SYNTHESIS OF HALOGEN DERIVATIVES OF 9-ARYLAMINO-1,2,3,4-TETRAHYDROACRIDINES

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A method has been proposed for obtaining halogen-substituted 9-arylamino-1,2,3,4-tetrahydroacridines from the anilides of the corresponding cyclohexylideneanthranilic acids.

Derivatives of 9-amino-1,2,3,4-tetrahydroacridine are attracting attention as physiologically active substances [1,2]. However, this group of compounds has been studied inadequately from the chemical point of view. In particular, halogen derivatives of 9-arylamino-1,2,3,4-tetrahydroacridines have not been studied at all. We have proposed a new method for obtaining 9-arylamino-1,2,3,4-tetrahydroacridines [3]. The present investigation was undertaken with the aim of broadening the limits of this method and extending it to halogen derivatives of 9-arylamino-1,2,3,4-tetrahydroacridines (see scheme page 638).

The initial anilides of 5-chloro- and 5-bromoanthranilic acids (I) (Table 1) were obtained by the method of Petyunin and Kozhevnikov [4]. The reaction of the anilides I with cyclohexanone gave good yields of the anilides of 5-chloro- and 5-bromo-N-cyclohexylideneanthranilic acids (II) (Table 2). Compounds I

TABLE 1. Anilides of 5-Chloro- and 5-Bromoanthranilic Acids (I)

R	R′	mp, °C	Empirical formula	N, % found	N, % calc.	Yield, %
H	Cl	140—142	$C_{13}H_{11}ClN_2O$	11,20; 11,16	11,36	48
p-CH_3	Cl	180	$C_{14}H_{13}ClN_2O$	10,70; 10,62	10,75	58
p-CH_3	Br	190—192	$C_{14}H_{13}BrN_2O$	9,01; 9,11	9,18	86
m-CH_3	Cl	148—151	$C_{14}H_{13}ClN_2O$	10,48; 10,51	10,75	57
m-CH_3	Br	160—162	$C_{14}H_{43}BrN_2O$	9,16; 9,04	9,18	78
p-CH_3O	Cl	154	$C_{14}H_{13}ClN_2O_2$	9,93; 10,04	10,15	72
p-CH_3O	Br	167	$C_{14}H_{13}BrN_2O_2$	8,50; 8,46	8,73	46
p-Cl	Br	193—194	$C_{13}H_{10}BrClN_2O$	8,40; 8,53	8,62	93
p-Br	Cl	188—190	$C_{13}H_{10}BrClN_2O$	8,42; 8,70	8,62	84
p-Br	Br	196—197	$C_{13}H_{10}Br_2N_2O$	7,50; 7,43	7,57	72

TABLE 2. Anilides of 5-Chloro- and 5-Bromo-N-cyclohexylidene-anthranilic Acids (II)

R	R′	mp, °C	Empirical formula	N, % found	N, % calc.	λ_{max}, nm	log ε	Yield, %
H	Cl	224	$C_{19}H_{19}ClN_2O$	8,86; 8,87	8,60	356	3,48	64
H	Br	225	$C_{19}H_{19}BrN_2O$	7,78; 7,91	7,55	357	3,55	95
p-CH_3	Cl	233—235	$C_{20}H_{21}ClN_2O$	8,57; 8,54	8,23	356	3,44	70
p-CH_3	Br	230—232	$C_{20}H_{21}BrN_2O$	7,36; 7,35	7,27	356	3,55	88
m-CH_3	Cl	200—202	$C_{20}H_{21}ClN_2O$	8,53; 8,42	8,23	356	3,46	94
m-CH_3	Br	204—207	$C_{20}H_{21}BrN_2O$	7,54; 7,34	7,27	356	3,49	70
o-CH_3	Cl	220—225	$C_{20}H_{21}ClN_2O$	8,35; 8,43	8,23	—	—	74
p-CH_3O	Cl	218—220	$C_{20}H_{21}ClN_2O_2$	8,12; 7,92	7,85	356	3,54	78
p-CH_3O	Br	214—216	$C_{20}H_{21}BrN_2O_2$	7,32; 7,04	6,98	356	3,35	90
p-Cl	Cl	225—230	$C_{19}H_{18}Cl_2N_2O$	7,73; 8,07	7,75	356	3,44	81
p-Cl	Br	235—237	$C_{19}H_{18}BrClN_2O$	7,08; 6,91	6,90	358	3,43	87
p-Br	Cl	230—232	$C_{19}H_{18}BrClN_2O$	6,58; 6,68	6,90	354	3,34	74

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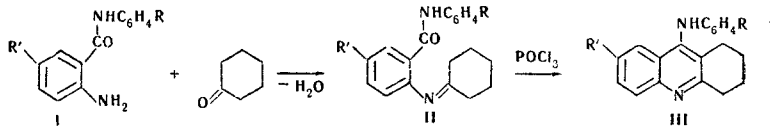
TABLE 3. Halogen Derivatives of 9-Arylamino-1,2,3,4-tetrahydroacridines (III)

R	R′	mp, °C	Empirical formula	Found, %		Calc.,%		λ_{max}, nm	log ε	Yield, %	mp of the hydrochloride, °C
				C	H	C	H				
H	Cl	190—191	$C_{19}H_{17}ClN_2$	74,02; 73,90	5,48; 5,30	73,89	5,54	258; 328; 356	4,34; 3,88; 3,95	64	268—270
H	Br	184—185	$C_{19}H_{17}BrN_2$	64,82; 64,70	5,08; 4,96	64,59	4,86	258; 328; 356	4,20; 3,75; 3,80	63	270
p-CH_3	Cl	140—141	$C_{20}H_{19}ClN_2$	74,20; 74,12	5,72; 5,64	74,48	5,88	258; 328; 356	4,40; 3,87; 3,99	70	273—275
p-CH_3	Br	158—160	$C_{20}H_{19}BrN_2$	65,08; 65,10	5,09; 5,03	65,40	5,21	258; 328; 358	4,39; 3,87; 3,97	72	282
m-CH_3	Cl	162—163	$C_{20}H_{19}ClN_2$	74,30; 74,25	5,70; 5,62	74,48	5,88	256; 328; 356	4,32; 3,86; 3,93	55	252—255
m-CH_3	Br	174—175	$C_{20}H_{19}BrN_2$	65,20; 65,12	5,52; 5,40	65,40	5,21	256; 328; 356	4,43; 3,83; 3,98	57	240—242
o-CH_3	Cl	144—145	$C_{20}H_{19}ClN_2$	74,23; 74,18	5,54; 5,63	74,48	5,88	254; 328; 348	4,47; 4,04; 4,05	71	292—295
p-CH_3O	Cl	118—120	$C_{20}H_{19}ClN_2O$	70,81; 70,65	5,43; 5,35	70,99	5,60	256; 358	4,40; 4,00	63	260—263
p-Cl	Cl	144	$C_{19}H_{16}Cl_2N_2$	66,30; 66,25	4,38; 4,35	66,50	4,67	256; 328; 350	4,40; 3,92; 4,07	74	260
p-Cl	Br	162—164	$C_{19}H_{16}BrClN_2$	61,45; 61,58	4,21; 4,17	61,80	4,12	256; 328; 354	4,06; 3,60; 3,63	63	260—262
p-Br	Cl	150	$C_{19}H_{16}BrClN_2$	61,52; 61,70	4,09; 4,20	61,80	4,12	256; 328; 354	4,06; 3,61; 3,65	51	265—269
p-CH_3O	Br	142—145	$C_{20}H_{19}BrN_2O$	62,38; 62,45	4,80; 4,92	62,70	4,95	258; 328; 358	4,27; 3,70; 3,86	84	263

react with cyclohexanone with greater difficulty than the anilides of anthranilic acid. This can be explained by the lower basicity of the amino group in the former case because of the I-effect of the halogen atoms.



When the anilides II are heated with phosphorus oxychloride in dry benzene they are smoothly converted into halogen derivatives of 9-arylamino-1,2,3,4-tetrahydroacridine (III) (Table 3). These are faintly yellowish crystalline substances possessing a basic nature and readily forming salts with mineral acids. The IR spectra of the anilides II, taken on a SF-4 spectrophotometer in ethanolic solution (Table 1) each have a maximum in the 354-358 nm region, and the UV spectra of the aminoacridines III (Table 3) each have three well-defined maxima in the 260, 328, and 356-358 nm regions which are shifted in the long-wave direction as compared with the spectra of the 9-arylamino-1,2,3,4-tetrahydro-acridines [3].

EXPERIMENTAL

Anilides of 5-Chloro- and 5-Bromoanthranilic Acids (I). To the dimagnesylamine obtained by the usual method from 0.4 mole of magnesium, 0.4 mole of ethyl bromide, and 0.2 mole of arylamine was added a solution of 0.1 mole of methyl 5-chloro- or 5-bromoanthranilate in 30 ml of ether, and the mixture was heated in the water bath for 30 min and decomposed with 10% acetic acid. The ethereal layer was separated off and treated with steam. The residue was crystallized from ethanol.

Anilides of Halogeno-N-cyclohexylideneanthranilic Acids (II). A mixture of 0.01 mole of an anilide I and 0.01 mole of cyclohexanone in 5 ml of benzene was boiled on a sand bath for 3-4 h. The precipitate that separated out after cooling was filtered off and crystallized from ethanol.

9-Arylamino-1,2,3,4-tetrahydroacridines (III). A mixture of 0.01 mole of an anilide II and 3 ml of phosphorus oxychloride in 15 ml of anhydrous benzene was heated in the water bath for 1 h, the benzene was distilled off in vacuum, and the residue was dissolved in ethanol and treated with ammonia. The precipitate that separated out was filtered off and crystallized from ethanol. The hydrochlorides were obtained by mixing an ethanolic solution of a compound III with an ethanolic solution of hydrogen chloride.

LITERATURE CITED

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