N-SUBSTITUTED 4-ISOTHIOCYANATOPHENYLSULFONAMIDES

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The synthesis of seven isothiocyanatophenylsulfonamides, which are used as chemotherapeutics, is described.

Schultz and Gauri[1] described the synthesis of therapeutics containing NCS group. In their work they started from known bacteriocidic and fungicidic effects of isothiocyanates towards various bacteria and fungi.

We now report on the synthesis of several other N-substituted 4-isothiocyanatophenylsulfonamides from amines with known bacteriostatic effects. Of the compounds of this group, the following derivatives were already synthesised: 4-isothiocyanatophenylsulfonamide (*I*) by thiophosgene[2] and dithiocarbamate[3] method (decomposition was effected with mercuric chloride), N-acetyl derivative (*II*) and 2-thiazolyl derivative (*III*) by thiophosgene method[2]. The results of microbiological studies of derivative *I* have been reported in literature[4].

Starting compounds for preparing the isothiocyanates were corresponding amines or amine hydrochlorides. Their thiophosgenation was effected both by the known procedure[2] (method A, derivatives *I*—*III*), and by the method worked out in this laboratory (see Experimental, method B). As follows from Table I in our hands the method A did not afford so high yields as reported[2], which led us to seek for another method of their synthesis for comparative purposes (method B). Derivatives *I*—*III* (method A) were obtained in analytical purity grade only after their threefold crystallization, which markedly reduced their final yields. For preparing derivatives *IV*—*VII* we used only method B, since it afforded higher yields also in the case of derivatives *I*—*III*. All the isothiocyanates were crystallized from mixed solvents (ethyl acetate–chloroform, acetone–water).

The structure of prepared substances was confirmed by elemental analysis, infrared and ultraviolet spectroscopy. The infrared spectra of these compounds show medium bands at 945 ± 3 cm^{-1} which correspond to ν_s(NCS) and characteristic complex band in the 2200—2000 cm^{-1} region, assigned to ν_{as}(NCS). The bands corresponding to ν_s(SO) and ν_{as}(SO) occur in the 1182—1149 cm^{-1} region and the 1359—1305 cm^{-1} region, respectively, the former ones being more intense than the latter. The ultraviolet spectra exhibit two absorption bands, λ_1 217—229 nm and λ_2 278—301 nm; with derivatives *I*, *III*, and *IV*, two maxima of equal intensity occur in the 278—301 nm region (Table I). The intensity of the above absorption bands indicates that they correspond to $\pi \rightarrow \pi^*$ transitions of respective conjugated systems.

TABLE I
Properties of $RNHSO_2C_6H_4NCS$

R	Formula (m.w.)	Yield, % (method)	M.p.[a], °C	Calc./Found % N	Calc./Found % S	$\lambda_{1\,max}$, nm (log ε)	$\lambda_{2\,max}$, nm (log ε)
H, *I*	$C_7H_6N_2O_2S_2$ (214·3)	46 (A)[b] 63 (B)	212–214	13·07 12·83	29·92 29·65	229 (4·47)	278[c] (4·31)
N-Acetyl, *II*	$C_9H_8N_2O_3S_2$ (256·3)	35 (A)[d] 52 (B)	156–159	10·92 10·66	25·02 25·33	220 (4·42)	295 (4·56)
2-Thiazolyl, *III*	$C_{10}H_7N_3O_2S_3$ (297·4)	35 (A)[e] 49 (B)	239–242	14·13 14·12	32·35 32·27	220 (4·37)	282[f] (4·45)
3-(6-Methoxy)pyridazinyl, *IV*	$C_{12}H_{10}N_4O_3S_2$ (319·4)	52 (B)	142–145[g]	17·54 17·34	20·07 19·65	224 (4·65)	291 (4·47)
5-(3,4-Dimethyl)isoxazoyl, *V*	$C_{12}H_{11}N_3O_3S_2$ (309·4)	77 (B)	149–151	13·58 13·82	20·72 20·30	217 (4·33)	295 (4·53)
2-(5-Methoxy)pyrimidinyl, *VI*	$C_{13}H_{11}N_3O_3S_2$ (321·4)	49 (B)	208–210[g]	13·07 13·19	19·96 20·04	225 (4·61)	286[h] (4·43)
2-(4,6-Dimethyl)pyrimidinyl,	$C_{13}H_{12}N_4O_2S_2$ (320·4)	58 (B)	182–185[g]	17·49 17·56	20·02 20·11	222 (4·49)	296 (4·56)

[a] Crystallized from acetone–water; [b] ref.[2] records 89% yield and m.p. 212–214°C (dec.); [c] λ_{max}, nm (log ε) 290 (4·33); [d] ref.[2] records 88% yield and m.p. 156–159°C; [e] ref.[2] records 98% yield and m.p. 239–242 °C (dec.); [f] $\lambda_{2,max}$, nm (log ε) 301 (4·48); [g] crystallized from ethyl acetate–chloroform; [h] $\lambda_{2,max}$, nm (log ε) 295 (4·45).

EXPERIMENTAL

Diprone, sulfathiazole, sulfisoxazole, sulfametoxydine, and sulfamidine were commercial products. N-acetyl-4-aminophenylsulfonamide was prepared by reported procedure[5,6]. Melting points were determined with Kofler hot stage microscope. Analytical samples were dried in Abderhalden apparatus. The infrared spectra were recorded on a double-beam Zeiss, Model UR 20, spectrophotometer (Jena), using KBr pellets (2 mg compound per 1 g KBr). The ultraviolet spectra were recorded on Specord UV–VIS Zeiss instrument, using $2 . 10^{-5}$M methanolic solutions of the compounds placed in 10 mm thick cells.

Synthesis of N-Substituted 4-Isothiocyanatophenylsulfonamides

A) To an efficiently stirred solution of appropriate N-substituted 4-aminophenylsulfonamide (0·12 mol, 150 ml H_2O and 50 ml conc. HCl), thiophosgene (0·12 mol) was added in one portion and the stirring was continued until the red colour of thiophosgene dissapeared and white crystals of the isothiocyanate began to precipitate (2—4 h). Then the product was filtered with suction, washed with water and crystallized from appropriate solvent.

B) To a stirred suspension of 0·105 mol of thiophosgene, 50 ml of chloroform and 10 ml of water, an aqueous solution of appropriate amine hydrochloride was added over a period of 20 min, together with such an amount of calcium carbonate which ensured that after the addition of the amine hydrochloride the reaction mixture was neutral. The stirring was continued for another 6 h and then the chloroform layer was separated, washed successively with dilute hydrochloric acid and water, dried over sodium sulphate and evaporated *in vacuo*. The residue was then crystallized from appropriate solvent.

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