# INVESTIGATION OF NAPHTHYRIDINES

## IV.* ARYLAMIDES OF 2-ANILINONICOTINIC ACID AND CYCLIZATION OF THEM TO 4-ARYLAMINO-2,3-BENZO-1,8-NAPHTHYRIDINES

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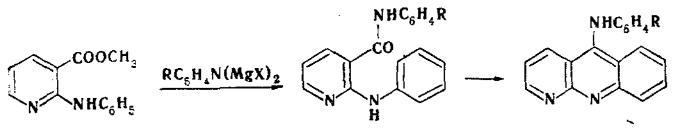
The corresponding arylamides were obtained from methyl 2-anilinonicotinate and dimagnesylamines, and the amides were converted to 4-arylamino-2,3-benzo-1,8-naphthyridines by the action of phosphorus oxychloride. The p$K_a$ values of the 2-anilinonicotinic acid arylamides were determined.

Substituted 4-amino-2,3-benzo-1,8-naphthyridines – analogs of the widely known 9-aminoacridines – are of interest as potential physiologically active substances. Such compounds have not been described in the literature. The present research is devoted to the synthesis of 4-arylamino-2,3-benzo-1,8-naphthyridines from 2-anilinonicotinic acid arylamides.



I–X XI–XVII

2-Anilinonicotinic acid arylamides (I-X, Table 1) were obtained in good yields by reaction of aryldimagnesylamines with methyl 2-anilinonicotinate. A $\nu_{CO}$ band at 1638 ± 2 cm$^{-1}$ is observed in the IR spectra of I-X. The UV spectra contain two maxima at 290-294 and 353-357 nm. The p$K_a$ values of arylamides I-VII in ethanol are close to one another and range from 2.48 to 2.72 p$K_a$ units. Because of the remoteness of the radical of the arylamide portion of the molecule from the nitrogen atom of the pyridine ring, its effect on the basicity is insignificant.

4-Arylamino-2,3-benzo-1,8-naphthyridines (XI-XVII, Table 2) are formed in satisfactory yields when I-V, VIII, and IX are refluxed in excess phosphorus oxychloride. It should be noted that 2-anilinonicotinic acid arylamides, in contrast to N-phenylanthranilic acid anilide [2], undergo cyclization with much greater difficulty. This is apparently associated with the decrease in the electron density on the phenyl group (the nucleophilic center of the reaction) due to the electron-acceptor properties of the protonated pyridine ring.

The structure of naphthyridines XI-XVII was confirmed by the IR spectra, in which the band of a secondary amino group is observed at 3426-3449 cm$^{-1}$ and, in contrast to the spectra of arylamides I-X, the band of a carbonyl group is absent.

## EXPERIMENTAL

The IR spectra of 0.005 M solutions of the compounds in carbon tetrachloride were recorded with an IKS-14 spectrometer.

The ionization constants of the 2-anilinonicotinic acid arylamides were determined potentiometrically by titration, with an 0.1 N ethanol solution of perchloric acid, of 0.01 M solutions of I-VII in ethanol (with an LPM-60M potentiometer). The p$K_a$ values were calculated by the method in [3].

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*See [1] for communication III.

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TABLE 1. 2-Anilinonicotinic Acid Arylamides (I-X)

| Compound | R | mp, deg C | Empirical formula | N, % |  | pK$_a$, in ethanol |  |
|---|---|---|---|---|---|---|---|
|  |  |  |  | found | calc. |  |  |
| I | H | 185—187 | $C_{18}H_{15}N_3O$ | 14,6 | 14,5 | 2,56±0,06 | 62 |
| II | *m*-$CH_3$ | 173—174 | $C_{19}H_{17}N_3O$ | 13,9 | 13,9 | 2,62±0,04 | 64 |
| III | *p*-Cl | 168—170 | $C_{18}H_{14}ClN_3O$ | 12,9 | 13,0 | 2,48±0,06 | 78 |
| IV | *p*-$CH_3O$ | 170—172 | $C_{19}H_{17}N_3O_2$ | 13,2 | 13,2 | 2,52±0,05 | 46 |
| V | *m*-$CH_3O$ | 163—164 | $C_{19}H_{17}N_3O_2$ | 13,3 | 13,2 | 2,68±0,02 | 83 |
| VI | *m*-Cl | 206—207 | $C_{18}H_{14}ClN_3O$ | 12,9 | 13,0 | 2,58±0,04 | 44 |
| VII | *p*-$CH_3$ | 170—172 | $C_{19}H_{17}N_3O$ | 14,0 | 13,9 | 2,72±0,03 | 50 |
| VIII | *o*-Cl | 174—176 | $C_{18}H_{14}ClN_3O$ | 13,0 | 13,0 | — | 72 |
| IX | *p*-Br | 183—184 | $C_{18}H_{14}BrN_3O$ | 11,5 | 11,4 | — | 69 |
| X | *o*-$CH_3O$ | 138—140 | $C_{19}H_{17}N_3O_2$ | 13,3 | 13,2 | — | 42 |

TABLE 2. 4-Arylamino-2,3-benzo-1,8-naphthyridines (XI-XVII)

| Compound | R | mp, deg C | Empirical formula | N, % |  | Yield, % |
|---|---|---|---|---|---|---|
|  |  |  |  | found | calc. |  |
| XI | H | 274—276 | $C_{18}H_{13}N_3$ | 15,6 | 15,5 | 47 |
| XII | *m*-$CH_3$ | 269—270 | $C_{19}H_{15}N_3$ | 14,8 | 14,7 | 44 |
| XIII | *p*-Cl | 278—280 | $C_{18}H_{12}ClN_3$ | 13,6 | 13,7 | 27 |
| XIV | *p*-$CH_3O$ | 225—228 | $C_{19}H_{15}N_3O$ | 13,7 | 13,9 | 24 |
| XV | *m*-$CH_3O$ | 290—292 | $C_{19}H_{15}N_3O$ | 13,9 | 13,9 | 23 |
| XVI | *o*-Cl | 276—279 | $C_{18}H_{12}ClN_3$ | 13,9 | 13,7 | 21 |
| XVII | *p*-Br | 280—283 | $C_{18}H_{12}BrN_3$ | 11,9 | 12,0 | 19 |

2-Anilinonicotinic Acid Arylamides (I-X). A solution of 0.02 mole of methyl 2-anilinonicotinate in 30 ml of absolute ether was added to 0.05 mole of dimagnesylamine, and the mixture was heated for 1.5 h. It was then decomposed with a saturated ammonium chloride solution, and the ether layer was worked up by steam distillation. The residue was crystallized from ethanol. Arylamides I-X were obtained as colorless crystalline substances that were soluble in the usual organic solvents (Table 1).

4-Arylamino-2,3-benzo-1,8-naphthyridines (XI-XVII). A 0.005 mole sample of arylamide I-V, VIII, or IX was added to 5 ml of phosphorus oxychloride, and the mixture was refluxed for 10 h. The excess phosphorus oxychloride was removed by vacuum distillation, and 10-15 ml of ice water was added to the residue. The aqueous mixture was neutralized with 10% sodium hydroxide solution, and the precipitate was removed by filtration and crystallized from aqueous pyridine. Naphthyridines XI-XVII were obtained as yellowish crystalline substances that were only slightly soluble in the usual organic solvents (Table 2).

## LITERATURE CITED

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