INVESTIGATIONS IN THE ACRIDINE SERIES.

I. The Synthesis and Properties of 9-Phenoxyacridines

A. C. Lebekhov and A. S. Samarin

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Condensation of 9-chloroacridines with substituted phenols has given a series of strongly bactericidal 9-phenoxyacridines, which have not previously been described in the literature.

According to the literature [1–6], many acridines containing amino-, alkoxy-, and halo-substituents in various positions in the acridine nucleus, possess strong bactericidal activity.

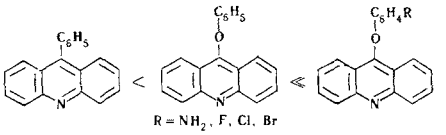
It was, therefore, thought worthwhile to synthesize and to examine the bactericidal activity of acridines containing these substituents, not in the acridine moiety, but in the 9-phenoxy radical. It is known that 9-chloroacridine reacts under very milk conditions (heating at 80° C) with phenol to give 9-phenoxyacridine [7], and substituted 9-chloroacridines react easily under similar conditions [8–10].

This paper describes the condensation of 9-chloroacridine with various substituted phenols by heating equimolar amounts of the reactants in a solvent (usually methanol) for 2–3 hr. Completion of the reaction was established by using a color reaction for 9-chloroacridine [11]. The 9-phenoxyacridines (Table 1, I–XXII) were high melting, amorphous solids, usually of a yellow color. The compounds were all odorless, insoluble in water, and sparingly soluble in the usual organic solvents; they were all readily soluble in concentrated sulfuric acid, the solutions showing an intense violet fluorescence.

The structure of the aminophenoxyacridines I and III were confirmed by alternate syntheses from the corresponding 9-nitrophenoxyacridines XVIII and XIX, by reduction with zinc and acetic or hydrochloric acid. In addition, compounds I–III could be diazotized and coupled with phenols to give brightly-colored substances, indicating the presence in these compounds of free amino-groups. The products of the reaction of 9-chloroacridine with hydroxybenzoic acid and phenolsulfonic acid must possess similar structures.

All the 9-phenoxyacridines were submitted for determination of their bactericidal activity. The results are given in Table 2. All the compounds showed powerful bactericidal effects on Bacteria coli and Staphylococus aureus. The following are worthy of special attention: the isomeric 9-aminophenoxyacridines I–III, which kill B. coli in concentrations of 0.005–0.001% after 30 min; 9-p-fluorophenoxyacridine (XI), lethal to B. coli at 0.02% after 30 min and to S. aureus at 0.003%; and 9-p-dimethylaminophenoxyacridine (VI), which kills Anthracoides spores at 2% after 30 min. Microbiological examination of the starting materials did not reveal any bactericidal activity in the concentrations used.

The experimental data on the effects of various functional groups on the bactericidal activity of 9-phenoxyacridines may be represented as follows:



It will be seen from this that the oxygen bridge between the acridine ring in the 9-position and the phenyl nucleus gives a weakly bactericidal compound (9-phenylacridine is nonbactericidal, and 9-phenoxyacridine kills S. aureus at concentrations of 0.25% after 60 min), but the amino group or halogens in the phenyl radical substantially increase the bactericidal properties of these compounds.

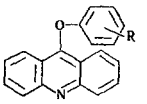
EXPERIMENTAL

9-Phenoxyacridines (I-XXIII, Table 1). Equivalent amounts (0.009 mole) of 9-chloroacridine [12] and the substituted phenol in 50 ml of methanol were boiled for 2–3 hr under reflux. The end of the reaction was determined by adding two drops of a saturated solution of barbituric acid to two drops of the reaction mixture and heating; in the presence of 9-chloroacridine, a bright red precipitate of acridinobarbituric acid separated. When the reaction was complete, the mixture was cooled to room temperature and diluted with water. The precipitated phenoxyacridine hydrochloride was basified with dilute ammonia to give the free base. The latter may also be obtained directly from the reaction mixture by basification with 25% ammonia. The precipitate was filtered off, washed with alcohol and water, and dried at 70° C. Purification was effected by recrystallization from alcohol to give 80–90% yields of the pure 9-phenoxyacridines.

9-Aminophenoxyacridines (I, III, Table 1). To a solution of 1.07 g (0.003 mole) of the 9-nitrophenoxyacridine in 50 ml of methanol was added 10 ml of conc HCl, and 2 g of zinc dust in small portions (such that it dissolved), with gentle heating on the water bath. When all the zinc had dissolved, the color of the solution changed. Treatment of the solution with concentrated ammonia gave an immediate precipitate of the corresponding 9-aminophenoxyacridine, which was filtered off, washed with alcohol and water, and dried at 70° C. Yield 0.5 g (52%). Acetic acid may be used in place of hydrochloric.

Diazotization of 9-aminophenoxyacridines and coupling with phenols. 1.75 g (0.006 mole) of 9-o-aminophenoxyacridine was dissolved in 30 ml of conc H_2SO_4, and diluted with 100 ml of water. The mixture was cooled to 0° C, and a saturated aqueous solution of 2.5 g (0.03 mole) of sodium nitrite added slowly with cooling and stirring. When diazotization was complete, the clear diazo solution was added with cooling to 10° C, to a solution of 2 g (0.01 mole) of β-naphthol in 36 ml of 2% NaOH. The bright yellow precipitate was filtered off and washed with alcohol and water. Recrystallization from alcohol gave 1.64 g (60%) of an amorphous yellow powder, mp 388° C. 9-p-Aminophenoxyacridine was diazotized and coupled similarly with β-naphthol.

Table 1



Compound	R	Mp, ° C (decomp.)	Molecular formula	Found, %			Calculated, %		
				C	H	halogen*	C	H	halogen*
I	*o*-H_2N	236	$C_{19}H_{14}N_2O$	78.98	4.98	(283.9)	79.70	4.93	(286.3)
II	*m*-H_2N	256	$C_{19}H_{14}N_2O$	80.01	4.90	(281.2)	79.70	4.93	(286.3)
III	*p*-H_2N	270	$C_{19}H_{14}N_2O$	79.35	4.87	(279.0)	79.70	4.93	(286.3)
IV	*o*-CH_3CONH	232	$C_{21}H_{16}N_2O_2$	76.43	4.87	(341.1)	76.81	4.91	(328.4)
V	*p*-CH_3CONH	216	$C_{21}H_{16}N_2O_2$	76.49	4.93	(347.0)	76.81	4.91	(328.4)
VI	*p*-$(CH_3)_2N$	146	$C_{21}H_{18}N_2O$	79.75	5.79	—	80.23	5.77	—
VII	*o*-Cl	238	$C_{19}H_{12}ClNO$	74.39	3.92	11.75	74.63	3.96	11.60
VIII	*o*-Br	240	$C_{19}H_{12}BrNO$	64.93	3.43	22.66	65.16	3.45	22.80
IX	*o*-Cl	215—218	$C_{19}H_{12}ClNO$	74.11	3.95	11.05	74.63	3.96	11.60
X	*p*-Br	244	$C_{19}H_{12}BrNO$	64.74	3.48	22.70	65.16	3.45	22.80
XI	*p*-F	255	$C_{19}H_{12}FNO$	78.21	4.14	6.14	78.88	4.18	6.57
XII	*o*-SO_3H	320	$C_{19}H_{13}NO_4S$	65.35	3.63	—	64.95	3.73	—
XIII	*p*-SO_3H	230	$C_{19}H_{13}NO_4S$	64.78	3.77	—	64.95	3.73	—
XIV	2-Cl-4-SO_3H	260	$C_{19}H_{12}ClNO_4S$	58.60	3.11	9.40	59.15	3.14	9.19
XV	2-Br-4-SO_3H	272	$C_{19}H_{12}BrNO_4S$	53.30	2.76	19.02	53.04	2.81	18.60
XVI	4-Cl-2-SO_3H	310	$C_{19}H_{12}ClNO_4S$	58.73	3.08	9.59	59.15	3.14	9.19
XVII	4-Br-2-SO_3H	258	$C_{19}H_{12}BrNO_4S$	52.51	2.77	18.30	53.04	2.81	18.60
XVIII	*o*-NO_2	191—195	$C_{19}H_{12}N_2O_3$	72.54	3.84	—	72.14	3.82	—
XIX	*p*-NO_2	175—179	$C_{19}H_{12}N_2O_3$	72.77	3.79	—	72.14	3.82	—
XX	*o*-COOH	242—244	$C_{20}H_{13}NO_3$	75.91	4.09	—	76.18	4.16	—
XXI	*p*-COOH	210—214	$C_{20}H_{13}NO_3$	76.48	4.09	—	76.18	4.16	—
XXII	*m*-H_3C	380—382	$C_{20}H_{15}NO$	83.84	5.28	(292.2)	84.18	5.20	(285.4)

*The molecular weight (determined by the Rast method) is given in parentheses.

Table 2

The Bactericidal Properties of 9-Phenoxyacridines

Compound	Bacteria coli			Staphylococcus aureus			Anthracoides	
	Bactericidal activity		Bacteriostatic activity	Bactericidal activity		Bacteriostatic activity	Bactericidal activity after 30 min	Bacteriostatic activity
	10 min.	30 min.		10 min.	30 min.			
I	0.03	0.005	++++	1	0.5	++	—	—
II	0.01	0.005	++++	0.05	0.03	++++	—	—
III	0.01	0.001	++++	0.5	0.5	++	—	—
IV	0.25	0.1	++++	0.25	0.1	++++	—	—
V	0.2	0.15	++++	0.2	0.15	++++	—	—
VI	0.5	0.25	++++	0.25	0.2	++++	2	++
VII	0.1	0.05	++++	0.05	0.025	++++	—	—
VIII	0.5	0.2	+++	0.5	0.25	+	—	—
IX	0.1	0.005	++++	0.05	0.025	++++	—	—
X	0.25	0.1	++	0.25	0.25	+	—	—
XI	0.05	0.02	++++	0.01	0.003	++++	—	—
XII	0.05	0.02	+++	—	0.15	++	—	—
XIII	—	0.2	+	—	—	+	—	—
XIV	—	0.1	++++	—	0.25	++	—	—
XV	—	0.5	+	—	0.5	+	—	—
XVI	—	0.5	+	—	0.5	+	—	—
XVII	0.05	0.01	+++	0.01	0.005	++++	—	—
XVIII	0.5	0.5	+++	0.5	0.5	+++	—	—
XIX	0.5	0.25	+++	0.25	0.25	+++	—	—
XX	0.1	0.05	++++	0.05	0.05	++++	—	—
XXI	0.5	0.5	+	1	0.5	+	—	—
XXII	—	0.25	+	0.25	0.1	++	—	—

Note: The table shows the percentage concentrations of compounds showing bactericidal activity; the sign + (or -) indicates that the compound is active (or inactive) in the case of the particular organisms.

The 9-phenoxyacridines were examined for bactericidal activity in solution in alcohol or dioxane, with the addition of an emulsifying agent (OP-7). The less soluble compounds were dissolved in conc H_2SO_4 and neutralized with sodium carbonate or hydroxide solution.

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Perm Polytechnic Institute