INVESTIGATION OF NAPHTHYRIDINES.

12.* SYNTHESIS OF SUBSTITUTED 5-OXO-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINES BY CYCLIZATION OF 2-STYRYLNICOTINIC ACID AMIDES

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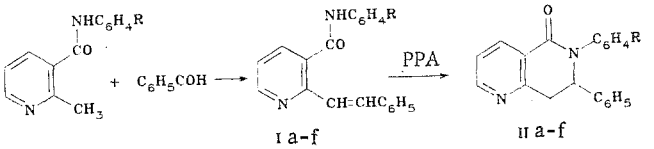
Substituted amides of 2-styrylnicotinic acid were obtained by condensation of 2-methylnicotinic acid arylamides with benzaldehyde, and it was found that they undergo cyclization to 5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridine derivatives when they are heated in polyphosphoric acid.

1,6-Naphthyridines are of interest for investigation in comparison with quinolines and also as biologically active compounds [2-4]. 5-Oxo-5,6,7,8-tetrahydro-1,6-naphthyridines have not been investigated. In [5] it was shown that 4-styrylnicotinamide undergoes cyclization to a 2,7-naphthyridine derivative when it is heated in polyphosphoric acid (PPA). The yield of the product was not indicated, and the reaction is the only example of this sort of cyclization. In the present paper we describe 2-styrylnicotinic acid arylamides (Ia-f, Table 1), which were obtained in order to ascertain the possibility of the synthesis of substituted 1,6-naphthyridines from them. Experiments showed that the synthesis of amides Ia-f can be realized by a previously proposed method for the preparation of stilbazole [6] by heating 2-methylnicotinic acid arylamides with benzaldehyde in the presence of benzoyl chloride in dimethylformamide (DMF). Attempts to carry out the reaction in acetic anhydride or in the presence of alkaline condensation catalysts (piperidine) were unsuccessful.



I a-f II a-f

Ia, IIa R=H; Ib, IIb R=*m*-CH_3; Ic, IIc R=*p*-CH_3; Id, IId R=*p*-CH_3O; Ie, IIe R=*p*-Cl; If, IIe R=*p*-Br

Amides Ia-f are colorless crystalline substances, the IR spectra of which contain absorption bands at 1690-1695 (CO), 3430-3440 (NH), and 3050-3065 cm^{-1} (CH). The signals of the chemical shifts of the protons (δ) in the PMR spectra of these amides are represented by a multiplet centered at 7.1-7.5 ppm (H of the aromatic rings and the CH=CH group), a doublet at 8.06-8.66 ppm [1H attached to the pyridine $C_{(6)}$ atom], and a singlet at 10.56 ppm (amide group 1H).

Intramolecular cyclization to give 6-aryl-5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridines (IIa-f, Table 2), the compositions and structures of which were confirmed by the results of elementary analysis and spectral data, is observed when amides Ia-f are heated in PPA (135°C) for 3.5 h. The IR spectra of naphthyridines IIa-f contain absorption bands at 1660-1675 (CO) and 2900-2915 cm^{-1} (CH_2) but, in contrast to the spectra of starting amides Ia-f, do not contain a band of the NH bond of an amide group. Signals of chemical shifts of protons at 3.36-3.76 ppm [2H attached to the $C_{(8)}$ atom], 5.13-5.23 ppm [1H attached to the $C_{(7)}$ atom], and 8.33-8.43 ppm [1H attached to the $C_{(2)}$ atom] are present in the PMR spectra of IIa-f; a multiplet at 7.09-7.26 ppm (H of the aromatic and pyridine rings) is also observed.

*See [1] for communication 11.

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TABLE 1. 2-Styrylnicotinic Acid Arylamides

Compound	R	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
Ia	H	172—173	80,21	5,55	9,47	$C_{20}H_{16}N_2O$	80,00	5,33	9,33	31
Ib	*m*-CH_3	172—173	80,46	5,75	8,96	$C_{21}H_{18}N_2O$	80,25	5,73	8,91	44
Ic	*p*-CH_3	160—162	80,07	5,81	9,23	$C_{21}H_{18}N_2O$	80,25	5,73	8,91	33
Id	*p*-CH_3O	171—172	76,48	5,61	8,25	$C_{21}H_{18}N_2O_2$	76,36	5,45	8,48	37
Ie	*p*-Cl	159—161	—	—	8,49	$C_{20}H_{15}ClN_2O$[a]	—	—	8,37	31
If	*p*-Br	179—181	—	—	7,55	$C_{20}H_{15}BrN_2O$[b]	—	—	7,38	60

[a]Found: Cl 10.64%. Calculated: Cl 10.61%. [b]Found: Br 21.22%. Calculated: Br 21.10%.

TABLE 2. 6-Aryl-5-oxo-7-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridines

Compound	R	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	H	144—146	80,19	5,48	9,51	$C_{20}H_{16}N_2O$	80,00	5,33	9,33	33
IIb	*m*-CH_3	125—126	80,50	5,89	8,71	$C_{21}H_{18}N_2O$	80,25	5,73	8,91	33
IIc	*p*-CH_3	145—147	80,43	5,89	8,60	$C_{21}H_{18}N_2O$	80,25	5,73	8,91	83
IId	*p*-CH_3O	98—99	76,53	5,66	8,31	$C_{21}H_{18}N_2O_2$	76,36	5,45	8,48	30
IIe	*p*-Cl	45—46	—	—	8,51	$C_{20}H_{15}ClN_2O$[a]	—	—	8,37	30
IIf	*p*-Br	106—108	—	—	7,57	$C_{20}H_{15}BrN_2O$[b]	—	—	7,38	44

[a]Found: Cl 10.43%. Calculated: Cl 10.61%. [b]Found: Br 21.35%. Calculated: Br 21.10%.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The PMR spectra of solutions in deuterochloroform were recorded with an Rya-2310 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

2-Styrylnicotinic Acid Arylamides (Ia-f). A solution of 16 mmole of the 2-methylnicotinic acid arylamide [7], 15.4 mmole of benzoyl chloride, and 16.6 mmole of benzaldehyde in 7 ml of DMF was heated at 155°C for 5 h, after which it was decomposed with concentrated HCl. The benzoic acid that formed during hydrolysis and the benzaldehyde were removed by steam distillation, and the precipitate in the distilling flask was separated, washed with hot water to remove the inorganic salts, and crystallized from ethanol.

6-Aryl-5-oxo-7-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridines (IIa-f). A mixture of 15 g of PPA containing 80-84% P_2O_5 and 1 mmole of the corresponding 2-styrylnicotinic acid arylamide was heated at 135°C for 3.5 h, after which it was poured into 50 ml of ice water, and the aqueous mixture was mixed with 10 ml of chloroform. The acidic layer was neutralized with sodium carbonate, and the mixture was extracted with chloroform. The residue was crystallized from hexane—benzene (1:1).

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