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SYNTHESIS AND DIURETIC ACTIVITY OF 3-SULFAMOYL-4-CHLOROBENZOYL HYDRAZONES OF AROMATIC ALDEHYDES

A. A. Lebedev, V. A. Smirnov, V. P. Posokhov, and L. V. Simerzina

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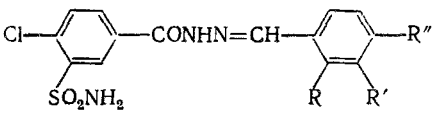
Hydrazides of 3-sulfamoyl-4-chlorobenzoic acid have been found to exhibit diuretic activity [3-9]. Compounds of that class which include N-(cis-2,6,-dimethylpiperidino)-3-sulfamoyl-4-chlorobenzamide – clopamide [2], and N-(3-sulfamoyl-4-chlorobenzoyl)-1-amino-2-methylindoline – indapamide [7], exhibit a high degree of natriuretic activity and antihypertensive action and have been employed in medical practice. At the same time practically no studies have been made of the 3-sulfamoyl-4-chlorobenzoyl hydrazones. The literature has some information about the diuretic action only of 3-sulfamoyl-4-chlorobenzoyl hydrazones of acetone (I) and benzaldehyde (II).

We felt it would be of interest to establish how diuretic activity would be affected by various substituents in the benzene ring of the aldehyde component of compound II. To that end we synthesized 3-sulfamoyl-4-chlorobenzoyl hydrazones of benzaldehyde and its derivatives (II-XI) and investigated their diuretic and saluretic activity. Compounds II-XI were obtained by boiling a solution of 3-sulfamoyl-4-chlorobenzoic hydrazide (XII) and an appropriate aldehyde in 2-propanol in the presence of acetic acid.



II – XI

R = H (II – VI, IX, X), OH (VII), OCH_3 (VIII, XI);
R′ = H (II – VIII, XI), Cl (IX), NO_2 (X);
R″ = H (II, VII – X), Br (III), NO_2 (IV), N $(C_2H_5)_2$ (V), OCH_3 (VI, XI).

The structures of II-XI were confirmed by element analysis and IR-spectroscopy. The IR-spectra of II-XI had the following absorption bands: 1665-1680 cm^{-1} (C=O, amide I), 1625-1660 cm^{-1} (C=N), 1329-1344 and 1160-1185 cm^{-1} (SO_2NH_2).

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TABLE 1. 3-Sulfamoyl-4-Chlorobenzoyl Hydrazones II-XI

Compound	Yield, %	mp, °C	$\nu_{C=O}$, cm^{-1}	Found, %		Empirical formula	Calculated, %	
				Cl	S		Cl	S
II	89	281—91	1668	10,6	9,4	$C_{14}H_{12}ClN_3O_3S$	10.5	9,5
III	98	298—300	1669	27,5*	7,5	$C_{14}H_{11}BrClN_3O_3S$	27,7	7,7
IV	94	328—9	1680	9,1	8,2	$C_{14}H_{11}ClN_4O_5S$	9,3	8,4
V	83	250—2	1666	8,8	7,8	$C_{18}H_{21}ClN_4O_3S$	8,7	7,8
VI	91	244—6	1672	9.8	8,6	$C_{15}H_{14}ClN_3O_4S$	9,6	8,7
VII	74	302—4	1667	10,2	9.2	$C_{14}H_{12}ClN_3O_4S$	10,0	9,1
VIII	95	257—9	1665	9,7	8,7	$C_{15}H_{14}ClN_3O_4S$	9,6	8,7
IX	85	305—6	1665	18.7	8,4	$C_{14}H_{11}Cl_2N_3O_3S$	19,0	8,6
X	84	308—10	1670	9,0	8,1	$C_{14}H_{11}ClN_4O_5S$	9,3	8,4
XI	84	266—8	1669	8.6	7.8	$C_{16}H_{16}ClN_3O_5S$	8,9	8,1

Note. Compounds III, IV, and X were recrystallized from 90% DMPA. The remaining compounds were recrystallized from 65% dioxane. Asterisk indicates total content of Cl and Br.

EXPERIMENTAL (CHEMICAL)

IR-spectra were recorded on a IKS-29 instrument in KBr pellets.

3-Sulfamoyl-4-chlorobenzoic Hydrazide (XII) was obtained by method [3]. Yield was 77%, mp 212-214°C (water). Literature data: mp 211-212°C.

3-Sulfamoyl-4-chlorobenzoyl Hydrazones (II-XI). A 10 mmole portion of aldehyde and 0.6 ml of glacial acetic acid was added to a hot solution of 2.5 g (10 mmole) of XII in 40 ml of 50% aq. 2-propanol, and the reaction mixture was boiled for 15 min. The precipitate was filtered off, washed with 20 ml of 50% aq. 2-propanol, and dried to yield compounds II-XI. Physicochemical characteristics of II-XI are given in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

The method in [10] was used to examine the effect that compounds II-XI had on diuresis and potassium and sodium ion excretion in white rats. The experiments were conducted on intact white rats weighing 180-300 g, as described earlier [1]. Diuresis and potassium and sodium ion excretion was measured 4 h after the start of the experiment, and ion concentration was measured by flame photometry on a PAZh-1 instrument. The diuretic activity of the tested compounds was compared to the activity of furosemide which was administered to the animals at the same dosage and in the same manner. Each compound was administered orally to 10 rats with a gastric probe in the form of a starch mucilage suspension at a dose of 25 mg/kg. The 10 control group animals were given the same amount of starch mucilage as was given to the test animals. The water load in the control and experimental animal groups was 2% of the animal's body weight. The experimental results are given in Table 2.

As can be seen from Table 2, compound II reliably increases diuresis, sodium, and potassium excretion in white rats by 1.32, 3, and 1.6 times, respectively. The introduction of a bromine atom or nitro group into the para-position of the benzene ring (compound III and IV) removes the diuretic and saluretic activity characteristic of compound II. The introduction of a nitro group into the meta-position of the benzene ring of compound II (compound X) results in increased natriuretic activity whereas diuretic and potassium excretion activity is reduced. In comparison to the control, compound X did not alter potassium excretion and diuresis in the white rats whereas natriuresis increased reliably by 6.5 times. Compound X exceeds the natriuretic activity of all the compounds we tested, including furosemide. The same characteristics were observed when a chlorine atom was introduced into the meta-position of the benzene ring of compound II. Both compounds (IX and X) exhibit a high level of natriuretic activity although they do not significantly affect diuresis and kaliuresis in white rats.

The introduction of a diethylamino group into the para-position or a methoxy group into the ortho-position of the benzene ring of compound II (compounds V and VIII) results in greater diuretic and saluretic activity: Compound V increases diuresis by 2.4 times, natriuresis by 6.2 times, and kaliuresis by 2.5 times, whereas compound VIII increases those actions by 1.8, 5, and 2.3 times, respectively. One should note that whereas the introduction of a methoxy group into the ortho-position of the benzene ring of II resulted in greater activity, a me-

TABLE 2. Effect of Compounds II-XI at a Dose of 25 mg/kg on Diuresis and Sodium–Potassium Excretion in White Rats (M ± m)

Compound	Diuresis over a 4 h period, ml	Natriuresis over a 4 h period, μequiv.	4 hr potassium excretion, μequiv.	Sodium–potassium coefficient
II	4,6±0,2*	339±16*	150±8*	2,26
III	3,8±0,4	205±33	83±12	2,47
IV	4,2±0,5	178±45	116±16	1,53
V	8,5±0,3*	901±55*	234±10*	3,85
VI	4,6±0,5*	267±44	167±22*	1,60
VII	0,7±0,1*	226±46	47±8*	4,81
VIII	6,4±0,4*	736±82*	208±20*	3,54
IX	2,3±0,4	852±17*	94±19	9,06
X	4,2±0,6	953±11*	125±15	7,62
XI	3,0±0,3	141±26	90±14	1,57
Furosemide	6,4±0,3*	505±35*	178±21*	2,84
Control	3,5±0,3	146±21	92±14	1,59

*$p < 0.05$.

thoxy group introduced into the para-position of the ring (compounds VI and XI) resulted in a reduction of the diuretic and saluretic activity that is characteristic of compounds II and VIII, respectively.

When a methoxy group in compound VIII was replaced by a hydroxy group (compound VII), the natriuretic activity characteristic of compound VIII was removed and antidiuretic and antikaliuretic action was observed. In comparison to the control, compound VII reduced kaliuresis and diuresis in white rats by 2 and 5 times, respectively.

The values for the sodium–potassium coefficients for compounds II, V, VIII, IX, and X which reliably increased natriuresis in white rats exceeded the control value by 2-9 times. This indicates that the natriuretic activity of the enumerated compounds is markedly greater than that of kaliuretic activity.

Our studies indicate that the 3-sulfamoyl-4-chlorobenzoyl hydrazones warrant further investigation in the search for effective diuretics.

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