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Synthesis of Sufamides of Indole Series

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Abstract—The reaction of indoles with chlorosulfonyl isocyanate yields indolylcarbonylsulfamoyl chlorides. Their reaction with amines afforded a series of indole-containing sulfamides.

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Compounds containing a fragment N–SO_2–N exhibit antiviral action [1], inhibit phosphodiesterase [2], are antagonists of dopamine D2 [3] and leucotriene [4].

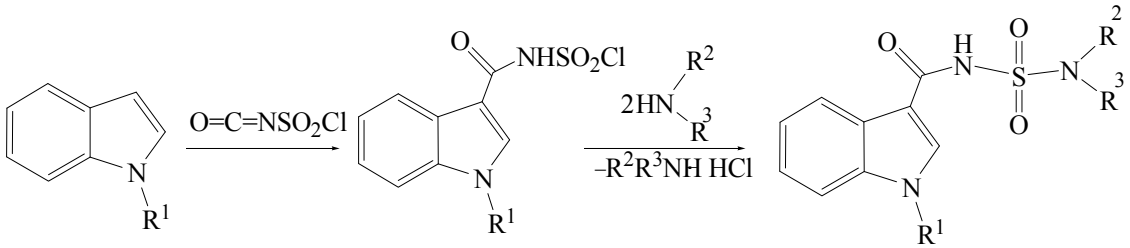
The high biological activity of indole derivatives is due to the fact that the indole bicycle belongs to important privileged structures [5]. This is evidently related to the molecular recognition of the exogenous compounds of the indole series since many endogenous substances, for instance, serotonin (a most important neuromediator) contain an indole fragment [6].

We investigated the possibility to prepare the indole derivatives containing an N–SO_2–N moiety. To this end a reaction was applied between indoles and a chlorosulfonyl isocyanate (CSI). The acylation of indoles **Ia** and **Ib** with the chlorosulfonyl isocyanate occurs at the position *3* leading to the formation of sulfonyl chlorides **IIa** and **IIb (**Scheme 1).

Compound **IIa** was described as an unstable intermediate in the preparation of a nitrile and an amide of indole-3-carboxylic acid [7, 8]. Substance **IIb** was obtained by us for the first time. It turned out that both compounds were relatively stable and could be stored in a refrigerator for about a month. However we failed to obtain their NMR spectra due to a low solubility in $CDCl_3$ and a high chemical activity toward the other solvents. The reaction of sulfamoyl chlorides **IIa** and **IIb** with amines occurs through a nucleophilic substitution of chlorine and results in the formation of sulfamides of the indole series **IIIa–IIIj** (Scheme 1) proving the structure of the initial compounds.

In the ^{1}H NMR spectra of compounds **IIIa–IIIj** proton signals appear of both indole and amine fragments. In the IR spectra peaks characteristic of NH group were present in the region 3407– 3060 cm^{-1}, and the peaks of carbonyl group, in the range 1687–1627 7 cm^{-1}.

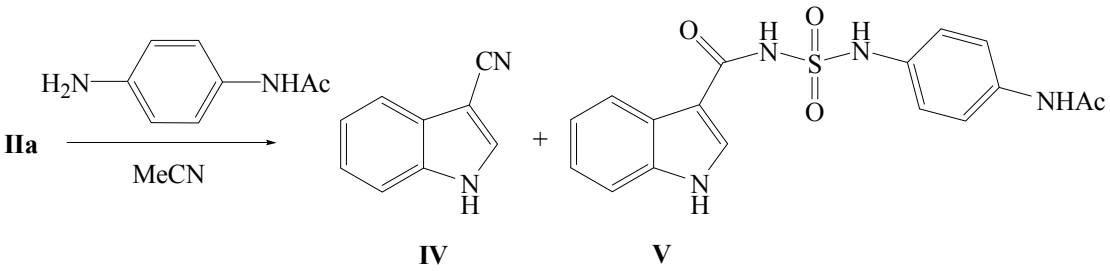
Scheme 1.



Ia, Ib **IIa, IIb** **IIIa–IIIj**

I, II, R^1 = H (**a**), Me (**b**); **III**, R^1 = Me, R^2 = H, R^3 = 1,3-thiazol-2-yl (**a**); R^1 = R^2 = H: R^3 = 4-FC_6H_4 (**b**), cyclohexyl (**c**), 4-ClC_6H_4 (**d**); R^1 = H.

Scheme 2.



IV **V**

With some strongly basic amines the reaction occurs not along Scheme 1. Carbonylsulfamoyl chloride **IIa** with an *N*-(4-aminophenyl)acetamide furnished a mixture of compounds **IV** and **V** (Scheme 2).

The IR spectrum of the mixture of compounds **IV** and **V** contained peaks of groups NH (3367 and 3233 cm^{-1}), C≡N (2227 cm^{-1}), C=O (1660 cm^{-1}). In the ^1H NMR spectrum the protons signal of NH groups of compound **V** was observed in the region 12.0 ppm, that of compound **IV**, in the region 11.6 ppm. The ratio of compounds **IV** and **V** was 1:2. The signals of nitrile **IV** were identified by superimposing with the spectrum of the mixture the spectrum of the pure compound **IV** prepared by an independent procedure [7].

Chloride **IIa** in reaction with imidazole did not undergo the nucleophilic substitution but formed only the known nitrile of indole-3-carboxylic acid (**IV**) identified by the NMR spectrum and melting point [7].

Thus based on the reaction of 1*H*-indol-3-ylcarbonylsulfamoyl chlorides with amines a wide range of indole-containing sulfamides can be obtained promising for the screening of their biological action.

EXPERIMENTAL

^1H NMR spectra were registered on a spectrometer Varian Unity 300 from solutions in DMSO-d_6. IR spectra were recorded on a spectrophotometer Specord 75-IR from mulls in mineral oil. The data of elemental analyses of the synthesized compounds are in agreement with the theoretically calculated values within the common experimental errors.

1*H*-Indol-3-yl-carbonylsulfamoyl chloride (IIa) was obtained by procedures [7, 8], mp 175–180°C (mp was not reported in [7, 8]).

(1-Methyl-1*H*-indol-3-yl)carbonylsulfamoyl chloride (IIb). To 0.1 mol of indole **Ib** in 200 ml of anhydrous ether was added dropwise within 1 h at constant stirring and temperature of 3–4°C 0.1 mol of CSI in 100 ml of anhydrous ether. Then the stirring of the reaction mixture cooled by an ice bath continued for 1 h more. The slightly colored precipitate was filtered off and dried in a vacuum-desiccator. Yield 85%, mp 160–162°C. Found, %: C 44.1; H 3.2; Cl 12.9; N 10.2; S 11.4. $C_{10}H_9ClN_2O_3S$. Calculated, %: C 44.0; H 3.3; Cl 12.9; N 10.3; S 11.3.

Indol-3-ylcarbonylsulfamides IIIa–IIIj. To a dispersion of 3 mmol of sulfamoyl chloride **IIa** or **IIb** in acetonitrile was added 6 mmol of amine, the mixture was heated to boiling, 2–3 ml of water was added causing the dissolution of precipitated amine hydrochloride, then more 10–15 ml of water was added till turbidity. Afterwards the precipitate separated that was filtered off and dried. According to ^1H NMR data the products obtained were pure and did not require recrystallization.

***N*-[(1-Methyl-1*H*-indol-3-yl)carbonyl]-*N*'-(1,3-thiazol-2-yl)sulfamide (IIIa).** Yield 31%, mp 150–153°C. IR spectrum, ν, cm^{-1}: 3227, 3060 (NH); 1633 (C=O). ^1H NMR spectrum, δ, ppm: 3.8 s (3H, CH_3), 6.7–7.4 m (5H_{arom}), 7.4 d (1H_{arom}), 8.1 m (1H_{arom}), 8.3 m (1H_{arom}), 11 s (1H, NHCO), 12 br.s (1H, NH_{amine}). Found, %: C 46.4; H 3.6; N 16.7; S 19.0. $C_{13}H_{12}N_4O_3S_2$. Calculated, %: C 46.4; H 3.7; N 16.6; S 19.0.

N-(1*H*-Indol-3-ylcarbonyl)-*N*'-(4-fluorophenyl)-sulfamide (IIIb). Yield 81%, mp 201–204°C. IR spectrum, ν, cm^{-1}: 3327, 3326 (NH); 1633 (C=O). ^1H NMR spectrum, δ, ppm: 6.9–7.4 m (7H_{arom}), 8.1 m (1H_{arom}), 8.2 m (1H_{arom}), 10.2 s (1H, NH_{amine}), 11.25 s (1H, NHCO), 11.6 s (1H, NH_{indole}). Found, %: C 54.1; H 3.6; N 12.6; S 9.6. $C_{15}H_{12}FN_3O_3S$. Calculated, %: C 54.0; H 3.6; N 12.6; S 9.7.

***N*-(1*H*-Indol-3-ylcarbonyl)-*N*'-cyclohexyl-sulfamide (IIIc).** Yield 47%, mp 220–223°C. IR spectrum, ν, cm^{-1}: 3307, 3260(NH); 1627(C=O). ^1H NMR spectrum, δ, ppm: 1.0–2.0 m (10H, 5CH_2),

3.1 m (1H, CH), 7.0–7.4 m (4H, H_{arom}, NH_{amine}), 8.1 m ($1H_{arom}$), 8.3 m ($1H_{arom}$), 11.0 s (1H, NHCO), 11.6 s (1H, NH_{indole}). Found, %: C 56.1; H 6.0; N 13.1; S 10.0. $C_{15}H_{19}N_3O_3S$. Calculated, %: C 56.0; H 5.9; N 13.0; S 9.9.

***N*-(1*H*-Indol-3-ylcarbonyl)-*N*'-(4-chlorophenyl)-sulfamide (IIId).** Yield 67%, mp 205–208°C. IR spectrum, ν, cm^{-1}: 3320, 3227 (NH); 1627 (C=O). ^1H NMR spectrum, δ, ppm: 7.0–7.4 m ($7H_{arom}$), 8.1 m ($1H_{arom}$), 8.3 m ($1H_{arom}$), 10.4 s (1H, NH_{amine}), 11.35 s (1H, NHCO), 11.6 s (1H, NH_{indole}). Found, %: C 51.5; H 3.5; Cl 10,1; N 12.0; S 9.2. $C_{15}H_{12}ClN_3O_3S$. Calculated, %: C 51.6; H 3.4; Cl 10.0; N 12.0; S 9.1.

2,3-Dihydroindol-1-yl-N-(1*H*-indole-3-carbonyl)-sulfonamide (IIIe). Yield 76%, mp 132–135°C. IR spectrum, ν, cm^{-1}: 3287, 3260 (NH); 1660 (C=O). ^1H NMR spectrum, δ, ppm: 3.2 t (2H, CH_2), 4.4 t (2H, CH_2N), 6.8–7.4 m ($7H_{arom}$), 8.0 d ($1H_{arom}$), 8.3 s ($1H_{arom}$), 11.5 s (1H, NHCO), 11.6 s (1H, NH_{indole}). Found, %: C 59.8; H 4.4; N 12.3; S 9.4. $C_{17}H_{15}N_3O_3S$. Calculated, %: C 59.8; H4.4; N 12.4; S 9.3.

***N*-(1*H*-Indol-3-ylcarbonyl)-4-morpholinosulfonamide (IIIf).** Yield 55%, mp 184–186°C. IR spectrum, н, cm^{-1}: 3310, 3227 (NH); 1640 (C=O). ^1H NMR spectrum, δ, ppm: 3.3 m (4H, CH_2NCH_{2morph}), 3.6 m (4H, CH_2OCH_{2morph}), 7.0 m ($2H_{arom}$), 7.4 d ($1H_{arom}$), 8.1 m ($1H_{arom}$), 8.3 m ($1H_{arom}$), 11.1 s (1H, NHCO), 11.7 s (1H, NH_{indole}). Found, %: C 50.5; H 4.9; N 13.6; S 10.4. $C_{13}H_{15}N_3O_4S$. Calculated, %: C 51.0; H 4.8; N 13.6; S 10.3.

***N*-Isopropyl-*N*'-(1*H*-Indol-3-ylcarbonyl)-sulfamide (IIIg).** Yield 31%, mp 201–204°C. IR spectrum, ν, cm^{-1}: 3293, 3253 (NH); 1633 (C=O). ^1H NMR spectrum, δ, ppm: 1.1 d (6H, $2CH_3$), 3.4 m (1H, CH), 7.0–7.4 m (4H, H_{arom}, NH_{amine},), 8.1 d ($1H_{arom}$), 8.3 m ($1H_{arom}$), 11.0 s (1H, NHCO), 11.6 s (1H, NH_{indole}). Found, %: C 51.2; H 5.4; N 15.0; S 11.4. $C_{12}H_{15}N_3O_3S$. Calculated, %: C 51.1; H 5.5; N 14.9; S 11.5.

***N*'-(1*H*-Indol-3-ylcarbonyl)-*N*,*N*-diethylsulfamide (IIIh).** Yield 49 %, mp 221–225°C. IR spectrum, ν, cm^{-1}: 3287, 3053 (NH); 1647 (C=O). ^1H NMR spectrum, δ, ppm: 1.2 m [6H, $N(CH_2–CH_3)_2$], 3.2 m [4H, $N(CH_2–CH_3)_2$], 7.0–8.3 m ($5H_{arom}$), 11.1 s (1H, NHCO), 11.6 s (1H, NH_{indole}). Found, %: C 52.9; H 5.8; N 14.2; S 10.7. $C_{13}H_{17}N_3O_3S$. Calculated, %: C 52.9; H 5.9; N 14.3; S 10.5.

Ethyl 4-({[(1*H*-indol-3-ylcarbonyl)amino]-sulfonyl}amino)benzoate (IIIi). Yield 60%, mp 165–168°C. IR spectrum, ν, cm^{-1}: 3187 (NH), 1713(CO_2Et), 1687 (C=O). ^1H NMR spectrum, δ, ppm: 1.3 t (3H, CH_2CH_3), 4.2 q (2H, CH_2CH_3), 7.0–8.3 m ($9H_{arom}$), 10.9 s (1H, NH_{amine}), 11.5 s (1H, NHCO), 11.6 s (1H, NH_{indole}). Found, %: C 53.4; H 3.7; N 11.7; S 8.9. $C_{16}H_{13}N_3O_5S$. Calculated, %: C 53.3; H 3.8; N 11.6; S 9.0.

Methyl 4-({[(1*H*-indol-3-ylcarbonyl)amino]-sulfonyl}amino)benzoate (IIIj). Yield 55%, mp 196°C. IR spectrum, ν, cm^{-1}: 3407, 3327, 3180(NH); 1707 (CO_2Me); 1687 (C=O). ^1H NMR spectrum, δ, ppm: 3.8 s (3H, CH_3), 7.0–8.3 m ($9H_{arom}$), 10.9 s (1H, NH_{amine}), 11.5 s (1H, NHCO), 11.6 s (1H, NH_{indole}). Found, %: C 54.7; H 4.1; N 11.3; S 8.6. $C_{17}H_{15}N_3O_5S$. Calculated, %: C 54.6; H 4.0; N 11.4; S 8.7.

REFERENCES

1. Esteban, A.I., De Clercq, E., and Martinez, A., *Bioorg. Med. Chem. Lett.,* 1997, vol. 7, p. 540.
2. Martinez, A., Castro, A., Gil, C., Abasolo, Ml., and Segarra, V., *J. Med. Chem*., 2000, vol. 43, p. 683.
3. Nordman, R. and Petcher, T.J., *J. Med. Chem.,* 1985, vol. 28, p. 367.
4. Serradell, M.N., Castaser, J., and Chu, S.S., *Drugs, Fut.,* 1985, vol. 10, no. 1, p. 42.
5. Horton, D.A., Bourne, G.T., and Smythe, M.L., *Chem. Rev.,* 2003, vol. 103, p. 893.
6. Desimone, R.W., Currie, K.R., Mitchell, S.A., Darrow, J.W., and Pippin, D.A., *Combinator. Chem. High Troughput Screening*, 2004, vol. 7, p. 473.
7. Dhar, D.N., Keshava, and Murthy, K.S., *Synthesis*, 1986, p. 437.
8. Vorbuggen, H. and Krolikiewicz, K., *Tetrahedron,* 1994, vol. 50, p. 6549.