DERIVATIVES OF 7-SULFODIETHYLAMIDOACRIDINE

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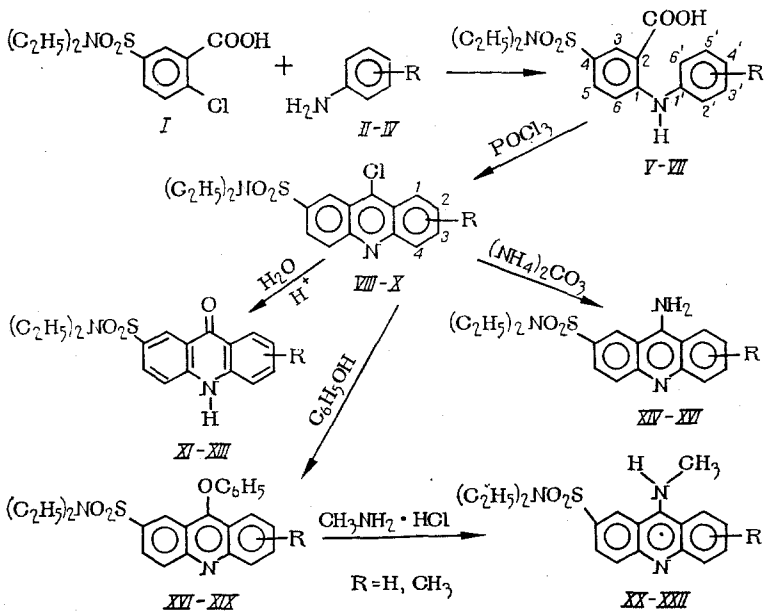
Combination of a sulfonamide group and the acridine nucleus is of particular interest in the search for new biologically active compounds. In continuation of investigations [1, 2] on the establishment of a link between chemical structure and antibacterial activity in the acridine series the synthesis has been achieved of 9-chloro-7-sulfodiethylamidoacridine and its 2- and 4-methyl-substituted derivatives from which the corresponding 9-phenoxyacridines, 9-aminoacridines, 9-methylaminoacridines, and acridones were obtained.

4-Sulfodiethylamidodiphenylamine 2-carboxylic acid (V) and its 2'- and 4'-methyl-substituted derivatives (VI, VII) served as starting materials. These were obtained by the condensation of 2-chloro-5-sulfodiethylamidobenzoic acid (I) [3] with aniline (II), o- or p-toluidine (III, IV) by the Ullman reaction [4].

On treatment of acids V-VII with an excess of phosphorus oxychloride by the method in [5] 9-chloro-7-sulfodiethylamidoacridine (VIII) and its 2- and 4-methyl-substituted derivatives (IX, X) were obtained. The corresponding acridones (XI-XIII) were obtained from compounds VIII-X by boiling with 1 N hydrochloric acid, and 9-amino-7-sulfodiethylamidoacridine (XIV) and its 2- and 4-methyl-substituted derivatives (XV, XVI) by treatment with ammonium carbonate. 9-Phenoxy-7-sulfodiethylamidoacridine (XVII) and its 2- and 4-methyl-substituted derivatives (XVIII, XIX) were synthesized by heating compounds VIII-X with an excess of phenol.

By the reaction of XVII-XIX with methylamine hydrochloride in benzene 9-methylamino-7-sulfodiethylamidoacridine (XX) and its 2- and 4-methyl-substituted derivatives (XXI-XXII) were obtained. Data on the compounds are given in Table 1.



The structures of the synthesized compounds were confirmed by data of IR spectra and

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TABLE 1. Characteristics of the Compounds Prepared

Compound	Yield, %	Melting point, °C	Found, %	Empirical formula	Calculated, %
V	28	128—31	8,12	$C_{17}H_{20}N_2O_4S$	8,04
VI	30	145—8	7,79	$C_{18}H_{22}N_2O_4S$	7,72
VII	36	150—3	7,83	$C_{18}H_{22}N_2O_4S$	7,72
VIII	82	147—8	8,12	$C_{17}H_{17}ClN_2O_2S$	8,03
IX	86	173—4	7,82	$C_{18}H_{19}ClN_2O_2S$	7,71
X	80	180—2	7,79	$C_{18}N_{19}ClN_2O_2S$	7,71
XI	96	>300(decomp.)	8,52	$C_{17}H_{18}N_2O_3S$	8,47
XII	92	>300(decomp.)	8,21	$C_{18}H_{20}N_2O_3S$	8,13
XIII	91	>300(decomp.)	8,07	$C_{18}H_{20}N_2O_3S$	8,13
XIV	72	255(decomp.)	12,86	$C_{17}H_{19}N_3O_2S$	12,75
XV	78	258(decomp.)	12,39	$C_{18}H_{21}N_3O_2S$	12,23
XVI	70	218—9	11,98	$C_{18}H_{21}N_3O_2S$	12,23
XVII	83	178—80	7,02	$C_{23}H_{22}N_2O_3S$	6,89
XVIII	88	180—1	6,72	$C_{24}H_{24}N_2O_3S$	6,66
XIX	85	148—50	6,75	$C_{24}H_{24}N_2O_3S$	6,66
XX	70	180—2	12,31	$C_{18}H_{21}N_3O_2S$	12,23
XXI	76	168—70	11,80	$C_{19}H_{23}N_3O_2S$	11,75
XXII	70	150—1	11,66	$C_{19}H_{23}N_3O_2S$	11,75

Note. Compounds V-VII were crystallized from glacial acetic acid, VIII-X and XVII-XIX from ethanol, XI-XIII from aqueous dimethylformamide, and XIV-XVI and XX-XXII from aqueous ethanol.

elemental analysis. Intense bands at 1650-1680 cm^{-1} for XIV-XVI and weak bands at 1615 cm^{-1} for XX-XXII were detected in the region of N—H deformation vibrations in the IR spectra of XIV-XVI and XX-XXII together with bands for the acridine ring. In the region of N—H stretching vibrations bands were detected at 2900-3200 cm^{-1} in the indicated compounds, the presence in this region of a wide low-frequency absorption made it possible to propose the presence of associated molecules as a result of intermolecular hydrogen bonds for XIV-XVI and XX-XXII. It was possible to distinguish intense bands corresponding to the stretching vibration of SO_2 group at 1160 and 1335 cm^{-1} (XIV), 1160 and 1340 cm^{-1} (XV), 1165 and 1350 cm^{-1} (XVI), 1150 and 1335 cm^{-1} (XX), 1153 and 1330 cm^{-1} (XXI), and 1170 and 1340 cm^{-1} (XXII).

Compounds XI-XIII have the following main bands in their IR spectra: ν C=O 1640 cm^{-1} (XI-XIII), several bands for the stretching vibrations of the associated NH group in the 2900-3280 cm^{-1} region; ν SO_2 1160 and 1340 cm^{-1} (XI), 1165 and 1340 cm^{-1} (XII), and 1155 and 1355 cm^{-1} (XIII).

The antibacterial activity of compounds XIV-XVI and XX-XXII was established by serial dilution against *Staphylococcus* 209-P, *Pseudomonas aeruginosa*, *Escherichia coli*, and hay bacillus in meat—peptone broth (pH 7.2). The bacteriostatic action was determined (with subsequent seeding on sectors of meat—peptone agar) after 24-h incubation of seedlings at 37° in a thermostat.

Compounds XIV and XXI did not show bacteriostatic action against the above-mentioned strains of microorganism. The remaining compounds showed insignificant bacteriostatic action only in relation to staphylococcus and hay bacillus. Thus XV, XX, and XXII inhibited growth of staphyloccus and hay bacillus at a dilution of 1:4000 and XVI showed bacteriostatic action towards staphylococcus at a dilution of 1:16,000.

EXPERIMENTAL

IR spectra were taken in potassium bromide disks on a UR-20 spectrophotometer with lithium fluoride and sodium chloride prisms. Concentration was 0.5%.

4-Sulfodiethylamidodiphenylamine 2-Carboxylic Acid and Its 2'- and 4'-Methyl-Substituted Derivatives (V-VII). A mixture of I (0.1 mole), aniline, or the corresponding toluidine (0.15 mole), potassium carbonate (0.11 mole), and powdered copper (1 g) was heated in n-amyl alcohol (250 ml) at 130-135° for 4-5 h. The alcohol and excess amine were steam distilled off, the solution was boiled with active carbon, filtered, hydrochloric acid was added to neutral reaction, the precipitate which separated was filtered off, and crystallized. After

recrystallization V-VII were crystalline substances, white or slightly greenish, insoluble in water, soluble in glacial acetic acid, alcohol, acetone, and dimethylformamide.

7-Sulfodiethylamido-9-chloroacridine and Its 2- and 4-Methyl-Substituted Derivatives (VIII-X). The appropriate acid (V-VII) (0.01 mole) was heated on the water bath with phosphorus oxychloride (6.1 g; 0.04 mole) for 3-4 h. On cooling the solution was poured onto a mixture of ice and ammonia, the solid which precipitated was separated, and dried in vacuum over potassium hydroxide. After recrystallization compounds VIII-X formed white or slightly yellow crystals insoluble in water, soluble in alcohol, acetone, and dimethylformadide.

7-Sulfodiethylamido-9-acridone and Its 2- and 4-Methyl-Substituted Derivatives (XI-XIII). The appropriate 9-chloroacridine (VIII-X) (0.005 mole) was boiled with 1 N hydrochloric acid (30 ml) for 2-3 h. The mixture was made alkaline with ammonia; the precipitate was filtered off, and crystallized. After recrystallization compounds XI-XIII formed with crystals, insoluble in alcohol and acetone, soluble in dimethylformamide.

7-Amino-9-sulfodiethylamidoacridine and Its 2- and 4-Methyl-Substituted Derivatives (XIV-XVI). Compounds VIII-X (0.01 mole) were dissolved at 70° in phenol (9.4 g: 0.1 mole) and finely ground ammonium carbonate (1.7 g) was added in portions with stirring. The mixture was heated at 100° for 1.5 h and 10% sodium hydroxide solution was added while cooling, the solid was separated, extracted with hot 5% acetic acid, and XIV-XVI were isolated from the acetic acid filtrate by the addition of ammonia. After recrystallization compounds XIV-XVI formed yellow crystals insoluble in water, soluble in alcohol and dimethylformamide.

7-Phenoxy-9-sulfodiethylamidoacridine and Its 2- and 4-Methyl-Substituted Derivatives (XVII-XIX). A mixture of the appropriate 9-chloroacridine (VIII-X) (0.02 mole) with phenol (10.0 g) was heated at 100°; an excess of 10% sodium hydroxide solution was added on cooling, the precipitate which separated was washed with water, dried, and crystallized. After crystallization compounds XVII-XIX formed white crystals, insoluble in water, soluble in alcohol, benzene, and dimethylformamide.

7-Methylamino-9-sulfodiethylamidoacridine and Its 2- and 4-Methyl-Substituted Derivatives (XX-XXII). The appropriate 9-phenoxyacridine (XVII-XIX) (0.01 mole) was dissolved in phenol (10 g) at 70° and methylamine hydrochloride (0.015 mole) was added with stirring. The temperature was quickly raised to 105-110° and stirring was continued for 1.5 h. While cooling 10% sodium hydroxide solution was added, the precipitate was separated, extracted with hot acetic acid, and XX-XXII were isolated from the acetic acid filtrate by the addition of ammonia. After recrystallization compounds XX-XXII formed yellow crystals insoluble in water, soluble in alcohol and dimethylformamide.

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