Synthesis of some benzopyranoquinoline derivatives

V V Mulwad* & B S Mahadalkar
Department of Organic Chemistry, Institute of Science, 15 Madam Cama Road, Mumbai 400 032, India
Received 1 January 1997; accepted (revised) 16 December 1997

4-Chlorocoumarins on condensation with anthranilic acid afford 4-(2'-carboxyphenylamino)-2H-1-benzopyran-2-ones 1 which on cyclisation with polyphosphoric acid yield 7,12-dihydro-6H-[1]benzopyrano[4,3-b]quinoline-6,7-diones 2. Compounds 1 on treatment with phosphoryl chloride yield 7-chlorobenzopyrano[4,3-b]quinolin-6(H)-ones 3. These chloro compounds on further treatment with various aromatic amines yield 7-anilinobenzopyrano[4,3-b]quinolin-6(H)-ones 4.

Polycyclic ring fused alkaloids have been isolated from a variety of marine sources including lunicates, sponges and mollusces. Many compounds of this class have been reported to have cytotoxic, antitumour and antiviral activities. The pentacyclic alkaloid derivatives isolated from the sponge Dericus are active against tumour cell lines and RNA/DNA viruses. Its hexacyclic analogue cyclodertin is active against P388 leukemia cell lines. The synthetic antiviral drug enviroxime has a broad spectrum features in common with the natural products. Due to the striking biological activities of the marine alkaloids and the synthetic drugs of this family, and since very few reports on benzopyranoquinolines are available in literature we were inspired to synthetise the above novel compounds.

4-Chlorocoumarins (cf. Scheme 1), were condensed with anthranilic acid by the Ullmann reaction to give 4-(2'-carboxy phenylamino)-2H-1-benzopyran-2-ones 1a-e. These compounds dissolved in sodium bicarbonate solution with effervescence indicating the presence of carboxylic acid. Their IR spectra in KBr showed bands at 3356 (NH), 3058 (-OH of acid) and 1655 (>C=O) cm⁻¹. The acids 1a-e on cyclisation with poly-phosphoric acid (PPA) yielded 7,12-dihydro-6H-[1]benzopyrano[4,3-b]quinoline-6,7-diones 2a-e which did not dissolve in sodium bicarbonate solution, and the absence of a broad IR band at 3058 cm⁻¹ confirmed the cyclisation.

Compounds 1a-e on treatment with phosphoryl chloride afforded 7-chlorobenzopyrano-[4,3-b]quinolin-6(H)-ones 3a-e. These compounds also did not dissolve in the sodium bicarbonate solution and gave positive Beilstein's test indicating the absence of halogen. The mass spectrum of 7-chloro-2-methylbenzopyrano[4,3-b]quinolin-6(H)-one 3b exhibited M⁺ peak at m/z 295 and M⁺² peak at m/z 297 due to isotopic chlorine Cl³⁵ and Cl³⁷ respectively. These chloro compounds on further treatment with various aromatic amines yielded 7-anilinobenzopyrano[4,3-b]quinolin-6(H)-ones 4a-e. These compounds showed negative Beilstein's test. The IR spectra of these compounds on KBr showed a band at 3449 cm⁻¹ due to NH stretching. Their ¹H NMR spectra in CDCl₃ showed a singlet at δ 11.64 due to -NH proton. Their mass spectra were devoid of M⁺² peak indicating the absence of halogen. The structures of all these compounds were established by elemental analyses and spectral data.

Experimental Section

General. Melting points of all the compounds were taken in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 257 spectrophotometer. ¹H NMR spectra were recorded on a Perkin-Elmer 300 MHz spectrometer. Homogeneity of the compounds was ascertained by TLC on silica gel plates.

4-(2'-Carboxy-phenylamino)-2H-1-benzopyran-2-ones 1a-e: General procedure. A mixture of an appropriate chlorocoumarin (0.013 mole), anthranilic acid (0.0145 mole), copper powder (26 mg), copper (I) chloride (50 mg), and triethylamine (8 mL) in 40 mL of dimethylformamide was refluxed at 150°-160 °C for about 20-22 hr. On cooling, it was poured over crushed ice and filtered. The filtrate was acidified with 3 N HCl and the resulting precipitate filtered, washed well with water and recrystallised from ethanol, Yield~ 45%.

1a: mp 252 °C. Anal. Caled for C₁₉H₁₁O₄: C, 68.32; H, 3.91; N, 4.90. Found : C, 67.92; H, 3.97; N,
Scheme I

1. $R_1 = R_2 = R_3 = H$

2a. $R_1 = R_2 = Cl$, $R_3 = H$

2b. $R_1 = R_3 = Cl$, $R_2 = H$

2c. $R_1 = R_2 = Cl$, $R_3 = Cl$

2d. $R_1 = R_2 = Cl$, $R_3 = Cl$

2e. $R_1 = R_2 = Cl$, $R_3 = Cl$

4a. $R_1 = R_2 = R_3 = H$

4b. $R_1 = R_2 = Cl$, $R_3 = H$

4c. $R_1 = R_2 = Cl$, $R_3 = Cl$

4d. $R_1 = R_2 = Cl$, $R_3 = Cl$

4e. $R_1 = R_2 = Cl$, $R_3 = Cl$

4f. $R_1 = R_2 = Cl$, $R_3 = Cl$

4g. $R_1 = R_2 = Cl$, $R_3 = Cl$

4h. $R_1 = R_2 = Cl$, $R_3 = Cl$

4i. $R_1 = R_2 = Cl$, $R_3 = Cl$

4j. $R_1 = R_2 = Cl$, $R_3 = Cl$

4k. $R_1 = R_2 = Cl$, $R_3 = Cl$

4l. $R_1 = R_2 = Cl$, $R_3 = Cl$

4m. $R_1 = R_2 = Cl$, $R_3 = Cl$

4n. $R_1 = R_2 = Cl$, $R_3 = Cl$

4o. $R_1 = R_2 = Cl$, $R_3 = Cl$

4p. $R_1 = R_2 = Cl$, $R_3 = Cl$

4q. $R_1 = R_2 = Cl$, $R_3 = Cl$

4r. $R_1 = R_2 = Cl$, $R_3 = Cl$

4s. $R_1 = R_2 = Cl$, $R_3 = Cl$

4t. $R_1 = R_2 = Cl$, $R_3 = Cl$

4u. $R_1 = R_2 = Cl$, $R_3 = Cl$

4v. $R_1 = R_2 = Cl$, $R_3 = Cl$

4w. $R_1 = R_2 = Cl$, $R_3 = Cl$

4x. $R_1 = R_2 = Cl$, $R_3 = Cl$

4y. $R_1 = R_2 = Cl$, $R_3 = Cl$

4z. $R_1 = R_2 = Cl$, $R_3 = Cl$

Scheme I

1b: mp 235 °C. Anal. Caled for C_{17}H_{13}O_4N: C, 69.15; H, 4.40; N, 4.74. Found: C, 69.18; H, 4.42; N, 4.74%. IR (KBr): 3356(-NH), 3059(-OH of -COOH), 2875, 1656 (-C=O), 1605, 1576, 1518, 1446, 1256, 1160, 1101, 757 cm^{-1}.

1c: mp 218 °C. Anal. Caled for C_{17}H_{13}O_4N: C, 69.15; H, 4.40; N, 4.74. Found: C, 69.18; H, 4.42; N, 4.74%. IR (KBr): 3356(-NH), 3059(-OH of -COOH), 2875, 1656 (-C=O), 1605, 1576, 1518, 1446, 1256, 1160, 1101, 757 cm^{-1}.

1d: mp 205 °C. Anal. Caled for C_{17}H_{13}O_4N: C, 69.15; H, 4.40; N, 4.74. Found: C, 69.18; H, 4.42; N, 4.74%. IR (KBr): 3332(-NH), 3110(-OH of -COOH), 2888, 1667, 1605, 1572, 1537, 1453, 1375, 1238, 1196, 1182, 1082, 1047, 968, 790, 760 cm^{-1}.

1e: mp 222 °C. Anal. Caled for C_{17}H_{13}O_4N: C, 69.89; H, 4.85; N, 4.52. Found: C, 69.90; H, 4.88; N, 4.53%. IR (KBr): 3328(-NH), 3089(-OH of -COOH), 2880, 1670, 1600, 1570, 1535, 1452, 1388, 1358, 1319, 1252, 1143, 804, 817, 727, 667, 544 cm^{-1}.

7,12-Dihydro-6H-1-benzopyrans[4,3-b]quinoline-6,7-diones 2a-e: General procedure.

Compound 1 (1g) was added to phosphorus pentoxide (10.67 g) and phosphoric acid (6.8 mL) mixed together and heated at 100 °C for 1 hr] and then heated at 110 °C for 2 hr. The reaction mixture was cooled and poured over crushed ice.

Neutralisation with aqueous ammonia yielded the product which was filtered, washed well with sodium bicarbonate solution and water. The compounds, thus prepared, were recrystallised from ethanol, yield ~90%.

2a: mp >284 °C. Anal. Caled for C_{17}H_{13}O_4N: C, 72.98; H, 3.42; N, 5.32. Found: C, 73.00; H, 3.42; N, 5.32%. IR (KBr): 3360 (-NH), 1685 (-C=O), 1660 (>C=O), 1580, 1520, 1447, 1261, 1116, 1101, 759, 654, 520 cm^{-1}.

2b: mp >260 °C. Anal. Caled for C_{17}H_{13}O_4N requires C, 73.64; H, 4.69; N, 5.05. Found: C, 73.65; H, 4.70; N, 5.06%. IR(KBr): 3352(-NH), 2945, 1687(-C=O), 1660(-C=O), 1580, 1524, 1444, 1259, 1157, 750, 660, 516 cm^{-1}. 1H NMR(DMSOd_6): δ 1.7(s,3H,CH_3), 8.8(d,1H,J=5.9Hz, C-H), 8.1(d,1H,J=5.9Hz, C-H), 7.1-7.7(m,4H, aromatic-H), 11.9(s,1H, NH); MS: m/z 277(M^+ 100%), 249(40%), 220(40%), 191(20%), 165(30%), 110(20%), 96(40%), 89(50%), 77(80%), 63(70%), 51(85%).
7-Chlorobenzopyran-4,3-b|quinolino- 6(H)-ones

3a-e: General procedure. A mixture of (2g) and phosphoril chloride (11.8 mL) was refluxed on an oilbath at 100-110 °C for 3 hr. The reaction mixture was cooled to room temperature and then the contents were slowly added to a large excess of ice-cold solution of ammonium hydroxide. Care was taken to maintain the alkalinity until all the remaining phosphoril chloride was hydrolysed with ammonium hydroxide. The resulting product was filtered, washed well with sodium bicarbonate solution and water, and then was crystallised from ethanol, yield ~ 80%.

3a: mp 235 °C. Anal. Caled: C, 73.65; H, 4.50; N, 4.50. Found: C, 73.66; H, 4.46; N, 4.46. IR(KBr): 3332(-NH), 2924, 1722 (>C=O), 1675 (>C=O), 1630, 1560, 1510, 1480, 1450, 1420, 1320, 1161, 1080, 1030, 891, 820, 770 cm⁻¹.

3b: mp 220 °C. Anal. Caled: C, 73.64; H, 4.69; N, 5.06. Found C, 73.65; H, 4.70; N, 5.06. IR(KBr): 3332(-NH), 2936, 1722 (>C=O), 1675 (>C=O), 1630, 1560, 1510, 1480, 1450, 1420, 1320, 1161, 1080, 1030, 891, 820, 770 cm⁻¹.

3c: mp 215 °C. Anal. Caled for C₁₇H₁₃O₂NCl: C, 73.64; H, 4.69; N, 5.06. Found: C, 73.66; H, 4.68; N, 5.06. IR(KBr): 3332 (-NH), 2925, 1720 (>C=O), 1678 (>C=O), 1630, 1560, 1510, 1480, 1450, 1420, 1320, 1160, 1070, 1040, 890, 760 cm⁻¹.

3d: mp 250 °C. Anal. Caled for C₁₇H₁₃O₂NCl: C, 73.64; H, 4.69; N, 5.06. Found C, 73.65; H, 4.70; N, 5.06. IR(KBr): 3332 (-NH), 2936, 1722 (>C=O), 1675 (>C=O), 1630, 1560, 1510, 1480, 1450, 1420, 1320, 1161, 1080, 1030, 891, 820, 770 cm⁻¹.

3e: mp 180 °C. Anal. Caled for C₁₇H₁₃O₂NCl: C, 69.90; H, 3.80; N, 4.50. Found: C, 69.96; H, 4.00; N, 4.50. IR(KBr): 2924, 1734 (>C=O), 1635, 1578, 1566, 1534, 1516, 1478, 1451, 1408, 1335, 1196, 1055, 771, 617 cm⁻¹.
1473, 1432, 1304, 1296, 1239, 590, 865, 803, 750 cm⁻¹.

4c: mp > 250 °C; reaction period 35 hr; IR (KBr): 3100, 2900, 1728(>C=O), 1637, 1577, 1557, 1511, 1475, 1449, 1418, 1329, 1283, 1241, 1131, 1069, 885, 767 cm⁻¹.

4d: mp 240 °C; reaction period 25 hr; IR (KBr): 3322(-NH), 2921, 1728(>C=O), 1633, 1578, 1514, 1265, 1194, 1153, 787 cm⁻¹.

4d₁: mp 200 °C; reaction period 35 hr; IR (KBr): 3322(-NH), 2921, 1728(>C=O), 1633, 1578, 1514, 1265, 1194, 1153, 787 cm⁻¹.

4d₂: mp > 260 °C; reaction period 35 hr; IR (KBr): 3001, 2936, 1728(>C=O), 1633, 1606, 1520, 1489, 1242, 1196, 1169, 1073, 844, 771 cm⁻¹.

4e: mp 245 °C; reaction period 30 hr; IR (KBr): 3332(-NH), 2920, 1674(>C=O), 1616, 1589, 1508, 1257, 1194, 758 cm⁻¹.

4e₁: mp > 260 °C; reaction period 30 hr; IR (KBr): 3334(-NH), 2924, 1685(>C=O), 1578, 1508, 1253, 1157, 762 cm⁻¹.

Acknowledgement
The authors are thankful to Mr S V Chiplunkar, UDCT, Mumbai for elemental analysis, to the Director, RSIC, Mumbai for the ¹H NMR spectra and to the Searle Industries Ltd. For recording the mass spectra of the compounds.

References