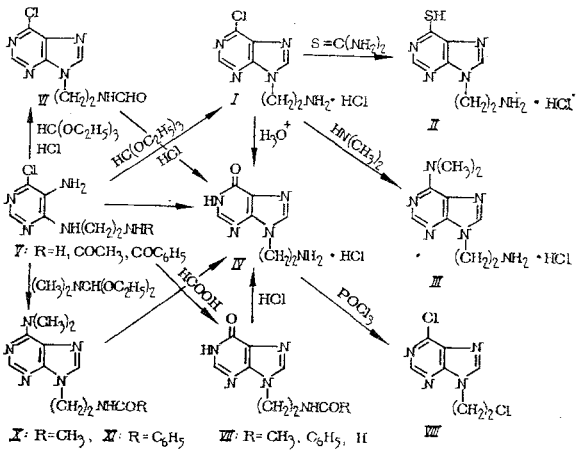
SYNTHESIS AND ANTITUMOR ACTIVITY OF 9-(β-AMINOETHYL)PURINES

R. G. Glushkov, L. A. Nikolaeva, O. V. Kozlova,
L. N. Dronova, V. A. Chernov, and S. M. Minakova

UDC 615.277.3:547.857/.012.1

Continuing our search for antitumor drugs [1], we have synthesized some 9-(β-amidino- or cycloamidinoethyl)purines with a hydroxy-, mercapto-, or amino-group in the 6-position of the purine molecule. These compounds are of interest as potential antimetabolites for naturally-occurring purines present in nucleic acids.

The 6-substituted 9-(β-aminoethyl)purines (I-IV) required as starting materials were synthesized from the pyrimidines (V) (R = H [2], $COCH_3$ [3], COC_6H_5), with triethyl orthoformate, formic acid, or DMF diethyl acetal as cyclizing agents, as follows:



In an examination of the cyclization of (V) (R = H) with triethyl orthoformate, we have found conditions which enable the yield of (I) to be raised from 39 [2] to 70%. Varying the amount of triethyl orthoformate used in this reaction resulted in formylation of the β-aminoethyl moiety in addition to cyclization to give 6-chloro-9-(β-formylaminoethyl)purine (VI). The latter is hydrolyzed by dilute HCl to the amine (IV), which was also synthesized by by cyclization of (V) (R = H) with formic acid, or by hydrolysis of the acyl derivatives (VII) (R = CH_3, C_6H_5), as for (VI). An anomalous reaction, which is the subject of a separate study, was observed when the aminoethylhypoxanthine (IV) was reacted with phosphoryl chloride. In this reaction, both the hydroxy-groups were replaced by chlorine to give 6-chloro-9-(β-chloroethyl)purine (VIII), the structure of which was confirmed by its elemental analysis and the identity of its IR and UV spectra and melting point with a sample of (VIII) obtained by treating 6-chloro-9-(β-hydroxyethyl)purine (IX) with thionyl chloride [4].

Interesting results were obtained when the chloropyrimidines V (R = $COCH_3$, COC_6H_5) were reacted with dimethylformamide diethyl acetal. In this reaction, which proceeds under mild conditions to give high yields (90%), in addition to cyclization of the diaminopyrimidine to the corresponding purine, replacement of the 6-chloro-substituent by the dimethylamino group occurred to give the substituted 6-dimethylaminopurines (X-XI). Hydrolysis of the acyl group in (X) and (XI) by treatment with acid or caustic alkali gave the hypoxanthine (IV). 6-Dimethylamino-9-(β-aminoethyl)purine (III) was synthesized in the usual way, by reacting the chloropurine (I) with dimethylamine. Reaction of (I) with thiourea also gave 6-mercapto-9-(β-aminoethyl)purine (II).

Reaction of 6-substituted 9-(β-aminoethyl)purines (II-IV) with lactim ethers or with DMF acetals and formylmorpholine afforded a new group of purines, the 9-(β-amidino- or cycloamidinoethyl)purines (XII-XXIII).

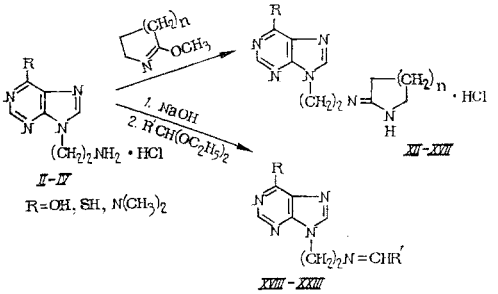
S. Ordzhonikidze All-Union Scientific-Research Institute for Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 6, pp. 674-679, June, 1984. Original article submitted November 15, 1983.

0091-150X/84/1806- 0387$08.50

TABLE 1. Properties of 9-(β-Aminoethyl)purines

Compound	Yield, %	mp, °C (solvent for crystallization)	Found, %					Empirical formula	Calculated, %				
			C	H	Cl	N	S		C	H	Cl	N	S
II	82,2	283—285	30,97	3,90	26,27	26,03	12,01	$C_7H_{11}Cl_2N_5S$	31,34	4,10	26,49	26,12	11,94
III	51,2	195—197 (ethanol)	44,37	6,21	14,52	34,56	—	$C_9H_{15}ClN_6$	44,53	6,18	14,64	34,63	—
V (R=COC_6H_5)	64,5	225—227 (abs. ethanol)	53,37	4,74	12,37	24,25	—	$C_{13}H_{14}ClN_5O$	53,52	4,80	12,18	24,01	—
VI	47,8	188—190 (water)	42,48	3,60	15,35	31,03	—	$C_8H_8ClN_5O$	42,57	3,54	15,74	31,04	—
VII (R CH_3)	79,6	280 (decomp., aq. ethanol)	48,46	4,87	—	31,73	—	$C_9H_{11}N_5O_2$	48,87	4,97	—	31,07	—
VII (R=C_6H_5)	85,4	300 (decomp., aq. ethanol)	59,07	4,67	—	24,97	—	$C_{14}H_{13}N_5O_2$	59,36	4,59	—	24,73	—
VIII	32,5	110—112,5 (ethanol)	38,78	2,73	32,69	26,19	—	$C_7H_6Cl_2N_4$	38,71	2,76	25,81	32,72	—
X	89,6	155—156 (ethyl acetate)	53,65	6,43	—	33,66	—	$C_{11}H_{16}N_6O$	53,23	6,45	—	33,87	—
XI	90,3	171—174 (ethyl acetate)	61,65	5,68	—	27,07	—	$C_{16}H_{18}N_6O$	61,94	5,81	—	27,09	—
XII	82,4	282—284 (aq. ethanol)	46,77	5,26	12,51	29,98	—	$C_{11}H_{15}ClN_6O$	46,72	5,31	12,57	29,73	—
XIII	59,7	304—305 (aq. ethanol)	50,12	6,13	11,52	27,01	—	$C_{13}H_{19}ClN_6O$	50,24	6,12	11,43	27,05	—
XIV	67,8	304 (decomp., aq. ethanol)	41,91	5,44	11,23	26,61	9,96	$C_{11}H_{15}ClN_6S \cdot H_2O$*	41,70	5,37	11,22	26,54	10,11
XV	74,0	336 (decomp., aq. ethanol)	47,58	5,61	11,08	25,86	9,89	$C_{13}H_{19}ClN_6S$	47,78	5,82	10,87	25,72	9,80
XVI	90,8	291—293 (methanol)	45,26	5,88	20,62	28,25	—	$C_{13}H_{20}Cl_2N_7$	45,08	6,08	20,52	28,32	—
XVII	89,3	300 (decomp., methanol)	48,28	6,79	18,96	26,40	—	$C_{15}H_{25}Cl_2N_7$	48,12	6,68	18,98	26,20	—
XVIII	78,3	285—286 (aq. ethanol)	44,28	5,61	12,83	31,12	—	$C_{10}H_{15}ClN_6O$	44,36	5,55	13,12	31,05	—
XIX	91,1	263—265 (aq. ethanol)	40,91	6,20	9,98	24,18	—	$C_{12}H_{17}ClN_6O_2$	41,31	6,03	10,19	24,10	—
XX	78,7	269 (decomp., aq. ethanol)	41,50	5,19	12,36	29,46	11,23	$C_{10}H_{15}ClN_6S$	41,88	5,24	12,39	29,32	11,17
XXI	88,2	275—277 (aq. ethanol)	41,58	5,60	10,19	24,58	9,10	$C_{12}H_{17}ClN_6OS \cdot H_2O$ †	41,56	5,48	10,25	24,24	9,23
XXII	70,1	257—258 (abs. ethanol)	43,08	6,12	21,38	29,38	—	$C_{12}H_{25}Cl_2N_7O_2$	43,11	6,28	21,25	29,34	—
XXIII	67,3	260—262 (abs. ethanol)	42,97	6,30	17,87	25,00	—	$C_{14}H_{23}Cl_2N_7O \cdot H_2O$ ‡	42,64	6,34	18,02	24,87	—

*Found, %: H_2O 5.89. Calculated, %: H_2O 5.69.
†Found, %: H_2O 5.31. Calculated, %: H_2O 5.19.
‡Found, %: H_2O 4.48. Calculated, %: H_2O 4.57.



XII: R = OH, $n = 1$
XIII: R = OH, $n = 3$
XIV: R = SH, $n = 1$
XV: R = SH, $n = 3$
XVI: R = $N(CH_3)_2$, $n = 1$
XVII: R = $N(CH_3)_2$, $n = 3$
XVIII: R = OH, R′ = $=N(CH_3)_2$
XIX: R = OH, R′ = morpholino
XX: R — SH, R′ = $=N(CH_3)_2$
XXI: R = SH, R′ = = morpholino
XXII: R = R′ = $N(CH_3)_2$,
XXIII: R = $N(CH_3)_2$ R′ = morpholino

EXPERIMENTAL CHEMISTRY

For the properties of the compounds prepared, see Table 1.

6-Chloro-9-(β-aminoethyl)purine Hydrochloride (I). To a mixture of 16.55 g of (V) (R = H) in 250 ml of freshly-distilled triethyl orthoformate was added 7.3 ml of concentrated hydrochloric acid, followed slowly over 2 h by the dropwise addition of a further 14.3 ml of the same acid. The mixture was heated to the boil, and when the temperature of the mixture reached 80°C boiling was continued for a further 2 h. The mixture was then cooled, kept at 20°C for 3-4 h, filtered, and the solid crystallized from aqueous alcohol to give 13.6 g (65.9%) of (I), mp 295°C (decomp.) [2].

6-Chloro-9-(β-formylaminoethyl)purine (VI). To a suspension of 12.36 g of (V) (R = H) in 150 ml of triethyl orthoformate was added with stirring 5.9 ml of concentrated hydrochloric acid, followed by the dropwise addition over 2 h of a further 13.2 ml of the same acid. The mixture was boiled for 2 h, cooled, and the solid which separated was isolated, dried, and crystallized.

4-Chloro-5-amino-6-(benzoylaminoethyl)aminopyrimidine (V, R = COC_6H_5). A mixture of 8.9 g of 4,6-dichloro-5-aminopyrimidine and 15.91 g of N-benzoylethylenediamine in 100 ml of propanol was boiled for 3 h. The mixture was cooled, filtered, the solid stirred with 30 ml of water, filtered, washed with alcohol, dried, and crystallized to give 10.2 g of (V) (R = COC_6H_5).

9-(β-Acetylaminoethyl)hypoxanthine (VII, R = CH_3). A mixture of 5 g of (V) (R = $COCH_3$) [3] and 25 ml of anhydrous formic acid was boiled for 4 h. The mixture was then cooled, and filtered to give 3.83 g of (VII) (R = CH_3).

Compounds (IV) and (VII) (R = C_6H_5) were obtained similarly.

6-Dimethylamino-9-(benzoylaminoethyl)purine (XI). A mixture of 10 g of (V) (R = COC_6H_5) and 15 ml of DMF diethyl acetal in 150 ml of DMF was boiled for 3 h. The solution was evaporated, and the residual solid was crystallized from ethyl acetate to give 9.6 g of (XI).

9-(β-Aminoethyl)hypoxanthine Hydrochloride (IV). A mixture of 2 g of (VI) and 50 ml of 18% hydrochloric acid was boiled. The solution was evaporated, and the residual solid was crystallized from aqueous alcohol to give 1.4 g of (IV).

Similarly obtained were (IV) from (VII) (R = CH_3, C_6H_5), (X), and (XI).

6-Mercapto-9-(β-aminoethyl)purine Dihydrochloride (II) [3]. A mixture of 2.9 g of (I) and 1.88 g of thiourea was boiled for 3 h in 42 ml of n-butanol. The mixture was then cooled (20°C), filtered, and dried to give 2.73 g of (II).

6-Dimethylamino-9-(β-aminoethyl)purine Hydrochloride (III). 30 g of (I) was added gradually at 20-22°C to 300 ml of 33% aqueous dimethylamine, and the mixture was stirred for 4 h at 20°C. The solution was then evaporated, and the residual solid filtered with 50 ml of ethanol, dried, and crystallized to give 16.2 g of (III).

Compound (III) (4 g) was dissolved in 7 ml of water, 40% NaOH added until the pH reached 10.0, and the mixture extracted with chloroform to give 3.22 g of (III) free base, mp 93-95°C. Found, %: N 40.65. $C_9H_{14}N_6$. Calculated, %: N 40.77.

6-Chloro-9-(β-chloroethyl)purine (VIII). A. A mixture of 2.45 g of 9-(β-aminoethyl)-hypoxanthine, 1.7 g of triethylamine hydrochloride, and 25 ml of phosphoryl chloride was boiled for 20 h. The mixture was evaporated, and the residue decomposed with ice and treated with sodium bicarbonate (pH 7.0). Filtration gave 0.8 g (32.5%) of (VIII), which was crystallized for analysis from alcohol, mp 110-112.5°C [4].

B. A mixture of 1 g of 6-chloro-9-(β-hydroxyethylamino)purine (IX) and 10 ml of thionyl chloride was boiled for 0.5 h. The solution was then evaporated, the residue decomposed with ice, and extracted at pH 7.0 with chloroform. The extract was evaporated, and the solid filtered with ether to give 0.7 g of (VIII), mp after crystallization from alcohol 111-112.5°C, mixed mp with (VIII) obtained by method A, 110.5-111.5°C.

9-β-[(Pyrrolidinylid-2-ene)amino]ethylhypoxanthine Hydrochloride (XII). A mixture of 1 g of (IV) and 2 g of O-methylbutyrolactim was boiled in 20 ml of absolute alcohol for 11 h, cooled (20°C), filtered, and the solid recrystallized from aqueous alcohol to give (XII).

Compounds (XIII-XVII) were obtained similarly.

N-[β-(Hypoxanth-9-yl)ethyl]-N'N'-dimethylformamidine Hydrochloride (XVIII). A mixture of 2.5 g of the free base (IV) and 8 ml of DMF diethyl acetyl was stirred in 40 ml of DMF for 2 h, then kept at room temperature for 20 h. The mixture was filtered, the solid stirred with 25 ml of absolute ethanol and alcoholic hydrogen chloride added until the pH reached 2.0. The resulting solid was filtered off and crystallized to give (XVIII).

Compound (XX) was obtained similarly.

9-[β-(N-Morpholinomethylene)aminoethyl]hypoxanthine Hydrochloride (XIX). A mixture of 2 g of the free base (IV) and 2.62 g of N-formylmorpholine diethyl acetal was stirred in 50 ml of absolute alcohol for 8 h at 20°C. The mixture was then filtered, and the solid washed with alcohol, dried, and crystallized to give (XIX).

Compound (XXI) was obtained similarly.

9-[β-(N-Morpholinomethylene)aminoethyl]-6-dimethylaminopurine Dihydrochloride (XXIII). A mixture of 1 g of free base (III) and 1.37 g of N-formylmorpholine diethyl acetal was stirred in 10 ml of absolute ethanol for 7 h. The solution was then evaporated, and the dry residue treated with 10 ml of absolute alcohol, and alcoholic HCl until the pH reached 2.0. The solid was isolated and crystallized, to give (XXIII).

Compound (XXII) was obtained similarly.

EXPERIMENTAL BIOLOGY

The antitumor activity of compounds (XII-XXIII) was studied in rats with transplanted Jensen's sarcoma. Treatment was commenced on the 5th day following transplantation of the tumor, the compounds being administered intraperitoneally in repeated doses (once daily for 4-7 days). One day subsequent to the last injection the animals were killed, and the inhibition index (I_i, %) was measured by comparing the change in mass of the tumor.

The results are shown in Table 2.

It will be seen that three compounds (XII, XIV, and XXIII) inhibited the growth of Jensen's sarcoma when given in repeated doses, the greatest antitumor activity being displayed by hypoxanthine and 6-mercaptopurine derivatives with a pyrrolidinylidene group in the 9-position (XII and XIV). In doses of 66 and 120 mg/kg, these compounds retarded the growth of Jensen's sarcoma by 32 and 39%, respectively.

Slightly greater activity was shown by the 6-dimethylaminopurine (XXIII). Repeated administration of this compound to rats with Jensen's sarcoma in the maximum tolerated dose retarded the growth of the tumor by 49%, whereas the analogous derivatives of hypoxanthine and 6-mercaptopurine were inactive.

TABLE 2. Toxicities and Antitumor Activity of Purines in Rats with Jensen's Sarcoma

Compound	LD_{50}, mg/kg (repeated dosage)	Dose, mg/kg	No. of doses	I_T, %	Changes in weight of animals, g	
					experimental	control
XII	110	66	7	+32	—5	—10
XIII	50	17	7	0	—12	—10
XVIII	120	76	7	0	—18	—10
XIX	90	45	4	0	—9	—10
XIV	150	126	6	+39	+2	—6
		85	6	0	—9	—6
XV	134	87	6	0	+1	—6
		37	6	0	—5	—6
XX	156	120	6	0	—5	—6
		80	6	0	—8	—6
XXI	102	75	6	0	—11	—6
		33	6	0	—14	—6
XVI	60	22	6	0	0	+15
XVII	35	21	4	0	+1	+15
XXII	60	21	6	+24	+10	+15
XXIII	55	20	6	+49	+11	+15

A study of the toxicities of the compounds in rats showed that the hypoxanthine and 6-mercaptopurine derivatives were of relatively low toxicity following repeated intraperitoneal administration, their LD_{50} ranging from 90-156 mg/kg (except for XIII). The 6-dimethylaminopurines were more toxic, with LD_{50} ranging from 35 to 60 mg/kg.

Thus, biological studies of the novel purines (XII-XXIII) has shown that some of them display antitumor activity, and are of moderate toxicity. These results encourage further searches for 9-aminoalkyl- and 9-amidinoalkylpurines with antitumor activity.

LITERATURE CITED

1. R. G. Glushkov, L. A. Nikolaeva, E. S. Golovchinskaya, et al., Khim.-farm. Zh., No. 3, 16-19 (1981).
2. S. K. Chakraborti, Ind. J. Chem., 7, 425-429 (1969).
3. T. P. Johnston, G. S. McCaleb, and J. A. Montgomery, J. Med. Chem., 6, 676-679 (1963).
4. J. A. Montgomery and C. Temple, J. Am. Chem. Soc., 83, 630 (1961).

SYNTHESIS AND ANTITUMOR ACTIVITY OF A COMPLEX OF CADMIUM CHLORIDE AND POLYVINYLIMIDAZOLE

G. G. Skvortsova, A. I. Skushnikova, E. S. Domnina, I. G. Veksler, K. P. Balitskii, and M. G. Voronkov

UDC 615.277.3:[547.77+546.443].012.1

The fundamental role of complexes in a variety of biological systems has stimulated the study of complexes of metals with compounds containing an imidazole ring. Metal-containing polyvinylimidazoles have been used in the development of models of hemoproteins [7] and polymeric hemochromes [6, 8]. An antitumor imidazole derivative is known, which is used in the treatment of breast cancer and melanoma [5].

In order to extend the range of antitumor drugs, we have studied for the first time the formation of complexes of cadmium chloride with polyvinylimidazoles. A new cadmium-containing complex of vinylimidazole with 1-vinyl-2-pyrrolidone has been obtained, and its antitumor activity examined. The required ligands were prepared by the radical copolymerization of 1-vinylimidazole (I) with 1-vinyl-2-pyrrolidone (II) in the presence of azobisisobutyronitrile [2]. The reaction of alcoholic solutions of the copolymer of 1-vinylimidazole with 1-vinyl-2-pyrrolidone (III, copolymer) with cadmium chloride affords complexes with different metal contents.

Institute of Organic Chemistry, Siberian Section, Academy of Sciences of the USSR, Irkutsk.

Translated from Khimiko-farmetsevticheskii Zhurnal, Vol. 18, No. 8, pp. 679-683, June, 1984. Original article submitted July 29, 1983.

0091-150X/84/1806-0391$08.50