SYNTHESIS AND ANTITUMOR ACTIVITY OF N-[2-(DIETHYLENEDIAMIDOPHOSPHONYL)VINYL]-N'-ARYLUREAS

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Although N-phosphorylated ureas have been fairly thoroughly investigated, their vinyl analogs have hitherto been unknown. They are of both theoretical and practical interest, since many phosphorylated urea derivatives possess high antitumor activity [1-3].

We have obtained phosphorylated vinylogs of urea from 2-isocyanatovinylphosphonyl dichloride, prepared as follows [4]:

$$CH_2=CHNCO \xrightarrow{2PCl_5} (Cl_3PCH=CHNHCOCl)^+ PCl_6^- \xrightarrow{SO_2}$$
$$Cl_2P(O)CH=CHNHCOCl \xrightarrow[-HCl]{} Cl_2P(O)CH=CHNCO.$$

The reaction between aromatic amines and 2-amino-5-methoxypyrimidine, and 2-isocyanatovinylphosphonyl dichloride, results initially in addition to the vinyl group to form N-dichlorophosphonylvinyl-N'-arylureas, which are colorless crystalline solids, readily hydrolyzed by moist air, and melting with decomposition (Table 1):

$$Cl_2P(O)CH=CHNCO \xrightarrow{ArNH_2} Cl_2P(O)CH=CHNHCONHAr.$$

The reaction was carried out in an atmosphere of nitrogen, the diacid chlorides being obtained in nearly quantitative yields in a state of analytical purity.

The N-dichlorophosphonylvinyl-N'-arylureas react with ethyleneimine in the presence of triethylamine to give N-[2-(diethylenediamidophosphonyl)-vinyl]-N'-arylureas, which are colorless, high-melting crystalline solids, soluble on heating in methanol and nitromethane, insoluble in ether–light petroleum and in water (cf. Table 1):

$$Cl_2P(O)CH\text{-}CHNHCONHAr \longrightarrow (\text{N})_2P(O)CH\text{-}CHNHCONHAr.$$

Intense bands occur in the IR spectrum in the 880-920 and 1210-1230 cm^{-1} regions, due to C–C deformational vibrations in the three-membered ethyleneimine ring [5], and at 1710 and 1260 cm^{-1}, due to C = O and P = O group stretching vibrations [6, 7].

The antitumor activity of the compounds was determined on two strains of rat tumors, Guerin's carcinoma, and sarcoma 45 (Table 2). Preliminary investigation of the acute toxicity showed that all the compounds were of low toxicity, the LD_{50} varying between 150 and 550 mg/kg. Compounds VIII and XV were virtually nontoxic. In investigating the antiblastic properties of the compounds, treatment was begun 6-8 cays after inoculation, when the tumors were 10-15 mm in diameter. The compounds were introduced daily in 8-10 doses by the subcutaneous route. The principal indication of antitumor activity was the percentage

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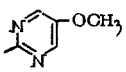
TABLE 1. N-(2-Phosphonylvinyl)-N'-arylureas RNHCONHCH-CHP(O)X_2

Compound	R	X	Yield (%)	Melting point (deg)	Calculated (%)	Molecular formula	Found (%)
I	C_6H_5	Cl	92	127–130	N 10,04	$C_9H_9Cl_2N_2O_2P$	N 9,98
II	C_6H_5	C_2H_4N	58	184–5 (181)	N 19,13	$C_{13}H_{17}N_4O_2P$	N 19,23
III	*n*-$CH_3C_6H_4$	Cl	95	126–8	P 10,57	$C_{10}H_{11}Cl_2N_2O_2P$	P 10,84
IV	*n*-$CH_3C_6H_4$	C_2H_4N	48	186–8 (180)	P 10,11	$C_{14}H_{19}N_4O_2P$	P 10,19
V	*n*-$CH_3C_6H_4$	Cl	96	132–4	Cl 22,94	$C_{10}H_{11}Cl_2N_2O_3P$	Cl 23,05
VI	*n*-$CH_3OC_6H_4$	C_2H_4	60	188–9 (185)	P 9,60	$C_{14}H_{19}N_4O_3P$	P 9,49
VII	2,4-$(CH_3)_2C_6H_3$	Cl	91	148–0	P 10,09	$C_{11}H_{13}Cl_2N_2O_2P$	P 10,15
VIII	2,4-$(CH_3)_2C_6H_3$	C_2H_4	50	184–6 (180)	P 9,67	$C_{15}H_{21}N_4O_2P$	P 9,45
IX		Cl	97	161–3	P 9,96	$C_8H_9Cl_2N_4O_3P$	P 9,96
X	p-ClC_6H_4	Cl	99	165–6	P 9,88	$C_9H_9Cl_3N_2O_2P$	P 9,94
XI	p-ClC_6H_4	C_2H_4	70	211–3 (205)	Cl 10,85	$C_{13}H_{16}ClN_4O_2P$	Cl 10,80
XII	p-BrC_6H_4	Cl	98	166–8	P 8,65	$C_9H_9BrCl_2N_2O_2P$	P 8,48
XIII	p-BrC_6H_4	C_2H_4	71	220–1 (215)	P 8,34	$C_{13}H_{16}BrN_4O_2P$	P 8,20
XIV	p-IC_6H_4	Cl	99	167–8	Cl 17,51	$C_9H_9Cl_2IN_2O_2P$	Cl 17,48
XV	p-IC_6H_4	C_2H_4	75	227–9 (224)	P 7,42	$C_{13}H_{16}IN_4O_2P$	P 7,37

Notes. The temperature of insertion of the capillary containing the substance into the mp apparatus is given in parentheses. Compounds I, III, V, VII-X, XII, and XIV were purified by repeated washing with ether; II, VI, XI, XIII, and XV by crystallization from methanol; and IV by crystallization from a mixture of methanol and ether.

TABLE 2. Activity of N-Substituted Ureas on Guerin's Carinoma and Sarcoma 45

Tumor type	Compound	LD_{50} (mg/kg)	Therapeutic dose (mg/kg) × number of admin.	Number of animals		Mean tumor weight (g)		Inhibition of tumor growth (T, %)
				exp.	cont.	exp.	cont.	
Guerin's carcinoma	II	200	33×8	10	12	39,0±2,6	59,0±5,0	34
	IV	550	100×10	10	10	3,1±0,9	10,6±1,9	71
	VI	150	30×9	10	10	51,4±4,0	55,7±4,1	8
	VIII	1500	100×9	10	10	23,3±4,1	46,0±3,7	50
	XI	300	60×10	10	10	9,7±2,6	10,6±1,9	8
	XIII	500	100×10	10	10	13,9±3,4	10,6±1,9	—32
	XV	1200	100×9	10	10	31,6±2,2	69,4±4,5	54
Sarcoma 45	II		33×9	10	12	30,0±3,7	23,0±1,4	—30
	IV		100×10	10	10	2,7±0,8	5,0±1,2	46
	VI		20×9	10	10	6,7±1,2	19,6±2,8	66
	VIII		100×10	10	15	12,8±4,7	23,3±4,9	45
	XI		60×9	10	10	8,9±3,5	14,8±4,4	40
	XIII		100×9	10	10	17,0±4,5	14,8±4,4	—15
	XV		100×9	10	10	5,4±3,1	14,8±4,4	63

Note: $T = M_c - M_e/M_c \cdot 100$, where M_c and M_e are the mean weights of the tumors in control and experimental animals, respectively.

reduction in the growth of the tumor (cf. Table 2). The results were evaluated statistically by the Student–Fisher method as modified by Sh. D. Moshkovskii [8]. The most active compound in tests on Guerin's carcinoma was IV, moderate activity being displayed by VIII and XV. In tests on sarcoma 45, the most pronounced inhibitory effects were observed in VI and XV.

Analysis of the relationship between chemical structure and antitumor activity shows that the introduction of such substituents as iodine, methyl, and methoxy into the p-position of the benzene ring increases the activity, whereas bromine reduces it.

EXPERIMENTAL

All reactions were carried out in anhydrous solvents.

N-[2-(Dichlorophosphonyl)vinyl]-N'-arylureas (I, III, V, VII, IX, X, XII, XIV). To a solution of 0.02 mole of 2-isocyanatovinylphosphonyl dichloride in 40 ml of ether in a nitrogen atmosphere was added gradually with stirring at 2-5° a solution of 0.2 mole of the amine in 50 ml of ether, and the mixture was kept at

20° for 5 h. The precipitate which separated was filtered off, washed with ether, and dried.

N-[2-(Diethylenediamidophosphonyl)vinyl]-N'-arylureas (II, IV, VI, VIII, XI, XIII, XV). To a solution of 0.021 mole of triethylamine and 0.021 mole of freshly distilled ethyleneimine in 100 ml of benzene was added slowly with vigorous stirring and cooling 0.01 mole of the N-dichlorophosphonylvinyl-N'-arylurea at such a rate that the temperature of the mixture remained at 4-5°. The mixture was stirred at 20° for 5 h and kept at the same temperature for 10 h. The precipitate which separated was filtered off, washed with benzene and ether, and dried. It was then washed with water, dried, and crystallized.

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