A Facile Synthesis of 1,3,4,6-Tetrahydro-1,6-benzodiazocine-2,5-diones

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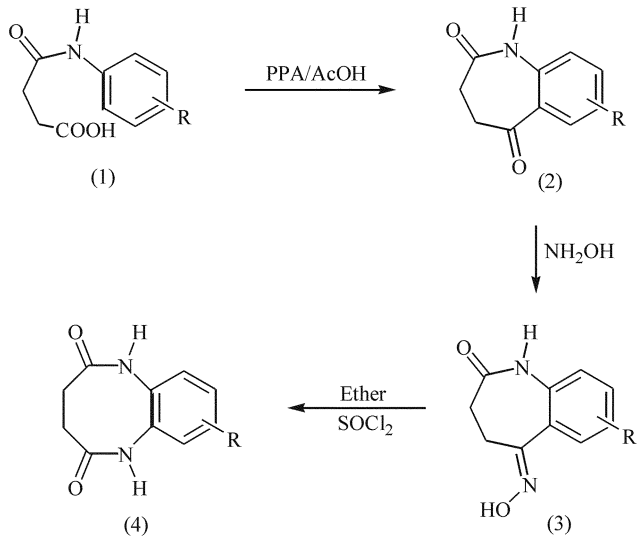
Derivatives of 5,6-dihydro-6,11-dioxomorphanthridine-6-oxime are useful as transquilizers and anticeteleptic agents.[1] For the preparation of large number of pharmacodynamic compounds 1,3,4-trihydro-2,5-dioxomorphanthrindines has been used as key intermediate.[2,3] Earlier workers have synthesized compounds (**2**) by Schmidt reaction on anthraquinone[4-6] and Beckmann rearrangement on anthraquinone mono-oxime.[7,8] The derivatives of diazocine are used as amoebicidal agents.[9] Several N-substituted aryl acids have been used as non-steroidal anti-inflammatory agents.[10,11] It was thus felt that the synthesis of dimeric compounds of anthranilic acids *i.e*. 7-substituted 1,3,4,6-tetrahydro-1,6-benzodiazocine-2,5-diones would be the considerable importance as they could possess pharmacological properties comparable to those of monomeric acids or could serve as prodrug capable of releasing anthranilic acid through slow hydrolysis in *vivo*. These 'slow release drugs' would thus help to obtain longer periods of action with smaller doses. We were interested in the synthesis of 1,3,4,6-tetrahydro-1, 6-benzodiazocine-2,5-diones (**4**).

The present context of studies introduced 3,4-dihydro-1-benzazepine-2,5 (1H)-diones (**2**) by the condensation of anilinic acids (**1**) with PPA/AcOH in 65-81% yield. Anilinic acid were obtained in quantitative yield by the condensation of cyclic anhydride with substituted aromatic amines.[12] The compounds (**2**) on treatment with hydroxylamine hydrochloride gives oxime derivatives (**3**) in good yield. These oximes on Beckmann rearrangement under condition afforded diazocines (**4**) in good yield (Scheme 1).



Scheme 1. Where R= H, 3-NO_2, 4-CH_3, 3-COOH, 4-Br.

Experimental Section

Melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected. IR spectra were recorded in nujol on Perkin-Elmer-237 spectrophotometer. ^{1}H NMR were recorded on a Perkin-Elmer R-32 spectrometer using TMS as internal standard (Chemical shift are given in δ ppm).

Preparation of 7-methyl-3,4-dihydro-1-benzazepine-2,5-(1H)-dione (2). A mixture of 3-(N-3-methyl aryl carbomyl) propionic acid (2.23 g, 0.01 mole) and PPA [prepared from P_2O_5 (10 g) and H_3PO_4 (3 mL)] or acetic acid (20 mL) was heated at 95-100 ^{o}C for 2 hrs. The reaction mixture was cooled and poured on crushed ice and left for 2 h. The solid was washed with water, dried and crystallized from acetic acid to afford **2**.

2a: 73%, m.p. 145 ^{o}C. IR: 3280, 1710, 1690, 1565 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.5 (t, 2H, C_4), 2.7 (t, 2H, C_3), 7.2-8.0 (m, 4H, Ar-H). Anal. Calcd for $C_{10}H_9NO_2$ (175.19): C, 68.58; H, 5.18; N, 8.00. Found: C, 68.55; H, 5.13; N, 7.97.

2b: 70%, m.p. 152 ^{o}C. IR: 3285, 1710, 1685, 1560 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.6 (t, 2H, C_4), 2.8 (t, 2H, C_3), 7.0-8.1 (m, 3H, Ar-H). Anal. Calcd for $C_{10}H_8N_2O_4$ (220.19): C, 54.55; H, 3.66; N, 12.72. Found: C, 54.50; H, 3.61; N, 12.75.

2c: 85%, m.p. 204 ^{o}C. IR: 3290, 1715, 1690, 1665 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.4 (t, 2H, C_4), 2.6 (t, 2H, C_4), 2.3 (s, 3H, Ar-CH_3), 7.2-8.2 (m, 3H, Ar-H). Anal. Calcd for $C_{11}H_{11}NO_2$ (189.22): C, 69.83; H, 5.86; N, 7.40. Found: C, 69.85; H, 5.83; N, 7.36.

2d: 80%, m.p. 196 ^{o}C. IR: 3280, 2850, 1710, 1680, 1665 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.5 (t, 2H, C_4), 2.8 (t, 2H, C_4), 7.2-8.4 (m, 3H, Ar-H), 10.8 (s, 1H, COOH). Anal. Calcd for $C_{11}H_9NO_4$ (219.20): C, 60.28; H, 4.14; N, 6.39. Found: C, 60.25; H, 4.10; N, 6.37.

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2e: 68%, m.p. 125 °C. IR: 3285, 1705, 1695, 1665 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.4 (t, 2H, C_4), 2.7 (t, 2H, C_4), 7.2-8.2 (m, 3H, Ar-H). Anal. Calcd for $C_{10}H_8NO_2Br$ (254.08): C, 47.27; H, 3.17; N, 5.51. Found: C, 47.22; H, 3.13; N, 5.57.

Preparation of oxime of 7-methyl-3,4-dihydro-1-benzazepine-2,5-(1H)-dione (3). A mixture of **2** (2.05 g, 0.01 mole), hydroxyl amine hydrochloride (0.7 g, 0.01 mole), ethanol (20 mL) and pyridine (0.5 mL) was refluxed on water bath for 20 min. The solvent ethanol was removed by distillation on water bath. The 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 oxime **3**.

3a: 85%, m.p. 167 °C. IR: 3510, 3272, 1680, 1555 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.0 (s, 1H, N-OH), 2.4 (t, 2H, C_3), 3.3 (t, 2H, C_4), 7.0-7.7 (m, 4H, Ar-H). Anal. Calcd for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 68.14; H, 5.25; N, 14.78.

3b: 93%, m.p. 138 °C. IR: 3485, 3285, 1693, 1545 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.8 (s, 1H, N-OH), 2.5 (t, 2H, C_3), 3.1 (t, 2H, C_4), 7.5-8.8 (m, 3H, Ar-H). Anal. Calcd for $C_{10}H_9N_3O_4$ (235.20): C, 51.07; H, 3.86; N, 17.87. Found: C, 51.10; H, 3.90; N, 17.97.

3c: 87%, m.p. 189 °C. IR: 3515, 3290, 1690, 1560 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.1 (s, 1H, N-OH), 2.3 (s, 3H, CH_3), 2.7 (t, 2H, C_3), 3.0 (t, 2H, C_4), 7.2-7.8 (m, 3H, Ar-H). Anal. Calcd for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.75; H, 5.83; N, 13.77.

3d: 75%, m.p. 155 °C. IR: 3525, 3275, 1685, 1570 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.0 (s, 1H, N-OH), 3.4 (t, 2H, C_4), 2.4 (t, 2H, C_3), 7.7-8.5 (m, 3H, Ar-H), 11.3 (s, 1H, COOH). Anal. Calcd for $C_{11}H_{10}N_2O_4$ (234.21): C, 56.41; H, 4.30; N, 11.96. Found: C, 56.35; H, 4.37; N, 12.10.

3e: 81%, m.p. 161 °C. IR: 3515, 3282, 1687, 1545 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.8 (s, 1H, N-OH), 2.8 (t, 2H, C_3), 3.2 (t, 2H, C_4), 7.2-7.8 (m, 3H, Ar-H). Anal. Calcd for $C_{10}H_9N_2O_2Br$ (269.09): C, 44.63; H, 3.37; N, 10.41. Found: C, 44.55; H, 3.44; N, 10.57.

Preparation of 8-methyl 1,3,4,6-tetrahydro-1,6-benzodiazocine 2,5-dione (4). Oxime **3c** (2.2 g, 0.01 mole) was dissolved in anhydrous ether (20 mL) in a small conical flask. Thionyl chloride (3 mL) was then added to it and stirred for 30 min. Solvent and other volatile products were distilled off on water bath. The residue was treated with water (25 mL) and boiled for few minutes. The precipitated product was then filtered, washed with water and recrystallised from acetic acid to give diazocine **4**.

4a: 76%, m.p. 172 °C. IR: 3285, 1680, 1650 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.5 (m, 4H, C_3 & C_4), 7.1-7.8 (m, 4H, Ar-H). Anal. Calcd for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.27; N, 14.69.

4b: 76%, m.p. 197 °C. IR: 3280, 1685, 1640 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.6 (m, 4H, C_3 & C_4), 7.0-8.0 (m, 3H, Ar-H). Anal. Calcd for $C_{10}H_9N_3O_4$ (235.20): C, 51.07; H, 3.86; N, 17.87. Found: C, 51.03; H, 3.80; N, 17.84.

4c: 80%, m.p. 131 °C. IR: 3285, 1685, 1655 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.8 (m, 4H, C_3 & C_4), 2.4 (s, 3H, Ar-CH_3), 7.1-7.9 (m, 3H, Ar-H). Anal. Calcd for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.61; H, 5.87; N, 13.69.

4d: 70%, m.p. 149 °C. IR: 3275, 1685, 1645 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.5 (m, 4H, C_3 & C_4), 7.1-8.2 (m, 3H, Ar-H), 10.5 (s, 1H, COOH). Anal. Calcd for $C_{11}H_{10}N_2O_4$ (234.21): C, 56.41; H, 4.30; N, 11.96. Found: C, 56.37; H, 4.27; N, 11.92.

4e: 72%, m.p. 204 °C. IR: 3285, 1685, 1655 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.5 (m, 4H, C_3 & C_4), 7.1-7.6 (m, 3H, Ar-H). Anal. Calcd for $C_{10}H_9N_2O_2Br$ (269.10): C, 44.63; H, 3.37; N, 10.41. Found: C, 44.58; H, 3.32; N, 10.35.

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