titer 5.5 log TCD_{50}/ml. The viruses were titrated in a tube culture of swine enbryo kidney virus (SEKV) by the cytopathic effect. The compounds were taken in the maximum tolerated concentrations (MTC).

After contact for 1 h of a tenfold dilution of the virus and the culture, the former was decanted off and 1 ml of the supporting nutrient medium (50% medium 199 + 50% of 0.5% lactalbumin) containing the compound in solution. The test results were determined 120 h following infection. The antiviral activity was assessed by the inhibition of the cytopathic effects of the viruses.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF DERIVATIVES OF DIBENZO-18-CROWN-6

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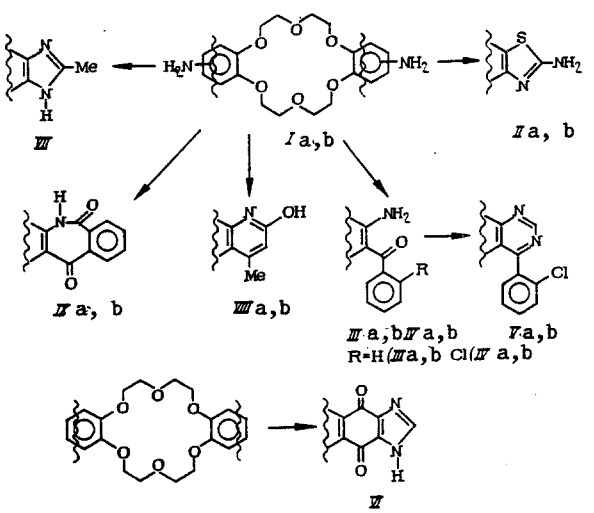
The continued interest of research workers in macroheterocycles is due partly to their uniqueness as complexones, and partly to their wide spectrum of biological activity.



Since some crown ethers are known to display antiviral activity [1], it was decided to synthesize some derivatives of dibenzo-18-crown-6 (DBC) and examine their antiviral activity.

The starting materials used for the syntheses were syn-2,14-diamino- and anti-2,13-diaminodibenzo-18-crown-6 (Ia, b) [4], together with unsubstituted DBC. The benzothiazole derivatives (IIa, b) were obtained by reacting (Ia) and (Ib) with dithiocyanogen in acetic acid [3]. Reaction of the diamines (I) with benzoyl chlorides under Friedel–Crafts conditions afforded the crown o-aminoketones (III) and (IV) [5], which on boiling in formamide

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TABLE 1. Physicochemical Properties of DBC Derivatives

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			IR spectrum, ν_{max}, cm^{-1}	M^+
			C	H	N		C	H	N		
III a	68	102—3	67,8	5,6	4,8	$C_{34}H_{34}N_2O_8$	67,9	5,7	4,7	3320, 3435 (NH), 1625 (C=O)	598
III b	68	106—7	68,0	5,6	4,7	$C_{34}H_{34}N_2O_8$	67,9	5,7	4,7	3330, 3460 (NH), 1630 (C=O)	598
IV a	70	113—4	61,3	4,8	4,3	$C_{34}H_{32}N_2O_8Cl_2$	61,2	4,8	4,2	3330, 3460 (NH), 1620 (C=O)	667
IV b	70	117—8	61,3	4,7	4,2	$C_{34}H_{32}N_2O_8Cl_2$	61,2	4,8	4,2	3320, 3450 (NH), 1615 (C=O)	667
V a	88	236	63,1	4,5	8,3	$C_{36}H_{30}N_4O_6Cl_2$	63,1	4,4	8,2	1640 (C=N), 1170 (>C—O—C<)	685
V b	94	248	63,3	4,3	8,2	$C_{36}H_{30}N_4O_6Cl_2$	63,1	4,4	8,2	1638 (C=N), 1175 (>C—O—C<)	685
VI	78	345	60,2	4,0	9,5	$C_{30}H_{24}N_4O_{10}$	60,0	4,0	9,3	3170 (NH), 1640 (C=O)	600

Note. a is the syn-isomer, and b the anti-isomer.

TABLE 2. Antiviral Activity of DBC Derivatives

Compound	Test virus	Concentrations used, μg/ml	Viral titer, log PFU/ml	Difference from controls, log PFU/ml	ED_{50}, μg/ml
IIa	VSV	100*	5,69	1,00	
		50	5,69	1,00	
		25	5,60	1,09	<12
		12	6,27	0,42	
IIIa	VVV	200*	<3,0	>1,59	
		100	<3,0	>1,59	
		50	3,77	0,82	<12
		0	4,59	0,42	
IIIb	VVV	200*	<3,0	>1,59	
		100	<3,0	>1,59	
		50	3,74	0,85	47,68
		25	4,31	0,28	
		0	4,59	—	
Va	VVV	200*	<3,2	>1,69	
		100	<3,2	>1,69	
		50	<3,2	>1,69	
		25	4,37	0,52	<12,5
		12,5	4,58	0,31	
		0	4,89	—	
	IV	200*	<3,91	>1,51	
		100	4,39	1,03	
		50	5,11	0,31	26,09
		25	5,23	0,19	
		0	5,42	—	
VI	VVV	400*	<3,2	>1,69	
		200	4,74	0,15	>323,47<400
		100	4,74	0,15	
		50	4,73	0,16	
		0	4,89	—	

Notes. 1) An asterisk denotes maximum tolerated dose.
2) IV denotes influenza virus.

gave the quinazolines (V). Condensation of DBC with imidazo-4,5-dicarboxylic acid in polyphosphoric acid results in the formation of the quinone (VI). Compounds (VII-IX) were synthesized as described in [3].

The structures of the products were confirmed by their IR and UV spectra, and their composition by elemental analysis, purity being checked by TLC. The molecular masses of (III-VI) as measured by mass spectrometry were in agreement with the calculated values. In the IR spectra of solid samples of the products, absorption was present for stretching vibrations of the carbon atoms of the benzene ring at 1560-1630 cm^{-1}, together with strong absorption for stretching of the ether group of the macroheterocycle at 1110-1250 cm^{-1}. The spectra of the corresponding compounds also contained characteristic absorption for stretching vibrations of the NH group at 3190-3460 cm^{-1}, and the carbonyl group at 1620-1680 cm^{-1}.

In the UV spectra of the compounds, three absorption bands are present with maxima at 205-230, 240-270, and 290-390 nm. The first two bands correspond to excitation of the aromatic chromophores, and the third (long wavelength) band is attributed to the carbonyl or azomethine group conjugated with the benzene ring. Some physicochemical data for the compounds obtained are given in Table 1.

EXPERIMENTAL (CHEMISTRY)

IR spectra were recorded on a Specord IR-75 spectrophotometer (East Germany), in KBr disks. Mass spectra were obtained on a Varian MAT-112 (Switzerland), UV spectra were recorded on a Specord UV-VIS spectrophotometer (East Germany). Silufol UV-254 plates were used for TLC, solvent systems methanol—ammonia (5:1) and benzene—acetone (5:1).

4,14-Di-(2'-chlorophenyl)diquinazolino[6,7-b;7',6'-k]-18-crown-6 (Va) and 4,17-Di-(2'-chlorophenyl)diquinazolino[6,7-b;6',7'-k]-18-crown-6 (Vb). The o-aminoketone (IVa) or (IVb) (0.667 g) was boiled for 1 h with formamide in a flask with a reflux condenser. On cooling the solution, a solid separated which was filtered off. The product was recrystallized from DMF.

4,14,18,28-Tetraoxodimidazo[5,6-b;5',6'-o]dibenzo-18-crown-6 (VI). To 20 ml of freshly-prepared polyphosphoric acid was added 1.8 g (0.005 mole) of DBC and 1.9 g (0.012 mole) of

imidazole-4,5-dicarboxylic acid. The mixture was stirred at 130-140°C for 2 h, then it was poured into cold water and the solid which separated was filtered off.

EXPERIMENTAL (BIOLOGY)

The antiviral activity of the test compounds was determined in tissue culture against variola vaccine virus (VVV), herpes simplex virus (HSV), classical avian plague virus (CAPV), Newcastel disease virus (NDV), vesicular stomatitis virus (VSV), Venezuelan equine encephalomyelitis virus (VEEN), and ECHO-6, using screening tests and reduction of platelets under an agar cover. In the case of ECHO virus, investigations were carried out with monolayer cultures of passivated human embryo musculocutaneous cells, and in the case of the remaining viruses, with primarily trypsinized chicken embryo fibroblasts.

Measures of antiviral activity were provided by the diameter of the zone of suppression of formation of platelets, and the reduction in viral titer in thepresence of the compound in a range of concentrations. The dose of the compound which inhibited platelet formation by 50% (the mean effective dose, ED_{50}) was calculated by the method of Reed and Mensch. The methods of examination and assessment of antiviral activity have been described in detail previously [2].

In this series of compounds, inhibitory activity against the variola vaccine virus is moderate or low (Table 2). Introducing a thiazole or quinazoline moiety into the DBC molecule gives rise to low antiviral activity against vesicular stomatitis virus (IIa) and influenza virus (Va) respectively. The remaining compounds failed to show antiviral activity in these tests.

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RADIOPROTECTIVE PROPERTIES OF PYRROLIDONE-CONTAINING HETEROCYCLIC ANALOGS OF S-AMINOALKYLISOTHIOUREAS

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There have been reports in [1, 2, 4, 5] about the synthesis, radioprotective activity, and some aspects concerning the radioprotective mechanism of aminoalkylthiol derivatives of pyrimidine and quinazoline, being heterocyclic analogs of S-aminoalkylisothioureas. Compounds in this series have radioprotective activity that is related to a reduction in oxygen consumption by the organism. A significant factor in their radioprotective mechanism is hydrolytic decomposition and generation of free aminothiol. It was of interest to study the radioprotective properties of heterocyclic analogs of isothioureas that contain pyrrolidone residues. The distinctive physicochemical properties of the latter – a combination of hydrophilic and lipophilic activity – could increase the biological availability of the compounds and have a positive effect on their biological activity.

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