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INVESTIGATION OF NAPHTHYRIDINES. 16*. SYNTHESIS OF DERIVATIVES OF 2,5-DIOXO-1,2,5,6,7,8-HEXAHYDRO-1,6-NAPHTHYRIDINE-3-CARBOXYLIC ACIDS FROM ANILIDES (HYDRAZIDES) OF 6-OXO-2-STYRYLNICOTINIC ACIDS

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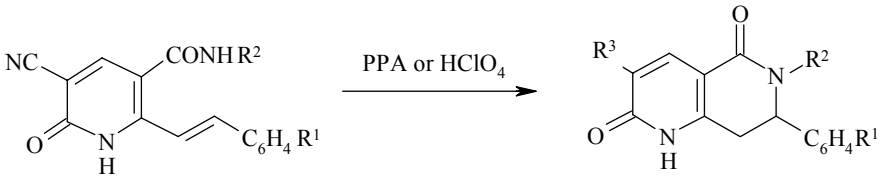
Heating anilides (hydrazides) of 5-cyano-6-oxo-2-styrylnicotinic acids in polyphosphoric acid (PPA) leads to amides of 7-aryl-2,5-dioxo-6-phenyl(amino)-1,2,5,6,7,8-hexahydro-1,6-naphthyridine-3-carboxylic acids, which on heating with perchloric acid in acetic acid give the corresponding acids.

Keywords: anilides, hydrazides, 2,5-dioxo-1,2,5,6,7,8-hexahydro-1,6-naphthyridines, 6-oxo-2-styrylnicotinic acids, cyclization.

Amides of 2-styrylnicotinic acid are cyclized on heating in PPA into derivatives of 5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridine [2]. The aim of the present work was to extend the limits of this reaction and to obtain new derivatives of 1,6-naphthyridine from anilides and hydrazides of 5-cyano-6-oxo-2-styrylnicotinic acid.

The investigations showed that ring closure in compounds **1a-d** occurs on heating them in PPA at 165°C for 3 h. Amides of 7-aryl-2,5-dioxo-6-phenyl(amino)-1,2,5,6,7,8-hexahydro-1,6-naphthyridine-3-carboxylic acids **2a-d** were formed in this way (Table 1).



1a – f **2a – i**

1, 2 a R^1 = 4-Me_2N, R^2 = Ph; **b** R^1 = 3-Br, R^2 =Ph; **c** R^1 = 4-Me_2N, R^2 = NH_2; **d** R^1 = 3-Br, R^2 = NH_2; **e** R^1 = 4-MeO, R^2 = Ph; **1f** R^1 = 4-Br, R^2 = NH_2; **2 f** R^1 = 4-Me_2N, R^2 = Ph, **g** R^1 = 3-Br, R^2 = Ph, **h** R^1 = 4-Me_2N, R^2 = NH_2; **i** R^1 = 4-Br, R^2 = NH_2; **a-d** R^3 = $CONH_2$, **e-i** R^3 = COOH

* For Part 15 see [1].

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TABLE 1. Characteristics of Compounds **2a-i**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %	Antimicrobial activity, minimum inhibitory concentration (MIC), μg/ml	
		C	H	Br	N			*St. aureus*	*E. coli*
2a	$C_{23}H_{22}N_4O_3$	68.64 / 68.71	5.51 / 5.33	—	13.92 / 14.20	262-263	41		
2b	$C_{21}H_{16}BrN_3O_3$	57.58 / 57.79	3.68 / 3.39	18.24 / 18.52	9.59 / 9.76	216-218	44		
2c	$C_{17}H_{19}N_5O_3$	59.81 / 60.04	5.61 / 5.49	—	20.52 / 20.50	213-215	42	500	1000
2d	$C_{15}H_{13}BrN_4O_3$	47.76 / 48.00	3.47 / 3.27	21.18 / 20.90	14.85 / 14.63	259-262	37		
2e	$C_{22}H_{18}N_2O_5$	67.69 / 67.40	4.65 / 4.92	—	7.18 / 6.87	276-278	41	500	500
2f	$C_{23}H_{21}N_3O_4$	68.47 / 68.76	5.25 / 5.33	—	10.42 / 10.66	268-270	34	500	500
2g	$C_{21}H_{15}BrN_2O_4$	57.40 / 57.67	3.44 / 3.28	18.19 / 18.25	6.38 / 6.50	240-242	48	125	500
2h	$C_{17}H_{18}N_4O_4$	59.64 / 59.76	5.30 / 5.01	—	16.36 / 16.49	238-241	62	1000	1000
2i	$C_{15}H_{12}BrN_3O_4$	47.64 / 47.67	3.20 / 2.95	21.13 / 21.39	10.11 / 10.84	201-204	69	500	1000

The IR spectra of naphthyridines **2a-d**, unlike the spectra of the corresponding compounds **1a-d** [3], did not contain absorption bands for nitrile group but had absorption bands at 1668-1676 cm^{-1} (C=O amide) and also bands for the stretching vibrations of the amide N–H group at 3462-3480 cm^{-1}. In the ^1H NMR spectra of compounds **2**, in difference to the spectra of the initial anilides and hydrazides **1**, proton signals appeared at 7.19-7.67 (2H, br. s, $CONH_2$), 3.32-3.48 (2H, d, CH_2), and 5.37-5.52 ppm (1H, t, CH).

In the mass spectrum of compound **2a** the molecular ion 402* $[M]^{+\cdot}$ splits off a molecule of water and is converted into the 384 ion $[M-H_2O]^{+\cdot}$. Further fragmentation of this ion is linked either with loss of a molecule of HCN, which is characteristic of nitriles [4], or with detachment of phenylnitrene. Detachment of a molecule of HCN leads to the formation of the stable 357 ion, the intensity of the peak of which is 100%, which is probably determined by the distribution of the positive charge inside the formed aromatic pyridine ring. Fragmentation of the 357 ion proceeds in three directions (fission of $O\cdot$, $CO\cdot$, and CH_2=N–Me) with the formation of 341, 329, and 314 ions respectively. The latter eliminates either phenyl and gives a 237 ion or phenylnitrene and forms the 223 ion. On detachment of phenylnitrene from the 384 $[M-H_2O]^{+\cdot}$ ion the 293 ion is formed which sequentially eliminates hydrogen cyanide and a fragment of dimethylamine with the emergence of the stable 266 and 223 ions.

It was further established that 7-aryl-2-oxo-1,2,5,6,7,8-hexahydro-6-phenyl(amino)-1,6-naphthyridine-3-carboxylic acids **2e-i** were formed on heating a solution of stilbazoles **1a-c,e,f** in glacial acetic acid in the presence of perchloric acid.

The ^1H NMR spectra of naphthyridines **2e-i** differed from the spectra of compounds **1a-c,e,f** [3] by the absence of a broadened singlet for the NH_2 group at 7.19-7.67 ppm and by the presence of a singlet for the carboxyl group proton at 8.68-9.31 ppm, and in the IR spectrum by the presence of bands at 1704-1744 (C=O carboxyl group) and at 3555-3580 cm^{-1} (O–H).

The antimicrobial activity of compounds **2c,e-i** was studied in relation to *Staphylococcus aureus* and *Escherichia coli*. The minimum inhibitory concentration (MIC) was determined by serial dilution [5]. Ethacridine lactate was used as reference standard and inhibits growth of both *St. aureus* and *E. coli* at concentration of 500 μg/ml. The investigations showed that the majority of the compounds did not supersede the reference standard in activity towards *St. aureus* but compound **2g** was 4 times more potent.

EXPERIMENTAL

The IR spectra were obtained on a UR 20 instrument in CCl_4, c = 0.05 M (compound **2e**) and in nujol (remaining compounds). The ^1H NMR spectra were recorded on a PC 60 (60 MHz) spectrometer in DMSO-d_6, internal standard was HMDS (δ 0.05 ppm). The mass spectra were obtained on a MX 1303 instrument with direct insertion of samples into the ion source, ionizing voltage was 70 eV, reference standard was ^{200}Hg.

Amides of 6-Amino(phenyl)-7-aryl-2,5-dioxo-1,2,5,6,7,8-hexahydro-1,6-naphthyridine-3-carboxylic Acids 2a-d. The appropriate compound **1a-d** (0.01 mol) was heated with PPA (10 ml) for 3 h at 165°C. The mixture was poured into water (100 ml) and neutralized with ammonia solution. The solid was filtered off, and crystallized from dioxane (compound **2a**) or aqueous ethanol (compounds **2b-d**). IR spectrum, ν, cm^{-1}: 3366-3396, 3172-3194 ($CONH_2$), 3360-3480 (N–H), 1668-1684 ($C_{(3)}$–C=O), 1656-1672 ($C_{(2)}$=O), 1632-1664 ($C_{(5)}$=O); compounds **2c,d** 3272-3280, 3208 (NH_2). ^1H NMR spectrum, δ, ppm: 8.43-8.78 (1H, s, H-4); 7.25-7.65 (1H, s, NH); 7.19-7.67 (2H, s, $CONH_2$); 5.08-5.37 (1H, t, H-7); 3.32-3.50 (2H, d, H-8); compounds **2a,b** 6.96-7.42 (9H, m, arom.); compounds **2c,d** 6.68-7.00 (4H, m, C_6H_4); 3.77-4.18 (2H, s, NH_2). Mass spectrum of compound **2a**, m/z (I_{rel}, %): 402 (97) $[M]^{+\cdot}$, 384 (26), 357 (100), 341 (12), 329 (25), 314 (19), 293 (67), 266 (98), 237 (52), 223 (99), 183 (25), 146 (26), 134 (66).

* Here and subsequently m/z values are given for ion peaks.

6-Amino(phenyl)-7-aryl-1,5-dioxo-1,2,5,6,7,8-hexahydro-1,6-naphthyridine-3-carboxylic Acids 2e-i. The appropriate compound **1a-c,e,f** (0.01 mol) was added to freshly prepared solution (30 ml) of perchloric acid in glacial acetic acid with a small amount of acetic anhydride (perchloric acid content 10-12%). The mixture was heated at ~100°C for 2 h, poured into water (150 ml), and neutralized with sodium bicarbonate solution. The solid was filtered off and crystallized from aqueous DMF. IR spectrum, ν, cm^{-1}: 3530-3589 (COOH), 3372-3452 (N–H), 1704-1744 ($C_{(3)}$–C=O), 1642-1682 ($C_{(2)}$=O), 1620-1668 ($C_{(5)}$=O), compounds **2h,i** 3280-3288, 3206-3212 (NH_2). ^{1}H NMR spectrum, δ, ppm: 8.68-9.31 (H, s, COOH); 8.46-8.78 (1H, s, H-4); 7.07-7.65 (1H, s, NH); 5.05-5.55 (1H, t, H-7); 3.24-3.76 (2H, d, 2H-8); compounds **2e-g** 6.87-7.48 (9H, m, arom.); compounds **2h,i** 6.68-6.97 (4H, m, C_6H_4); 4.01-4.39 (2H, s, NH_2).

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