C–N	7.25–7.30(m,2H,CH=CH) 7.48–7.85(m,8H,arom) 13.50(s,2H,2 NH–C=S)
XXI	C_2H_5	$C_{10}H_{14}N_6S_2$ 282.380	16	142–144	42.53 42.38	4.99 4.76	29.76 29.58	2930, 1440 CH aliph. 1670 CH=CH trans 1620 C=N 1540 C–N	1.20–1.31(t,6H,2CH_3) 3.91–4.05(q,4H,2CH_2) 7.57–7.96(m,2H,CH=CH) 13.48(s,2H,2 NH–C=S)
XXII	CH_2COOH	$C_{10}H_{10}N_6S_2O_4$ 342.348	17	242–244	35.08 35.21	2.94 2.80	24.55 24.48	2920, 1420 CH aliph. 1718 C=O 1646 CH=CH trans 1640 C=N 1560 C–N	3.80(s,4H,2CH_2) 5.55(s,2H,2OH) 7.10–7.38(m,2H,CH=CH) 13.39(s,2H,2 NH–C=S)