Synthesis of 1,2-Di-(4-pyridyl)ethylenediamine and Related Compounds

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Hydrolysis of *N,N'*-diacyl-1,2-di(4-pyridyl)ethylenediamines **1** in aqueous sulfuric acid gave the corresponding imidazolines **3**. 1,2-Di-(4-pyridyl)ethylenediamine **2** was prepared in 61% yield by treating *N,N'*-di-*t*-butyloxycarbonyl-1,2-di(4-pyridyl)ethylenediamine **4** with trifluoroacetic acid or in 94% yield by the hydrolysis under basic conditions of *N,N'*-diphthaloylglycyl-1,2-di(4-pyridyl)ethylenediamine **13**.

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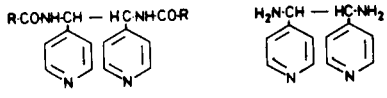
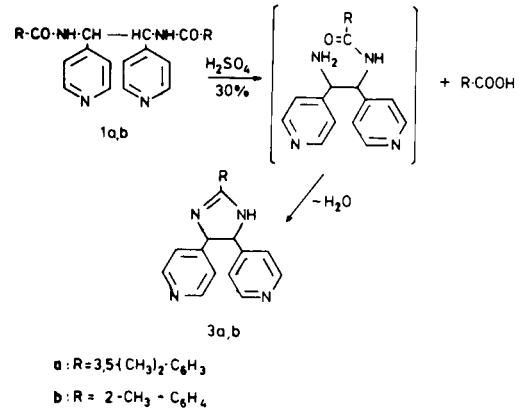
In previous papers [1-3] we reported the synthesis and pharmacological properties of a series of *N,N'*-diacyl-1,2-di(4-pyridyl)ethylenediamines **1**. Due to the low solubility of these compounds in aqueous media, we have been interested in the synthesis of soluble analogues, which might act as prostaglandin synthetase inhibitors.



1 2

As a point of departure we chose the simplest compound, *i.e.*, 1,2-di(4-pyridyl)ethylenediamine **2**. Initially, we attempted the synthesis of **2** by hydrolysis of **1**.

In the several attempts to hydrolize **1a** (R = 3,5-$(CH_3)_2$-C_6H_3) under basic conditions, only 3,5-dimethylbenzoic acid could be isolated. However, hydrolysis of **1** (**a**, R = 3,5-$(CH_3)_2$-C_6H_3; **b**, 2-CH_3-C_6H_4) in 30% aqueous sulfuric acid led to the formation of the imidazoline **3** and the corresponding benzoic acid (Scheme 1). Compounds **3a,b** were characterized by their ir, nmr and ms.



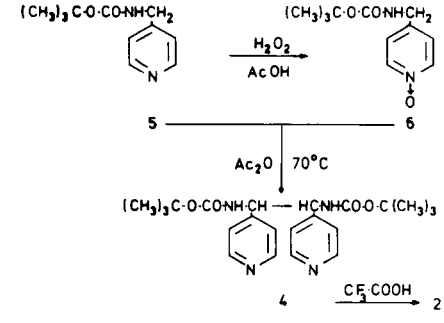
1a,b 3a,b

a : R = 3,5-$(CH_3)_2$-C_6H_3

b : R = 2-CH_3-C_6H_4

SCHEME 1

Secondly, it was decided to attempt the synthesis of **2** by treatment of *N,N'*-di-*t*-butyloxycarbonyl-1,2-di(4-pyridyl)-ethylenediamine **4** with trifluoracetic acid; in this way compound **4** has been prepared by reaction of *N*-*t*-butyloxycarbonyl-4-pyridylmethylamine **5** with its *N*-oxide **6** in presence of acetic anhydride [3]. Treatment of **4** with trifluoroacetic acid at room temperature provided the desired product **2** in 61% yield (Scheme 2).

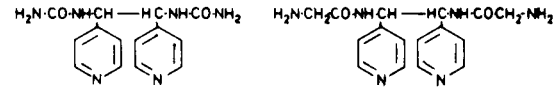


5 6 4 2

SCHEME 2

The infrared (ir) spectrum of **2** exhibited an absorption band for amine group. The ^1H nmr spectrum showed signals at δ 2.4 (s, 4H, $2NH_2$), 3.9 (s, 2H, 2CH), 7.0 (d, 4H, $2H_3$ and $2H_5$-pyridine), 8.3 (d, 4H, $2H_2$ and $2H_6$-pyridine).

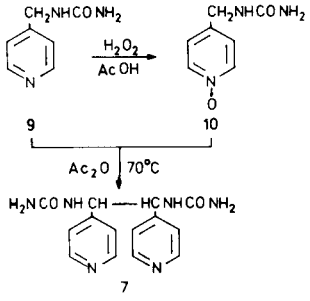
Continuing our interest in the synthesis of soluble ethylenediamines analogues, compound **7**, which might be transformed in the corresponding dihidrazino derivative by Hofmann rearrangement, has also received attention as well as the diglycylderivative **8**.



7 8

The synthesis of *N,N'*-dicarbamoyl-1,2-di(4-pyridyl)ethylenediamine **7** was accomplished by reaction of *N*-(4-pyri-

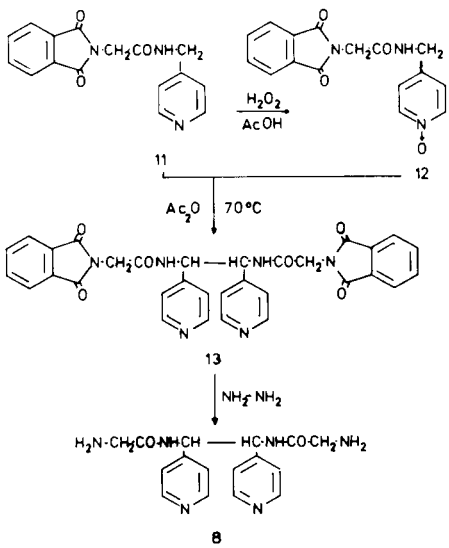
dylmethyl)urea **9** [4] with its *N*-oxide **10** in presence of acetic anhydride [3] (Scheme 3).



SCHEME 3

The ir spectrum of **7** showed absorption bands for amide group. The ^{1}H nmr spectrum showed signals at δ 4.8 (d, 2H, 2NH), 5.3 (s, 4H, $2NH_2$), 6.3 (d, 2H, 2CH), 6.9 (d, 4H, $2H_3$ and $2H_5$-pyridine), 8.2 (d, 4H, $2H_2$ and $2H_6$-pyridine). All attempts to convert **7** in the dihidrazino derivative were unsuccessful.

For the preparation of *N,N'*-diglycyl-1,2-di(4-pyridyl)ethylenediamine **8**, we considered the synthetic path-way represented in the Scheme 4.



SCHEME 4

The reaction of phthaloylglycine with ethyl chloroformate under basic conditions followed by treatment with 4-aminomethylpyridine lead to the formation of *N*-(4-pyridylmethyl)phthaloylglycinamide **11**. The oxidation of **11** with hydrogen peroxide in acetic acid afforded the *N*-oxide **12**.

Heating to 70° a mixture of **11** (1 equivalent) with **12** (1 equivalent) and acetic anhydride furnished the *N,N'*-diphthaloylglycyl-1,2-di(4-pyridyl)ethylenediamine **13** in practically quantitative yield.

Finally, when **13** was treated with hidrazine under different reaction conditions, only phthalazone could be isolated. Attempts to obtain **8** by hydrolysis of **13** under basic conditions were unsuccessful, resulting 1,2-di(4-pyridyl)-ethylenediamine **2** as the sole isolated product (in 94% yield).

EXPERIMENTAL

The melting points were obtained on a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer (potassium bromide disc). The ^{1}H nmr spectra were determined with a Varian T-60 and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT 711 spectrometer. The elemental analyses were performed by Centro Nacional de Química Orgánica, Madrid.

Hydrolysis of *N,N*-Di(3,5-dimethylbenzoyl)-1,2-di(4-pyridyl)ethylenediamine.

A solution of **1a** [3] (2 g, 0.004 mole) in 200 ml of 30% sulfuric acid was refluxed for 6 hours, and the resulting precipitate was collected by suction filtration. Recrystallization from ethanol/water afforded 0.4 g (64%) of 3,5-dimethylbenzoic acid.

The above aqueous solution was made basic with 30% sodium hydroxide, extracted with chloroform and the chloroform layer was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure provide an oil which was treated with petroleum ether to give 2-(3,5-dimethylphenyl)-4,5-di(4-pyridyl)-2-imidazoline **3a** (0.9 g, 66%), mp > 275° (benzene-petroleum ether); ir: ν cm^{-1} 3200 (NH), 1600, 1570, 1500 (C=C, C=N); ^{1}H nmr (deuterated dimethylsulfoxide): 2.3 (s, 6H, $2CH_3$), 4.7 (s, 2H, H_4 and H_5-imidazoline), 7.0-7.2 (m, 5H, H_4-phenyl, $2H_3$ and $2H_5$-pyridine), 7.5 (s, 2H, H_2 and H_6-phenyl), 8.4 (d, 4H, $2H_2$ and $2H_6$-pyridine); ms: m/e 328 (M^+).

Anal. Calcd. for $C_{21}H_{20}N_4$: C, 76.80; H, 6.14; N, 17.06. Found: C, 76.94; H, 6.16; N, 17.14.

Hydrolysis of *N,N'*-Di(2-methylbenzoyl)-1,2-di(4-pyridyl)ethylenediamine.

A solution of **1b** [3] (5 g, 0.11 mole) in 350 ml of 30% sulfuric acid was refluxed for 6 hours, and the resulting precipitate was collected by suction filtration. Recrystallization from water afforded 1.1 g (73%) of *o*-toluic acid.

The above aqueous solution was made basic with 30% sodium hydroxide, extracted with chloroform and the chloroform layer was dried over anhydrous sulfate. Removal of the solvent under reduced pressure provide an oil which was treated with *n*-hexane to give 2-(2-methylphenyl)-4,5-di(4-pyridyl)-2-imidazoline **3b** (0.7 g, 20%), mp 205-206° (ethanol/ethyl acetate); ir: ν cm^{-1} 3000 (NH), 1600, 1570, 1500 (C=C, C=N); ^{1}H nmr (deuterated dimethylsulfoxide): 2.5 (s, 3H, CH_3), 4.7 (s, 2H, H_4 and H_5-imidazoline), 7.0-7.5 (m, 8H, 4H-phenyl, $2H_3$ and $2H_5$-pyridine), 8.3 (d, 4H, $2H_2$ and $2H_6$-pyridine); ms: m/e 314 (M^+).

Anal. Calcd. for $C_{20}H_{18}N_4$: C, 76.40; H, 5.77; N, 17.82. Found: C, 76.11; H, 5.67; N, 17.50.

N-t-Butyloxycarbonyl-4-pyridylmethylamine (**5**).

To a solution of 4-aminomethylpyridine (10.8 g, 0.1 mole) and triethylamine (40 g, 0.4 mole) in water/dioxane (500 ml, 1:1) was added *t*-butyloxycarbonylazide (17 ml). The reaction mixture was stirred at room temperature for 30 hours, diluted with 300 ml of water, extracted with chloroform and the chloroform layer was dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure afforded **5** (17.7 g, 85%), mp 88-89° (cyclohexane); ir: ν cm^{-1} 3220 (NH), 1700 (CO), 1600, 1570 (C=C, C=N), 1390, 1360 ($C(CH_3)_3$); ^{1}H nmr (deuteriochloroform): 1.4 (s, 9H, $C(CH_3)_3$), 4.2 (d, 2H, CH_2), 5.0 (m, 1H, NH), 7.0 (d, 2H, H_3 and H_5-pyridine), 8.4 (d, 2H, H_2 and H_6-pyridine).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.65; H, 7.80; N, 13.57.

N-t-Butyloxycarbonyl-4-pyridylmethylamine *N*-Oxide (**6**).

To a solution of **5** (5 g, 0.024 mole) in glacial acetic acid (100 ml) was added hydrogen peroxide (20 ml, 36% w/v). The solution was heated on a water bath and the completion of the reaction was determined by tlc. The solution was then reduced *in vacuo*, diluted with water and the solvent was evaporated *in vacuo*. The resulting oil **6** was dried and this material was used in the next step without further purification.

N,N'-Di-*t*-butyloxycarbonyl-1,2-di(4-pyridyl)ethylenediamine (**4**).

A mixture of **5** (1 g, 0.0048 mole) and **6** (1 g, 0.0048 mole) in acetic anhydride (3 ml) was heated to 70° on a water bath for 3 hours. The resulting precipitate was collected and washed with ethyl acetate to give **4** (1.3 g, 65%), mp 253° (*N,N*-dimethylformamide); ir: ν cm^{-1} 3380 (NH), 1680 (CO), 1600, 1520 (C=C, C=N), 1390, 1360 ($C(CH_3)_3$); ^1H nmr (trifluoroacetic acid): 1.5 (s, 18H, 2 $C(CH_3)_3$), 6.0 (s, 2H, 2CH), 8.4 (d, 4H, $2H_3$ and $2H_5$-pyridine), 8.8 (d, 4H, $2H_2$ and $2H_6$-pyridine).

Anal. Calcd. for $C_{22}H_{30}N_4O_4$: C, 63.74; H, 7.29; N, 13.51. Found: C, 63.92; H, 7.58; N, 13.40.

1,2-Di(4-pyridil)ethylenediamine (**2**).

A solution of **4** (2.5 g, 0.006 mole) in trifluoroacetic acid (7 ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into water (100 ml), washed with chloroform and the aqueous layer was made alkaline. The resulting precipitate **2** (0.8 g, 61%) was filtered off and recrystallized from water, mp 160-162°; ir: ν cm^{-1} 3500-3000 (NH_2), 1630, 1560 (C=C, C=N); ^1H nmr (deuterated dimethylsulfoxide): 2.4 (s, 4H, $2NH_2$), 3.9 (s, 2H, 2CH), 7.0 (d, 4H, $2H_3$ and $2H_5$-pyridine), 8.3 (d, 4H, $2H_2$ and $2H_6$-pyridine).

Anal. Calcd. for $C_{12}H_{14}N_4 \cdot 2H_2O$: C, 57.58; H, 7.25; N, 22.38. Found: C, 57.51; H, 7.56; N, 22.27.

N-(4-Pyridylmethyl)urea (**9**).

A mixture of 4-aminomethylpyridine (10 g, 0.09 mole) and potassium cyanate (20 g, 0.24 mole) in water (70 ml) was refluxed for 3 hours. The reaction mixture was allowed to stand at room temperature for 1 hour and the precipitate obtained was filtered. Crystallization from water yielded **9** (9.8 g, 72%), mp 190-192°, reported [4] mp 187-191°. ir: ν cm^{-1} 3400, 3300 (NH_2, NH), 1660 (C=O), 1610, 1500 (C=C, C=N); ^1H nmr (deuterated dimethylsulfoxide): 4.1 (d, 2H, CH_2), 5.5 (s, 2H, NH_2), 6.4 (t, 1H, NH), 7.0 (d, 2H, H_3 and H_5-pyridine), 8.3 (d, 2H, H_2 and H_4-pyridine).

N-(4-Pyridylmethyl)urea *N*-Oxide (**10**).

To a solution of **9** (3 g, 0.02 mole) in glacial acetic acid (75 ml) was added hydrogen peroxide (15 ml, 40% w/v). The solution was heated on a water bath and the completion of the reaction was determined by tlc. The solution was then reduced *in vacuo* to 1/3 of its volume, diluted with water and ethanol and the solvents were evaporated *in vacuo*. The residue was washed with acetone and recrystallized from *N,N'*-dimethylformamide to give **10** (2.6 g, 78%), mp 200-201°; ir: ν cm^{-1} 3390, 3300 (NH_2, NH), 1660 (CO), 1570 (Ar), 1240 (N→O); ^1H nmr (trifluoroacetic acid): 4.8 (s, 2H, CH_2), 7.8 (d, 2H, H_3 and H_5-pyridine), 8.6 (d, 2H, H_2 and H_6-pyridine).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.42; N, 25.13. Found: C, 49.98; H, 5.46; N, 24.92.

N,N'-Dicarbamoyl-1,2-di(4-pyridyl)ethylenediamine (**7**).

A mixture of **9** (1.4 g, 0.009 mole) and **10** (1.5 g, 0.009 mole) in acetic anhydride (4 ml) was heated to 70° on a water bath for 3 hours. The resulting precipitate was collected and washed with ethyl acetate to give **7** (1.4 g, 52%), mp 248-250° (dimethylsulfoxide/ethanol); ir: ν cm^{-1}, 3440, 3300 (NH_2, NH), 1670 (CO), 1600, 1530 (C=C, C=N), ^1H nmr (deuterated dimethylsulfoxide): 4.8 (d, 2H, 2NH), 5.3 (s, 4H, $2NH_2$), 6.3 (d, 2H, 2CH), 6.9 (d, 4H, $2H_3$ and $2H_5$-pyridine), 8.2 (d, 4H, $2H_2$ and $2H_6$-pyridine).

Anal. Calcd. for $C_{14}H_{16}N_6O_2$: C, 55.99; H, 5.37; N, 27.98. Found: C, 55.87; H, 5.40; N, 27.88.

N-(4-Pyridylmethyl)phthaloylglycinamide (**11**).

A solution of phthaloylglycine (10.3 g, 0.05 mole) and triethylamine (5 g, 0.05 mole) in anhydrous acetone (50 ml) was cooled to −10° and ethyl chloroformate (5.4 g, 0.05 mole) was added dropwise. The mixture was stirred at −10° for 1 hour and then 4-aminomethylpyridine (5.4 g, 0.05 mole) in water (25 ml) was added. The mixture was stirred 4 hours at room temperature. The precipitate obtained was filtered and then treated with 20% hydrochloric acid. The aqueous solution was made basic with sodium carbonate to precipitate **11** (9 g, 61%), mp 216-217° (ethanol); ir: ν cm^{-1} 3300 (NH), 1770, 1720 (NCO), 1660 (CONH), 1610, 1600, 1570 (C=C, C=N); ^1H nmr (deuterated dimethylsulfoxide): 4.2 (s, 4H, $2CH_2$), 7.1 (d, 2H, H_3 and H_5-pyridine), 7.7 (s, 4H, 4H-phthaloyl), 8.3 (d, 2H, H_2 and H_6-pyridine), 8.7 (t, 1H, NH).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.21; H, 4.32; N, 14.43.

N-(4-Pyridylmethyl)phthaloylglycinamide *N*-Oxide (**12**).

To a solution of **11** (10 g, 0.034 mole) in glacial acetic acid (250 ml) was added hydrogen peroxide (40 ml, 36% w/v). The solution was heated on a water bath and the completion of the reaction was determined by tlc. The solution was then reduced *in vacuo* to 1/3 of its volume and alkalinized with sodium carbonate. The precipitate product **12** (5.1 g, 49%) was filtered off and recrystallized from *N,N*-dimethylformamide/ethanol, mp 252-253°; ir: ν cm^{-1} 3300 (NH), 1770, 1720 (NCO), 1660 (CONH), 1560, 1550 (C=C, C=N), 1240 (N-O); ^1H nmr (trifluoroacetic acid): 4.8 (m, 4H, $2CH_2$), 7.9 (m, 6H, 4H-phthaloyl, H_3 and H_5-pyridine), 8.6 (d, 2H, H_2 and H_6-pyridine).

Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.49. Found: C, 61.59; H, 4.22; N, 13.42.

N,N'-Diphthaloylglycyl-1,2-di(4-pyridyl)ethylenediamine (**13**).

A mixture of **11** (3.8 g, 0.013 mole) and **12** (4 g, 0.013 mole) in acetic anhydride (10 ml) was heated to 70° on a water bath for 3 hours. The resulting precipitate was collected and washed with ethyl acetate to give **13** (7.32 g, 96%), mp 323° (acetic acid); ir: ν cm^{-1} 3300 (NH), 1770, 1720 (NCO), 1670 (CONH), 1600, 1540 (C=C, C=N); ^1H nmr (trifluoroacetic acid): 4.4 (s-broad, 4H, $2CH_2$), 6.2 (s-broad, 2H, 2CH), 7.6 (s, 8H, 8H-phthaloyl), 8.2 (d, 4H, $2H_3$ and $2H_5$-pyridine), 8.7 (d, 4H, $2H_2$ and $2H_6$-pyridine).

Anal. Calcd. for $C_{32}H_{24}N_6O_6$: C, 65.30; H, 4.11; N, 14.28. Found: C, 64.96; H, 4.29; N, 14.44.

Hydrolysis of **13**.

A solution of **13** (4 g, 0.0068 mole) in 100 ml of 30% sodium hydroxide was refluxed for 6 hours, and the resulting precipitate was collected by suction filtration. Recrystallization from water afforded 1.6 g (94%) of **2**.

REFERENCES AND NOTES

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[4] T. Gostea, G. Nicoara and A. Maza, *Rev. Chim. (Bucharest)*, **22**, 711 (1971).