SYNTHESIS AND INVESTIGATIONS OF CERTAIN IMIDAZOLE DERIVATIVES.

V. ACYL DERIVATIVES OF THE ETHYL ESTER OF 4(5)-AMINO-5(4)-IMIDAZOLECARBOXYLIC ACID

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As potential antagonists of 4(5)-amino-5(4)-imidazolecarboxamide one of the predecessors of purine nucleotides in the organism is described a series of compounds similar to it: 4-nitro- and 4-amino-5-imidazole sulfones and sulfides [1], 4(5)-diazo- and 4(5)-triazeno-5(4)-imidazolecarboxamides [2,3]. Some of them produce an antitumorigenic effect [2,4,5].

It should be noted that an antitumorigenic activity was detected experimentally in the structurally similar to aminoimidazolecarboxamide ethyl ester of 4(5)-amino-5(4)-imidazolecarboxylic acid, obtained by us from the ester of nitroimidazolecarboxylic acid by a known method [6].

On the basis of these data, we undertook the synthesis of several derivatives of 4(5)-amino-5(4)-imidazolecarboxylic acid, and in particular, the acyl derivatives of its ethyl ester. 4(5)-Carbethoxy-5(4)-imidazolylamides of sulfonic and carboxylic acids were obtained by the reaction of the ethyl ester of 4(5)-amino-5(4)-imidazolecarboxylic acid (I) with the acid chloride of the corresponding acids in the presence of hydrohalide-accepting agents (pyridine, triethylamine) or without them. In isolated cases, in the preparation of the amide of p-bis-(2-chloroethyl)-aminobenzoic acid (VI) in particular, the role of the hydrogen chloride acceptor role was fulfilled by the amino acid ester used in excess.

4(5)-Carbethoxy-5(4)-imidazolylamides are colorless crystalline materials, which are soluble in acetone, hot alcohol, and with the exception of the dichloroacetyl derivative (IX), insoluble in water. In contrast to amides of aliphatic acids, which are very poorly soluble in aromatic hydrocarbons, the derivatives of aromatic acids dissolve in them quite well.

The carbethoxyimidazolylamide of benzoic acid (IV), described earlier by L. P. Kulev and V. R. Koroleva [6], was synthesized by us in better yield using a slightly modified method.

The greater portion of the obtained amidoesters was investigated for antitumorigenic effect (compounds (IV) and (VII) were not examined). Examinations were carried out on mice with ascitic Ehrlich tumors of sarcoma 180 and on rats with sarcoma 45. Medical treatment was begun on the fifth to seventh day after interruption of intumescence and was continued for ten days in rats and for eight days in mice. Mice with ascitic Ehrlich tumors began to be cured on the next day after interruption of intumescence. The antitumorigenic activity was evaluated by the index of inhibition of tumor growth, calculated as the ratio of the difference of the weight of the tumor in the control and in the experiment to the average weight in the control in percent. The toxicity was evaluated by the effect on the change in weight of the animals in the experiment (with deduction of the weight of tumor) and the weight of the spleen at the end of the experiment.

Examinations showed that antitumorigenic activity is possessed by the hydrochloride of the ethyl ester of amino acid (I), which upon subcutaneous introduction in a dose of 250 mg/kg inhibits the growth of sarcoma 45 by 57%, and by the 4(5)-carbethoxy-5(4)-imidazolylamide of N,N-bis-(2-chloroethyl)sulfanilic acid (V). The latter compound upon oral introduction in a dose of 300 mg/kg depresses the growth of sarcoma 45 by 64%. The remaining compounds did not show an antitumorigenic activity on any one of the strains used, and 4(5)-carbethoxy-5(4)-imidazolylamide of acetic acid (II) in a dose of 500 mg/kg also causes a small (50%) stimulating effect on the growth of sarcoma 45.

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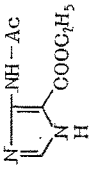
TABLE 1. 4(5)-Carbethoxy-5(4)-imidazolylamides



Compounds	Ac	Yield (%)	Mp (°C)	Found (%)				Empirical formula	Calculated (%)			
				C	H	N	Cl		C	H	N	Cl
II	CH_3CO	50,5	217—8	48,76	5,73	21,51	—	$C_8H_{11}N_3O_3$	48,73	5,58	21,32	—
III	CH_3CH_2CO	76,6	193—4	53,21	6,34	18,37	—	$C_{10}H_{15}N_3O_3$	53,35	6,66	18,66	—
IV	C_6H_5CO	68,5	188—9	59,99	4,86	15,87	—	$C_{13}H_{13}N_3O_3$	60,23	5,02	16,21	—
V	$(ClC_2H_4)_2C_6H_4SO_2$	55,3	175	44,16	4,71	12,99	—	$C_{16}H_{20}Cl_2N_4O_4S$	44,14	4,60	12,87	—
VI	$(ClC_2H_4)_2NC_6H_4CO$	42,7	130—2	51,13	5,37	13,90	—	$C_{17}H_{20}Cl_2N_4O_3$	51,13	5,01	14,01	—
VII	$HO—C_6H_4CO$	70,9	231—2	56,65	4,85	15,47	—	$C_{13}H_{13}N_3O_4$	56,72	4,72	15,27	—
VIII·HCl	$ClCH_2CO$	79,0	262—7 (dec.)	—	—	15,95	25,99	$C_8H_{10}ClN_3O_3 \cdot HCl$	—	—	15,67	26,5
IX	Cl_2CHCO	24,0	189—90	36,07	3,46	16,02	26,20	$C_8H_9Cl_2N_3O_3$	36,09	3,38	15,79	26,69
X	Cl_3CCO	51,6	164—5	31,74	2,77	13,98	—	$C_8H_6Cl_3N_3O_3$	31,94	2,66	13,97	—
X·HCl	Cl_3CCO	—	174—5	28,32	2,92	12,70	—	$C_8H_8Cl_3N_3O_3 \cdot HCl$	28,49	2,67	12,46	—

The investigated compounds do not have a toxic effect on the organism.

Of the synthesized compounds, only the 4(5)-carbethoxy-5(4)-imidazolylamide of monochloroacetic acid (VIII) has pharmacological activity, having an antispasmodic effect upon intraperitoneal introduction in mice in a dose of 140 mg/kg (1/5 of the half-death dose) (prevents the extensor phase of maximum electroshock in half of the experimental mice).

EXPERIMENTAL

4(5)-Carbethoxy-5(4)-imidazolylamides of Acetic (II) and Butyric (III) Acids. To a suspension of 0.06 mole of carefully pulverized (I) in 150-200 ml of anhydrous benzene was added in portions with stirring over $1^1/_2$-2 h 0.07 mole of the acid chloride in 25 ml of benzene and 5 ml (0.06 mole) of pyridine in 25 ml of benzene. The reaction mixture was boiled for 2 h, left overnight, and filtered. The precipitate was treated with a solution of sodium carbonate, washed with water, and dried in air. The compound was crystallized from alcohol. Crystals of (II) are colorless microplates; crystals of (III) are colorless light plates.

4(5)-Carbethoxy-5(4)-imidazolylamide of Benzoic Acid (IV). To a boiling suspension of 2.98 g (0.0192 mole) of ground (I) in 100 ml of anhydrous xylene was poured 2.03 ml (0.0244 mole) of benzoyl chloride and 2.4 ml (0.03 mole) of pyridine in 8 ml of xylene. The mixture was boiled for 1 h and filtered while hot. Upon cooling, a light yellow finely-crystalline precipitate separated from the filtrate. The mixture was filtered. The precipitate was dried at 50-70°C. The compound was crystallized from alcohol. Crystals of (IV) are almost colorless.

4(5)-Carbethoxy-5(4)-imidazolylamide of N,N-bis-(2-chloroethyl)sulfanilic Acid (V). We suspended 2.9 g (0.0187 mole) of (I) in a solution of 6.5 g (0.0206 mole) of lymphochin sulfochloride, the acid chloride of N,N-bis-(2-chloroethyl)sulfanilic acid, in 100 ml of benzene. To the hot mixture was poured dropwise with stirring 7.8 ml (0.056 mole) of triethylamine. The mixture was boiled for ½ to 1 h. The mixture was filtered while hot from the precipitate of triethylamine hydrochloride. The light yellow precipitate of (V) separated from the filtrate upon cooling. The mixture was filtered. The precipitate was dried at 50-70°. The material was crystallized from alcohol.

4(5)-Carbethoxy-5(4)-imidazolylamide of p-Bis(2-chloroethyl)-aminobenzoic Acid (VI). To a suspension of 15.5 g (0.1 mole) of finely pulverized (I) in 250 ml of benzene was added over 2 h a solution of 15.5 g (0.055 mole) of the acid chloride of p-bis(2-chloroethyl)aminobenzoic acid in 200 ml of benzene. The mixture was boiled for 2 h. The mixture was filtered while hot from the precipitate of (I) hydrochloride. Benzene was distilled from the filtrate. The tarry residue was crystallized twice from acetone containing activated carbon. Crystals of (VI) are light yellow microprisms.

4(5)-Carbethoxy-5(4)-imidazolylamide of Salicylic Acid (VII). To a suspension of 3.1 g (0.02 mole) of (I) in 40 ml of benzene was poured over 2 h, 11 g of 58% (0.04 mole recalculated to 100%) of the acid chloride

of salicylic acid in 15 ml of benzene with cooling and stirring. The mixture was boiled for 2 h. The mixture was cooled and filtered. The precipitate, a mixture of the amide and salicylic acid, was treated with boiling ether to remove the latter. The precipitate was crystallized from alcohol.

4(5)-Carbethoxy-5(4)-imidazolylamide of Monochloroacetic (VIII), Dichloroacetic (IX), and Trichloroacetic (X) Acids. To a suspension of 3.1 g (0.02 mole) of (I) in 100 ml of benzene was added a solution of 0.03-0.04 mole of the acid chloride of the corresponding acid in 20 ml of benzene with cooling and stirring. In the preparation of (VIII), the mixture was boiled for 3-4 h; of (IX), for 13 h; of (X), for 15 h. The mixture was filtered.

The precipitate of (VIII) was washed with benzene, rubbed with acetone in a mortar, and washed several times with acetone. The material was crystallized from alcohol. The crystal are colorless and fine. Upon saturating a solution of (VIII) in anhydrous alcohol with dry hydrogen chloride, the hydrochloride of (VIII) precipitated as colorless fine crystals. After filtration of (IX), more impure (IX) precipitated from the mother solution upon standing, which together with the main precipitate was crystallized from water. Crystals of (IX) are colorless silky needles. Compound (X) is a light powdery precipitate. The precipitate was dried in a vacuum extractor. Compound (VIII) was transformed analagously into a finely crystalline hydrochloride.

Yields of acids, melting points, and analysis data are presented in Table 1.

LITERATURE CITED

1. L. L. Bennett and H. T. Baker, J. Am. Chem. Soc., 79, 2188 (1957).
2. J. F. Shealy, R. F. Struck, L. B. Holum, et al., J. Org. Chem., 26, 2396 (1961).
3. J. F. Shealy, C. A. Krauth, and J. A. Montgomery, ibid., 27, 2150 (1962).
4. J. F. Shealy and C. A. Krauth, Nature, 210, 208 (1966).
5. J. F. Shealy, J. A. Montgomery, and W. R. Laster, Biochem. Pharmacol., 11, 674 (1962).
6. L. P. Kulev and V. R. Koroleva, Zh. Obshch. Khim., 29, 2401 (1959).