2R,4R'-7,8-Benzo- (XIV, XV) and 2,4-Diphenyl-5,6-benzohexahydrothiochromenes (XVI). To a solution of 0.02 mole of the benzodihydrothiochromene (VI-VIII) in 0.04 mole of triethylsilane was added 0.06 mole of dry trifluoroacetic acid. The reaction mixture was warmed to 60-80°C, and after 3-5 min the starting material had been completely converted into the corresponding sulfide (XIV-XVI), which separated as colorless crystals. These were isolated, washed with alcohol, and dried to give 95-98% of the sulfide (XIV-XVI), the melting points of which corresponded with those of the sulfides obtained by reacting the diketone (I, II, or V) with H_2S in trifluoroacetic acid. 2-Phenyl-4-p-methoxyphenyl-7,8-benzo-5,6-dihydro- (XIX) and 2,4-diphenyl-5,6-benzo-7,8-dihydrochromylium fluoroborates were synthesized as described in [1], purification being effected by reprecipitation from chloroform with ether (Table 2).

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PYRROLO[3,2-d]PYRIMIDINES.

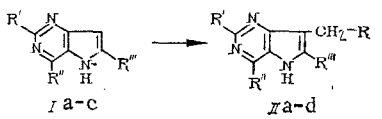
III. 7-AMINOMETHYL-SUBSTITUTED PYRROLO[3,2-d]PYRIMIDINES

G. A. Modnikova, O. S. Sizova,
K. Yu. Novitskii,* N. A. Ryabokon',
T. M. Vlasova, and V. A. Chernov

UDC 615.281:547.853.3

Some previously-synthesized amino-derivatives of pyrrolo[3,2-d]pyrimidines have been found to possess bacteriostatic activity [1].

Continuing investigations in this series of compounds, we have synthesized some aminomethyl derivatives of pyrrolo[3,2-d]pyrimidines. The standard Mannich reaction was used to synthesize the 7-aminomethyl-substituted compounds (IIa-d), isolated as their hydrochlorides (IIa, b), base (IIc), and picrate (IId).



I a-c II a-d

a) $R' = R''' = H$, $R'' = OH$;
b) $R' = R''' = CH_3$, $R'' = OH$;
c) $R' = R''' = CH_3$, $R'' = OCH_3$;

a) $R' = R''' = H$, $R'' = OH$, $R = N(C_2H_5)_2$;
b) $R' = R''' = CH_3$, $R'' = OH$, $R = N(C_2H_5)_2$;
c) $R' = R''' = CH_3$, $R'' = OCH_3$, $R = N(CH_2)_5$;
d) $R' = R''' = CH_3$, $R'' = OCH_3$, $R = N(CH_3)_2$;

The aminomethyl derivatives (Va-e) were synthesized from pyrrolo[3,2-d]pyrimidines containing an aldehyde group in the 7-position [2]. Reaction of the aldehydes (IIIa-c) with amines first gave the Schiff's bases (IVa-e), which were subsequently reduced with alcoholic sodium borohydride to the amines (Va-e). The IR spectra of the Schiff's bases showed characteristic absorption for the >C=N group at 1630 cm^{-1}, which disappeared on reduction to (Va-e). Reaction of 4-chloro-2-phenylpyrrolo[3,2-d]pyrimidine-7-aldehyde (IIIb) with an excess of cyclohexenylethylamine in aqueous solution resulted in replacement of the chlorine atom in addition to reaction at the aldehyde group, giving (IVe), which was reduced to the corresponding diamine (Ve).

*Deceased.

All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 5, pp. 548-552, May, 1982. Original article submitted October 29, 1981.

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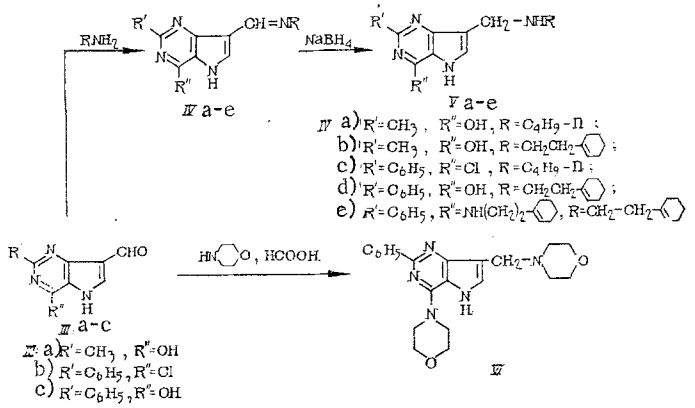
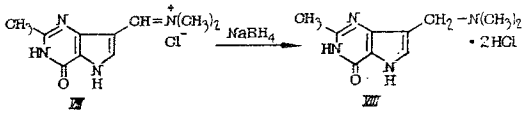
The Wallach reaction with the aldehyde (IIIb) and morpholine also resulted in replacement of the chlorine atom by an amino group, affording the pyrrolo[3,2-d]pyrimidine (VI).



2-Methyl-4-oxo-7-dimethylaminomethyl-3,4-dihydropyrrolo[3,2-d]pyrimidine (VIII) was synthesized by reducing (2-methyl-4-oxo-3,4-dihydropyrrolo[3,2-d]pyrimidin-7-yl)methyleneammonium chloride (VII) [3] with alcoholic sodium borohydride.



The yields, melting points, and elemental analyses of the compounds prepared are given in Table 1.

It is known that pyrimidine derivatives, including condensed systems in which the pyrimidine is annelated to a five-membered ring (imidazole or pyrrole), exert an inhibitory effect on the enzyme dihydrofolate reductase (DFR) [4]. We therefore studied the antireductase activity of the pyrrolo[3,2-d]pyrimidines. DFR was isolated from the livers of healthy animals (rats). DFR activity was determined by a colorimetric method [5].

The highest antireductase activity was exhibited by 4-oxo-2-phenyl-7-(β-cyclohexen-1'-yl)ethylaminomethyl-3,4-dihydropyrrolo[3,2-d]pyrimidine (Vd), which at a concentration of $1 \cdot 10^{-5}$ mole inhibited the activity of the enzyme to the extent of 95%, and at a concentration of $1 \cdot 10^{-6}$ mole to the extent of 48% (Table 2). 4-Oxo-2-methyl-7-(β-cyclohexen-1'-yl)ethylaminomethyl-3,4-dihydropyrrolo[3,2-d]pyrimidine (Vb) was slightly less active, reducing DFR activity by 82% at a concentration of $1 \cdot 10^{-5}$ mole, and by 12% at $1 \cdot 10^{-6}$ mole.

The *in vivo* antitumor activity of some of the 7-aminomethyl derivatives of pyrrolo[3,2-d]pyrimidines was also studied. Of the compounds examined, weak antitumor activity was shown by 4-chloro-2-phenyl-7-n-butylaminomethylpyrrolo[3,2-d]pyrimidine (Vc). Administration *per os* in a dose of 250 mg/kg resulted in 30% inhibition of the growth of sarcoma 180 in mice, and 38% inhibition in a toxic dose (500 mg/kg). The remaining compounds had no antitumor activity.

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer 457.

4-Oxo-7-diethylaminomethyl-3,4-dihydropyrrolo[3,2-d]pyrimidine Hydrochloride (IIa). Sodium acetate (0.72 g, 0.009 mole) and 0.96 g (0.009 mole) of diethylamine hydrochloride were dissolved in 5 ml of water, and to the solution were added 1.0 g (0.007 mole) of (Ia) [2] and 0.75 g (0.009 mole) of 40% aqueous formaldehyde. The reaction mixture was stirred at 80-85°C for 4 h. The solution was evaporated to dryness, the residue dissolved in ethanol, and the insoluble inorganic material filtered off. The solution was treated with alcoholic HCl to pH 1.0, and the precipitated hydrochloride was filtered off and recrystallized from 80% ethanol to give 1.55 g of (IIa).

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

Compound	mp, °C	Yield, %	Found, %				Molecular formula	Calculated, %			
			C	H	N	Cl		C	H	N	Cl
IIa	242—4	72	44,84	6,40	19,51	24,18	$C_{11}H_{16}N_4O \cdot 2HCl$	45,06	6,19	19,11	24,18
IIb	223—5	75	54,55	7,30	—	12,35	$C_{13}H_{20}N_4O \cdot HCl$	54,83	7,43	—	12,16
IIc	199—201	49	65,41	7,88	20,32	—	$C_{15}H_{12}N_4O$	65,64	8,08	20,42	—
IId	151—3	42	46,75	4,89	21,55	—	$C_{12}H_{18}N_4O \cdot C_6H_2OH(NO_2)_3$	46,65	4,57	21,65	—
IVa	300	67	62,10	7,38	23,90	—	$C_{12}H_{16}N_4O$	62,04	6,94	24,12	—
IVb	266—8	87	67,56	7,12	19,81	—	$C_{16}H_{20}N_4O$	67,58	7,09	19,70	—
IVd	224—6	83	73,00	6,52	16,14	—	$C_{21}H_{22}N_4O$	72,79	6,36	16,15	—
IVe	154—6	68	77,00	7,80	15,66	—	$C_{29}H_{35}N_5$	76,78	7,77	15,43	—
Va	270—2	63	46,86	6,75	18,33		$C_{12}H_{18}N_4O \cdot 2HCl$	46,91	6,56	18,23	
Vb	162—4	93	62,81	8,20	18,31	—	$C_{16}H_{22}N_4O \cdot H_2O$	63,13	7,95	18,41	—
Vb·HCl	255—7	56	62,00	6,98	15,05		$C_{16}H_{22}N_4O \cdot 2HCl \cdot 0,5H_2O$	52,17	6,84	15,21	
Vc	122—4	30	61,43	6,26	16,98		$C_{17}H_{19}N_4Cl \cdot H_2O$	61,35	6,36	16,83	
Vd	132—5	70	70,54	6,58	15,53	—	$C_{21}H_{24}N_4O \cdot 0,5H_2O$	70,57	6,76	15,67	—
Ve	261—2	68	66,08	7,52	13,20	13,49	$C_{29}H_{37}N_5 \cdot 2HCl$	66,02	7,44	13,27	13,44
VI	212—5	18	66,52	6,62	18,41	—	$C_{21}H_{25}N_5O_2$	66,47	6,64	18,46	—
VIII	295—7	69	42,93	5,61	19,78		$C_{10}H_{14}N_4O \cdot 2HCl$	42,98	5,74	20,02	

Note: Compounds (IIa), (Va-b), (Ve), and (VIII) were crystallized from ethanol, (IIb) and (Vd) from DMF, (IVa) from dioxane, and (IVd) and (VI) from benzene.

TABLE 2. Antireductase Activity of 7-Aminomethyl-pyrrolo-[3,2-d]pyrimidine

Compound	Concentration	
	$1 \cdot 10^{-5}$ mole	$1 \cdot 10^{-6}$ mole
	suppression of DFR activity, %	
IIa	22	0
Va	16	0
Vb	82	12
Vd	95	48

Compound (IIb) was obtained similarly, the reaction being carried out at 50-60°C. On cooling to room temperature, the precipitate of (IIb) which separated was filtered off.

4-Methoxy-2,6-dimethyl-7-piperidinomethylpyrrolo[3,2-d]pyrimidine (IIc). To a suspension of 1.9 g (0.01 mole) of (Ic) [6] in 4.0 ml of CH_3COOH was added with cooling a mixture of 0.95 g (0.01 mole) of 40% aqueous formalin, 1.1 g (0.01 mole) of piperidine, and 4.0 ml of CH_3COOH. The mixture was stirred for 20 min at room temperature, then for 2 h at 70-80 °C. The resulting solution was cooled, diluted with 16 ml of water, and extracted with ether to remove nonbasic impurities. The aqueous layer was basified with 10% NaOH until strongly alkaline, and the solid which separated was filtered off and recrystallized from ethanol to give 1.43 g of (IIc).

4-Methoxy-2,6-dimethyl-7-dimethylaminomethylpyrrolo[3,2-d]pyrimidine Picrate (IId). To a solution of 0.5 g (0.003 mole) of 4-methoxy-2,6-dimethylpyrrolo[3,2-d]pyrimidine (Ic) in 13.5 ml of n-butanol was added 0.1 g (0.003 mole) of paraformaldehyde and 0.66 g (0.008 mole) of dimethylamine hydrochloride. The reaction mixture was boiled for 15 min, then the butanol was removed *in vacuo*, the residue treated with 12 ml of 5% HCl, and nonbasic impurities extracted with ether. The aqueous solution was neutralized with 50% K_2CO_3 solution to pH 7.0, and the oil which separated was extracted with ether. The extract was dried over K_2CO_3, and the ether distilled off. The residue was dissolved in water, and the solution treated with a saturated aqueous solution of picric acid. After 10 h, the solid which had separated was filtered off and recrystallized from 50% ethanol to give 0.55 g of picrate (IId).

4-Oxo-2-methyl-7-n-butylaminomethylene-3,4-dihydropyrrolo[3,2-d]pyrimidine (IVa). A solution of 1.1 g (0.006 mole) of 4-oxo-2-methyl-3,4-dihydropyrrolo[3,2-d]pyrimidine-7-aldehyde (IIIa) [3], 0.6 g (0.008 mole) of n-butylamine, and 25 ml of dry dioxane was boiled for 1 h. After cooling, the solid was filtered off to give 1.0 g of (IVa).

4-Oxo-2-methyl-7-(β-cyclohexene-1-yl)ethylaminomethylene-3,4-dihydropyrrolo[3,2-d]-pyrimidine (IVb). A mixture of 1.15 g (0.006 mole) of 4-oxo-2-methyl-3,4-dihydropyrrolo-[3,2-d]pyrimidine-7-aldehyde (IIIb), 1.8 g (0.014 mole) of β-cyclohexen-1-yl-ethylamine, 2.0 g (0.014 mole) of K_2CO_3, and 60 ml of water was boiled for 4 h. After cooling, the solid was filtered off, washed with light petroleum ether, and recrystallized from DMF to give 1.6 g of (IVb).

4-Oxo-2-methyl-7-(β-cyclohexen-1'-yl)ethylaminomethyl-3,4-dihydropyrrolo[3,2-dipyrimidine (Vb). To a solution of 0.5 g (0.002 mole) of (IVb) in 10 ml of absolute methanol was added gradually 0.07 g (0.002 mole) of $NaBH_4$. The reaction mixture was boiled for 15 min, cooled, and poured into 15 ml of water. The solid which separated was filtered off and washed with water to give 0.5 g of (Vb). This (0.5 g) was dissolved in 4 ml of absolute ethanol, and alcoholic HCl was added to pH 1.0. The solid which separated was filtered off, and washed with light petroleum ether to give 0.34 g of (Vb) hydrochloride.

Compounds (Va, d, and e) were obtained similarly, boiling being continued for 2 h in the case of (Va) and (Ve). When the reaction was complete, alcoholic HCl was added to the solution until the pH was 1.0. The precipitated hydrochlorides of (Va, d, and e) were filtered off.

4-Chloro-2-phenyl-7-n-butylaminomethylpyrrolo[3,2-d]pyrimidine (Vc). A mixture of 1 g (0.004 mole) of 4-chloro-2-phenylpyrrolo[3,2-d]pyrimidine-7-aldehyde (IIIb) [2], 0.3 g (0.004 mole) of n-butylamine, and 4 ml of dry dioxane was boiled for 30 min. The solution was evaporated to dryness, the residues (0.5 g) dissolved in 5 ml of absolute methanol, and 0.06 g

(0.002 mole) of $NaBH_4$ added portionwise. After boiling for 15 min, the solution was cooled, poured into 10 ml of water, and the solid filtered off, and washed with water to give 0.4 g of (Vc).

2-Phenyl-4-morpholino-7-morpholinomethylpyrrolo[3,2-d]pyrimidine (VI). Morpholine (1.0 g, 0.0012 mole) was added to 0.6 g (0.0012 mole) of formic acid, the mixture cooled, and 1.5 g (0.0006 mole) of 4-chloro-2-phenylpyrrolo[3,2-d]pyrimidine-7-aldehyde (IIIb) added portionwise. The reaction mixture was heated on the water bath for 1 h, dissolved in 25 ml of concentrated hydrochloric acid, and unreacted amine extracted with ether. The hydrochloric acid solution was treated with 40% NaOH solution to pH 8.0, and extracted with chloroform. The chloroform extract was dried over Na_2SO_4, and the chloroform evaporated. The residue was recrystallized from carbon tetrachloride to give 0.4 g of (VI).

4-Oxo-2-methyl-7-dimethylaminomethylpyrrolo[3,2-d]pyrimidine Hydrochloride (VIII). To a suspension of 2 g (0.008 mole) of (4-oxo-2-methyl-3,4-dihydropyrrolo[3,2-d]pyrimidin-7-yl)methyleneammonium chloride (VII) [3] in 15 ml of absolute methanol was added gradually 0.7 g (0.02 mole) of $NaBH_4$, and the reaction mixture was heated at 65-70°C for 1 h. The mixture was cooled, inorganic solids filtered off, and the solution treated with alcoholic HCl to pH 1.0. The precipitate was filtered off to give 1.6 g of (VIII).

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