SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 9-METHYLAMINOACRIDINE DERIVATIVES

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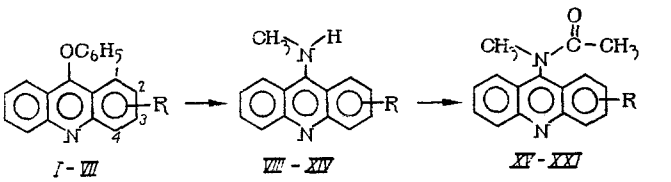
In continuation of our investigations [1, 2] into the relation between the chemical structure and biological activity of substituted acridines, we have synthesized 9-methylaminoacridine (VIII) and its 2- and 4-methoxy, 2- and 4-methyl, and 2- and 4-chloro derivatives (IX and X, XI and XII, and XIII and XIV, respectively), and also 9-methylacetylaminoacridine (XV) and its 2- and 4-methoxy, 2- and 4-methyl, and 2- and 4-chloro derivatives (XVI and XVII, XVIII and XIX, and XX and XXI, respectively), and studied their antimicrobial activity.



I-VII VIII-XIV XV-XXI

I, VIII, XV: R=H;
II, IX, XVI: R=2-CH_3O;
III, X, XVII: R=4-CH_3O;
IV, XI, XVIII: R=2-CH_3;
V, XII, XIX: R=4-CH_3;
VI, XIII, XX: R=2-Cl
VII, XIV, XXI: R=4-Cl

The synthesis of 9-phenoxyacridine (I) and its 2- and 4-methoxy derivatives (II and III), and of VIII and IX, was carried out by methods described in the literature [3-5]. The other compounds were synthesized using the corresponding 9-chloroacridines [5, 6] as starting materials. Reaction of these with phenol by the method described in [1] gave the 2- and 4-methyl and 2- and 4-chloro derivatives of 9-phenoxyacridine (IV and V, and VI and VII, respectively). Reaction of the corresponding 9-phenoxyacridines with methylamine hydrochloride in phenol by the method described in [1] gave X-XIV. Acylation of VIII-XIV with excess acetic anhydride in pyridine gave compounds XV-XXI. The readily water-soluble hydrochloride salts of 9-methylaminoacridine (VIIIa) and its 2- and 4-methoxy, 2- and 4-methyl, and 2- and 4-chloro derivatives (IXa and Xa, XIa and XIIa, and XIIIa and XIVa, respectively) were prepared by adding acetone saturated with dry hydrogen chloride to solutions of VIII-XIV in acetone (Table 1).

The structure of IX-XXI was confirmed by elementary analysis data and IR spectroscopy. The spectra of IX-XIV contain bands in the region of the N—H bending (1570-1580 cm^{-1}) and stretching (3250-3350 cm^{-1}) vibrations of secondary amines. In addition, the N—H stretching region contains a broad low-frequency band, indicating the formation of intermolecular hydrogen bonds in the case of IX-XIV. Intense singlet bands, belonging to the carbonyl group, can be distinguished in the 1650-1680 cm^{-1} region of the spectra of compounds XVI-XXI. It was not possible to distinguish unequivocally the bands corresponding to the C—OCH_3, C—CH_3, and C—Cl stretching vibrations, because they lie in the region of the aromatic C—H bending vibrations [7, 8].

The antibacterial activity of compounds VIIIa-XIVa and XV-XXI was determined with respect to Gram-positive and Gram-negative microorganisms in a meat—peptone broth (pH 7.2). by serial dilution. Their bacteriostatic action was determined by keeping the cultures in a thermostat at 37° for 24 h and then transferring them to meat—peptone agar sectors (Table 2). The data on the antimicrobial activity of compounds XV-XXI is not given because these com-

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TABLE 1. Substituted Derivatives of 9-Phenoxy- and 9-Methylamino-acridine

Compound	Yield (%)	Melting point (deg)*	Found N (%)	Empirical formula	Calculated N (%)
IV	73	129—30	5,00	$C_{20}H_{15}NO$	4,91
V	68	115—6	4,98	$C_{20}H_{15}NO$	4,91
VI	75	145—6	4,96	$C_{19}H_{12}ClNO$	4,83
VII	69	123—5	4,88	$C_{19}H_{12}ClNO$	4,83
X	67	205—7	11,79	$C_{15}H_{14}N_2O$	11,75
XI	80	181—3	12,65	$C_{15}H_{14}N_2$	12,60
XII	72	124—6	12,70	$C_{15}H_{14}N_2$	12,60
XIII	84	136—8	11,72	$C_{14}H_{11}ClN_2$	11,54
XIV	75	165—9	11,60	$C_{14}H_{11}ClN_2$	11,54
XV	84	225	11,18	$C_{16}H_{14}N_2O$	11,20
XVI	74	240—2	10,20	$C_{17}H_{16}N_2O_2$	9,99
XVII	70	255—8	10,18	$C_{17}H_{16}N_2O_2$	9,99
XVIII	81	243	10,63	$C_{17}H_{16}N_2O$	10,59
XIX	71	224	10,69	$C_{17}H_{16}N_2O$	10,59
XX	86	251	10,02	$C_{16}H_{13}ClN_2O$	9,84
XXI	69	238	9,99	$C_{16}H_{13}ClN_2O$	9,84
Xa	84	240—2	10,27	$C_{15}H_{14}N_2O \cdot HCl$	10,19
XIa	81	294—6	11,03	$C_{15}H_{14}N_2 \cdot HCl$	10,82
XIIa	80	272—4	10,99	$C_{15}H_{14}N_2 \cdot HCl$	10,82
XIIIa	83	300—2	10,21	$C_{14}H_{11}ClN_2 \cdot HCl$	10,03
XIVa	80	288—90	10,18	$C_{14}H_{11}ClN_2 \cdot HCl$	10,03

*Compounds XX, Xa, XIa, XIIa, XIIIa, and XIVa melt with decomposition. Compounds IV-VII were crystallized from ethanol, X-XIV from benzene, and XV-XXI from aqueous ethanol.

TABLE 2. Antibacterial Activity of Hydrochlorides of 9-Methylaminoacridine and Its Methoxy, Methyl, and Chloro Derivatives

Compound	Microorganism			
	Staphylococcus 209 P	B. pyocyaneous	E. coli	hay bacillus
VIIIa	1:32 000	1:500	1:32 000	1:128 000
IXa	1:64 000	1:1 000	1:16 000	1:500 000
Xa	1:64 000	1:500	1:16 000	1:256 000
XIa	1:32 000	—	1:8 000	1:64 000
XIIa	1:128 000	1:500	1:32 000	1:50 000
XIIIa	1:64 000	—	1:32 000	1:128 000
XIVa	1:16 000	1:500	1:16 000	1:25 000

pounds showed insignificant bacteriostatic activity. The antibacterial activity of the compounds studied proved to be somewhat lower than that of analogous derivatives containing a nitro group in the 6 and 7 positions of the acridine system [1, 2].

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrophotometer with lithium fluoride and sodium chloride prisms using potassium bromide pellets with a concentration of 0.5%.

Compounds IV-VII. The corresponding 9-chloroacridine (1.5 g) is dissolved in 10.0 g of phenol at 70°. The solution is heated at 100° for 30 min, cooled, and treated with 10% sodium hydroxide solution. The precipitate is filtered off, washed with cold water, dried, and crystallized.

Compounds X-XIV. The corresponding phenoxy derivative IV-VII (1.5 g) is dissolved in phenol and 0.5 g of methylamine hydrochloride added while stirring. The temperature is rapidly raised to 100° and stirring continues for 1.5 h. On cooling, the mixture is treated with 10% sodium hydroxide solution. The precipitate is filtered off, washed with warm water, dried, and recrystallized twice.

Hydrochlorides VIIIa-XIVa were prepared by adding acetone saturated with dry hydrogen chloride to solutions of compounds VIII-XIV in acetone.

Compounds XV-XXI. Compounds VIII-XIV (0.5 g) are dissolved in 5 ml of pyridine, treated with 3 ml acetic anhydride, and boiled for 1 h. The resulting solution is poured into water, and the precipitate filtered off, washed with 5% sodium bicarbonate solution and water, dried, and crystallized.

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AZACYCLOALKANES

XIX. SYNTHESIS AND ANESTHETIC ACTIVITY OF THE MESIDIDES OF PYRROLIDINE-2-CARBOXYLIC ACIDS

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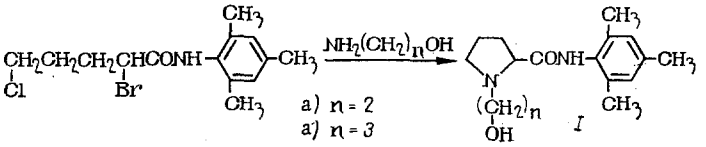
In [1-3] we synthesized a number of aromatic amides of N-alkyl, N-cycloalkyl, and N-aralkyl derivatives of α-azacycloalkanecarboxylic acids, studied the relation between their structure and anesthetic activity, and found new anesthetics with high activity, viz., pyromecaine and cyclomecaine. The anesthetic pyromecaine has successfully passed clinical tests and has been authorized for medical use [4-6].

In the present work we will describe the synthesis of a number of new mesidides of N-substituted α-pyrrolidinecarboxylic acids which differ from those prepared previously in that they contain functional groups (OH or NH_2) in the N-alkyl radical. We have studied the effect of these functional groups on the anesthetic activity of the compounds. At the same time, the presence of these groups has made it possible to introduce new substituents typical of anesthetics into the molecule, which is important for evaluating the significance of the principle of accumulation of active groups in molecules in the search for new anesthetics.

In accordance with the fact that two main types of anesthetics are used in medicine, viz., esters of dialkylaminoalkanols and aromatic acids (novocaine and its analogs) and aromatic amides of α-amino acids (xylocaine and its analogs) [7], we prepared derivatives containing both these groupings in the same molecule.

The N-hydroxyalkyl derivatives of α-pyrrolidinecarboxylic acid mesidide (I) were synthesized by amination of α-bromo-δ-chlorovaleric acid mesidide (II) with the corresponding amino alcohols.



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