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DERIVATIVES OF ARYLSULFONIC ACIDS. SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF 4-ALKOXYBENZENESULFONYLCARBAMIDES AND 4-ALKOXYBENZENESULFONYLTHIOSEMICARBAZIDES

M. A. Kaldrikyan, V. A. Geboyan, A. A. Aroyan,* N. O. Stepanyan, and Zh. M. Bunatyan

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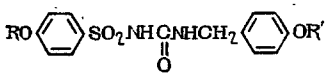
In order to find a link between the chemical structure and the hypoglycemic activity of 4-alkoxybenzenesulfonic acids [1], we have prepared some alkoxybenzenesulfonylcarbamides I and sulfonylthiosemicarbazides II.



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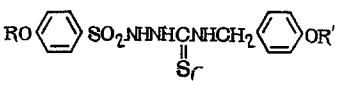
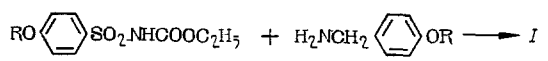


Compounds I and II differ from those synthesized earlier [2] in that they contain an alkoxybenxyl radical so that the effect of this group on the hypoglycemic activity can be determined.

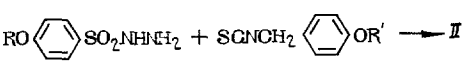
One of the most suitable and convenient methods of synthesizing I [3] is by the reaction of the ethyl esters of 4-alkoxybenzenesulfonylcarbamic acids with alkoxybenzylamines:



The ethyl 4-alkoxybenzenesulfonylcarbamates were prepared by heating 4-alkoxybenzenesulfonylamides with ethyl chlorocarbonate in the presence of dry potash [4]. The 4-alkoxybenzylamines were synhesized by the condensation of alkoxybenzyl chlorides with potassium phthalimide with subsequent hydrolysis of the alkoxybenzylphthalimides [5].

Structures of the 4-alkoxybenzenesulfonylcarbamides I were confirmed by IR spectroscopy; the SO_2 group gives rise to absorption bands at 1170 and 1370, 1180 and 1335, 1185 and 1340 cm^{-1}, and the associated NH group gives characteristic bands at 3240-3380 cm^{-1}.

The sulfonylthiosemicarbazides II were prepared by heating 4-alkoxybenzenesulfonylhydrazides [1] and 4-alkoxybenzeneisothiocyanates [6] for two h:



In the IR spectra of the latter, the C=S group absorbs at 1565, 1180, and 975 cm^{-1}, the SO_2 group at 1160 and 1380 cm^{-1}, and 1175 and 1340 cm^{-1}, and the NH group at 3160, 3265, and 3370 cm^{-1}.

*Deceased.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Erevan. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 10, pp. 54-57, October, 1978. Original article submitted January 13, 1978.

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TABLE 1. 4-Alkoxybenzenesulfonylcarbamides I and Their Hypoglycemic Action

R	R′	Yield, %	Melting point, °C	R_f	Found, %		Empirical formula	Calculated, %		Level of glucose in blood, mg/100 ml				
										before injection of compound	after injection of compound			
					N	S		N	S		100 mg/kg		250 mg/kg	
CH_3	C_2H_5	73,3	193—4	0,61	7,98	9,19	$C_{17}H_{20}N_2O_5S$	7,68	8,79	79±2,7	86±5,7		95±2,5	(<0,02)
CH_3	C_3H_7	79,9	162—3	0,56	7,59	8,18	$C_{18}H_{22}N_2O_5S$	7,40	8,47	83±2,1	83±2,8		74±4,1	(>0,05)
CH_3	iso-C_3H_7	76,5	175—6	0,60	7,33	8,20	$C_{18}H_{22}N_2O_5S$	7,40	8,47	85±1,5	100±6,0		100±1,2	(<0,01)
CH_3	C_4H_9	75,0	149—5	0,49	7,39	8,34	$C_{19}H_{24}N_2O_5S$	7,13	8,17	71±4,9	85±4,2	(>0,05)	89±8,6	(>0,05)
C_2H_5	CH_3	65,0	195—6	0,74	7,41	9,01	$C_{17}H_{20}N_2O_5S$	7,68	8,79	60±0,55	65±3,6		59±13	
C_2H_5	C_2H_5	50,0	208—9	0,66	7,73	8,18	$C_{18}H_{22}N_2O_5S$	7,40	8,47	85±1,5	78±2,0		82±3,0	
C_2H_5	C_3H_7	80,0	204—5	0,52	7,26	8,30	$C_{19}H_{24}N_2O_5S$	7,13	8,17	90±1,0	72±8,0	(>0,05)	86±6,2	(>0,05)
C_2H_5	iso-C_3H_7	64,3	193—4	0,72	7,08	8,02	$C_{19}H_{24}N_2O_5S$	7,13	8,17	92±1,6	103±3,0	(<0,001)	108±8,0	(<0,01)
C_2H_5	C_4H_9	78,5	182—3	0,52	7,17	8,16	$C_{20}H_{26}N_2O_5S$	6,89	7,88	72±1,4	125±2,1	(<0,001)	145±4,7	(<0,001)
C_3H_7	C_2H_5	65,5	197—8	0,60	7,04	8,39	$C_{19}H_{24}N_2O_5S$	7,13	8,17	99±0,6	79±4,2		81±4,4	(<0,01)
C_3H_7	C_3H_7	81,2	199—200	0,65	6,74	7,62	$C_{20}H_{26}N_2O_5S$	6,89	7,88	99±1,0	88±7,1		88±1,1	(>0,05)
C_3H_7	iso-C_3H_7	66,6	177—8	0,63	7,16	7,53	$C_{20}H_{26}N_2O_5S$	6,89	7,88	77±1,0	68±2,3		79±2,0	
C_3H_7	C_4H_9	76,8	173—4	0,61	6,96	7,48	$C_{21}H_{28}N_2O_5S$	7,22	7,62	95±2,9	105±3,7		93±7,6	
C_4H_9	CH_3	64,4	159—60	0,60	6,79	8,50	$C_{19}H_{24}N_2O_5S$	7,13	8,17	96±4,1	82±3,7		100±1,2	
C_4H_9	C_2H_5	56,5	164—5	0,67	6,71	8,10	$C_{20}H_{26}N_2O_5S$	6,89	7,88	75±1,0	72±6,4		105±8,8	(<0,002)
C_4H_9	C_3H_7	78,8	174—5	0,64	6,48	7,23	$C_{21}H_{28}N_2O_5S$	6,66	7,62	78±2,0	116±8,5	(<0,001)	147±12	(<0,001)
C_4H_9	iso-C_3H_7	75,3	154—6	0,73	6,83	8,18	$C_{21}H_{28}N_2O_5S$	6,66	7,62	82±4,3	72±3,0		90±4,6	
C_4H_9	C_4H_9	85,7	175—6	0,56	6,52	7,25	$C_{22}H_{30}N_2O_5S$	6,44	7,37	105±3,0	110±1,4		106±2,2	
iso-C_4H_9	CH_3	50,7	133—4	0,65	7,10	8,44	$C_{19}H_{24}N_2O_5S$	7,13	8,17	74±6,7	81±3,1		82±5,6	(>0,05)
iso-C_4H_9	C_2H_5	54,3	174—5	0,70	7,15	7,50	$C_{20}H_{26}N_2O_5S$	6,89	7,88	85±8,2	85±4,8		114±5,0	(>0,05)
iso-C_4H_9	C_3H_7	74,6	176—7	0,66	6,73	8,00	$C_{21}H_{28}N_2O_5S$	6,66	7,62	115±7,7	108±1,0	(>0,05)	128±6,4	(>0,05)
iso-C_4H_9	iso-C_3H_7	72,1	116—7	0,75	6,95	7,50	$C_{21}H_{28}N_2O_5S$	6,66	7,62	115±7,7	124±2,0		153±1,0	(<0,01)
iso-C_4H_9	C_4H_9	89,5	168—9	0,58	6,21	7,50	$C_{22}H_{30}N_2O_5S$	6,44	7,37	90±1,5	83±1,2		86±2,2	(>0,05)

Note. Values of P are given in parentheses.

TABLE 2. 4-Alkoxybenzenesulfonylthiosemicarbazides II

R	Yield, %	Melting point, °C	R_f	Found, %		Empirical formula	Calculated, %	
				N	S		N	S
CH_3	63.1	163—4	0,58	10,38	16.91	$C_{16}H_{19}N_3O_4S$	10,00	16.80
C_2H_5	60.0	171—2	0,55	10,19	15.33	$C_{18}H_{23}N_3O_4S$	10,20	15,60
C_3H_7	55.7	163—4	0,66	9,73	14.56	$C_{20}H_{27}N_3O_4S$	9,60	14,65
C_4H_9	43.4	165—6	0,77	9,36	13.55	$C_{22}H_{31}N_3O_4S$	9,02	13.77
iso-C_4H_9	51.3	168—9	0,76	9.26	13.67	$C_{22}H_{31}N_3O_4S$	9.02	13.77

Structures of the individual compounds were verified by thin-layer chromatography and elemental analysis.

The hypoglycemic activity was determined using the glucose reagent o-toluidine. The compounds were injected intraperitoneally into rats (100 and 250 mg/kg) and after 2-2.5 h the animals were decapitated and blood samples were taken.

As can be seen from Table 1, almost all of the sulfonylcarbamides with R = CH_3 or C_2H_5 had a hyperglycemic effect. Derivatives of 4-propoxybenzenesulfonylcarbamide exhibited the greatest hypoglycemic activity; of these, the most active were compounds I with R = C_3H_7; R' = C_2H_5; C_3H_7 (100 mg/kg) which lowered the blood glucose by 18 and 11% respectively. When R was increased to C_4H_9 and iso-C_4H_9, the hypoglycemic activity decreased and disappeared.

For the sulfonylcarbamides I with R = C_4H_9 and iso-C_4H_9, a change of R' from CH_3 to iso-C_4H_9 gave compounds with hyperglycemic activity.

This study of 4-alkoxybenzenesulfonylthiosemicarbazides II showed that only one of them (R = C_2H_5; R' = CH_3) showed any appreciable hypoglycemic activity.

EXPERIMENTAL

Thin-layer chromatography was carried out on UV-254 silufol plates using ether—petroleum ether (3 : 1) as solvent; the plates were developed in UV light. IR spectra were taken in mineral oil suspension on a UR-10 spectrometer with sodium and lithium chloride prisms.

Ethyl 4-alkoxybenzenesulfonylcarbamates. A mixture of 0.044 mole of the 4-alkoxybenzenesulfamide, 15.1 g (0.11 mole) of anhydrous potash, and 60 ml of absolute acetone was refluxed for 3 h; 6.3 g (0.058 mole) of ethyl chlorocarbonate was added and heating continued for 18 h. The reaction mixture was filtered, the precipitate dissolved in water, and the solution filtered. The filtrate was acidified with concentrated hydrochloric acid and the crystalline precipitate filtered off.

Yield of ethyl 4-propoxybenzenesulfonylcarbamate 72.8% mp 70-80°C. Found, %: N 4.53; S 11.35. $C_{42}H_{17}NO_5S$. Calculated, %: N 4.89; S 11.25.

Yield of ethyl 4-butoxybenzenesulfonylcarbamate 60.7% mp 61-62°C. Found, %: N 4.22; S 11.00. $C_{13}H_{19}NO_5S$. Calculated, %: N 4.51; S 10.63.

Yield of ethyl 4-iso-butoxybenzenesulfonylcarbamate 75.4%, mp 65-66°C. Found, %: N 4.25; S 10.51. $C_{13}H_{19}NO_5S$. Calculated, %: N 4.51; S 10.63.

N(4-alkoxybenzenesulfonyl)-N'-(4-alkoxybenzyl)carbamides(I). A mixture of 0.0035 mole of ethyl 4-alkoxybenzenesulfonylcarbamate 0.003 mole of 4-alkoxybenzylamine, and 10 ml of toluene was refluxed for 5-6 h. The crystals which separated on cooling were filtered off and recrystallized from ethanol (see Table 1).

4-Alkoxybenzenesulfonyl-4-alkoxybenzenethiosemicarbazides (II). A mixture of 0.01 mole of 4-alkoxybenzenesulfonylhydrazide, 0.012 mole of freshly prepared 4-alkoxybenzylisothiocyanate, and 20 ml of ethanol was refluxed for 2 h. On cooling crystals separated and were filtered off and recrystallized from ethanol (Table 2).

4-Alkoxybenzenesulfonylbenzoylthiosemicarbazide was obtained by the same method using 0.01 mole of 4-alkoxybenzenesulfonylhydrazide and 0.012 mole of benzoylisothiocyanate.

Yield of 4-methoxybenzenesulfonylbenzoylthiosemicarbazide 63.5%, mp 149-150°C. Found, %: N 11.62; S 17.76. $C_{15}H_{15}N_3O_4S$. Calculated, %: N 11.49; S 17.54.

Yield of 4-ethoxybenzenesulfonylbenzoylthiosemicarbazide 60.4%, mp 151-152°C. Found, %: N 11.31; S 16.76. $C_{16}H_{17}N_3O_4S$. Calculated, %: N 11.07; S 16.90.

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CORONARY DILATING ACTIVITY OF SOME N-DERIVATIVES OF 2,2-DIMETHYL-3-OXY-8-AZASPIRO[5,5]UNDECANE

R. A. Aleksanyan, É. S. Marashyan, and A. S. Noravyan

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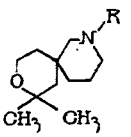
A new method of synthesizing β-aminoalcohols of the tetrahydropyran series, by the interaction of 4-cyanotetrahydropyranols-4 with ketones in the presence of Raney nickel catalyst under pressure and with heating, was previously reported [1]. Those investigations were extended among derivatives of six-membered heterocyclic compounds; it was shown that in the reduction of 2,2-dimethyl-4-formyl-4-β-cyanoethyltetrahydropyran under those conditions there is cyclization with the formation of 8,8-dimethyl-2-azo-9-oxy[5,5]-undecane [2, 3] whose derivatives show coronary dilating activity.



I: R=H
II: R=$COCH_3$
III: R=C_2H_5

The present report contains results of the pharmacological investigation of those compounds.

EXPERIMENTAL

Coronary dilating activity of the specified compounds was investigated in cats, narcotized with urethane (ethyl carbamate) and chlorazol. The volume rate of coronary blood flow was registered by the method of Moravits and Tsan, using N. V. Kaverina's modification [4]. The point of the method consists of measuring the blood rate volume flowing through the coronary vessels of the heart. The compounds used were introduced into the femoral vein. Compound I and II were investigated in 3 cats, and the comparatively active substance III was investigated in 12 cats. The investigations were conducted in the fall.

The compounds investigated were active with respect to coronary blood circulation. We determined that compound I has weak coronary dilating activity. After intravenous introduction of that compound we noted an increase in the rate volume of coronary flow by 20 ± 5.1% within 15 to 17 min. Compound II shows biphasic activity. At first it lowers the rate volume of coronary flow by 50 ± 9.2% within 45 to 95 min, then it increases

A. L. Mndzhoyan Institute of Micro-Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan.

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