The Synthesis of Pyrimido[4,5-*b*][1,4]diazocines and Pyrido[2,3-*b*][1,4]diazocines

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The reaction conditions for the preparation of 7*H*,8*H*-1,3-dimethyl-2,4,6,9-tetraoxopyrimidino[4,5-*b*][1,4]-diazocine (**9**), 1,3-dimethyl-2,4,6,11-tetraoxobenzo[*f*]pyrimidino[4,5-*b*][1,4]diazocine (**10**), 7*H*,8*H*-1,3-dimethyl-2,4,6,10-tetraoxopyrimidino[4,5-*b*][1,4]diazonine (**16**), and 7*H*,8*H*-6,9-dioxopyridino[2,3-*b*][1,4]diazocine (**19**) were determined. The mechanism of the formation of these compounds was established. The scope of these reactions was found to be general for eight and nine ring formation from 2,3-diamino-*N*-heterocycles.

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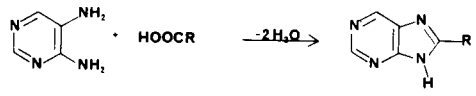
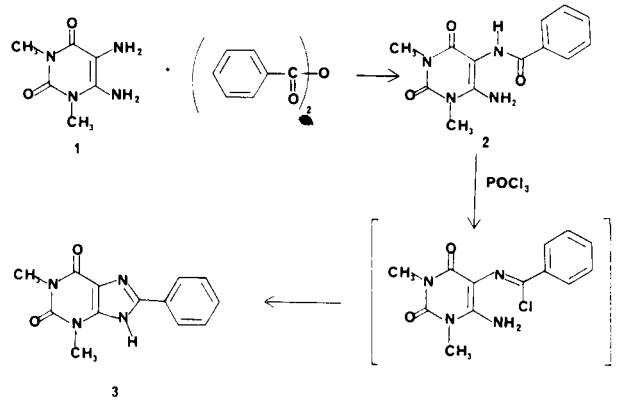
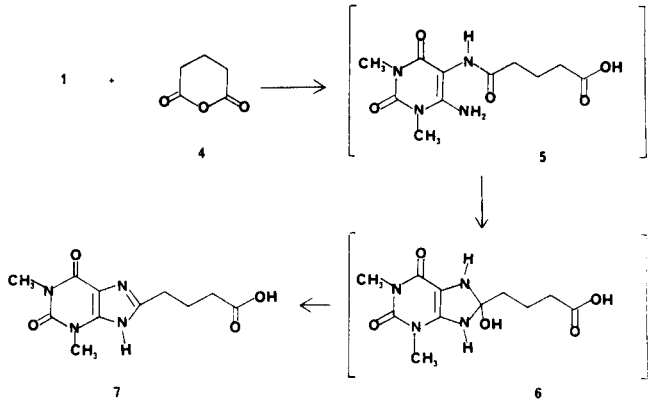
A variety of purines exist in nature including caffeine, theophylline, adenine, and other biologically important chemicals. A large volume of chemistry has been devoted to exploring the properties of this class of compounds. One well-known reaction is the synthesis of 8-substituted purines, the Traube synthesis [1,2]. This reaction is accomplished by condensing a 4,5-diaminopyrimidine with a



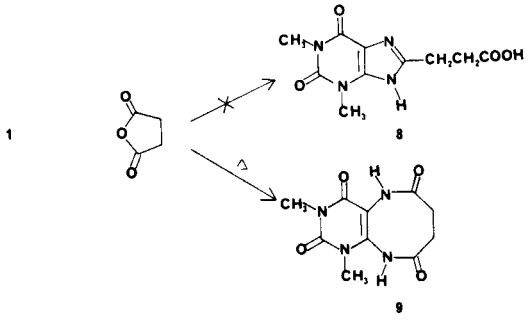
carboxylic acid to give an 8-substituted purine, where the substituent on the 8-position is determined by the type of carboxylic acid used. The condensation of the carboxylic acid with the diaminopyrimidine is generally accomplished using either a condensing agent (*i.e.*, phosphorus oxychloride), or elevated temperatures (usually greater than 200°) [3,4]. An example of this reaction is the condensation



of benzoic anhydride with 5,6-diamino-1,3-dimethylpyrimidine-2,4-dione (**1**) giving an amide, **2**. When treated with phosphorus oxychloride, **2** gives rise to a purine, **3** [5]. The amide linkage is mostly likely converted to an imidoyl chloride which undergoes rapid cyclization to the aromatic product. In another example of the Traube reaction, the condensation is accomplished with heat. The condensation of **1** with glutaric anhydride gives **7** in 38% yield [6]. An amide (**5**) is formed on initial heating which



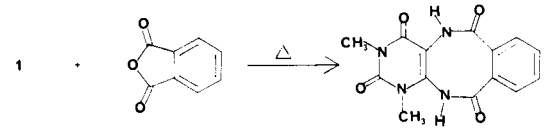
then cyclizes to the purine product **7**. If this same reaction is attempted with succinic anhydride instead of glutaric anhydride, the expected 8-substituted theophylline **8** is not obtained. Instead, a fused pyrimido[4,5-*b*][1,4]diazocine (**9**) is formed in 55% yield. This unexpected reaction seemed intriguing and the formation of the 1,4-diazocine ring



deserved closer inspection. Reported herein is the synthesis and mechanistic proposal for the formation of the

fused pyrimido[4,5-*b*][1,4]diazocines and related compounds.

Since 1,4-diazocines have been prepared in moderate yields in the past, [7,8] the formation of **9** was not without precedence. The unusual aspect of this reaction was that **9** had been prepared using the Traube conditions. To determine whether this reaction was specialized for succinic anhydride, phthalic anhydride was used as a reactant. Again, as in the previous case, purine ring formation did not occur, but the fused pyrimido[4,5-*b*][1,4]diazocine, **10** was obtained in 52% yield. It appeared from these examples that under certain conditions, the reaction clearly



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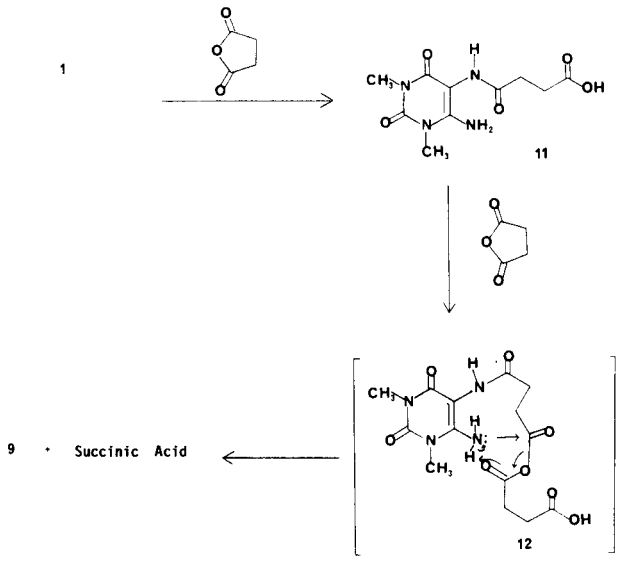
gives fused diazocine products in preference to the purine. A reasonable explanation for this is shown in the Scheme 1. As in the previous example with glutaric anhydride, succinic anhydride and **1** should give amide **11** when heated

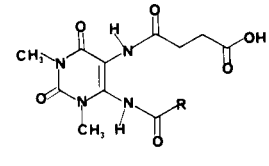
Scheme 1



together. It is unlikely that the amine function of **11** will react directly with the carbonyl of the acid for cyclization. Since the reaction conditions call for two moles of succinic anhydride, it would be more likely that an activated acid is formed such as an anhydride, before the reaction takes place. The second mole of succinic anhydride would then react with **11** to give **12**. This would be followed by cyclization through the six membered transition state shown, to give the diazocine product **9**. Before this could be established as the most acceptable mechanism, several details needed to be examined more closely.

First, **11** needed to be prepared and isolated. This was accomplished in 63% yield by refluxing **1** with succinic anhydride in toluene. Product **11** was heated to reflux in *N,N*-dimethylaniline for 4 hours, but only unreacted **11** was present in the reaction mixture. Since the original reaction conditions called for two equivalents of succinic anhydride, **11** was heated with one equivalent of succinic anhydride in *N,N*-dimethylaniline to reflux. This gave diazocine **9** in the same yield as the original conditions. To determine whether high temperatures were necessary, an excess of succinic anhydride was refluxed with **1** in toluene. A 75% yield of diazocine **9** was obtained. It was clear that the high temperatures required for purine formation were not necessary for the preparation of the diazocine ring. The above results establish the presence of **11** as an intermediate. The facts that two equivalents of succinic anhydride were necessary for the reaction to take place, extremely high temperatures were not necessary for the reaction to take place, and **11** would not condense readily without succinic anhydride preclude the possibility that the acid of **11** would condense with the amine to give the amide linkage of the diazocine directly. If an activated acid (such as an anhydride) was an intermediate; any anhydride prepared from **11** should cyclize to a diazocine. To test this idea, **11** was treated with acetic anhydride in pyridine to successfully give **9** in 79% yield.

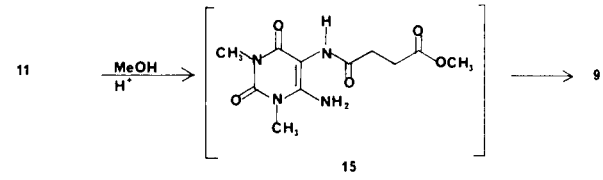
So far all of these results are consistent with the proposed mechanism, but this does not rule out the possible formation of a diamide intermediate such as **13** or **14**. Although **13** and **14** are unlikely intermediates in the condensation to form the diazocine, it is possible that their



13 R = CH_2CH_2COOH

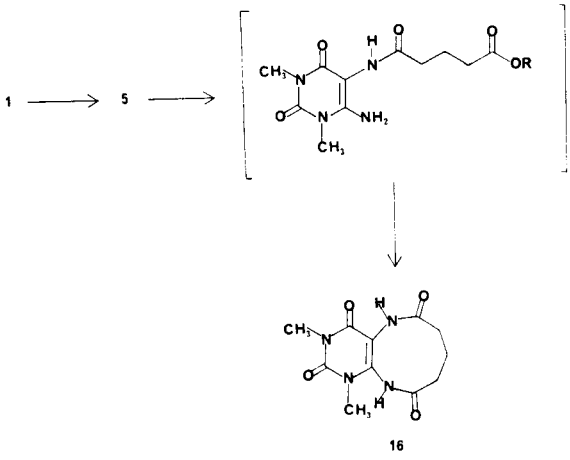
14 R = CH_3

formation would interfere with the formation of **9**. To help establish the idea that **13** and **14** were not intermediates, an indirect examination of the reaction was necessary. Previously, only anhydride derivatives of **11** were prepared. The preparation of a less reactive acid derivative, such as an ester, would not alter the amine functionality and should cyclize to the diazocine **9** on heating. The preparation of the methyl ester (**15**) was attempted by refluxing the acid (**11**) with *p*-toluenesulfonic



acid in methanol. Unexpectedly, although not unwelcomed, **15** was not isolated, instead a 55% yield of the diazocine **9** was obtained. This demonstrates that any reactive carboxylic acid derivative would condense with the amino functionality to form the diazocine product. This also implies that any reaction of the carboxylic acid which results in a reactive intermediate such as an anhydride or ester would result in cyclization to give the diazocine. Again this gives support for the mechanism in Scheme 1.

In the reaction, the condensation to form the eight-membered ring competes with the condensation which gives the five-membered ring. Since the five-ring is generally formed at high reaction temperatures (> 200°), and the activated acid derivative gives the eight-ring at low temperatures, the condensation of **1** with glutaric anhydride should also give the nine-membered ring **16** at lower temperatures. When **1** was heated with glutaric anhydride in toluene, **5** was obtained in 44% yield. When



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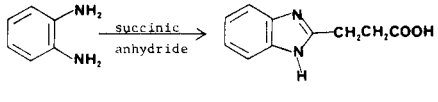
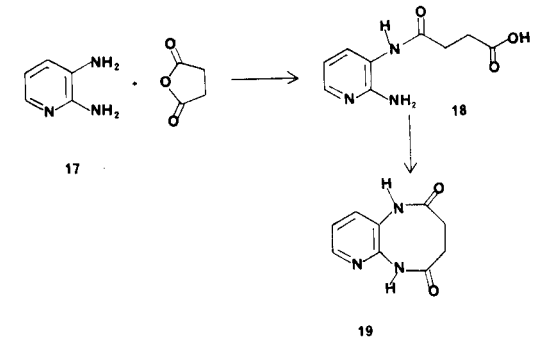
the mixed anhydride of **5** was prepared using acetic anhydride, **16** was subsequently formed in 32% yield (14% from **1**).

One factor of the reaction which has not been discussed yet is the nature of the nitrogen nucleophile which condenses with the carbonyl to give the cyclic purine or diazocine ring. If both nitrogens are similar nucleophiles, as in 1,2-diaminobenzene, reaction with succinic anhydride gives the benzimidazole [9]. This reaction is



similar to the Traube synthesis of purines; however, it is a more facile reaction. The conditions for condensation are simply heating in toluene (110°) and azeotroping the water out of solution. This condensation is much more difficult when one amine nitrogen is a poor nucleophile. It is known that the amine nitrogen at the 6-position of the starting pyrimidine is a very weak nucleophile [2] due to the adjacent nitrogen within the ring; this makes the amine as poor a nucleophile as the nitrogen of an amide. In contrast to the benzimidazole synthesis, the condensation to form an eight-ring should be general for vicinal diamines where one amine is a weak nucleophile. To determine the general nature of this reaction, another vicinal diamine, 2,3-diaminopyridine (**17**), was used in diazocine formation. Here, the NH_2 in the 2 position is weakly nucleophilic, but the NH_2 in the 3 position is a good nucleophile. When **17** was treated with succinic anhydride in refluxing pyridine, **18** was prepared in 55% yield. The crude product, **18**, was then treated with acetic anhydride



in pyridine, and **19** was formed in 46% yield. These results help demonstrate that the reaction is general to a variety of 2,3-diamino-*N*-heterocycles where one amine exhibits a more typical nucleophilic character, while the other is weakly nucleophilic.

In summary, reaction conditions for the preparation of two fused pyrimido[1,4]diazocines, a pyrimido[1,4]diazonine, and a pyrido[1,4]diazocine were determined. The mechanism of the formation of these compounds has been established (Scheme 1). And finally, the general scope of these reactions was shown for eight and nine ring formation from 2,3-diamino-*N*-heterocycles.

EXPERIMENTAL

Melting points were obtained on a Buchi 510 melting point apparatus utilizing open capillary tubes and are uncorrected as reported. Infrared spectra were obtained on a Nicolet MX-1 infrared spectrophotometer, and all absorptions were reported in wave numbers (cm^{-1}). The nmr spectra were obtained on Varian EM-360, Perkin-Elmer R-32, or Varian FT-80 A (^{13}C) spectrophotometers. Both proton and carbon spectra were reported in parts per million (ppm) downfield from internal tetramethylsilane. Chemical ionization (ci) and electron impact (ei) mass spectra were obtained using a Fennigan series 4000 mass spectrometer.

7*H*,8*H*-1,3-Dimethyl-2,4,6,9-tetraoxopyrimido[4,5-*b*][1,4]diazocine (**9**). Method A.

A mixture of 5.10 g (27.1 mmoles) of 5,6-diamino-1,3-dimethyluracil hydrate (Aldrich) and 6.00 g (60.0 mmoles) of succinic anhydride (Aldrich) was heated to reflux in 30 ml of *N*,*N*-dimethylaniline under

nitrogen as water was removed using a Dean-Stark trap. After 1.5 hours, the mixture was cooled to room temperature and filtered. The resulting crude product was recrystallized with water (1 g in 10 ml of water) giving 4.00 g (14.8 mmoles, 55% yield) of white crystals (dihydrate), mp 131-133° dec; ir (0.5% potassium bromide): 3500, 3375, 3120, 1725, 1675, 1640, 1600, 1525, 1425, 1390, 1200, and 775 cm^{-1}; ^1H nmr (d_6DMSO): δ 7.05 (2H, brs, N*H*), 3.55 (4H, s, H_2O), 3.50 (3H, s, CH_3), 3.22 (3H, s, CH_3), and 2.77 (4H, s, CH_2); ^{13}C nmr (d_6DMSO): 177.8 (2C), 158.3, 152.7, 150.6, 82.4, 30.1, 28.7 (2C), and 27.8 ppm; ms: (ei) m/e (relative intensity) 252 (100, M^+), 224 (23), 207 (37), 169 (65), 155 (24), and 83 (32).

Anal. Calcd. for $C_{10}H_{12}N_4O_4 \cdot 2H_2O$: C, 41.67; H, 5.59; N, 19.44; H_2O, 12.50. Found: C, 41.50; H, 5.59; N, 19.11; H_2O (Karl Fischer) 12.50.

Method B.

A mixture of 1.90 g (10.1 mmoles) of 5,6-diamino-1,3-dimethyluracil hydrate (Aldrich) and 5.00 g (50.0 mmoles) of succinic anhydride (Aldrich) in 35 ml of toluene was heated to reflux for 3 hours. While the mixture was still hot, the toluene was decanted off of the remaining solid. The solid was dissolved in 20 ml of boiling water and cooled to room temperature. Refrigeration gave a newly formed solid which was filtered. Air drying gave 1.90 g (7.54 mmoles, 75% yield) of white crystals, mp 135-137° dec. The spectral data was the same as the spectra for the product from Method A.

Method C.

A mixture of 4.45 g (23.6 mmoles) of 5,6-diamino-1,3-dimethyluracil hydrate (Aldrich) and 2.38 g (23.8 mmoles) of succinic anhydride in 40 ml of toluene was heated to reflux. After 1 hour, the mixture was cooled to room temperature and filtered giving 5.96 g of yellow powder. This was recrystallized with 75 ml of water giving 4.01 g (14.9 mmoles, 63% yield) of off-white crystals (acid, **11**), mp 248-249°; ir (0.5% potassium bromide): 3375, 3210, 3000 (br), 1720, 1690, 1660, 1625, 1590, 1500, 1250, 1200, and 775 cm^{-1}; ^1H nmr (d_6DMSO): δ 11.4 (1H, brs, COO*H*), 8.71 (1H, s, N*H*CO), 6.62 (2H, s, NH_2), 3.41 (3H, s, NCH_3), 3.19 (3H, s, NCH_3), and 2.55 (4H, s, CH_2); ^{13}C nmr (d_6DMSO): 174.2, 171.5, 159.3, 151.9, 150.3, 87.2, 30.0, 29.9, 29.3 and 27.4 ppm; ms: (ei) m/e (relative intensity) 270 (10, M^+), 252 (53), 207 (33), 170 (80), 169 (100), 142 (28), and 83 (58).

Anal. Calcd. for $C_{10}H_{14}N_4O_5$: C, 44.45; H, 5.22; N, 20.73. Found: C, 44.25; H, 5.26; N, 20.87.

A mixture of 1.00 g (3.70 mmoles) of this solid (**11**) and 334 ml (361 mg, 3.50 mmoles) of acetic anhydride (Fischer) in 5 ml of pyridine was heated to reflux. After 30 minutes the mixture was filtered, the pyridine was removed under reduced pressure and the remaining solid was recrystallized with 10 ml of water giving 794 mg (2.8 mmoles, 79% yield, 50% from 5,6-diamino-1,3-dimethyluracil) of white crystals, mp 131-134° dec. The spectral data was the same as the spectra for the product from Method A.

Method D.

A mixture of 2.04 g (7.56 mmoles) of succinamide **11** (from Method C) and 0.53 g of *p*-toluenesulfonic acid hydrate (Aldrich) in 150 ml of methanol was heated at reflux for 30 hours. To the cooled mixture, 0.217 g of anhydrous sodium bicarbonate was added. After warming to reflux for 5 minutes, the mixture was cooled to 0°. This was filtered, and the solvent was removed under reduced pressure. The solid residue was dissolved in 10 ml of boiling water and cooled to 0°. The white solid which precipitated was filtered and air dried giving 1.20 g (4.18 mmoles, 55% yield) of white crystals, mp 131-134° dec. The spectral data was the same as the spectra for the product from Method A.

1,3-Dimethyl-2,4,6,11-tetraoxobenzo[*f*]pyrimido[4,5-*b*][1,4]diazocine (**10**).

A mixture of 5.00 g (26.5 mmoles) of 5,6-diamino-1,3-dimethyluracil hydrate (Aldrich) and 7.90 g (26.5 mmoles) of phthalic anhydride (Aldrich) and 60 ml of *N,N*-dimethylaniline was treated under the conditions of Method A. Recrystallization of the solid product from 800 ml of 95% ethanol gave 4.50 g (13.8 mmoles, 52% yield) of pale yellow needles. An analytical sample was prepared by recrystallization from water (0.5 g in 300 ml) as a hydrated solid (1.5 moles of water), mp > 250°; ir (0.5% potassium bromide): 3400 (br), 3225, 1725, 1625 (br), 1510, 1380, 890, 750, and 660 cm^{-1}; ^1H nmr (d_6DMSO): δ 8.10 (4H, s, Ar*H*), 7.46 (2H, brs, N*H*), 3.39 (3H, s, CH_3), and 3.18 (3H, s, CH_3); ^{13}C nmr (TFA): 176.0, 171.2, 163.6, 157.2, 152.3, 137.1 (2C, Ar), 133.0 (2C, Ar), 125.8 (2C, Ar), 84.1, 31.7, and 30.3 ppm; ms: (ei) m/e (relative intensity) 300 (71, M^+), 256 (30), 132 (40), 104 (100), and 76 (62).

Anal. Calcd. for $C_{14}H_{12}N_4O_4 \cdot 1.5H_2O$: C, 54.69; H, 4.20; N, 18.22; H_2O, 2.34. Found: C, 54.57; H, 4.04; N, 18.08; H_2O (Karl Fischer) 2.32.

7*H*,8*H*-1,3-Dimethyl-2,4,6,10-tetraoxopyrimido[4,5-*b*][1,4]diazonine (**16**).

A mixture of 3.01 g (16.0 mmoles) of 5,6-diamino-1,3-dimethyluracil hydrate (Aldrich) and 1.82 g (16.0 mmoles) of glutaric anhydride in 40 ml of toluene was treated as in Method B. Filtration gave 4.10 g of off-white powder. Recrystallization from water gave 2.00 g (7.0 mmoles, 44% yield) of off-white powder, mp 227-228° dec. An analytical sample was prepared by recrystallization from 95% ethanol giving white crystals of **5**, mp 227-228° dec; ir (0.5% potassium bromide): 3425, 3350, 2995, 1725, 1705, 1655, 1640, 1610, 1510, 1235, 1190 and 775 cm^{-1}; ^1H nmr (d_6DMSO): δ 11.5 (1H, brs, COO*H*), 8.42 (1H, s, N*H*), 6.64 (2H, brs, NH_2), 3.35 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 2.1-2.3 (4H, m, $COCH_2$), and 1.7-2.0 (2H, brm, $CH_2CH_2CH_2$); ^{13}C nmr (d_6DMSO): 174.2, 172.4, 159.0, 151.8, 150.1, 87.1, 34.0, 32.8, 29.6, 27.1, and 20.1 ppm; ms: (ci) m/e (relative intensity) 285 (100, MH^+), 267 (86), 249 (32), 171 (23), and 115 (17).

Anal. Calcd. for $C_{11}H_{16}N_4O_5$: C, 46.48; H, 5.68; N, 19.71. Found: C, 46.09; H, 5.84; N, 19.43.

A mixture of 1.34 g (4.70 mmoles) of this solid **5** and 570 ml (6.03 mmoles) of acetic anhydride in 7.0 ml of pyridine was treated as in Method C. The solid residue was recrystallized by dissolving in 25 ml of boiling methanol, then treating with darco to remove color. After filtration, 100 ml of acetone was added and the mixture was concentrated to 15 ml. After cooling in the freezer, filtration gave 0.40 g (1.50 mmoles, 32% yield) of a white powder, mp > 275°; ir (0.5% potassium bromide): 3400 (br), 3240, 1700, 1660, 1630, 1590, 1525, 1370, 1260, 1190, 1150, 1010, and 780 cm^{-1}; ^1H nmr (d_6DMSO): δ 6.90 (1H, s, N*H*), 3.37 (3H, s, CH_3), 3.14 (3H, s, CH_3), 2.68 (4H, m, CH_2CO), and 1.8-2.1 (2H, brm, $CH_2CH_2CH_2$); ^{13}C nmr (d_6DMSO): 172.5 (2C), 157.7, 151.6, 150.2, 85.8, 32.1 (2C), 29.7, 27.2 and 16.3 ppm; ms: (ei) m/e (relative intensity) 266 (66, M^+), 207 (64), 194 (70), 170 (93), 169 (100), 155 (37), and 83 (30).

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.36; H, 5.36; N, 21.19.

7*H*,8*H*-6,9-dioxopyrido[2,3-*b*][1,4]diazocine (**19**).

A mixture of 1.54 g (14.1 mmoles) of 2,3-diaminopyridine (Aldrich) and 1.41 g (14.1 mmoles) of succinic anhydride (Aldrich) in 8 ml of pyridine was heated to reflux for 5 minutes. After cooling, the pyridine was removed under reduced pressure and the remaining solid was recrystallized from 95% aqueous ethanol giving 1.60 g (7.7 mmoles, 55% yield) of off-white needles (acid, **18**), mp 185-186°; ir (0.5% potassium bromide): 3290 (br), 3000 (br), 1690, 1675, 1560, 1530, 1405, 1380, 1300, 790, and 750 cm^{-1}; ^1H nmr (d_6DMSO): δ 9.22 (1H, s, N*H*), 7.88 (1H, dd, J = 1, 7 Hz, C(6)-Ar*H*), 7.67 (1H, dd, J = 1, 7 Hz, C(4)-Ar*H*), 6.58 (1H, dd, J = 7, 11 Hz, C(5)-Ar*H*), 5.7 (2H, brs, NH_2), and 2.40 (4H, s, CH_2CH_2); ^{13}C nmr (d_6DMSO): 173.8, 170.3, 153.1, 143.7, 131.4, 118.4, 111.9, 30.5, and 28.9 ppm; ms: (ci) m/e (relative intensity) 210 (100, MH^+), and 192 (47).

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.33; H, 5.33; N, 19.96.

A mixture of this solid (375 mg, 1.79 mmoles) and 175 ml of acetic anhydride in 5 ml of pyridine was refluxed for 30 minutes. The resulting mixture was cooled to room temperature and the solvent was removed under reduced pressure. The solid residue was treated with charcoal and recrystallized from water giving 158 mg (0.83 mmoles, 46% yield) of white needles, mp 224-226°; ir (0.5% potassium bromide): 3460, 3425, 3360, 1710, 1640, 1475, 1390, 1200 and 780 cm^{-1}; ^1H nmr (d_6DMSO): δ 8.17 (1H, dd, J = 1, 7 Hz, C(6)-Ar*H*), 7.42 (1H, dd, J = 1, 11 Hz, C(4)-Ar*H*), 6.72 (1H, dd, J = 7, 11 Hz, C(5)-Ar*H*), 6.22 (2H, s, N*H*), and

2.79 (4H, s, CH_2CH_2); ^{13}C nmr (d_6DMSO): 176.9 (2C), 156.2, 148.3, 137.1, 112.5, 111.5, and 28.8 (2C) ppm; ms: (ei) m/e (relative intensity) 192 (43, MH^+), 191 (100, M^+), 146 (44), 136 (96), 135 (35), 109 (54) and 108 (38).

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.57; H, 4.80; N, 21.87.

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