ORIENTATION IN THE AMINOARYLATION OF ACRIDINE

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UDC 547.835.9:542.953

A number of 9-aminoarylacridines were obtained by the condensation of acridine hydrochloride with various aromatic amines in the presence of sulfur. The orientation of the arylamines was established by determination of the structures of the products by alternative synthesis or measurement of the dipole moments.

Addition at the 9 position of acridine and the para position of the arylamine [2] occurs in the reaction of quaternary and protic salts of acridine with ring-unsubstituted aromatic amines in the presence of sulfur [1]. The introduction of substituents makes it possible for the reaction to occur in several directions. The establishment of the effect of the orientation of such compounds during the aminoarylation of acridine makes it possible to obtain products with known structures; in addition, the accumulation of data on the effect of substituents on the course of the process makes it possible to draw some conclusions relative to the mechanism of the reaction.

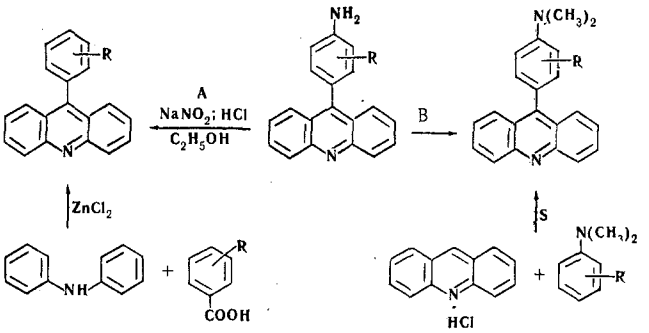
In the present paper, the effect of orientation was investigated in the case of the condensation of acridine hydrochloride with various phenylamines containing donor and acceptor substituents and also with amines of the diphenyl and naphthalene series (Table 1). When arylamines with donor substituents in the ring were used, a side product – thioacridone – and unchanged acridine were isolated in several cases in addition to 9-aminoarylacridine. The yield of thioacridone increases as the yield of 9-aminoarylacridine decreases, i.e., as the primary reaction is hindered.

The presence of acceptor substituents in the ring (o-nitroaniline) or attached to the nitrogen atom (acetanilide, N-methylacetanilide, and diphenylamine) leads to deactivation of the arylamines, and the aminoarylation reaction does not occur. This sort of effect of acceptor substituents may be evidence for reaction via an ionic mechanism, since these sorts of substituents do not obstruct the reaction during radical processes [3]. Under the conditions of the aminoarylation reaction, anthranilic acid is decarboxylated, and the aniline formed undergoes reaction. Some data on the synthesis and properties of the compounds obtained are given in Table 1.

The structures of the reaction products were proved by alternative synthesis and determination of the dipole moments. The PMR spectra recorded for several compounds did not give adequate information regarding the structure. The structures of VI, IX, and XV were proved by alternative synthesis (A). The 9-aminoarylacridines were deaminated to the corresponding 9-arylacridines, which were compared with compounds obtained via the method in [4] by closing the acridine ring (see the scheme below).

The structures of I, IV, V, VII, VIII, X, XI, and XIV were proved by alternative synthesis B. Route B is the reaction of acridine hydrochloride with dimethylarylamines, for which one can exclude the possibility of alternative ortho products of coupling with acridine.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 216-219, February, 1972. Original article submitted June 30, 1971.



According to the literature [5], the dimethylamino group creates steric hindrance, for example, during azo coupling. It is natural to assume that it will also shield the ortho position from the entry of a more bulky substituent than the azo group – acridine. In fact, in the case of the reaction of acridine hydrochloride with N,N-dimethyl-p-toluidine and N,N-dimethyl-4-aminodiphenyl, in which the para position is occupied, the reaction does not occur, although addition products were obtained for the corresponding N-unmethylated compounds – p-toluidine and 4-aminodiphenyl. The meta orientation is unlikely in both the ionic and radical mechanisms of the reaction [3]. Thus only para addition with respect to the dimethylamino group is possible for meta-substituted dimethylanilines. The structures of the 9-aminoarylacridines were established by alternative synthesis – by methylation to the corresponding 9-dimethylaminoarylacridines, which are obtained via reaction of sulfur and have known structures (see scheme above).

The dipole moments were determined for II, III, VI, and IX. Their structures were proved by a comparison of the theoretical dipole moments with the experimental values. The dipole moments could not be determined for the remaining compounds because of their poor solubility in benzene.

Thus an investigation of the structure of the products of the reaction of acridine hydrochloride with the indicated arylamines demonstrates that the amino group is the determining factor in the orientation and, as a rule, directs to the para position. When the para position is occupied, the reaction proceeds at the ortho position relative to the amino group, and if the ortho and para positions are occupied, the reaction does not occur. Aminoalkylation also does not occur when acceptor substituents are introduced into the ring and into the nitrogen of the amino group. The acridine residue adds to the β-position in the reaction with α-naphthylamine.

EXPERIMENTAL

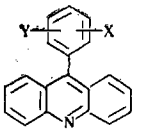
The dielectric permeabilities of dilute benzene solutions were measured at 25°C by the heterodyne method with a Tangens precision capacitance measurer. The refractive indexes of the same solutions were measured with an IRF-22 refractometer. The experimental dipole moments were calculated from the Guggenheim equation [6]. The theoretical dipole moments were calculated via the vector-additive scheme with allowance for the geometry of the acridine molecule, and the angle of rotation of the benzene ring relative to the plane of the acridine system was taken as 60° [7]. Thin-layer chromatography was performed on activity II aluminum oxide with elution by chloroform.

Preparation of 9-Aminoarylacridines. A mixture of 0.1 mole of acridine hydrochloride, 0.15-0.2 mole of arylamine, and 0.3 g-atom of sulfur was stirred at 120-140° until the reaction mass no longer thickened and hydrogen sulfide evolution decreased appreciably. The mixture was then cooled, and the resinous melt was washed with ether and treated three times with 10% hydrochloric acid. The acid extracts were neutralized with ammonia, and the resulting precipitate was filtered, dried, and crystallized (Table 1). The residue from the acid extraction was dissolved in concentrated hydrochloric acid, and the sulfur was removed by filtration. The filtrate was diluted with water, and the precipitated thioacridone was removed by filtration and dried.

Methylation of 9-Aminoarylacridines. A 0.005 mole sample of 9-aminoarylacridine was dissolved in 15 ml of methanol containing 1.5 g of KOH. A 0.01 mole sample of dimethyl sulfate was added carefully, and the mixture was refluxed for 45 min. The precipitate was removed by filtration, dried, and crystallized.

Deamination of 9-Aminoarylacridines. A 0.005 mole sample of 9-aminoarylacridine was diazotized in the usual way [8], 80 ml of ethanol was added to the diazonium salt solution, and the mixture was re-

TABLE 1. 9-Aminoarylacridines



Compound	Starting arylamine	X, Y	Reaction temp., °C	Reaction time, h	Mp, °C (crystallization solvent)	R_f	Empirical formula	Found, %			Calc., %			μ exp	μ th	Yield, %	
								C	H	N	C	H	N			9-aminoarylacridine	thioacridone
I	m-Toluidine	2-CH_3-4-NH_2	120	4,5	233—234 (propanol)	0,17	$C_{20}H_{16}N_2$	84,3	6,0	10,3	84,5	5,7	9,9			70	20
II	o-Toluidine	3-CH_3-4-NH_2	125	2	290—292 (propanol)	0,21	$C_{20}H_{16}N_2$	84,8	5,7	10,0	84,5	5,7	9,9	3,90	3,45	90	8
III	p-Toluidine	2-NH_2-5-CH_3	125—135	7	235—236 (propanol)	0,15	$C_{20}H_{16}N_2$	84,7	5,7	10,1	84,5	5,7	9,9	2,72	2,84	25	43
IV	N,N-Dimethyl-o-toluidine	3-CH_3-4-$N(CH_3)_2$	125—135	1	285—287 (propanol)	0,27	$C_{22}H_{20}N_2$	84,8	6,3	9,0	84,6	6,4	9,0			80	10
V	N,N-Dimethyl-m-toluidine	2-CH_3-4-$N(CH_3)_2$	125—135	4,5	221—223 (xylene)	0,31	$C_{22}H_{20}N_2$	84,3	6,2	9,3	84,6	6,4	9,0			66	28
VI	m-Chloroaniline	2-Cl-4-NH_2	125—135	4	250—251 (propanol)	0,28	$C_{19}H_{13}N_2Cl$	74,8	4,4	9,0	74,9	4,2	9,2	4,53	4,29	32	34,5
VII	m-Aminophenol	2-OH-4-NH_2	135	1	344—346 (xylene)	—	$C_{19}H_{14}N_2O$	79,9	4,9	9,7	79,7	4,9	9,8			95	4
VIII	o-Aminophenol	3-OH-4-NH_2	135	1	304—306 (xylene)	—	$C_{19}H_{14}N_2O$	79,8	5,2	10,0	79,7	4,9	9,8			85	None
IX	o-Anisidine	3-OCH_3-4-NH_2	125	2,5	243—244 (xylene)	0,19	$C_{20}H_{16}N_2O$	80,1	5,3	9,1	80,0	5,4	9,3	3,64	3,45	84	4
X	N,N-Dimethyl-o-anisidine	3-OCH_3-4-$N(CH_3)_2$	120	3	242—243 (xylene)	0,20	$C_{22}H_{20}N_2O$	80,1	5,9	9,0	80,4	6,1	8,6			86	0,5
XI	N,N-Dimethyl-m-anisidine	2-OCH_3-4-$N(CH_3)_2$	125	2	234—236 (propanol)	0,20	$C_{22}H_{20}N_2O$	80,0	6,3	8,8	80,4	6,1	8,6			91	1
XII	m-Phenylenediamine	2,4-$(NH_2)_2$	130	1	294—296 (xylene)	0,12	$C_{19}H_{15}N_3$	80,0	5,2	14,8	80,0	5,3	14,7			91	1
XIII	o-Phenylenediamine	3,4-$(NH_2)_2$	135	1	279—281 (xylene)	0,07	$C_{19}H_{15}N_3$	80,2	5,7	14,6	80,0	5,3	14,7			80	None
XIV	4-Aminodiphenyl	2-NH_2-5-C_6H_5	130—140	4	259—260 (ethanol)	—	$C_{25}H_{18}N_2$	86,5	5,5	7,8	86,7	5,2	8,1			15	45
XV	α-Naphthylamine	2-NH_2=3,4-benzo	120	1,5	305—307 (DMF)	0,16	$C_{23}H_{16}N_2$	86,0	5,3	9,1	86,2	5,0	8,7			85	5

fluxed for 1 h. The solution was cooled, diluted with an equal volume of water, and treated with excess ammonia. The precipitated 9-arylacridine was removed by filtration, dried, and crystallized.

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