SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF SOME 1-NITRO-9-AMINOACRIDINE DERIVATIVES

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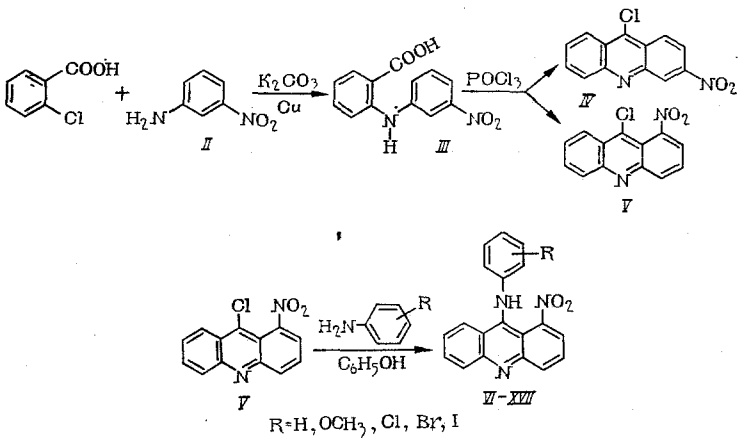
Among the acridine nitro derivatives, compounds are found which exert an antimicrobial, local anesthetic, antidepressant, and oncostatic activity [1-6].

Searching for biologically active compounds and studying the relation between the structure and antimicrobial activity, we synthesized 1-nitro-9-arylaminoacridines and studied their antimicrobial action. The synthesis was carried out according to the following scheme:



1-Nitro-9-chloroacridine (V) and 9-N-derivatives (VI-XVII) were obtained according to the literature [7-9]. o-Chlorobenzoic acid (I) and m-nitroaniline (II) were condensed according to Ullmann [8] to 3'-nitrodiphenylamine-2-carboxylic acid (III) from which, by cyclization with phosphorus oxychloride, isomeric nitro derivatives (IV and V) were obtained and isolated. The reaction of 1-nitro-9-chloroacridine (V) with the corresponding arylamines in the presence of phenol yielded 1-nitro-9-arylaminoacridines (VI-XVII) which are red or brown crystalline substances, insoluble in water, sparingly soluble in organic solvents, and readily soluble in dimethyl formamide (see Table 1).

Antimicrobial activity of preparations (VI-XVII) was tested with both gram-positive bacteria (staphylococcus 209, mycoides, hay bacillus) and gram-negative bacteria (Escherichia coli, proteus X-19, blue-green pus bacillus No. 11) according to the generally accepted procedure of serial dilutions in meat-peptone broth (pH 7.2-7.4).

Determinations were made of both bacteriostatic and bactericidal activity (with a subsequent seeding per sector of meat-peptone agar) after keeping the seedings 20-24 h in a thermostat at a temperature of 37° as compared with ethacridine and 9-aminoacridine.

The strongest bacteriostatic activity toward staphylococcus 209, hay bacillus, and Escherichia coli was shown by compound XI in dilutions of 1:8000, 1:4000, and 1:2000, respectively; substance X showed a bacteriostatic effect toward staphylococcus 209 and Escherichia coli in a dilution of 1:1000. Bactericidal action was shown only by compound XI toward staphylococcus 209 in a dilution of 1:2000.

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TABLE 1. 1-Nitro-9-arylaminoacridines

Compound	R	Yield, %	mp, deg	Found N, %	Empirical formula	Calc. N, %
VI	H	82	197—9	13,24 13,27	$C_{19}H_{13}N_3O_2$	13,33
VII	o-CH_3O	92	180—2	11,90 11,96	$C_{20}H_{15}N_3O_3$	12,16
VIII	m-CH_3O	88	183—5 (decomp.)	12,21 12,26		
IX	p-CH_3O	88	184—6 (decomp.)	12,15 12,18		
X	o-Cl	85	229—31	12,10 12,14	$C_{19}H_{12}ClN_3O_2$	12,03
XI	m-Cl	96	250—2	12,18 12,26		
XII	p-Cl	85	226—9 (decomp.)	12,29 12,36		
XIII	o-Br	91	200—02	10,97 11,00	$C_{19}H_{12}BrN_3O_2$	10,65
XIV	m-Br	94	233—5	10,73 10,82		
XV	p-Br	96	238—40	10,47 10,58		
XVI	m-I	86	239—41 (decomp.)	9,76 9,81	$C_{19}H_{12}IN_3O_2$	9,51
XVII	p-I	94	259—61 (decomp.)	9,71 9,87		

Thus, the synthesized compounds are weak inhibitors of the growth of both Gram-positive and Gram-negative microorganisms.

EXPERIMENTAL

1-Nitro-9-arylaminoacridines (VI-XVII). Compound V (0.005 mole) was dissolved in 5 g of phenol at 70° and, with stirring, 0.006 mole of arylamine was added. The stirring was continued for 2 h at 100°. On cooling, the mixture was treated with 10% sodium hydroxide solution. The precipitate was filtered off, washed with water, extracted with 10% acetic acid, and filtered. The filtrate was leached out with dilute sodium hydroxide solution. The precipitate was separated, washed with water, dried, and crystallized from aqueous dimethyl formamide.

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