SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF VARIOUS DERIVATIVES OF 5-NITROACRIDINE

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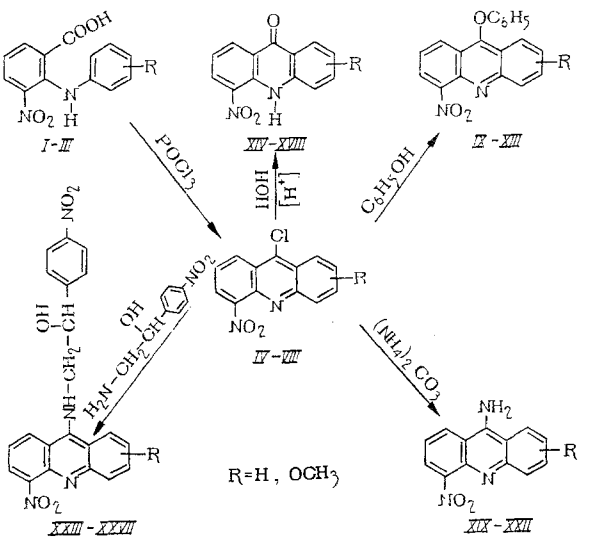
Many substituted acridines have a high biological activity [1-6]. With the aim of discovering new antibacterial substances and determining the connection between their structure and activity, we have synthesized the isomeric methoxy derivatives of 5-nitro-9-chloro-, 5-nitro-9-phenoxy-, 5-nitro-9-amino-, and 5-nitro-9-[2'-hydroxy-2'-(p-nitrophenyl)ethylamino]acridine and 5-nitroacridone-9. The synthesis was carried out as follows:



6-Nitrodiphenylamine-2-carboxylic acid and its 2'-,3'-, and 4'-methoxy derivatives [7] (I-III) were cyclized by the action of phosphorus oxychloride [8] to 5-nitro-9-chloroacridine (IV) and its 1-, 2-, 3-, and 4-methoxy derivatives (V-VIII). 3'-Methoxy-6-nitrodiphenylamine-2-carboxylic acid (II) gave a mixture of isomeric 1- and 3-methoxy-5-nitro-9-chloroacridines (V, VII) which was separated [9]. Reaction of IV-VIII with phenol gave 9-phenoxy derivatives (IX-XIII) in a yield of 66-93% [10]. The methoxy derivatives of 5-nitroacridone-9 (XV-XVIII) were obtained by hydrolysis of V-VIII with dilute hydrochloric acid [11]. The methoxy derivatives of 5-nitro-9-aminoacridine (XX-XXII) were synthesized by reaction of VI-VIII with ammonium carbonate in a phenol medium [12]. Condensation of IV-VIII in a phenol medium with 2-amino-1-p-nitrophenylethanol gave 5-nitro-9-[2'-hydroxy-2'-(p-nitrophenyl)ethylamino] acridine and its 1-, 2-, 3-, and 4-methoxy derivatives (XXIII-XXVII, Table 1) [3].

The antibacterial properties of the substances synthesized were investigated by the usual method of serial dilution in meat-peptone broth (pH 7.2-7.4) with respect to gram-positive and gram-negative microorganisms. Both the bacteriostatic and bactericidal (with subsequent seeding on sectors of a meat-peptone agar) actions were determined after 20-24 h incubation at 37°C.

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TABLE 1. Derivatives of 5-Nitroacridine

Compound	R	Yield (%)	Melting point (°C)	N found (%)	Empirical formula	N calculated (%)
IV	H	91	196	10,92	$C_{13}H_7ClN_2O_2$	10,80
V	1-CH_3O	8	194—6	9,74		
VI	2-CH_3O	93	243—4	9,78		
VII	3-CH_3O	78	215—7	9,96	$C_{14}H_9ClN_2O_3$	9,70
VIII	4-CH_3O	91	242—3	9,81		
IX	H	66	239—41	9,13	$C_{19}H_{12}N_2O_3$	8,86
X	1-CH_3O	86	226—8	8,20		
XI	2-CH_3O	93	222—3	8,16		
XII	3-CH_3O	92	201—3	8,29	$C_{20}H_{14}N_2O_4$	8,08
XIII	4-CH_3O	83	210	8,34		
XIV	H	90	262	11,80	$C_{13}H_8N_2O_3$	11,69
XV	1-CH_3O	96	218(decomp.)	10,49		
XVI	2-CH_3O	92	229—30	10,19	$C_{14}H_{10}N_2O_4$	10,37
XVII	3-CH_3O	94	242—4	10,46		
XVIII	4-CH_3O	94	246	10,43		
XIX	H	73	191—3	17,38	$C_{13}H_9N_3O_2$	17,50
XX	2-CH_3O	80	212—4	15,55		
XXI	3-CH_3O	84	201—3	15,81	$C_{14}H_{11}N_3O_3$	15,61
XXII	4-CH_3O	91	217—8	15,83		
XXIII	H	84	254	14,02	$C_{21}H_{16}N_4O_5$	13,85
XXIV	1-CH_3O	75	237—8	13,14		
XXV	2-CH_3O	94	120	12,53		
XXVI	3-CH_3O	75	235	13,08	$C_{22}H_{18}N_4O_6$	12,89
XXVII	4-CH_3O	88	208—10	13,12		

Note: Compound IV was recrystallized from ethyl acetate, compounds V, VII, and VIII from benzene, VI from amyl acetate, IX from toluene, X-XIII, XXI, XXII from aqueous dimethylformamide, XIX from xylene, and XX from aqueous ethanol.

TABLE 2. Antibacterial Activity of the Derivatives of 5-Nitro-9-aminoacridine

Microorganism culture		Compound			
		Ethacridine	9-amino-acridine	XXI	XXII
Staphylococcus 209	a	1:32 000	1:32 000	1:128 000	1:128 000
	b	1:6 000	1:2 000	1:8 000	1:2 000
Hay bacillus	a	1:64 000	—	1:128 000	1:64 000
	b	1:64 000	—	1:2 000	1:16 000
Blue-green pus bacillus	a	1:8 000	—	1:8 000	1:16 000
	b	1:4 000	—	1:4 000	1:4 000
Escherichia coli	a	1:32 000	—	1:128 000	1:128 000
	b	1:16 000	—	1:16 000	1:8 000

Note: a represents the bacteriostatic influence and b the bactericidal influence.

The data obtained indicate that the derivatives of 5-nitroacridine have an antibacterial effect with respect to the majority of the microorganisms used. The introduction of the methoxy group to the benzene nucleus of 5-nitro-9-aminoacridine causes a considerable increase in biological activity. Thus, 3- and 4-methoxy-5-nitro-9-aminoacridines (XXI and XXII) are more active than ethacridine (Table 2).

EXPERIMENTAL

Compounds IV-VIII

A mixture of 0.04 mole of appropriately substituted diphenylamine-2-carboxylic acid, 20 ml phosphorus oxychloride, and 40 ml chloroform was heated on a water bath for 4 h. Excess phosphorus oxychloride was driven off and the dark-red mass introduced to a mixture of ice and ammonia. The crystals formed were removed and dried in a vacuum desiccator. Recrystallization gave yellow, acicular crystals which were soluble in the majority of organic solvents and insoluble in water.

Compounds IX-XIII

A mixture of 0.02 mole of the appropriate chloroacridine and 10 g phenol was stirred for 30 min at 100°C. On cooling, 30 ml ether and 30 ml 10% aqueous sodium hydroxide were added to the solution. The

precipitate formed was separated, dried in a vacuum desiccator and recrystallized. The yellow or yellow-orange crystals obtained are insoluble in water but soluble in benzene, ethanol, dimethylformamide, and dioxane.

Compounds XIV-XVIII

A mixture of 0.02 mole of the appropriate chloracridine and 100 ml 0.5 N hydorchloric acid was boiled for 1 h. The hot solution was poured into a mixture of ammonia and ice. The crystals formed were separated, washed with water and dried. Recrystallization from aqueous dimethylformamide gave orange needles which were insoluble in water, hexane, chloroform, and benzene and soluble in dimethylformamide, acetone, and dioxane.

Compounds XIX-XXII

0.02 mole of the appropriate chloroacridine was dissolved in 15 g phenol at 70°C and 0.04 mole powdered ammonium carbonate added with stirring. The temperature of the reaction mixture was raised rapidly to 120°C and held at this point with stirring for 2 h. On cooling, the mixture was treated with a 5% aqueous solution of sodium hydroxide. The precipitate formed was removed, washed with water, dried, and recrystallized. Red or brownish crystals were obtained which were insoluble in water, benzene, and hexane and soluble in dioxane, dimethylformamide, and ethanol.

Compounds XXIII-XXVII

0.1 mole of the appropriate chloroacridine was dissolved in 9 g phenol at 70°C and 0.012 mole 2-amino-1-p-nitrophenylethanol added with stirring. Stirring was continued for 2 h at 115-120°C. After cooling, the mass was treated with a 5% aqueous solution of sodium hydroxide. The precipitate formed was removed, washed with water, dried, and recrystallized from aqueous dimethylformamide. Red crystals were obtained which were insoluble in water, sparingly soluble in ethanol, and readily soluble in dioxane and dimethylformamide.

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