2,3-POLYMETHYLENEQUINOLINES

XI.* 6-CHLORO-9-ARYLAMINO-1,2,3,4-TETRAHYDROACRIDINES

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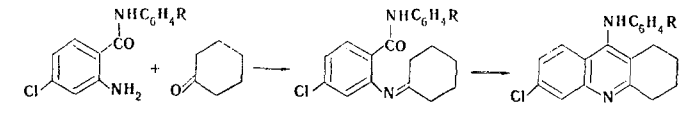
6-Chloro-9-arylamino-1,2,3,4-tetrahydroacridines were synthesized by intramolecular cyclization of arylamides of N-cyclohexylidene-4-chloroanthranilic acid. A number of new compounds were obtained, and their properties and biological activity were studied.

We have previously [2, 3] proposed a method for the synthesis of 9-arylamino- and 9-alkylamino-1,-2,3,4-tetrahydroacridines from substituted amides of N-cyclohexylideneanthranilic acids. To extend the scope of this method we obtained 6-chloro-9-arylamino-1,2,3,4-tetrahydroacridines.



I a-h II a-h III-X

I, II a R=H; b R=*p*-CH_3; c R=*m*-CH_3; d R=*o*-CH_3; e R=*p*-OCH_3; f R=*p*-Cl; g R=*p*-Br; h R=*m*-Br; III R=H; IV R=*p*-CH_3; V R=*m*-CH_3; VI R=*o*-CH_3; VII R=*p*-Cl; VIII R=*p*-Br; IX R=*m*-Br; X R=*p*-OCH_3.

The arylamides of 4-chloroanthranilic acid (I) (Table 1) were obtained by the magnesylamine method [4]. When I were heated with cyclohexane in benzene solution, arylamides of N-cyclohexylidene-4-chloroanthranilic acid (II) (Table 2) were obtained in good yields.

We also attempted to condense anilides of 3,5-dichloro- and 3,5-dibromoanthranilic acids with cyclohexane. The reaction was carried out by refluxing solutions of the starting substances in ethanol, butanol, and benzene, and also by heating the anilides with excess cyclohexanone at its boiling point. However, we were unable to effect the condensation in any case. The reason for this is apparently the low basicity of the arylamides of 3,5-dihaloanthranilic acids as compared with the arylamides of 4-chloroanthranilic acid and the steric hindrance from the two o-substituents, which shield the amino group.

Intramolecular cyclization accompanied by the formation of 6-chloro-9-arylamino-1,2,3,4-tetrahydroacridines (III-X) (Table 3) is observed when II are heated briefly with phosphorus oxychloride.

Compounds III-X are colorless or slightly yellowish crystalline substances that display weak basic properties. There are four absorption maxima in the UV spectra of these compounds.

We studied the acute toxicity and character of the interrelationships of III-X† with muscle relaxants with concurrent (diplatsin) and depolarizing (ditilin) action. The investigated substances were introduced intraperitoneally into white mice as a suspension in 2% starch mucilage. None of the compounds were toxic. Their LD_{50} exceeds 1500 mg/kg. Only IV has anticurare activity. Compounds IV, VI, VII, and X have proditilin activity, which is most clearly expressed in the case of VI.

*See [1] for communication X.

†The tests were made by Professor A. S. Zaks and L. G. Zil'bermints (Master of Medical Sciences), to whom the author extends his thanks.

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TABLE 1. Arylamides of 4-Chloroanthranilic Acid

Compound	mp, °C	Empirical formula	N, % found	N, % calc.	Yield, %
Ia	132	$C_{13}H_{11}ClN_2O$	10,8	11,3	60
Ib	153	$C_{14}H_{13}ClN_2O$	10,4	10,8	69
Ic	132—133	$C_{14}H_{13}ClN_2O$	10,5	10,8	81
Id	130	$C_{14}H_{13}ClN_2O$	10,7	10,8	67
Ie	156—158	$C_{14}H_{13}ClN_2O_2$	9,8	10,1	54
If	165—166	$C_{13}H_{10}Cl_2N_2O$	9,7	10,0	54
Ig	173—175	$C_{13}H_{10}BrClN_2O$	8,4	8,6	60
Ih	150—151	$C_{13}H_{10}BrClN_2O$	8,2	8,6	57

TABLE 2. Arylamides of N-Cyclohexylidene-4-Chloroanthranilic Acid

Compound	mp, °C	Empirical formula	N, % found	N, % calc.	λ_{max}, nm	lg ε	Yield, %
IIa	238	$C_{19}H_{19}ClN_2O$	8,6	8,60	232, 334	4,50; 3,36	70
IIb	217—220	$C_{20}H_{21}ClN_2O$	8,0	8,23	232, 344	4,52; 3,44	65
IIc	218—220	$C_{20}H_{21}ClN_2O$	8,5	8,23	232, 344	4,40; 3,53	59
IId	227—229	$C_{20}H_{21}ClN_2O$	8,2	8,23	232, 342	4,63; 3,58	60
IIe	230—232	$C_{20}H_{21}ClN_2O_2$	8,1	7,85	232, 340	4,89; 3,73	52
IIf	220—222	$C_{19}H_{18}Cl_2N_2O$	7,9	7,75	232, 334	4,54; 3,59	56
IIg	225—228	$C_{19}H_{18}BrClN_2O$	6,8	6,90	234, 344	4,70; 3,44	60
IIh	200—201	$C_{19}H_{15}BrClN_2O$	7,0	6,90	230, 344	4,60; 3,51	67

TABLE 3. 6-Chloro-9-arylamino-1,2,3,4-tetrahydroacridines

Compound	mp, °C	Empirical formula	N, % found	N, % calc.	λ_{max}, nm	lg ε	Yield, %
III	220	$C_{19}H_{17}ClN_2$	9,0	9,06	234, 254, 328, 354	4,5; 4,07; 3,62; 3,7	63
IV	187	$C_{20}H_{19}ClN_2$	8,2	8,34	234, 258, 328, 352	4,6; 4,3; 3,73; 3,86	78
V	165—167	$C_{20}H_{19}ClN_2$	8,2	8,34	234, 256, 328, 346	4,95; 4,59; 4,15; 4,18	70
VI	130	$C_{20}H_{19}ClN_2$	8,0	8,34	234 — 352 —	4,87 — 4,38	53
VII	184	$C_{19}H_{16}Cl_2N_2$	8,2	8,04	230, 262, 330, 352	4,32; 4,07; 3,57; 3,61	81
VIII	167	$C_{19}H_{16}BrClN_2$	7,1	7,24	232, 258, 328, 350	4,9; 4,6; 4,1; 4,18	78
IX	168	$C_{19}H_{16}BrClN_2$	7,1	7,24	232, 252, 328, 348	5,0; 4,7; 4,3; 4,2	47
X	136—140	$C_{20}H_{19}ClN_2O$	8,2	8,26	232, 258, 328, 355	4,9; 4,5; 4,1; 4,14	53

EXPERIMENTAL

Anilides of 4-Chloroanthranilic Acid (I). The dimagnesylamine was obtained from 0.4 g-atom of magnesium, 0.4 mole of ethyl bromide, and 0.2 mole of the arylamine in anhydrous ether. An ether solution of methyl 4-chloroanthranilate was added to the reagent, and the mixture was heated on a water bath for 30 min. It was then decomposed with 10% acetic acid, and the ether layer was separated and treated with steam. The residue was crystallized from alcohol.

Anilides of N-Cyclohexylidene-4-chloroanthranilic Acid (II). A 0.01-mole sample of cyclohexanone was added to a solution of 0.01 mole of anilide I in 5 ml of benzene, and the mixture was refluxed for 4 h. It was then cooled, and the precipitate was removed by filtration and crystallized from alcohol.

9-Arylamino-6-chloro-1,2,3,4-tetrahydroacridines (III-X). A mixture of 0.01 mole of anilide II and 4 ml of phosphorus oxychloride was heated on a water bath for 1 h, after which it was cooled and poured into water. The precipitate was then removed by filtration and dissolved in alcohol, and the solution was treated with ammonia. The precipitated base (III) was removed by filtration and crystallized from alcohol.

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