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NITROPYRIDINES. 8.* SYNTHESIS OF SUBSTITUTED 5-NITRONICOTINAMIDES

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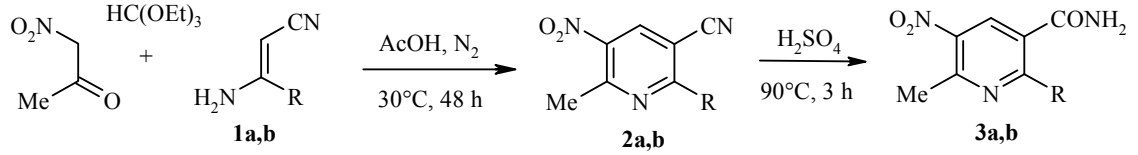
Previously unreported nitriles of 5-nitronicotinic acid were synthesized by various types of cyclocondensation using nitrocarbonyl compounds and their derivatives. The partial hydrolysis of these nitriles in concentrated sulfuric acid and in alkali solution in the presence of hydrogen peroxide leads to nitronicotinamides.

Keywords: enamines, 5-nitro-1,4-dihydropyridines, nitropyridines, 5-nitronicotinic acid nitriles, 5-nitronicotinamides.

Most substituted nicotinamides containing a nitro group at various positions of the pyridine ring display anticoccidial activity and are heterocyclic analogs of coccidine, an effective means against various types of bird-parasite coccidia [2, 3]. Substituted 2-nitro- and 5-nitronicotinamides display the greatest anticoccidial activity [4].

In the present work, a synthesis is described for previously unreported nitriles of 5-nitronicotinic acid and 5-nitronicotinamides.

A one-pot cyclocondensation of nitroacetone, ethyl orthoformate, and enamines **1a**,**b** described in our previous work [5] was used to prepare 3-cyano-5-nitropyridines **2a**,**b**.



1–3 **a** R = Me, **b** R = Ph

When nitroacetone is replaced by nitroacetophenone, the cyclocondensation with ethyl orthoformate and 3-aminocrotononitrile **1a** does not give the expected nitrile of 2-methyl-5-nitro-6-phenylnicotinic acid (**9c**), but rather leads to complete conversion to tar. Hence, nitropyridine **9c** was obtained in two steps by the Hantsch

* For Communication 7, see [1].

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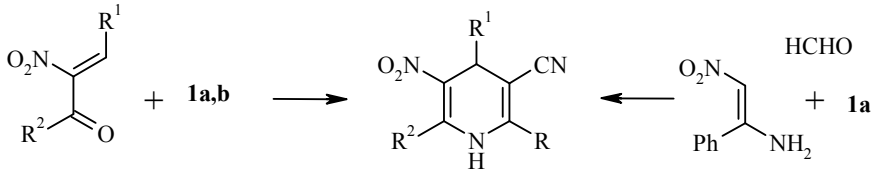
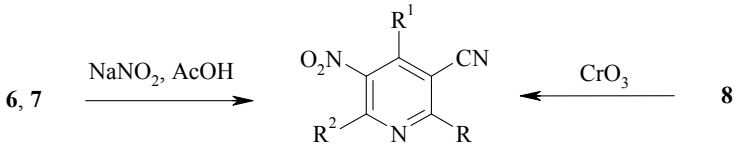
reaction involving cyclocondensation of nitroacetophenone, 3-aminocrotononitrile, and formaldehyde with subsequent aromatization of 1,4-dihydronitropyridine **8**. The two-component Hantsch synthesis also gave asymmetrical 1,4-dihydronitropyridines **6** and **7** with an aryl or hetaryl substituent at C-4 in the pyridine ring.



4, **5** **6–8**

4 R^1 = 2-Fur, R^2 = Me; **5** R^1 = *p*-$MeOC_6H_4$, R^2 = Ph; **6** R = Ph, R^1 = 2-Fur, R^2 = Me; **7** R = Me, R^1 = *p*-$MeOC_6H_4$, R^2 = Ph; **8** R = Me, R^1 = H, R^2 = Ph

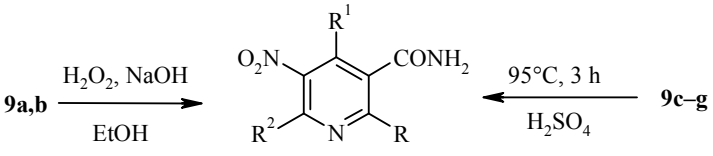
5-Nitronicotinic acid nitriles **9a,b** were synthesized by the oxidation of dihydropyridines **6** and **7** by sodium nitrite in acetic acid. The aromatization of 1,4-dihydropyridine **8** was carried out using chromic trioxide, CrO_3, as the oxidizing agent.



9a–c

9 **a** R = Ph, R^1 = 2-Fur, R^2 = Me; **b** R = Me, R^1 = *p*-$MeOC_6H_4$, R^2 = Ph; **c** R = Me, R^1 = H, R^2 = Ph

Cyanopyridines **9d-g** and nicotinamide **10d** were described in our previous work [1, 6, 7]. The partial hydrolysis of cyanopyridines **2a**,**b, 9c-g**, and **11** upon heating in concentrated sulfuric acid gave substituted amides of 5-nitronicotinic acid **3a**,**b, 10c-g**, and **12**. The synthesis of amides **10a**,**b** from nitriles **9a**,**b**, which contain an acidophobic furyl substituent at C-4 of the pyridine ring and a 4-methoxyphenyl substituent capable of sulfonation upon heating in sulfuric acid, was carried out by the Radziszewski reaction.



10a–g

9, **10 a** R = Ph, R^1 = 2-Fur, R^2 = Me; **b–f** R = Me, **b** R^1 = *p*-$MeOC_6H_4$, R^2 = Ph, **c** R^1 = H, R^2 = Ph; **d** R^1 = R^2 = Ph; **e** R^1 = Ph, R^2 = Me; **f** R^1 = R^2 = H; **g** R = Ph, R^1 = R^2 = H

Nitronicotinamide **13** was obtained by reductive dechlorination of 2-chloropyridine **12**.

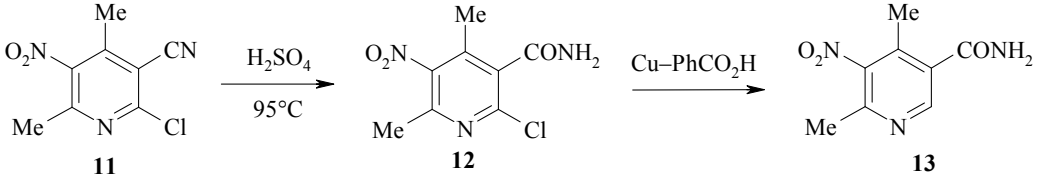


TABLE 1. Spectral Characteristics of Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)*
3a	1337, 1552 (NO_2), 1650, 1690 (CO), 3188, 3306, 3450 ($CONH_2$)	2.64 (3H, s, 2-CH_3); 2.75 (3H, s, 6-CH_3); 7.78 (1H, s, $CONH_2$-*cis*); 8.11 (1H, s, $CONH_2$-*trans*); 8.38 (1H, s, H-4)
3b	1327, 1556 (NO_2), 1601, 1660 (CO), 3193, 3307, 3375, 3438 ($CONH_2$)	2.83 (3H, s, 6-CH_3); 7.46-7.51 (3H, m, C_6H_5); 7.71-7.77 (3H, m, C_6H_5, $CONH_2$-*cis*); 8.11 (1H, s, $CONH_2$-*trans*); 8.45 (1H, s, H-4)
6	1320, 1485 (NO_2), 2210 (CN), 3420 (NH)	2.59 (3H, s, 6-CH_3); 5.34 (1H, s, H-4); 6.33 (1H, d, $^3J_{3,4}$ = 3.2, H-3 Fur); 6.37 (1H, dd, $^3J_{4,3}$ = 3.2, $^3J_{4,5}$ = 1.7, H-4 Fur); 6.55 (1H, br. s, NH); 7.36 (1H, dd, $^3J_{5,4}$ = 1.7, $^4J_{5,3}$ = 0.7, H-5 Fur); 7.46-7.59 (5H, m, C_6H_5)
7	1330, 1480 (NO_2), 2205 (CN), 3410 (NH)	2.11 (3H, s, 2-CH_3); 3.79 (3H, s, OCH_3); 5.02 (1H, s, H-4); 6.08 (1H, br. s, NH); 6.85-6.93 (2H, m, J_{AX} = 8.8, 4-C_6H_4, AA′XX′); 7.26-7.33 (2H, m, J_{AX} = 8.8, 4-C_6H_4, AA′XX′); 7.32-7.50 (5H, m, C_6H_5)
8	1319, 1495 (NO_2), 2203 (CN), 3262 (NH)	2.01 (3H, t, $^5J_{C(4)\text{-}H,\ C(2)\text{-}CH_3}$ = 1.1, CH_3); 3.64 (2H, q, $^5J_{C(4)\text{-}H,\ C(2)\text{-}CH_3}$ = 1.1, CH_2); 7.32-7.39 (2H, m, C_6H_5); 7.44-7.50 (3H, m, C_6H_5); 9.62 (1H, br. s, NH)
9a	1360, 1550 (NO_2), 2230 (CN)	2.72 (3H, s, 6-CH_3); 6.68 (1H, dd, $^3J_{4,3}$ = 3.7, $^3J_{4,5}$ = 1.7, H-4 Fur); 7.52 (1H, d, $^3J_{3,4}$ = 3.7, H-3 Fur); 7.54-7.61 (3H, m, C_6H_5); 7.69 (1H, d, $^3J_{5,4}$ = 1.7, H-5 Fur); 7.86-7.93 (2H, m, C_6H_5)
9b	1360, 1550 (NO_2), 2230 (CN)	2.95 (3H, s, 2-CH_3); 3.88 (3H, s, OCH_3); 7.02-7.08 (2H, m, J_{AX} = 8.8, 4-C_6H_4, AA′XX′); 7.35-7.41 (2H, m, J_{AX} = 8.8, 4-C_6H_4, AA′XX′); 7.48-7.55 (3H, m, C_6H_5); 7.63-7.69 (2H, m, C_6H_5)
9c	1347, 1547 (NO_2), 2227 (CN)	2.93 (3H, s, CH_3); 7.46-7.63 (5H, m, C_6H_5); 8.37 (1H, s, H-4)
10a	1349, 1528 (NO_2), 1604, 1681 (CO), 3120, 3312 ($CONH_2$)	2.58 (3H, s, 2-CH_3); 6.71 (1H, dd, $^3J_{4,3}$ = 3.7, $^3J_{4,5}$ = 1.7, H-4 Fur); 7.05 (1H, dd, $^3J_{3,4}$ = 3.7, $^4J_{3,5}$ = 0.7, H-3 Fur); 7.45-7.50 (3H, m, C_6H_5); 7.69 (1H, s, $CONH_2$-*cis*); 7.70-7.75 (2H, m, C_6H_5); 7.95 (1H, dd, $^3J_{5,4}$ = 1.7, $^4J_{5,3}$ = 0.7, H-5 Fur); 8.02 (1H, s, $CONH_2$-*trans*)
10b	1359, 1517 (NO_2), 1609, 1656 (CO), 3196, 3301, 3432 ($CONH_2$)	2.63 (3H, s, 2-CH_3); 3.79 (3H, s, OCH_3); 6.98-7.03 (2H, m, J_{AX} = 8.8, 4-C_6H_4, AA′XX′); 7.24-7.29 (2H, m, J_{AX} = 8.8, 4-C_6H_4, AA′XX′); 7.50-7.54 (5H, m, C_6H_5); 7.62 (1H, s, $CONH_2$-*cis*); 7.91 (1H, s, $CONH_2$-*trans*)
10c	1347, 1530 (NO_2), 1602, 1687 (CO), 3392, 3510 ($CONH_2$)	2.70 (3H, s, CH_3); 7.47-7.56 (5H, m, C_6H_5); 7.85 (1H, s, $CONH_2$-*cis*); 8.15 (1H, s, $CONH_2$-*trans*); 8.42 (1H, s, H-4)
10e	1347, 1525 (NO_2), 1660, 1698 (CO), 3178, 3375 ($CONH_2$)	2.50 (3H, s, 2-CH_3); 2.55 (3H, s, 6-CH_3); 7.26-7.31 (2H, m, C_6H_5); 7.40-7.47 (3H, m, C_6H_5); 7.58 (1H, s, $CONH_2$-*cis*); 7.87 (1H, s, $CONH_2$-*trans*)
10g	1346, 1533 (NO_2), 1604, 1674 (CO), 3161, 3363 ($CONH_2$)	7.52-7.53 (3H, m, C_6H_5); 7.76-7.79 (2H, m, C_6H_5); 7.85 (1H, s, $CONH_2$-*cis*); 8.21 (1H, s, $CONH_2$-*trans*); 8.59 (1H, d, ^4J = 2.44, H-4); 9.47 (1H, d, ^4J = 2.44, H-6)
12	1327, 1538 (NO_2), 1605, 1701 (CO), 3389, 3510 ($CONH_2$)	2.25 (3H, s, 2-CH_3); 2.47 (3H, s, 4-CH_3); 8.02 (1H, s, $CONH_2$-*cis*); 8.16 (1H, s, $CONH_2$-*trans*)
13	1354, 1510 (NO_2), 1580, 1674 (CO), 3398, 3505 ($CONH_2$)	2.31 (3H, s, 2-CH_3); 2.48 (3H, s, 4-CH_3); 7.80 (1H, s, $CONH_2$-*cis*); 8.10 (1H, s, $CONH_2$-*trans*), 8.62 (1H, s, H-6)

* The ^1H NMR spectra were taken in DMSO-d_6 for **3a**,**b, 10a-g**, **12,** and **13** and in $CDCl_3$ for **6-8** and **9a-c**.

TABLE 2. Mass Spectra of Compounds **3a,b, 9c, 10c,g, 12** and **13**

Compound	*m/z* (I_{rel}, %)*
3a	195 $[M]^{+\bullet}$ (100), 179 (33), 178 (22), 131 (19), 106 (56), 105 (18), 104 (21), 79 (30), 77 (36), 63 (21), 44 (22)
3b	257 $[M]^{+\bullet}$ (95), 256 (41), 241 (30), 240 (84), 227 (24), 226 (16), 211 (100), 210 (36), 168 (21), 167 (30), 166 (19), 153 (16), 141 (28), 140 (18), 115 (25), 77 (21), 44 (20)
9c	239 $[M]^{+\bullet}$ (71), 211 (97), 210 (100), 209 (47), 208 (38), 195 (16), 194 (50), 193 (21), 192 (38), 183 (30), 182 (49), 181 (31), 180 (18), 179 (30), 178 (27), 169 (25), 166 (37), 165 (19), 164 (22), 155 (28), 152 (19), 151 (30), 140 (59), 139 (36), 127 (28), 115 (16), 81 (89), 77 (40), 76 (20), 75 (17), 63 (19), 51 (25)
10c	257 $[M]^{+\bullet}$ (88), 229 (59), 228 (35), 212 (22), 184 (32), 183 (35), 182 (45), 169 (18), 168 (33), 167 (52), 166 (38), 156 (24), 155 (18), 154 (32), 153 (69), 141 (32), 140 (36), 139 (26), 137 (15), 128 (20), 127 (24), 126 (33), 115 (54), 109 (17), 105 (18), 80 (100), 77 (36), 76 (19), 63 (25), 53 (24), 51 (22), 44 (52), 40 (19)
10g	243 $[M]^{+\bullet}$ (100), 242 (38), 227 (38), 226 (51), 213 (24), 197 (79), 196 (26), 181 (19), 169 (23), 153 (21), 127 (24), 126 (18), 105 (15), 77 (31), 44 (16)
12	229 $[M]^{+\bullet}$ (10), 213 (16), 196 (17), 183 (15), 167 (23), 154 (30), 142 (35), 141 (21), 140 (100), 139 (16), 105 (16), 99 (33), 77 (30), 63 (26), 51 (24), 44 (41), 43 (29), 42 (20), 39 (16)
13	195 $[M]^{+\bullet}$ (11), 179 (15), 162 (13), 149 (14), 136 (15), 133 (28), 132 (20), 120 (42), 107 (33), 105 (100), 104 (16), 92 (25), 80 (15), 79 (18), 78 (18), 77 (33), 65 (47), 64 (29), 63 (28), 53 (18), 52 (21), 51 (2), 44 (44), 43 (18), 42 (33), 39 (23)

* Peaks given with $I > 15\%$.

The signals of the *cis* and *trans* protons of the amide group in the ^{1}H NMR spectra of nicotinamides **3a**,**b**, **10a-g**, and **13** are seen as broadened singlets of different intensity at 7.58-8.02 (H-*cis*) and 7.87-8.62 ppm (H-*trans*).

The spectral data for newly synthesized **3a**,**b**, **6-8, 9a-c**, **10a-c**,**e**,**g**, **12,** and **13** are given in Tables 1 and 2. The elemental analysis data for these compounds are given in the Experimental.

EXPERIMENTAL

The IR spectra of **6**, **7**, **9a-c**, **10c**, **12,** and **13** were obtained on a Specord IR-75 spectrometer in $CHCl_3$, while the spectra for **3a**,**b**, **8**, **10a**,**b**,**e**,**g** were taken on an Infralum FT-80 spectrometer with a device for singly perturbed internal reflection. The ^{1}H NMR spectra of **3a**,**b,** and **10g** were taken on a Bruker AC-200 spectrometer at 200 MHz with TMS as the internal standard. The ^{1}H NMR spectra of **6-8**, **9a-c**, **10a-c**,**e**, **12**, and **13** were taken on a Bruker AC-250 spectrometer at 250 MHz using the solvent as the internal standard. The mass spectra were taken on an Agilent 5973N mass spectrometer. The injector temperature was 230-250°C and the ionizing electron energy was 70 eV. The elemental analysis was carried out on a Perkin-Elmer C,H,N-analyzer. Column chromatography was performed using Merck 60A silica gel, 0.060-0.200 mm. The reaction course and purity of the products were monitored by thin-layer chromatography using Silufol UV-254 plates.

3-Amino-2-butenonitrile (**1a**) was obtained from Fluka. 3-Amino-3-phenylacrylonitrile (**1b**) was obtained using the Thorpe reaction [8]. 4-(2-furyl)-3-nitrobut-3-en-2-one (**4**) was obtained according to Berestovitskaya [9], while 3-(4-methoxyphenyl)-2-nitro-1-phenylprop-2-en-1-one (**5**) was obtained according to Sokolov [10] and 2-nitro-1-phenyletheneamine was obtained according to Tokumitsu [11] and Sokolov [12]. 2-Chloro-4,6-dimethyl-5-nitronicotinonitrile (**11**) was synthesized according to Wibaut [13].

1,4-Dihydropyridines 6 and 7 (General Method). A solution of α,β-unsaturated nitro ketone **4** or **5** (10 mmol) and corresponding enamine **1** (10 mmol) in glacial acetic acid (15 ml) was stirred for 20 h at room temperature. The crystalline precipitate was filtered off and recrystallized from ethanol. An additional amount of reaction product was obtained upon removing the solvent in vacuum.

4-(2-Furyl)-6-methyl-5-nitro-2-phenyl-1,4-dihydropyridine-3-carbonitrile (6) was obtained in 81% yield; mp 202-204°C. Found, %: C 66.25; H 4.25; N 13.57. $C_{17}H_{13}N_3O_3$. Calculated, %: C 66.44; H 4.26; N 13.67.

4-(4-Methoxyphenyl)-2-methyl-5-nitro-6-phenyl-1,4-dihydropyridine-3-carbonitrile (7) was obtained in 62% yield; mp 166-167°C. Found, %: C 68.97; H 5.03; N 11.96. $C_{20}H_{17}N_3O_3$. Calculated, %: C 69.15; H 4.93; N 12.10.

2-Methyl-5-nitro-6-phenyl-1,4-dihydropyridine-3-carbonitrile (8). Formalin 40% (1 ml) was added to a suspension of nitroacetophenone enamine (1.97 g, 12 mmol) and compound **1a** (0.98 g, 12 mmol) in glacial acetic acid (2 ml) and stirred for 48 h at room temperature. The oil formed was then poured into water and washed with 5% aqueous sodium carbonate. The oil was dried in vacuum and purified by column chromatography using 9:1 benzene–ethyl acetate as the eluent to give compound **8** in 30% yield; mp 113-114°C (ethanol). Found, %: C 64.57; H 4.67; N 17.31. $C_{13}H_{11}N_3O_2$. Calculated, %: C 64.72; H 4.60; N 17.42.

Cyanopyridines 9a and 9b (General Method). $NaNO_2$ (15 mmol) was added in portions with stirring to a suspension of corresponding 1,4-dihydropyridine **6** or **7** (10 mmol) in glacial acetic acid (25 ml) at 65-70°C. After addition of all the oxidizing agent, the reaction mixture was stirred for an additional 1 h at the same temperature and then poured into 100 ml ice water. The crystalline precipitate of **9c** or **9h** was filtered off, washed with water, dried, and recrystallized from ethanol.

4-(2-Furyl)-6-methyl-5-nitro-2-phenylnicotinonitrile (9a) was obtained in 75% yield; mp 106-107°C. Found, %: C 67.00; H 3.69; N 13.95. $C_{17}H_{11}N_3O_3$. Calculated, %: C 66.88; H 3.63; N 13.76.

2-Methyl-4-(4-methoxyphenyl)-5-nitro-6-phenylnicotinonitrile (9b) was obtained in 81% yield; mp 179-180°C. Found, %: C 69.35; H 4.55; N 11.98. $C_{20}H_{15}N_3O_3$. Calculated, %: C 69.56; H 4.38; N 12.17.

2-Methyl-5-nitro-6-phenylnicotinonitrile (9c). CrO_3 (1.5 g, 15 mmol) in water (12 ml) was added with stirring to a suspension of dihydropyridine **8** (2.41 g, 10 mmol) in acetic acid (5 ml) at a temperature not exceeding 30°C. After addition of the CrO_3, the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was poured onto ice and neutralized by adding 25% ammonium hydroxide. The crystalline precipitate was filtered off to give compound **9c** in 90% yield; mp 89-90°C (petroleum ether 40-70°C). Found, %: C 65.20; H 3.75; N 17.52. $C_{13}H_9N_3O_2$. Calculated, %: C 65.27; H 3.79; N 17.56.

Nicotinamides 10a and 10b by the Radziszewski reaction **(General Method)**. A sample of 3 ml 40% aq. H_2O_2 followed after an interval by a second sample of 3 ml aq. H_2O_2 were added with stirring to a solution of corresponding nicotinonitrile **9a** or **9b** (3 mmol) and NaOH (0.14 g, 3.4 mmol) in ethanol (23 ml) at room temperature over 1 h. The reaction mixture was heated at 55-60°C for 24 h. The crystalline precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

4-(2-Furyl)-6-methyl-5-nitro-2-phenylnicotinamide (10a) was obtained in 62% yield; mp 258-259°C (dec.). Found, %: C 62.97; H 4.06; N 12.82. $C_{17}H_{13}N_3O_4$. Calculated, %: C 63.16; H 4.05; N 13.00.

2-Methyl-4-(4-methoxyphenyl)-5-nitro-6-phenylnicotinamide (10b) was obtained in 83% yield; mp 246-247°C. Found, %: C 66.35; H 4.66; N 11.57. $C_{20}H_{17}N_3O_4$. Calculated, %: C 66.11; H 4.72; N 11.56.

Nicotinamides 3a, 3b, 10c-10g, and 12 (General Method). A solution of corresponding nicotinonitrile **2a, 2b, 9c-9g,** or compound **11** (15 mmol) in concentrated sulfuric acid (10 ml) was heated at 90-95°C for 3 h. The reaction mixture was cooled, poured onto ice, and neutralized by adding 25% ammonium hydroxide. The crystalline precipitate was filtered off, dried, and recrystallized from ethanol.

2,6-Dimethyl-5-nitronicotinamide (3a) was obtained in 68% yield; mp 210-211°C. Found, %: C 49.40; H 4.62; N 21.10. $C_8H_9N_3O_3$. Calculated, %: C 49.23; H 4.65; N 21.53.

6-Methyl-5-nitro-2-phenylnicotinamide (3b) was obtained in 88% yield; mp 196-197°C. Found, %: C 60.10; H 4.41; N 15.95. $C_{13}H_{11}N_3O_3$. Calculated, %: C 60.70; H 4.31; N 16.33.

2-Methyl-5-nitro-4-phenylnicotinamide (10c) was obtained in 95% yield; mp 197-198°C. Found, %: C 60.93; H 4.29; N 16.13. $C_{13}H_{11}N_3O_3$. Calculated, %: C 60.70; H 4.31; N 16.33.

2,6-Dimethyl-5-nitro-4-phenylnicotinamide (10e) was obtained in 89% yield; mp 213-215°C. Found, %: C 62.25; H 5.02; N 15.66. $C_{14}H_{13}N_3O_3$. Calculated, %: C 61.99; H 4.83; N 15.49.

2-Methyl-5-nitronicotinamide (10f) was obtained in 87% yield; mp 190-191°C (mp 190-191°C [14]).

5-Nitro-2-phenylnicotinamide (10g) was obtained in 95% yield; mp 214-215°C. Found, %: C 59.02; H 3.71; N 16.92. $C_{12}H_9N_3O_3$. Calculated, %: C 59.26; H 3.73; N 17.28.

2-Chloro-4,6-dimethyl-5-nitro-nicotinamide (12) was obtained in 79% yield; mp 203-204°C. Found, %: C 41.58; H 3.48; N 18.20. $C_8H_8ClN_3O_3$. Calculated, %: C 41.85; H 3.51; N 18.30.

4,6-Dimethyl-5-nitronicotinamide (13). Electrolytic copper powder (GOST State Standard 4960-75 PMS-1) from Uralelektromed' (1.5 g, 22.5 mmol) was added in portions with stirring to a mixture of amide **12** (1 g, 4.4 mmol) and benzoic acid (2 g, 16.4 mmol) heated to 150°C and stirred for 15 min. After cooling with stirring, the mixture was dissolved in ethyl acetate. The organic layer was washed with aqueous sodium carbonate and then water, dried over magnesium sulfate, and evaporated to give compound **13** in 55% yield; mp 183-184°C (ethanol). Found, %: C 49.20; H 4.72; N 21.41. $C_8H_9N_3O_3$. Calculated, %: C 49.23; H 4.65; N 21.53.

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