SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF SULFONAMIDO-1,3,4-THIADIAZOLES

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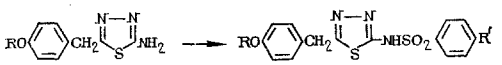
In continuing a search for new compounds with hypoglycemic activity (HA) [1], we accomplished the synthesis of several sulfonamides incorporating the 1,3,4-thiadiazole ring. The HA of compounds frequently is connected with the presence of a thiadiazole ring, such as, for example, the earlier-described [2] HA of the antibacterial sulfonamide 2-(4-aminobenzoylsulfonamido)-5-isopropyl-1,3,4-thiadiazole, which also was used for the treatment of diabetes [3]. Furthermore, these studies were expanded [4-6], and the authors proposed that the manifestation of HA is inherent in derivatives of 1,3,4-thiadiazole carrying a 3-5 carbon alkyl substituent in position 5. On the basis of this information we undertook the synthesis of analogous biologically active derivatives of 1,3,4-thiadiazoles to study the influence of substituents in position 5 on HA. Specifically, in the compounds we prepared, we introduced an alkoxybenzyl group instead of an alkyl group in position 5 of the thiadiazole ring. The synthesis was accomplished according to the scheme:



I II-XIX

II — VII: R = CH_3, C_2H_5, C_3H_7, iso-C_3H_7, C_4H_9, iso-C_4H_9, R = CH_3;
VIII — XIII: R = CH_3, C_2H_5, C_3H_7, iso-C_3H_7, C_4H_9, iso-C_4H_9, R = OCH_3;
XIV — XIX: R = CH_3, C_2H_5, C_3H_7, iso-C_3H_7, C_4H_9, iso-C_4H_9, R = $NHCOCH_3$.

2-Amino-5-(4-alkoxybenzyl)-1,3,4-thiadiazole (I) was prepared by cyclization of 1-(4-alkoxyphenylaceto)-thiosemicarbazide in acidic medium [8]. The interaction of thiadiazole (I) with the corresponding arylsulfonyl chloride took place to give sulfonamidothiadiazoles (II-XIX). The latter were stable, crystalline substances identified by mass-spectrometric and elemental analyses, and TLC.

In the mass-spectra of sulfonamidothiadiazoles (II), (VIII), and (XIV) were of the SO_2-group. In addition, the presence in the spectrum of peaks from fragments characteristic for these compounds permits the acceptance of the proposed structures. Thus, for compound (II), the following characteristics were found (the numbers before the parentheses denote the mass of the ion, in the parentheses are given the relative intensities in % of the most intense peak): 375 (36), 311 (24), 220 (53), 179 (18), 147 (41), 146 (42), 121 (100), 91 (13), for compound (VIII): 391 (22), 376 (8), 327 (28), 220 (47), 179 (21), 147 (52), 146 (28), 121 (100), 91 (20), and for compound (XIV): 418 (13), 376 (31), 375 (11), 354 (28), 220 (43), 179 (13), 147 (32), 146 (23), 121 (100), 91 (18).

The HA results for compounds (II-XIX) are shown in Table 1. Some of the studied compounds showed a moderate HA. Thus, compound (II) (R = CH_3, R' = CH_3) reduced the level of sugar in the blood by 19.7%, an increase in the alkyl substituent in this series leads to a reduction of HA, i.e., compounds (IV) (R = C_3H_7, R' = CH_3) and (V) (R = iso-C_3H_8, R' = CH_3) reduce the blood sugar level by an average of 12.7% and compounds (III), (VI), and (VII) (R = C_2H_5, C_4H_9, and iso-C_4H_9, R' = CH_3) are devoid of activity. By substitution of methoxy for the methyl group (R') (thiadiazoles VIII-XIII), produces activity in only one compound (IX), which decreases the blood sugar by 16%. Among the thiadiazoles (XIV-XIX) (R = $NHCOCH_3$), significant HA (18%) is shown only by compound (XIV) (R = CH_3). Enlargement or branching of the alkyl radical R in this series does not have a positive influence on HA.

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TABLE 1. Sulfonamido-1,3,4-thiadiazoles (II-XIX)

Compound	R	R′	Yield, %	mp, °C	R_f	Found, %		Empirical formula	Calculated, %		Level of glucose in blood, mg/100 ml (M ± t)		
						N	S		N	S	before introduction of the preparation	after introduction of the preparation dose: 100 mg/kg	after introduction of the preparation dose: 250 mg/kg
II	CH_3	CH_3	71,5	222—3	0,79	11,31	17,36	$C_{17}H_{17}N_3O_2S_2$	11,19	17,08	96±3,5	90±3,15	77±3,3‡
III	C_2H_5	CH_3	73,2	207—8	0,78	10,57	16,71	$C_{18}H_{19}N_3O_3S_2$	10,78	16,46	106±6,68	106±6,6	113±6,65
IV	C_3H_7	CH_3	73,9	216—7	0,76	10,23	15,58	$C_{19}H_{21}N_3O_3S_2$	10,41	15,89	102±2,68	100±2,74	89±3,93†
V	iso-C_3H_7	CH_3	66,7	229—31	0,77	10,06	15,76	$C_{19}H_{21}N_3O_3S_2$	10,41	15,89	102±3,04	98±3,26	89±2,77*
VI	C_4H_9	CH_3	64,8	210—1	0,75	9,88	15,07	$C_{20}H_{23}N_3O_3S_2$	10,06	15,36	100±1,1	94±5,35	88±5,32
VII	iso-C_4H_9	CH_3	65,3	216—7	0,74	10,08	15,20	$C_{20}H_{23}N_3O_3S_2$	10,06	15,36	105±5,3	110±2,2	105±5,32
VIII	CH_3	OCH_3	68,1	247—8	0,85	10,61	16,02	$C_{17}H_{17}N_3O_4S_2$	10,73	16,38	105±5,32	94±5,65	94±5,72
IX	C_2H_5	OCH_3	68,3	217—8	0,84	10,23	15,63	$C_{18}H_{19}N_3O_4S_2$	10,38	15,81	116±2,73	100±1,2	97±3,58**
X	C_3H_7	OCH_3	62,7	224—5	0,81	9,88	14,93	$C_{19}H_{21}N_3O_4S_2$	10,01	15,28	89±5,3	83±9,5	84±1,3
XI	iso-C_3H_7	OCH_3	61,9	235—6	0,83	10,21	15,06	$C_{19}H_{21}N_3O_4S_2$	10,01	15,28	84±1,0	89±5,3	89±5,1
XII	C_4H_9	OCH_3	74,0	218—9	0,80	9,45	14,41	$C_{20}H_{23}N_3O_4S_2$	9,69	14,79	100±4,2	106±6,7	86±6,7
XIII	iso-C_4H_9	OCH_3	67,7	223—4	0,82	9,71	14,56	$C_{20}H_{13}N_3O_4S_2$	9,69	14,79	100±2,2	110±5,3	110±5,3
XIV	CH_3	$NHCOCH_3$	62,3	237—8	0,67	13,52	15,18	$C_{18}H_{18}N_4O_4S_2$	13,39	15,32	98±2,0	96±3,9	80±3,2*
XV	C_2H_5	$NHCOCH_3$	67,5	221—2	0,68	13,16	14,56	$C_{19}H_{20}N_4O_4S_2$	12,95	14,82	105±3,6	115±6,7	102±4,8
XVI	C_3H_7	$NHCOCH_3$	59,1	215—6	0,71	12,25	14,18	$C_{20}H_{22}N_4O_4S_2$	12,54	14,36	124±1	134±1,2	135±1,3*
XVII	iso-C_3H_7	$NHCOCH_3$	54,8	203—5	0,69	12,75	14,15	$C_{20}H_{22}N_4O_4S_2$	12,54	14,36	114±4,3	118±4,8	125±1,1*
XVIII	C_4H_9	$NHCOCH_3$	63,7	196—8	0,72	12,50	13,75	$C_{21}H_{24}N_4O_4S_2$	12,16	13,92	117±2,7	114±6,0	114±1,4
XIX	iso-C_4H_9	$NHCOCH_3$	58,6	188—90	0,70	12,38	13,69	$C_{21}H_{24}N_4O_4S_2$	12,16	13,92	118±5,5	122±2,3	121±7,6
Butazolamide	—	—	—	—	—	—	—	—	—	—	85±2,2	71±1,7***	64±2,7*

*P < 0.01
†P < 0.02
‡P < 0.05

Toxic effects in animals were not observed on introduction of the compounds showing HA in doses of 750 mg/kg or more.

Thus, in the above series of sulfonamidothiadiazoles, HA primarily is shown by compounds with R = CH_3.

From the results obtained, the presence of an alkyl substituent on position 5 of the sulfonamidothiadiazole ring is optional with regard to HA. In this series, the activity indicated was assured by the alkoxybenzyl substituent.

EXPERIMENTAL (CHEMICAL)

Mass spectra were obtained on an MX-1303 instrument with direct introduction of the sample at an ionization potential of 30 eV and an introduction temperature of 30-40°C lower than the melting point of the substance. The melting points were obtained with a Boethius 72/2064 hot stage. TLC was carried out on Silufol UV-254 plates, and the spots were observed in an Ultrachemoscope or in iodine vapor.

2-Tosylamido-5-(4-alkoxybenzyl)-1,3,4-thiadiazoles (II-VII). Toluene sulfonyl chloride (0.95 g, 5 mmoles) was added portionwise over 15 min to a solution prepared by gently heating a mixture of the corresponding I (5 mmoles) and 5 ml of pyridine. The mixture was heated at 50-60°C for 30 min. The cooled solution was poured into 50 ml of cold water, and the resulting precipitate was filtered off and recrystallized from acetic acid. TLC system, acetone–benzene, 1:1 (Table 1).

2-(4-Methoxybenzenesulfonamido)-5-(4-alkoxybenzyl)-1,3,4-thiadiazoles (VIII-XIII). Prepared analogously with thiadiazoles (II-VII) from 5 mmoles of the corresponding (I) and 1.03 g (5 mmoles) of 4-methoxybenzenesulfonyl chloride by heating at 70-80°C for 2 h. TLC system, acetone–benzene, 1:1 (Table 1).

2-(4-Acetamidobenzenesulfonamido)-5-(4-alkoxybenzyl)-1,3,4-thiadiazoles (XIV –XIX). To a solution of 5 mmoles of the corresponding (I) in 10 ml of pyridine was added portionwise with shaking 1.10 g (5 mmoles) of 4-acetamido-benzenesulfonyl chloride over a period of 20 min. The mixture was heated in a water bath for 3 h, and allowed to stand for 5-6 h. The resulting precipitate was filtered, washed with water, and dried. Recrystallization was carried out with acetic acid, after treatment with activated charcoal. TLC system; methanol–ether, 1:1 (see Table 1).

EXPERIMENTAL (PHARMACOLOGICAL)

The HA of the compounds was determined by the orthotoluidine method. The preparations were introduced into the rats intraperitoneally in dosages of 100 and 250 mg/kg. Blood samples were taken by decapitation 2-2.5 h after introduction of the preparations. The activity of each dose was studied in an average of 6-8 animals.

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