SYNTHESIS AND BIOLOGICAL ACTIVITY OF 9-ARYLAMINO DERIVATIVES OF 7-NITRO- AND 7-AMINOACRIDINE

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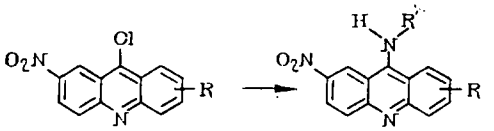
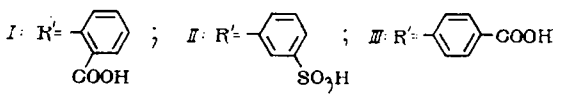
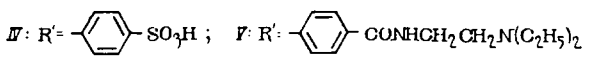
It is known that 9-arylacridine derivatives are often biologically more active than the unsubstituted compounds [1]. Continuing our search for a link between chemical structure and biological activity [2], we have synthesized a number of 9-arylamino derivatives of 7-nitroacridine with the following substituents: anthranilic, metanilic, p-aminobenzoic, sulfanilic acids, p-carbomethoxyaminobenzenesulfamide, and also novocainamid. It was thought that among these compounds there would be some with both antibacterial and antiinflammatory properties [3, 4].



Ia-g; IIa-g; III b, d
IVb; Va-c, e-g





a) R=H, *b)* R=2-CH_3O, *c)* R=4-CH_3O, *d)* R=2-CH_3
e) R=4-CH_3, *f)* R=2-Cl, *g)* R=4-Cl

TABLE 1. 9-Arylaminosubstituted 7-Nitroacridines

Compound	Yield, %	Melting point, °C	Found, % N	Empirical formula	Calculated, % N
Ia	91	193—4	10,31	$C_{20}H_{13}N_3O_4 \cdot HCl$	10,61
Ib	88	267	9,98	$C_{21}H_{15}N_3O_5 \cdot HCl$	9,87
Ic	81	271	10,11	$C_{21}H_{15}N_3O_5 \cdot HCl$	9,87
Id	87	>300 (with decomp.)	10,07	$C_{21}H_{15}N_3O_4 \cdot HCl$	10,25
Ie	77	>300 (with decomp.)	10,50	$C_{21}H_{15}N_3O_4 \cdot HCl$	10,25
If	79	>300 (with decomp.)	9,64	$C_{20}H_{12}N_3ClO_4 \cdot HCl$	9,76
Ig	75	272	9,80	$C_{20}H_{12}N_3ClO_4 \cdot HCl$	9,76
IIa	91	>300 (with decomp.)	9,60	$C_{19}H_{13}N_3O_5S \cdot HCl$	9,73
IIb	89	>300 (with decomp.)	9,28	$C_{20}H_{15}N_3O_6S \cdot HCl$	9,10
IIc	90	>300 (with decomp.)	9,23	$C_{20}H_{15}N_3O_6S \cdot HCl$	9,10
IId	76	>300 (with decomp.)	8,96	$C_{20}H_{15}N_3O_5S \cdot HCl$	9,42
IIe	91	>300 (with decomp.)	9,22	$C_{20}H_{15}N_3O_5S \cdot HCl$	9,42
IIf	87	>300 (with decomp.)	9,28	$C_{19}H_{12}ClN_3O_5S \cdot HCl$	9,01
IIg	83	>300 (with decomp.)	8,77	$C_{19}H_{12}ClN_3O_5S \cdot HCl$	9,01
IIId	96	286	10,62	$C_{21}H_{15}N_3O_4 \cdot HCl$	10,25
IIIb	92	303—5	9,60	$C_{21}H_{15}N_3O_5 \cdot HCl$	9,87
IVb	52	>300 (with decomp.)	9,22	$C_{20}H_{15}N_3O_6S \cdot HCl$	9,10
Va	57	148	12,96	$C_{26}H_{27}N_5O_3 \cdot 2HCl$	13,20
Vb	66	205	12,36	$C_{27}H_{29}N_5O_4 \cdot 2HCl$	12,49
Vc	79	209	12,21	$C_{27}H_{29}N_5O_4 \cdot 2HCl$	12,49
Ve	59	238	12,99	$C_{27}H_{29}N_5O_3 \cdot 2HCl$	12,86
Vf	56	180	12,47	$C_{26}H_{26}ClN_5O_3 \cdot 2HCl$	12,40
Vg	71	167	12,51	$C_{26}H_{26}ClN_5O_3 \cdot 2HCl$	12,40
VIa	92	237	12,27	$C_{21}H_{16}N_4O_8$	12,38
VIb	64	132	11,90	$C_{22}H_{18}N_4O_7$	11,63
VIc	82	238	11,83	$C_{22}H_{18}N_4O_6$	12,01
VIIc	92	238	12,96	$C_{20}H_{14}N_4O_6$	12,78
VIII	54	224	11,24	$C_{23}H_{20}N_4O_7$	11,30

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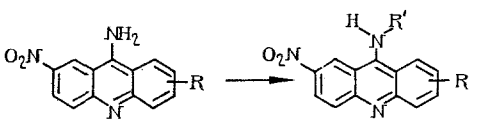
TABLE 2. 9-Arylaminosubstituted 7-Aminoacridines

Compound	Yield, %	Melting point, °C	Found, % N	Empirical formula	Calculated
IXa	65	74	11,12	$C_{26}H_{29}N_5O \cdot 2C_2H_2O_4$	11,53
IXb	63	67	11,12	$C_{27}H_{31}N_5O_2 \cdot 2C_2H_2O_4$	10,98
IXc	67	71	10,80	$C_{27}H_{31}N_5O_2 \cdot 2C_2H_2O_4$	10,98
IXe	80	72	11,42	$C_{27}H_{31}N_5O \cdot 2C_2H_2O_4$	11,27
IXf	67	66	11,02	$C_{26}H_{28}N_5ClO \cdot 2C_2H_2O_4$	10,90
IXg	58	62	11,09	$C_{26}H_{28}N_5ClO \cdot 2C_2H_2O_4$	10,90
Xa	68	243	12,96	$C_{19}H_{16}N_4O_2S \cdot 2HCl$	12,81
Xb	54	237	12,12	$C_{20}H_{18}N_4O_2S \cdot 2HCl$	11,99
Xc	59	131	9,87	$C_{20}H_{18}N_4O_2S \cdot 2C_2H_2O_4$	9,75
Xd	71	154—5	9,74	$C_{20}H_{18}N_4O_2S \cdot 2C_2H_2O_4$	10,03
Xe	72	265	12,20	$C_{20}H_{18}N_4O_2S \cdot 2HCl$	12,41
Xf	54	250	11,80	$C_{19}H_{15}N_4ClO_2S \cdot 2HCl$	11,87
Xg	64	91	11,62	$C_{19}H_{15}ClN_4O_2S \cdot 2HCl$	11,87
XIa	93	201	16,35	$C_{25}H_{22}N_6O_2S \cdot HCl$	16,57
XIb	54	200	15,41	$C_{26}H_{24}N_6O_3S \cdot HCl$	15,65
XIc	94	205	15,52	$C_{26}H_{24}N_6O_3S \cdot HCl$	15,65
XId	96	225—7	16,21	$C_{26}H_{24}N_6O_2S \cdot HCl$	16,13
XIe	94	202	16,08	$C_{26}H_{24}N_6O_2S \cdot HCl$	16,13
XIf	57	203—4	15,77	$C_{25}H_{21}ClN_6O_2S \cdot HCl$	15,52
XIg	72	159	14,27	$C_{25}H_{21}ClN_6O_2S \cdot C_2H_2O_4$	14,12
XIIa	72	145	10,81	$C_{26}H_{26}N_4O_4 \cdot 2HCl$	10,54
XIIb	64	191	10,12	$C_{27}H_{28}N_4O_5 \cdot 2HCl$	9,98
XIIc	53	180—2	9,74	$C_{27}H_{28}N_4O_5 \cdot 2HCl$	9,98
XIId	64	142	10,36	$C_{27}H_{28}N_4O_4 \cdot 2HCl$	10,27
XIIe	59	148	9,88	$C_{27}H_{28}N_4O_4 \cdot 2HCl$	10,27
XIIf	76	230—1	9,73	$C_{26}H_{25}ClN_4O_4 \cdot 2HCl$	9,90
XIIg	50	95	9,98	$C_{26}H_{25}ClN_4O_4 \cdot 2HCl$	9,90
XIII	71	271	11,76	$C_{20}H_{18}N_4O_2 \cdot 2HCl$	11,48

The compounds were prepared by the reaction between 7-nitro-9-chloroacridine and its 2- and 4-methoxy-methyl- and chloro-derivatives [5-7] and the corresponding acids in dimethylformamide; the following compounds were prepared: 7-nitro-9-(o-carboxyphenylamino)acridine hydrochloride (Ia) and its 2- and 4-methoxy-, methyl-, and chloro-derivatives (Ib-g); 7-nitro-9-(m-sulfophenylamino)acridine hydrochloride (IIa) and its 2- and 4-methoxy-, methyl-, and chloro-derivatives (IIIb-g); the hydrochlorides of 2-methoxy- and 2-methyl-7-nitro-9-(p-carboxyphenylamino)acridine (IIIb and IIId); the hydrochloride of 2-methoxy-7-nitro-9-(p-sulfophenylamino)acridine (IVb). The reaction between 7-nitro-9-chloroacridine and its substituted derivatives with the base of novocainamid in phenol gave 7-nitro-9-[p-(2'-diethylaminoethylcarboxyamidophenylamino)]-acridine dihydrochloride (Va), its 2- and 4-methoxy (Vb-c), 4-methyl- (Ve), and 2- and 4-chloroderivatives (Vf-g).

The compound 7-nitro-9-[p-(methoxycarbonylaminophenylsulfonamido)]acridine (VIa), and its 2-methoxy- (VIb), and 2-methyl- (VIc) derivatives, and 2-methyl-7-nitro-9-(p-nitrophenylsulfamido)acridine (VIIc) were obtained by the reaction of 7-nitro-9-aminoacridine and its 2-methoxy- and 2-methyl-substituted derivatives [8] with carbomethoxyaminobenzenesulfonylchloride and p-nitrobenzenesulfochloride in pyridine.



V a-c; VI c

VI: R' = $-O_2S-C_6H_4-NHCOOCH_3$; VII: R' = $-O_2S-C_6H_4-NO_2$

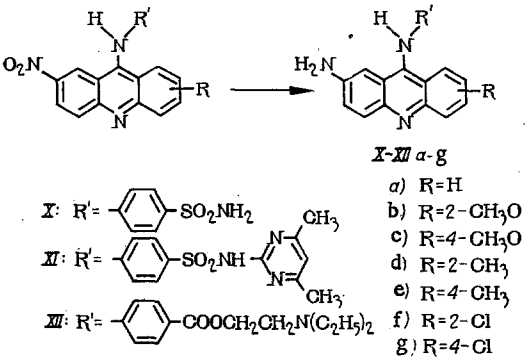
a) R = H b) R = 2-CH_3O c) R = 2-CH_3

To determine the effect of the methyl group on the biological activity, 2-methoxy-7-nitro-9-[p-(methoxy-carbonylaminophenylsulfonamidomethyl)acridine (VIII) was synthesized by reacting 2-methoxy-7-nitro-9-methylaminoacridine [9] with carbomethoxyaminobenzenesulfonylchloride.

The characteristics of the 9-arylamino derivatives of 7-nitroacridine are given in Table 1.

The reduction of compounds Va-c and e-g with stannous chloride [10, 11] gave the dioxalate of 7-amino-9-[p-(2'-diethylaminoethyl carboxyaminophenylamino)]acridine (IXa), and the corresponding methoxy-, methyl-, and chloro-derivatives (IXb-c, e-g).

The compounds 7-amino-9-(p-sulfonamidophenylamino)acridine (Xa), 7-amino-9-[p-(4',6'-dimethylpyrimidino-2'-sulfonamidophenylamino)] acridine (XIa), 7-amino-9-[p-(2'-diethylaminoethylcarboxylatophenylamino)]acridine (XIIa) and their 2- and 4-methoxy-, methyl- and chloroderivatives (X-XIIb-g) were prepared by the reduction of the corresponding 7-nitrosubstituted compounds [2].



The trihydrochloride of 2-methyl-7-amino-9-(p-aminophenylsulfamido)acridine (XIII) was obtained by reduction of VIIc. Characteristics of 9-arylamino derivatives of 7-aminoacridine are given in Table 2.

EXPERIMENTAL

Pharmacological

The antibacterial activity of the test compounds was determined by the method of double serial dilutions in liquid nutrient medium (meat–peptone broth). The microorganisms used for the tests were 24-hour agar cultures of gram-positive (Staphylococcus 209 and Bacillus subtilis) and gram-negative (Escherichia coli and Bacillus pyocyaneus) bacteria, and these were introduced in quantities of fifty thousand microorganisms into test tubes containing broth and a suitable amount of the test compound. After incubation for 18-20 hours at 37°C, the minimum inhibiting concentration of the compounds was visually determined by the amount of turbidity in the test tube. At the same time, the antibacterial activity of the pharmaceutical preparation ethodin (Table 3) was also determined.

The most active compounds were those with a p-aminobenzoic or anthranilic acid group in the 9-position and a methoxy group in the 2-position, and also those with a p-nitrobenzene sulfamide group in the 9-position. Compound VII had the largest antibacterial action although the analogous compound VIb, without a methyl group in the 9-position, was inactive, which can be explained by the removal of substituents from the plane of the acridine ring in the 9-N-methyl derivative VIII. Substituted 7-nitroacridines with a novocainamid residue in the 9-position were less active than the corresponding novocain derivatives [2], and reduction of the 7-nitro group did not lead to a decrease in antibacterial action. The 9-arylamino-7-aminoacridines had a lower antibacterial activity than the corresponding 7-nitro derivatives. In some cases reduction of the nitro group gave a compound which was active against Bacillus pyocyaneus, but it was less effective than ethodin.

The antiinflammatory activity was determined by Strel'nikov's method [12]. Antiinflammatory properties were displayed by compounds Id, IId, and IIId, which have, respectively, an anthranilic, metanilic, and p-aminobenzoic acid group in the 9 position. The decrease in edematous inflammation 24 hours after the introduction of formalin was 37, 28, and 27% for compounds Id-IIId respectively (dose 0.15 g/kg); the value for mephenamic acid under the same conditions was 30%.

Chemical

Derivatives of 7-Nitro-9-(o-carboxyphenylamino)acridine (Ia-g) and the Hydrochlorides of 2-Methoxy- and 2-Methyl-7-nitro-9-(p-carboxyphenylamino)acridine (IIIb and d). To a solution of 0.01 mole of the appropriate 7-nitro-9-chloroacridine in 50 ml of dimethylformamide, was added 0.01 mole of anthranilic or p-aminobenzoic acid, and the reaction mixture was heated on the water bath for 1 hour. After cooling, the reaction mixture was poured into 350 ml of ice water and allowed to stand overnight. The precipitate was filtered off and dissolved in a 10% solution of ammonia, filtered, and acidified to pH 3.0 with concentrated hydrochloric acid. The precipitated material was washed with water and recrystallized from aqueous dimethylformamide.

TABLE 3. Antibacterial Activity of 9-Arylamino Derivatives of 7-Nitro- and 7-Aminoacridine

Microorganism	Dilution	Compound
Staphylococcus	1:500	XIIb
	1:2 000	Id Ig, IIa, IIb, IId, IIe, IIf, IIg, IVb, VIa, VIc, IXa, IXb, IXf, IXg, Xa, Xb, Xc, Xd, Xe, Xf, XIc, XIe, XId, XIg
	1:4 000	Ie, IIc, IIId, VIb, Va, Vb, Ve, Vf, Vg, IXe, IXe, XId, XIIc
	1:8 000	Ia, Vc, Xg, XIa XIId, XIIf
	1:16 000	Ib, Ic If, XIf, XIIa, XIId, XIIg, XIII
	1:32 000	Ethodin, VIIc, VIII
	1:256 000	IIIb
Bacillus subtilis	1:500	XIIb
	1:1 000	XIe XIg
	1:2 000	Ig, IIa, IIb, IId, IIe, IIg, VIa VIc, IXa, IXg, Xa, Xb, Xf, XIa, Xe, XIIc
	1:4 000	Id, Ie, IIf, IVb, VIb, Va IXb IXc, Xc, Xd, IXf, XIb, XIIf
	1:8 000	Ic, IIc, IIId, Vb Vc Vf Vg, XIc, XId, XIId, XIIe, XIII
	1:16 000	Ia, IXe, Xg, XIf XIIa XIIg
	1:32 000	If
	1:64 000	Ethodin, IIIb, Ve VIIc
	1:128 000	Ib VIII
Escherichia coli	1:1 000	XIg, XIIb, XIIc
	1:2 000	Ic, Ie, Ig, IIa, IIc, IId, IIf, IIId IVb, IXa, IXb, IXd, IXg IXd, Xa, Xb, Xd, Xe, XIa, XIb, XIe, XIf, XIIg
	1:4 000	Ia, Ib, Id, If, IIb, IIe, IIg, IIIb, VIa, Va, Vb, Ve, IXc, Xc, Xf, XIc, XId, XIIa, XIId, XIIe
	1:8 000	Vc, Vf, Vg, VIb, XIII
	1:16 000	VIIc, VIII, Xg
	1:32 000	Ethodin
Bacillus pyocyaneus	1:500	XIIb, XIIc, XIIf, XIIg
	1:1 000	XIIa
	1:2 000	Ig, IId, IIId, IXb, IXe, IXf, IXg, Xa, Xc, Xe, Xg, XIb, XIe, XVf, XIg, XIII
	1:4 000	Ia, Ib, Ic, Id, Ie, IIa, IIb, IIc, IIe, IIf, IIg, IIIb, IVb, VIa, VIb, VIc, VIIc, Va, Vb, Vc Vf, Ve, Vg, IXa, Xb, Xf, XIa, XIc, XId, XIId, XIIe
	1:8 000	Ethodin If, VIII, IXc

Derivatives of 7-Nitro-9-(m-sulfophenylamino)acridine (IIa-g) and the Hydrochloride of 2-Methoxy-7-nitro-9-(p-sulfophenylamino) acridine (IVb). A solution of 0.01 mole of the corresponding 7-nitro-9-chloroacridine in 100 ml of dimethylformamide, 0.01 mole of triethylamine, and 0.01 mole of methanylic acid or sulfanilic acid were heated on a water bath for 2 hours. After cooling, 500 ml of ice water was poured into the reaction mixture. The precipitate was filtered off and dissolved in a 10% solution of sodium hydroxide, filtered, and the filtrate acidified to pH 3.0 with concentrated hydrochloric acid. The precipitate was washed with water and recrystallized from aqueous dimethylformamide.

Derivatives of 7-Nitro-9-[p(2^1-diethylaminoethylcarboxamidophenylamino)]acridine (Va-c, e-g). A mixture of 0.01 mole of the appropriate 7-nitro-9-chloroacridine, 20 g of phenol and 2.35 g (0.01 mole) of the base of novocainamid was heated at 100°C for 3 hours. After cooling, the mixture was treated with ether and the hydrochloride converted to the base with aqueous ammonia. The hydrochloride was obtained by adding a saturated alcoholic solution of hydrogen chloride to an alcoholic solution of the base.

Derivatives of 7-Nitro-9-[p-(methoxycarbonylaminophenylsulfonamido)]acridine (VIa-c). To a solution of 0.01 mole of the appropriate 7-nitro-9-aminoacridine in pyridine, was added 0.015 mole of carbomethoxy-aminobenzenesulfonylchloride and 0.01 mole of triethylamine, and the reaction mixture heated at 125°C with mixing for 3 hours. After cooling, the reaction mixture was diluted with water and acidified to pH 2.0 with 10% hydrochloric acid. The residue was filtered off, washed with water and 10% sodium hydroxide solution, and recrystallized from aqueous acetone. The same method was used to prepare compound VIII from 2-methoxy-7-nitro-9-methylaminoacridine, and compound VIIc from 2-methyl-7-nitro-9-aminoacridine and p-nitrobenzene-sulfochloride. Compounds VIIc and VIII were recrystallized from aqueous acetone.

Compounds IXa-c, e-g, Xa-g, XIa-g, XIIa-g, and XIII. The reducing agent was first prepared in the following manner: 7 g anhydrous stannous chloride and 7 ml of acetic anhydride were diluted to 30 ml with glacial acetic acid and the solution saturated with dry hydrogen chloride until the stannous chloride had com-

pletely dissolved. To this solution was added with mixing over a period of 1 hour, 1 g of 7-nitro-9-aryl-aminoacridine and the reaction mixture allowed to stand overnight. The precipitated material was filtered, washed with glacial acetic acid and the base liberated by the addition of 20% sodium bicarbonate solution. The final products were isolated as the hydrochlorides (for IXa-g, Xc and d, and XIg, as the oxalates since the hydrochlorides are hygroscopic). The hydrochlorides were obtained by adding a saturated alcoholic solution of hydrogen chloride to an alcoholic solution of the base. The oxalates were obtained by adding the calculated amount of oxalic acid dissolved in dry acetone to an alcoholic solution of the base.

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