SYNTHESIS AND DIURETIC ACTIVITY OF 3-SULFAMOYL-4-CHLOROBENZOYLHYDRAZONE DERIVATIVES OF CARBONYL COMPOUNDS

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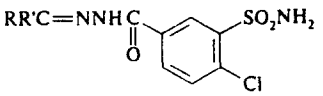
Earlier we reported [1] that 3-sulfamoyl-4-chlorobenzoylhydrazones of some aromatic aldehydes exhibited a short-time (2 – 3 h) diuretic and saluretic activity, which could be related to a rapid hydrolysis of these hydrazones in the organism with the formation of a 3-sulfamoyl-4-chlorobenzoic acid hydrazide (I) and the corresponding aldehydes.

It was therefore of interest to synthesize and study 3-sulfamoyl-4-chlorobenzoylhydrazones of carbonyl compounds that are more stable with respect to hydrolyzing enzymes. For this purpose, we obtained 3-sulfamoyl-4-chlorobenzoylhydrazones of some aliphatic, aromatic, and heterocyclic aldehydes and ketones (II – XIV) using the condensation reaction between hydrazide I and the corresponding carbonyl compounds in a 2-propanol medium in the presence of acetic acid.

Hydrazones II – XIV appear as colorless or yellowish fine-crystalline powders, which are virtually insoluble in water, poorly soluble in alcohols, and soluble in DMF, DMSO, and dioxane.



II – XIV

II: R = H, R' = 2-furyl;
III: R = H, R' = *i*-Pr;
IV: R = H, R' = *i*-Bu;
V: R = H, R' = *n*-C_6H_{13};
VI: R = H, R' = *n*-C_7H_{15};
VII: R = R' = Me;
VIII: R = Me, R' = Ph;
IX: R = Me, R' = C_6H_4OH-4;
X: R = Me, R' = 4-hydroxy-3-chlorophenyl;
XI: R = Me, R' = 4-methoxy-3-chlorophenyl;
XII: R = Me, R' = 1-adamantyl;
XIII: CRR' = cyclohexylidene;
XIV: CRR' = 2-adamantylidene.

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The structures of compounds II – XIV were confirmed by data of elemental analyses and the results of UV, IR, and ^{1}H NMR spectroscopic measurements. The UV spectra of III – VII, XII – XIV, which are derivatives of aliphatic aldehydes and ketones, have a single absorption maximum at 280 – 286 nm. The same absorption band is observed in the spectrum of the initial hydrazide I. The UV spectra of the other hydrazones, which are derivatives of aromatic aldehydes and ketones, exhibit two absorption maxima: at 272 – 287 and 313 – 333 nm. The longwave band is due to absorption of the aromatic core conjugated with the N=C bond. The IR spectra of compounds II – XIV display the following absorption bands (cm^{-1}): 3450 – 3360, 3375 – 3230, 3215 – 3180 (N–H in SO_2NH_2 and CONH), 1680 – 1660 (C=O, amide I), 1660 – 1620 (C=N), 1345 – 1325, 1190 – 1160 (SO_2NH_2). The ^{1}H NMR spectra of II – XIV are characterized by a signal at 10.60 – 12.01 ppm (δ scale) attributed to protons of the CONHN=C group.

EXPERIMENTAL CHEMICAL PART

The IR spectra of the synthesized compounds were measured on a Specord M-80 spectrophotometer using samples pelletized with KBr. The ^{1}H NMR spectra were recorded on a Bruker W-80 spectrometer (working frequency, 80 MHz) using DMSO-d_6 as the solvent and HMDS as the internal standard. The UV spectra were measured on a SF-26 spectrophotometer in acetonitrile solutions.

3-Sulfamoyl-4-chlorobenzoic acid hydrazide (I) was synthesized as described in [2]: yield, 77% m.p., 212 – 214°C (water); reported m.p., 211 – 212°C [2].

3-Sulfamoyl-4-chlorobenzoylhydrazones of carbonyl compounds (II – XIV).

To a hot solution of 2.5 g (10 mmole) of compound I in 40 ml of 50% aqueous 2-propanol was added 10 mmole of the corresponding carbonyl compound and 0.6 ml of glacial acetic acid. The reaction medium was boiled during 15 min (for the condensation with aldehydes) or 30 min (for the condensation with ketones) and cooled to room temperature. The

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TABLE 1. Physicochemical Properties of the Synthesized 3-Sulfamoyl-4-chlorobenzoylhydrazones

Compound	Yield, %	M.p., °C	Empirical formula	^{1}H NMR spectrum	UV spectrum	
				CONH (δ, ppm)	λ, nm	log ε
II	87	258 – 260	$C_{12}H_{10}ClN_3O_4S$	11.83	272, 314	4.31, 4.63
III	55	211 – 213	$C_{11}H_{14}ClN_3O_3S$	11.78	286	4.53
IV	56	215 – 217	$C_{12}H_{16}ClN_3O_3S$	11.75	285	4.51
V	42	228 – 230	$C_{14}H_{20}ClN_3O_3S$	11.70	284	4.52
VI	48	233 – 235	$C_{15}H_{22}ClN_3O_3S$	11.69	284	4.50
VII	76	243 – 245	$C_{10}H_{12}ClN_3O_3S$	11.69	286	4.45
VIII	87	255 – 256	$C_{15}H_{14}ClN_3O_3S$	12.01	278, 313	4.31, 4.66
IX	64	297 – 299	$C_{15}H_{14}ClN_3O_4S$	11.10	286, 319	4.38, 4.69
X	67	294 – 296	$C_{15}H_{13}Cl_2N_3O_4S$	11.08	285, 333	4.36, 4.78
XI	62	268 – 270	$C_{16}H_{15}Cl_2N_3O_4S$	11.06	287, 330	4.32, 4.82
XII	92	273 – 275	$C_{19}H_{24}ClN_3O_3S$	10.60	280	4.37
XIII	62	189 – 191	$C_{13}H_{16}ClN_3O_3S$	11.48	284	4.43
XIV	79	245 – 247	$C_{17}H_{20}ClN_3O_3S$	10.84	285	4.49

TABLE 2. Diuretic and Saluretic Activity of Compounds II – XIV

Compound	Diuresis	Natriuresis	Kaliuresis
II	4.0 ± 0.2 / 2.1 ± 0.2 = 1.9*	231 ± 34 / 77 ± 16 = 3.0*	72 ± 14 / 48 ± 15 = 1.5
III	3.8 ± 0.3 / 1.3 ± 0.3 = 2.9*	291 ± 66 / 63 ± 7 = 4.6*	267 ± 10 / 68 ± 5 = 3.9*
IV	5.1 ± 0.8 / 2.1 ± 0.1 = 2.4*	336 ± 59 / 52 ± 9 = 6.5*	152 ± 24 / 50 ± 12 = 3.0*
V	3.4 ± 0.8 / 1.3 ± 0.3 = 2.6*	945 ± 91 / 63 ± 7 = 15.0*	117 ± 10 / 68 ± 5 = 1.7*
VI	4.2 ± 0.4 / 1.2 ± 0.3 = 3.5*	292 ± 10 / 63 ± 20 = 4.6*	164 ± 5 / 68 ± 9 = 2.4*
VII	6.1 ± 0.1 / 3.1 ± 0.1 = 2.0*	140 ± 10 / 70 ± 15 = 2.0*	170 ± 10 / 85 ± 20 = 2.0*
VIII	3.3 ± 0.5 / 1.6 ± 0.5 = 2.1*	208 ± 39 / 66 ± 17 = 3.2*	78 ± 10 / 47 ± 20 = 1.7
IX	3.0 ± 0.4 / 1.6 ± 0.5 = 1.9*	73 ± 28 / 66 ± 17 = 1.1	12 ± 2 / 47 ± 20 = 0.3*
X	5.0 ± 0.1 / 2.9 ± 0.2 = 1.7*	91 ± 14 / 69 ± 11 = 1.3	90 ± 10 / 50 ± 10 = 1.8*
XI	3.2 ± 0.2 / 2.1 ± 0.1 = 1.5*	116 ± 32 / 52 ± 9 = 2.2*	112 ± 24 / 50 ± 12 = 2.2*
XII	6.0 ± 0.5 / 2.6 ± 0.3 = 2.3*	292 ± 18 / 70 ± 18 = 4.2*	85 ± 15 / 77 ± 18 = 1.1
XIII	4.5 ± 0.4 / 2.8 ± 0.3 = 1.6*	316 ± 32 / 98 ± 15 = 3.2*	126 ± 16 / 87 ± 18 = 1.4
XIV	5.0 ± 0.4 / 2.8 ± 0.3 = 1.8*	346 ± 30 / 98 ± 15 = 3.5*	106 ± 18 / 87 ± 18 = 1.2

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

precipitate was filtered, washed with 20 ml of 50% aqueous 2-propanol, crystallized from 65% aqueous dioxane (II, VII – XII, XIV) or 50% aqueous 2-propanol (III – VI, XIII), and dried at 105°C. The yield and physicochemical characteristics of compounds II – XIV are listed in Table 1.

EXPERIMENTAL PHARMACOLOGICAL PART

The effect of compounds II – XIV on diuresis, natriuresis, and kaliuresis was studied on intact white rats weighing 200 – 300 g as described in [3, 4]. Total diuresis and the excretion of sodium and potassium ions were determined 4 h after the beginning of experiment. The concentrations of sodium and potassium ions in the urine were determined by flame photometry on an PAZh-1 spectrophotometer. Each compound was introduced into the tested animals via a gastric tube at a dose of 25 mg/kg in the form of a mucous starch suspension; the control group obtained the same amount of pure starch mucus. The aqueous load in the test and control groups amounted to 2% of the animal bode weight. The diuretic, natriuretic, and kaliuretic activities were evaluated by the ratios of the magnitudes of diuresis, natriuresis, and kaliuresis of test animals to the corresponding values in the control.

As is seen from data presented in Table 2, all the synthesized compounds produced a reliable increase in the level of diuresis (1.5 – 3.5 times). Compounds II – VIII and XI – XIV reliably increased the level of natriuresis. The effect is most pronounced in the case of 3-sulfamoyl-4-chlorobenzoylhydrazones of aliphatic aldehydes (III – VI). The natriuretic activity initially increases with elongation of the chain of aliphatic substituent R′, reaching a maximum for 3-sulfamoyl-4-chlorobenzoylhydrazones of enanthic aldehyde (V), and then drops. Note that the kaliuretic activity in the same group of compounds (III – VI) varies in the inverse manner with increasing length of aliphatic substituent R′, reaching the minimum for compound V. The diuretic (and, hence, natriuretic) activity of 3-sulfamoyl-4-chlorobenzoylhydrazones of acetophenone (VIII) and its substituents (IX – XI) is generally lower as compared to that of aliphatic aldehydes (III – VI). The hydrazones of cyclic ketones (XIII, XIV) exhibit a lower diuretic and saluretic activity as compared to that of the hydrazones of aliphatic aldehydes and ketones (III – VII).

Note that the duration of diuretic action of the compounds studied in this work is generally longer (3 – 4 h, and even 5 h for compound XII) than that observed for the compounds studied in [1]. A comparative analysis of the data obtained in this work and those reported in [1] suggests that the diuretic and saluretic activity can be affected by both steric and electronic factors.

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