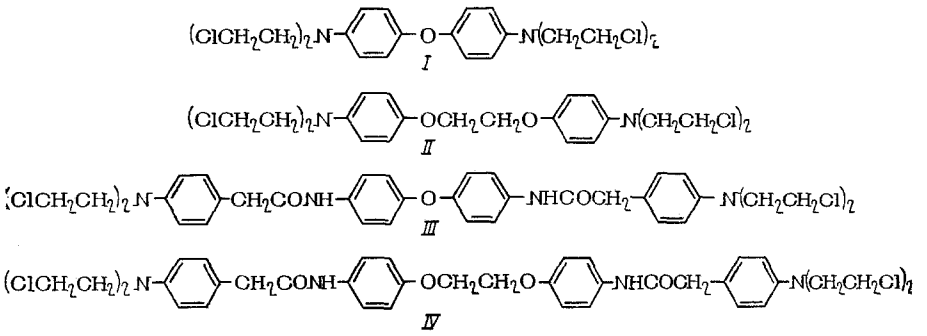
BIS(2-CHLOROETHYL)AMINO DERIVATIVES OF DIPHENYL ETHERS

R. N. Gireva, L. F. Mal'tseva,
L. N. Trappel', T. V. Zykina,
and M. Yu. Mogilevskii

UDC 615.277.3:547.652

We synthesized some chloroethylamino derivatives of diphenyl ethers in a search for substances with anticancer activity. The synthesis of four derivatives of N,N-bis(2-chloroethyl)amine is described in this paper as possible antitumorigenic substances: 4,4'-tetra(2-chloroethyl)diaminodiphenyl ether (I), ethyleneglycol 4,4'-tetra(2-chloroethyl)diaminodiphenyl ether (II), 4,4'-di[p-bis(2-chloroethyl)aminophenylacetamido]-diphenyl ether (III), and ethyleneglycol 4,4'-di[p-bis(2-chloroethyl)aminophenylacetamido]diphenyl ether (IV)



I

II

III

IV

4,4'-Diaminodiphenyl ether (V) and ethyleneglycol 4,4'-diaminodiphenyl ether (VI), which we prepared by reducing the corresponding nitro compounds [1] with cast iron filings in an aqueous–acetone (3:2) solution of an electrolyte (ammonium chloride and hydrochloric acid), were used as the starting substances for preparing I-IV.

Methods of obtaining V by the catalytic reduction of 4,4'-dinitrodiphenyl ether over Raney nickel and Pd/C or Pt/C at an increased pressure have been described in the literature [2, 3]. The method we used is characterized by simplicity, does not require the use of expensive catalysis (platinum or palladium), and provides a satisfactorily high yield of the desired product with good quality.

Compounds I and II were obtained from V and VI by reacting them with ethylene oxide in dilute acetic acid followed by treatment of the tetrahydroxyethyl derivatives formed with phosphorus oxychloride. Compounds III and IV were synthesized by acylating the appropriate diamines with p-bis(2-chloroethyl)aminophenylacetyl chloride (VII) [4, 5] in the presence of triethylamine as a hydrogen chloride acceptor.

The antitumorigenic activity of substances I-IV was investigated in therapeutic experiments on three strains of transplantable tumors (sarcoma 45, sarcoma 180, and Ehrlich's ascitic tumor). It was established in preliminary experiments on white mice that these compounds possess low acute toxicity: the maximum bearable dose is more than 500-1000 mg/kg for a single injection. All the preparations were injected as a suspension in a 1% starch paste. Medical treatment of the solid tumors began on the 5th-7th day; treatment of the ascitic tumors began on the next day after transplantation. The duration of treat-

Novokuznets Chemical and Pharmaceutical Scientific-Research Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 5, pp. 5-7, May, 1972. Original article submitted September 15, 1970.

TABLE 1. Effect of Bis(2-Chloroethyl)amino Derivatives of Diphenyl Ethers When Administered Internally on the Growth of Experimental Tumors

Strain of tumor	Preparation	Dose, mg/kg	No. of animals		Average weight of tumors (in g)*		Index of inhibition, %
			exp.	control	exp.	control	
Sarcoma 45	I	500	7	7	7,8±1,1	27,8±1,7	72
	II	200	9	9	9,7±1,5	19,3±2,0	48
	III	100	7	7	23,5±1,6	16,7±3,9	—42
	IV	100	7	7	10,9±2,1	21,1±3,4	48
Sarcoma 180	I	500	7	7	3,3±0,7	5,8±0,8	43
	II	100	7	8	1,7±0,6	2,7±0,2	0
	III	100	7	7	2,8±0,6	3,4±0,5	0
	IV	50	8	9	5,1±0,9	6,0±0,6	0
Ehrlich's tumor (ascitic form)	I	250	7	7	2,2±0,6	4,3±0,3	48
	II	100	7	7	3,0±0,8	5,3±0,3	47
	III	100	7	7	5,0±0,7	4,9±0,5	0
	IV	100	7	7	5,1±0,9	3,8±0,4	0

*The volume of ascitic liquid (in ml) is indicated for Ehrlich's tumor.

ment amounted to 8-10 days. The results were evaluated by an index of inhibition of the growth of the tumors, which was calculated as the ratio of the difference in the weight of the tumor in the control and in the experiment to the average weight of the tumors in the control. The volume of ascitic liquid and the length of life of the animals were recorded in the experiments with Ehrlich's tumor.

It was established (see Table 1) that preparation I possesses moderate antitumorigenic activity, having depressed the growth of sarcoma 45 by 72%, sarcoma 180 by 43%, and Ehrlich's ascitic tumor by 48%. In addition, this substance proves to have a negative effect on the organism by substantially decreasing the weight of the spleen and the body weight of the animals toward the end of the experiment. Some antitumorigenic activity in relation to sarcoma 45 was also displayed by preparations II and IV. Substance III, on the other hand, stimulated the growth of this tumor. Not one of the preparations affected the length of life of the mice with Ehrlich's tumor.

EXPERIMENTAL

4,4'-Diaminodiphenyl Ether (V). A mixture of 102 g of degreased ground iron filings, 360 ml of water, 240 ml of acetone, 20 g of ammonium chloride, and 10 ml of 33% hydrochloric acid was heated with agitation to 60°C; 64 g of 4,4'-dinitrophenyl ether was gradually added over the period of 1 h while maintaining the temperature at 60-64°C. The reaction mixture was maintained under these conditions for 3 h. The acetone was distilled off. A 10% sodium carbonate solution was added to the cooled residue until the iron salts had completely precipitated out (test with sodium sulfide) and they were filtered off. The base V was extracted from the iron sludge with acetone. The acetone was distilled from the extract. In order to purify V, the residue was dissolved in dilute hydrochloric acid (500 ml of water and 50 ml of 33% hydrochloric acid). The solution of the hydrochloride of V was boiled with carbon and filtered. The base V was precipitated from the filtrate with a 10% sodium carbonate solution, filtered off, washed with water, air dried, then dried in vacuo at 100°C. The yield was 35-37 g (87.5-92.5%), grayish crystals, mp 187-189°C.

Ethylene Glycol 4,4'-Diaminodiphenyl Ether (VI). This compound was prepared the same way V was from 16.1 g of ethyleneglycol 4,4'-dinitrodiphenyl ether, 26 g of iron fillings, 4.8 g of ammonium chloride, and 3.3 ml of concentrated hydrochloric acid in a mixture of 90 ml of water and 60 ml of acetone. The purification operation of the finished product was repeated twice. The yield was 9 g (83.3%), light brown crystals, mp 174-175°C. Found %: C 68.62, 68.94; H 6.48, 6.62; N 11.52, 11.61. $C_{14}H_{16}N_2O_2$. Calculated %: C 68.65; H 6.56; N 11.47.

4,4'-Tetra(2-hydroxyethyl)diaminodiphenyl Ether (VIII). To a cooled mixture of 10 g of V and 150 ml of 10% acetic acid was carefully added 21 ml of ethylene oxide. The flask was tightly sealed with a stopper and allowed to sit for a day at room temperature. To the reaction mixture was added a solution of sodium carbonate until the mixture was slightly alkaline, the precipitate was filtered off, and crystallized

from water to which carbon was added. The yield was 12 g (64%), colorless crystals, mp 99°C. Found %: C 63.37, 62.98; H 7.62, 7.41; N 7.49, 7.69. $C_{20}H_{28}N_2O_5$. Calculated %: C 63.83; H 7.45; N 7.45.

Ethylene Glycol 4,4'-Tetra(2-hydroxyethyl)diaminodiphenyl Ether (IX). This compound was obtained similarly to VIII from 10 g of VI, 150 ml of 10% acetic acid, and 18 ml of ethylene oxide. The yield was 13.6 g (79.02%), colorless crystals, mp 108°C (from water). Found %: C 62.9, 62.71; H 7.98, 8.02; N 6.69, 6.55. $C_{22}H_{32}N_2O_6$. Calculated %: C 62.85; H 7.62; N 6.67.

4,4'-Tetra(2-chloroethyl)diaminodiphenyl Ether (I). Five grams of VIII was gradually added while cooling and with agitation to 9.7 ml of phosphorus oxychloride which had been cooled. The mixture was gradually heated to boiling on a water bath and boiled for 1 h; at this time, VIII had completely dissolved. The mixture was cooled and poured onto 100 g of crushed ice. After decomposing the excess phosphorus oxychloride, a sodium carbonate solution was added to the reaction mixture until it was slightly acid. The precipitate was filtered off and crystallized from isopropanol to which activated carbon was added. The yield was 5 g (83%), lustrous plates with a faint brownish tinge, mp 77-78°C, soluble in alcohol, insoluble in water. Found %: C 53.34, 53.09; H 5.56, 5.40; N 6.26, 6.26. $C_{20}H_{24}Cl_4N_2O$. Calculated %: C 53.33; H. 5.33; N 6.22.

Ethylene Glycol 4,4'-Tetra(2-chloroethyl)diaminodiphenyl ether (II). This compound was prepared similarly to I from 5 g of IX and 8.7 ml of phosphorus oxychloride. The yield was 4.2 g (72.4%), lustrous plates with a very faint brownish tinge, mp 72-73°C (from methanol), soluble in alcohol, insoluble in water. Found %: C 53.42, 53.29; H 5.84, 5.67; Cl 28.17, 28.04; N 5.51, 5.61. $C_{22}H_{28}Cl_4N_2O_2$. Calculated %: C 53.44; H 5.67; Cl 28.74; N 5.67.

4,4'-Di[p-bis(2-chloroethyl)aminophenylacetamido]diphenyl Ether (III). To a mixture of 7.7 g of the hydrochloride of VII, 2 g of V, and 600 ml of anhydrous benzene, which was heated to boiling, was added 8 ml of triethylamine. The reaction mixture was boiled 1 h and filtered free of the triethylamine hydrochloride while hot. Compound III, which precipitated when the filtrate was cooled (5.1 g, 71.2%), mp 160°C, was recrystallized twice from acetone. The yield was 2.5 g (34.9%), colorless crystals, mp 186-187°C, soluble in alcohol, benzene, acetone, insoluble in water. Found %: C 60.49; H 5.62; Cl 20.03, 20.22; N 8.25, 8.05. $C_{36}H_{38}Cl_4N_4O_3$. Calculated %: C 60.34; H 5.31; Cl 19.83; N 7.82.

Ethylene Glycol 4,4'-Di-[p-bis(2-chloroethyl)aminophenylacetamido]diphenyl Ether (IV). To a suspension of 1.22 g of VI and 3.31 g of the hydrochloride of VII in 300 ml of chloroform, cooled to 5-6°C, was added dropwise 3.4 ml of triethylamine. The mixture was boiled 1 h, cooled, and the precipitate (IV) was filtered off. The yield was 2.1 g (55.2%), mp 185°C. It was crystallized from acetone. Fine, colorless crystals were obtained, 1.7 g (44.7%), mp 194-195°C, soluble in alcohol, benzene, acetone, insoluble in water. Found %: C 59.64, 59.69; H 5.28, 5.28; Cl 18.65, 18.57; N 7.02, 7.19. $C_{38}H_{42}Cl_4N_4O_4$. Calculated %: C 60.00; H 5.53; Cl 18.67; N 7.37.

LITERATURE CITED

1. M. Yu. Mogilevskii and N. V. Gudalina, Letter of Invention No. 202,911, Izobreteniya, No. 20, 30 (1967).
2. USA Patent No. 3,140,316; Ref. Zh. Khim., No. 8H 169 (1966).
3. USA Patent No. 3,192,263; Ref. Zh. Khim., No. 24H 414 (1966).
4. I. Guben, Methods of Organic Chemistry [in Russian], Vol. 2, No. 1, Moscow-Leningrad (1941), p. 526; Vol. 4, No. 1 (1949), p. 243.
5. J. L. Everett, J. J. Roberts, and W. C. J. Ross, J. Chem. Soc. (1953), p. 2386.