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

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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-COOCC₆H₄, 2-OCC₆H₄, 4-OCC₆H₄) in acetic acid at room temperature or toluene under reflux afforded arylocarbamoylpyridinecarboxylic 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-dicarboxylic anhydride with some nucleophilic reagents [16-21], we studied herein the effect of nucleophilic nitrogenous compounds with pyridine-2,3-dicarboxylic 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 S300 spectrometer (v, cm⁻¹). ¹H NMR spectra were recorded using Varian mercury 300 MHz & Varian Gemini 200 MHz with chemical shift in δ from Me₃Si 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.

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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 C; IR: ν/cm⁻¹: 3448 (OH), 3278 (NH) and 1726, 1674 (C=O); ¹H NMR (DMSO-d₆): 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 C₁₄H₁₀N₂O₂: C, 65.74; H, 3.82; N, 10.44. Found: C, 65.80; H, 3.40; N, 9.70.

2-(4-Carboxyphenylcarbamoyl)nicotinic acid (6b) Yield: 70%; M.P.: 273-275 C; IR: ν/cm⁻¹: 3434 (NH,OH), 1687 (C=O); MS, m/z 286 (M⁺); 242 (M-CO; 64.12%), 241 (M-COOH; 15.22%), 268 (M-H₂O; 21.44%), 120 (C₈H₅N=CO=O; 12.0%), 106 (C₆H₅NO; 100), 78 (pyridinyl moiety; 90.71%), 77 (pyridine; 14.8%). Anal. Calcd for C₁₄H₁₀N₂O₄: C, 63.81; H, 3.56; N, 10.79. Found: C, 63.80; H, 3.60; N, 9.70.

2-(4-Ethoxycarbonylphenylcarbamoyl)nicotinic acid (6c) Yield: 65%; M.P.: 158-160 C; IR: ν/cm⁻¹: 3370, 3320(NH,OH), 1714, 169(C=O); ¹H NMR (DMSO-d₆): δ/ppm: 1.30 (t, 3H, CH₃), 4.29 (q, 2H, CH₂), 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 C₁₄H₁₀N₂O₄: C, 64.86; H, 3.01; N, 10.44. Found: C, 64.80; H, 3.40; 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, 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 C; IR: ν/cm⁻¹: 1726, 1688 (C=O); MS, m/z 268 (M⁺; 38.6%), 240 (M-CO; 7.2%), 224 (M-CO₂; 23%), 77 (C₆H₅; 100%). Anal. Calcd for C₁₄H₉N₂O₄: 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 C; IR: ν/cm⁻¹: 1796, 1728 (C=O); ¹H NMR (DMSO-d₆): δ/ppm: 7.63-8.69 (m, 7H, Ar-H), 10.82 (s, 1H, OH). Anal. Calcd for C₁₄H₁₀N₂O₄: 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 C; IR: ν/cm⁻¹: 2924 (CH- aliph.) 1720(C=O); ¹H NMR (DMSO-d₆): δ/ppm: 1.3 (t, 3H, CH₃), 4.3 (q, 2H, CH₂), 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 C₁₄H₁₀N₂O₄: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.80; H, 4.00; N, 9.46.

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6-(2-Ethoxyphenyl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (7d) Yield: 80%; M.P.: 134-135°C; IR: ν/cm⁻¹: 2986 (CH-aliph.), 1728 (C=O); ¹HNMR (DMSO-d₆): δ/ppm: 1.2 (t, 3H, CH₃), 4.1 (q, 2H, CH₂), 7.7-7.6 (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 C₁₅H₁₂N₂O₃: C, 67.16; H, 4.16; N, 10.46. Found: C, 67.20; H, 4.50; N, 10.50.

6-(4-Ethoxyphenyl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (7e) Yield: 80%; M.P.: 229-230°C; IR: ν/cm⁻¹: 2978 (CH-aliph.) and 1722 (C=O); ¹HNMR (DMSO-d₆): δ/ppm: 3 (t, 3H, CH₃), 4.0 (q, 2H, CH₂), 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 C₁₅H₁₂N₂O₂: C, 68.71; H, 4.50; N, 11.46. Found: C, 68.80; H, 4.60; N, 11.60.

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

**Method A:**

A mixture of 2,3-pyridine dicarboxylic anhydride (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°C; IR: ν/cm⁻¹: 3416 (OH), 3252 (NH) and 1682, 1622 (C=O); MS, m/z 242 (M⁺; 23.2%), 137 (17%), 106 (100%), 78 (73%). Anal. Calcd for C₁₅H₁₁O₄N: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.50; H, 4.20; N, 11.60.

4-(Nicotinamido)benzoic acid (8b) Yield: 50%; M.P.: >300°C; IR: ν/cm⁻¹: 3306 (NH,OH), 1672 (C=O); Anal. Calcd for C₁₅H₁₀O₄N: 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°C; IR: ν/cm⁻¹: 3256(NH), 2980, 2928 (CH-aliph.), 1696, 1684 (C=O); ¹HNMR (DMSO-d₆): δ/ppm: 1.31 (t, 3H, CH₃), 4.8 (q, 2H, CH₂), 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 C₁₅H₁₂N₂O₃: 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°C; IR: ν/cm⁻¹: 3290 (NH), 2926 (CH-aliph.), 1660 (C=O); ¹HNMR (DMSO-d₆): δ/ppm:1.31 (t, 3H, CH₃), 4.9 (q, 2H, CH₂), 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 C₁₅H₁₂N₂O₂: 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°C; IR: ν/cm⁻¹: 3248 (NH), 2978 (CH-aliph.) and 1670 (C=O); ¹HNMR (DMSO-d₆): δ/ppm:1.33 (t, 3H, CH₃), 4.9 (q, 2H, CH₂), 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 C₁₅H₁₂N₂O₂: 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)carbamoyl)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.

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N3-(2-ethoxyphenyl)-N2-(4-ethoxyphenyl)pyridine-2,3-dicarboxamide (9a) Yield: 85%; M.P.: 208-210°C; IR: v/cm⁻¹: 3329 (NH), 2978 (CH-aliph.) and 1704, 1674 (C=O). MS, 433 (M⁺; 1.1%) 137(100%). Anal. Calcd for C₂₅H₂₁N₂O₄: 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: v/cm⁻¹: 3320 (NH), 2972 (CH-aliph.) and 1668 (C=O). ¹H NMR (DMSO-d₆): δ/ppm: 1.3 (t, 6H, 2CH₃), 3.8 (q, 4H, 2CH₂), 6.3-8.4 (m, 11H, Ar-H), 10.2, 10.8 (2s, 2H, 2NH). Anal. Calcd for C₂₅H₂₁N₂O₄: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.20; H, 5.80; N, 10.40.

Synthesis of 6-(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: v/cm⁻¹: 3420, 3334 cm⁻¹ (NH) and 1728 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ/ppm: 5.0 (b, 2H, NH), 7.3-8.9 (m, 11H, Ar-H), MS, 315 (19.3%), 77 (100%). Anal. Calcd for C₁₆H₁₂N₂O₂: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.40; H, 4.10; N, 13.40.

6-(4’-Aminobiphenylsulfonyl)phenyl-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (11b) Yield: 80%; M.P.: 218-220°C; IR: v/cm⁻¹: 3463, 3371 cm⁻¹ (NH), 3062 cm⁻¹ (CH-aromat.), and 1689.5 cm⁻¹ (C=O); MS, 379 (18.8%), 106 (100%). Anal. Calcd for C₁₆H₁₂N₂O₂S: C, 60.15; H, 3.45; N, 11.08. Found: C, 60.10; H, 3.40; N, 11.00.

Synthesis of N-(4-(aminobiphenylsulfonyl)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); ¹H NMR (DMSO-d₆): δ/ppm: 4.9 (b, 2H, NH), 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 C₂₀H₁₈N₂O₂S: 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: v/cm⁻¹: 1660 cm⁻¹ (C=O); ¹H NMR (DMSO-d₆): δ/ppm: 7.2-9.0 (m, 10H, Ar-H), MS: m/z 370 (3.8%), 107 (100%). Anal. Calcd for C₂₀H₁₈N₂O₂: C, 64.87; H, 4.10; N, 15.13. Found: C, 64.90; H, 2.70; N, 15.10.

6,6’-(Biphenyl-4,4’-dilyl)bis(5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione) (14b) Yield: 80%; M.P.: >300°C; IR: v/cm⁻¹: 1728 cm⁻¹ (C=O). MS: 446 (100%). Anal. Calcd for C₂₉H₂₃N₄O₄: 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: v/cm⁻¹: 3328 (NH) and 1714, 1646 (C=O); ¹H NMR (DMSO-d₆): 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 C₂₅H₂₁N₂O₄: C, 66.28; H, 3.51; N, 16.27. Found: C, 66.30; H, 3.50; N, 16.30.

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Synthesis of 6,6'-[(4-chloro-1,2-phenylene)bis(5H-pyrrrolo[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). ¹H NMR (DMSO-d₆): δ/ppm: 7.2-8.9 (m, 9H, Ar-H); MS, m/z (%), 404 (M⁺;1.2%) 229(100). Anal. Calcd for C₂₅H₁₈N₂O₅: 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-amidoquinaxaline-3-carboxylic acid derivatives 2; while fusion with 1 of the same amines afforded 2-aminoquinoxaline derivatives 3. This reaction involved nucleophilic attack of amine at position-2 of anhydride forming 2 which loses CO₂ to form 3 (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 arylcarbamoylpyridine carboxylic 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, ¹H NMR 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 1746-1712 cm⁻¹ for C=O group. Additionally, compounds 6c-e showed bands in region compatible with aliphatic protons. ¹H NMR spectrum of 6a in (DMSO-d₆) 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, D₂O-exchangeable), 8.71 (s, 1H, OH, D₂O-exchangeable), 10.71 (s, 1H, OH, D₂O-exchangeable). ¹H NMR spectrum of the 6c showed signals at: δ = 1.30 (t, 3H, CH₃), 4.29 (q, 2H, CH₂), 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-C=O); 64.12%), 241 (M-COOH; 15.22%), 268 (M-H₂O; 21.44%), 120 (C₆H₄N=N=C=O; 12.0%), 106 (C₆H₄NO; 100), 78 (pyridinyl moiety; 90.71%), 77 (pyridyne; 14.8%).

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Pyrrrolo[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 reflux. 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.¹¹H NMR spectrum (DMSO-d₆) of 7c displayed the following signals at δ: 1.3 (t, 3H, CH₃), 4.3 (q, 2H, CH₂), 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-CO₂; 23%), 77 (C₆H₅; 100%).

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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 nicotiamide 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 nicotiamide derivatives 8a-e was characterized chemically and by their elemental analysis and careful inspection of their spectral IR, 1H NMR, 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 for NH,OH groups and band in 1696-1660 cm⁻¹ for C=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. 1H NMR spectrum of 8a displayed the following signals at: δ = 1.33 (t, 3H, CH₂), 4.9 (q, 2H, CH₂), 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 1H NMR spectrum of 9b were at: δ = 1.3 (t, 6H, 2CH₃), 3.8 (q, 4H, 2CH₂), 10.2, 10.8 (2s, 2H, 2NH). The mass spectrum of compound (9b; C₁₉H₁₂N₂O₃) revealed a molecular ion peak at m/z 433 (M⁺; 11%) 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 (pyridine; 8.9%).

The present investigation was extended to cover the behavior of 2,3-pyridine dicarboxylic anhydride 4 towards some binculeophiles. 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 binculeophiles.](image)

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 C₁₉H₁₂N₂O₃ 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 C₁₉H₁₃N₃O₄S 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 (NH₂-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 C₁₈H₁₅N₃O₃S 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](http://astonjournals.com/csj)

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: C₁₇H₁₀N₄O₄) 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: C₁₉H₁₁N₄O₃) 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: C₂₅H₁₆N₄O₃) 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 range.
1, characteristic of the carbonyl group. Also, the mass spectrum of compound (17: C_{20}H_{9}ClN_{4}O_{4}) showed a molecular ion peak at m/z 404 (M⁺; 1.2%) with base peak at m/z 229.

![Scheme 5](http://astonjournals.com/csj)

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>
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<th>Gram -ve</th>
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Table 1: Antimicrobial activity data of some synthesized compounds.
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.

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