SYNTHESIS AND DIURETIC ACTIVITY OF 3-NITRO(AMINO)-4-CHLORO-5-SULFAMOYLSALICYLIC ACIDS AND THEIR DERIVATIVES

V. A. Smirnov[1]

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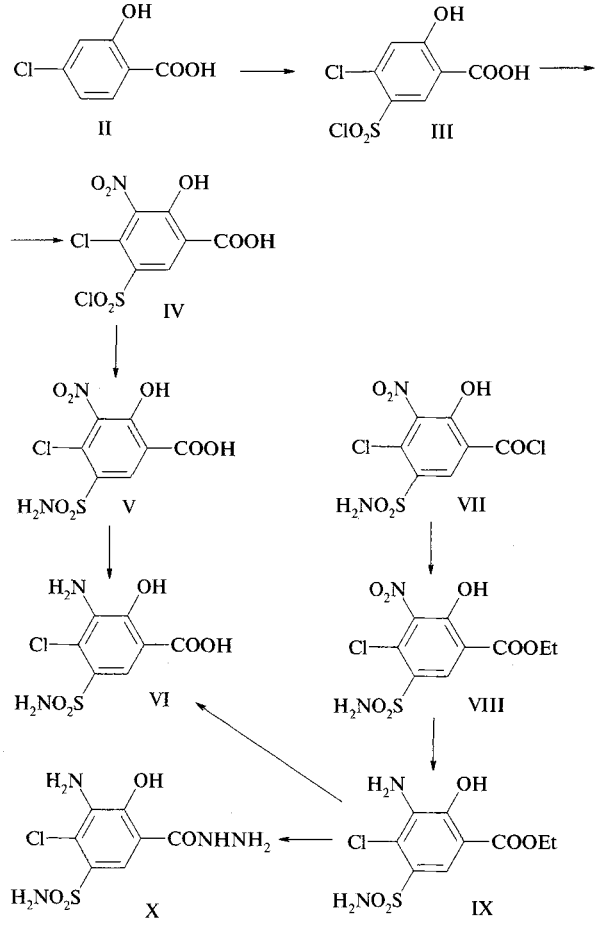
Previously [1 – 3], it was demonstrated that 4-chloro-5-sulfamoylsalicylic acid (I) and its derivatives possess diuretic activity. In connection with this, it was also of interest to study the diuretic and saluretic activity of the derivatives of compound I containing electron donor and acceptor groups in position 3. For this purpose, we have synthesized 3-nitro- and 3-amino-4-chloro-5-sulfamoylsalicylic acids (V, VI) and their derivatives substituted at the carboxy group (VII – X) according to the following scheme.

The initial compound in these syntheses was 4-chlorosalicylic acid (II) which, in contrast to its derivatives alkylated at the phenolic hydroxy group [3], is readily sulfochlorinated by interaction with chlorosulfonic acid at 80°C. This reaction leads to the formation of an isomerically pure 4-chloro-5-chlorosulfonylsalicylic acid (III) with a rather high yield. It should be noted that the yield of sulfochloride III sharply decreases if the process involves less than 5 mole of chlorosulfonic acid per mole of compound II. The action of nitriding mixture upon compound III at 65 – 70°C leads to the formation of 3-nitro-4-chloro-5-chlorosulfonylsalicylic acid (IV) with a 80% yield.

Because of the high mobility of the chlorine atom bound to the benzene ring, the conversion of sulfochloride IV into 3-nitro-4-chloro-5-sulfamoylsalicylic acid (V) has to be performed under very mild conditions by interaction with an ether solution of ammonia at 0 ± 5°C. Under these conditions, the yield of amide V reaches 62 – 64%. Conducting the process at a higher temperature with an aqueous ammonia solution sharply decreases the yield of compound V.

Boiling amide V with a seven-fold molar excess of thionyl chloride in anhydrous dioxane leads to 3-nitro-4-chloro-5-sulfamoylsalicylic acid chloroanhydride (VII) with a yield of 90%. When compound VII is boiled with ethanol, no significant substitution of chlorine atoms in the benzene ring takes place and 3-nitro-4-chloro-5-sulfamoylsalicylic acid ethyl ether (VIII) is obtained with a yield of 77 – 79%.



The hydrogenation of compounds V and VIII is significantly affected by the nature of solvent. Nitro acid V is not hydrogenated in a sodium carbonate solution in the presence of 10% palladium supported on activated charcoal. Neither V

[1] Samara State Medical University, Samara, Russia.

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nor VIII can be hydrogenated in a DMF solution and both are very slowly hydrogenated in dioxane and isopropyl alcohol. Acceptable results were obtained for the hydrogenation of V and VIII in methanol at 40 – 50°C and a hydrogen pressure of 1.1 atm in the presence of 10% palladium supported on activated charcoal. Under these conditions, compound V converts into 3-amino-4-chloro-5-sulfamoylsalicylic acid ethyl ether (IX) with a yield of 70%.

The saponification of ether IX with a 10% aqueous potassium hydroxide solution leads to acid VI. Heating ether IX with hydrazine hydrate at 70 – 75°C yields 3-amino-4-chloro-5-sulfamoylsalicylic acid hydrazide (X).

The proposed structures of the synthesized compounds were confirmed by IR-spectroscopic data and by the results of elemental analyses.

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on a Specord M-80 spectrophotometer (Germany) in KBr pellets. The data of elemental analyses of compounds III – X agree with the results of analytical calculations.

4-Chloro-5-chlorosulfonylsalicylic acid (III). To 170 ml (304 g, 2.6 mole) of chlorosulfonic acid cooled to – 5°C were added by portions with stirring 86.3 g (0.5 mole) of 4-chlorosalicylic acid (II), so that the temperature would not rise above 0°C. Upon completely introduction of II, 20 ml of thionyl chloride were immediately added and the mixture was stirred for 2 h at 0°C. Then the mixture was slowly (over 1 h) heated to 80°C and stirred at this temperature for 2.5 h, with periodical addition by small portions of 50 ml of thionyl chloride. Finally, the mixture was cooled to room temperature, poured into 1.5 kg of crushed ice, stirred for 1.5 h, and filtered. The precipitate was washed with ice-cold water, dried in vacuum at room temperature, and crystallized from toluene to obtain 115 – 118 g (85 – 87%) of a finely-crystalline product having a white color with a pink-yellowish tint; m.p., 181 – 183°C [4]; $C_7H_4Cl_2O_5S$.

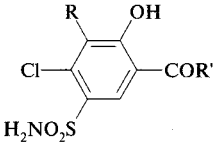
3-Nitro-4-chloro-5-chlorosulfonylsalicylic acid (IV). To a solution of 81.3 g (0.3 mole) of compound III in 690 ml of 92% sulfuric acid at 65 – 70°C were slowly (over 1 h) added 17.5 ml (0.35 mole) of 85.5% nitric acid. Then the mixture was stirred at 65 – 70°C for 2 h and cooled to 0°C. The precipitate was separated by filtration, washed with ice-cold water, dried in vacuum at 50°C, and crystallized from benzene to obtain 75 – 77 g (79 – 81%) of a white crystalline product; m.p., 226 – 228°C; $C_7H_3Cl_2NO_7S$.

3-Nitro-4-chloro-5-sulfamoylsalicylic acid (V). To 400 ml of an ether solution of ammonia saturated at –10°C were added at –5 ± 0.5°C, with intensive stirring and dry ammonia bubbling, a solution of 63.2 g (0.2 mole) of compound IV in 200 ml of ether. After the mixture was stirred at 0°C for 2 h, the precipitate was filtered, washed with ether, and added by small portions at 0 – 5°C to 250 ml of a 20% hydrochloric acid. The mixture was stirred at 0 – 5°C for 30 min and filtered. The precipitate was separated by filtration, washed with ice-cold water, and dried in vacuum at 80°C to obtain 37 – 38 g (62 – 64%) of a white crystalline product; m.p., 252 – 254°C (water); $C_7H_5ClN_2O_7S$; IR spectrum (ν_{max}, cm^{-1}): 3410, 3295 (NH_2), 3100 ($C–H_{arom.}$), 1684 (CO), 1552, 1340 (NO_2), 1360, 1160 (SO_2).

3-Nitro-4-chloro-5-sulfamoylsalicylic acid chloroanhydride (VII). A mixture of 17.8 g (0.06 mole) of acid V, 30 ml (0.42 mole) of thionyl chloride, and 30 ml of anhydrous dioxane was boiled for 2 h. Then 30 ml of the solvent was distilled off and the residue cooled to room temperature. To this residue was added 150 ml of dry chloroform and the mixture was stirred for 10 min. The precipitate was separated by filtration, crystallized from benzene, and dried in vacuum at 50°C to obtain 17.0 – 17.2 g (90 – 91%) of a finely-crystalline product having white color with a yellowish tint; m.p., 214 – 216°C [4]; $C_7H_4Cl_2N_2O_6S$.

3-Nitro-4-chloro-5-sulfamoylsalicylic acid ethyl ether (VIII). A mixture of 12.6 g (0.04 mole) of chloroanhydride VII with 30 ml of absolute ethanol was boiled for 2 h. To this hot solution were added 50 ml of water and the mixture was cooled to 0°C. The precipitate was separated by filtration, washed with water, and dried at 105°C to obtain 10.0 – 10.3 g (77 – 79%) of a white finely-crystalline product; m.p., 144 – 146°C; $C_9H_9ClN_2O_7S$; IR spectrum (ν_{max},

TABLE 1. The Diuretic and Natriuretic Activity of 3-R-4-Chloro-5-sulfamoylsalicylic Acids and Their Derivatives Upon Intragastric Introduction to White Rats at a Dose of 24 mg/kg



Compound	R	R'	Activity*	
			diuretic	natriuretic
I	H	OH	$\frac{5.9 \pm 0.6}{2.1 \pm 0.1} = 2.8$*	$\frac{145 \pm 26}{58 \pm 12} = 2.5$*
V	NO_2	OH	$\frac{5.3 \pm 0.4}{2.4 \pm 0.2} = 2.2$*	$\frac{130 \pm 22}{71 \pm 14} = 1.8$*
VI	NH_2	OH	$\frac{5.1 \pm 0.4}{1.5 \pm 0.1} = 3.4$*	$\frac{196 \pm 32}{52 \pm 10} = 3.8$*
VIII	NO_2	OC_2H_5	$\frac{2.0 \pm 0.2}{2.4 \pm 0.2} = 0.8$	$\frac{110 \pm 24}{86 \pm 14} = 1.3$
IX	NH_2	OC_2H_5	$\frac{4.6 \pm 0.3}{2.4 \pm 0.2} = 1.9$*	$\frac{165 \pm 25}{71 \pm 14} = 2.3$*
X	NH_2	$NHNH_2$	$\frac{3.1 \pm 0.1}{1.5 \pm 0.1} = 2.0$*	$\frac{518 \pm 72}{52 \pm 10} = 10.0$*

* $p < 0.05$; the diuretic and natriuretic activity values were calculated as the ratios of diuresis (ml/kg) and natriuresis (μmole/kg) measured within 4 h upon drug introduction to the corresponding values in the control.

cm^{-1}): 3330, 3260 (NH_2), 3105 ($C–H_{arom.}$), 2990 ($C–H_{al.}$), 1692 (CO), 1552, 1350 (NO_2), 1380, 1152 (SO_2).

3-Amino-4-chloro-5-sulfamoylsalicylic acid ethyl ether (IX). A solution of 6.5 g (0.02 mole) of ether VIII in 100 ml of methanol was hydrogenated at 40 – 45°C and a hydrogen pressure of 1.1 atm in the presence of 0.5 g of 10% palladium supported on activated charcoal. The subsequent standard treatment yields 4.1 – 4.3 g (70 – 73%) of a white finely-crystalline product with grayish tint; m.p., 202 – 204°C (80% aqueous isopropanol); $C_9H_{11}ClN_2O_5S$; IR spectrum (ν_{max}, cm^{-1}): 3460, 3420,3355, 3290 (NH_2, SO_2NH_2), 3100 ($C–H_{arom.}$), 1680 (CO), 1465, 1385 ($C–H_{al.}$) 1335, 1150 (SO_2).

3-Amino-4-chloro-5-sulfamoylsalicylic acid (VI).

(A). A solution of 8.9 g (0.03 mole) of acid V in 90 ml of methanol was hydrogenated as described above to obtain 7.0 – 7.2 g (87 – 90%) of amino acid VI in the form of a white finely-crystalline product with grayish tint; m.p., 244 – 246°C (water); $C_7H_7ClN_2O_5S$.

(B) A mixture of 2.95 g (10 mmole) of ether IX and 50 ml of a 10% aqueous potassium hydroxide solution was kept for 1 h at 45 – 50°C and acidified with glacial acetic acid to pH 3 to precipitate compound VI with a yield of 1.0 g (38%).

3-Amino-4-chloro-5-sulfamoylsalicylic acid hydrazide (X). A mixture of 1.2 g (4 mmole) of ether IX and 4.0 g (80 mmole) of hydrazine hydrate was kept for 10 min at 70 – 75°C, cooled to room temperature, acidified with glacial acetic acid to pH 7, and cooled down to 0°C. The precipitate was crystallized from water to obtain 1.0 g (85%) of a white finely-crystalline product; m.p., 213 – 215°C; $C_7H_9ClN_4O_4S$.

EXPERIMENTAL BIOLOGICAL PART

The diuretic and natriuretic activity of the synthesized compounds was studied on intact white rats weighing 180 – 300 g as described in [5, 6]. The total diuresis and the excretion of sodium ions were determined 4 h after the beginning of the experiment. The concentration of sodium ions was determined by flame photometry on a PAZh-1 instrument. Each compound was studied in a group of 10 animals, to which the samples suspended in a starch jelly were introduced via a gastric tube at a dose of 24 mg/kg. Animals in the control group received the same amount of pure starch jelly. The aqueous load in the test and control groups amounted to 2% of the animal body weight.

As seen from the experimental data summarized in Table 1, the presence of a nitro group in position 3 of the benzene ring decreases the diuretic and natriuretic activity, while the introduction of an amino group at the same position increases the activity. Etherification of the carboxy group led to a decrease in the activity. These results are indicative of a certain role of the electronic factor in the diuretic activity manifestation, in agreement with the data reported previously for 3-sulfamoyl-4-chlorobenzoylhydrazones of aromatic aldehydes [6] and 3-sulfamoyl-4-chlorobenzoic acid amides [7]. Note that compound X exhibits a high natriuretic activity at a rather low diuretic activity, which is probably explained by localization of the drug action within a cortical branching segment of the loop of Henle.

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