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Synthesis of (1*H*-Pyrrol-2-ylsulfanyl)alkanoic Acids

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Abstract—(1-Benzyl-1*H*-pyrrol-2-ylsulfanyl)acetic acid, 2- and 3-(1-benzyl-1*H*-pyrrol-2-ylsulfanyl)propionic acids, 1,1′-[1,4-phenylenebis(methylene)]bis[(1*H*-pyrrol-2-ylsulfanyl)acetic acid], and 1,1′-(hexane-1,6-diyl)bis-[(1*H*-pyrrol-2-ylsulfanyl)acetic acid] were synthesized for the first time by reactions of 1-benzyl-1*H*-pyrrole, 1,1′-[1,4-phenylenebis(methylene)]bis(1*H*-pyrrole), and 1,1′-(hexane-1,6-diyl)bis(1*H*-pyrrole) with thiourea, iodine, and the corresponding halogen-substituted alkanoic acids. 1-(4-Nitrophenyl)-1*H*-pyrrole failed to react with thiourea and iodine.

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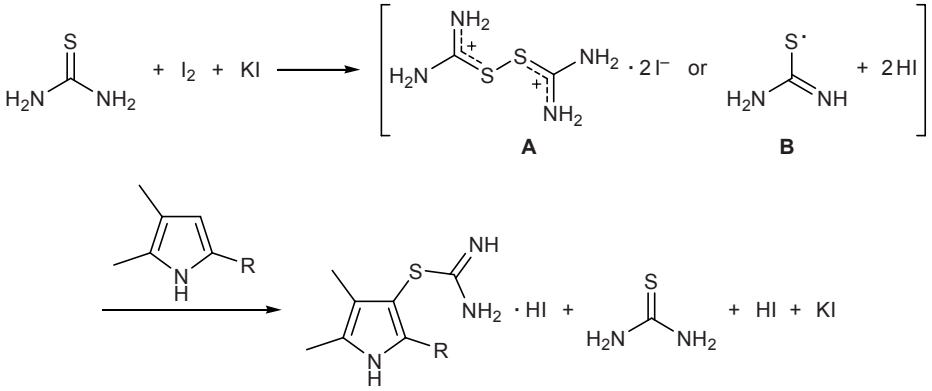
Pyrrolyl-substituted carboxylic acids are widely used as intermediate products and biologically active substances [1]. Pyrrolylsulfanyl-substituted alkanoic acids also attract strong interest from the practical viewpoint since their closest analogs, hetaryl- and indolylsulfanylalkanoic acids and hydroxyalkylammonium salts derived therefrom are known to act as growth stimulators toward microorganisms, herbicides, and immunostimulatory, adaptogenic, and antiphlogistic agents [2, 3]. Therefore, development of methods for the preparation of pyrrolylsulfanylalkanoic acids is an important problem. However, pyrrolethiols that could be used as starting compounds for the synthesis of pyrrolylsulfanyl-substituted alkanoic acids remain so far almost inaccessible.

With the goal of developing a synthetic route to pyrrolylsulfanylalkanoic acids as promising biologically active substances and intermediate products, we continued our studies on reactions of pyrroles with iodine and thiourea and of the isothiuronium iodides thus obtained with halogen-substituted carboxylic acids. It is known that ethyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate reacts with an equivalent amount of thiourea, imidazolidine-2-thione, and imidazole-2-thiol in the presence of 1 equiv of bromine or potassium triiodide to give the corresponding isothiuronium salts in more than 75% yield; no sulfanyl-substituted pyrrole was isolated upon alkaline decomposition of these salts [4]. Two mechanisms were proposed for the formation of *S*-pyrrolylisothiuronium salts. The first of these involves initial oxidation of thiourea with halogen to produce dithiobis(formimidamide), reaction of the latter with the remaining halogen to give sulfenyl halide, and electrophilic substitution of hydrogen in the pyrrole ring. According to the second mechanism, initial halogenation of pyrrole is followed by nucleophilic replacement of the halogen atom by thiourea or its analogs. As shown in [5], preliminarily prepared iodopyrrole failed to react with thiourea under analogous conditions; therefore, the proposed mechanisms for formation of pyrrolylisothiuronium salts [4, 5], as well as of those derived from indole [6], via halogenation of hetarenes and subsequent reaction with thiourea was not confirmed.

We previously studied [7] reactions of indole and its substituted derivatives with thiourea and iodine and found optimal conditions for the synthesis of *S*-indolylisothiuronium iodides and their subsequent transformation into the corresponding indolylsulfanylalkanoic acids. In the same publication we also described for the first time reactions of chloroacetic acid with *S*-pyrrolylisothiuronium iodides generated *in situ* from unsubstituted pyrrole and 1-methyl-1*H*-pyrrole, thiourea, and iodine at a ratio of 1:2:1. The reactions were carried out both with addition of hydrazine hydrate and without it. We found that addition of hydrazine hydrate (0.2 equiv with respect to initial hetarene) at the stage of reaction of isothiuronium salts with halocarboxylic acids ensures improved yield and purity of the final products, presumably as a result of elimina-

Scheme 1.

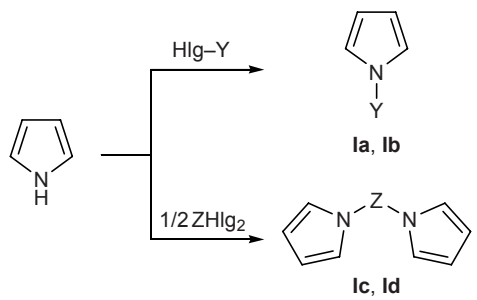


tion of side oxidation of thiols and isothiuronium salts. However, the yield of the corresponding (1*H*-pyrrol-2-yl)sulfanylacetic acids (which were identified by the IR and ^{1}H NMR spectra) did not exceed 5–20%, and we failed to separate them from unidentified impurities by column chromatography.

We examined the effect of the reactant ratio and order of their mixing on the yield of *S*-indolylisothiuronium iodide and found that the use of 2 equiv of thiourea rules out intermediate formation of sulfenyl halide $NH_2C(=NH)SCl$ or 3-iodoindole. Our results allowed us to propose two possible paths for the formation of *S*-indolylisothiuronium salt: (1) through intermediate of dithiobis(formimidamide) dihydroiodide **A** and its reaction *in statu nascendi* with indole (it should be emphasized that preliminarily isolated disulfide **A** is inactive as electrophile toward indole); (2) via formation of radical species **B** and radical substitution of hydrogen in the indole ring (Scheme 1). At the optimal reactant ratio, the entire amount of iodine is consumed for the oxidation of thiourea.

The present work continues our studies on reactions of 1-substituted pyrroles with iodine, thiourea, and halocarboxylic acids. Initial pyrroles **Ia**–**Id** were synthesized according to the procedure described previously for the synthesis of 1-methyl-1*H*-indole [8], i.e., by alkylation of pyrrole with benzyl chloride and arylation with 4-fluoronitrobenzene in DMSO in the presence of alkali. Unlike the original procedure, we used considerably lower amounts of the solvent (by a factor of 2 to 3) and alkali (by a factor of 1.5). 1,1′-(Hexane-1,6-diyl)bis(1*H*-pyrrole) (**Ic**) and 1,1′-[1,4-phenylenebis(methylene)]bis(1*H*-pyrrole) (**Id**) were obtained under analogous conditions from pyrrole and 1,6-dichlorohexane or 1,4-bis(chloromethyl)benzene, respectively. The yields of N-substituted pyrroles **Ia**–**Id** were 85–95% (Scheme 2).

Scheme 2.

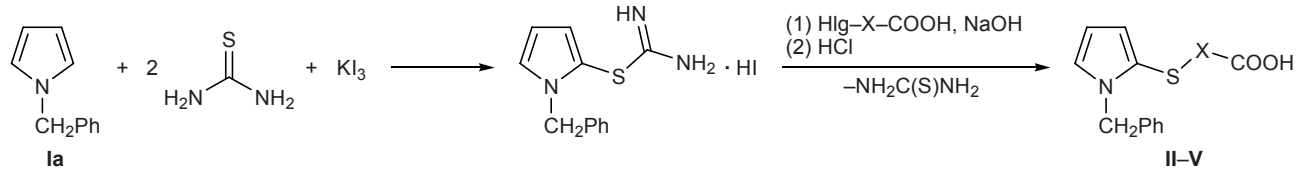


Hlg = Cl, Y = $PhCH_2$ (**a**); Hlg = F, Y = 4-$O_2NC_6H_4$ (**b**);
Hlg = Cl, Z = $(CH_2)_6$ (**c**), *p*-$CH_2C_6H_4CH_2$ (**d**).

Pyrroles **Ia**–**Id** were brought into reactions with thiourea, potassium triiodide, and haloalkanoic acids under the conditions reported in [7]. The reactions were carried out in lower alcohols (methanol, ethanol, or propan-2-ol), the ratio pyrrole–thiourea–iodine–potassium iodide–haloalkanoic acid being 1:2:1:1:1.2. From 1-benzyl-1*H*-pyrrole (**Ia**) and chloroacetic and 2-chloropropionic acids we obtained, respectively, (1-benzyl-1*H*-pyrrol-2-ylsulfanyl)acetic and 2-(1-benzyl-1*H*-pyrrol-2-ylsulfanyl)propionic acids **II** and **III** in 59–68% yield (Scheme 3). 2-(1-Benzyl-1*H*-pyrrol-2-ylsulfanyl)butanoic acid (**IV**) and 2-(1-benzyl-1*H*-pyrrol-2-ylsulfanyl)propionic acid (**III**) were also formed with a fairly good yield, but they were contaminated with unidentified impurities which we failed to separate by recrystallization or chromatography.

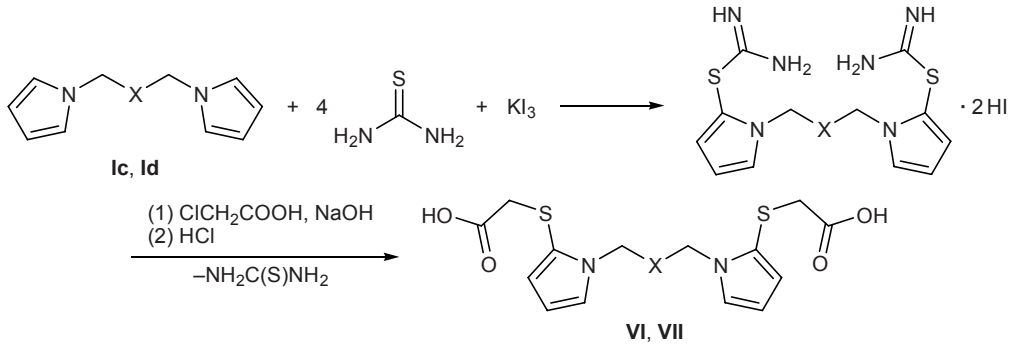
Thus, the presence of a benzyl group on the pyrrole nitrogen atom ensures chemoselective reactions of compound **Ia** with thiourea and iodine at a ratio of 1:2:1 and subsequent reactions with halocarboxylic acids to obtain α-(1-benzyl-1*H*-pyrrol-2-ylsulfanyl)-substituted acetic and propionic acids **II** and **III**. Presumably, the benzyl group on the pyrrole nitrogen atom stabilizes both transition states and intermediate

Scheme 3.



II, X = CH_2; **III**, X = CH(Me); **IV**, X = CH(Et); **V**, X = CH_2CH_2; Hlg = Cl, Br.

Scheme 4.



VI, X = $(CH_2)_4$; **VII**, X = *p*-C_6H_4.

isothiuronium salts, and the process is also favored by high reactivity of halogen atom in the α-position of acetic and propionic acids. Lower selectivity in the reactions with 2-bromobutanoic and 3-bromopropionic acids is likely to be related to steric hindrances in the first case and weak electrophilicity of the β-carbon atom in the latter.

Electron-withdrawing substituents on the pyrrole nitrogen atom reduce nucleophilicity of the pyrrole ring, thus preventing formation of isothiuronium salts. 1-(4-Nitrophenyl)-1*H*-pyrrole (**Ib**) failed to react with thiourea and potassium triiodide even on prolonged heating (3 h at 68–70°C) and was recovered from the reaction mixture (75%) together with a small amount of tars. Using bridged bis-pyrroles **Ic** and **Id** as initial compounds we obtained 59–73% of bis-pyrrolylsulfanylacetic acids **VI** and **VII**, respectively (Scheme 4).

The IR spectra of acids **II**–**VII** contained absorption bands belonging to vibrations of the carboxy groups, pyrrole rings, and alkyl groups. Pyrrolylsulfanylacetic acids **II**, **VI**, and **VII** displayed in the ^{1}H NMR spectra signals from protons in positions *3–5* of the pyrrole ring, OH group, and SCH_2 fragment with an intensity ratio corresponding to the assumed structures. In the ^{1}H NMR spectrum of acid **III** signals from protons in the CH_3CH and OH groups were present. Molecule **III** possesses a chiral center; therefore, double sets of signals from the SCH_2 protons and protons in the pyrrole ring are observed. Likewise, 2-(1-benzyl-1*H*-pyrrol-2-ylsulfanyl)butanoic acid (**IV**) showed a complex pattern in the ^{1}H NMR spectrum.

Thus we were the first to obtain a series of 1*H*-pyrrol-2-ylsulfanyl-substituted alkanoic acids by reactions of 1-substituted pyrroles with iodine, thiourea, and chloroacetic and 2-chloropropionic acids. These compounds attract interest as potential biologically active substances and intermediate products for their preparation.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer from samples prepared as KBr pellets or thin films. The ^{1}H NMR spectra were measured on a Bruker DPX-400 spectrometer (400.13 MHz); the ^{1}H–^{1}H coupling constants were determined with an accuracy of ±0.1 Hz.

General procedure for N-alkylation of pyrrole. Pyrrole, 6.70 g (0.1 mol), was added to a solution of 12 g (0.3 mol) of sodium hydroxide in 50 ml of DMSO, the mixture was stirred for 20–30 min and cooled to 10–15°C, and the corresponding halogen derivative [0.05 mol of 1,6-dichlorohexane, 0.05 mol of 1,4-bis(chloromethyl)benzene, or 0.1 mol of benzyl chloride or 4-fluoronitrobenzene] was slowly added. The mixture was stirred for 3 h at 20–22°C and poured into 200 ml of ice water, and the precipitate was filtered off, washed with water, and dried (liquid prod-

ucts were extracted into diethyl ether, the extract was dried and evaporated, and the residue was distilled under reduced pressure).

1-Benzyl-1*H*-pyrrole (Ia). Yield 13.4 g (85%), bp 134–135°C (15 mm); published data [9]: bp 245–247°C, 137–139°C (27 mm). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.22 s (2H, CH_2), 6.42 br.s (2H, 3-H, 4-H), 6.87 br.s (2H, 2-H, 5-H), 7.31 d and 7.49 m (5H, C_6H_5).

1-(4-Nitrophenyl)-1*H*-pyrrole (Ib). Yield 15.0 g (80%) (from 6.70 g of pyrrole and 14.11 g of 4-fluoronitrobenzene), mp 186–187°C; published data [10]: mp 181°C. IR spectrum, ν, cm^{-1}: 3140, 3075 (=CH); 1600, 1595 (C=C); 1500, 1330 (NO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.32 br.s (2H, 3-H, 4-H), 7.52 br.s (2H, 2-H, 5-H), 7.80 d and 8.22 d (4H, C_6H_4, *AA′BB′* system, J = 8.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 112.20, 119.21, 119.47, 125.39, 144.25, 144.76. Found, %: C 63.27; H 4.23; N 14.81. $C_{10}H_8N_2O_2$. Calculated, %: C 63.83; H 4.28; N 14.89.

1,1′-(Hexane-1,6-diyl)bis(1*H*-pyrrole) (Ic). Yield 6.47 g (60%) (from 6.70 g of pyrrole and 7.75 g of 1,6-dichlorohexane), bp 102–105°C (3 mm). IR spectrum, ν, cm^{-1}: 3145, 3075 (=CH), 1600, 1595 (C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20 m (4H, CH_2), 1.65 m (4H, CH_2), 3.73 t (4H, CH_2), 6.07 br.s (4H, 3-H, 4-H), 6.54 s (4H, 2-H, 5-H). Found, %: C 77.20; H 9.30; N 12.92. $C_{14}H_{20}N_2$. Calculated, %: C 77.73; H 9.32; N 12.95.

1,1′-[1,4-Phenylenebis(methylene)]bis(1*H*-pyrrole) (Id). Yield 8.12 g (69%) [from 6.70 g of pyrrole and 8.75 g of 1,4-bis(chloromethyl)benzene], mp 118–120°C; published data [11]: mp 117–118°C. IR spectrum, ν, cm^{-1}: 3110, 3090, 3050 (=CH); 2920 (CH); 1500 (C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.08 s (4H, CH_2), 6.23 s (4H, 3-H, 4-H), 6.57 s (4H, 2-H, 5-H), 6.97 s (4H, H_{arom}). Found, %: C 81.75; H 6.92; N 11.86. $C_{16}H_{16}N_2$. Calculated, %: C 81.32; H 6.82; N 11.85.

General procedure for the synthesis of (1*H*-pyrrol-2-ylsulfanyl)alkanoic acids. Substituted pyrrole **Ia**, **Ic**, or **Id**, 0.1 mol, and thiourea, 15.20 g (0.2 mol), were dissolved in 30 ml of alcohol, and a solution of 25.38 g (0.1 mol) of iodine and 16.60 g (0.1 mol) of potassium iodide in 50 ml of 50% alcohol was added in portions under argon at such a rate that the temperature did not exceed 40°C. The mixture was kept for 3 h at 30–40°C, 5.00 g (0.1 mol) of hydrazine hydrate was added, a solution of 20.00 g (0.5 mol) of sodium hydroxide in 30 ml of water and a solution of 0.12 mol of the corresponding haloalkanoic acid in 5 ml of water were slowly added, and the mixture was heated for 2 h on a boiling water bath. When the reaction was complete, the alcohol was evaporated, the precipitate was dissolved in water on heating to 50°C, the solution was treated with activated charcoal (0.5–1 h) and filtered, the filtrate was acidified with 10% hydrochloric acid until complete precipitation (pH 1–2), the mixture was kept for at least 12 h at 5°C, and the precipitate was filtered off or separated by decanting, purified by reprecipitation from 5% alkali, and dried in a vacuum desiccator over P_2O_5.

(1-Benzyl-1*H*-pyrrol-2-ylsulfanyl)acetic acid (II) was obtained using 15.72 g (0.1 mol) of 1-benzyl-1*H*-pyrrole (**Ia**), 15.22 g (0.2 mol) of thiourea, 25.38 g (0.1 mol) of iodine, 16.60 g (0.1 mol) of potassium iodide, 5.00 g (0.1 mol) of hydrazine hydrate, 20.00 g (0.5 mol) of NaOH, and 11.40 g (0.12 mol) of chloroacetic acid. Yield 16.83 g (68%), mp 88–92°C. IR spectrum, ν, cm^{-1}: 3100, 3050, 3010 (=CH); 2980, 2900 (C–H); 1700 (C=O); 1500 (C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.05 s (2H, SCH_2), 5.24 s (2H, NCH_2), 6.15 t (1H, 4-H, J = 3.1 Hz), 6.50 m (1H, 3-H, J = 1.7 Hz), 6.80 d (1H, 5-H, J = 1.7 Hz), 7.04 m and 7.25 m (5H, H_{arom}), 11.11 s (1H, OH). Found, %: C 63.25; H 5.32; N 5.62; S 13.00. $C_{13}H_{13}NO_2S$. Calculated, %: C 63.14; H 5.30; N 5.66; S 12.96.

2-(1-Benzyl-1*H*-pyrrol-2-ylsulfanyl)propionic acid (III) was obtained using 15.72 g (0.1 mol) of 1-benzy-1*H*-pyrrole (**Ia**), 15.22 g (0.2 mol) of thiourea, 25.38 g (0.1 mol) of iodine, 16.60 g (0.1 mol) of potassium iodide, 5.00 g (0.1 mol) of hydrazine hydrate, 20.00 g (0.5 mol) of sodium hydroxide, and 13.02 g (0.12 mol) of 2-chloropropionic acid. Yield 17.23 g (66%), tarry substance. IR spectrum, ν, cm^{-1}: 3010 (=CH); 2920, 2980 (C–H); 1700 (C=O); 1440, 1500, 1600 (C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 d (3H, CH_3, J = 7.1 Hz), 3.27 q (1H, SCH, J = 7.1 Hz), 5.25 d.d (2H, NCH_2, J = 5.4 Hz), 6.15 m (1H, 4-H, J = 3.7, 2.9, 1.0 Hz), 6.50 m (1H, 3-H), 6.80 m (1H, 5-H), 7.31 m and 7.08 m (5H, H_{arom}), 10.70 s (1H, OH). Found, %: C 64.30; H 5.81; N 5.34; S 12.28. $C_{14}H_{15}NO_2S$. Calculated, %: C 64.34; H 5.79; N 5.36; S 12.27.

2-(1-Benzyl-1*H*-pyrrol-2-ylsulfanyl)butanoic acid (IV) was obtained using 15.72 g (0.1 mol) of 1-benzyl-1*H*-pyrrole (**Ia**), 15.22 g (0.2 mol) of thiourea, 25.38 g (0.1 mol) of iodine, 16.60 g (0.1 mol) of potassium iodide, 5.00 g (0.1 mol) of hydrazine hydrate, 20.00 g (0.5 mol) of sodium hydroxide, and 20.04 g (0.12 mol) of 2-bromobutanoic acid. We

isolated 16.80 g of a tarry material containing 70% of compound **IV** (yield 43%). IR spectrum, ν, cm^{-1}: 3100 (=CH); 2920, 2980 (C–H); 1700 (C=O); 1500 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.91 t (3H, CH_3), 1.63 m and 1.75 m (2H, CH_2), 2.99 m (1H, SCH), 5.21 d.d (2H, NCH_2), 6.15 d (1H, 3-H), 6.50 m (1H, 4-H), 6.80 br.s (1H, 5-H), 7.31 m and 7.08 m (5H, H_{arom}), 9.4 br.s (1H, OH). Found, %: C 64.30; H 5.81; N 5.34; S 12.28. $C_{14}H_{15}NO_2S$. Calculated, %: C 64.34; H 5.79; N 5.36; S 12.27.

3-(1-Benzyl-1*H*-pyrrol-2-ylsulfanyl)propionic acid (V) was obtained using 15.72 g (0.1 mol) of 1-benzyl-1*H*-pyrrole (**Ia**), 15.22 g (0.2 mol) of thiourea, 25.38 g (0.1 mol) of iodine, 16.60 g (0.1 mol) of potassium iodide, 5.00 g (0.1 mol) of hydrazine hydrate, 20.00 g (0.5 mol) of sodium hydroxide, and 18.36 g (0.12 mol) of 3-bromopropionic acid. We isolated 15.40 g (59%) of a tarry material containing 70% of compound **V** (yield 41%). IR spectrum, ν, cm^{-1}: 3100 (=CH); 2980, 2940 (C–H); 1700 (C=O); 1500 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.19 t (2H, CH_2), 3.27 q (1H, SCH), 5.20 s (2H, NCH_2), 6.14 t (1H, 3-H), 6.53 m (1H, 4-H), 6.89 br.s (1H, 5-H), 7.10 m and 7.30 m (5H, H_{arom}), 11.35 s (1H, OH). Found, %: C 64.30; H 5.81; N 5.34; S 12.28. $C_{14}H_{15}NO_2S$. Calculated, %: C 64.34; H 5.79; N 5.36; S 12.27.

2,2′-[Hexane-1,6-diylbis(1*H*-pyrrole-1,2-diyl)]diacetic acid (VI) was obtained using 10.81 g (0.05 mol) of 1,1′-(hexane-1,6-diyl)bis(1*H*-pyrrole) (**Ic**), 15.22 g (0.2 mol) of thiourea, 25.38 g (0.1 mol) of iodine, 16.60 g (0.1 mol) of potassium iodide, 5.00 g (0.1 mol) of hydrazine hydrate, 20.00 g (0.5 mol) of sodium hydroxide, and 11.40 g (0.12 mol) of chloroacetic acid. Yield 14.46 g (73%), decomposes above 180°C. IR spectrum, ν, cm^{-1}: 2900, 2950 (C–H); 1700 (C=O); 1410, 1490 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 br.s (4H, CH_2), 1.75 br.s (4H, CH_2), 3.35 s (4H, SCH_2), 4.04 t (4H, NCH_2), 6.15 br.s (2H, 4-H), 6.47 br.s (2H, 3-H), 6.82 br.s (2H, 5-H), 10.97 s (2H, OH). Found, %: C 54.47; H 6.07; N 7.09; S 16.19. $C_{18}H_{24}N_2O_4S_2$. Calculated, %: C 54.52; H 6.10; N 7.06; S 16.17.

2,2′-[1,4-Phenylenebis(methylene-1*H*-pyrrole-1,2-diyl)]diacetic acid (VII) was obtained using 11.81 g (0.05 mol) of 1,1′-[1,4-phenylenebis(methylene)]bis(1*H*-pyrrole) (**Id**), 15.22 g (0.2 mol) of thiourea, 25.38 g (0.1 mol) of iodine, 16.60 g (0.1 mol) of potassium iodide, 5.00 g (0.1 mol) of hydrazine hydrate, 20.00 g (0.5 mol) of sodium hydroxide, and 11.40 g (0.12 mol) of chloroacetic acid. Yield 14.80 g (71%), mp 80–84°C. IR spectrum, ν, cm^{-1}: 3100 (=C–H); 2950, 2900 (C–H); 1700 (C=O); 1490 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.21 s (4H, SCH_2), 5.23 s (4H, NCH_2), 6.08 t (2H, 4-H), 6.35 br.s (2H, 3-H), 7.01 br.s (2H, 5-H), 7.03 s (4H, H_{arom}), 10.80 s (2H, OH). Found, %: C 57.68; H 4.86; N 6.77; S 15.42. $C_{20}H_{20}N_2O_4S_2$. Calculated, %: C 57.67; H 4.84; N 6.73; S 15.39.

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