EXPERIMENTAL

The spectra in the UV and visible regions were measured on an SF-4A instrument in ethanol and 0.1 N alkali at concentrations of $1 \cdot 10^{-5}$-$2 \cdot 10^{-5}$ mole/liter.

Benzoylformamide Phenylhydrazone (IIIa). A solution of 0.02 mole of Ia in 10 ml of benzene was added to 0.02 mole of II (R = H). The mixture was heated on the water bath for 10-15 min until a precipitate separated, then filtered, and the solid crystallized from benzene. All the compounds (III) were obtained in this way.

LITERATURE CITED

1. M. S. Mashevskaya and P. A. Petyunin, Khim. Farmats. Zh., No. 7, 9 (1970).
2. P. A. Petyunin, M. S. Mashevskaya, et al., Khim. Farmats. Zh., No. 11, 11 (1972).
3. M. S. Mashevskaya, P. A. Petyunin, et al., Inventor's Certificate No. 447,401; Otkrytiya, No. 39 (1974).
4. I. S. Berdinskii and P. A. Petyunin, Zh. Obshch. Khim., 26, 2592 (1956).
5. O. V. Sverdlov, Electronic Spectra in Organic Chemistry [in Russian], Leningrad (1973), p. 120.
6. G. N. Pershin (editor), Methods of Experimental Chemotherapy [in Russian], Moscow (1959), p. 109.

SYNTHESIS AND INVESTIGATION OF IMIDAZOLE DERIVATIVES.

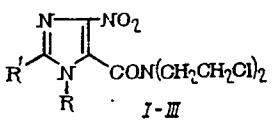
IX. AMIDES CONTAINING THE DI(2-CHLOROETHYL)AMINO GROUP

R. N. Gireva, G. A. Aleshina,
L. A. Reznichenko, G. V. Zykina,
L. F. Mal'tseva, and P. M. Kochergin

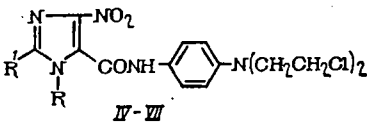
UDC 615.277.3:547.781.1].012.1

In continuation of our earlier search for potential antitumor compounds amongst imidazone derivatives containing the di(2-chloroethyl)amino group [1, 2], we have synthesized some di(2-chloroethyl)amides and p-di(2-chloroethyl)aminoanilides of 4-nitroimidazole-5-carboxylic acids, together with ethoxycarbonyl- and carbamoylimidazolylamides of N,N-di(2-chloroethyl)sulfanilic acid and carbamoylimidazolylamides of p-di(2-chloroethyl)aminophenylacetic acid.

The di(2-chloroethyl)amides (I-III) and di(2-chloroethyl)aminoanilides (IV-VII) of 1-methyl- and 1,2-dialkyl-4-nitroimidazole-5-carboxylic acids were obtained by reaction of the nitro acid chlorides [3, 4] with di(2-chloroethyl)amine [5] or p-N,N-di(2-chloroethyl)phenylenediamine hydrochlorides [6] in the presence of pyridine as hydrogen chloride acceptor.



I-III



IV-VII

The 1-methyl-, 1,2-dialkyl-5-ethoxycarbonyl-, and 1,2-dialkyl-5-carbamoylimidazole-4-amides of N,N-di(2-chloroethyl)sulfanilic acid (VIII-X and XI-XIII), and the 1,2-dialkyl-5-carbamoyl-4-amides of p-di(2-chloroethyl)aminophenylacetic acid (XIV-XVI) were obtained by reaction of the corresponding acid chlorides [7, 8] with the esters and amides of 4-aminoimidazole-5-carboxylic acid [9] in the presence of a hydrogen chloride acceptor (pyridine or triethylamine).

Novokuznets Scientific-Research Institute of Pharmaceutical Chemistry. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 9, pp. 48-51, September, 1976. Original article submitted January 22, 1976.

TABLE 1. Imidazole Amides Containing the Di(2-chloroethyl)amino Group

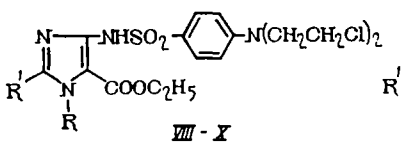
Compound	R	R¹	Yield, %	Melting point, deg*	Found, %				Molecular formula	Calculated, %			
					C	H	Cl	N		C	H	Cl	N
I	CH_3	H	74,7	114,5—5,0	37,09	4,20	23,79	19,09	$C_9H_{12}Cl_2N_4O_3$	36,61	4,68	24,07	18,98
II	CH_3	CH_3	78,8	162,5—3,5	38,64	4,57	22,86	18,21	$C_{10}H_{14}Cl_2N_4O_3$	38,83	4,53	22,98	18,12
III	C_4H_9	C_3H_7	80,3	55—6	48,00	6,31	18,48	14,34	$C_{15}H_{24}Cl_2N_4O_3$	47,49	6,33	18,73	14,77
IV	CH_3	H	38,2	188,5—9,0	46,12	4,66	—	18,20	$C_{15}H_{17}Cl_2N_5O_3$	46,63	4,44	—	18,13
V	CH_3	CH_3	40,0	220—1	47,73	4,85	18,50	17,28	$C_{16}H_{19}Cl_2N_5O_3$	48,00	4,75	17,75	17,50
VI	C_3H_7	C_2H_5	55,2	171—2	51,54	5,87	16,32	15,40	$C_{19}H_{25}Cl_2N_5O_3$	51,58	5,67	16,06	15,84
VII	C_4H_9	C_3H_7	57,6	170—1	53,11	6,20	—	14,59	$C_{21}H_{29}Cl_2N_5O_3$	53,62	6,17	—	14,89
VIII	CH_3	H	51,2	133—4	45,36	5,10	—	12,47	$C_{17}H_{22}Cl_2N_4O_4$	45,43	4,90	—	12,47
IX	CH_3	CH_3	30,2	143,5—4,0	46,47	5,13	—	12,12	$C_{18}H_{24}Cl_2N_4O_4$	46,65	5,18	—	12,10
X	C_3H_7	C_2H_5	36,6	123—4	49,77	6,25	—	11,07	$C_{21}H_{30}Cl_2N_4O_4$	49,90	5,94	—	11,09
XI	CH_3	CH_3	30,5	236,5—7,5	43,86	5,00	16,32	16,55	$C_{16}H_{21}Cl_2N_5O_3$	44,24	4,88	16,32	16,13
XII	C_3H_7	C_2H_5	37,8	220,5—1,5	47,28	5,81	—	14,88	$C_{19}H_{27}Cl_2N_5O_3$	47,90	5,67	—	14,71
XIII	C_4H_9	C_3H_7	33,7	210,5—1,5	49,65	6,15	14,35	14,24	$C_{21}H_{31}Cl_2N_5O_3$	49,99	6,21	14,05	13,88
XIV	CH_3	CH_3	23,0	197	52,31	5,67	17,18	16,89	$C_{18}H_{23}Cl_2N_5O_2$	52,43	5,63	17,19	16,99
XV	C_3H_7	C_2H_5	25,4	197	55,42	6,43	15,31	14,96	$C_{21}H_{29}Cl_2N_5O_2$	55,50	6,44	15,60	15,41
XVI	C_4H_9	C_3H_7	45,3	196	57,02	6,90	14,36	14,11	$C_{23}H_{33}Cl_2N_5O_2$	57,25	6,91	14,52	14,52

*The compounds were purified by crystallization from: alcohol (I, VIII-XIII), absolute alcohol (II), alcohol with addition of water until turbid (III), and acetone (IV-VII and XIV-XVI).

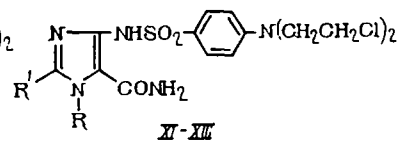
TABLE 2. Results of Testing Compounds I-XVI for Antitumor Activity

Compound	MTD,* mg/kg	Inhibition index, %		
		Ehrlich's ascites carcinoma	sarcoma 180	sarcoma 45
I	100	40	25	40
II	250	0	0	0
III	250	40	50	0
IV	500	60	0	0
V	500	0	0	0
VI	500	30	30	0
VII	500	0	40	40
VIII	500	0	60	0
IX	500	0	40	0
X	500	0	30	20
XI	500	0	0	0
XII	500	0	0	0
XIII	1000	0	0	31
XIV	500	0	50	100
XV	500	45	0	0
XVI	500	0	0	0

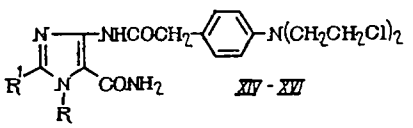
*MTD) Minimum tolerated dose for mice on a single administration.



VIII - X



XI - XIII



XIV - XVI

The properties of the compounds are shown in Table 1.

The IR spectra of these compounds (in paraffin oil, IR-10 spectrophotometer) showed absorption bands in the 1655-1650 cm^{-1} region characteristic of the tertiary amide group (I-III) and at 1520-1510 cm^{-1} and 1330 cm^{-1} corresponding to symmetrical valence vibrations of the nitro group (I-VII). Bands are also present typical of sulfonamides at 1164-1160 cm^{-1} (VIII-XIII), C—O—C grouping of esters at 1260-1208 and 1100 cm^{-1} (VIII-X), and for secondary amides at 1663-1655 cm^{-1} (NHCO group; IV-VII and XIV-XVI).

Initial tests for antitumor activity were carried out in therapeutic tests on three strains of tumors (Ehrlich's ascites carcinoma, sarcoma 180, and sarcoma 45). It was shown that some of the compounds had no antitumor effect, and the rest showed activity only at moderately high doses (Table 2).

EXPERIMENTAL

Di(2-chloroethyl)amides of 1-Methyl- and 1,2-Dialkyl-4-nitroimidazole-5-carboxylic Acids (I-III). To a mixture of the nitro acid chloride, obtained from 0.02 mole of the acid and a 9-11-fold excess of thionyl chloride [4], 100-150 ml of dry benzene, and 3.13 g (0.017 mole) of di(2-chloroethyl)amine hydrochloride was added dropwise with stirring and cooling 6.4 ml (6.3 g, 0.08 mole) of pyridine (dried over solid potassium hydroxide). The mixture was stirred for 2-3 h, then kept overnight. The precipitated pyridine hydrochloride was filtered off, the benzene removed from the filtrate, and the residue treated with dilute hydrochloric acid. The crystals were filtered off, washed with water, dilute sodium carbonate, and again with water. The yellowish crystals of the amide were air dried and crystal-

lized from alcohol (Table 1). The amides were colorless crystalline solids, soluble in alcohol on heating, acetone, and benzene, but insoluble in water.

Di(2-chloroethyl)aminoanilides of 1-Methyl- and 1,2-Dialkyl-4-nitroimidazole-5-carboxylic Acids (IV-VII). To a mixture of the acid chloride of the nitro acid obtained from 0.02 mole of the acid, 5.39 g (0.02 mole) of N,N-di(2-chloroethyl)phenylenediamine hydrochloride, and 100 ml of dry benzene was added dropwise with stirring and cooling in an ice bath 6.4 ml (0.08 mole) of pyridine (dried over solid potassium hydroxide). The reaction mixture was stirred for 3-4 h at room temperature. After 12-16 h, the precipitate was filtered off, suspended in alcohol, filtered again, and washed on the filter with small amounts of alcohol. A further quantity of the amide was obtained from the mother liquors on evaporation of the benzene. Crystallized from acetone. Brightly colored (yellow or reddish orange) crystals, sparingly soluble in alcohol, benzene, and insoluble in water.

1-Methyl- and 1,2-Dialkyl-5-ethoxycarbonylimidazole-4-amides of N,N-Di(2-chloroethyl)-sulfanilic Acid (VIII-X). To a mixture of 0.02 mole of the ethyl-1-methyl- or 1,2-dialkyl-4-aminoimidazole-5-carboxylate, 7.8 g (0.024 mole) of N,N-di(2-chloroethyl)sulfanilyl chloride, and 150 ml of dry benzene was added dropwise with stirring 6.4 ml (0.08 mole) of dry pyridine. The reaction mixture was heated slowly to the boil, boiled for 2-2.5 h, and kept at room temperature for 12-15 h. The pyridine hydrochloride which separated was filtered off, and the benzene was removed from the mother liquors. The gummy residue was crystallized twice from alcohol. The di(2-chloroethyl)sulfanilamides were colorless, crystalline solids which were readily soluble in acetone, benzene, and hot alcohol.

1,2-Dialkyl-5-carbamoylimidazole-4-amides of N,N-Di(2-chloroethyl)sulfanilic Acid (XI-XIII). To a mixture of 0.02 mole of 1,2-dialkyl-4-aminoimidazole-5-carbonamide, 6.32 g (0.02 mole) of N,N-di(2-chloroethyl)sulfanilic acid, and 300 ml of dry benzene was added slowly with stirring (15-20 min) 4.8 ml (0.06 mole) of dry pyridine. The reaction mixture was heated to the boil, boiled for 5-7 h, cooled to room temperature, and kept for several hours in the refrigerator. The precipitate which separated was filtered off, suspended in distilled water, filtered, and the solid washed on the filter with a small amount of alcohol. The off-white or grayish finely crystalline powder of the sulfonamide was crystallized from alcohol to give colorless crystals, readily soluble in acetone but sparingly so in benzene and hot alcohol.

1,2-Dialkyl-5-carbamoyl-4-amides of p-Di(2-chloroethyl)aminophenylacetic Acid (XIV-XVI). To a mixture of 4.96 g (0.015 mole) of finely ground p-di(2-chloroethyl)aminophenylacetyl chloride hydrochloride, 0.012 mole of the 1,2-dialkyl-4-aminoimidazole-5-carbonamide, and 400-500 ml of dry benzene was added dropwise with stirring 5.9 ml (0.052 mole) of triethylamine. The mixture was gradually brought to the boil, and boiled for 1.5 h, then filtered hot from triethylamine hydrochloride. The amide separated from the filtrate on cooling as a colorless solid. Crystallization from acetone gave colorless crystals, soluble in alcohol, benzene, and acetone, but insoluble in water and light petroleum.

LITERATURE CITED

1. R. N. Gireva, N. N. Gavrilov, G. A. Aleshina, et al., Khim. Geterotiskl. Soedin., 123-125 (1967).
2. R. N. Gireva, G. A. Aleshina, L. F. Mal'tseva, et al., in: Proceedings of the 1st All-Union Conference on the Chemotherapy of Malignant Tumors, Riga (1968) [in Russian], p. 146.
3. F. G. Mann and J. W. G. Porter, J. Chem. Soc., 751-760 (1945).
4. R. N. Gireva, G. A. Aleshina, L. A. Reznichenko, et al., Khim. Farmats. Zh., No. 10, 24-29 (1974).
5. M. I. Goryaev and E. V. Zhikulina, Tr. Kaz. Inst. Klin. Éksp. Khir., 6, 200-203 (1960).
6. J. L. Everett and W. C. J. Ross, J. Chem. Soc., 1972-1983 (1949).
7. J. F. Danielli and L. N. Owen, US Patent No. 3057850 (1962); Chem. Abstr., 58, 6751 (1963).
8. E. N. Shkodinskaya, E. M. Kurdyukova, O. S. Vasina, et al., Zh. Obshch. Khim., 32, 959-961 (1962).
9. R. N. Gireva, G. A. Aleshina, L. A. Reznichenko, et al., Khim. Farmats. Zh., No. 11, 25-29 (1974).