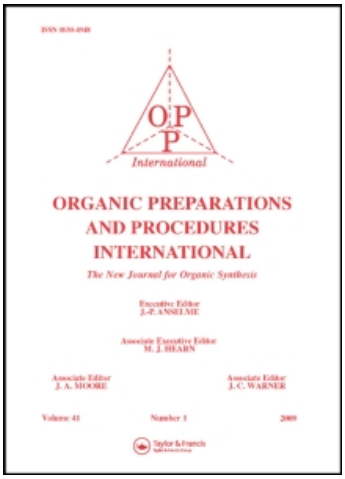

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4-IODO-6-METHOXYQUINOLINE

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OPPI BRIEFS

4-IODO-6-METHOXYQUINOLINE

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(08/06/08)

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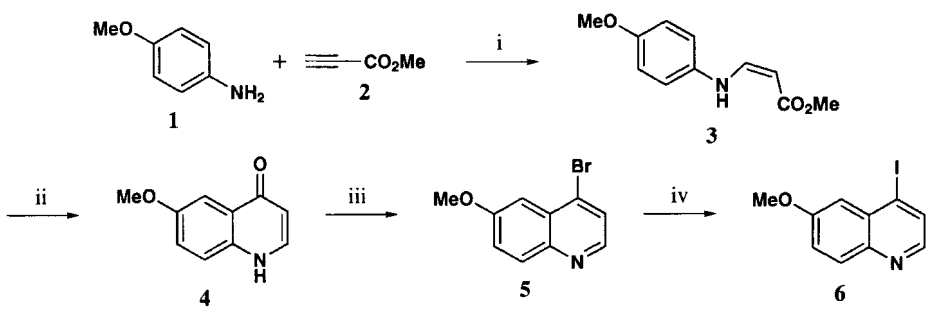
As part of a project directed towards establishing a fully stereocontrolled total synthesis of the anti-malarial agent quinine[1] we required access to the title compound (**6**). The only reported synthesis is a rather lengthy one published in 1930.[2] Accordingly we sought to establish a new route. An examination of the literature suggested the best approach might involve making the corresponding bromide **5**, a compound that appeared accessible by at least two distinct and relatively efficient routes,[3,4] then converting it into the target iodide (**6**) using one of a number of available *trans*-halogenation protocols.[5–7] In the event, this strategy proved successful although a number of significant modifications to reported procedures was required to ensure an efficient process was established. Details are provided herein.

The route used to obtain target **6** is shown in *Scheme 1* and started with the stereoselective Michael addition of *p*-anisidine (**1**) to methyl propiolate (**2**).[3] When this reaction was conducted at 18°C then a *ca.* 9:1 mixture of acrylate **3**[3] and the corresponding *E*-isomer was obtained. In contrast, when the same reaction was carried out at 30°C then compound **3** was essentially the only product of reaction and was obtained in near quantitative yield. Following a



i) MeOH, 18–30°C, 15 h; ii) Ph_2O, 260°C, 0.5 h; iii) PBr_3, DMF, 18°C, 1 h; iv) Ac_2O, NaI, MeCN, microwave irradiation, 80°C, 3 h.

Scheme 1

reported procedure[3] that was expected to result in the β-anilinoacrylate **3** undergoing a Conrad–Limpach reaction[8] to give 4-quinolone **4**, a *ca.* 0.4 M solution of compound **3** in diphenyl ether was heated at *ca.* 260°C for 0.5 h. However, under such conditions only polymeric products were obtained. After a great deal of experimentation, it was established that heating a *ca.* five-fold diluted solution of the substrate under the same conditions led to an efficient cyclization reaction thus providing the target 4-quinolone **4**[3,4] as a fine, tan-colored powder in 93% yield. The conversion of this compound into bromide **5** proceeded smoothly when PBr_3 in dimethylformamide (DMF) was used[4] and the desired product was obtained as a light-yellow crystalline solid in 88% yield. The physical and spectroscopic properties of this material were in full accord with the assigned structure and in agreement with the analogous data reported in the literature.[3,4]

Various protocols are available for the *trans*-halogenation of electron-deficient heterocycles.[5–7] For the purposes of effecting the conversion **5** → **6**, we chose to use that one involving a mixture of acetyl chloride and sodium iodide.[5,6] When the relevant reaction was carried out using microwave irradiation then the target compound **6** was indeed produced but the major product of reaction was the corresponding chloride. Accordingly, the acetyl chloride was replaced with acetic anhydride and while the ensuing reaction was a little slower, the required iodide could be obtained, after column chromatography, in 94% yield and as a crystalline solid. The spectral data of compound **6** were in full accord with the assigned structure but the melting point of this material was significantly higher (126°C) than that reported[2] (85°C) for the material prepared by John and Andraschko. The origins of this discrepancy remain unclear.

The time-efficient protocols described here should have utility in the preparation of other 4,6-disubstituted quinolines for which straightforward and rapid methods of access are lacking.[3b]

EXPERIMENTAL SECTION

Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 18°C in base-filtered $CDCl_3$ on a Varian Mercury or Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on NaCl plates. A VG Fisons AutoSpec three sector (E/B/E) double focusing mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple quadrupole MS instrument operating in positive ionization mode. Melting points were measured on an Optimelt automated melting point system and are uncorrected. All microwave irradiation experiments were carried out in the CEM Explorer™ microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilizing the standard absorbance level of 300 W maximum power. The reactions were carried out in 80 mL sealed Pyrex vessels (working volume of 50 mL) equipped with a magnetic stirrer. The temperature was measured with a fiber optic temperature sensor immersed in the reaction vessel. After the irradiation period, the reaction vessel was cooled rapidly (1–2 min) to ambient temperature by N_2 jet cooling.

(*Z*)-Methyl 3-(4-methoxyphenylamino)acrylate (3).- Compound **3** was prepared using the method detailed by Nicolaou *et al.*[3a] Thus, methyl propiolate (**2**) (4.45 mL, 49.9 mmol) was added to a magnetically stirred solution of *p*-anisidine (**1**) (6.15 g, 49.9 mmol) in methanol (125 mL) maintained under a nitrogen atmosphere at 18°C. The ensuing mixture was warmed to 30°C and after 15 h at this temperature it was cooled then concentrated under reduced pressure. The crude solid thus obtained was dissolved in boiling ethyl acetate (200 mL) and the resulting mixture filtered through a 5 cm deep pad of TLC-grade silica sitting on a sintered-glass funnel. The solids thus retained were washed with ethyl acetate (150 mL) and the combined filtrates were concentrated under reduced pressure to afford compound **3**[3a] (10.3 g, 99%) as a yellow solid, mp 126–128°C. ^{1}H NMR: δ 9.79 (d, J = 12.0 Hz, 1H), 7.15 (dd, J = 12.0 and 8.1 Hz, 1H), 6.92–6.83 (AB system, J = 9.3 Hz, 4H), 4.78 (d, J = 8.1 Hz, 1H), 3.77 (s, 3H), 3.70, (s, 3H); ^{13}C NMR δ 170.8, 155.5, 144.2, 134.3, 116.9, 114.8, 85.5, 55.5, 50.5; IR (NaCl): ν_{max} 3315, 2959, 2838, 1622, 1589, 1515, 1484, 1297, 1233, 1207, 1180, 1034, 1017 828, 782 cm^{-1}; MS: *m/z* 230 [(M + Na)$^+$, 94%], 208 [(M + H)$^+$, 9], 176 (100), 148 (30), 124 (36); HRMS: $C_{11}H_{13}NO_3$ requires (M + H)$^+$, 208.0974. Found: (M + H)$^+$, 208.0970.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76

Found: C, 63.72; H, 6.28; N, 6.79

6-Methoxy-1*H*-quinolin-4-one (4).- Compound **4** was prepared using a modification of a procedure described by Nicolaou *et al.*[3a] So, compound **3** (4.70 g, 22.7 mmol) was added, in one portion and with magnetic stirring, to refluxing diphenyl ether (275 mL). After 0.5 h the reaction mixture was cooled to 18°C then poured into hexane (300 mL). The ensuing precipitate was removed by filtration and washed with diethyl ether (500 mL) to afford compound **4**[3a,9] (3.70 g, 93%) as tan-colored solid, mp 234–237°C (lit.[9] mp 237–238°C). ^{1}H NMR (DMSO-d_6): δ 7.97 (d, J = 7.2 Hz, 1H), 7.57 (m, 1H), 7.48 (m, 1H), 7.33 (m, 1H), 6.16 (d, J = 7.2 Hz, 1H), 3.82, (s, 3H), 3.53 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 176.7, 156.6, 139.7, 135.7, 127.5, 123.4, 121.2, 108.3, 104.9, 56.3; IR (NaCl): ν_{max} 3075, 2978, 1592, 1555, 1514, 1386, 1232, 1208, 1029, 812 cm^{-1}; MS: *m/z* 198 [(M + Na)$^+$, 5%], 176 [(M + H)$^+$, 100], 161 (10), 102 (8); HRMS: $C_{10}H_9NO_2$ requires (M + H)$^+$, 176.0712. Found: (M + H)$^+$, 176.0711.

4-Bromo-6-methoxyquinoline (5).- Compound **5** was prepared using a protocol described by Margolis.[4] Thus, phosphorus tribromide (110 μL, 1.18 mmol) was added to a magnetically stirred solution of 6-methoxy-1*H*-quinolin-4-one (**4**) (200 mg, 1.14 mmol) in DMF (5 mL) maintained under a nitrogen atmosphere at 0°C. The ensuing mixture was warmed to 18°C and after 1 h at this temperature ice was added. After 0.5 h sodium bicarbonate (5 mL of a saturated aqueous solution) and dichloromethane (15 mL) were added and the phases separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow residue was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions afforded compound **5**[3b,4] (239 mg, 88%) as a light-

yellow, crystalline solid, mp 86°C (*lit.*[3b] mp 78–80°C), R_f 0.3 (in 1:1 v/v hexane/ethyl acetate). ^{1}H NMR: δ 8.52 (d, J = 4.8 Hz, 1H), 7.99 (m, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.42–7.38 (complex m, 2H), 3.98 (s, 3H); ^{13}C NMR δ 158.4, 146.7, 144.5, 132.0, 131.0, 128.5, 124.8, 122.8, 103.8, 55.3; IR (NaCl): ν_{max} 3083, 2961, 1618, 1622, 1573, 1558, 1497, 1424, 1352, 1263, 1231, 1160, 1064, 1028, 844, 817 cm^{-1}; MS (EI): *m/z* 239 and 237 ($M^{+\bullet}$, 39 and 38%), 207 (12), 194 (20), 158 (4), 149 (42); HRMS: $C_{10}H_8{}^{79}BrNO$ requires $M^{+\bullet}$, 236.9789. Found: $M^{+\bullet}$, 236.9793.

4-Iodo-6-methoxyquinoline (6).- Acetic anhydride (300 μL, 3.15 mmol) was added to a magnetically stirred suspension of 4-bromo-6-methoxyquinoline (**5**) (300 mg, 1.26 mmol) and sodium iodide (565 mg, 3.78 mmol) in acetonitrile (2 mL) maintained at 18°C. The ensuing reaction mixture was heated, for 3 h, at 80°C in a microwave reactor then cooled and treated with potassium carbonate (1.5 mL of a 10% aqueous solution), sodium sulfite (1.5 mL of a 5% aqueous solution) and dichloromethane (10 mL). The phases were separated, the aqueous layer extracted with dichloromethane (3 x 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow solid was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions afforded title compound **6**[2] (337 mg, 94%) as a colorless, crystalline solid, mp 126°C (lit.[2] mp 85°C), R_f 0.3 (in 1:1 v/v hexane/ethyl acetate). ^{1}H NMR: δ 8.29 (br s, 1H), 7.99–7.89 (complex m, 2H), 7.65 (dd, J = 9.0 and 2.7 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR: δ 158.9, 146.9, 143.7, 132.4, 131.4, 131.3, 122.9, 110.2, 109.2, 55.4; IR (NaCl): ν_{max} 3344, 2953, 1617, 1555, 1498, 1452, 1423, 1350, 1264, 1232, 1159, 1028 cm^{-1}; MS (EI): *m/z* 285 ($M^{+\bullet}$, 100%); HRMS: $C_{10}H_8{}^{127}INO$ requires $M^{+\bullet}$, 284.9651. Found: $M^{+\bullet}$, 284.9651. *Anal.* Calcd for $C_{10}H_8INO$: C, 42.13; H, 2.83; I, 44.51; N, 4.91. Found: C, 42.45; H, 3.19; I, 44.22; N, 4.96.

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A SHORT SYNTHESIS OF THE NATURALLY OCCURRING 2,3,3',4,4',5,5'-HEPTACHLORO- ("Q1") AND HEPTABROMO-1'-METHYL-1,2'-BIPYRROLES

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(09/04/08)

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Of the more than 4,500 known naturally occurring organohalogen compounds[1] the halogenated bipyrroles are among the most interesting. For example, hexabromo-1,1'-dimethyl-2,2'-bipyrrole and 3,3',4,4'-tetrabromo-5,5'-dichloro-1,1'-dimethyl-2,2'-bipyrrole are present in the eggs of Pacific and Atlantic Ocean seabirds (albatross, puffin, gull, petrel, auklet) and in bald eagle liver samples,[2,3] and, more recently, 2,3,3',4,4',5,5'-heptachloro-1'-methyl-1,2'-bipyrrole (designated "Q1") (**1**) is found to be a ubiquitous marine natural product, detected in over 100 environmental marine samples from virtually all over the world (sea bird eggs, fish, the blubber of marine mammals, Antarctic air, and, remarkably, human milk from Eskimo women who consume whale blubber).[4] Although we established the structure of Q1 by total synthesis in 2002, the yield was very low due to the difficulty of synthesis and instability of the key intermediate 1,2'-bipyrrolyl **4**.[5] Subsequently, many mixed halogenated 1,2'-bipyrrolyls have been detected in a myriad of marine sources.[6] For example, 2,3,3',4,4',5,5'-heptabromo-1'-methyl-1,2'-bipyrrole (**2**) was tentatively identified in 2006.[6b,c]

To provide a more efficient synthesis of Q1 (**1**) for much needed analytical comparison and biological evaluation in view of its structural similarity to anthropogenic polychlorinated