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LETTERS TO THE EDITOR

Reaction of Amides of Sulfanyl, Thio-, and Carbonic Acids with Tropylium Salts

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Abstract—By the reaction of urea, thiourea, sulfanilamide or sulfadimethoxine with tropylium tetrafluoroborate new products of substitution of hydrogen atom by the tropylium motif at the amide nitrogen atom or at the amino group of the benzene ring have been obtained.

Keywords: urea, thiourea, 4-aminobenzenesulfonamide, 4-amino-*N*-(2,6-dimethoxy-4-pyrimidinyl)benzenesulfonamide, tropylium tetrafluoroborate

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Sulfanilamide and its derivatives, as well as urea and thiourea belong to the group of antimicrobial drugs [1–5]. In view of resistance of microorganisms with respect to drugs, trans-formation of molecules of the known antimicrobial compounds is a state-of-the-art problem [6].

Earlier by the reaction of aniline with tropylium perchlorate 4-(7-cyclohepta-1,3,5-trienyl)aniline was obtained [7], which upon further tropylation with tropylium perchlorate [8] or tetrafluoroborate [9] gave 4-(7-cyclohepta-1,3,5-trienyl)-*N*-(1-cyclohepta-2,4,6-trienyl)aniline. The latter product contains two tropylium moieties resulting from substitution of hydrogen atoms in the *para*-position of the benzene ring and in the amino group. Both compounds possess a pronounced antibacterial activity with respect to *Staphylococcus aureus 906* and antimicotic activity with respect to *Candida albicans*, the compound with two tropylium rings having a higher activity with respect to *Staphylococcus aureus 906* [8]. Based on the above, it is presumable that to impart new pharmacological properties to compounds having amino group in the molecule tropylium salts containing a 1,3,5-cycloheptatriene ring are quite suitable.

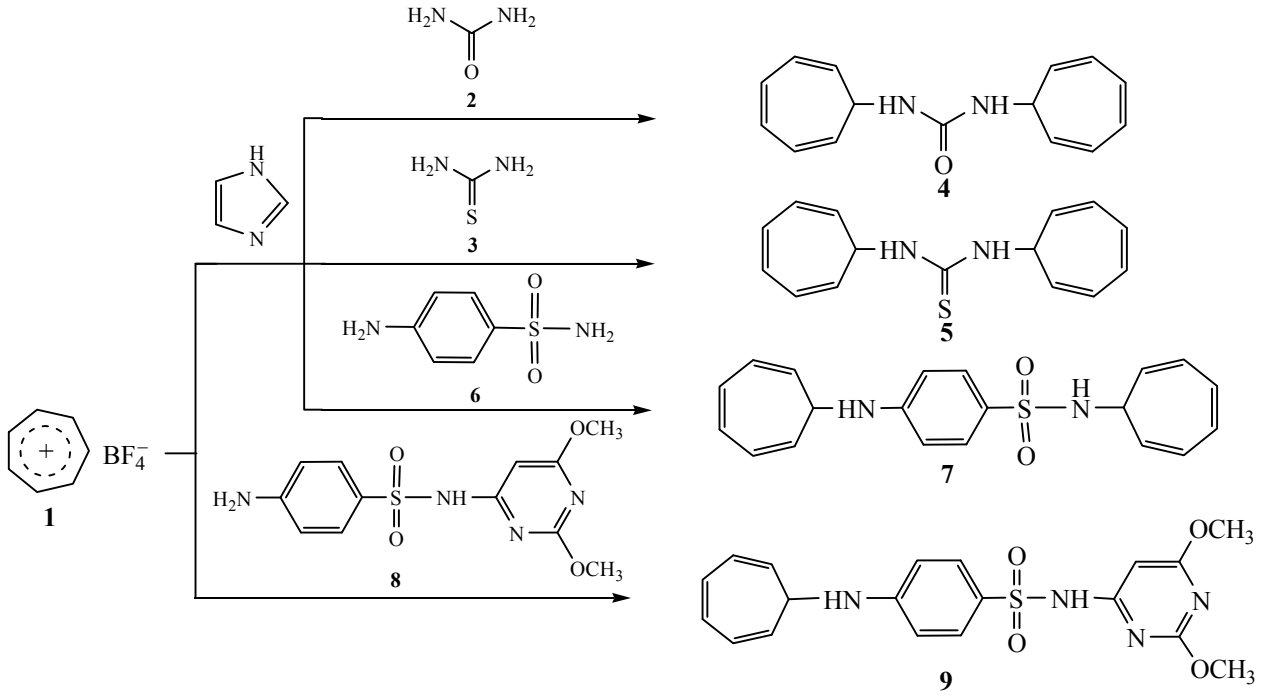
The goal of this work was to expand the tropylation reaction to the group of well known antimicrobial compounds: full amides of carbonic and thiocarbonic acids (urea and thiourea), and 4-aminobenzenesulfamide (sulfanilamidum), containing free or substituted amide groups, which may be of interest for the design of new biologically active compounds in view of the problem of microbial resistance.

The reaction of tropylium tetrafluoroborate **1** with urea **2** or thiourea **3** in 2 : 1 ratio in the presence of imidazole in aqueous medium was found to proceed as substitution of hydrogen atoms in two amide groups by tropylium rings. *N,N'*-Di(cyclohepta-2,4,6-trien-1-yl)-urea **4** and *N,N'*-di(cyclohepta-2,4,6-trien-1-yl)thiourea **5** have been synthesized.

Unlike compounds **2** and **3**, the molecule of 4-aminobenzenesulfonamide **6** (sulfanilamide) contains the sulfonamide group SO_2NH_2 and the amino group in the *para*-position of the benzene ring. Both amino groups were shown to be active in the studied reaction. As a result, the reaction carried out in the same conditions gave the product of substitution in both amino groups, *N*-(cyclohepta-2,4,6-trien-1-yl)-4-(cyclohepta-2',4',6'-trien-1-ylamino)benzenesulfonamide **7** (Scheme 1).

For comparison, we have also studied a related drug, sulfadimethoxine [4-amino-*N*-(2,6-dimethoxy-4-pyrimidinyl)benzenesulfonamide] **8** containing a secondary sulfonamide group and a primary amino group in the aromatic ring. It was found that the reaction of compound **8** with tropylium tetrafluoroborate **1** in 1 : 1 ratio in DMSO solution affords the

Scheme 1.



product of substitution in the amino group, 4-(cyclohepta-2,4,6-trien-1-ylamino)-*N*-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide **9**.

Therefore, the hydrogen atom of the amide groups of urea, thiourea and the amide group of sulfanilamide is readily replaced by biogenic tropylium fragment. Besides, in sulfanilamide and sulfadimethoxine, substitution of hydrogen in the amino groups of the benzene ring also takes place.

***N,N'*-Di(cyclohepta-2,4,6-trien-1-yl)urea (4).** To a solution of 0.115 g (0.6 mmol) of tropylium tetrafluoroborate **1** in 5 mL of water 0.04 g (0.6 mmol) of imidazole was added with stirring till the solution became transparent. Then in one portion 0.019 g (0.3 mmol) of urea **2** was added. The reaction mixture was stirred for 1 h at room temperature, the precipitate was filtered off, washed with water, and treated with 10% solution of ammonium hydroxide to pH 7. Yield 0.045 g (64%), mp 174–175°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 3.57 d.t (2H, $C^1H + C^{1'}H$, C_7H_7, J = 8.0, 5.2, 1.4 Hz), 5.30 d.d (4H, C^2H, $C^7H + C^{2'}H$, $C^{7'}H$, C_7H_7, J = 9.1, 5.2 Hz), 6.13 q.d (4H, C^3H, $C^6H + C^{3'}H$, $C^{6'}H$, C_7H_7, J = 9.2, 3.9, 2.6, 1.4 Hz), 6.46 d (2H, NH, J = 7.6 Hz), 6.61–6.72 m (4H, C^4H, $C^5H + C^{4'}H$, $C^{5'}H$, C_7H_7). Mass spectrum, *m/z*: 241.1333 $[M + H]^+$ (calculated for $C_{15}H_{16}N_2O$: 241.1335.

***N,N'*-Di-(cyclohepta-2,4,6-trien-1-yl)thiourea (5)** was prepared similarly from 0.115 g (0.6 mmol) of tropylium tetrafluoroborate **1**, 0.04 g (0.6 mmol) of imidazole and 24.5 mg (0.3 mmol) of thiourea **4**. Yield 0.03 g (38%), mp 107–108°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 4.34 q (2H, $C^1H + C^{1'}H$, C_7H_7, J = 6.1 Hz), 5.38 t.d (4H, C^2H, $C^7H + C^{2'}H$, $C^{7'}H$, C_7H_7, J = 10.0, 5.3, 0.8 Hz), 6.19 q.d (4H, C^3H, $C^6H + C^{3'}H$, $C^{6'}H$, C_7H_7, J = 9.2, 3.9, 2.6, 1.3 Hz), 6.66 d.d (4H, C^4H, $C^5H + C^{4'}H$, $C^{5'}H$, C_7H_7, J = 3.8, 2.7 Hz), 7.80 d (2H, 2NH, J = 7.4 Hz). Mass spectrum, *m/z*: 257.1107 $[M + H]^+$ (calculated for $C_{15}H_{16}N_2S$: 257.1107).

***N*-(Cyclohepta-2,4,6-trien-1-yl)-4-(cyclohepta-2',4',6'-trien-1-ylamino)benzenesulfonamide (7).** To a solution of 0.089 g (0.5 mmol) of tropylium tetrafluoroborate **1** in 5 mL of water 0.034 g (0.5 mmol) of imidazole, and then in one portion 0.043 g (0.25 mmol) of sulfanilamide **6** was added, the reaction mixture was stirred for 2 h at room temperature. After 0.5 h light-yellow precipitate was filtered off, washed with water, and treated with 10% solution of ammonium hydroxide to pH 7. Yield 0.06 g (68%), mp 134–136°C [EtOH–C_6H_{14}, 1 : 1]. ^{1}H NMR spectrum, δ, ppm: 2.75–2.83 m (1H, C^1H, C_7H_7), 3.14–3.22 m (1H, $C^{1'}H$, C_7H_7), 5.17 d.d (2H, C^2H, C^7H, C_7H_7, J = 9.3, 4.7 Hz), 5.39 d.d (2H, $C^{2'}H + C^{7'}H$, C_7H_7, J = 9.3, 4.8 Hz), 6.03 d (2H, $C^3H + C^6H$, C_7H_7, J = 9.0 Hz),

6.26 d (2H, $C^{3'}H + C^{6'}H$, C_7H_7, J = 7.7 Hz), 6.55 d (2H, C_6H_4, J = 8.8 Hz), 6.61 t (2H, $C^4H + C^5H$, C_7H_7, J = 3.2 Hz), 6.76 t (2H, $C^{4'}H + C^{5'}H$, C_7H_7, J = 3.1 Hz), 7.11 d (1H, NHC_7H_7, J = 5.8 Hz), 7.44 d (2H, C_6H_4, J = 8.8 Hz), 8.00 d (1H, $NHSO_2$, J = 6.8 Hz). Mass spectrum, *m/z*: 375.1136 $[M + Na]^+$ (calculated for $C_{20}H_{20}N_2NaO_2S$: 375.1138).

4-(Cyclohepta-2,4,6-trien-1-ylamino)-*N*-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide 9. To 0.15 g (0.50 mmol) of compound **8** dissolved in 3 mL of DMSO at heating 0.1 g (0.55 mmol) of tropylium tetrafluoroborate **1** was added, the reaction mixture was stirred for 1.5 h at room temperature, then 10% solution of NH_4OH was added till alkaline reaction of the solution. After 24 h the mixture was diluted with excess of water, the formed light-yellow precipitate was separated and dried. Yield 0.14 g (74%), mp 193–194°C (DMSO). ^{1}H NMR spectrum, δ, ppm: 3.12 t.t (1H, C^1H, C_7H_7, J = 5.1, 1.6 Hz), 3.71 s (3H, OCH_3), 3.84 s (3H, OCH_3), 5.13 d.d (2H, $C^2H + C^7H$, C_7H_7, J = 8.8, 5.0 Hz), 5.91–5.94 m (2H, CH_{Het} + NH), 6.13 q.d (2H, $C^4H + C^5H$, C_7H_7, J = 8.9, 3.8, 2.6, 1.5 Hz), 6.58 d (2H, C_6H_4, J = 8.8 Hz), 6.62–6.69 m (2H, $C^3H + C^6H$, C_7H_7), 7.57 d (2H, C_6H_4, J = 8.8 Hz), 10.41 s (1H, $NHSO_2$). Mass spectrum, *m/z*: 401.1275 $[M + H]^+$ (calculated for $C_{19}H_{20}N_4O_4S$: 401.1278).

^{1}H NMR spectra were registered on a Mercury 400 spectrometer (400 MHz) in DMSO-d_6, internal reference HMDS. Mass spectra were recorded on a maXis Impact HD Bruker Daltonik GmbH mass spectrometer.

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