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ANTIMICROBIAL ACTIVITY OF HETEROCYCLIC DERIVATIVES OF DIBENZO-18-CROWN-6

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We have previously shown that crown-annelated nitrogeneous heterocycles, derivatives of dibenzo-18-crown-6, have antispasmodic, antiviral and pesticidal properties. The degree of activity of these crown ethers is most of all determined by the character of the heterocyclic nuclei, and also their steric disposition in the molecule [3-5].

It is known that certain simpler macroheterocycles and their derivatives have antimicrobial activity, like many nitrogen-containing heterocycles and quinone derivatives [1]. Therefore, the study of the antimicrobial activity of crown-ethers containing azoheterocyclic and quinone fragments and the clarification of its dependence on the structure and composition of these compounds are clearly of interest.

Syn- and anti-isomers of dibenzo-18-crown-6 (I) derivatives, containing thiazole (II and III), imidazole (IV), triazole (V), pyridine (VI and VII) and azepine (VIII-IX) rings annelated with the benzene rings, were obtained from syn- and anti-diaminodibenzo-18-crown-6 according to the methods that we have previously developed [2, 6].

The crown-annelated quinone (X) was synthesized as a result of the reaction of I with phthalic anhydride in polyphosphoric acid at 80-90°C. Its physicochemical characteristics are given in the experimental part.

The results of the investigation of the biological activity of the synthesized compounds given in Table 1 show that they display a moderate antibacterial and antifungal activity. It is important to note the predominance of the antifungal properties in crown-annelated quinone X, while dibenzo-18-crown-6 (I) itself and its thiazolo derivatives (II and III) display antibacterial activity to a greater degree. This indicates the expedience of a drug search in this series of compounds.

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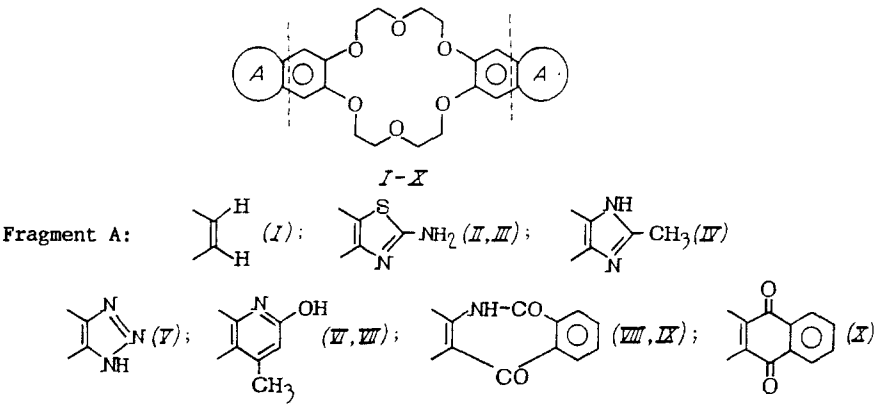
TABLE 1. Minimal Inhibiting Concentrations of Dibenzo-18-Crown and Its Derivatives (in μg per 1 ml of the medium) Inhibiting the Growth of Microorganisms

Compound	St. aureus	E. coli	P. aeruginosa	B. subtilis	Asp. niger	C albicans	S. cerevisiae	T. rubrum	T. mentagrophytes var. gypseum
I	125	500	250	250	250	500	125	250	250
II	250	500	250	15,6	250	250	125	250	250
III	125	500	250	7,8	250	250	31,2	500	500
IV	500	500	500	500	250	500	250	500	500
V	250	500	250	125	250	250	250	250	500
VI	250	n/a	250	500	250	62,5	125	500	500
VII	250	n/a	250	500	250	62,5	62,5	500	n/a
VIII	250	n/a	250	250	250	125	250	500	500
IX	500	500	500	500	125	250	250	500	250
X	250	500	250	125	125	125	15,6	62,5	15,6

Note. Concentration of 500 μg/ml was accepted as the initial dilution of the compound; n/a – inactive; microbial load – 1-2 million microbial bodies in 1 ml.



EXPERIMENTAL (CHEMICAL)

The monitoring of the course of the reaction and the evaluation of the individual compounds was carried out by TLC on "Silufol UV-254" plates in a methanol–ammonia–chloroform (5:2:2) system with development of the spots in UV light or by iodine. The IR spectra were run on a Perkin-Elmer 580 B spectrophotometer in KBr tablets, the UV spectra on a Specord UV-vis spectrophotometer in an ethanol solution, and mass spectra on a Varian MAT CH-5 spectrometer (Switzerland). The elemental analysis data corresponded to the calculated values.

5,15,20,30-Tetraoxodianthraquinono[6,7-b;6',7'-k]-18-crown-6 (X). A 1.8 g portion (0.005 mole) of dibenzo-18-crown and 1.8 g (0.012 mole) of phtalic anhydride were added to 20 ml of freshly prepared polyphosphoric acid. The reaction mixture was stirred at 80-90°C for 4 h, and was then poured into ice and the precipitate was filtered off. The product was recrystallized from DMFA. Yield, 1.9 g (62%), mp 141-146°C. IR spectrum, ν_{max}, cm^{-1}: 1110 (C–O–C), 1670 (C=O). UV spectrum, ν_{max}, nm: 208, 280, 435. Mass spectrum: m/e_{max} 620 (M^+). $C_{36}H_{28}O_{20}$.

EXPERIMENTAL (BIOLOGICAL)

The biological activity of the synthesized compounds was studied with respect to prokaryote and eukaryote cells. The antibacterial activity was determined by the method of double serial dilutions in a meat peptone agar at pH 7.2 with respect to St. aureus ATCC 25923, E. coli 25922, P. aeruginosa, and B. subtilis. The minimal inhibiting concentrations of the compounds for the Asp. niger, C. albicans, T. rubrum, T. mentagrophytes var. gypseum, S. cerevisiae fungi were determined by the method of double serial dilutions in a liquid Saburo medium (pH 5.6) [7].

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