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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SUBSTITUTED 5-CYANO-6-OXO-2-STYRYLNICOTINIC ACIDS

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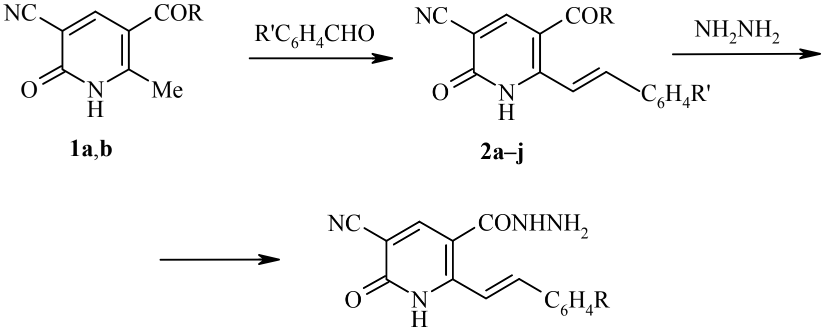
Derivatives of the anilide or ethyl ester of 5-cyano-6-oxo-2-styrylnicotinic acid are formed in the reaction of the anilide or ethyl ester of 5-cyano-2-methyl-6-oxonicotinic acid with aromatic aldehydes. On interaction with hydrazine hydrate the products are converted into hydrazides of 5-cyano-6-oxo-2-styrylnicotinic acid derivatives.

Keywords: anilides, hydrazides, 5-cyano-6-oxo-2-(substituted styryl)nicotinic acid, esters, antimicrobial activity, synthesis.

Amides and hydrazides of 2-styrylnicotinic acids are of interest as intermediates for the synthesis of 1,6-naphthiridines [1] and also as potential biologically active substances.

The present work was undertaken with the aim of clarifying the possibility of synthesizing derivatives of 5-cyano-6-oxo-2-styrylnicotinic acid by reacting the ethyl ester and anilide of 5-cyano-2-methyl-6-oxonicotinic acid with aromatic aldehydes and studying their antimicrobial activity.

The investigations showed that the ethyl ester and anilide of 5-cyano-2-methyl-6-oxonicotinic acid **1a,b** react with aromatic aldehydes on boiling (3 h) a solution of the starting materials in xylene in the presence of piperidine as catalyst or on boiling (8 h) in acetic anhydride.



1 a R = EtO, **b** R = PhNH; **2 a-e** R = EtO, **f-j** R = PhNH; **a** R' = 4-MeO, **b** R' = 4-Me$_2$N, **c** R' = 4-Br, **d** R' = 3-Br, **e** R'= 2-F, **f** R'= 4-MeO, **g** R' = 4-Me$_2$N, **h** R' = 4-Br, **i** R' = 3-Br, **j** R' = 2-F; **3 a** R = 4-MeO, **b** R = 4-Me$_2$N, **c** R = 4-Br, **d** R = 3-Br

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % Calculated, %				mp, °C	Yield, %
		C	H	N	Hal		
2a	$C_{18}H_{16}N_2O_4$	66.66 66.42	4.97 4.92	8.64 8.89		262-263	53
2b	$C_{19}H_{19}N_3O_3$	67.64 67.78	5.68 5.96	12.45 12.32		296-297	62
2c	$C_{17}H_{13}BrN_2O_3$	54.71 55.03	3.51 3.40	7.51 7.52	21.41 21.30	309-311	40
2d	$C_{17}H_{13}BrN_2O_3$	54.71 54.95	3.51 3.36	7.51 7.40	21.41 21.67	292-294	67
2e	$C_{17}H_{13}FN_2O_3$	65.38 65.50	4.20 4.01	8.97 8.94	6.08 6.32	260-262	48
2f	$C_{22}H_{17}N_3O_3$	71.15 71.20	4.61 4.44	11.31 11.45		277-279	56
2g	$C_{23}H_{20}N_4O_2$	71.86 72.13	5.24 5.37	14.57 14.46		210-212	72
2h	$C_{21}H_{14}BrN_3O_2$	60.02 59.81	3.36 3.69	10.00 10.28	19.01 19.30	274-276	71
2i	$C_{21}H_{14}BrN_3O_2$	60.02 60.31	3.36 3.23	10.00 9.73	19.01 19.28	291-293	66
2j	$C_{21}H_{14}FN_3O_2$	70.19 69.97	3.93 4.18	11.69 12.00	5.29 5.00	244-247	41
3a	$C_{16}H_{14}N_4O_3$	61.93 62.10	4.55 4.82	18.05 18.27		183-185	89
3b	$C_{17}H_{17}N_5O_2$	63.15 63.29	5.30 5.28	22.57 22.41		233-236	86
3c	$C_{15}H_{11}BrN_4O_2$	50.16 49.92	3.09 2.90	15.60 15.66	22.24 22.53	322-325	90
3d	$C_{15}H_{11}BrN_4O_2$	50.16 50.48	3.09 2.87	15.60 15.85	22.24 22.30	240-243	92

In both cases ethyl esters or anilides of substituted 5-cyano-6-oxo-2-styrylnicotinic **2a-j** are formed (see Table 1), but in the first case the reaction products were obtained in higher yield.

In the ^1H NMR spectra of compounds **2**, in difference to the spectra of compounds **1** (see Experimental), the signal for the methyl group protons disappeared and a multiplet for the aromatic protons was displayed (in the case of compounds **2f-j** the integrated intensity of this multiplet was increased) as were signals for the two protons of the ethylenic fragment at 7.28-7.60 ppm.

In the mass spectrum of compound **2g** a peak was observed for the molecular ion* with mass 384. Breakdown of the molecular ion was linked with fission of hydrogen and with conversion into a 382 ion which probably is obtained on cyclization due to the *ortho*-positioning of the dimethylaminostyryl residue and the heterocyclic nitrogen atom of the 384 ion, and has the structure of a benzo[1,2-*b*]quinolizine. Fission of a molecule of isocyanate from the 382 ion gives a 263 ion or eliminates aniline, undergoing a McLafferty rearrangement [2], and forms a 289 ion. The latter subsequently either splits off a molecule of CO or a dimethylamine fragment with the formation of 261 or 245 ions respectively.

It was shown that the synthesis of hydrazides of 5-cyano-6-oxo-2-styrylnicotinic acids **3a-d** may be carried out successfully on boiling ethyl esters **2a-d** with hydrazine hydrate in ethanol for 5-6 h. Only the ester group reacts and the nitrile is unchanged.

Four bands were observed in the IR spectrum of these compounds for the stretching vibrations of the N-H bond at 3250-3290, 3285-3315, 3310-3355, and 3405-3420 cm^{-1}. In the ^1H NMR spectrum of compounds **3a-d**, compared with the initial esters **2a-d**, the ethyl group signals had disappeared. A broadened signal appeared at 4.42-5.48 (1H, NH) and also a signal at 8.18-8.24 ppm (2H, NH_2).

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

The presence of antimicrobial activity for the hydrazides of 2-methyl-6-phenylnicotinic acid [3] was the basis for determining the activity of compounds **2f-j** and **3a-d***. The investigations were carried out in relation to standard strains of *Escherichia coli* and *Staphylococcus aureus* by serial dilution [4].

All the compounds studied displayed antimicrobial activity towards *Escherichia coli* and *Staphylococcus aureus* at concentrations of 500-1000 μg/ml, but hydrazide **3b** inhibited growth of the former culture at a dilution of 250 μg/ml, which is double the activity of ethacridine lactate. However it is half as active as the comparison standard on the culture of *Staphylococcus aureus.*

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument for compound **3a** in CCl_4 (c = 0.05 M), for **3b,c** in $CHCl_3$ (c = 0.05 M), and for the remainder in nujol. The ^{1}H NMR spectra were obtained on a RS-60 (60 MHz) spectrometer for compounds **2b,d** in $CDCl_3$, and for the remainder in DMSO-d_6, internal standard was HMDS. The mass spectra were obtained on a MX-1303 instrument with direct insertion of samples into the ion source at an ionizing voltage of 70 eV, the standard for comparison was ^{200}Hg.

5-Cyano-2-methyl-6-oxonicotinic Acid. Compound **1** (20.6 g, 0.1 mol) was boiled in a 15% NaOH solution in alcohol for 4 h. The mixture was poured into water (200 ml), and the solution acidified with acetic acid to a weakly acid reaction. The solid was filtered off, and crystallized from aqueous DMF. Yield 15.1 g (85%); mp 273-274°C. ^{1}H NMR spectrum, δ, ppm: 10.62 (1H, s, COOH); 8.38 (1H, s, =$C_{(4)}$–H); 8.20 (1H, s, NH); 2.58 (3H, s, Me). IR spectrum, ν, cm^{-1}: 3520 (O-H), 3445 (N–H), 2240 (C≡N), 1675 ($C_{(3)}$–C=O), 1625 ($C_{(6)}$=O). Found, %: C 53.94; H 3.39; N 15.72. $C_8H_6N_2O_3$. Calculated, %: C 54.13; H 3.26; N 16.01.

Anilide of 5-Cyano-2-methyl-6-oxonicotinic Acid (1b). Aniline (9.3 g, mol) and phosphorus oxychloride (10 ml, 16.7 g, 0.11 mol) was added to a solution of 5-cyano-2-methyl-6-oxonicotinic acid (17.8 g, 0.1 mol) in anhydrous dioxane (50 ml). The mixture was heated for 30 min, cooled, and poured into water (200 ml). The solution was neutralized with ammonia solution, the solid was filtered off, and crystallized from aqueous DMF. Yield 14.7 g (58%); mp 216-218°C. ^{1}H NMR spectrum, δ, ppm: 10.58 (1H, s, CONH); 8.68 (1H, s, =$C_{(4)}$–H); 7.78 (1H, s, NH); 7.45 (5H, m, Ph); 2.65 (3H, s, Me). IR spectrum, ν, cm^{-1}: 3270 (CON–H), 3390 (N–H), 2240 (C≡N), 1645 ($C_{(3)}$–C=O), 1620 ($C_{(6)}$=O). Found, %: C 66.40; H 4.38; N 16.59. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.27; H 4.22; N 16.46.

Ethyl Esters and Anilides of 5-Cyano-6-oxo-2-styrylnicotinic Acids (2a-j). A. A solution of compound **1a** or **1b** (0.01 mol) and substituted benzaldehyde (0.015 mol) in a mixture of xylene (10 ml) and piperidine (1 ml) was boiled for 3 h. The solvent and the excess of the benzaldehyde were steam distilled off, the solid was recrystallized from aqueous DMF (compounds **2a-g,i**) or a mixture of DMF–dioxane–water, 5:2:1 (compounds **2h,j**). ^{1}H NMR spectrum, δ, ppm: compounds **2a-e,** 8.42-8.52 (1H, s, =$C_{(4)}$–H); 7.78-7.91 (1H, s, NH), 7.42-7.60 (6H, m, Ph, –CH=CH–); 4.22-4.30 (2H, q, CH_2 in COOEt); 1.28-1.32 (3H, t, Me in COOEt); compounds **2f-j,** 10.32-10.40 (1H, s, CONH); 8.32-8.48 (1H, s, =$C_{(4)}$–H); 7.65-7.86 (1H, s, NH); 7.28-7.57 (11H, m, Ph, –CH=CH–). IR spectrum, ν, cm^{-1}: compounds **2a-e,** 3310-3340 (N–H), 2235-2240 (C≡N), 1700-1715 ($C_{(3)}$–C=O), 1650-1660 ($C_{(6)}$=O); compounds **2f-j,** 3290-3310 (N–H), 3260-3275 (PhNH), 2230-2240 (C≡N), 1620-1630 ($C_{(3)}$–C=O), 1645-1660 ($C_{(6)}$=O). Mass spectrum of compound **2g**, m/z (I_{rel}, %): 384 (97) $[M]^+$, 382 (100), 289 (99), 273 (17), 263 (68), 261 (49), 245 (20), 234 (45), 207 (36), 191 (45), 146 (33).

B. A solution of compound **1a** or **1b** (0.01 mol) and 3-bromobenzaldehyde (1.3 ml, 2.06 g, 0.011 mol) in acetic anhydride (5 ml) was boiled for 8 h. The mixture was poured into water (100 ml), the solution was neutralized, and the precipitated solid was crystallized sequentially from acetic acid and aqueous DMF. Compounds **2d** (yield 0.37 g, 10%) and **2i** (yield 1.97 g, 44%) were obtained.

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* Tests were carried out by G. N. Novoselova.

Hydrazides of 5-Cyano-6-oxo-2-styrylnicotinic Acids (3a-d). Hydrazine hydrate (7.5 ml, 0.1 mol) was added to a solution of the appropriate compound **2a-d** (0.01 mol) in ethanol (20 ml) and the mixture boiled for 6 h. The mixture was then poured into water (150 ml), the precipitated solid was filtered off, and crystallized from DMF. ^{1}H NMR spectrum, δ, ppm: 8.32-8.39 (1H, s, $=C_{(4)}$–H); 8.18-8.24 (2H, s, NH_2); 7.40-7.64 (1H, s, NH); 6.95-7.58 (6H, m, Ph, –CH=CH–). IR spectrum, ν, cm^{-1}: 3405-3420, 3310-3355, 3250-3290 ($NHNH_2$), 3285-3315 (N–H), 2230-2240 (C≡N), 1600-1620 ($C_{(3)}$–C=O), 1630-1635 ($C_{(6)}$=O).

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