SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SOME AMIDES OF SALICYLIC ACID — α-AMINO ACID DERIVATIVES

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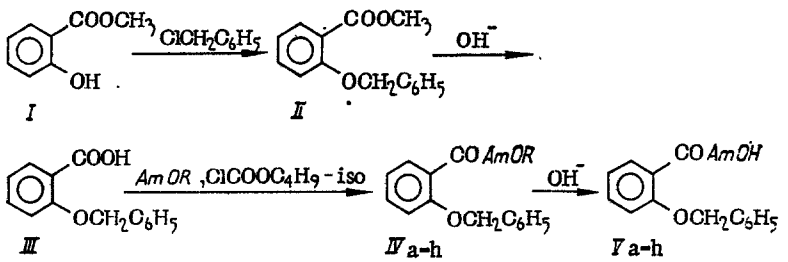
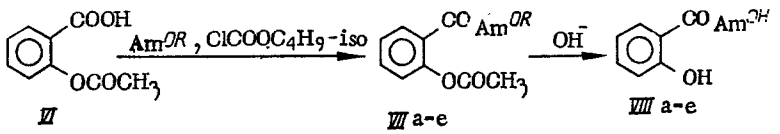
Salicylic acid and its derivatives have fever-reducing and anti-inflammatory activity [1].

With the objective of studying the connection between chemical structure and biological activity in the salicylic acid series, we have prepared amino acid derivatives by the following scheme:



where R = CH_3 or C_2H_5, and Am = glycyl, L-alanyl, LD-valyl, LD-leucyl, L-phenylalanyl, L-tryptophyl, p-aminobenzoyl, or glycylglycyl, as well as the o-acetoxy derivatives, by the scheme:



where R = C_2H_5, and Am = glycyl, L-alanyl, DL-valyl, DL-leucyl, or L-phenylalanyl.

The methyl ester of o-benzyloxybenzoic acid (II) was prepared by the action of benzyl chloride on methyl salicylate (I) in the presence of sodium alcoholate; by subsequent hydrolysis of this compound, o-benzyloxybenzoic acid (III) was prepared.

Synthesis of esters of N-(o-benzyloxybenzoyl) (IV) and N-(o-acetoxybenzoyl) (VII) amino acids was effected by the mixed anhydride method of [2], by the action of isobutyl chloroformate on III or VI, then by the action of an alkyl ester of the amino acids in dry tetrahydrofuran medium. Derivatives of the N-(o-acetoxybenzoyl)-amino acid (VII) were obtained by the same method.

The corresponding N-(o-benzyloxybenzoyl) amino acids (V) were obtained by the hydrolysis of IV); and the N-(o-hydroxybenzoyl) amino acids (VIII), by the hydrolysis of VII.

The hydrazides (IX) of the acids (V) were also prepared by the action of hydrazine of IV in absolute alcohol medium.

The purity and identity of the compounds prepared were established by thin-layer chromatography (TLC), elemental analysis, and IR and mass spectrometry.

In the IR spectra of IV and VII, absorption is observed in the regions of 1750, 1680, and 1560 cm^{-1} (ester and amide carbonyl), 3420-3350 cm^{-1} (NH), and 1265 cm^{-1} (C=O=C); and in the IR spectrum of VIII, at 3580 cm^{-1} (OH).

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Intense peaks of molecular ions and peaks corresponding to fragments are observed in the mass spectra of IVb and VIIIa.

The fever-reducing and anti-inflammatory properties of compounds prepared from the N-(o-benzyloxybenzoyl) amino acid and N-(o-hydroxybenzoyl) amino acid groups were studied on the models of yeast fever [3] and carrageenan inflammation in rats [4]. The preparations were administered to the animals orally in doses of 50, 75, and 100 mg/kg. Each dose of the preparations was studied on 4 to 6 animals. Of all the compounds, only N-(o-benzyloxybenzoyl)-DL-leucine and -DL-valine in doses of 75 and 100 mg/kg reliably reduced fever by 1°C ($P = 0.01$) and exerted no action on carrageenan inflammation. In the indicated doses, the rest of the compounds had no anti-inflammatory or fever-reducing properties.

A control aspirin preparation in a dose of 75 mg/kg reduced the temperature in yeast fever by 1°C ($P < 0.05$) and suppressed carrageenan edema to the extent of 57% ($P = 0.02$).

EXPERIMENTAL

Chemical

For the TLC we used Silufol UV-254 plates (from Czechoslovakia); the mobile phase was propanol-water (7:3); and detection was with UV light or iodine vapor. The IR spectra were taken on a UR-20 spectrometer in vaseline oil (sodium chloride or lithium fluoride prism); the mass-spectra, on an MKh-1303 instrument with direct injection of the substances at temperatures which exceeded their mp by 10°C, and with an ionizing electron energy of 40-45 eV.

Methyl-o-Benzyloxybenzoate (II). To the sodium ethoxide prepared from 23.0 g (1 mole) of sodium and 500 ml of absolute alcohol was added 152.15 g (1 mole) of I, at room temperature. After 10-minute stirring, 164.5 g (1.3 mole) of benzyl chloride was added. The mixture was boiled for 20 h, and the precipitate was filtered off. The alcohol was evaporated, the residue was extracted with ether, and the extract was washed with a 10% sodium hydroxide solution and dried with sodium sulfate. After the solvent had been stripped off, the residue was distilled under vacuum at 205-207°C/4 mm. Compound II was obtained (145 g, 60%). $R_f = 0.65$. Found, %: C 74.50; H 5.55. $C_{15}H_{14}O_3$. Calculate, %: C 74.36; H 5.82. IR spectrum (ν, cm^{-1}): 1610 (C=C aromatic ring), 1680-1720 (C=O).

o-Benzyloxybenzoic acid (III). Sodium hydroxide (30 ml of 1 N) was added to a solution of 2.42 g (0.01 mole) of II in 40 ml of methanol at 20°C. The mixture was stirred at 45-50°C for 5-6 h. The methanol was distilled off, 50 ml of water was added, the contents was extracted with ether, and the water layer was acidified at 0°C with 1 N hydrochloric acid, to a pH of 4.0-5.0. The precipitate of III which fell was filtered off and recrystallized from a methanol-ether (1:3) mixture. It had mp 56-57°C; the yield was 1.49 g (65.5%). After recrystallization from an alcohol–water (1:2) mixture, it had mp 58-50°C. $R_f = 0.40$. Found, %: C 73.40; H 5.60. $C_{14}H_{12}O_3$. Calculate, %: C 73.66; H 5.29. Compound Va-h were prepared from IVa-h under similar conditions (Table 1).

Ethyl N-(o-Benzyloxybenzoyl)glycylglycine (IVh). Isobutyl chloroformate (1.36 g, 0.01 mole) was added at −5 to −7°C to a solution of 2.28 g (0.01 mole) of III and 1.01 g (0.01 mole) of triethylamine in 30 ml of tetrahydrofuran. The mixture was stirred for 15-20 min, after which a mixture of 1.93 g (0.01 mole) of ethyl glycylglycinate hydrobromide and 1.01 g (0.01 mole) of triethylamine in 20 ml of dry dimethylformamide was added to it dropwise. After 3 to 4 h of stirring at room temperature, the solvent was distilled off. The residue

TABLE 1. N-(o-Benzyloxybenzoyl) amino acids (Va-h)

Compound	Am	Yield, %	mp, °C	R_f	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
Va	Gly	63,5	86—8	0,42	67,50	5,60	4,48	$C_{16}H_{15}NO_4$	67.35	5,29	4,90
Vb	L-Ala	73,6	162—3	0,82	68,32	5,50	4,80	$C_{17}H_{17}NO_4$	68,21	5,72	4,67
Vc	DL-Val	78,8	165—7	0,50	69,79	6,58	4,44	$C_{19}H_{21}NO_4$	69,70	6,46	4,27
Vd	DL-Leu	74,3	179—80	0,55	70,40	6,45	4,42	$C_{20}H_{23}NO_4$	70,36	6,79	4,10
Ve	L-Phe	65,3	158—9	0,49	73,80	5,80	3,90	$C_{23}H_{21}NO_4$	73,58	5,63	3.73
Vf	p-Aminobenzoyl	79,9	159—60	0,63	72,80	4,20	4,80	$C_{21}H_{17}NO_4$	72,61	4.93	4,03
Vg	L-try	72,2	74—5	0,82	72,60	5,60	6,50	$C_{25}H_{24}N_2O_4$	72,09	5,80	6,72
Vh	Empirical	68,8	71—2	0,65	63,50	5,50	8,00	$C_{18}H_{18}N_2O_5$	63,14	5,29	8,18

TABLE 2. Methyl and Ethyl Esters of N-(o-Benzyloxybenzoyl) and N-(o-Acetoxybenzoyl) Amino Acids (IVa-h, VIIa-e).

Compound	Am	R	R'	Yield, %	R_f	Found, %			Empirical formula	Calculated, %		
						C	H	N		C	H	N
IVa	Gly	CH_3	$CH_2C_6H_5$	75,3	0,76	68,30	5,50	4,50	$C_{17}H_{17}NO_4$	68,21	5,72	4,67
IVb	L-Ala*	CH_3	$CH_2C_6H_5$	73,6	0,74	68,75	6,00	4,30	$C_{18}H_{15}NO_4$	68,99	6,17	4,46
IVc	DL-Val	CH_3	$CH_2C_6H_5$				6,49	4,30	$C_{20}H_{23}NO_4$	70,36	6,79	4,10
IVd	DL-Leu	C_2H_5	$CH_2C_6H_5$				7,36	3,99	$C_{21}H_{25}NO_4$	71,		79
IVe	L-Phe	CH_3	$CH_2C_6H_5$						$C_{24}H_{23}NO_4$	74,		59
IVf	p-Aminobenzoyl	CH_3	$CH_2C_6H_5$						$C_{22}H_{18}NO_4$	73,	5,27	3,
IVg	L-Try	C_2H_5	$CH_2C_6H_5$						$C_{27}H_{27}N_2O_4$	73,11	6,13	6,31
IVh	Empirical	C_2H_5	$CH_2C_6H_5$						$C_{24}H_{22}N_2O_5$			56
VIIa	Gly	C_2H_5	$COCH_3$						$C_{13}H_{15}NO_5$	58,86	6,69	5,28
VIIb	L-Ala	C_2H_5	$COCH_3$						$C_{14}H_{17}NO_5$	60,20	6,13	5,01
VIIc	DL-Val	C_2H_5	$COCH_3$					83	$C_{16}H_{21}NO_5$	62,09	6,88	1,55
VIId	DL-Leu	C_2H_5	$COCH_3$					06	$C_{17}H_{23}NO_5$	63,53	7,21	4,35
VIIe	p-Aminobenzoyl	C_2H_5	$COCH_3$				04	4,5	$C_{18}H_{17}NO_5$			

*Mass spectrum of IVb: 313 (10) M^+; 298 (33); 211 (22); 120 (33); 91 (100); 57 (35).

TABLE 3. Hydrazides of N-(o-Benzyloxybenzoyl) Amino Acids (IXa-h)

Compound	Am	Yield, %	mp, °C	R_f	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
IXa	Gly	93,9	158—9	0,43	64,45	5,95	14,75	$C_{16}H_{17}N_3O_3$	64.20	5,72	14,03
IXb	L-Ala	89,9	167—8	0,50	65,30	6,28	13,60	$C_{17}H_{19}N_3O_3$	65.15	6,11	13,41
IXc	DL-Val	95,6	122—3	0,39	66,56	6.70	13,60	$C_{19}H_{23}N_3O_3$	66.84	6,79	12,30
IXd	DL-Leu	87,3	138—9	0,33	67,40	7.21	11,53	$C_{20}H_{25}N_3O_3$	67.58	7,08	11,82
IXe	L-Phe	87,4	112—3	0,73	70,25	6,20	11,30	$C_{23}H_{23}N_3O_3$	70,93	5,95	10,79
IXf	p-Aminobenzoyl	76,7	138—40	0,79	69,90	5,60	11,32	$C_{21}H_{19}N_3O_3$	69.79	5,29	11,62
IXg	L-Try	83,5	166—8	0,73	70,56	5,60	13,45	$C_{25}H_{26}N_4O_3$	69,74	6,08	13,01
IXh	Empirical	86,6	163—4	0,56	60.90	6,00	15,40	$C_{18}H_{20}N_4O_4$	60,66	5,65	15,72

TABLE 4. N-(o-Hydroxybenzoyl) Amino Acids (VIIIa-e)

Compound	Am	Yield, %	mp, °C	R_f	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
VIIIa	Gly*	51,85		0,87	55,80	5,01	6,9	$C_9H_9NO_4$	55.38	4,64	7,17
VIIIb	L-Ala	57,7	Oil	0,88	57,7	5,8	6,01	$C_{10}H_{11}NO_4$	57.41	5,30	6,69
VIIIc	DL-Val	43,1	"	0,83	60,70	6,63	5,97	$C_{12}H_{15}NO_4$	60,74	6,37	5,90
VIIId	DL-Leu	80,3	"	0,9	61,68	6,15	4,97	$C_{13}H_{17}NO_4$	62,13	6,81	5,57
VIIIe	p-Aminobenzoyl	43,2	"	0,9	64,93	4,05	4,7	$C_{14}H_{11}NO_4$	65,36	4,31	5,44

*Mass-spectrum of VIIIa: 195 (17), M^+; 138 (40); 121 (100); 91 (20); 57 (95).

was dissolved in 50 ml of water and was extracted with ethyl acetate (3 × 50 ml). The extract was shaken with 0.1 N hydrochloric acid and with a 5% solution of sodium bicarbonate, washed with water, and dried over sodium sulfate. After distilling off the solvent, there was obtained 2 g (55.3%) of IVh. R_f = 0.55. Found, %: C 64.70; H 5.70; N 7.30. $C_{20}H_{22}N_2O_5$. Calculate, %: C 64.85; H 5.98; N 7.56. Compounds IVa-g and VIIa-e were prepared by the same method (Table 2). The esters were obtained as oils.

N-(o-Benzyloxybenzoyl)glycylglycyl Hydrazine (IXh). A solution of 1.5 g (0.05 mole) of hydrazine hydrate in 5 ml of ethanol was added to a solution of 1.85 g (0.05 mole) of IVh in 10 ml of ethanol. The mixture was heated for 1.5-2 h at 40-45°C. After cooling, IXh was filtered off in the form of white needles. mp 163-164°C; yield, 1.54 g (86.6%). R_f = 0.56. Found, %: C 60.90; H 6.00; N 15.40. $C_{18}H_{20}N_4O_4$. Calculate, %: C 60.66; H 5.56; N 15.72. Compounds IXa-g were prepared by the same method (Table 3).

N-(o-Hydroxybenzoyl)glycine (VIIIa). Sodium hydroxide (60 ml of 1 N) was added to a solution of 16 g (0.06 mole) of VIIa in 100 ml of ethanol at 20°C. The mixture was stirred for 5-6 h at 45-50°C. The ethanol was distilled off, 50 ml of water was added, the contents was extracted with ether (3 × 50 ml), and the water layer was acified with 1 N hydrochloric acid at 0°C to pH 4.0-5.0. The precipitate which fell was filtered off and was recrystallized from an ethanol-ether mixture (1:3). mp 165-166°C; yield 5.6 g (51.85%). R_f = 0.87. Found, %: C 55.80; H 5.01; N 6.9. $C_9H_9NO_4$. Calculate, %: C 55.38; H 4.64; N 7.17. Compounds VIIIa-e were prepared under similar conditions (Table 4).

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A STUDY OF THE HYPOGLYCEMIC ACTIVITY OF SUBSTITUTED SULFONYLOXAMIDES

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The high and many-sided physiological activity of oxamic acid derivatives has drawn the steady attention of biologists and chemists [1-3] to this class of substances in recent times. In the development of these studies it was of interest to carry out the synthesis of sulfonyloxamide derivatives [4, 5] and study their sugar-reducing activity.

The following compounds were subjected to pharmacological testing: substituted amides of 3,5-dichloro-4-aminobenzenesulfonyloxamic acid — 3,5-Cl_2-4-$NH_2C_6H_2SO_2NHCOCONHR$ (Ia-b); the n-butylamide of α-naphthylsulfonyloxamic acid — α-$C_{10}H_7SO_2NHCOCONHC_4H_9$-n (II); some β-naphthylsulfonyloxamides — β-$C_{10}H_7SO_2NHCOCONHR$ (IIIa-f); N-arylaminoethylamides of an arenesulfonyloxamic acid — $RC_6H_4SO_2NHCOCONHCH_2CH_2NHC_6H_4R'$ (IVa-i); N-acyl-N-phenylaminoethylamide of p-toluenesulfonyloxamic acid — p-$CH_3C_6H_4SO_2NHCOCONHCH_2CH_2N(C_6H_5)COR$ (Va-c); benzylsulfonyloxamides — $C_6H_5CH_2SO_2NHCOCONHR$ (VIa-f); and alkansulfonyloxamides — $RSO_2NHCOCONHR'$ (VIIa-k).

Determination of the hypoglycemic activity of the compounds synthesized made it possible to discover the relationship between chemical structure and activity of the substances. It is evident from Table 1 that the sugar-reducing effect in substituted sulfonyloxamides depends on the structure of the radicals bonded to the sulfonyl and amide groups. Thus, the introduction of two chlorine atoms into the o-position to the amino group in the benzenesulfonyloxamides Ia-b retains the sugar-reducing effect without lowering the accessory antimicrobial effect which is manifested on the side of the substituted amides of p-aminobenzenesulfonyloxamic acids.

On comparing the hypoglycemic activity of I-V, attention is drawn to the fact that the activity in arenesulfonyloxamic acids disappears when the benzene ring is replaced by a naphthalene ring (II, III). The introduction of basic substituents in the oxamoyl radical of the arenesulfonyloxamides does not change their sugar-reducing activity. Of the nitro-isomers of the β-phenylaminoethylamides of benzenesulfonyloxamic acid, the m-isomer, IVd, has the

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