Quinoline Alkaloids: Synthesis of Pyrano[2,3-*b*]quinolines, Khaplofoline, Lunacrine, and Demethoxylunacrine

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Polyphosphoric acid (PPA)-catalyzed cyclization of 2-ono-3-vinylquinolinecarboxylic acid (**1**) yielded 3,4-dihydro-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinoline (**4**). The same reaction of 4-methoxy-2-oxo-3-vinylquinolinecarboxylic acid (**1g**) afforded 4-methoxy-2,2-dimethylpyrano[2,3-*b*]-quinoline (**4g**), which on hydrolysis with ethanolic hydrochloric acid gave khaplofoline (**5**). The Prevost reaction of 4-methoxy-3-prenylquinolin-2-one (**6**) using I_2/HgO in acetic acid yielded 4-methoxy-2-isopropylfuro[2,3-*b*]quinoline (**7**). Compound **7** on reduction with H_2/Pd−C followed by *N*-methylation and de-*O*-methylation afforded lunacrine (**10a**). A similar reaction sequence on **6b** gave demethoxylunacrine (**10b**).

The plant family Rutaceae is known[1,2] to be a prolific source of pyrano[2,3-*b*]quinoline and furo[2,3-*b*]quinoline alkaloids. These alkaloids have been reported[3−11] to be associated with interesting pharmacological as well as biological properties and have been synthesized by several methods. The synthetic method for the preparation of the pyranoquinoline system is based on either oxidative cyclization of 4-hydroxy-3-(3′-methybut-1′-enyl)-2-quinolinones with DDQ[12] or the Prevost reaction of 3-prenyl-2-quinolones.[13] Though these methods have proven to be fairly satisfactory, the overall yield of the alkaloids was only 15−35% because the routes to obtain the precursor prenylquinolines gave low yields (21−35%)[14,15] and often were attended by undesired side reactions (such as the formation of unwanted 3-(3′-methylbut-1′-enyl)-2-quinolinones as the major product[15]). This note reports a facile novel one-pot synthesis of 3,4-dihydro-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinolines (**4**). khaplofoline (**5**), lunacrine (**10a**), and demethoxylunacrine (**10b**) utilizing 3-(1′-carboxy-3′-methylbut-1′-enyl)-2-quinolinones[14] (**1**).

Treatment of the carboxy derivative of the 2-quinolinone[14] **1a** with polyphosphoric acid (PPA) at 140 °C for 4 h furnished in 60% yield the desired 6-methyl-3,4-dihydro-2,2-dimethylpyrano[2,3-*b*]quinoline (**4a**), identical with an authentic sample.[14] Extension of this method to compounds **1b**−**f** gave the respective pyranoquinolines **4b**−**f**. Analytical and spectroscopic data were consistent with the proposed structures **4** (Scheme 1).

The formation of **4** from **1** can be assumed to proceed via the decarboxylated product **2** formed in situ under acidic condition at high temperature.[16,17] Compound **2** is isomerized to a more stable isoprenyl cation, which then cyclizes to product **4**.

A similar polyphosphoric acid reaction of 4-methoxy-2-ono-3-vinylquinolinecarboxylic acid (**1g**) yielded the quinoline derivative **4g**, identical with an authentic sample[12] in all respects. Compound **4g** was refluxed with 10% ethanolic hydrochloric acid for 30 h to give khaplofoline (**5**), identical with the natural product by mixed mp and superimposable IR spectra.

The 4,8-dimethoxy-3-prenyl-2-quinolinone (**6a**)[23] on reaction with Prevost reagent (I_2/HgO) in acetic acid afforded 4,8-dimethoxy-2-isopropylfuro[2,3-*b*]quinoline (**7a**).[23] Catalytic hydrogenation of **7a** using Pd−C (5%) in ethanol solution at 50 psi gave 2-isopropyldihydrofuroquinoline (**8a**).[24] Compound **8a** was heated with methyl iodide for 20 min and then allowed to stand overnight. The lunasine (**9a**) obtained was directly converted into lunacrine, 8-methoxy-*N*-methyl-2,3-dihydro-2-isopropylfuro[2,3-*b*]quinoline (**10a**), by treatment with anhydrous lithium bromide in acetonitrile. The physical and spectroscopic data of compounds **7a**, **8a**, **9a**, and **10a** were identical with those of the authentic samples.

The same procedure yielded demethoxylunacrine (**10b**) from the starting quinolinone **6b**.

Experimental Section

General Experimental Procedures. Melting points were determined on a Boetius microheating table or a Mettler FP5 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian EM-360 (90 MHz) XL 100 (100 MHz) and General Electric QE-300 (300 MHz) spectrometers in $CDCl_3$. Chemical shifts are reported downfield from TMS, and coupling constants are in Hz. IR spectra were recorded on a Perkin-Elmer 597 spectrophotometer in KBr or Nujol. Mass spectra were recorded on Finnigan MAT-8230 and JEOL-JMS-D 300 instruments. Microanalyses were performed on Carlo-Erba 1106 and Perkin-Elmer Model 240 CHN analyzers.

Preparation of 2-Oxo-3-vinylquinolinecarboxylic Acids 1a−g. A mixture of quinolineacetic acid (0.02 mol), isobutyraldehyde (0.2 mol), sodium acetate (4.5 g), acetic acid (20 mL), and acetic anhydride (25 mL) was heated on a steam bath for 1.5 h and then poured into ice−water. The aqueous solution was then extracted with $CHCl_3$, washed with aqueous $NaHCO_3$ and water, and then dried over anhydrous Na_2SO_4. The residue obtained was mixed with aqueous NaOH (2 N, 75 mL), and the reaction mixture was heated on a steam bath

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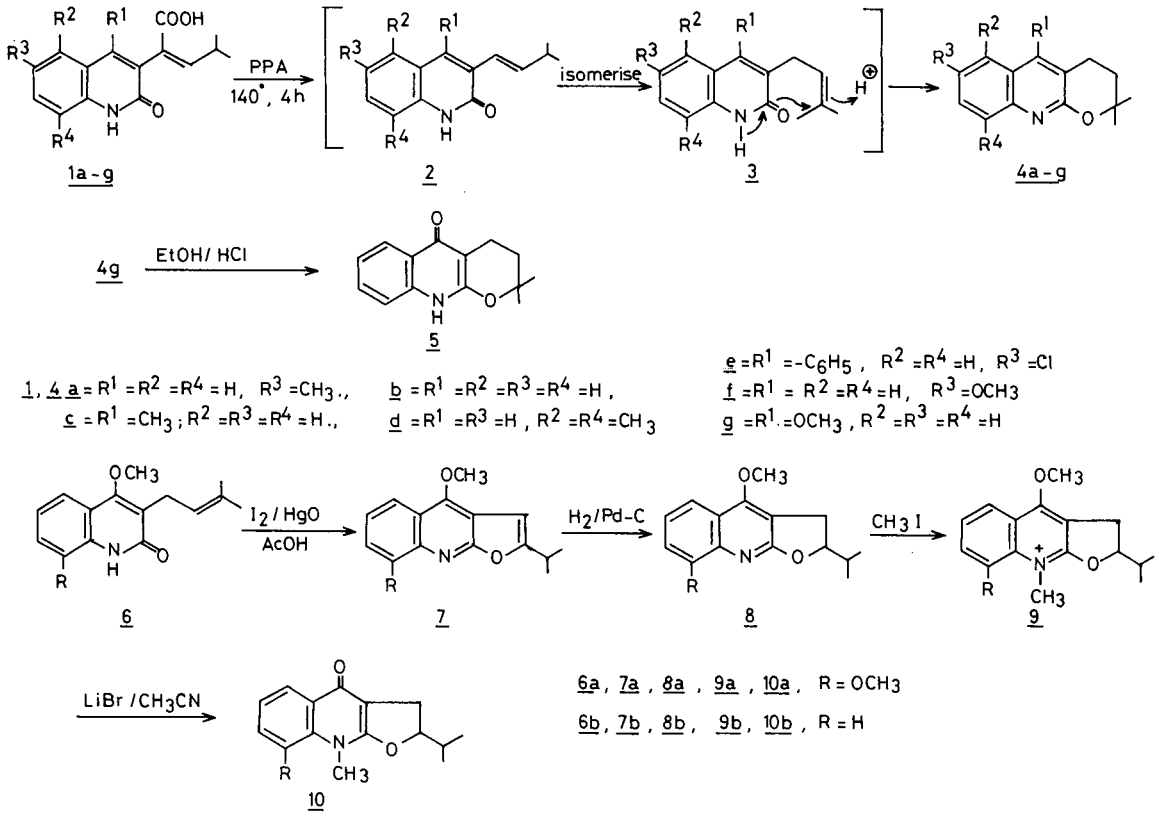
Scheme 1



for 1 h. It was cooled and acidified with dilute hydrochloric acid. The solid obtained was filtered, dried, and recrystallized with a C_6H_6−EtOH mixture. **1a**: mp 240 °C (lit.[14] mp 241−242 °C). **1b**: mp 234−235 °C (lit.[14] mp 235−236 °C). **1c**: mp 234 °C (lit.[14] mp 235−236 °C). **1d**: mp 227−229 °C (lit.[14] mp 229−230 °C). **1e**: mp 252−254 °C (lit.[14] mp 253−254 °C). **1f**: mp 218−220 °C (lit.[14] mp 220−221 °C). **1g**: mp 314 °C.

Synthesis of 3,4-Dihydro-2,2-dimethylpyrano-[2,3-*b*]quinolines 4a−g. The 2-ono-3-vinylquinolinecarboxylic acid (**1a−g**, 2 mmol) was heated with freshly prepared polyphosphoric acid (1 g) (2.5 g of P_4O_{10} and 1 mL of H_3PO_4) in an oil bath at 140 °C under a nitrogen atmosphere. The course of the reaction was followed by TLC analysis on silica gel with petroleum ether (60−80 °C)−EtOAc (3:1) as solvent system. The reaction was usually complete within about 4 h. After completion, the solution was cooled in an ice bath and poured into crushed ice (100 g). The yellow pyranoquinoline that separated was filtered, washed, dried, and chromatographed over alumina with petroleum ether (60−80 °C)−EtOAc (2:1, 3 × 100 mL). The solvent mixture was evaporated under reduced pressure to give solid **4a−g**. **4a:** yield 60%; mp 148−150 °C (lit.[15] mp 150−151 °C);^{1}H NMR ($CDCl_3$, 100 MHz) δ 7.30−7.90 (4H, m, H-5,6,8,9), 3.00 (2H, t, J = 7 Hz, H-4), 2.50 (3H, s, 7-CH_3), 1.90 (2H, t, J = 7 Hz, H-3), 1.50 (6H, s, CMe_2); *anal.* C 79.18%, H 7.44%, N 6.14%, calcd for $C_{15}H_{17}NO$, C 79.26%, H 7.54%, N 6.16%.

4b: yield 60%; mp 93−95 °C (lit.[15] mp 95−96 °C);^{1}H NMR ($CDCl_3$, 100 MHz) δ 7.20−7.93 (5H, m, H-5,6,7,8,9), 2.93 (2H, t, J = 6.9 Hz, H-4), 1.86 (2H, t, J = 6.9 Hz, H-3), 1.50 (6H, s, CMe_2); *anal.* C 78.78%, H 7.16%, N 6.48%, calcd for $C_{14}H_{15}NO$, C 78.84%, H 7.09%, N 6.56%.

Synthesis of Khaplofoline (5). The 4-methoxypyranoquinoline **4g** (250 mg) was refluxed with 10% ethanolic hydrochloric acid (10 mL) for 30 h. The solution was concentrated to a small bulk and poured into water. The precipitated product was collected by filtration and recrystallized from EtOAc to yield khaplofoline (**5**) as fine crystals: yield 96%; mp 270−272 °C (lit.[22] mp 272−274 °C); IR (KBr) ν_{max} 3340, 2995, 1635 cm^{-1}; *anal.* C 73.32%, H 6.59%, N 6.11%, calcd for $C_{14}H_{15}NO_2$, C 73.36%, H 6.64%, N 5.98%.

Synthesis of 4,8-Dimethoxy-2,3-dihydro-2-isopropylfuro[2,3-*b*]quinoline (8a). 4,8-Dimethoxy-2-isopropylfuro[2,3-*b*]quinoline[23] (**7a**, 0.270 g, 0.001 mol) in pure ethanol (50 mL) was shaken with 5% Pd/C (100 mg) in an atmosphere of hydrogen at 50 psi in a Parr hydrogenator for 3.5 h. The catalyst was removed by filtration, and the filtrate was concentrated to a small bulk under reduced pressure. The residue obtained was placed over a column of neutral alumina and eluted with petroleum ether−EtOAc mixture (96:4) to yield 4,8-dimethoxy-2,3-dihydro-2-isopropylfuro[2,3-*b*]quinoline (**8a**) (58%) after evaporation of the solvent: mp 130−132 °C (lit.[24] mp 130−131 °C). Treatment of **7b**[23] yielded **8b**: 60%; mp 124−126 °C (lit.[24] mp 125−126 °C).

Synthesis of Lunasine (9a). A solution of **8a** (136 mg, 0.5 mol) and methyl iodide (15 mL) was heated on a steam bath for 20 min and then allowed to stand overnight. Evaporation of the excess reagent followed by crystallization from benzene yielded lunasine (**9a**) as fine crystals in 58% yield: mp 130−132 °C (lit.[24] mp 130−131 °C); *anal.* C 71.08%, H 7.28%, N 4.74%, calcd for $C_{17}H_{21}NO_3$, C 71.04%, H 7.37%, N 4.80%. Similar treatment of **8b** yielded (**9b** 60%): mp 124−126 °C (lit.[25] mp 125−126 °C); *anal.* C 73.76%, H 7.38%, N 5.78%, calcd for $C_{15}H_{18}NO_2$, C 73.73%, H 7.43%, N 5.73%.

Synthesis of Lunacrine (10a). A mixture of lunasine (**9a**, 125 mg) and anhydrous LiBr (2.5 g) in CH_3CN (20 mL) was refluxed for 4 h and then poured into ice−water. It was extracted with $CHCl_3$ and then dried over anhydrous Na_2SO_4. The residue obtained from the extract was purified by passing through a column of alumina and eluting with petroleum ether−EtOAc mixture (95:5) to afford 8-methoxy-*N*-methyl-2,3-dihydro-2-isopropylfuro[2,3-*b*]quinoline (**10a**) (95%): mp 145−147 °C (lit.[24] mp 146−148 °C); IR (KBr) ν_{max} 1620, 1590, 1500, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 8.00 (1H, dd, J = 1.6, 5.5 Hz, H-5), 7.05−7.75 (2H, m, H-6 and H-7), 4.75 (1H, m, H-2), 3.90 (3H, s, OCH_3), 3.80 (3H, s, $N-CH_3$), 3.30 (2H, m, 2H-3), 2.05 (1H, m, $-CHMe_2$), 1.00 (6H, d, J = 6 Hz, $CHMe_2$); *anal.* C 70.34%, H 7.04%, N 5.16%, calcd for $C_{16}H_{19}NO_3$, C 70.29%, H 7.01%, N 5.12%.

Similar treatment of **9b** gave **10b** (95%): mp 152−153 °C (lit.[24] mp 152−154 °C); IR (KBr) ν_{max} 2990, 1610, 1550, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 7.90 (1H, d, J = 8.2 Hz, H-5), 7.00−7.65 (3H, m, H-6, H-7, H-8), 4.50 (1H, m, H-2), 3.65 (3H, s, NCH_3), 3.50 (2H, dd, J = 16, 5.5 Hz, 2H-3), 2.20 (1H, m, $CHMe_2$), 1.00 (6H, d, J = 6 Hz, $-CHMe_2$); *anal.* 74.38%, H 6.62%, N 5.86%, calcd for $C_{15}H_{17}NO_2$, C 74.34%, H 6.66%, N 5.78%.

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