RESEARCH ON NAPHTHYRIDINES

I. SYNTHESIS OF (2-AMINO-3-PYRIDYL)DIPHENYLCARBINOLS AND THEIR CYCLIZATION TO 4-PHENYL-2,3-BENZO-1,8-NAPHTHYRIDINES

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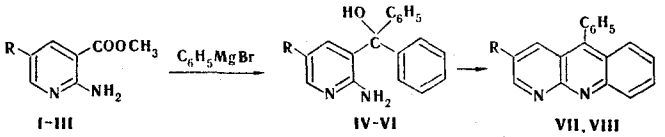
(2-Amino-3-pyridyl)diphenylcarbinols, obtained from esters of the corresponding 2-aminonicotinic acids by means of the Grignard reaction, are cyclized to 4-phenyl-2,3-benzo-1,8-naphthyridines on refluxing in nitrobenzene.

The search for new methods for the synthesis of difficult-to-obtain [1] naphthyridines and their derivatives is of both practical and theoretical interest. In the present study we have synthesized (2-amino-3-pyridyl)diphenylcarbinols with the aim of cyclizing them to 4-phenyl-2,3-benzo-1,8-naphthyridines via the scheme proposed for the preparation of acridines [2].

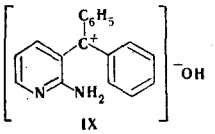
(2-Amino-3-pyridyl)diphenylcarbinols IV-VI were obtained from methyl 2-aminonicotinate (I) and its 5-chloro and 5-bromo derivatives (II, III) and phenylmagnesium bromide.



I, IV, VII R = H; II, V, VIII R = Cl; III, VI R = Br

2,3-Benzo-1,8-naphthyridines VII and VIII are formed as a consequence of intramolecular cyclization when carbinols IV and V are refluxed in nitrobenzene. We were unable to cyclize VI.

In contrast to the starting carbinols, benzonaphthyridines VII and VIII do not have bands of the stretching vibrations of amino and hydroxyl groups in their IR spectra and do not give halochromic salts with concentrated sulfuric acid.



IX

In the light of concepts regarding the mechanism of cyclization of 2-aminotriphenylcarbinol to 9-phenylacridine [2], it can be assumed that cyclization of alcohols IV and V proceeds through a step involving the formation of ionic complex IX. The success of the reaction is determined by the magnitude of the charge on the carbonium carbon atom and the degree of nucleophilicity of the amino group. Because of conjugation with the pyridine ring, the amino group in (2-amino-3-pyridyl)diphenylcarbinols is much less nucleophilic than the amino group in 2-aminotriphenylcarbinols. Because of this, (2-amino-3-pyridyl)diphenylcarbinols are less inclined to undergo cyclization than their benzene analog; this is confirmed by the experiments performed.

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EXPERIMENTAL

Methyl 2-Amino-5-chloronicotinate (II). A 10-ml sample of 30% hydrogen peroxide was added to a solution of 0.1 mole of ester I [3] in 75 ml of 35% hydrochloric acid, and the mixture was held at 55-60° for 2 h. It was then diluted with water and neutralized with 10% sodium carbonate solution. The precipitate was removed by filtration to give a product with mp 133-134° (from ethanol) in 50% yield. Found,%: N 14.9. $C_7H_7ClN_2O_2$. Calculated,%: N 15.0.

Methyl 2-Amino-5-bromonicotinate (III). A solution of 5.2 ml of bromine in 20 ml of glacial acetic acid was poured into a solution of 0.1 mole of ester I in 20 ml of glacial acetic acid. When the bromine color disappeared, the mixture was diluted with water, and the precipitated III was worked up in the usual manner to give a product with mp 148° (from ethanol) in 70% yield. Found,%: Br 34.3; N 12.3. $C_7H_7BrN_2O_2$. Calculated,%: Br 34.6; N 12.1.

(2-Amino-3-pyridyl)diphenylcarbinol (IV). An ether solution of 0.025 mole of ester I was added to phenylmagnesium bromide, obtained from 0.1 mole of bromobenzene and 0.1 g-atom of magnesium, and the mixture was heated for 2 h and decomposed with a saturated solution of ammonium chloride. The ether layer was separated and treated with steam. The residue was crystallized from ethanol to give 4.85 g (70%) of carbinol IV with mp 133-134°. IR spectrum (0.005 M solution in CCl_4): 3615, 3440 (free and intramolecularly bonded hydroxyl groups), 3506, 3412, 3348 cm^{-1} (amino group). Found,%: N 10.2; H_{act} 3.0; Mol. wt. 279. $C_{18}H_{16}N_2O$. Calculated,%: N 10.1; H_{act} 3.0; Mol. wt. 276.

Similarly obtained were (2-amino-5-chloro-3-pyridyl)diphenylcarbinol [in 63% yield, mp 174-176° (from ethanol)]. IR spectrum: 3611, 3440 (hydroxyl group), 3503, 3416, 3348 cm^{-1} (amino group). Found, %: Cl 11.1; N 8.7. H_{act} 3.0; Mol. wt. 305. $C_{18}H_{15}ClN_2O$. Calculated,%: Cl 11.4; N 9.0; H_{act} 3.0; Mol. wt. 311, and (2-amino-5-bromo-3-pyridyl)diphenylcarbinol (VI) [in 64% yield, mp 187-189° (from ethanol). IR spectrum: 3611, 3440 (hydroxyl group), 3518, 3348 cm^{-1} (amino group). Found,%: Br 22.8; N 7.8; H_{act} 3.0; Mol. wt. 363. $C_{18}H_{15}BrN_2O$. Calculated,%: Br 22.5; N 7.9; H_{act} 3; Mol. wt. 355].

4-Phenyl-2,3-benzo-1,8-naphthyridine (VII). A mixture of 1 g of IV and 2 ml of nitrobenzene was heated on a metal bath at 210-215° for 2 h, after which the nitrobenzene was removed by steam distillation, and the residue was dissolved in dilute hydrochloric acid. The solution was filtered and neutralized with 10% ammonium hydroxide, and the liberated base (VII) was crystallized from ethanol to give 0.6 g (64%) of a product with mp 208-210°. Found,%: N 10.8; Mol. wt. 260. $C_{18}H_{12}N_2$. Calculated,%: N 10.9; Mol. wt. 256.

Under similar conditions, 0.5 g (54%) of 4-phenyl-6-chloro-2,3-benzo-1,8-naphthyridine (VIII) with mp 248-250° (from ethanol) was obtained from 1 g of carbinol V. Found,%: N 9.5; Mol. wt. 287. $C_{18}H_{11}ClN_2$. Calculated,%: N 9.7; Mol. wt. 290.

LITERATURE CITED

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3. A. Philips, Ann., 288, 253 (1895).