SYNTHESIS AND ANTIMICROBIC ACTIVITY OF 6-NITRO-9-AMINOACRIDINE DERIVATIVES

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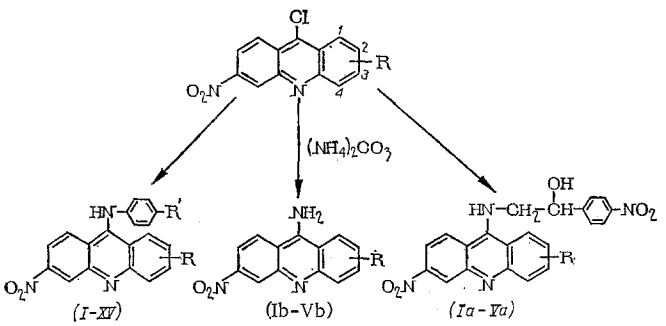
UDC 615.28:547.835.3

Substituted 9-aminoacridines have shown significant antimicrobic activity [1-3]. In a search for new biologically active materials and to determine the connection between structure and antimicrobic activity we synthesized aryl- and nitroarylethanolyl derivatives of 6-nitro-9-aminoacridine and its isomeric methoxy-substituted derivatives and studied their antimicrobic effect. The syntheses were carried out by the following scheme:



6-Nitro-9-chloroacridine, 6-nitro-9-aminoacridine, and their isomeric methoxy-substituted derivatives were obtained by known methods [4-6]. Reaction of 6-nitro-9-chloroacridine and its 1-, 2-, 3-, and 4-methoxy derivatives in a phenol medium with p-chloro-, p-bromo, p-iodoanilines, or 1-p-nitrophenyl-2-aminoethanol yielded the corresponding 9-N-substituted 6-nitro-9-aminoacridines, crystalline materials

TABLE 1. 6-Nitro-9-p-halophenylaminoacridines

Compound	R	R'	Yield (%)	mp (deg)	Found N (%)	Empirical formula	Calculated N (%)
I	H	Cl	64	225—8	12,00	$C_{19}H_{12}ClN_3O_2$	12,02
II	H	Br	71	228—30	10,70	$C_{19}H_{12}BrN_3O_2$	10,66
III	H	I	60	256	9,48	$C_{19}H_{12}IN_3O_2$	9,52
IV	1-OCH_3	Cl	62	216(decomp.)	11,10	$C_{20}H_{14}ClN_3O_3$	11,07
V	1-OCH_3	Br	65	228(decomp.)	9,88	$C_{20}H_{14}BrN_3O_3$	9,90
VI	1-OCH_3	I	61	235(decomp.)	8,78	$C_{20}H_{14}IN_3O_3$	8,85
VII	2-OCH_3	Cl	66	239—40	11,08	$C_{20}H_{14}ClN_3O_3$	11,07
VIII	2-OCH_3	Br	68	203(decomp.)	9,82	$C_{20}H_{14}BrN_3O_3$	9,90
IX	2-OCH_3	I	63	233—4	8,86	$C_{20}H_{14}IN_3O_3$	8,85
X	3-OCH_3	Cl	67	239—40	11,03	$C_{20}H_{14}ClN_3O_3$	11,07
XI	3-OCH_3	Br	69	233—4	9,82	$C_{20}H_{14}BrN_3O_3$	9,90
XII	3-OCH_3	I	64	235—7	8,73	$C_{20}H_{14}IN_3O_3$	8,85
XIII	4-OCH_3	Cl	56	264(decomp.)	11,10	$C_{20}H_{14}ClN_3O_3$	11,07
XIV	4-OCH_3	Br	58	268(decomp.)	10,03	$C_{20}H_{14}BrN_3O_3$	9,90
XV	4-OCH_3	I	55	280(decomp.)	8,90	$C_{20}H_{14}IN_3O_3$	8,85

Kharkov Pharmaceutical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 1, pp. 29-32, January, 1972. Original article submitted December 30, 1970.

TABLE 2. 6-Nitro-9-p-(2'-hydroxy-2'-p-nitrophenylamino)acridines

Compound	R	Yield (%)	mp (deg)	Found N (%)	Calculated N (%)*
Ia	H	85	197—8	13,88	13,86
IIa	1-OCH_3	70	188—90	12,96	12,90
IIIa	2-OCH_3	77	222—4	13,11	12,90
IVa	3-OCH_3	75	205—6	12,98	12,90
Va	4-OCH_3	73	212	12,96	12,90

*Empirical formula Ia: $C_{21}H_{16}N_4O_5$; IIa-Va: $C_{22}H_{18}N_4O_6$.

TABLE 3. Antibacterial Activity of 6-Nitro-9-aminoacridine Derivatives

Compound	Microorganism culture													
	staphylococcus		streptococcus		hay bacillus		mycoides		yeasts		Escherichia coli		Bacillus pyocyaneus	
	a	b	a	b	a	b	a	b	a	b	a	b	a	b
Ethacridine	1:32	1:16	1:8	1:4	1:64	1:64	1:64	1:64	1:8	1:8	1:32	1:16	1:8	1:4
I	1:2	1:2	—	—	1:2	1:2	1:2	1:2	—	—	1:1	1:1	1:2	1:2
II	1:1	1:1	—	—	1:1	1:1	1:8	1:8	—	—	1:1	1:1	1:1	1:1
III	1:1	1:1	—	—	1:1	1:1	1:2	1:2	—	—	1:1	1:1	1:1	1:1
VII	1:2	1:2	—	—	1:2	1:2	1:4	1:4	—	—	1:1	1:1	1:2	1:2
VIII	1:1	1:1	—	—	1:2	1:2	1:8	1:8	—	—	1:1	1:1	1:1	1:1
IX	1:4	1:1	—	—	1:8	1:4	1:4	1:4	—	—	1:4	1:1	1:8	1:1
X	1:16	1:16	—	—	1:8	1:4	1:16	1:4	—	—	1:16	1:16	1:8	1:4
XI	1:4	1:2	—	—	—	—	1:8	1:4	—	—	—	—	1:8	1:2
XII	1:4	1:4	—	—	1:4	1:4	1:4	1:2	—	—	1:4	1:1	1:2	1:2
XIII	1:2	1:2	—	—	1:2	1:2	1:4	1:4	—	—	1:2	1:2	1:2	1:2
XIV	1:4	1:4	—	—	1:4	1:4	1:1	1:2	—	—	1:4	1:4	1:4	1:4
XV	1:2	1:2	—	—	1:4	1:4	1:4	1:4	—	—	1:2	1:2	1:2	1:2
Ia	1:16	1:16	1:2	1:2	1:4	1:4	1:8	1:8	1:1	1:1	1:4	1:4	1:4	1:4
IIa	1:4	1:4	1:2	1:2	1:8	1:8	1:4	1:4	1:1	1:1	1:4	1:4	1:2	1:2
IIIa	1:2	1:2	1:1	1:1	1:4	1:4	1:4	1:4	1:2	1:2	1:2	1:2	1:4	1:4
IVa	1:32	1:32	1:4	1:4	1:8	1:8	1:32	1:32	1:4	1:4	1:32	1:32	1:2	1:2
Va	1:2	1:2	1:1	1:1	1:8	1:8	1:4	1:4	1:1	1:1	1:4	1:4	1:2	1:2
Ib	1:32	1:32	1:16	1:8	1:64	1:64	1:16	1:16	1:16	1:16	1:16	1:16	1:8	1:8
IIb	1:8	1:8	1:1	1:1	1:32	1:32	1:16	1:8	1:2	1:2	1:1	1:1	1:1	1:1
IIIb	1:64	1:64	1:4	1:1	1:64	1:32	1:64	1:32	1:2	1:2	1:8	1:4	1:4	1:2
IVb	1:32	1:64	1:16	1:2	1:256	1:256	1:256	1:256	1:8	1:8	1:16	1:16	1:8	1:8
Vb	1:64	1:64	1:4	1:1	1:128	1:128	1:32	1:8	1:8	1:8	1:32	1:2	1:16	1:4

Note. Dilutions given in parts per thousand (for example, 1:32 means 1:32,000).

which are insoluble in water, poorly soluble in organic solvent, and highly soluble in dimethylformamide (Tables 1, 2).

The antibacterial activity of the synthesized compounds was established by the method of serial dilutions in relation to gram-positive and gram-negative microorganisms in a meat-peptone broth (pH 7.2). Both the bacteriostatic and bactericidal effect were determined (with subsequent seeding on MPA sectors) after 24, 48, and 72 h of residence of inoculations in the thermostat at a temperature of 37°C (Table 3) in comparison with ethacridine. Compounds (Ib-Vb), (Ia), and (IVa) were the most active in relation to the majority of the examined microorganisms. Introduction of p-chloro-, p-bromo-, and p-iodoaniline groups into position 9 of 6-nitroacridine and its isomeric methoxy-substituted derivatives significantly decreases the activity of the preparations, which is evidently associated with their poor solubility; the most effective among them were found to be compounds containing the p-chloroaniline group in position 9. Of all the studied compounds the most active in relation to the majority of the microorganisms was found to be the 3-methoxy isomer. It should be noted that the highly water-soluble hydrochloride salts of 6-nitro-9-[p-(1'-hydroxy-2'-diethylaminoethyl)phenyl]aminoacridine and its 1-, 2-, 3-, and 4-methoxy-substituted derivatives [7] showed an antimicrobic activity 10-15 times higher than that in ethacridine at a low toxicity.

EXPERIMENTAL

Compounds (I-XV). We dissolved 0.01 mole of 6-nitro-9-chloroacridine or its 1-, 2-, 3-, and 4-methoxy-substituted derivatives in 9 g of phenol at 70° and added with stirring 0.012 mole of p-chloro-, p-bromo-, or p-iodoaniline. Stirring was continued for 1.5 h at 100°. Upon cooling the mixture was treated with a 10% solution of sodium hydroxide. The precipitate was filtered, washed with water, dried, and crystallized from 70% aqueous dimethylformamide.

Compounds (Ia-Va). We dissolved 0.01 mole of the corresponding 6-nitro-9-chloracridine in 9 g of phenol at 70° and with stirring added 0.012 mole of 1-p-nitrophenyl-2-aminoethanol. Stirring was continued for 2 h at 110-120°. Upon cooling, the mixture was treated with a 5% aqueous solution of sodium hydroxide and the precipitate was separated, washed with water, dried, and recrystallized from 70% aqueous dimethylformamide.

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