9-ARYLAMINO-SUBSTITUTED DERIVATIVES OF 7-NITROACRIDINE AND THEIR ANTIBACTERIAL ACTIVITY

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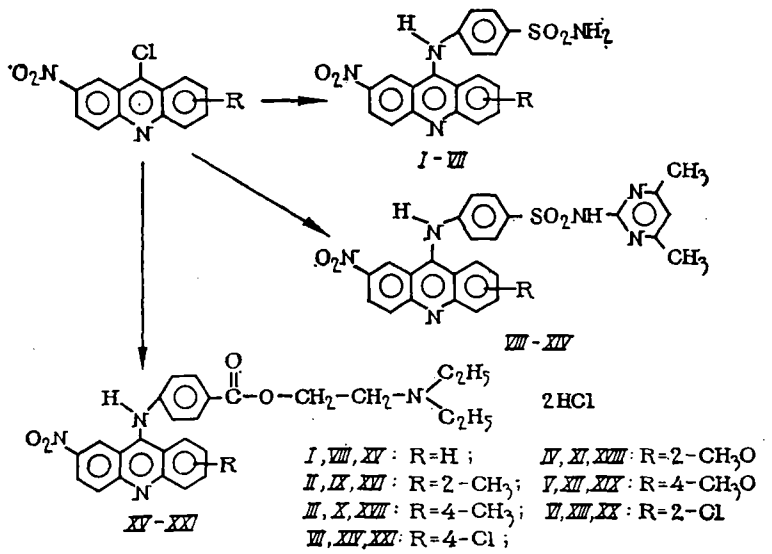
Compounds possessing antimicrobial activity have been discovered among the nitro derivatives of acridine [1-3]. We have synthesized 9-methylamino-substituted derivatives of 7-nitroacridine which showed insignificant bacteriostatic activity [4].

It is known that the introduction of a substituted aromatic group into the 9 position of the acridine molecule increases biological activity in this series of compounds [5].

In a continuing investigation to relate chemical structure and antibacterial properties, the synthesis of a series of 9-arylamino-substituted 7-nitroacridines was accomplished. Sulfanilamide, sulfamethazine, and procaine were introduced as substituents in position 9, thus allowing the combination of two biologically active moieties in one molecule. The selection of procaine as a substituent is explained by other data which indicate that similar derivatives of acridine hydrolyzed comparatively easily to give substituted p-aminobenzoic acids which must therefore be present with the heterocyclic antimetabolites, a series of similarly substituted acridines which showed significant antibacterial and anesthetic activity [6]. Therefore, condensation products of substituted 7-nitro-9-chloroacridines with the above compounds ought to show bacteriostatic activity.

The synthesis of 9-arylamino-substituted 7-nitroacridines was carried out as indicated in the following scheme:



The starting materials, 7-nitro-9-chloroacridine and its 2- and 4-methyl, methoxy, and chloro derivatives [7-9], were dissolved in phenol and treated with sulfanilamide or sulfamethazine to form the corresponding 9-N-substituted derivatives of 7-nitro-9-aminoacridines (I-XIV). Interaction of the corresponding chloroacridine with procaine base gave the diethyl-

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TABLE 1. 9-Arylaminosubstituted 7-Nitroacridines

Compound	Yield, %	Melting point, °C	% N, Found	Empirical formula	% N, Calculated
I	87	290	13,91	$C_{19}H_{14}N_4O_4S$	14,20
II	82	278	13,49	$C_{20}H_{16}N_4O_4S$	13,72
III	67	282—3	13,58	$C_{20}H_{16}N_4O_4S$	13,72
IV	79	264	12,99	$C_{20}H_{16}N_4O_5S$	13,20
V	71	308	13,36	$C_{20}H_{16}N_4O_5S$	13,20
VI	62	284	13,24	$C_{19}H_{13}ClN_4O_4S$	13,06
VII	59	275	13,32	$C_{19}H_{13}ClN_4O_4S$	13,06
VIII	79	216	16,53	$C_{25}H_{20}N_6O_4S$	16,79
IX	87	236	16,07	$C_{26}H_{22}N_6O_4S$	16,33
X	69	265	16,51	$C_{26}H_{22}N_6O_4S$	16,33
XI	90	185	16,01	$C_{26}H_{22}N_6O_5S$	15,84
XII	72	284	15,60	$C_{26}H_{22}N_6O_5S$	15,84
XIII	80	245—6	15,86	$C_{25}H_{19}ClN_6O_4S$	15,71
XIV	79	265	15,55	$C_{25}H_{19}ClN_6O_4S$	15,71
XV	72	145	10,81	$C_{26}H_{26}N_4O_4 \cdot 2HCl$	10,54
XVI	64	142	10,36	$C_{27}H_{28}N_4O_4 \cdot 2HCl$	10,27
XVII	59	148	9,98	$C_{27}H_{28}N_4O_4 \cdot 2HCl$	10,27
XVIII	64	191	10,12	$C_{27}H_{28}N_4O_5 \cdot 2HCl$	9,98
XIX	53	180—2	9,74	$C_{27}H_{28}N_4O_5 \cdot 2HCl$	9,98
XX	76	230—1	9,73	$C_{26}H_{25}ClN_4O_4 \cdot 2HCl$	9,90
XXI	50	95	9,98	$C_{26}H_{25}ClN_4O_4 \cdot 2HCl$	9,90

Note. Compounds I, III-V were crystallized from aqueous dimethylformamide; II, VI-XIV from aqueous dioxane.

aminoethyl ester of N-(7-nitroacridinyl-9)-p-aminobenzoic acid as the dihydrochloride (XV) and its substitution products (XVI-XXI), containing a methyl, methoxyl, or chlorine atom in position 2 or 4 of the acridine nucleus (Table 1). All synthesized compounds failed to form diazonium salts since colors were not obtained with an alkaline solution of β-naphthol, indicating an interaction between the 7-nitro-9-chloroacridines and only the primary aromatic amino groups of sulfanilamide, sulfamethazine, and procaine.

EXPERIMENTAL

Pharmacological

Antibacterial activity of the compounds obtained was tested by two-stage serial culture in a liquid nutritive medium against some common microorganisms. The substances were diluted from 1:500 to 1:256,000 in the nutritive medium (meat–peptone broth). The test microbes used were daily agar cultures of gram-positive (*Staphylococcus* 209, hay bacillus) and gram-negative (*Escherichia coli, Bacillus pyocyaneous*) bacteria, 50,000 of which were introduced into a test tube with broth and the corresponding test compound. The contents were incubated in a thermostat for 18-20 h at 37°C, after which the minimal inhibiting concentration of the substance was visually defined by the intensity or absence of turbidity in the test medium.

As indicated in Table 2, introduction of sulfanilamide or sulfamethazine into a molecule of 7-nitroacridine does not lead to an appreciable increase in antibacterial activity by comparison with the corresponding 9-methylaminosubstituted 7-nitroacridine [4]. The most activity against gram-positive microorganisms was shown by compounds XVI-XVIII, XX, and XXI, containing the procaine residue in position 9 of the 7-nitroacridine molecule. Practically all of the compounds studied did not show bacteriostatic activity against *Bacillus pyocyaneous*.

Chemical

Compounds I-VII. To a stirred solution of 0.01 mole of the corresponding 7-nitro-9-chloroacridine in 20 g of phenol at 70°C was added 1.72 g (0.01 mole) of sulfanilamide. The mixture was heated for 3 h at 100-110°C, added when cool to a 10% solution of sodium hydroxide, and the precipitate was separated and washed with water. After recrystallization, compounds I-VII were isolated as orange crystals, insoluble in water, difficultly soluble in alcohol, and easily soluble in dimethylformamide (cf. Table 1).

Compounds VIII-XIV. To a stirred solution of 0.01 mole of the corresponding 7-nitro-9-chloroacridine in 25 g of phenol at 70°C was added 2.78 g (0.01 mole) of sulfamethazine.

TABLE 2. Antibacterial Activity of 9-Arylaminosubstituted 7-Nitroacridines

Compound	Microorganism		
	Staphylococcus	hay Bacillus	Escherichia coli
I, II	1:4000	1:4000	1:4000
III	—	—	1:4000
IV	1:4000	1:4000	1:4000
V—VII	—	—	1:4000
VIII—XII	—	—	—
XIII—XV	—	1:4000	—
XVI	1:128 000	1:64 000	1:4000
XVII	1:128 000	1:128 000	1:4000
XVIII	1:32 000	1:16 000	1:4000
XIX	—	1:4000	1:4000
XX—XXI	1:8000	1:128 000	1:4000

Note. None of these compounds showed bacteriostatic activity against *Bacillus pyocyaneous*.

The mixture was heated for 3 h at 100-110°C, cooled, and treated with ether. The resulting hydrochloride was washed with ether and converted to the free base by treatment with a solution of ammonia. Recrystallization gave compounds VIII-XIV as orange-red crystals, insoluble in water, easily soluble in dimethylformamide (cf. Table 1).

Diethylaminoethyl N-(7-Nitroacridin-9-yl)-p-aminobenzoate Dihydrochloride (XV) and Its Derivatives (XVI-XXI). A mixture of 0.01 mole of the corresponding 7-nitro-9-chloroacridine, 25 g of phenol, and 2.47 g (0.01 mole) of procaine base was heated at 100°C for 3 h. After the cooled mixture was treated with ether, the precipitate obtained was washed with ether. The resulting hydrochloride salt was converted to the free base with a solution of ammonia. The dihydrochloride was obtained by addition of a saturated solution of hydrogen chloride in acetone to an acetone solution of the free base. Compounds XV-XXI were obtained as orange-red crystals, soluble in water, alcohol, and dimethylformamide (cf. Table 1).

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