SYNTHESES OF DRUG ON THE BASIS OF 3-SULFAMOYL-4-CHLOROBENZOYLAZIDE. DIURETIC ACTIVITY OF 3-SULFAMOYL-4-CHLOROBENZOIC ACID AMIDES

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An analysis of data available in the literature on the diuretic properties of 3-sulfamoyl-4-chlorobenzoic acid amides [1 – 12] and hydrazides [13 – 29] suggests that a condition necessary for the diuretic activity of these compounds consists in the presence of a –CO–NH– fragment in the *meta* position with respect to the sulfamoyl group. In particular, Lebedev et al. [30] showed that the diuretic and natriuretic activity of 3-sulfamoyl-4-chlorobenzoylhydrazones of aromatic aldehydes depend on the polarity of N–H bonds in this fragment.

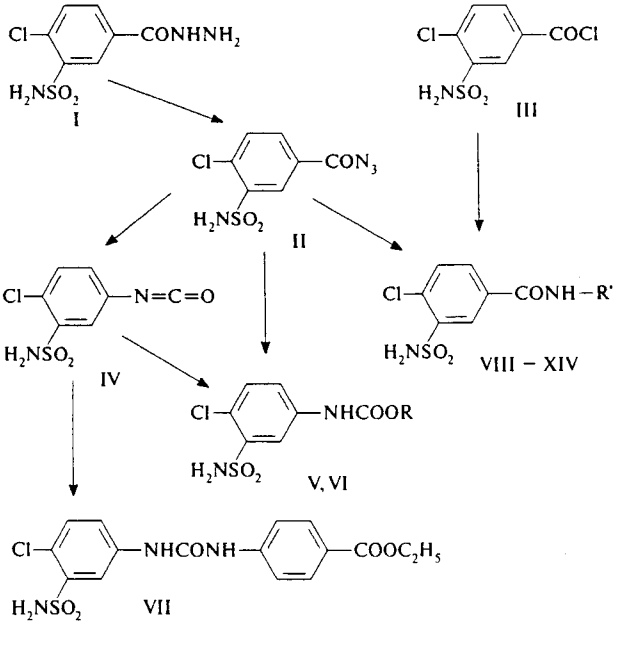
It was therefore of interest to study the diuretic activity of compounds in which, first, the distance of hydrogen atom in the –CO–NH– group from the benzene ring containing the sulfamoyl group differs from the corresponding values in 3-sulfamoyl-4-chlorobenzoyl acid amides, hydrazides, and hydrazones and, second, the character of the electronic influence of substituents on the N–H bond differs from that in 3-sulfamoyl-4-chlorobenzoylhydrazones of aromatic aldehydes.

For this purpose, we have synthesized a series of N-(3-sulfamoyl-4-chlorophenyl)carbamates, N-(3-sulfamoyl-4-chlorophenyl)-N′-R-ureas, and 3-sulfamoyl-4-chlorobenzoic acid amides and characterized their diuretic activity. The compounds were synthesized proceeding from 3-sulfamoyl-4-chlorobenzoylazide (II) according to the scheme.

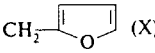
The initial azide II was obtained with high yield (94 – 96%) by a reaction between 3-sulfamoyl-4-chlorobenzoic acid hydrazide (I) and sodium nitrite in a hydrochloric medium. The structure of compound II was confirmed by data of the elemental analyses and by the synthesis of two known 3-sulfamoyl-4-chlorobenzoyl acid amides (VIII, IX) [5] on the basis of azide II.

The synthesis of 3-sulfamoyl-4-chlorobenzoyl acid amides (VIII – XIV) was conducted by two pathways. First, by interaction of 3-sulfamoyl-4-chlorobenzoic chloroanhydride (III) with the corresponding amines using a procedure similar to that described in [5] (Method A). Second, by reactions of water-soluble amines with azide II in an aqueous-alkaline solution under controlled pH conditions (Method B). Amides VIII – X obtained by the two methods were identical.

Scheme



R = C_2H_5 (V), $CH_2CH(CH_3)_2$ (VI).

R′ = CH_2CH_2OH (VIII), $CH_2C_6H_5$ (IX),  (X), C_6H_5 (XI), $C_6H_4CH_3$-2 (XII), $C_6H_4OCH_3$-2 (XIII), $CH(COOH)CH_2C_6H_5$ (XIV).

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Azide II decomposes on heating in toluene (beginning with 80°C), which is accompanied by the evolution of nitrogen and the formation of 3-sulfamoyl-4-chlorophenylisocyanate (IV). The proposed structure of compound IV was confirmed by IR spectroscopic data and by its conversion into carbamates V, VI and the urea derivative VII (identical with those obtained directly from azide II).

Table 1 gives the yields and melting temperatures of amides VIII – XIV.

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on a Shimadzu spectrophotometer (Japan) using samples prepared by pelletizing with KBr. The data of elemental analyses agree with the empirical formulas proposed.

3-Sulfamoyl-4-chlorobenzoylazide (II). To a solution of 5.0 g (0.02 mole) of compound I in 65 ml of an 0.5 M aqueous HCl was added dropwise with stirring during 10 min at 0 ± 3°C a solution of 1.4 g (20.3 mmole) of sodium nitrite in 5 ml water. The mixture was stirred for another 5 min at 0°C and filtered. The precipitate was washed with ice-cold water until we obtained a negative reaction for chloride ions and dried in vacuum at room temperature to obtain 4.9 – 5.0 g (94 – 96%) of a white substance; m.p., 129 – 130°C (violent decomp.). The product was crystallized using the following procedure. A weighted amount of the compound (1 g) was dissolved in 10 ml of 50% aqueous acetone at a temperature not exceeding 15°C. The solution was placed into a vacuum drying box and kept at a pressure of 400 – 500 Torr. The precipitate formed upon slow evaporation of acetone was filtered, washed with a cold 10% aqueous acetone solution, and dried in vacuum at room temperature to obtain azide II in the form of long colorless needles; m.p., 130.5 – 131°C (violent decomp.); $C_7H_5ClN_4O_3S$.

3-Sulfamoyl-4-chlorophenylisocyanate (IV). A mixture of 2.6 g (0.01 mole) of compound II and 80 ml of dry toluene was heated to 105 – 110°C, kept at this temperature until termination of the nitrogen evolution (1 – 1.5 h), and cooled to room temperature. The precipitate was filtered, washed with 20 ml acetone, and dried in vacuum at room temperature to obtain 1.8 g (78%) of compound II the form of fine crystals having white color with a yellowish tint; m.p., 185 – 187°C (decomp.); $C_7H_5ClN_2O_3S$; IR spectrum (ν_{max}, cm^{-1}): 2260 (N=C=O), 1350, 1175 (SO_2, NH_2).

Ethyl-N-(3-sulfamoyl-4-chlorophenyl)carbamate (V). A mixture of 2.6 g (10 mmole) of compound II or 2.3 g (10 mmole) of compound IV and 10 ml of absolute ethanol was boiled for 2 h and cooled to room temperature. To this mixture was added 100 ml of water and the precipitate was filtered, crystallized from 50% aqueous methanol, and dried at 105°C to obtain 1.8 – 1.9 g (65 – 68%) of white finely crystalline compound V; m.p., 201 – 203°C; $C_9H_{11}ClN_2O_4S$; IR spectrum (ν_{max}, cm^{-1}): 3355, 3335, 3235 (N–H), 3105 (C–H_{arom}), 1725 (C=O), 1346, 1170 (SO_2NH_2), 1386, 1370 (C–H_{aliph}), 1602, 1548, 1475, 1242, 1124, 1085, 1035, 920, 890, 830 (a group of bands characteristic of 1,3,4-substituted benzene derivatives).

Isobutyl-N-(3-sulfamoyl-4-chlorophenyl)carbamate (VI) was obtained similarly by boiling compound II or IV in isobutyl alcohol; yield (white crystalline product), 52%; m.p., 179 – 181°C; $C_{11}H_{15}ClN_2O_4S$; IR spectrum (ν_{max}, cm^{-1}): 3355, 3320, 3230 (N – H), 3100 (C – H_{arom}), 2870, 1400, 1380 (C–H_{aliph}), 1715 (C=O), 1345, 1168 (SO_2NH_2), 1600,

TABLE 1. Physicochemical Characteristics of 3-Sulfamoyl-4-chlorobenzoic Acid Amides VIII – XIV

Compound	Yield, %		M.p.,* °C	Empirical formula
	Method A	Method B		
VIII**	64	45	175 – 177	$C_9H_{11}ClN_2O_4S$
IX**	74	53	192 – 194	$C_{14}H_{13}ClN_2O_3S$
X	47	52	244 – 246	$C_{12}H_{11}ClN_2O_4S$
XI**	78	–	248 – 250	$C_{13}H_{11}ClN_2O_3S$
XII**	82	–	238 – 240	$C_{14}H_{13}ClN_2O_3S$
XIII	86	–	214 – 216	$C_{14}H_{13}ClN_2O_4S$
XIV	–	42	253 – 256	$C_{16}H_{15}ClN_2O_5S$

* All compounds recrystallized from ethanol.
** Published data: VIII, m.p., 177°C [5]; IX, m.p., 193°C [5]; XI, m.p., 247 – 249°C [3]; XII, m.p., 237 – 238°C [3].

TABLE 2. Diuretic and Natriuretic Activity of Compounds V – XIV in Experiments on Rats (Dose 25 mg/kg, p.o.)

Compound	Diuretic activity*	Natriuretic activity*
V	$\frac{2.2 \pm 0.3}{2.1 \pm 0.2} = 1.0$	$\frac{190 \pm 30}{148 \pm 18} = 1.3$
VI	$\frac{2.3 \pm 0.3}{2.1 \pm 0.2} = 1.1$	$\frac{208 \pm 42}{148 \pm 18} = 1.4$
VII	$\frac{3.7 \pm 0.4}{2.2 \pm 0.1} = 1.7$**	$\frac{145 \pm 24}{71 \pm 12} = 2.0$**
VIII	$\frac{5.4 \pm 1.0}{2.1 \pm 0.1} = 2.6$**	$\frac{353 \pm 81}{52 \pm 9} = 6.8$**
IX	$\frac{4.9 \pm 0.6}{2.4 \pm 0.2} = 2.0$**	$\frac{326 \pm 58}{87 \pm 14} = 3.7$**
X	$\frac{5.6 \pm 0.8}{2.1 \pm 0.1} = 2.7$**	$\frac{387 \pm 62}{52 \pm 9} = 7.4$**
XI	$\frac{4.8 \pm 0.5}{1.5 \pm 0.1} = 3.2$**	$\frac{395 \pm 74}{59 \pm 7} = 6.7$**
XII	$\frac{6.4 \pm 0.3}{1.5 \pm 0.1} = 4.3$**	$\frac{483 \pm 72}{59 \pm 7} = 8.2$**
XIII	$\frac{6.7 \pm 0.5}{1.5 \pm 0.1} = 4.5$**	$\frac{467 \pm 56}{59 \pm 7} = 7.9$**
XIV	$\frac{4.3 \pm 0.4}{2.4 \pm 0.2} = 1.8$**	$\frac{188 \pm 52}{87 \pm 14} = 2.2$**

* Figures in the numerator and denominator give the values of diuresis (ml / 4 h) and natriuresis (μmole / 4 h) in the test and control groups of animals, respectively.
** $p < 0.05$.

1545, 1472, 1235, 1120, 1080, 1035, 975, 885, 820 (a group of bands characteristic of 1,3,4-substituted benzene derivatives).

N-(3-Sulfamoyl-4-chlorophenyl)-N′-(4-ethoxycarbonylphenyl)urea (VII). A mixture of 2.6 g (10 mmole) of compound II or 2.3 g (10 mmole) of compound IV, 1.7 g (10.3 mmole) of *para*-aminobenzoic acid ethyl ester, and 80 ml of dry toluene was heated to 100°C. The resulting transparent solution was stirred at 100 – 105°C for 2 h, cooled to room temperature, and filtered. The precipitate was washed with 20 ml dioxane dried at 105°C to obtain 3.0 – 3.1 g (75 – 77%) of compound II in the form of white fine crystals; m.p., 234 – 235°C (isopropyl alcohol). A mixed sample of the products obtained proceeding from compounds II and IV showed no depression of the melting temperature; $C_{16}H_{16}ClN_3O_5S$.

3-Sulfamoyl-4-chlorobenzoyl acid amides (VIII – XIV).

Method A. To a mixture of 0.02 mole of amine and 2 g of triethylamine in 20 ml of dry chloroform at 20 – 25°C was added with stirring during 30 min a solution of 5.1 g (0.02 mole) of freshly prepared compound III in 20 ml of dry chloroform. After stirring the mixture for 5 h at 20 – 25°C, chloroform was distilled off. The residue was mixed with 10 ml of a 1 M hydrochloric acid solution and stirred for 5 min. The precipitate was washed with ice-cold water to a negative reaction for chloride ions, crystallized from ethanol, and dried in vacuum to obtain a target compound (VIII – XIII).

Method B. To a solution of 0.01 mole of amine in 10 ml of 1 M sodium hydroxide at 0 – 5°C were added simultaneously by small portions with stirring 2.6 g (0.01 mole) of compound II and a 1 M sodium hydroxide solution so as to provide pH within 7.5 – 8.0. After completely introducing compound II, the reaction mixture was stirred for 12 h at 20 – 25°C, with the pH value maintained within 7.5 – 8.0. After this exposure, the reaction mass was treated with hydrochloric acid to pH 2. The product (VIII – X, XIV) was isolated and purified as in Method A.

EXPERIMENTAL PHARMACOLOGICAL PART

The diuretic and natriuretic activity of compounds V – XIV were studied on white rats using the methods described in [31, 32].

As seen from the data presented in Table 2, all the synthesized 3-sulfamoyl-4-chlorobenzoyl acid amides produced a statistically reliable increase in the level of diuresis and natriuresis. The maximum diuretic and natriuretic activity was observed for compounds XII and XIII containing electron-donor substituents (CH_3 and OCH_3) in the *ortho* position of a benzene ring bound to nitrogen. This result agrees with the dependence found in our previous work with a series of 3-sulfamoyl-4-chlorobenzoylhydrazones of carbonyl compounds. Introducing the electron-acceptor COOH group into a vicinal position with respect to nitrogen atom of the reactive center (cf. compounds IX and XIV) leads, as expected, to a decrease in the diuretic and natriuretic activity.

A change in the structure of the reactive center, namely, conjugation of the N–H (rather than C=O) fragment of the reactive –CONH– group to the benzene ring containing the sulfamoyl group, leads to to a sharp drop or even complete loss of diuretic and natriuretic activity.

Thus, the experimental data confirm our hypothesis that a necessary condition for the diuretic activity manifestation in the series of sulfamide compounds studied is the presence of a CO–NH functional group in the *meta* position with respect to the sulfamoyl group. The role of this CO–NH group apparently consists in forming an intermolecular hydrogen bond with the receptor.

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