Reactivity of 2,3-Pyridine Dicarboxylic Anhydride Towards some Nitrogen Nucleophilic Reagents: Synthesis and Antimicrobial Evaluation of some Pyridine Carboxamide and Pyrrolo[3,4-B]Pyridine-5,7-Dione Derivatives

YA Ammar[1], YA Mohamed[2], AMSh El-Sharief[2], MSA El-Gaby[1], *SY Abbas[3]

[1]King Khalid University, Faculty of Science, Chemistry Department, Abha, Saudi Arabia
[2]Al-Azhar University, Faculty of Science, Cairo, Egypt.
[3]National Research Centre, Dokki, Cairo, Egypt.

*Correspondence to: Samir Y Abbas, samiryoussef98@yahoo.com

Accepted: January 2, 2011; Published: June 27, 2011

Abstract

The reactivity of 2,3-pyridine dicarboxylic anhydride towards some nitrogen nucleophiles under different conditions was studied. Thus, the reaction of anhydride with substituted anilines (X = 3-COOH, 4-COOH, 4-$COOC_2H_5$, 2-OC_2H_5, 4-OC_2H_5) in acetic acid at room temperature or toluene under reflux afforded arylcarbamoylpyridinecarboxylic acid. Repeating the same reaction under heating gave rise to a mixture of cyclic imide and nicotinamides. On the other hand, treatment of anhydride with binucleophiles (1,4-phenylenediamine, benzidine, 4,4`-diaminodiphenyl-sulfone) in glacial acetic acid at room temperature (or toluene under reflux) afforded pyrrolopyridine derivatives rather than carboxamide derivatives. The reaction of anhydride with binucleophiles in acetic acid under reflux afforded nicotinamide derivatives. Antimicrobial activities of some selected compounds were screened.

Keywords: 2,3-pyridine dicarboxylic anhydride; nicotinamide; pyrrolopyridine; antimicrobial activities.

1. Introduction

The relationship between chemical structure and biological activity has been of interest to pharmacologists and medicinal chemists. Large number of compounds which contain pyridine moiety are known in medicinal chemistry world as important compounds. Furthermore, pyridine nucleus is well known to be found in a broad variety of drugs such as nicotinamide (3-pyridinecarboxamide), a well-known drug used as respiratory analeptic [1]. Moreover, various substituted nicotinamides are used as fungicides [2,3], pesticides [4-9] or for treatment of benign prostatic hyperplasia [10]. Nikethamide 'N,N-diethyl-3-pyridinecarboxamide' is also a well-known drug used as respiratory analeptic [1]. Also, pyrrolo[3,4-b]pyridine derivatives are important as antibacterial [11], anti-inflammatory [12], anticonvulsant [13], antiviral [14] and herbicidal [15] agents. On the basis of these reports and in continuation of our program directed towards the reactivity of quinoxaline-2,3-dicarboxtylic anhydride with some nucleophilic reagents [16-21], we studied herein the effect of nucleophilic nitrogenous compounds with pyridine-2,3-dicarboxilic anhydride under different conditions.

2. Methods

All melting points are uncorrected. Microanalyses were carried out by the Microanalytical Laboratory, National Research Centre, Cairo, Egypt and the Microanalytical Center, Faculty of Science, Cairo University. Infrared spectra (KBr-disc) were recorded using a JASCO FT/IR-300E spectrophotometer and FTIR 5300 spectrometer (ν, cm^{-1}). ^1H NMR spectra were recorded using Varian mercury 300 MHz & Varian Gemini 200 MHz with chemical shift in δ from Me_4Si and JEOL 270, 500 MHz. Mass spectra were recorded on GC/MS Finnigan SSQ 7000 spectrophotometer & GC Ms-QP 1000 EX mass spectrometer at 70 ev.

General procedure for synthesis of the 2-arylcarbamoyl-3-pyridine carboxylic acids (6a-e)

Method A:

A mixture of 2,3-pyridine dicarboxylic anhydride **4** (0.01 mol) and aromatic amine derivatives (0.01 mol) in glacial acetic acid (30 ml) was stirred at room temperature for 1 hr. The solid product was collected and recrystallized from ethanol to give **6a-e**.

Method B:

A mixture of 2,3-pyridine dicarboxylic anhydride **4** (0.01 mol) and aromatic amine derivatives (0.01 mol) in toluene (30 ml) was heated under reflux for 1 hr, then allowed to cool. The solid product was collected and recrystallized from ethanol to give **6a-e**.

2-(3-Carboxyphenylcarbamoyl)nicotinic acid (6a) Yield: 65%; M.P.: 243-245 ^{o}C; IR: ν/cm^{-1}: 3448 (OH), 3278 (NH) and 1726, 1674 (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 7.38 (t, 1H, CH-pyridine), 7.43-7.60 (m, 4H, Ar-H), 7.90 (d, 1H, CH-pyridine), 8.10 (d, 1H, CH-pyridine), 8.45 (s, 1H, OH), 8.71 (s, 1H, NH), 10.71 (s, 1H, OH). Anal. Calcd for $C_{14}H_{10}N_2O_5$: C,58.74; H,3.52; N,9.79. : Found: C, 58.60; H, 3.40; N, 9.70.

2-(4-Carboxyphenylcarbamoyl)nicotinic acid (6b) Yield: 70%; M.P.: 273-275^{o}C; IR: ν/cm^{-1}: 3343 (NH,OH), 1687 (C=O); MS, m/z 286 (M^{+}; 4.001%), 242 (M-CO_2; 64.12%), 241 (M-COOH; 15.22%), 268 (M-H_2O; 21.44%), 120 (C_5H_4N-N=C=O; 12.0%), 106 (C_6H_4NO; 100), 78 (pyridinyl moiety; 90.71%), 77 (pyridyne; 14.8%). Anal. Calcd for $C_{14}H_{10}N_2O_5$: C,58.74; H,3.52; N,9.79. : Found: C, 58.80; H, 3.60; N, 9.70.

2-(4-(Ethoxycarbonyl)phenylcarbamoyl)nicotinic acid (6c) Yield: 65%; M.P.: 158-160^{o}C; IR: ν/cm^{-1}: 3370, 3320(NH,OH), 1714, 169(C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 1.30 (t, 3H, CH_3), 4.29 (q, 2H, CH_2), 7.45 (t, 1H, pyridine-H), 7.9 (m, 4H, Ar-H), 8.11 (d, 1H, pyridine-H), 8.53 (d, 1H, pyridine-H), 9.12 (hump, 1H, NH), 11.04 (hump, 1H, OH); Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.10; H, 4.50; N, 8.91.

2-(2-Ethoxyphenylcarbamoyl)nicotinic acid (6d) Yield: 60%; M.P. 129-130^{o}C; IR: ν/cm^{-1}: 3236 (NH), 2983, 2942, 2894 (CH-aliph.), 1720 (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 1.29 (t, 3H, CH_3), 4.10 (q, 2H, CH_2), 7.35-8.6 (m, 7H, Ar-H), 9.11 (s, 1H, NH), 11.05 (b, 1H, OH);Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93;H, 4.93; N, 9.79. Found: C, 62.90; H, 4.90; N, 9.80.

2-(4-Ethoxyphenylcarbamoyl)nicotinic acid (6e) Yield: 60%; M.P.: 203-205^{o}C; IR: ν/cm^{-1}: 3322 (NH), 2978, 2870 (CH-aliph.) and 1672(C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 1.30 (t, 3H, CH_3), 4.09 (q, 2H, CH_2), 7.45-8.5 (m, 7H, Ar-H), 9.12 (s, 1H, NH), 11.04 (b, 1H, OH); Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93;H, 4.93; N, 9.79. Found: C, 63.00; H, 5.00; N, 9.70.

General procedure for synthesis of 6-(substituted phenyl)-pyrrolo[3,4-b]pyridine-5,7-diones (7a-e)

A solution of compound **6a-e** (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 1 hr, and then allowed to cool. The solid product was collected and recrystallized from the proper solvent to give **7a-e**.

3-(5,7-Dioxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)benzoic acid (7a) Yield: 75%; M.P.: 279-281^{o}C; IR: ν/cm^{-1}: 1726, 1688 (C=O); MS, m/z 268 (M^{+}; 38.6%), 240 (M-CO; 7.2%), 224 (M-CO_2; 23%), 77 (C_6H_5; 100%). Anal. Calcd for $C_{14}H_8N_2O_4$: C,62.69; H,3.01; N,10.44. Found: C, 62.70; H, 3.00; N, 10.40.

4-(5,7-Dioxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)benzoic acid (7b) Yield: 70%; M.P.: 294-295^{o}C; IR: ν/cm^{-1}: 1796, 1728 (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 7.63-8.69 (m, 7H, Ar-H), 10.82 (s, 1H, OH). Anal. Calcd for $C_{14}H_8N_2O_4$: C,62.69; H,3.01; N,10.44. Found: C, 62.60; H, 3.00; N, 10.50.

Ethyl 4-(5,7-dioxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)benzoate (7c) Yield: 75%; M.P.: 139-140^{o}C; IR: ν/cm^{-1}: 2924 (CH- aliph.) 1720(C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 1.3 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 7.6 (d, 2H, AB-system, Ar-H), 7.8 (t, 1H, CH-pyridine), 8.1 (d, 2H, AB-system, Ar-H), 8.41 (d, 1H, CH-pyridine), 9.0 (d, 1H, CH-pyridine). Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.80; H, 4.00; N, 9.46.

6-(2-Ethoxyphenyl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (7d) Yield: 80%; M.P.: 134-135^{o}C; IR: ν/cm^{-1}: 2986 (CH-aliph.), 1728 (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 1.2 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 7-7.6 (m, 4H, Ar-H), 7.7 (t, 1H, CH-pyridine), 8.4 (d, 1H, CH-pyridine), 9.2 (d, 1H, CH-pyridine). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16;H, 4.51; N, 10.44. Found: C, 67.10; H, 4.50; N, 10.40.

6-(4-Ethoxyphenyl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (7e) Yield: 80%; M.P.: 229-230^{o}C; IR: ν/cm^{-1}: 2978 (CH-aliph.) and 1722(C=O). ^{1}HNMR (DMSO-d_6): δ/ppm: 3 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 7.0 (d, 2H, AB-system, Ar-H), 7.3 (d, 2H, AB-system, Ar-H), 7.8 (t, 1H, CH-pyridine), 8.4 (d, 1H, CH-pyridine), 9.0 (d, 1H, CH-pyridine), Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16;H, 4.51; N, 10.44. Found: C, 67.20; H, 4.50; N, 10.50.

General procedure for synthesis of 3-(1-substituted-phenyl carbamoyl) pyridines (8a-e)

Method A:

A mixture of 2,3-pyridine dicarboxylic anhydride **4** (0.01 mol) and substituted aniline (0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for 3 hrs, then allowed to cool and poured into cold water (100 ml). The solid product was collected and recrystallized from the proper solvent to give **8a-e** as major product.

Method B:

To a solution of nicotinyl chloride (0.01 mole) in toluene (30 ml), substituted aniline (0.01 mole) was added, the reaction mixture was heated under reflux for 0.5 hr.

3-(Nicotinamido)benzoic acid (8a) Yield: 50%; M.P.: >300^{o}C; IR: 3416 (OH), 3252 (NH) and 1698, 1682 (C=O); MS, m/z 242 (M^+; 23.2%), 137 (17%), 106 (100%), 78 (73%). Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.40; H, 4.10; N, 11.60.

4-(Nicotinamido)benzoic acid (8b) Yield: 50%; M.P.: >300 ^{o}C; IR: ν/cm^{-1}: 3306 (NH,OH), 1672 (C=O); Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.50; H, 4.20; N, 11.60.

Ethyl 4-(nicotinamido)benzoate (8c) Yield: 60%; M.P.: 213-215^{o}C; IR: ν/cm^{-1}: 3256(NH), 2980, 2928 (CH- aliph.) 1696, 1684 (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm:1.24 (t, 3H, CH_3), 4.8 (q, 2H, CH_2), 6.8 (d, 2H, AB-system, Ar-H), 7.7 (d, 2H, AB-system, Ar-H), 7.8 (t, 1H, CH-pyridine), 8.5 (d, 1H, CH-pyridine), 8.8 (d, 1H, CH-pyridine), 9.1 (s, 1H, CH-pyridine), 10.7 (s, 1H, NH); Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.60; H, 5.20; N, 10.40.

N-(2-ethoxyphenyl)nicotinamides (8d) Yield: 45%; M.P.: 159-160^{o}C; IR: ν/cm^{-1}: 3290 (NH), 2926 (CH-aliph.), 1660 (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm:1.31 (t, 3H, CH_3), 4.9 (q, 2H, CH_2), 6.9 - 8.5 (m, 6H, Ar-H), 8.8 (d, 1H, CH-pyridine), 9.2 (s, 1H, CH-pyridine), 10.6 (s, 1H, NH); Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41;H, 5.82; N, 11.56. Found: C, 69.40; H, 5.80; N, 11.50.

N-(4-ethoxyphenyl)nicotinamides (8e) Yield: 40%; M.P.: 179-180^{o}C; IR: ν/cm^{-1}: 3248 (NH), 2978 (CH-aliph.) and 1670 (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm:1.33 (t, 3H, CH_3), 4.9 (q, 2H, CH_2), 6.9 (d, 2H, AB-system, Ar-H), 7.7 (d, 2H, AB-system, Ar-H), 7.8 (t, 1H, CH-pyridine), 8.5 (d, 1H, CH-pyridine), 8.8 (d, 1H, CH-pyridine), 9.2 (s, 1H, CH-pyridine), 10.6 (s, 1H, NH); Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41;H, 5.82; N, 11.56. Found: C, 69.50; H, 5.90; N, 11.50.

Synthesis of 3-(arylcarbamoyl)-2-(4-ethoxy-phenyl)carbamol)pyridines (9a,b)

A mixture of compound **7d,e** (0.01 mol) and 4-ethoxyaniline (0.01 mol) in dimethylformamide (30 ml) was refluxed for 3 hrs, then allowed to cool and poured into cold water (40 ml). The solid product was collected and recrystallized from the proper solvent to give **9a,b.**

N3-(2-ethoxyphenyl)-N2-(4-ethoxyphenyl)pyridine-2,3-dicarboxamide (9a) Yield: 85%; M.P.: 208-210°C; IR: ν/cm^{-1}: 3329 (NH), 2978 (CH-aliph.) and 1704, 1674 (C=O). MS, 433 (M^+; 1.1%) 137(100%) Anal. Calcd for $C_{23}H_{23}N_3O_4$: C,68.13; H,5.72; N,10.36 Found: C, 68.10; H, 5.70; N, 10.40.

N3-(4-ethoxyphenyl)-N2-(4-ethoxyphenyl)pyridine-2,3-dicarboxamide (9b) Yield: 80%; M.P.: 198-200°C; IR: ν/cm^{-1}: 3320 (NH), 2972 (CH-aliph.) and 1668 (C=O). ^{1}HNMR (DMSO-d_6): δ/ppm: 1.3 (t, 6H, $2CH_3$), 3.8 (q, 4H, $2CH_2$), 6.3-8.4 (m, 11H, Ar-H), 10.2, 10.8 (2s, 2H, 2NH). Anal. Calcd for $C_{23}H_{23}N_3O_4$: C,68.13; H,5.72; N,10.36 Found: C, 68.20; H, 5.80; N, 10.40.

Synthesis of 6-(4-(4'-aminobiphenyl-4-yl) or (4-aminophenylsulfonyl)phenyl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (11a,b)

A mixture of compound **4** (0.01 mol) and benzidine or 4,4`-diaminodiphenylsulfone (0.01 mol) in toluene (30 ml) was refluxed for 1 hr, then allowed to cool. The solid product was collected and recrystallized from ethanol to give **11a,b**.

6-(4'-Aminobiphenyl-4-yl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (11a) Yield: 70%; M.P.: 159-160°C; IR: ν/cm^{-1}: 3420, 3334 cm^{-1} (NH) and 1728 cm^{-1} (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 5.0 (b, 2H, NH_2), 7.3-8.9 (m, 11H, Ar-H), MS, 315 (19.3%), 77 (100 %). Anal. Calcd for $C_{19}H_{13}N_3O_2$: C,72.37; H,4.16; N,13.33 Found: C, 72.40; H, 4.10; N, 13.40.

6-(4-(4-Aminophenylsulfonyl)phenyl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (11b) Yield: 80%; M.P.: 218-220°C; IR: ν/cm^{-1}: 3463, 3371 cm^{-1} (NH_2), 3062 cm^{-1} (CH-arom.), and 1689.5 cm^{-1} (C=O); MS, 379 (18.8%), 106 (100%). Anal. Calcd for $C_{19}H_{13}N_3O_4S$: C, 60.15; H, 3.45; N, 11.08. Found: C, 60.10; H, 3.40; N, 11.00.

Synthesis of N-(4-(4-aminophenylsulfonyl)phenyl)nicotinamide (12)

A mixture of compound **4** (0.01 mol) and 4,4-diaminodiphenylsulfone (0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 3 hrs., then allowed to cool. The solid product was collected and recrystallized from ethanol to give **12** as pale yellow crystals, yield 75%, m.p. 255°C. The IR spectrum of compound **12** showed absorption bands at 3364, 3184 cm^{-1} (NH), and 1684 cm^{-1} (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 4.9 (b, 2H, NH_2), 7.4-8.9 (m, 12H, Ar-H), 10.2 (s, 1H, NH). MS: 379(M^+), 353 (31.7%), 290 (13.9%), 248 (13.5%), 140 (12.5%), 106 (100 %). Anal. Calcd for $C_{18}H_{15}N_3O_3S$: C, 60.15; H, 3.45; N, 11.08. Found: C, 60.20; H, 3.40; N, 11.10.

Synthesis of 1,4-bis(pyrrolo[3,4-b]pyridine-5,7-diones-6-yl)benzene (or biphenyl) (14a,b)

A mixture of compound **4** (0.02 mol) and 1,4-phenylenediamine or benzidine (0.01 mol) in toluene (30 ml) was refluxed for 1 hr, then allowed to cool. The solid product was collected and recrystallized from EtOH to give **14a,b**.

1,4-Bis(pyrrolo[3,4-b]pyridine-5,7-diones-6-yl)benzene (14a) Yield: 75%; M.P.: 203-205°C; IR: ν/cm^{-1}: 1660 cm^{-1} (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 7.2-9.0 (m, 10H, Ar-H), MS: m/z 370 (3.8%), 107 (100%). Anal. Calcd for $C_{20}H_{10}N_4O_4$: C,64.87; H,2.72; N,15.13. Found: C, 64.90; H, 2.70; N, 15.10.

6,6'-(Biphenyl-4,4'-diyl)bis(5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione) (14b) Yield: 80%; M.P.: >300°C; IR: ν/cm^{-1}: 1728 cm^{-1} (C=O). MS: 446 (100%). Anal. Calcd for $C_{26}H_{14}N_4O_4$: C, 69.95; H, 3.16; N, 12.55. Found: C, 69.90; H, 3.20; N, 12.50.

Synthesis of N-(4-(5,7-dioxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)phenyl or biphenyl-4-yl)nicotinamides (16a,b)

A mixture of compound **4** (0.02 mol) and 1,4-phenylenediamine or benzidine (0.01 mol) in glacial acetic acid (30 ml) was refluxed for 3 hrs., then allowed to cool, the solid product was collected and recrystallized from ethanol to give **16a,b**.

N-(4-(5,7-dioxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)phenyl)nicotinamides (16a) Yield: 70%; M.P.: 268-270°C, IR: ν/cm^{-1}: 3328 (NH) and 1714, 1646 (C=O); ^{1}HNMR (DMSO-d_6): δ/ppm: 7.2-9.0 (m, 11H, Ar-H), 10.3 (s, 1H, NH). m/z (/%) 344(M^+;15), 318 (42.8%), 107 (19.2%), 106 (100%), 79 (12.1), 78 (63.7%). Anal. Calcd for $C_{19}H_{12}N_4O_3$: C, 66.28; H, 3.51; N, 16.27. Found: C, 66.30; H, 3.50; N, 16.30.

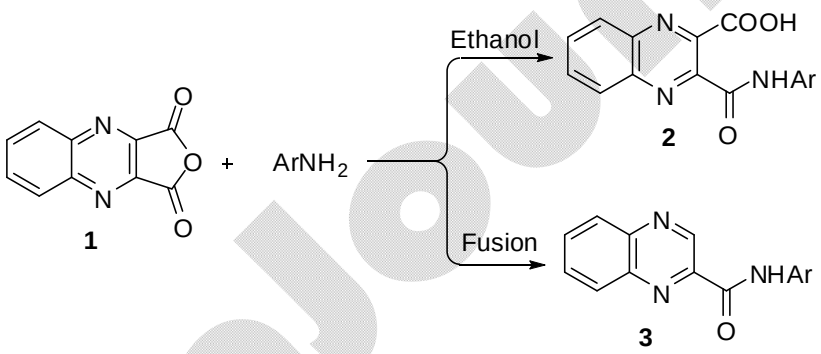
N-(4'-(5,7-dioxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)biphenyl-4-yl)nicotinamides (16b) Yield: 75%; M.P.: >300 ^{o}C; IR: ν/cm^{-1}: 3338 (NH), and 1718, 1652 cm^{-1} (C=O). MS: 420 394 (M-CO; 18.5%), 314 (M-C_6H_4NCO; 0.5%), 196 (0.2%), 120 (0.2%), (M^+;2.1%) 106(100%), 78 (2-pyridinyl; 72%). Anal. Calcd for $C_{25}H_{16}N_4O_3$: C, 71.42; H, 3.84; N, 13.33. Found: C, 71.40; H, 3.80; N, 13.30.

Synthesis of 6,6'-(4-chloro-1,2-phenylene)bis(5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione) (17)

A solution of compound **4** (0.02 mol) and 4-chloro-1,2-phenylenediamine (0.01 mol) in toluene was heated under reflux for 1 hr, then allowed to cool. The solid product was collected and recrystallized from ethanol to give **17** as brown crystals, yield 60%, m.p. 160°C. IR: ν/cm^{-1}: 1676 (C=O). ^{1}HNMR (DMSO-d_6): δ/ppm: 7.2-8.9 (m, 9H, Ar-H); MS, m/z (%), 404 (M^+;1.2%) 229(100). Anal. Calcd for $C_{20}H_9ClN_4O_4$: C, 59.35; H, 2.24; N, 13.84. Found: C, 59.30; H, 2.20; N, 13.80.

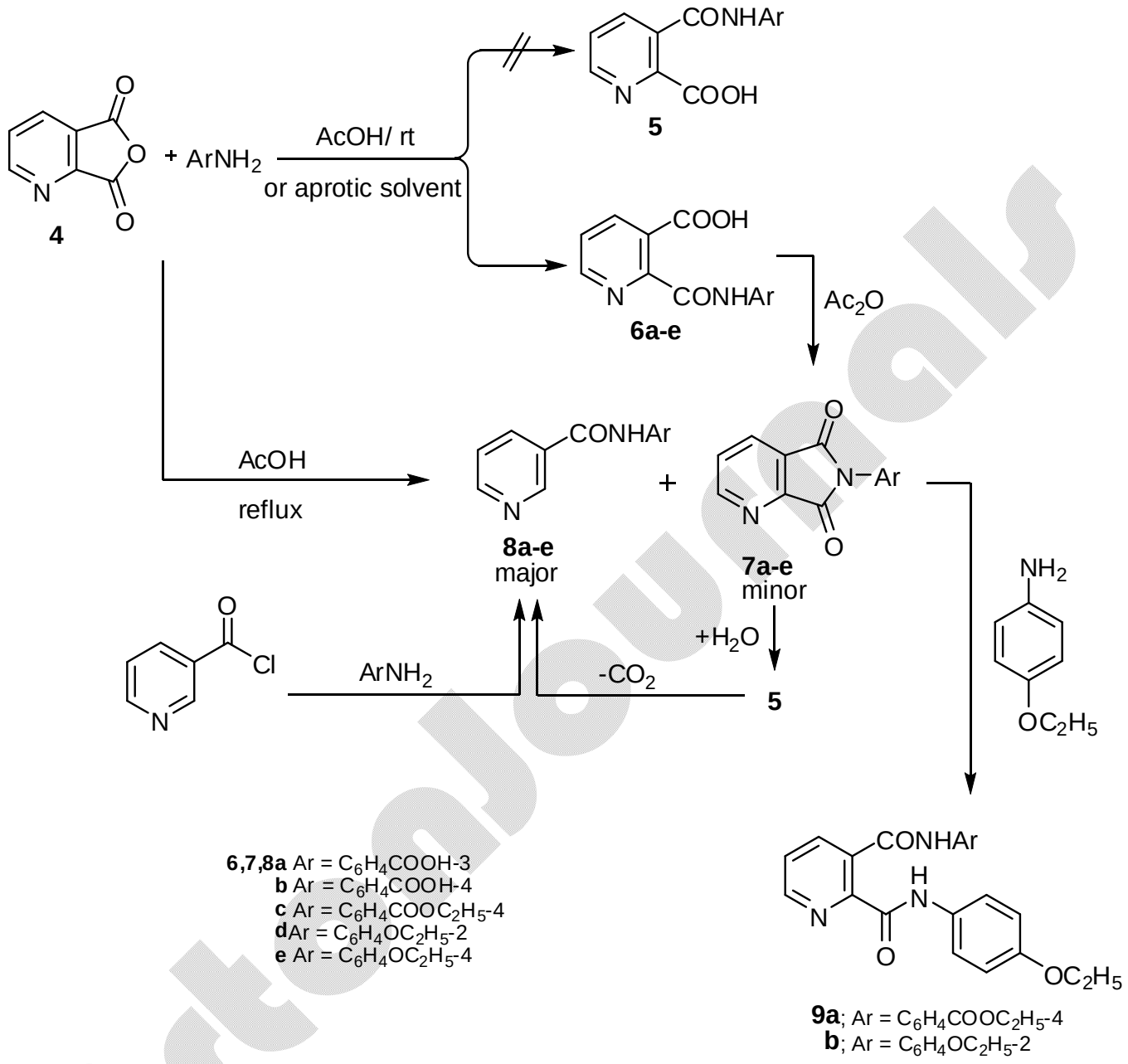
3. Results and Discussion

Previously, we reported that condensation of quinaxaline-2,3-dicarboxylic acid anhydride **1** with aromatic amine in ethanol caused opening of the lactone ring to give 2-amidoquinaxoline-3-carboxylic acid derivatives **2**; while fusion with **1** of the same amines afforded 2-aminoquinoxalkine derivatives **3**. This reaction involved nucleophilic attack of amine at position-2 of anhydride forming **2** which loses CO_2 to form **3** (Scheme 1).



Scheme 1

In view of these facts and as a continuation of our previous efforts carried out in our laboratories [16-21], the reactivity of 2,3-pyridine dicarboxylic anhydride towards some nitrogen nucleophiles under different conditions was studied with the objective of obtaining biologically active compounds. Thus, the reaction of equimolar amounts of pyridine dicarboxylic anhydride **4** with aromatic amines in glacial acetic acid at room temperature provides a single product that could be formulated as arylcarbamoylpyridinecarboxylic acid. Two possible isomeric structures could be considered (**5** or **6**). Structure **6a-e** was considered for such a reaction product based on that the carbonyl group at C-2 of the anhydride is the more reactive center in the molecule which subjected to the nucleophilic attack of aromatic amines. The same products **6a-e** were obtained on repeating the same reaction in toluene as aprotic solvent at reflux conditions (m.p. and mixed m.p.). Structure of the amide **6a-e** was supported on the basis of correct analytical data and by studying the IR, ^{1}HNMR and mass spectral data. Their IR spectra were characterized by appearance of strong bands in the 3448-3320 cm^{-1}, characteristic to NH, OH groups and bands in 1746-1672 cm^{-1} for C=O group. Additionally, compounds **6c-e** showed bands in region compatible with aliphatic protons. ^{1}HNMR spectrum of **6a** in (DMSO-d_6) revealed the following signals at: δ = 7.38 (t, 1H, CH-pyridine), 7.43-7.60 (m, 4H, Ar-H), 7.90 (d, 1H, CH-pyridine), 8.10 (d, 1H, CH-pyridine), 8.45 (s, 1H, NH, D_2O-exchangeable), 8.71 (s, 1H, OH, D_2O-exchangeable), 10.71 (s, 1H, OH, D_2O-exchangeable) . ^{1}HNMR spectrum of the **6c** showed signals at: δ = 1.30 (t, 3H, CH_3), 4.29 (q, 2H, CH_2), 7.45 (t, 1H, CH-pyridine), 7.9 (m, 4H, Ar-H), 8.11 (d, 1H, CH-pyridine), 8.53 (d, 1H, CH-pyridine), 9.12 (hump, 1H, NH), 11.04 (hump, 1H, OH). The mass spectrum of compound **6b** afforded the following: 286 (M^+; 4.01%), 242 (M-CO_2; 64.12%), 241 (M-COOH; 15.22%), 268 (M-H_2O; 21.44%), 120 (C_5H_4N-N=C=O; 12.0%), 106 (C_6H_4NO; 100), 78 (pyridinyl moiety; 90.71%), 77 (pyridyne; 14.8%).



Scheme 2: Reactivity of anhydride towards some aromatic amines.

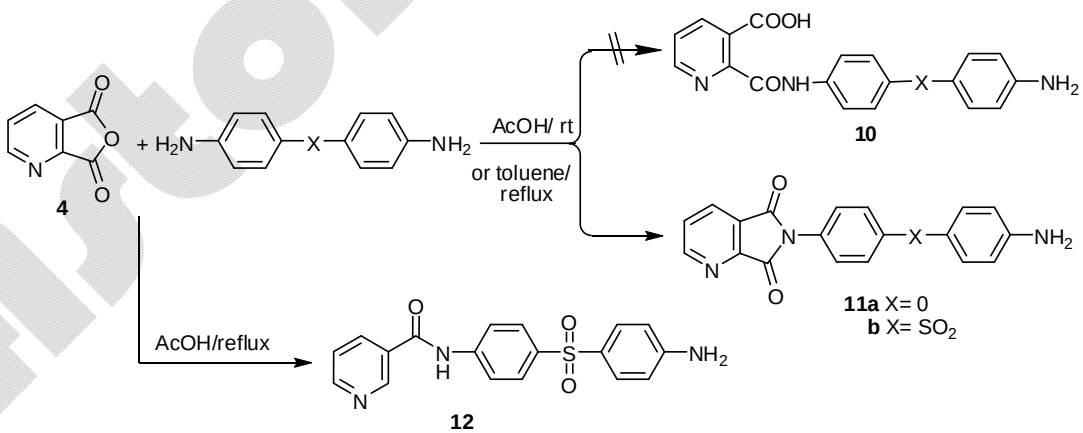
Pyrrolo[3,4-b]pyridine derivatives **7a-e** were typically prepared in stepwise fashion by cyclization of nicotinic acid derivatives **6a-e** through heating in acetic anhydride under reflex. Structure of pyrrolopyridine derivatives **7a-e** was confirmed by elemental analysis and spectral data. IR spectra of **7a-e** were characterized by disappearance of the bands of OH, NH groups and appearance of strong bands in the 1796-1720 cm^{-1}, characteristic of the C=O of pyrrone. ^{1}HNMR spectrum (DMSO-d_6) of **7c** displayed the following signals at: δ = 1.3 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 7.6 (d, 2H, AB-system, Ar-H), 7.8 (t, 1H, CH-pyridine), 8.1 (d, 2H, AB-system, Ar-H), 8.41 (d, 1H, CH-pyridine), 9.0 (d, 1H, CH-pyridine). The mass spectrum of compound **7a** afforded the following: 268 (M^+; 38.6%), 240 (M-CO; 7.2%), 224 (M-CO_2; 23%), 77 (C_6H_5; 100%).

On the other hand, interaction of anhydride **4** with the same previous aromatic amines in glacial acetic acid under reflux condition, yielding a mixture of two compounds which one of them was formulated as the nicotinamide derivatives **8a-e** (major product) while the other product was proved as pyrrolo[3,4-b]pyridine derivatives **7a-e** minor product (m.p. and mixed m.p.). These results were compatible with studies by Philip M. Harrington [22] for similar reaction (Scheme 2). The structural elucidation of the nicotinamide derivatives **8a-e** was characterized chemically and by their elemental analysis and careful inspection of their spectral IR, ^{1}HNMR, MS data. An important evidence for structure **8** was arrived at through its synthesis from nicotinyl chloride with aromatic amines (Scheme 2). Spectral data and previous work are in agreement with structure **8,** IR spectra of **8a-e** showed bands in 3416-3248 cm^{-1} region for NH,OH groups and band in 1696-1660 cm^{-1} for 2C=O groups. The lower frequency of C=O of carboxylic acid function group was suggested to be due to intramolecular hydrogen bonding. Also, IR spectra of **8c-e** showed bands in 2980-2926 cm^{-1} region for aliphatic protons. ^{1}HNMR spectrum of **8a** displayed the following signals at: δ = 1.33 (t, 3H, CH_3), 4.9 (q, 2H, CH_2), 6.9 (d, 2H, AB-system, Ar-H), 7.7 (d, 2H, AB-system, Ar-H), 7.8 (t, 1H, CH-pyridine), 8.5 (d, 1H, CH-pyridine), 8.8 (d, 1H, CH-pyridine), 9.2 (s, 1H, CH-pyridine), 10.6 (s, 1H, NH), The mass spectrum of compound **8b** afforded the following: 242 (M^+; 23.2%), 137 (17%), 106 (100%), 78 (73%).

Formation of nicotiamide **8** is assumed to proceed *via* the formation of nicotinic acid derivatives **6** which are subjected to intramolecular cyclodehydration to give the imide derivatives **7**, then hydrolysis to the picolinic acid derivatives **5** followed by decarboxylation to the final product **8**. It appears that water plays a critical role in this equilibration and its concentration affects the overall product distribution.

The behavior of **7** towards some nitrogenous compounds has also been investigated. Thus, compounds **7c,d** were reacted with *p*-phenatidine in dimethylformamide causing opening of the pyrrole ring to give the dicarboxamide derivatives **9a,b** (Scheme 2). Structure of dicarboxamide derivatives **9a,b** was demonstrated based on elemental analyses and spectroscopic studies. Their IR spectra were characterized by appearance of the bands at 3329 and 3320 cm^{-1} respectively, characteristic of the NH group. Diagnostically important signals in ^{1}HNMR spectrum of **9b** were at: δ=1.3 (t, 6H, $2CH_3$), 3.8 (q, 4H, $2CH_2$), 10.2, 10.8 (2s, 2H, 2NH). The mass spectrum of compound (**9a**; $C_{24}H_{23}N_3O_5$) revealed a molecular ion peak at m/z 433 (M^+; 1.1%) and base peak at m/z 137 which is characteristic for 4-ethoxyaniline. Other significant peaks were observed at m/z: 296 (M - ethoxyaniline; 6.6%) and 77 (pyridyne; 8.9%).

The present investigation was extended to cover the behavior of 2,3-pyridine dicarboxylic anhydride **4** towards some binucleophiles. Thus, treatment of one mole of benzidine or 4,4`-diaminodiphenyl-sulfone with one mole of compound **4** in glacial acetic acid at room temperature (or toluene under reflux) afforded pyrrolopyridine derivatives **11a,b** rather than carboxamide derivatives **10**. On the other hand, the reaction of one mole of compound **4** with 4,4`-diaminodiphenylsulfone in glacial acetic acid under reflux afforded nicotinamides **12** (Scheme 3).

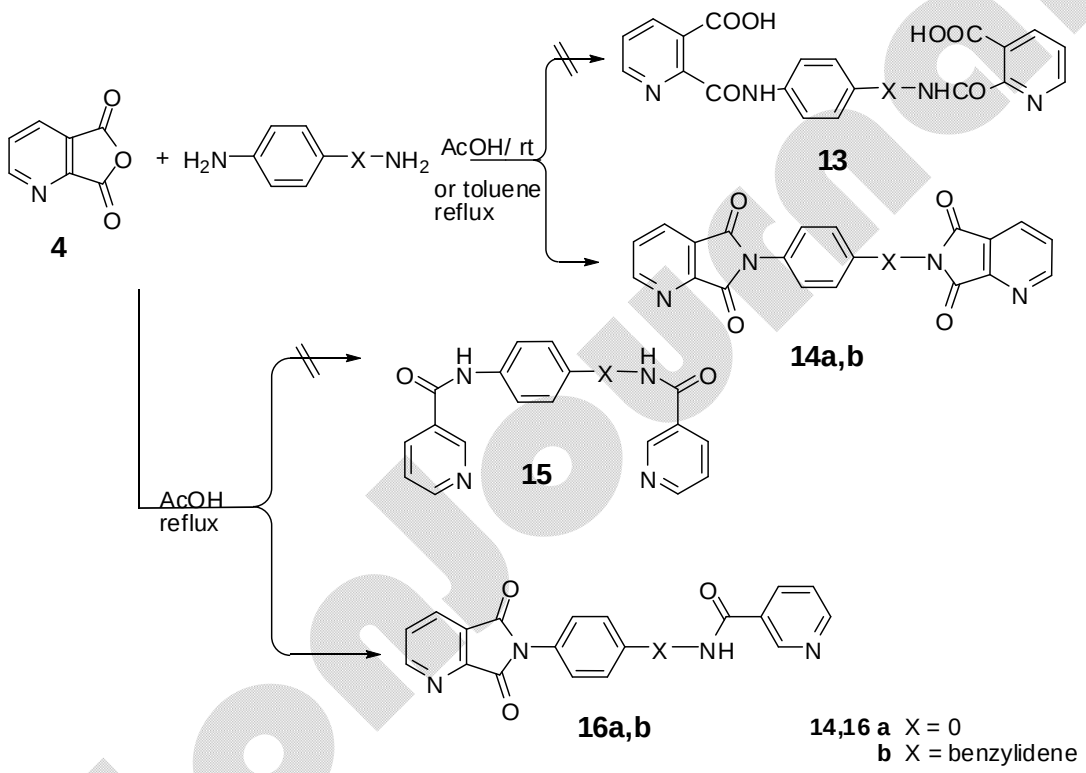


Scheme 3: Reactivity of anhydride towards some binucleophiles.

The structures of compounds **11a,b** and **12** were established on the basis of elemental analysis and spectral data. IR spectra of **11a,b** were compatible with the assigned structure. Mass spectrum of compounds **11a** showed a molecular ion peak at: m/z = 315 (M^+; 19.3%) corresponding to the molecular formula $C_{19}H_{13}N_3O_2$ and the base peak was observed in the spectrum at m/z 77 (100 %),

which is characteristic for pyridine moiety. Mass spectrum of **11b** exhibited a molecular ion peak at: m/z 379 (M^+;18.8%) corresponding to the molecular formula $C_{19}H_{13}N_3O_4S$ and the base peak was observed in the spectrum at m/z 106 (100%). The IR spectrum of compound **12** showed absorption bands at 3364, 3184 cm^{-1} (NH_2,NH), and 1684 cm^{-1} (C=O). Its mass spectrum showed a molecular ion peak at m/z = 353(M^+; 31.7%) corresponding to the molecular formula $C_{18}H_{15}N_3O_3S$ and the base peak was observed in the spectrum at: m/z = 106 (100 %).

In addition, the present investigation was extended to include the reaction of two moles of anhydride **4** with some binucleophiles. Thus, treatment of one mole of 1,4-phenylenediamine or benzidine with two moles of compound **4** in glacial acetic acid at room temperature (or toluene under reflux) afforded bispyrrolopyridine derivatives **14a,b** rather than biscarboxamide derivatives **13**. On the other hand, the reaction of two moles of compound **4** with 1,4-phenylenediamine or benzidine in glacial acetic acid under reflux afforded nicotinamide derivatives **16a,b** rather than bisnicotinamide derivatives **15** (Scheme 4).

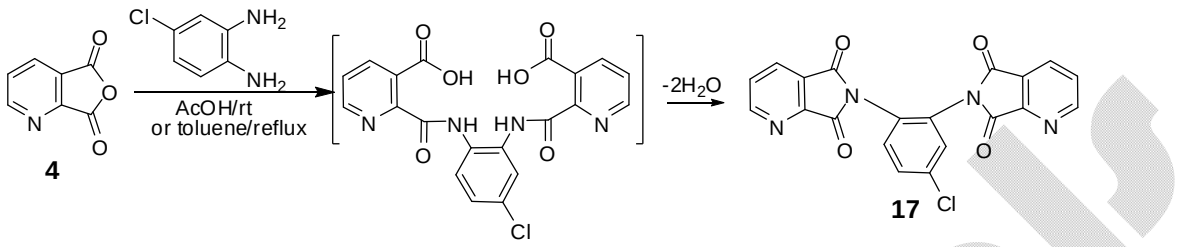


Scheme 4: Reactivity of two mole of anhydride towards some binucleophiles.

The structure of the bispyrrolopyridine **14a,b** was inferred from their microanalysis and spectral data. Their IR spectra characterized by absence of bands of OH, NH groups and presence of strong bands (about 1728 cm^{-1}) characteristic of the carbonyl group. The mass spectrum of compound (**14a**; $C_{20}H_{10}N_4O_4$) showed a molecular ion peak at m/z 370 (M^+; 3.8%) with base peak at m/z 107 (100%). The mass spectrum of **14b** displayed a molecular ion peak at m/z 446 which is the base peak in the spectrum. IR spectrum of compound **16a** showed bands at 3328 cm^{-1} (NH) and 1714, 1646 cm^{-1} (C=O). The mass spectrum of compound (**16a**; $C_{19}H_{11}N_4O_3$) showed a molecular ion peak at m/z: 344 (M^+; 15.2%). Other significant peaks were observed at m/z: 318 (42.8%), 106 (100%), 78 (63.7%), The IR spectrum of compound **16b** showed the bands at 3338 (NH) and 1718, 1652 cm^{-1} (C=O). Mass spectrum of compound (**16b**; $C_{25}H_{16}N_4O_3$) revealed a molecular ion peak at m/z 420 (M^+; 2.1%) and base peak at: m/z 106. Other significant peaks appeared at m/z: 394 (M-CO; 18.5%) and 78 (2-pyridinyl; 72%).

Moreover, when two moles of compound **4** was allowed to react with 4-chloro-1,2-phenylenediamine in toluene, the bispyrrolopyridine **17** was achieved (Scheme 5). The structure of bispyrrolopyridine **17** was inferred from its microanalysis and spectral data. Its IR spectrum was characterized by absence of bands of OH, NH groups and presence of strong band in the 1676 cm^{-}

[1], characteristic of the carbonyl group. Also, the mass spectrum of compound (**17**; $C_{20}H_9ClN_4O_4$) showed a molecular ion peak at m/z 404 (M^+; 1.2%) with base peak at m/z 229.



Scheme 5

The preliminary *in vitro* antimicrobial activity screening for some selected synthesized compounds was carried out using paper disc method [23] against six test organisms representing three different microbial groups: Group 1: (Gram positive bacteria) *Bacillus subtilis* and *Sarcina* sp.; Group 2: (Gram negative bacteria) *Salmonella typhi* and *Klebsiella pneumonia*; Group 3: (Fungi) *Aspergillus ochraceus* Wilhelm and *Penicillium chrysogenum thom*. Fresh stock solutions (1mg/ml) of the tested compounds were prepared in redistilled DMSO according to the required concentrations. It is obvious from the obtained results that most of the tested compounds showed a moderate antimicrobial activity, in which compounds **6d, 7a, 11b** and **17** showed high activities against some tested organisms. The results are represented in the Table 1.

Table 1: Antimicrobial activity data of some synthesized compounds.

Compound No.	Gram +ve		Gram –ve		Fungi	
	B. sub.	***Sarcina* sp.**	***Klebsiella pneumoniae***	***Salmonella typhi***	***Penicillium* sp.**	***Aspergillus* sp.**
6a	6	13	7	8	7	12
6c	8	6	6	7	9	8
6d	13	16	14	14	13	13
7a	7	16	8	8	13	13
7c	-	-	-	-	-	-
7d	-	6	7	6	7	7
7e	-	-	-	-	-	-
8b	6	-	7	-	-	-
9a	7	7	-	-	6	8
9b	-	6	-	-	-	-
11a	-	8	8	6	-	-
11b	11	6	6	15	9	6
14a	6	8	8	11	13	6
14b	-	-	-	-	-	-
16b	-	-	-	-	-	-
17	13	17	14	16	7	7
Erthromycin	30	19	15	16	-	-
Noroxin	35	27	17	15	-	-
Nystatin	-	-	-	-	16	20

4. Conclusion

The reaction of 2,3-pyridine dicarboxylic anhydride with substituted anilines in acetic acid under reflux afforded nicotinamides as unexpected product. On the other hand, treatment of anhydride with the same substituted anilines in glacial acetic acid at room temperature (or toluene under reflux) afforded nicotinic acid derivatives.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

YAA, YAM and AME were involved in the preparation of manuscript. MSAE and SYA carried out experimental work at Plant and Microbiology Department, Faculty of Science, Al-Azhar University.

References

[1] Kleemann A, Engel J, Kutscher B, Reichert D, 1999. *In* Pharmaceutical Substances: Syntheses, Patents, Applications, 3rd ed.; Thieme: Stuttgart, New York, 1332–1341.

[2] Neubert TD, Piotrowski DW, Walker MP, 2002. Preparation of pyridinyl amides and imides for use as fungicides. PCT Int. Appl. WO 02 22,583 pp 105; ChemInform Abstract, 136: 263098.

[3] Taniguchi M, Imamura K, Hannaka O, Iinuma K, 1999. Preparation of 3-hydroxypicolinic acid amides and 2-hydroxynicotinic acid amides as fungicides. Jpn. Kokai Tokkyo Koho JP 11 228,542 [99 228,542] pp 6; ChemInform Abstract, 131: 157713.

[4] Mio S, Okui H, 2003. PCT Int. Appl. WO 03 44,013; ChemInform Abstract, 139: 6876.

[5] Kornuta PP, Shermolovich YG, Doeller U, Ort O, Schaper W, Jans D, Sanft U, Thoenessen MT, Beckmann M, Waibel JM, Pazenok S, 2001. Preparation of pyridinyl acylsulfinides as insecticides, acaricides and nematocides. PCT Int. Appl. WO 01 70,692 pp 119; ChemInform Abstract, 135: 272885.

[6] Maienfisch P, Farooq S, 2001. Preparation of trifluoromethyl pyri(mi)dine carboxamides as pesticides. PCT Int. Appl. WO 01 09,104; ChemInform Abstract, 134: 147503.

[7] Gesing ERF, Mueller KH, Kysela E, Drewes MW, Dahmen P, Feucht D, Pontzen R, 2001. Preparation of N-phenylnicotinamides for use as herbicides. PCT Int. Appl. WO 01 23,356 pp 66; ChemInform Abstract, 134: 266207.

[8] Linker KH, Mueller KH, Drewes MW, Feucht D, Pontzen R, Wetcholowsky I, 2000. Preparation of N-pyrazolyl phenoxynicotinic acid (thio) amides as herbicides. Ger. Offen. DE 19,854,081 pp 42; ChemInform Abstract, 132: 347567.

[9] Sugihara K, Shudo A, Tsuchiya S, 1999. Preparation of pyridine carbonyl amidines as pesticides. Jpn. Kokai Tokkyo Koho JP 11 180,957 [99 180,957]; ChemInform Abstract, 131: 73560.

[10] Kuo GH, Murray WV, Prouty CP, 1999. Preparation of N-pyridinyl carbonyl aminoalkyl-N'-arylpiperazines for treatment of benign prostatic hyperplasia. PCT Int. Appl. WO 99 42,448 pp 45; ChemInform Abstract, 131: 184970.

[11] Mohamed TA, Kandeel MM, Awad IMA, Youssef MSK, 1991. Synthesis of some new N-substituted quinolimides with antibacterial activities. Collection of Czechoslovak Chemical Communications, 56: 2999-3005.

[12] Bacha, C. T. M. ; Ferreira, I. P. ; Loiseau, P. ; Elfrides E. S. Schapoval; Schapoval, Elfrides E. S . 1987. Nouveaux n-arilpyridinecarboximides -2,3: etude chimique et pharmacologique. Pharmaceutica Acta Helvetia, 62: 292-297.

[13] Bailleux V, Valle I, Nuyts J, Vamecq J, 1995. Synthesis and anticonvulsant activity of two N-(2,6-dimethylphenyl)pyridinedicarboximides. Biomedicine & Pharmacotherapy, 49: 75-78.

[14] Rashan LJ, Ahmed BA, Hussein SH, AL-Khayat R, Al-Omar L, 1989. Synthesis and antiviral evaluation of 6-p-ethylphenyl-5H-pyrrolo [3,4-b]pyridine-5,7-dione. II Farmaco, 44: 893-896.

[15] Amprecht GH, Fuchs E, Gerber M, Walter H, Westphalen K, 1995. 471/04, 29 Jun, Appl. 22 Dec. 1993; ChemInform Abstract, 123: 228163z.

[16] Ammar YA, 1990. Some reactions with N-(p-carbethoxyphenyl)quinoxaline-2,3-dicarboxyimides, Journal of Serbian Chemical Society, 55: 515.

[17] Ammar YA, Mohamed YA, El-Sharief AMS, Zahran MA, 1991. Curtius degradation of quinoxaline acid azides. Egyptian Journal of Chemistry, 34: 361.

[18] Mohamed YA, Ammar YA, El-Sharief AMS, Zahran MAJ, 1993. A facile synthesis and reactions of 6,7-dimethylquinoxaline-2,3-dicarboxyimides. Affinidad Chemistry, L444, Marzo-April, 123.

[19] Zahran MA, Ismail MMF, El-Gaby MSA, Shemiss NAMM, Ammar YA, 2002. Synthesis of novel quinoxaline carboxylic acid derivatives for antimicrobial investigation. Indian Journal of Chemistry, 41B: 1481-1485.

[20] Ammar YA, Ismail MMF, El-Gaby MSA, Zahran MA, 2002. Some reactions with quinoxaline-2,3-dicarboxylic acid anhydride: Novel synthesis of thieno[2,3-d]pyrimidines and pyrrolo[3,4-b]quinoxalines as antimicrobial agents. Indian Journal of Chemistry, 41B: 1486-1491.

[21] Ammar YA, Mohamed YA, El-Sharief AM, El-Gaby MSA, Abbas SY, 2011. Synthesis of some biologically active 4(3H)-quinazolinones derived from 2,3-pyridine dicarboxylic anhydride. Chemical Sciences Journal, 2011: CSJ-15.

[22] Philip M, 1993. An unusual synthesis of nicotinamides. Heterocycles, 35 (2): 683-687.

[23] Performance Standards for Antimicrobial Disk Susceptibility Tests, 1993. Approved Standard NCCLS Publication M2-A5, Villanova, PA, USA, pp. 1.