PYRROLO[3,2-d]PYRIMIDINES.

IV. SYNTHESIS AND ANTIBACTERIAL AND ANTITUMOR ACTIVITY OF 2,4,7-SUBSTITUTED PYRROLO[3,2-d]PYRIMIDINES

O. S. Sizova, N. E. Britikova, K. Yu. Novitskii,*
L. I. Shcherbakova, G. N. Pershin, A. I. Kravchenko,
and V. A. Chernov

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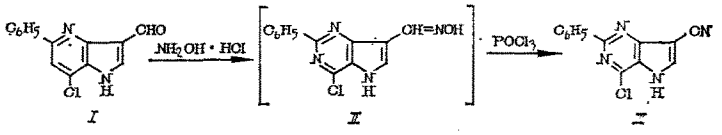
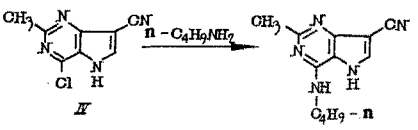
In continuation of the search for biological activity in pyrrolo[3,2-d]pyrimidines [1], we have synthesized some 2,4,7-substituted pyrrolopyrimidines (Table 1), and studied their antibacterial and antitumor activity.

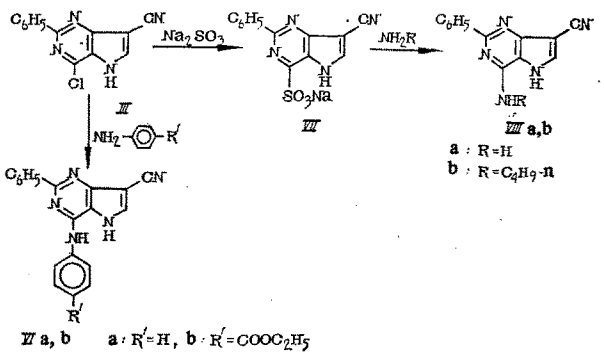
We have synthesized 2-phenyl-4-chloro-7-cyanopyrrolo[3,2-d]pyrimidine (III) from the aldehyde (I) (2), by conversion of the oxime (II) followed by dehydration of the latter with phosphoryl chloride. The oxime (II) could not be isolated in an analytically pure state, but its structure was proved unambiguously by IR spectroscopy as well as by the preparation of its nitrile (III).



The 4-n-butylaminopyrrolopyrimidine (V), which has a methyl group in the 2-position, was obtained from the chloro-compound (IV) [1] and n-butylamine in boiling ethanol. Under these conditions, replacement of the chlorine atom by an amino group in 2-phenyl-4-chloro-7-cyanopyrrolo[3,2-d]pyrimidine (III) did not occur.



The 4-aminopyrrolopyrimidines (IVa-b) were obtained by heating (III) with aromatic amine hydrochlorides in aqueous solution, but this compound failed to react with aliphatic amines. The introduction of amino- and alkylamino-groups into the 4-position of 2-phenyl-7-cyanopyrrolo[3,2-d]pyrimidine was accomplished via the sodium salt of the corresponding sulfonic acid (VII) [3].



*Deceased.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 11, pp. 1338-1343, November, 1982. Original article submitted March 23, 1982.

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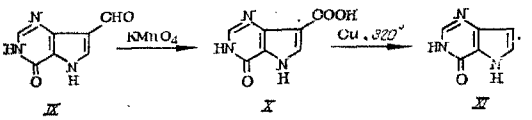
TABLE 1. 2,4,7-Substituted Pyrrolo[3,2-d]pyrimidines

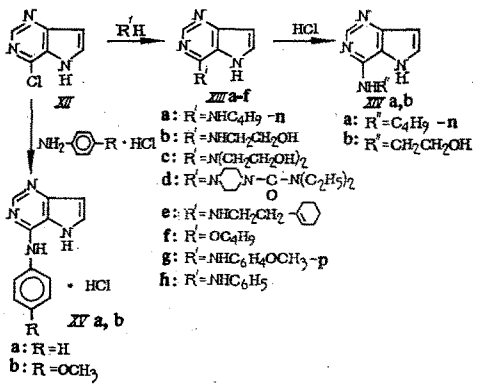
Compound	Yield, %	Mp deg C	Found, %					Molecular formula	Calculated, %				
			C	H	N	Cl	S		C	H	N	Cl	S
III	70	288—290	61,61	2,89	22,08	13,91		$C_{13}H_7N_4Cl$	61,29	2,75	22,03	13,93	
V	56	320	63,08	6,50	30,54			$C_{12}H_{15}N_5$	62,88	6,55	30,56		
VIa	69	305—307	73,31	3,92	22,54			$C_{19}H_{13}N_5$	73,38	4,20	22,43		
VIb	50	320	68,64	4,48	17,85			$C_{22}H_{17}N_5O_2$	68,93	4,43	18,27		
VII	53	320	48,33	2,34	17,01		9,53	$C_{13}H_7N_4O_3SNa$	48,44	2,17	17,39		9,93
VIIIa	82	320	66,41	3,77	29,56			$C_{13}H_9N_5$	66,38	3,83	29,78		
VIIIb	73	278—280	70,13	5,87	24,06			$C_{17}H_{17}N_5$	70,10	5,84	24,05		
X	80	320	46,81	2,82	23,32			$C_7H_5O_3N$	46,93	2,81	23,46		
XI*	64	300	52,97	3,30	31,20			$C_6H_5ON_3$	53,35	3,70	31,11		
XIIIa	50	176	63,33	7,49	29,56			$C_{10}H_{14}N_4$	63,14	7,42	29,45		
XIIIb	65	296—298	53,91	5,74	31,50			$C_8H_{10}ON_4$	53,77	5,60	31,37		
XIIIc	35	260—262	54,29	6,31	25,51			$C_{10}H_{14}O_2N_4$	54,05	6,35	25,21		
XIIId	51	150	59,41	7,32	27,66			$C_{15}H_{22}ON_6$	59,58	7,34	27,79		
XIIIe	52	190	69,35	7,67	23,09			$C_{14}H_{18}N_4$	69,39	7,49	23,12		
XIIIf	53	100	63,08	6,74	21,86			$C_{10}H_{13}ON_3$	62,81	6,85	21,97		
XIVa	84	145—147	52,86	6,69	24,72	15,82		$C_{10}H_{14}N_4 \cdot HCl$	52,98	6,67	24,71	15,64	
XIVb	85	262—264	44,86	5,12	26,31	16,63		$C_8H_{10}ON_4 \cdot HCl$	44,76	5,17	26,10	16,52	
XVa	75	285	58,49	4,67	22,86			$C_{12}H_{10}N_4 \cdot HCl$	58,42	4,50	22,71		
XVb	50	226	56,65	4,85	20,09			$C_{13}H_{12}ON_4 \cdot HCl$	56,43	4,73	20,25		

*Literature value for the mp [4], 300°C.

For the synthesis of pyrrolopyrimidines unsubstituted in the 2 and 7-positions, the aldehyde (IX) [2] was oxidized with potassium permanganate in alkaline solution to the acid (X), decarboxylation of which afforded 4-oxo-3,4-dihydropyrrolo[3,2-d]pyrimidine (XI) [4].



In a study of the nucleophilic replacement of the chlorine atom in 4-chloropyrrolo[3,2-d]-pyrimidine (XIV) [4], it was found that reaction with aliphatic amines afforded 4-alkylaminopyrrolo-pyrimidines (XIIIa-e). Under the same conditions, sodium butoxide gave 4-butoxypyrrolo[3,2-d]-pyrimidine (XIIIe). In order to obtain the water-soluble hydrochlorides for biological study, the aminopyrrolopyrimidines (XIII) were treated with alcoholic hydrogen chloride. The hydrochlorides (XIVa-b) could be isolated, but the remaining compounds were unstable. The hydrochlorides of the 4-arylaminopyrrolopyrimidines (XVa, b) were obtained by reacting the chloro-compound (XII) with the aromatic amine hydrochlorides.



The antibacterial activities of the compounds were tested *in vitro*, and their antitumor activities *in vivo*. Antibacterial activity was examined in synthetic and semisynthetic media against the lactic acid bacterium *L. casei* 7469, human tuberculosis bacillus strain H37Rv, and *E. coli* strain 335. The results of the *in vitro* studies are shown in Table 2. Selected compounds were tested for antitumor activity and toxicity *in vivo*. The experiments were carried out with 400 male mice weighing 20-22 g with sarcoma 180 (solid type). It was found that compounds (II-IV), (VI), and (VIII) (Table 3) inhibited the growth of the tumor by 30-50% when administered two days after transplantation of the sarcoma 180. The toxicities of the compounds differed considerably, depending on their structure and route of administration. Thus, (III), (VI), and (VIII) in vegetable oil by the gastric route were of low toxicity, their LD_{10} and MTD_7 (maximum tolerated dose by daily administration for 7 days) values being greater than 1000 and 500 mg/kg respectively. Of the compounds administered intraperitoneally (I, II, IV, V, and VIII), the most toxic were (II) and (VIII), the MTD_7 values for which were 10 and 25 mg/kg. By this route of administration, (VI) and (VIII) had an irritant effect on the mucous lining of the peritoneum, causing peritonitis.

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer 457 instrument (Sweden) in the crystalline state, as a paste in vaseline oil.

2-Phenyl-4-chloro-7-cyanopyrrolo[3,2-d]pyrimidine (III). A mixture of 4.4 g (0.017 mole) of the aldehyde (I) and 3.0 g (0.043 mole) of hydroxylamine hydrochloride was boiled in 150 ml of 30% aqueous ethanol for 4 h. The precipitate of (II) which separated on cooling was filtered off, washed with hot ethanol, and dried to constant weight. mp 198-200°C. IR spectrum, ν, cm^{-1}: 1645 (>C-N), 3500 (OH). The oxime (II) thus obtained (4 g) was boiled with 100 ml of $POCl_3$ until the solid had dissolved completely. The phosphoryl chloride was distilled off *in vacuo*, and the residue treated with a mixture of ice and water. The resulting solid was filtered off and crystallized from ethanol to give 3 g of the nitrile. IR spectrum, ν, cm^{-1}: 2230 (-C≡N). The constants, yields, and elemental analyses for all the compounds prepared are given in Table 1.

TABLE 2. Antibacterial Activity of 2,4,7-Substituted Pyrrolo[3,2-d]-pyrimidines

Compound	Test microorganism		
	E. coli strain 335	H 37 R_V	L. casei 7469
	Dilution at which the compound displayed activity		
V		1 : 512 000	
VIa		1 : 2 000 000	1 : 10 000
VII		1 : 8 000	1 : 1 000
VIIIa*	1 : 256 000	1 : 8 000	1 : 10 000
XIIIb		1 : 1 000	1 : 10 000
XIIIc	1 : 64 000	1 : 1 000 000	1 : 10 000
XIIId		1 : 32 000	
XIIIf	1 : 4 000	1 : 4 000	
XIIIg	1 : 128 000	1 : 128 000	1 : 1 000
XIIIe	1 : 256 000	1 : 64 000	1 : 100 000

*Hydrochloride.

TABLE 3. Toxicities and Antiblastic Activity of Some Pyrrolo[3,2-d]pyrimidines in Mice with Sarcoma 180

Compound	Route of administration	% inhibition of sarcoma 180	Toxicity	
			LD_{10}	MTD_7
			mg/kg	
XIIIg	Intraperitoneal	0	333	40
XIIIa	Same	35	67	10
XIIIe	Peroral	35	>1000	>500
XIIIb	Intraperitoneal	30—50	>500	35
XIIIh	Same	0	400	37,5
VIa	Peroral	30	>1000	>500
V	Same	55	>1000	>500
VII	Intraperitoneal	30—50	>500	>25 <100

2-Methyl-4-n-butylamino-7-cyanopyrrole[3,2-d]pyrimidine (V). A solution of 0.6 g (0.003 mole) of (IV) and 0.4 g (0.005 mole) of n-butylamine in 25 ml of 50% aqueous ethanol was boiled for 6 h. The solution was evaporated to dryness, and the residue treated with water. The resulting solid was filtered off and crystallized from aqueous ethanol to give 0.4 g of (V).

2-Phenyl-4-phenylamino-7-cyanopyrrole[3,2-d]pyrimidine (VIa). A solution of 0.6 g (0.002 mole) of (III) and 0.62 g (0.005 mole) of aniline hydrochloride in 10 ml of 50% aqueous ethanol was boiled for 6 h. The solution was then cooled, and the solid which separated was filtered off and crystallized from 50% aqueous DMF to give 0.5 g of (VIa).

2-Phenyl-4-p-ethoxycarbonylphenylamino-7-cyanopyrrolo[3,2-d]pyrimidine (VIb). A solution of 0.8 g (0.003 mole) of (III) and 0.72 g (0.004 mole) of ethyl p-aminobenzoate in 20 ml of water and 3 ml of concentrated hydrochloric acid was boiled for 6 h. The solid which separated on cooling was filtered off, washed with water, and crystallized from 50% aqueous DMF to give 0.6 g of (VIb).

Sodium 2-Phenyl-7-cyanopyrrolo[3,2-d]pyrimidine-4-sulfonate (VII). A solution of 0.6 g (0.002 mole) of (III) and 0.66 g (0.005 mole) of Na_2SO_3 in 10 ml of water and 5 ml of ethanol was boiled for 4 h. The reaction mixture was cooled, and the solid which separated was filtered off and recrystallized from water to give 0.4 g of the salt (VII).

2-Phenyl-4-amino-7-cyanopyrrolo[3,2-d]pyrimidine (VIIIa). A solution of 0.5 g (0.0015 mole) of (VII) in 15 ml of 18% alcoholic ammonia was heated for 2.5 h in an autoclave at 110°C. The alcohol was distilled off, and the residue crystallized from aqueous DMF to give 0.3 g of (VIIIa).

2-Phenyl-4-n-butylamino-7-cyanopyrrolo[3,2-d]pyridine (VIIIb). A solution of 0.3 g (0.001 mole) of (VII) and 0.18 g (0.025 mole) of n-butylamine in 20 ml of 50% aqueous ethanol was boiled for 6 h. The reaction mixture was cooled, and the solid which separated was filtered off and crystallized from ethanol to give 0.2 g of (VIIIb).

4-Oxo-3,4-dihydropyrrolo[3,2-d]pyrimidine-7-carboxylic Acid (X). A solution of 1.2 g (0.007 mole) of (IX) and 0.59 g (0.0015 mole) of NaOH in 25 ml of water was heated to 40°C, and at this temperature there was added slowly a solution of 0.67 g (0.004 mole) of $KMnO_4$ in 15 ml of water. The mixture was stirred for 40 min at 40°C, and the solid was then filtered off, and the filtrate acidified with hydrochloric acid to pH 1.0. The solid which separated was filtered off and washed with water to give 1.05 g of the acid (X).

4-Oxo-3,4-dihydropyrrolo[3,2-d]pyrimidine (XI). A mixture of 2.9 g (0.016 mole) of the acid (X) and 0.3 g (0.005 mole) of copper powder was heated at 320°C under reduced pressure (15 mm Hg) for 1 h. The reaction mixture was then treated with 16 ml of 1 N NaOH, and stirred for 15 min at room temperature. The insoluble solid was filtered off, and the filtrate acidified with acetic acid to pH 6.0. The solid which separated was filtered off and crystallized from water to give 1.4 g of (XI).

4-n-Butylaminopyrrolo[3,2-d]pyrimidine (XIIIa). A solution of 0.3 g (0.002 mole) of (XII) [3] and 0.29 g (0.004 mole) of n-butylamine in 10 ml of ethanol was boiled for 3 h. The alcohol was then evaporated off, and the residue treated with water. The solid which separated was filtered off and crystallized from 50% aqueous ethanol to give 0.18 g of (XIIIa).

Similarly obtained were the 4-aminopyrrolopyrimidines (XIIIb-e)

4-Butoxypyrrolo[3,2-d]pyrimidine (XIIIf). 0.6 g (0.0026 mole) of metallic sodium was dissolved in 15 ml of n-butanol, and to the resulting solution of sodium butoxide was added 0.3 g (0.002 mole) of (XII) [3]. The mixture was boiled for 5 h, and the solvent was then distilled off, and the residue treated with water. The solid which separated was filtered off and crystallized from 60% aqueous ethanol to give 0.2 g of (XIIIf).

4-n-Butylaminopyrrolo[3,2-d]pyrimidine Hydrochloride (XIVa). A suspension of 0.3 g of (XIIIa) in 5 ml of alcoholic HCl was kept for 10 min. The solid was then filtered off and washed with ethanol to give 0.3 g of the hydrochloride (XIVa).

Similarly obtained was the hydrochloride of 4-ethanolaminopyrrolo[3,2-d]pyrimidine (XIVb).

Attempts to prepare the hydrochlorides of the bases (XIIIc-e) resulted in recovery of the starting materials.

4-Phenylaminopyrrolo[3,2-d]pyrimidine (XVa) Hydrochloride. A mixture of 0.3 g (0.002 mole) of (XII) [3] and 0.5 g (0.004 mole) of aniline hydrochloride in 10 ml of water was heated at 80°C for 3 h. The reaction mixture was cooled, and the solid filtered off to give 0.3 g of (XVa).

Similarly obtained was 4-p-methoxyphenylaminopyrrolo[3,2-d]pyrimidine (XVb).

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AZAINDOLES. LXIV.

SEARCH FOR β-ADRENOBLOCKERS IN THE 5-AZAINDOLE SERIES

N. N. Bychikhina, V. A. Azimov, V. G. Granik, A. M. Zhidkova, N. B. Marchenko, R. G. Glushkov, M. D. Mashkovskii, S. D. Yuzhakov, A. V. Morozov, and L. N. Yakhontov

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β-Adrenoblockers play an important part in the current therapy of cardiovascular diseases. Nevertheless, clinical experience with drugs of this type shows that in 40-50% of patients with hypertonic disease they cause an increase in the overall peripheral resistance, and are less effective than methyldopa and guanethidine [1-4]. For this reason, the search for new β-adrenoblockers which are safer and more effective is of current interest. There have been recent reports [5, 6] of increasd β-adrenoblocking activity together with vasodilating and hypotensive properties when, in addition to the usual 3-isopropylamino-2-hydroxypropoxy group, typical of β-adrenoblockers, there is also introduced into the benzene or pyridine nucleus the cyano-group. Similar effects have been reported also in the indole series [7]. Azaindoles containing the 3-isopropylamino-2-hydroxypropoxy group have not been described, and there is

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.

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