SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF CHLORO- AND NITROCHLORO DERIVATIVES OF THIOACRIDINE AND 9-SEMICARBAZIDOACRIDINE

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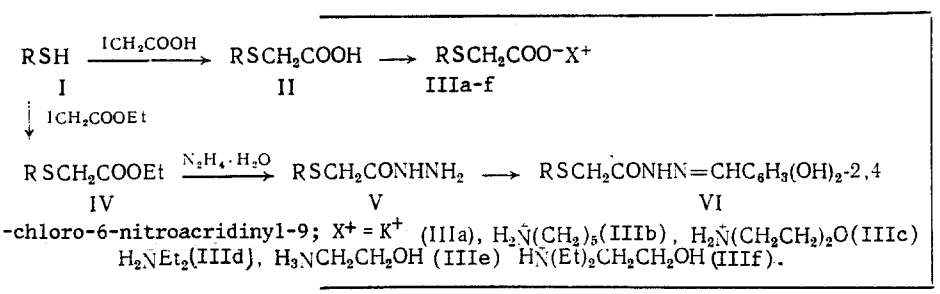
The available literature on the synthesis of 9-thioacridines and some of their derivatives [6, 9, 11, 12, 14] as well as information about their physicochemical and biological properties [2, 3, 10, 13] indicate that an examination of this class of compounds for the purpose of finding biologically active substances would be promising.

We selected the 6-nitro-9-thioderivatives of acridine and the 9-semicarbazidoacridines [1, 8] substituted by a chlorine atom in positions 2, 3, and 6 of the acridine ring to be our objects of investigation.

We synthesized 2-chloro-6-nitroacridinyl-9-thioacetic acid (II) [7] and its ethyl ester (IV) by alkylating 2-chloro-6-nitro-9-thioacridine (I) with monoiodoacetic acid or its ethyl ester in an alkaline organic solvent medium. Neutralization of acid II with a base in dioxane or ethanol resulted in the formation of the water-soluble salts (IIIa-f). By reacting $N_2H_4 \cdot H_2O$ with the ester IV [5] we obtained the hydrazide (V) which with 2,4-dioxybenzaldehyde formed the N-arylidine hydrazides VI. The structure of the resultant substances was confirmed by UV-, IR-, and mass-spectra, element analysis, and purity was confirmed by TLC.



R = 2-chloro-6-nitroacridinyl-9; $X^+ = K^+$ (IIIa), $H_2\overset{+}{N}(CH_2)_5$(IIIb), $H_2\overset{+}{N}(CH_2CH_2)_2O$(IIIc) $H_2\overset{+}{N}Et_2$(IIId), $H_3\overset{+}{N}CH_2CH_2OH$ (IIIe) $H\overset{+}{N}(Et)_2CH_2CH_2OH$ (IIIf).

The IR-spectrum of compound (II) exhibited an intensive absorption band in the 1730 cm^{-1} region associated with the carboxyl C=O stretching vibrations as well as $-CH_2-S-$ vibrations band in the 675 cm^{-1} region. The IR-spectra of the salts IIIa-f are characterized by two intensive bands in the 1630-1610 and 1430-1410 cm^{-1} region that correspond to asymmetric and symmetric vibrations of the COO^- group as well as absorption bands caused by vibrations in the cation: the broad band of NH_2 stretching vibrations (3280-2870 cm^{-1}) and the NH band of deformation vibrations (1630 cm^{-1}).

The water-soluble salts of 2-chloro, 3-chloro, 2,6-dichloro-9-semicarbazidoacridines (VIIIa-c) were obtained by reacting 2,9-dichloro, 3,9-dichloro-, and 2,6,9-trichloroacridines (VIIa-c) with semicarbazide HCl in an aqueous dioxane medium. The corresponding bases (IXa-c) were obtained by neutralizing the aqueous solutions of the indicated salts with $NaHCO_3$ (see scheme on following page).

The IR-spectra of the chloro derivatives of 9-semicarbazidoacridine has a band of C=O stretching vibrations in the 1690-1670 cm^{-1} region where there are also absorption bands that are characteristic of C=N stretching vibrations (1660-1640 cm^{-1}) and C=C stretching vibrations (1620-1605 cm^{-1}).

Fragmentation of the 9-semicarbazidoacridines by electron impact confirmed that the semicarbazide molecule reacts with the 9-chloroacridine amino group that is furthest from the carbonyl.

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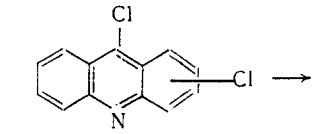
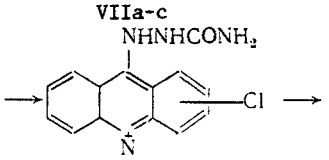
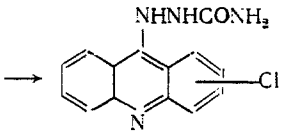


VIIa-c



VIIIa-c Cl-



IXa-c

2-Cl (VIIa, IXa), 3-Cl (VIIb, IXb)
2,6-Cl (VIIc, IXc)

The mass spectrum of IXa recorded a molecular ion peak with m/z 286:288 ($^{35}Cl:^{37}Cl$) at an intensity ratio of 3:1 which proves the presence of a single chlorine atom in the molecule. The presence of a semicarbazide residue in position 9 of the acridine ring was controlled by the following fragmentation ions (m/z): 269:271 $[M-NH_3]^+$, 243:245 $[M-NHCO]^+$, 242:244 $[M-CONH_2]^+$, 228:230 $[M-NCONH_2]^+$ (rupture of the weakest amide bonds was accompanied by the migration of a hydrogen atom from the α-position relative to the carbonyl group).

EXPERIMENTAL CHEMICAL

UV-spectra were recorded on a Pyc Unicam (England) instrument, IR-spectra recorded on a Perkin-Elmer instrument (England), and mass-spectra on a Varian MAT 311A (USA, Switzerland, FRG). The found element analysis values corresponded to the calculated ones.

2-Chloro-6-nitroacridinyl-9-thioacetic acid (II). A 0.02 mole portion of NaOH or Na_2CO_3 and 0.01 mole of monoiodoacetic acid was added to a solution of 0.01 mole of 2-chloro-6-nitro-9-thioacridine [4] in 80 ml of DMPA and heated on a water bath for 10-15 min, cooled, and decanted into water and acidified with 10% AcOH to pH ~6.0. The precipitate was separated and dissolved in a 2% solution of $NaHCO_3$, filtered, and the filtrate was acidified with 10% AcOH to pH ~6.0. The precipitate was separated, washed with water, and dried.

Calcium 2-Chloro-6-nitroacridinyl-9-thioacetate (IIIa). A 0.01 mole portion of 2-chloro-6-nitroacridinyl-9-thioacetic acid was added to an aqueous solution of 0.01 mole of K_2CO_3, heated on a water bath for 5-7 min, cooled, and evaporated at 40-50°C to dryness.

TABLE 1. Derivatives of 9-Thioacridine and 9-Semicarbazidoacridine

Compound	Yield, %	mp, °C	Empirical formula
II	77	185—7	$C_{15}H_9ClN_2O_4S$
IIIa	85	350	$C_{15}H_8ClN_2O_4S$
IIIb	69	164—6	$C_{20}H_{20}ClN_3O_4S$
IIIc	65	153—5	$C_{19}H_{18}ClN_3O_5S$
IIId	73	175—7	$C_{19}H_{20}ClN_3O_4S$
IIIe	77	98—101	$C_{21}H_{24}ClN_3O_5S$
IIIf	63	63—65	$C_{17}H_{17}ClN_3O_5S$
IV	76	106—8	$C_{17}H_{13}ClN_2O_4S$
V	67	280—2	$C_{16}H_{11}ClN_4O_3S$
VIa	69	245—7	$C_{22}H_{15}ClN_4O_5S$
VIIIa	72	226—8	$C_{14}H_{12}Cl_2N_4O$
VIIIb	77	231—3	$C_{14}H_{12}Cl_2N_4O$
VIIIc	65	212—4	$C_{14}H_{11}Cl_3N_4O$
IXa	63	205—7	$C_{14}H_{11}ClN_4O$
IXb	72	208—10	$C_{14}H_{11}ClN_4O$
IXc	73	210—12	$C_{14}H_{10}Cl_2N_4O$

TABLE 2. Antimicrobial Activity of Synthesized Compounds and Minimal Suppressive Concentration (in μg/ml)

Compound	Staphylococcus aureus	E. coli	Bac. anthracoides	Pseudomonas aeruginosa	Candida albicans	Shigella flexneri	Proteus vulgaris	S. thyphi
Ethacridine lactate	31,2	31,2	125	250	125	125	7,8	125
II	31,2	—	15,6	—	31,2	—	—	—
IIIa	62,5	—	125	—	62,5	—	—	—
IIIb	31,2	—	125	—	62,5	—	—	—
IIIc	31,2	—	125	—	31,2	—	—	—
IIId	31,2	—	62,5	—	15,6	—	—	—
IIIe	31,2	—	62,5	—	31,2	—	—	—
IIIf	31,2	250	15,6	—	125	250	250	—
VIIIa	125	—	31,2	—	62,5	—	—	—
VIIIb	62,5	—	62,5	250	15,6	260	250	250
VIIIc	31,2	—	31,2	—	31,2	—	—	—
IXa	125	—	125	—	62,5	—	250	—
IXb	62,5	250	62,5	250	31,2	250	250	—
IXc	15,6	—	62,5	250	62,5	—	250	—

The precipitate was collected on a filter, washed with ether, and dried. The product constituted brown flakelets (from ethanol).

The IIIb-f salts were obtained in the same manner as compound IIIa except that organic solvents (dioxane, ethanol) were used instead of water. Upon heating the reaction mixture for 7-10 min and cooling, the salt IIIb precipitated immediately, whereas the salts IIId, e precipitated only after the solvent was evaporated.

Ethyl 2-Chloro-6-nitroacridinyl-9-thioacetate (IV). A 0.01 mole portion of NaOH and 0.01 mole of ethyl monoiodoacetate was added to a solution of 0.01 mole of compound I in 100 ml of DMPA, heated on a water bath for 5-7 min, cooled, and decanted into water. The resultant product was brown flakelets (from 70% aqueous alcohol).

2-Chloro-6-nitroacridinyl-9-thioacetic hydrazide (V). A 0.04 mole portion of hydrazine hydrate was added to a solution of 0.01 mole of compound IV in 30 ml of ethanol, and heated on a water bath for 10-12 min, and cooled. The precipitate was separated and dried.

2-Chloro-6-nitroacridinyl-9-thioacetic (2-4-dioxybenzylidene)hydrazide (VIa). A 0.01 mole portion of 2,4-dioxybenzaldehyde and 1 drop of concentrated H_2SO_4 was added to a solution of 0.01 mole of compound V in 80 ml of DMPA or DMSO, heated for 20 min, cooled, diluted with water, and the precipitate was separated and dried, resulting in a brown needle-like product (from aqueous DMPA).

2-Chloro-9-semicarbazidoacridine HCl (VIIIa). A solution of 0.01 mole of semicarbazide HCl in 30 ml of ethanol was added to a solution of 0.01 mole of 2,9-dichloroacridine VII in 100 ml of dioxane, and boiled for 5-10 min, then cooled. The precipitate was separated and dried. The product was yellow flakelets (from aqueous 70% alcohol).

Compounds VIIIb, c were obtained in the same manner as VIIIa.

The bases of IXa-c were separated by treating the aqueous solutions of the VIIIa-c salts with a 2% solution of $NaHCO_3$ to pH ~6.0.

EXPERIMENTAL BIOLOGICAL

The microbiological tests of the synthesized substances were made on eight strains of pathogenic bacteria and fungi by the double series dilution method in a liquid nutrient (aminopeptide). Daily agar cultures of microbial bodies (500,000 per 1 ml) were placed into the nutrient medium with a known dilution of the test compound and the contents were incubated for 18 h after which the minimum concentration of the substance required to retard microorganism growth was visually assayed by the amount of turbidity in the test tube.

The experimental results showed that the synthesized substances exhibit bacteriostatic activity against Staphylococcus aureus and anthracoid spores as well as fungistatic activity against Candida albicans within the range of 15.6-31.2 μg/ml.

An examination of the structure-action relationship showed that the introduction of a nitro group into position 6 of the 2-chloro-acridinyl-9-thioacetic acid molecule and its

derivatives enhances antimicrobial action against Staphylococcus aureus and anthracoid spores. Blockage of the ether residue in the ethyl ester of this acid by hydrazine or hydrazone groups also resulted in greater antimicrobial activity.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF NITROGEN-CONTAINING ADAMANTANE DERIVATIVES

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It is known [1, 2, 5] that nitrogenous functional derivatives of the adamantane series have distinct antiviral activity which, apparently, is caused by the high lipophilicity of the adamantyl radical. For example, N-adamantyl substituted ureas [5], carbamates [3], and carboxylic amides [6] are active. Therefore, the synthesis and study of the antiviral activity of compounds containing both adamantyl and amide fragments in their molecules seemed to be an important task.

To determine the relationship of the virus-inhibiting effect and the structure, we have synthesized acylamino, carbamoylamino, and alk(thio)oxycarbonylamino derivatives of adamantane.

Reaction of adamantane with an excess of 98% HNO_3 in AcOH with subsequent addition of aliphatic and aromatic nitriles to the reaction mixture leads to the formation of acylaminoadamantanes (I-VII) (see scheme on following page).

In the reaction with an excess of succinonitrile, concurrent with addition of the adamantyl cation according to Ritter [7], a conversion of the second C≡N group to an amide group takes place through subsequent protonation and hydrolysis, which leads to the preparation of 1-[(2-carbamoylethyl)carbonylamino]adamantane (II). In case of shortage of

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