The results of the study of toxicity and antitumor activity are given in Table 2. Of the tested substances, the most toxic were compounds containing γ-aminobutyric acid (IX), proline (X), and L-leucine (III) in their structure; the LD_{100} of these compounds was 400-750 mg/kg. Compounds III and I, containing sarcosine and glycine, were considerably less toxic (LD_{100} 2500 mg/kg); the rest of the compounds were intermediate in toxicity.

In chemotherapeutic experiments, it was established that the majority of compounds possessed moderate antitumor activity against sarcoma 45, retarding growth by 32-49%. Compounds containing β-phenyl-β-alanine (VIII), L-α-alanine (V), and glycine (I), were ineffective. Only compounds II, IV, V, and X exhibited significant antitumor activity towards Pliss lymphosarcoma (retardation of growth, 32-55%). Sarcoma 180 was found to be relatively resistant to the therapeutic action of the test compounds; only compounds containing L-α-alanine (V) and β-phenyl-β-alanine (VIII) groups showed some growth-inhibiting activity (30-50%).

Thus, some compounds in the oxazolo[5,4-d]pyrimidyl-7-amino acid series, in addition to their low toxicity, possessed significant activity against transplanted tumors; further research in this area is therefore recommended.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF 4,6-DIAZATRYPTOPHAN AND 4,6-DIAZAHETEROAUXIN

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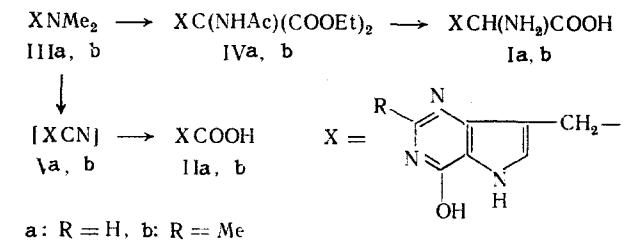
Pyrrolo(3,2-4)pyrimidines (9-desazapurines) have attracted attention for study because of the discovery of anti-tumor activity in some compounds of this series [4]. In continuing studies in a search for a substance with anti-tumor activity, the present work describes the synthesis of diaza-analogs of tryptophan (Ia and b) and heteroauxin (IIa and b) starting from our previously-described 2-R-4-hydroxy-7-dimethylaminomethylpyrrolo(3,2-d)pyrimidine hydrochlorides (IIIa and b) [3] according to the scheme:



a: R = H, b: R = Me

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TABLE 1. Characteristics of the Pyrrolo(3,2-d)pyrimidines

Compound	Yield, %	mp, °C (from water)	Found, %			Empirical formula	Calc., %		
			C	H	N		C	H	N
IVa	46*	>300	52,70	5,43	15,61	$C_{16}H_{20}N_4O_6$	52,74	5,53	15,38
IVb	50*	255—7	52,71	5,95	14,85	$C_{17}H_{22}N_4O_6 \cdot O,5H_2O$	52,71	5,99	14,46
Ia	91	>320	48,24	4,51	25,21	$C_9H_{10}N_4O_3$	48,65	4,54	25,21
Ib	62	334—6	47,15	5,60	22,41	$C_{10}H_{12}N_4O_3 \cdot H_2O$	47,24	5,55	22,04
IIa	21	326—7	49,68	3,68	21,92	$C_8H_7N_3O_3$	49,74	3,66	21,75
IIb	19	>300	51,80	3,98	20,57	$C_9H_9N_3O_3$	52,17	4,38	20,28

*From the reaction of IIIa and b.

Condensation of IIIa and b with acetylaminomalonic ester in the presence of 3 equivalents of NaOEt gave the diesters (IVa and b) which were hydrolyzed with hydrochloric acid to give Ia and b. The heteroauxin analogs IIa and b were synthesized by the condensation of KCN in alcohol with subsequent acidic hydrolysis of the intermediate nitriles (Va and b).

The structures of the synthesized compounds agreed well with IR spectral data.

The IR spectra of the 4,6-diazatryptophans Ia and b showed absorption bands at 3100-2920 cm^{-1} corresponding to valence vibrations of the NH_3^+ group, and at 1580 and 1410 cm^{-1} for the asymmetrical and symmetrical vibrations of the COO^- group, which indicates that the amino acids Ia and b exist as the zwitterions [1].

IR spectral data also indicated the existence of hydrogen bonds in compounds IIa and b by the presence of absorption bands in the 3500 cm^{-1} region and in the 2820-2500 cm^{-1} region, characteristic of the —OH of a hydrogen-bonded carboxyl group. Absorption bands of 1700 and 1605 cm^{-1} corresponding to the valence and deformation vibrations of the COO^- group as well as 1430 and 1380 cm^{-1} bands for the CH_2COOH group also were observed. Intense bands occurred in the 1290 and 1260 cm^{-1} regions for the planar deformation vibrations of the —OH and the valence vibrations of the C—O groups [2].

Absorption at 1680 cm^{-1} in Ia and b and 1650 in IIa and b indicate that the pyrrolopyrimidines exist in the form of amides.

The IR spectra of diazaheteroauxins IIa and b also show strong absorptions in the 3240-2980 cm^{-1} region for the NH group.

Compound IVa showed weak anti-tumor activity; it inhibited the growth of sarcoma 180 in mice by 30-38%. The other compounds did not possess anti-tumor activity, and did not show dihydrofolate reductase inhibition.

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer 457 instrument in KBr tablets.

Ethyl 2-Acetylamino-2-carboethoxy-3(4-hydroxypyrrolo[3,2-d]pyrimidyl-7)propionate (IVa). To a solution of NaOEt from 0.7 g (0.03 mole) of Na in 50 ml of absolute ethanol was added 3 g (0.014 mole) of acetylaminomalonic ester and 2.3 g (0.01 mole) of 4-hydroxy-7-dimethylaminomethylpyrrolo(3,2-d)pyrimidine hydrochloride (IIIa). The reaction mixture was boiled for 24 h, the ethanol was distilled and to the residue was added 50 ml of water and AcOH to pH 6.0. The resulting precipitate was filtered off and washed to give 1.1 g of IVa.

The mother liquor was evaporated to dryness and the residue was boiled with 200 ml of ethanol, the insoluble precipitate was filtered off, and half of the ethanol was distilled. The alcoholic solution was cooled and 9.6% alcoholic HCl was added to pH 1.0. The resulting precipitate was filtered off and recrystallized from 90% ethanol to give 0.8 g of IIIa, mp 268-269°C.

IVb was prepared analogously.

d,l-7-Hydroxy-4,6-diazatryptophan (Ia). A solution of 0.9 g of IVa in 10 ml of concentrated hydrochloric acid was boiled for 8 h and then evaporated to dryness. The residue was dissolved in 15 ml of water, treated with HOAc to pH 6.0, and the resulting precipitate was filtered off and washed with water to give 0.5 g of Ia.

Ib was prepared analogously.

7-Hydroxy-4,6-diazaheteroauxin (IIa). A mixture of 5 g (0.022 mole) of IIIa, 7 g (0.11 mole) of KCN, 60 ml of water and 15 ml of ethanol was heated at 80°C for 80 h. The solution was evaporated to dryness and the residue was treated with 20 ml of concentrated hydrochloric acid. After heating for 5 h, the solution was cooled and the resulting precipitate was filtered off to give 0.9 g of IIa.

IIb was prepared analogously.

The characteristics of the synthesized compounds are presented in Table 1.

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MACROHETEROCYCLIC COMPOUNDS.

XXIII. ANTIHYPOXIC AND ANTIAMNESTIC PROPERTIES OF AZACROWN ETHERS WITH PHARMACOPHORE GROUPS

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The ability to change the permeability of biological membranes to metal ions and certain organic molecules (amines, amino acids) is one of the most interesting of the biological properties of the crown ethers. This process modifies biomembranes so that the selective transport of ions and molecules can occur [2, 3]. In this respect, of special interest are crown ethers with pharmacophore groups, since the action of "traditional" biologically active substances can be greatly improved by increased ease of transport through hematoencephalic barriers.

In particular, it is suggested that γ-aminobutyric acid, which normally does not readily penetrate the hematoencephalic barrier, when introduced into a crown ether passes through the barrier more easily; the pharmacological activity of this amino acid (a mediator of retardation) is thereby improved.

During our search for new psychotropic agents, we have synthesized N,N'-bispyrollidonomethyl-diaza-17-crown-6 (I), N,N'-bissuccinimidomethyldiaza-18-crown-6 (II), N,N'-bis-γ-aminobutyryl-diaza-18-crown-6 (III) and studied their antihypoxic and antiamnestic properties.

CHEMICAL EXPERIMENTAL

Infrared spectra were taken on a Perkin-Elmer 580 B (USA), NMR spectra on a Tesla BS 467 spectrometer (ChSSR) with a working frequency of 60 MHz; internal standard, tetramethylsilane.

N,N'-Bis-pyrrolidonomethyl-diaza-18-crown-6 (I). A mixture of 0.31 g (0.9 moles) of N,N'-bis-methoxymethyl-diaza-18-crown-6 [1], 0.13 g (1.8 mmoles) of pyrrolidone-2, and 3 ml of dry CCl_4 were refluxed for 3 hours. The reaction mixture was filtered, and the solvent

*Deceased.

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