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Synthesis and Properties of *N*-(2,2,2-Trichloroethyl)-2-thiophenesulfonamides

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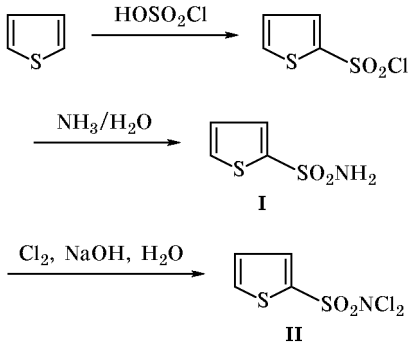
Abstract—Chlorination of 2-thiophenesulfonamide gave unstable *N*,*N*-dichloro-2-thiophenesulfonamide which was brought into reactions with 1,2-polyhaloethenes. The condensation of 2-thiophenesulfonamide with trichloroacetaldehyde afforded *N*-(2,2,2-trichloro-1-hydroxyethyl)-2-thiophenesulfonamide which reacted with benzene, toluene, 2-chlorothiophene, and phenol to form the corresponding *N*-(1-aryl-2,2,2-trichloroethyl)-2-thiophenesulfonamides. Under more severe conditions, the latter were converted into 1,1-diaryl-2,2,2-trichloroethanes. The reaction of *N*-(2,2,2-trichloro-1-hydroxyethyl)-2-thiophenesulfonamide with substituted arenes, including phenol, was regioselective: only the corresponding *para*-substituted products were obtained. Hydrolysis of *N*-[2,2,2-trichloro-1-(4-tolyl)ethyl]-2-thiophenesulfonamide yielded *N*-(2-thienylsulfonyl)-2-(4-tolyl)glycine.

Design of compounds possessing sulfonamide, polyhaloalkyl, and thienyl fragments in a single molecule is an important problem, for such derivatives are promising from the viewpoint of their biological activity due to the presence of pharmacophoric groups. Moreover, they can also be used as intermediate products in fine organic synthesis.

While continuing our systematic studies in the field of synthetic approaches to *N*-polyhaloethyl amides on the basis of the reaction of *N*,*N*-dihalo amides with polyhaloethenes [1], we have synthesized *N*,*N*-dichloro-2-thiophenesulfonamide (**II**) by chlorination of 2-thiophenesulfonamide (**I**) (Scheme 1) and examined its behavior in reactions with tri- and 1,2-dichloroethenes. 2-Thiophenesulfonamide was obtained as shown in Scheme 1 without isolation of 2-thiophenesulfonyl chloride, which considerably simplified the experimental procedure and increased the yield of **I**. The chlorination of 2-thiophenesulfonamide in aqueous alkali gave up to 70% of dichloro amide **II**.

Scheme 1.



The formation of *N*,*N*-dichloro amide **II** was confirmed by the data of IR spectroscopy and elemental analysis (see Experimental). In the IR spectrum we observed two absorption bands belonging to the sulfonyl group, while NH_2 absorption typical of 2-thiophenesulfonamide was absent.

N,*N*-Dichloro-2-thiophenesulfonamide (**II**) turned out to be unstable. It readily undergoes decomposition in 20 h at room temperature or instantaneously on heating with formation of tar-like compounds of unknown composition. For that reason we failed to synthesize *N*-(2-polychloroethylidene)-2-thiophenesulfonamides and their derivatives via reaction of **II** with trichloroethylene and 1,2-dichloroethenes. No reaction occurred in the cold, whereas heating of the reaction mixture resulted in tarring.

With the goal of developing synthetic approaches to *N*-(trichloroethyl)thiophenesulfonamides we were the first to effect condensation of 2-thiophenesulfonamide with trichloroacetaldehyde. As a result, we obtained *N*-(2,2,2-trichloro-1-hydroxyethyl)-2-thio-

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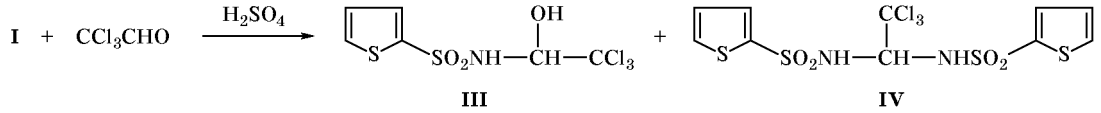
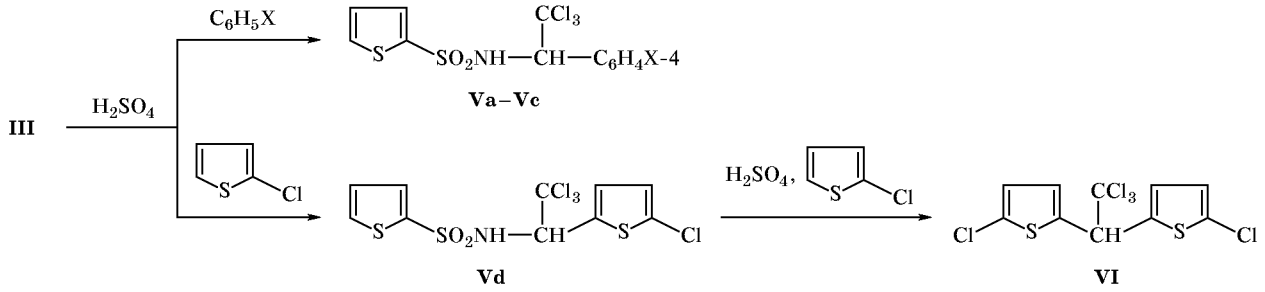
Scheme 2.



III **IV**

Scheme 3.



Va–Vc **Vd** **VI**

X = H (**a**), CH_3 (**b**), OH (**c**).

phenesulfonamide (**III**) which was then brought into reactions with aromatic and heteroaromatic substrates. We have found that 2-thiophenesulfonamide reacts with trichloroacetaldehyde in the presence of a catalytic amount of sulfuric acid. The use of a large amount of sulfuric acid, as well as prolonging the reaction over 3 h and overheating of the reaction mixture, favors formation of 1,1,1-trichloro-2,2-bis-(2-thienylsulfonylamino)ethane (**IV**) as by-product (Scheme 2).

By analogy with *N*-(1-hydroxy-2-polychloroethyl)-arenesulfonamides [2], amide **III** readily reacts under similar conditions with benzene, toluene, phenol, and 2-chlorothiophene, yielding the corresponding substituted arenes **Va**–**Vc**. In the reaction with toluene, the substitution occurs in a regioselective fashion, at the *para* position of the benzene ring. Likewise, the C-amidoalkylation of 2-chlorothiophene afforded the corresponding 5-substituted derivative (Scheme 3).

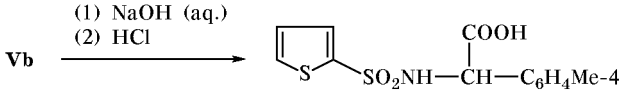
Increase of the reaction time, e.g., in the C-amidoalkylation of 2-chlorothiophene, leads to formation of 1,1,1-trichloro-2,2-bis(2-chlorothienyl)ethane (**VI**). This result indicates that amides **V** are capable of alkylating arenes and that the thiophenesulfonamide fragment is a departing group in this process. We can also state that the 2-thienylsulfonylamino group is a better nucleofuge than arylsulfonylamino, for analogous derivatives of benzenesulfonic acids do not give rise to 1,1-diaryl-2,2,2-trichloroethanes under similar conditions [2, 3].

The structure of compounds **III**–**VI** was determined by IR and ^{1}H NMR spectroscopy and elemental analysis. The IR spectra of thiophenesulfonamides **III**–**V** contain absorption bands due to vibrations of the SO_2 and NH groups, which are absent in the spectrum of **VI**. Amide **III** also showed in the IR spectrum absorption of the hydroxy group.

The –NH–CH– fragment in compounds **III**–**V** gives two characteristic doublets in the ^{1}H NMR spectra. In addition, the spectra of **III**–**VI** contain signals from the thiophene ring protons, amides **Va** and **Vb** display signals from the benzene ring protons, and a singlet from the CH proton is observed in the spectrum of **VI**. The relative intensities of the above signals are consistent with the assigned structures.

We previously showed [4] that *N*-(2,2,2-trichloroethyl)arenesulfonamides can be used in the synthesis of *N*-sulfonyl-α-arylglycines. We have found that compounds like **V** can also be involved in analogous syntheses. Alkaline hydrolysis of amide **Vb** afforded *N*-(2-thienylsulfonyl)-2-(4-tolyl)glycine sodium salt which was treated with hydrochloric acid to isolate amino acid **VII** in 35% yield (Scheme 4).

Scheme 4.



VII

In the IR spectrum of **VII** absorption bands belonging to the COOH, OH, NH, and SO_2 groups were present. Its ^{1}H NMR spectrum contained signals from protons of the *para*-substituted benzene ring, thiophene ring, and NCH group; signals from the NH

and OH protons were not observed due to fast H–D exchange.

Compounds **III**–**VII** are crystalline substances, which are soluble in acetone, dimethyl sulfoxide, and aqueous alkali and insoluble in water.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 MHz) from 5–10% solutions in deuterated solvents; hexamethyldisiloxane was added as internal reference. The IR spectra were obtained on a Specord 75IR spectrometer from samples pelleted with KBr.

2-Thiophenesulfonamide (I). Thiophene, 8 ml (0.1 mol), was added dropwise over a period of 1 h under vigorous stirring and cooling to a mixture of 39.88 ml (0.6 mol) of chlorosulfonic acid and 40 ml of carbon tetrachloride. The rate of addition was controlled in such a way that the temperature did not exceed –5°C. The mixture was diluted with 20 ml of carbon tetrachloride, stirred for 10–15 min, and poured onto ice. The organic phase was separated, the aqueous phase was extracted with carbon tetrachloride (3 × 10 ml), the extracts were combined with the organic phase and evaporated under reduced pressure, the tarry residue was mixed with 50 ml of 20% aqueous ammonia, and the mixture was left to stand for 20 h on exposure to air. The mixture was then neutralized to pH 6.5 with 10% hydrochloric acid and kept for 2–3 h, and the precipitate of amide **I** was filtered off and purified by reprecipitation from 10% aqueous ammonia, followed by recrystallization from ethanol–chloroform (1 : 3). Yield 13.53 g (83%), mp 141–142°C [5]. IR spectrum, ν, cm^{-1}: 1160, 1320 (SO_2); 1560 ($C{=}C_{arom}$); 3090–3105 ($C{-}H_{arom}$); 3240, 3310 (NH_2).

***N*,*N*-Dichloro-2-thiophenesulfonamide (II).** Amide **I**, 1.63 g (0.01 mol), was added in small portions under stirring to a solution of 0.80 g (0.02 mol) of sodium hydroxide in 15 ml of water. The solution was filtered, and gaseous chlorine was passed through the filtrate, maintaining the temperature below 10°C, until a solid no longer precipitated. The product was filtered off, washed with cold water until a negative test for chloride ion in the washings, and dried over P_2O_5 under reduced pressure. Yield 1.62 g (70%), decomposes above 30°C. IR spectrum, ν, cm^{-1}: 1160, 1370 (SO_2); 3100, 3110 ($C{-}H_{arom}$). Found, %: C 24.33; H 1.52; Cl 18.51; N 7.23; S 32.48. $C_4H_3Cl_2NO_2S_2$. Calculated, %: C 24.43; H 1.54; Cl 18.03; N 7.12; S 32.61.

***N*-(2,2,2-Trichloroethyl-1-hydroxy)-2-thiophenesulfonamide (III).** A mixture of 1.47 g (0.01 mol) of trichloroacetaldehyde, 1.63 g (0.01 mol) of 2-thiophenesulfonamide, and one drop of concentrated sulfuric acid was heated under thorough stirring until it melted. It was then heated for 20 min at 60–70°C and repeatedly washed with water, and the residue was dried in air. Yield 3.04 g (98%), mp 124–126°C. IR spectrum, ν, cm^{-1}: 1160, 1340 (SO_2); 2850–2950 ($C{-}H_{aliph}$); 3080–3105 ($C{-}H_{arom}$); 3200 (NH), 3470 br (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.22 d (1H, CH, J = 8.8 Hz); 7.17 t, 7.68 d, and 7.92 d (3H, 2-thienyl); 7.95 br.s (1H, OH); 9.16 d (1H, NH, J = 8.8 Hz). Found, %: C 23.36; H 1.72; Cl 35.18; N 4.43; S 20.48. $C_6H_6Cl_3NO_3S_2$. Calculated, %: C 23.20; H 1.95; Cl 34.24; N 4.51; S 20.64.

1,1,1-Trichloro-2,2-bis(2-thienylsulfonylamino)-ethane (IV). A mixture of 1.47 g (0.01 mol) of trichloroacetaldehyde, 1.63 g (0.01 mol) of 2-thiophenesulfonamide, 5 ml of dry benzene, and 2 ml of concentrated sulfuric acid was heated for 30 min at 80°C. The mixture was evaporated under reduced pressure, and the solid residue was repeatedly washed with water and dried. According to the ^{1}H NMR data, the product was a mixture of amides **III** and **IV** at a ratio of 2.5 : 1; the calculated yield of **IV** was 1.17 g (50%). ^{1}H NMR spectrum of **IV** (DMSO-d_6), δ, ppm: 5.65 t (1H, CH); 7.08 t, 7.58 d, and 7.83 d (6H, 2-thienyl); 9.53 d (2H, NH, J = 9.2 Hz).

***N*-(2,2,2-Trichloro-1-phenylethyl)-2-thiophenesulfonamide (Va).** A mixture of 3.11 g (0.01 mol) of amide **III**, 8 ml of benzene, and 1 ml of concentrated sulfuric acid was vigorously stirred for 4 h at room temperature. Excess benzene was removed under reduced pressure, and the residue was washed first with 10 ml of 5% aqueous ammonia and then with water until neutral washings. Yield 3.30 g (90%), mp 142–143°C. IR spectrum, ν, cm^{-1}: 1160, 1330 (SO_2); 2940–2960 ($C{-}H_{aliph}$); 3080–3095 ($C{-}H_{arom}$); 3260 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.30 d (1H, CH, J = 10.2 Hz); 6.84 t, 7.32 d, and 7.56 d (3H, 2-thienyl); 7.25 m and 7.60 m (5H, Ph); 9.11 d (1H, NH, J = 10.2 Hz). Found, %: C 38.56; H 2.74; Cl 28.37; N 3.58; S 17.43. $C_{12}H_{10}Cl_3NO_2S_2$. Calculated, %: C 38.88; H 2.72; Cl 28.69; N 3.78; S 17.30.

***N*-[2,2,2-Trichloro-1-(4-tolyl)ethyl]-2-thiophenesulfonamide (Vb)** was synthesized as described above for compound **Va** from 3.11 g (0.01 mol) of amide **III** and 8 ml of toluene. Yield 3.71 g (96%), mp 149–150°C. IR spectrum, ν, cm^{-1}: 1160, 1340 (SO_2); 2900–2980 ($C{-}H_{aliph}$); 3060–3100 ($C{-}H_{arom}$); 3250 br (NH). ^{1}H NMR spectrum (DMSO-d_6), δ,

ppm: 2.22 s (3H, Me); 5.18 d (1H, CH, J = 10.4 Hz); 6.85 t, 7.32 d, and 7.67 d (3H, 2-thienyl); 7.01 and 7.40 (4H, C_6H_4 *AA′BB′* system); 9.37 d (1H, NH). Found, %: C 40.51; H 3.22; Cl 27.37; N 3.68; S 16.54. $C_{13}H_{12}Cl_3NO_2S_2$. Calculated, %: C 40.59; H 3.14; Cl 27.65; N 3.64; S 16.67.

***N*-[2,2,2-Trichloro-1-(4-hydroxyphenyl)ethyl]-2-thiophenesulfonamide (Vc).** A mixture of 3.11 g (0.01 mol) of amide **III**, 1.88 g (0.02 mol) of phenol, 10 ml of carbon tetrachloride, and 0.5 ml of concentrated sulfuric acid was stirred for 3 h. The precipitate was filtered off and washed first with 20 ml of carbon tetrachloride and then repeatedly with water until neutral washings. Yield 3.02 g (78%), mp 194–196°C. IR spectrum, ν, cm^{-1}: 1170, 1345 (SO_2); 2930–2960 ($C-H_{aliph}$); 3080–3100 ($C-H_{arom}$); 3280 (NH); 3430 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.04 d (1H, CH, J = 10.5 Hz); 6.83 t, 7.29 d, and 7.61 d (3H, 2-thienyl); 6.53 and 7.25 (4H, C_6H_4, *AA′BB′* system); 9.23 d (1H, NH). Found, %: C 37.33; H 2.65; Cl 27.41; N 3.72; S 16.43. $C_{12}H_{10}Cl_3NO_3S_2$. Calculated, %: C 37.27; H 2.61; Cl 27.50; N 3.62; S 16.58.

***N*-[2,2,2-Trichloro-1-(5-chloro-2-thienyl)ethyl]-2-thiophenesulfonamide (Vd)** was synthesized as described above for compound **Va** from 3.11 g (0.01 mol) of amide **III** and 4.60 ml (0.05 mol) of 2-chlorothiophene (reaction time 3 h). Yield 2.96 g (72%), mp 112–116°C. IR spectrum, ν, cm^{-1}: 1170, 1350 (SO_2); 2950 ($C-H_{aliph}$); 3240 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.55 d (1H, CH, J = 10.0 Hz); 7.11 t, 7.50 d, and 7.81 d (3H, 2-thienyl); 6.86 and 7.01 (2H, 5-chloro-2-thienyl); 9.51 d (1H, NH, J = 10.0 Hz). Found, %: C 29.31; H 1.75; Cl 34.31; N 3.51; S 23.49. $C_{10}H_7Cl_4NO_2S_3$. Calculated, %: C 29.21; H 1.72; Cl 34.49; N 3.41; S 23.39.

1,1,1-Trichloro-2,2-bis(5-chloro-2-thienyl)ethane (VI). Following the above procedure, a mixture of 3.11 g (0.01 mol) of amide **III**, 4.60 ml (0.05 mol) of 2-chlorothiophene, and 1 ml of concentrated sulfuric acid was stirred for 6 h. The solution was evaporated under reduced pressure, and the residue was washed first with 30 ml of 10% aqueous ammonia and then with water until neutral washings. According to the ^1H NMR data, the product was a mixture of amides **Vd** and **VI** at a ratio of 1.7 : 1; calculated yield of **VI** 1.30 g (35%). ^1H NMR spectrum of **VI** (DMSO-d_6), δ, ppm: 6.30 s (1H, CH); 7.07 d and 7.23 d (4H, 5-chloro-2-thienyl).

***N*-(2-Thienylsulfonyl)-2-(4-tolyl)glycine (VII)**. A mixture of 1.92 g (0.005 mol) of amide **Vb**, 0.80 g (0.02 mol) of NaOH, and 50 ml of water was stirred for 3 h at the boiling point. The mixture was filtered while hot, the filtrate was cooled to room temperature, and 10% hydrochloric acid was added dropwise until a solid no longer precipitated. The mixture was kept for 2 h, and the precipitate was filtered off, washed with water until neutral washings, and dried. Yield 0.54 g (35%), mp 48–55°C (from acetone–chloroform, 1 : 3). IR spectrum, ν, cm^{-1}: 1170, 1350 (SO_2); 1700 (C=O); 3080–3100 ($C-H_{arom}$); 3220 br (NH); 3450 br (OH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (3H, Me); 4.08 s (1H, CH); 7.04 t, 7.63 d, and 7.82 d (3H, 2-thienyl); 7.05 and 7.20 (4H, C_6H_4, *AA′BB′* system). Found, %: C 37.33; H 2.65; Cl 27.41; N 3.72; S 16.43. $C_{12}H_{10}Cl_3NO_3S_2$. Calculated, %: C 37.27; H 2.61; Cl 27.50; N 3.62; S 16.58.

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