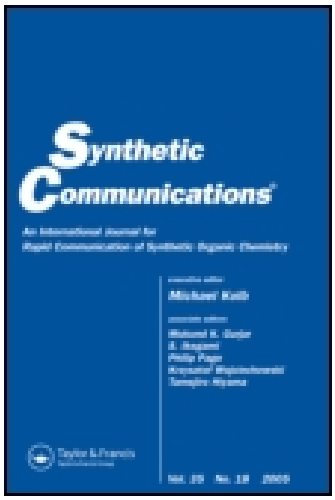

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STUDIES IN LARGE RING COMPOUNDS: SYNTHESIS OF SOME NEW MORPHANTHRINDINES AND DIAZOCINES

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STUDIES IN LARGE RING COMPOUNDS: SYNTHESIS OF SOME NEW MORPHANTHRINDINES AND DIAZOCINES

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ABSTRACT

A novel method for the synthesis of 2 or 3-substituted 5,6-dihydro-6,11-dioxo-morphanthridines (**2**) involving the cyclisation of anilinic acid (**1**) with PPA/AcOH has been developed. A new heterocyclic system, 2 or 3-Substituted 5,6,11,12-tetrahydrodibenzo[b, f][1,4]diazocine-6,11-diones (**4**) has been synthesized with excellent yields.

Key Words: Phthalic anhydride; Morphanthrindines; PPA; Diazocine

Derivatives of 5,6-dihydro-6,11-dioxomorphanthridine-6-oxime (**3**) are useful as a transquilizers and anticeteleptic agents.[1] In the preparation of large number of pharmacodynamic compounds,[2,3] 5,6-dihydro-6,11-dioxomorphanthridines (**2**) has been used as a key intermediate. Earlier

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workers have synthesized compound diazocinedione (**4**) by the Schmidt reaction on anthraquinone[4,5] and Beckmann rearrangement on anthraquinone mono-oxime.[6,7] The derivatives of diazocine are used as a amoebicidal agents.[8] Several N-substituted aryl acids have been used as nonsteriodal anti-inflammatory agents.[9–12] It was thus felt that the synthesis of dimeric compounds of anthranilic acids i.e., 5,11-disubstituted dibenzo [b, f] [1,4] diazocine 6,11-diones (**4**) would be of considerable importance as they could posses pharmacological properties comparable to those of monomeric acids and could serve as prodrug capable of releasing anthranilic acid as slow hydrolysis in vivo. These 'slow release drugs' would thus help to obtain longer periods of action with smaller doses. We were interested to synthesize some new derivatives of morphanthridines and diazocines.

Here we report the synthesis of some new morphanthridines (**2**) by cyclisation of anilinic acids with PPA/AcOH and their conversion to diazocines (**4**) via Beckmann rearrangement. Anilinic acid (**1**) were obtained in almost quantitative yield by the condensation of cyclic anhydride with aromatic amines.[13] The anilinic acid on condensation with PPA/AcOH affords dioxomorphanthridines (**2**) in 65–81% yield.

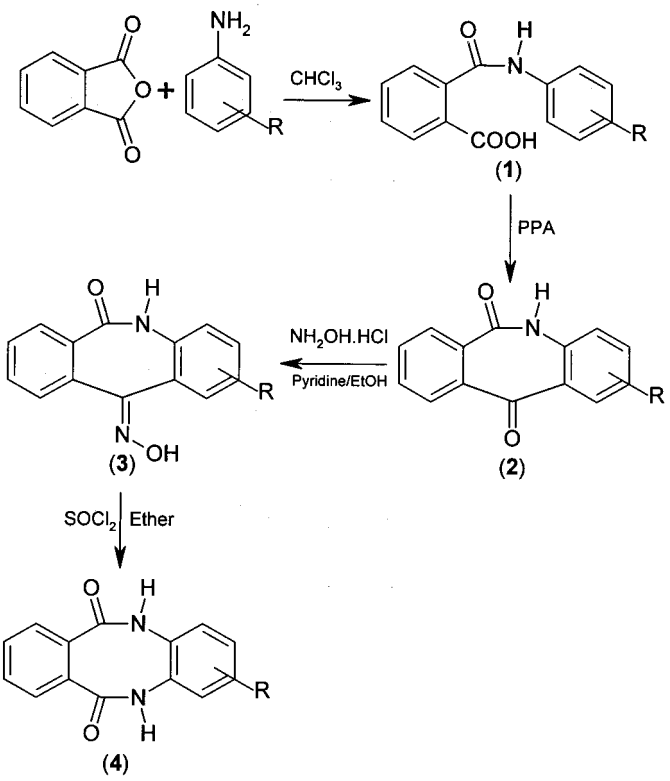
Treatment with hydroxylamine hydrochloride yields the oxime derivative (**3**) in 65–85% yield. These oximes on Beckmann rearrangement under condition afforded diazocines (**4**) in good yield (Scheme 1).

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in nujol on Perkin-Elmer 237 Spectrophotometer. ^{1}H-NMR was recorded in $CDCl_3$ on Perkin-Elmer-R-32 Spectrophotometer using TMS as an internal standard. (Chemical shift is given in δ-ppm). Purity of all compounds was 80–95% recorded on GC.

Synthesis of 3-Methyl-6,11-dioxo-5,6-dihydro-morphanthridine (2g)

A mixture 3-(N-3-methyl aryl carbomyl) benzoic acid (2.55 g, 0.01 mol) and PPA (prepared from 10 g P_2O_5 and 3 mL H_3PO_4) was kept at 95–100°C for 2 h. The reaction mixture was cooled and poured on crushed ice left for 2 h and filtered. The solid was washed with water and crystallized from acetic acid to afford 1.54 g (65%) of morphanthridine (**2g**), m.p. 145°C.



Scheme 1.

IR (neat): 3200, 1700, 1685, 1650 cm^{-1}. **^{1}H NMR ($CDCl_3$)** δ**:** 1.7 (s, 1H, CONH), 7.27–8.0 (m, 7H, Ar–H), 2.3 (s, 3H, Ar-CH_3). Anal. Calcd for $C_{15}H_{11}NO_2$ (237.26): C, 75.94; H, 4.67; N, 5.90. Found: C, 75.91; H, 4.64; N, 5.85.

2a. 73%, m.p. 203°C; IR (neat): 3200, 1705, 1680, 1655 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.8 (s, 1H, CONH), 7.0–8.0 (m, 8H, Ar–H).

Anal. Calcd for $C_{14}H_9NO_2$ (223.23): C, 75.33; H, 4.06; N, 6.27. Found: C, 75.31; H, 4.10; N, 6.25.

2b. 79%, m.p. 262°C; IR (neat): 3210, 1705, 1680, 1645 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.7 (s, 1H, CONH), 7.2–8.0 (m, 7H, Ar–H).

Anal. Calcd for $C_{15}H_9NO_4$ (267.24): C, 67.42; H, 3.39; N, 5.24. Found: C, 67.41; H, 3.40; N, 5.25.

2c. 80%, m.p. 215°C; IR (neat): 3205, 1710, 1685, 1650 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.8 (s, 1H, CONH), 7.3–8.0 (m, 7H, Ar–H).

Anal. Calcd for $C_{15}H_9NO_4$ (267.24): C, 67.42; H, 3.39; N, 5.24. Found: C, 67.45; H, 3.42; N, 5.30.

2d. 75%, m.p. 220°C; IR (neat): 3215, 1710, 1680, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.9 (s, 1H, CONH), 6.8–7.8 (m, 7H, Ar–H), 9.4 (s, 1H, OH).

Anal. Calcd for $C_{14}H_9NO_3$ (239.23): C, 70.29; H, 3.79; N, 5.85. Found: C, 70.31; H, 3.81; N, 5.87.

2e. 70%, m.p. 186°C; IR (neat): 3200, 1707, 1690, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.1 (s, 1H, CONH), 7.2–7.8 (m, 7H, Ar–H).

Anal. Calcd for $C_{14}H_8N_2O_4$ (268.23): C, 62.69; H, 3.01; N, 10.44. Found: C, 62.65; H, 3.05; N, 10.45.

2f. 81%, m.p. 181°C; IR (neat): 3210, 1695, 1685, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.9 (s, 1H, CONH), 7.2–8.2 (m, 7H, Ar–H).

Anal. Calcd for $C_{15}H_{11}NO_2$ (237.26): C, 75.94; H, 4.67; N, 5.90 Found: C, 75.91; H, 4.71; N, 5.95.

2h. 77%, m.p. 168°C; IR (neat): 3220, 1702, 1680, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.2 (s, 1H, CONH), 7.0–8.0 (m, 7H, Ar–H), 3.9 (s, 3H, OCH_3).

Anal. Calcd for $C_{15}H_{11}NO_3$ (253.26): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.11; H, 4.35; N, 5.55.

2i. 68%, m.p. 172°C; IR (neat): 3200, 1702, 1685, 1653 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.8 (s, 1H, CONH), 7.0–7.8 (m, 7H, Ar–H).

Anal. Calcd for $C_{14}H_8NO_2Br$ (302.13): C, 55.66; H, 2.67; N, 4.64; Br, 26.45. Found: C, 55.61; H, 2.63; N, 4.60; Br, 26.42.

2j. 70%, m.p. 132°C; IR (neat): 3200, 1710, 1680, 1647 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.9 (s, 1H, CONH), 7.0–8.0 (m, 7H, Ar–H).

Anal. Calcd for $C_{14}H_8NO_2Cl$ (257.68): C, 65.26; H, 3.13; N, 5.44; Cl, 13.76. Found: C, 65.31; H, 3.10; N, 5.45; Cl, 13.78.

Synthesis of Oxime of Dioxomorphanthridines (3g)

A mixture of dioxomorphanthridines **2g** (2.37 g, 0.01 mol), hydroxyl amine hydrochloride (0.7 g, 0.01 mol), ethanol (20 mL) and 0.5 mL of pyridine was refluxed on water bath for 20 min ethanol was removed by distillation on water bath. Residue was treated with water (5 mL) and stirred in an ice bath until the crystals appear. The solid was filtered, washed with water and recrystallised from alcohol to give 1.76 g (70%) of monoxime (**3g**), m.p. 254°C. IR (neat): 3585, 3225, 3010, 1680, 1662 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.2 (s, 3H, CH_3), 2.7 (s, 2H, CONH), 7.5–8.5 (m, 7H, Ar–H), 9.2 (s, 1H, =N–OH).

Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.28): C, 71,42; H, 4.79; N, 11.10. Found: C, 71.51; H, 4.60; N, 11.12.

3a. 85%, m.p. 136°C; IR (neat): 3575, 3230, 3005, 1675, 1640 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.8 (s, 2H, CONH), 7.5–8.2 (m, 8H, Ar–H), 9.1 (s, 1H, =N–OH).

Anal. Calcd for $C_{14}H_{10}N_2O_2$ (238.25): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.52; H, 4.35; N, 11.73.

3b. 70%, m.p. 155°C; IR (neat): 3580, 3220, 3010, 2675, 1685, 1645 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.75 (s, 2H, CONH), 7.1–8.2 (m, 7H, Ar–H), 8.8 (s, 1H, =N–OH), 12.5 (s, 1H, OH).

Anal. Calcd for $C_{15}H_{10}N_2O_4$ (282.26): C, 63.83; H, 3.57; N, 9.92. Found: C, 63.82; H, 3.60; N, 9.85.

3c. 80%, m.p. 95°C; IR (neat): 3590, 3220, 2690, 1685, 1648 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.6 (s, 2H, CONH), 7.0–8.5 (m, 7H, Ar–H), 9.5 (s, 1H, =N–OH), 12.2 (s, 1H, COOH).

Anal. Calcd for $C_{15}H_{10}N_2O_4$ (282.26): C, 63.83; H, 3.57; N, 9.92. Found: C, 63.80; H, 3.65; N, 9.83.

3d. 78%, m.p. 72°C; IR (neat): 3582, 3230, 3015, 1680, 1649 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.8 (s, 2H, CONH), 7.2–8.5 (m, 7H, Ar–H), 9.3 (s, 1H, =N–OH), 8.3 (s, 1H, Ar-OH).

Anal. Calcd for $C_{14}H_{10}N_2O_3$ (254.25): C, 66.14; H, 3.0; N, 11.02. Found: C, 66.11; H, 3.06; N, 11.10.

3e. 75%, m.p. 168°C; IR (neat): 3584, 3235, 3010, 1680, 1653 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.75 (s, 2H, CONH), 7.1–8.6 (m, 7H, Ar–H), 9.4 (s, 1H, =N–OH).

Anal. Calcd for $C_{14}H_9N_3O_4$ (283.25): C, 59.37; H, 3.20; N, 14.84. Found: C, 59.32; H, 3.16; N, 14.82.

3f. 60%, m.p. 198°C; IR (neat): 3585, 3225, 3010, 1685, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.2 (s, 3H, CH_3), 2.8 (s, 2H, CONH), 7.2–8.7 (m, 7H, Ar–H), 9.1 (s, 1H, =N–OH).

Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.28): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.52; H, 4.69; N, 11.06.

3h. 70%, m.p. 158°C; IR (neat): 3590, 3250, 3020, 1690, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.2 (s, 3H, OCH_3), 2.73 (s, 2H, CONH), 7.0–7.9 (m, 7H, Ar–H), 9.0 (s, 1H, =N–OH).

Anal. Calcd for $C_{15}H_{12}N_2O_3$ (268.27): C, 67.16; H, 4.51; N, 10.44. Found: C, 67.11; H, 4.62; N, 10.42.

3i. 65%, m.p. 192°C; IR (neat): 3575, 3230, 3000, 1680, 1655 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.65 (s, 2H, CONH), 7.2–8.2 (m, 7H, Ar–H), 9.6 (s, 1H, =N–OH).

Anal. Calcd for $C_{14}H_9N_2O_2Br$ (317.14): C, 53.02; H, 2.86; N, 8.83. Found: C, 53.08; H, 2.76; N, 8.92.

3j. 67%, m.p. 145°C; IR (neat): 3585, 3225, 3010, 1675, 1652 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.82 (s, 2H, CONH), 7.3–8.2 (m, 7H, Ar–H), 9.2 (s, 1H, =N–OH).

Anal. Calcd for $C_{14}H_9N_2O_2Cl$ (272.69): C, 61.66; H, 3.33; N, 10.27. Found: C, 61.41; H, 3.30; N, 10.19.

Synthesis of 2-Methyl 5,6,11,12 Tetrahydrodibenzo (b–f) [1,4] Diazocine-6,11-dione (4g)

Oxime **3g** (2.52 g 0.01 mol) was dissolved in anhydrous ether (20 mL) in a small conical flask and pure thionyl chloride (3 mL) was added to it and stirred for half-hours. Solvent and other volatile products were distilled off on water bath. The reaction mixture was treated with (25 mL) of water and boiled for few minutes. Then precipitated product was filtered, washed and recrystallised from acetic acid to give 1.71 g (68%) of diazocine (**4g**), m.p. 124°C.

IR (neat): 3230, 1680, 1647 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ: 6.5–7.5 (m, 8H, Ar–H), 2.5 (3H, s, Ar–CH_3).

Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.28): C, 71.42; H, 4.79; N, 11.10; Found: C, 71.41; H, 4.75; N, 11.14.

4a. 76%, m.p. 115°C; IR (neat): 3200, 1685, 1642 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.75 (s, 2H, CONH), 6.5–7.5 (m, 7H, Ar–H).

Anal. Calcd for $C_{14}H_{10}N_2O_2$ (238.25): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.51; H, 4.20; N, 11.72.

4b. 75%, m.p. 230°C; IR (neat): 3220, 1680, 1648 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.7 (s, 2H, CONH), 6.5–7.5 (m, 7H, Ar–H).

Anal. Calcd for $C_{15}H_{10}N_2O_4$ (228.26): C, 63.83; H, 3.57; N, 9.92. Found: C, 63.81; H, 3.50; N, 9.85.

4c. 70%, m.p. 158°C; IR (neat): 3210, 1675, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.8 (s, 2H, CONH), 6.5–7.7 (m, 7H, Ar–H).

Anal. Calcd for $C_{15}H_{10}N_2O_4$ (228.26): C, 63.83; H, 3.57; N, 9.92. Found: C, 63.89; H, 3.60; N, 9.96.

4d. 69%, m.p. 172°C; IR (neat): 3200, 1680, 1645 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.75 (s, 2H, CONH), 6.7–7.5 (m, 7H, Ar–H), 9.6 (s, 1H, OH).

Anal. Calcd for $C_{14}H_{10}N_2O_3$ (254.25): C, 66.14; H, 3.96; N, 11.02. Found: C, 66.18; H, 3.92; N, 11.05.

4e. 74%, m.p. 150°C; IR (neat): 3225, 1685, 1635 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.75 (s, 2H, CONH), 6.6–7.5 (m, 7H, Ar–H).

Anal. Calcd for $C_{14}H_9N_3O_4$ (283.25): C, 59.37; H, 3.20; N, 14.84. Found: C, 59.31; H, 3.22; N, 14.82.

4f. 80%, m.p. 152°C; IR (neat): 3210, 1690, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.65 (s, 2H, CONH), 6.5–7.5 (m, 7H, Ar–H), 2.4 (s, 3H, CH_3).

Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.28): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.41; H, 4.75; N, 11.12.

4h. 78%, m.p. 173°C; IR (neat): 3200, 1685, 1652 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.75 (s, 2H, CONH), 6.5–7.5 (m, 7H, Ar–H), 4.1 (s, 3H, OCH_3).

Anal. Calcd for $C_{15}H_{12}N_2O_3$ (268.27): C, 67.16; H, 4.51; N, 10.44. Found: C, 67.12; H, 4.52; N, 10.43.

4i. 72%, m.p. 135°C; IR (neat): 3225, 1675, 1645 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.8 (s, 2H, CONH), 6.7–7.7 (m, 7H, Ar–H).

Anal. Calcd for $C_{14}H_9N_2O_2Br$ (317.14): C, 53.02; H, 2.86; N, 8.83; Br, 25.19. Found: C, 53.10; H, 2.80; N, 8.85; Br, 25.15.

4j. 75%, m.p. 119°C; IR (neat): 3200, 1685, 1651 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.9 (s, 2H, CONH), 6.6–7.8 (m, 7H, Ar–H).

Anal. Calcd for $C_{14}H_9N_2O_2Cl$ (272.69): C, 61.66; H, 3.33; N, 10.27; Cl, 13.00. Found: C, 61.63; H, 3.30; N, 10.25; Cl, 13.04.

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