SYNTHESIS AND BIOLOGICAL INVESTIGATION OF FURAN-CONTAINING MACROCYCLES

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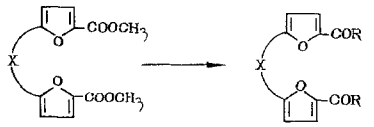
Crown ethers, which are synthetic complexones, are macrocyclic polyethers containing benzene, cyclohexane [1], furan [2], and other rings. Natural products include the highly active alkaloids morphine, halantamine, and the nonactin group of antibiotics which contain furan, di- and tetrahydrofuran heterocycles. New crown ethers have been synthesized by us with the aim of investigating their biological properties. The furan ring enters into the composition of these. Methyl esters of furan carboxylic acids (I-III) served as starting materials [3, 4]. Acids (IV, VI, VIII), their corresponding diacid chlorides (V, VII) [5, 6], and the diacid chloride of di-(5-carboxyfurfuryl)acetal (IX) have been obtained.



I-III IV-IX

I: X = CH_2; II: X = CH_2OCH_2; III: X = $CH_2OCH_2OCH_2$; IV: X = CH_2, R = OH;
V: X = CH_2, R = Cl; VI: X = CH_2OCH_2, R = OH; VII: X = CH_2OCH_2, R = Cl;
VIII: X = $CH_2OCH_2OCH_2$, R = OH; IX: X = $CH_2OCH_2OCH_2$, R = Cl.

The compounds 1,4,6,9-tetraoxa-12,15-diazadifuro[2,1,5a,q:2,1,5-h,i]cyclohectadecane-11,16-dione (X), 1,4,7-trioxa-10,13-diazadifuro[2,1,5-*a*,o:2,1,5-f,g]cyclopentadecane-9,14-dione (XI), 1,5-dioxa-8,11-diazadifuro[2,1,5-*a*,m:2,1,5-d,e]cyclotridecane-7,12-dione (XII), 1,4,6,9-tetraoxa-12,15,18,21,24-pentaazadifuro[2,1,5-*a*,z:2,1,5-h,i]cyclohexacosane-11,25-dione (XIII), 1,4,7-trioxa-10,13,16,19,22-pentaazadifuro[2,1,5-*a*,x:2,1,5-f,g]cyclotetraeicosane-9,23-dione (XIV), 1,5-dioxa-8,11,14,17,20-pentaazadifuro[2,1,5-*a*,v:2,1,5-d,e]cyclodocosane-7,21,dione (XV), and 1,5-dioxa-8,15-diazadifuro[2,1,5-*a*,q:2,1,5-d,e]cycloheptadecane-7,16-dione (XIV) were obtained by the interaction of di-(5-carbomethoxyfuryl)methane (I), di-(5-carbomethoxyfurfuryl)ether (II), and di-(5-carbomethoxyfurfuryl)acetal (III) with ethylenediamine, tetraethylenepentamine, and hexamethylenediamine.

The compounds 1,5,8,11,14-pentaoxadifuro[2,1,5-*a*,p:2,1,5-d,e]cyclohexadecane-7,15-dione (XVII), 1,4,7,10,13,16-hexaoxadifuro[2,1,5-*a*,r:2,1,5-f,g]cyclooctadecane-9,17-dione (XVIII), 1,5,8,11,14,17-hexaoxadifuro[2,1,5-*a*,s:2,1,5-d,e]cyclononadecane-7,8-dione (XIX), 1,4,7,10,13,16,19-heptaoxadifuro[2,1,5-*a*,u:2,1,5-f,g]cycloheneicosane-9,20-dione (XX), 1,4,6,9,12,15,18,21-octaoxadifuro[2,1,5-*a*,w:2,1,5-h,i]cyclotricosane-11,22-dione (XXI), 1,5,8,11-tetraoxa-9,10-benzodifuro[2,1,5-*a*,m:2,1,5-d,e]cyclotrideca-9-ene-7,12-dione (XXII), and 1,5,11-trioxa-trifuro[2,1,5-*a*,p:2,1,5-d,e:2,1,5-j,k]cyclohexadecane-7,15-dione (XXIII) were synthesized by the action of diacid chlorides (V, VII, IX), on di, and triethyleneglycol, pyrocatechol, and 2,5-dihydroxymethylfuran under conditions of high dilution in dimethylformamide (DMF). Substance 1,4,6,9-tetraoxa-12-aza(phenyl)difuro[2,1,5-*a*,n:2,1,5-h,i]cyclotetradecane-11,13-dione (XXIV) was formed on interaction of aniline with (IX) and had the illustrated general structure (see top, following page).

The structures of the synthesized compounds were confirmed by data of elemental analysis, IR, and mass spectrometry. There were absorption bands in the IR spectra of the macrocyclic amides in the 1660-1680 cm^{-1} region whichwere characteristic for amide group carbonyls and in the 1690-1720 cm^{-1} region for macrocyclic esters. The purity of the compounds was checked by TLC.

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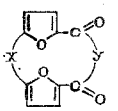
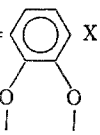
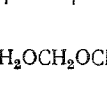
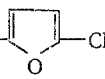


X: X = $CH_2OCH_2OCH_2$, V = NH—$(CH_2)_2$NH; XI: X = CH_2OCH_2, Y = HN—$(CH_2)_2$—NH; XII: X = CH_2, Y = HN $(CH_2)_6$ NH; X = $CH_2OCH_2OCH_2$, Y = $(CH_2)_2$ (HN) $(CH_2)_2$ NH_2; XIV: X = CH_2OCH_2, Y = $[(CH_2)_2NH(CH_2)_2NH]_2NH$; XY: X = CH_2, Y = $(CH_2)_2$ NH $(CH_2)_2$ $(NH)_2$ NH; XVI: X = CH_2, Y = HN—$(CH_2)_6$ NH; XVII: X = CH_2, Y = $(OCH_2CH_2)_2O$; XVIII: X = CH_2OCH_2, Y = $(OCH_2CH_2)_2O$; XIX: X = CH_2, Y = $(OCH_2CH_2)_3O$; XX: X = CH_2OCH_2, Y = $(OCH_2CH_2)_3O$; XXI: X = $CH_2OCH_2OCH_2$, Y = $(OCH_2CH_2)_3O$; XXII: X = CH_2 Y =  XXIII: X = CH_2,



Y = OCH_2—  —CH_2O; XXIV: X = $CH_2OCH_2OCH_2$, Y = NC_6H_5.

The antibacterial and mutagenic properties of the synthesized compounds have been investigated.

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a UR-20 (GDR) spectrophotometer in Nujol mulls. Mass spectrometric analysis was carried out on an MS-1303 instrument with direct insertion of the sample into the ionizing region at an ionization energy of the electrons of 30 eV and at an inlet temperature 40-50°C less than the melting point of the substance.

Aluminum oxide of Brockman grade II was used for column chromatography. The column had a length of 30 cm and a diameter of 4 cm. The eluent was chloroform. TLC was carried out on Silufol UV-254 plates (CSSR) in the systems pyridine—water—ethyl acetate (30:1:1) for compounds (X, XI, XIII, XIV, XV) and pyridine—water (30:1) for compounds (XII, XVI-XXIV). Visualization was performed by ultrachemoscopy. R_f values were within the limits 0.74-0.80.

Di-(5-carbomethoxyfurfuryl)ether (II). The methyl ester of 5-hydroxymethylfuran 2-carboxylic acid (15.6 g, 0.1 mole) [4] was added slowly with stirring to metallic sodium (2.3 g, 0.1 mole) in absolute ether (100 ml). The mixture was boiled for 20 h, then the methyl ester of 5-chloromethylfuran 2-carboxylic acid (17.4 g, 0.1 mole) was added slowly and the mixture was boiled for 20 h. The solid was filtered off, washed with absolute ether, and purified from unreacted metallic sodium. Water (50 ml) was added to the solid. The precipitated crystals were filtered, washed with water, dried, and (II) obtained. Yield was 4.9 g (16.6%), mp 155-156°C (from a mixture of acetone—water, 2:3). Found, %: C 56.87; H 4.75. $C_{14}H_{14}O_7$. Calculated, %: C 57.15; H 4.79. R_f 0.72.

Di-(5-carboxyfurfuryl)ether (VI). A mixture of (II) (5.8 g, 0.02 mole) and 15% sodium hydroxide solution (10 ml) was boiled with stirring for $2^1/_2$-3 h. The solution was extracted with a small amount of ether and acidified with hydrochloric acid. The precipitated crystals were filtered, washed with water (10 ml), dried, and (VI) was obtained. Yield was 4.6 g (90.9%), mp 214-215°C (from water). Found, %: C 54.28; H 3.84. $C_{12}H_{10}O_7$. Calculated, %: C 54.15; H 3.78. R_f 0.75.

Diacid Chloride of Di-(5-carboxyfurfuryl)acetal (IX). Thionyl chloride (40 ml) was added slowly while stirring and boiling to a suspension of (VIII) (9.8 g, 0.03 mole) in benzene (50 ml). The mixture was boiled for 4 h until the end of hydrogen chloride evolution. Benzene and the excess of thionyl chloride were distilled off. The residue was redistilled in vacuum and (IX) was obtained. Yield was 8 g (72.0%), bp 205-208°C (1 mm), mp 48-49°C. Found, %: C 42.55; H 2.84; Cl 21.06. $C_{13}H_{10}Cl_2O_8$. Calculated, %: C 42.76; H 2.76; Cl 21.29.

Preparation of Macrocycles (X-XVI). A mixture of the appropriate diether (0.01 mole), the appropriate diamine or tetraethylenepentamine (0.01 mole), and absolute ethanol (20 ml) was boiled under reflux for 18-20 h. The solvent was distilled off, the residue dissolved in chloroform (50 ml), and passed through a column of aluminum oxide. The chloroform solution was then concentrated to 10 ml and poured into absolute ether (100 ml). The precipitated crystals of (X-XVI) were filtered, washed with absolute ether (20 ml), and dried in a desiccator.

TABLE 1. Macrocycles (X-XIV)

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
X	13,1	140—1	56,35	5,18	8,71	$C_{15}H_{16}N_2O_6$	56,24	5,03	8,75
XI	76,5	104—5	57,86	4,79	9,97	$C_{14}H_{14}N_2O_5$	57,93	4,86	9,65
XII	15,4	173—4	59,78	4,89	10,49	$C_{13}H_{12}N_2O_4$	60,00	4,64	10,76
XIII	63,3	99—100	56,34	6,76	15,32	$C_{21}H_{31}N_5O_6$	56,11	6,95	15,58
XIV	73,8	58—9	57,45	7,07	16,88	$C_{20}H_{29}N_5O_5$	57,26	6,96	16,69
XV	53,5	50—2	58,76	7,11	17,84	$C_{19}H_{27}N_5O_4$	58,60	6,98	17,98
XVI	29,0	212—3	64,83	6,12	9,12	$C_{17}H_{20}N_2O_4$	64,55	6,37	8,85
XVII	40,1	238—240	58,88	4,38	—	$C_{15}H_{14}O_7$	58,82	4,60	—
XVIII	49,9	196—8	57,40	4,96	—	$C_{16}H_{16}O_8$	57,12	4,79	—
XIX	11,5	238—9	58,26	5,39	—	$C_{17}H_{18}O_8$	58,28	5,17	—
XX	36,0	190—1	56,58	5,37	—	$C_{18}H_{20}O_9$	56,83	5,30	—
XXI	13,4	187—8	55,35	5,17	—	$C_{19}H_{22}O_{10}$	55,60	5,40	—
XXII	9,5	112—3	65,63	3,46	—	$C_{17}H_{10}O_6$	65,82	3,25	—
XXIII	25,0	228—9	61,99	3,91	—	$C_{17}H_{12}O_7$	62,21	3,69	—
XXIV	37,1	53—5	64,76	4,39	3,85	$C_{19}H_{15}NO_6$	64,59	4,28	3,96

Macrocycles (XVI-XXIII) were obtained similarly to [7] and (XXIV) similarly to [8] (Table 1).

EXPERIMENTAL (BIOLOGICAL)

The antibacterial properties of the synthesized compounds were studied by serial dilutions in meat—peptone agar in relation to *Staphylococcus aureus* and *Flexner dysenteric* bacillus.

Compounds (XI, XII, XVI-XIX, XXIII, XXIV) had no influence on the growth of the test microorganisms at concentrations of 5 mg/ml and below. Compounds (XIII, XIV, XV), which contain a tetraethylene pentamine residue, inhibited growth of them at a concentration of 0.7 mg/ml.

The mutagenic action of the crown ethers was studied by the "dose-effect" method on the biochemical strains of *Escherichia coli* P-678 thr^- and *Actinomyces rimosus* 222 lys^- (initial strain Bs-21).

The mutagenic and antimutagenic activity of the investigated polyethers were studied regarding the frequency of occurrence of revertants from the auxotrophic to the prototrophic state at the locus responsible for the synthesis of threonine and lysine [9]. The activity of compounds was compared with the genetic action of the known-chemical mutagens hydroxylamine and ethylenimine and with the protectors 2-mercaptoethylamine and dimethyl sulfoxide (DMSO).

Results of the study of the toxic and genetic action of the investigated polyethers are presented in Table 2. From Table 2 it is seen that marked mutagenic action was shown only by compounds (XI, XIII, XIV) which induced the reverse mutation at the threonine locus of *Escherichia coli* 190, 250, and 715 times more, respectively, than the controls (spontaneous mutation). Compounds (XI) and (XIII) proved to be the most active in relation to the lysine locus of Actinomycetes and induced reversion only 72 and 249 times more than the controls. Among the investigated polyethers compounds (II) and (XXIII) showed a contrary antimutagenic action and reduced the number of revertants in experimental variants below the level of those arising spontaneously in control variants by 28.6 and 14.3% (at the threonine locus) and 43 and 28.6% (at the lysine locus), respectively.

Compounds have been made among the crown ethers which were active in mutagenic action on the two test objects and which surpassed hydroxylamine, and in other cases ethyleneimine, when studied under the same conditions.

Substances have been made which either showed action equal to that of 2-mercaptoethylamine and DMSO or were exceeded by them in antimutagenic action.

The obtained results make it possible to draw the conclusions that firstly the investigated substances show more marked mutagenic action in relation to the threonine locus of *Escherichia coli* and a stronger antimutagenic action in relation to the lysine locus of Actinomycetes. Secondly, compounds containing amide groups in the molecule possess only mutagenic

TABLE 2. Influence of Investigated and Control Compounds on the Generation of Mutations in the Test Objects (M ± m)

Compound	Escherichia coli P-678 thr⁻			Actinomyces rimosus 222 lys⁻		
	Dose, mmole	Time, min	survival, %	frequency of occurrence of revertants per 10^6 surviving cells	Dose, mmole	Time, min	survival, %	frequency of occurrence of revertants per 10^5 surviving spores
II	10	10	100±6	5±0,3 (71,4)	20	10	100±8	2,87±0,3 (57)
VIII	10	10	100±9	9,8±0,8 (140)	20	10	50±4,5	8±0,7 (160)
X	100	40	0,9±0 06	381±19,5 (5 440)	100	40	50±6,5	14±1,3 (280)
XI	100	40	0,6±0,04	1393±141 (19 000)	100	120	1,7±0,4	360±27,5 (7 200)
XIII	1	40	0,08±0,01	1750±18 (25 000)	10	80	0,3±0,02	1250±76 (24 900)
XIV	2,5	10	0,14±0,03	5005±420 (71 500)	20	10	12±0,9	25±1,8 (500)
XIX	10	10	70±4,7	12±0,9 (170)	20	10	48±3,8	19±2 (380)
XX	10	10	18±1,4	12±0,9 (170)	20	10	5±0,4	60±4,6 (1 200)
XXII	10	10	59±7,5	14±1,1 (200)	20	10	54±6,2	15,5±1,2 (310)
XXIII	10	10	100±10	6±0,5 (85,7)	20	10	100±8	3,57±0,4 (71,4)
Hydroxylamine	250	30	1,0±0,1	2702±312 (3 860)	250	80	2±0,2	87±5,6 (1 740)
Ethylenimine	100	25	0,1±0,02	2555±122 (36 490)	100	30	1±0,15	405±36 (8 100)
2-Mercaptoethylamine	100	10	100±4,7	3,72±0,65 (53,1)	100	10	97±2,9	2,53±0,3 (50,7)
DMSO	500	10	87,5±4,1	4,37 ±0,5 (62,5)	500	10	93±4,1	4,74±0,5 (94,9)
Control (spontaneous mutation)	—	—	100	7+0,6 (100)	—	—	100	5±0,5 (100)

Note. The percentage of the control figure is shown in parentheses.

activity while the larger the amount of nitrogen contained in a molecule of the substance the more strongly was its action expressed.

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SYNTHESIS AND ANTITUMOR ACTIVITY OF CERTAIN BERBERINE-ETHYLENAMIDES OF PHOSPHORIC ACID

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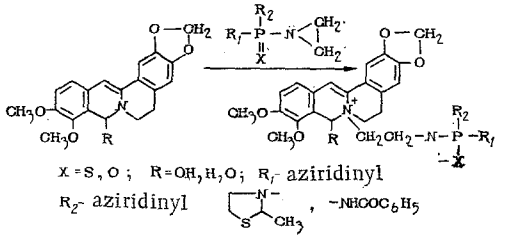
Substances have been discovered among berberine derivatives which possess antitumor properties [1-3]. The present work is devoted to the synthesis of new berberine derivatives, to a study of their toxicity, antitumor activity, and to the establishment of a relationship between the structure of the synthesized substances and their biological activity.

The compounds mentioned were obtained by the interaction of berberine, dihydroberberine, and hydroxyberberine with derivatives of phosphoric acid ethylenamides such as thiophosphamide, imiphos, and benzotef, in an organic solvent without a catalyst (compounds I-XI), the synthesis of some of which has been described previously [4, 5].

Under the conditions of the given reaction it is apparent that fission occurs of ethylenimine rings in thiophosphamide, imiphos, or benzotef by the withdrawal of electrons from the nitrogen atom to the oxygen or sulfur atom as a result of which a reactive ion is formed which interacts with reactive centers of the alkaloid possessing nucleophilic properties in accordance with the scheme:



Since thiophosphamide is a complex alkylating agent containing 3 aziridine groups in the molecule not all rings may be subject to fission at one time and depending on the reaction conditions there may be formed a mono-N'-[2-(N-berberinyl)ethylamide] of diaziridinylthiophosphoric acid (I) [4], compound (IX), di-N',N"-di-[2-(N-berberinyl)ethylamide of aziridinylthiophosphoric acid (II) [4], compound (X), and the trisubstituted derivatives N',N",N"'-tri-

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