ANTIMICROBIAL ACTIVITY OF DERIVATIVES OF BENZIMIDAZOLO[1,2-a]QUINOLINES

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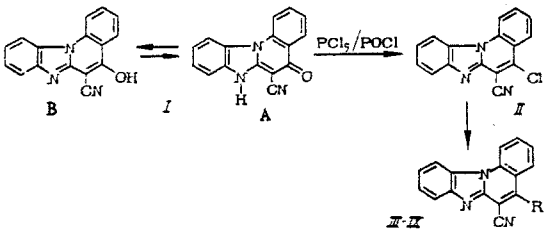
In connection with the presence of high antimicrobial activity in derivatives of benzimidazole [2, 4, 5], we synthesized the 5-substituted benzimidazolo[1,2-a]quinolines (III)-(IX). The heating of 5-oxo-6-cyanobenzimidazolo[1,2-a]quinoline (I) with the mixture of PCl_5 and $POCl_3$ resulted in the isolation of a high yield of 5-chloro-6-cyanobenzimidazolo-[1,2-a]quinoline (II). The chlorine atom, which occurs conjugated with the nitrogen atom of the heterocyclic nucleus and the nitrile group, is available and is substituted by the action of amines [1]. Thus, when the chloroderivative (II) is boiled in dioxane with the twofold excess of the corresponding amines, the nucleophilic substitution of the chlorine atom with the formation of the amines (III)-(IX) occurs.



R = $NH(CH_2)_3NMe_2$ (III), $NH(CH_2)_2NEt_2$ (IV),
$NH(CH_2)_2N(CH_2CH_2)_2O$ (V), $NH(CH_2)_2NHPh$ (VI),
$NH(CH_2)_2C_6H_3(OMe)_2$-3,4 (VII), $NHCH_2CH_2N(CH_2)_5$ (VIII),
$N(CH_2CH_2)_2NMe$ (IX).

The IR spectra of (I)-(IX) contain the absorption band of the nitrile group at 2220-2198 cm^{-1}, the absorption band of the secondary amino group [the compounds (III-IX)] in the region of 3300 cm^{-1}, and that of the aliphatic C-H bonds at 3000-2800 cm^{-1}.

The PMR spectrum of compound (I), recorded in DMSO-d_6, contains a broad signal at 13.53 ppm (one H is exchanged with D_2O), which may be assigned to the N—H or O—H group of the tautomers A and B correspondingly, besides the signals of the aromatic protons. The signal of the exchangeable proton is absent from the PMR spectrum of the compound (II). The intense bands at the λ_{max} = 336 nm, log ε = 4.26 and the λ_{max} = 287 nm, log ε = 4.05 are present in the UV spectrum of the compound (I).

TABLE 1. Minimal Inhibitory Concentrations (in μg/ml)

Compound	S. aureus, 209	S. aureus, 746	E. coli, ATCC 25922	P. aeruginosa	M. luteus	S. marcescens	B. subtilis	T. mentagrophytes var. gypseum 90	M. gypseum, 33/M1-12	C. albicans, 3	A. niger, 1119	M. canis, 4	T. rubrum
I	500	—	500	—	—	—	—	250	—	500	—	500	250
II	62,5	500	—	—	250	—	31,5	250	—	n/a	—	125	250
III	62,5	250	500	12,5	7,8	125	3,9	500	—	250	500	500	—
IV	62,5	250	500	250	31,2	31,2	3,9	62,5	—	250	500	250	—
V	31,2	250	500	500	62,5	500	500	500	—	125	500	250	—
VI	62,5	500	500	250	62,5	31,2	250	250	31,2	125	500	250	—
VII	31,2	500	500	500	62,5	31,2	500	500	500	500	500	125	—
VIII	250	500	500	—	500	—	500	250	—	250	—	250	125
IX	31,2	500	62,5	125	62,5	31,2	7,8	125	3,9	31,2	500	250	—

Notes. The concentration of 500 μg/ml was employed for initial dilution of the substance; n/a indicates inactive.

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TABLE 2. Characteristics of the Derivatives of Benzimidazolo[1,2-a]quinoline (I)-(IX)

Compound	Yield, %	mp, °C (solvent for recrystallization)	Empirical formula
I	78	300 (nitrobenzene)	$C_{14}H_9N_3O$
II	94	288 (DMF)	$C_{14}H_8ClN_3$
III	85	246–47 (toluene)	$C_{21}H_{21}N_5$
IV	80	229–30 (toluene)	$C_{22}H_{23}N_5$
V	83	295 (dioxane)	$C_{22}H_{21}N_5O$
VI	74	144 (toluene)	$C_{24}H_{19}N_5$
VII	65	187 (toluene)	$C_{28}H_{22}N_4O_2$
VIII	81	252 (o-xylene)	$C_{28}H_{23}N_5$
IX	73	259 (toluene)	$C_{21}H_{19}N_5$

As can be seen from Table 1, the activity of the compounds studied was mainly shown in regard to the Gram-positive bacteria and yeast-resembling fungi.

It is interesting to note the sharp broadening of the spectrum of antimicrobial activity for compound (IX). The most effective compounds proved to be (III) and (IV), inhibiting the growth of B. subtilis at the concentration of 3.9 μg/ml, and the produce (IX) which delays the growth of B. subtilis at the concentration of 7.8 μg/ml and that of M. gypseum at the concentration of 3.9 μg/ml.

EXPERIMENTAL (CHEMICAL)

The PMR spectra of the compounds (I) and (II) were recorded in DMSO-d_6 using the "Bruker CXP-200" instrument with the working frequency of 200 MHz and with TMS as the internal standard. The IR spectra were taken on the UR-20 instrument (GDR) using KBr tablets. The UV spectra were recorded on the "Specord UV-VIS" instrument (GDR) in PrOH. The homogeneity of all substances was monitored by chromatography on plates of "Silufol UV-254" utilizing the 9:1 mixture of $CHCl_3$–MeOH as the eluent. The characteristics of the compounds (I)-(IX) are presented in Table 2. The values found for the elemental analyses correspond with the calculated values.

The 5-oxo-6-cyanobenzimidazolo[1,2-a]quinoline (I) and 5-chloro-6-cyanobenzimidazolo-[1,2-a]quinoline (II) were obtained according to [1].

Isolation of the Amino Derivatives (III)-(IX). To the solution of 2.77 g of 5-chloro-6-cyanobenzimidazolo[1,2-a]quinoline (II) in 80 ml of dioxane is added the twofold excess of the corresponding amine. In the isolation of the compounds (VI) and (VII), an equimolecular amount of the amine and freshly calcined potassium carbonate, as the base to neutralize the liberated HCl, is utilized. The mixture is boiled for 1 h [for the compounds (III)-(V), (VIII), (IX)] and 4 h for the compounds (VI) and (VII). The solvent is evaporated in vacuo; the residue is triturated with 100 ml of water, and the residue is filtered off. The substance obtained is dried and recrystallized from the corresponding solvent.

EXPERIMENTAL (BIOLOGICAL)

The biological activity of the compounds (I)-(IX) in relation to the bacteria and fungi S. aureus, E. coli, P. aeruginosa, C. albicans, A. niger, M. canis, T. metagrophytes var. gypseum, M. gypseum, M. luteus, S. marcescens, B. subtilis, and T. rubrum, which are pathogenic in man, was determined by the method of twofold serial dilutions in liquid nutrient medium [3]. The initial dilutions of the investigated substances were prepared in DMSO. The highest dilution of the subtance completely suppressing the development of the test microbe was assumed to be the minimal inhibiting concentration; the microbial load was $1.2 \cdot 10^6$ colony-forming units in 1 ml of broth.

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