INVESTIGATION OF NAPHTHYRIDINES

VI.* METHOD FOR THE SYNTHESIS OF 9-AMINO-4-AZAACRIDINES

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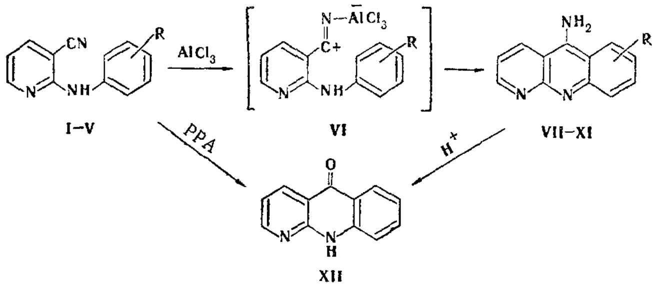
A method for the synthesis of 9-amino-4-azaacridines by cyclization of 2-arylaminonicotinonitriles by heating with aluminum chloride is proposed. The 2-arylaminonicotinonitriles were obtained by condensation of 2-chloronicotinonitrile with arylamines.

2-Arylaminonicotinonitriles (I-V, Table 1) were obtained in the present research by reaction of 2-chloronicotinonitrile with arylamines in order to study the possibility of the synthesis from them of 9-amino-4-azaacridines, which are of interest as potential physiologically active substances. Despite the data in [2], the reaction of 2-chloronicotinonitrile proceeds successfully with arylamine bases but not with their salts.



We were able to accomplish the cyclization of I-V to 9-amino-4-azaacridines (VII-XI, Table 2) by heating them with anhydrous aluminum chloride. Attempts to cyclize nitrile I by means of polyphosphoric acid (PPA) gave 4-aza-9-acridone (XII).

The structure of VII-XI was confirmed by analytical data and hydrolytic cleavage of derivative VII to give 4-aza-9-acridone. Because of the low solubility of the products in most solvents, the IR spectrum was obtained only for a solution of VII in chloroform; the spectrum of this solution contains NH_2 bands at 3450 and 3380 cm^{-1}.

The cyclization of nitriles I-V is apparently an intramolecular electrophilic substitution reaction that proceeds through a step involving the formation of ionic complex VI, in which the positively charged carbon atom attacks the adjacent benzene ring.

EXPERIMENTAL

2-Arylaminonicotinonitriles (I-V). A mixture of 0.01 mole of 2-chloronicotinonitrile [3] and 0.01 mole of arylamine was heated at 150-180° for 20-30 min, after which it was treated with hot water, and the residue was crystallized from methanol.

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*See [1] for communication V.

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TABLE 1. 2-Arylaminonicotinonitriles (I-V)

Compound	R	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
				C(Hal)	H	N	C(Hal)	H	N	
I	H	129[2]	$C_{12}H_9N_3$	—	—	—	—	—	—	43
II	*p*-CH_3	114—115	$C_{13}H_{11}N_3$	74,5	5,3	20,0	74,6	5,3	20,1	41
III	*o*-CH_3	102—103	$C_{13}H_{11}N_3$	74,6	5,5	20,1	74,6	5,3	20,1	56
IV	*p*-Br	141—142	$C_{12}H_8BrN_3$	(29,5)	—	15,1	(29,2)	—	15,3	58
V	*p*-Cl	135—137	$C_{12}H_8ClN_3$	(15,5)	—	18,0	(15,3)	—	18,3	55

TABLE 2. 9-Amino-4-azaacridines (VII-XI)

Compound	R	mp, °C	Empirical formula	Found*				Calculated				Yield, %
				C, %	H, %	N, %	*M*	C, %	H, %	N, %	*M*	
VII	H	277—280	$C_{12}H_9N_3$	73,8	4,8	21,8	205,5	73,9	4,6	21,5	195,1	42
VIII	7-CH_3	295—297	$C_{13}H_{11}N_3$	74,6	5,2	19,8	211	74,6	5,3	20,1	209	57
IX	5-CH_3	278—280	$C_{13}H_{11}N_3$	74,7	5,2	20,0	218,9	74,6	5,3	20,1	209	45
X	7-Br	300—301	$C_{12}H_8BrN_3$	—	—	15,2	280	—	—	15,3	274	50
XI	7-Cl	308—309	$C_{12}H_8ClN_3$	—	—	18,3	233,7	—	—	18,3	229,6	65

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*In the case of VII and XI, 2 and 2.1% active hydrogen are found, respectively.

9-Amino-4-azaacridines (VII-XI). A 1.5-g sample of anhydrous aluminum chloride was added to 0.01 mole of 2-arylaminonicotinonitrile, and the mixture was heated at 180-200° for 30-40 min. It was then decomposed in the cold with 10% HCl solution, and excess 30% NaOH solution was added. The resulting precipitate was removed by filtration and crystallized from ethanol.

4-Aza-9-acridone (XII). A mixture of 0.01 mole of 2-anilinonicotinonitrile and 10 ml of polyphosphoric acid was heated at 150° for 5 h, after which it was diluted with water and neutralized with 10% ammonium hydroxide. The resulting precipitate was crystallized from methanol to give 0.45 g (45%) of 4-aza-9-acridone with mp 278-279° [4]. A mixture of this product with VII melted at 250°.

Hydrolysis of VII. A solution of 0.7 g of VII in 10 ml of 15% HCl was refluxed on a sand bath for 5 h, after which it was cooled and neutralized with 10% ammonium hydroxide. The resulting precipitate was removed by filtration and crystallized from methanol to give 0.24 g (34%) of a product with mp 278-279°. No melting-point depression was observed for a mixture of this product with a sample of XII obtained in the preceding experiment.

LITERATURE CITED

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