Synthesis and Conformation of 2-[[3-(1-Hydroxyhexyl)phenoxy]methyl]quinoline, a 5-Lipoxygenase Inhibitor and Leukotriene Antagonist

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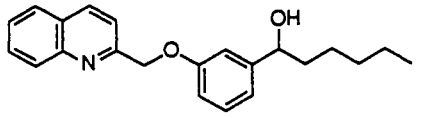
The quinoline derivative **1** is an orally active, specific inhibitor of 5-lipoxygenase,[1] and is also reported to be an orally effective peptidoleukotriene antagonist.[2] Recently **1** has been shown to inhibit platelet-activating factor (PAF)



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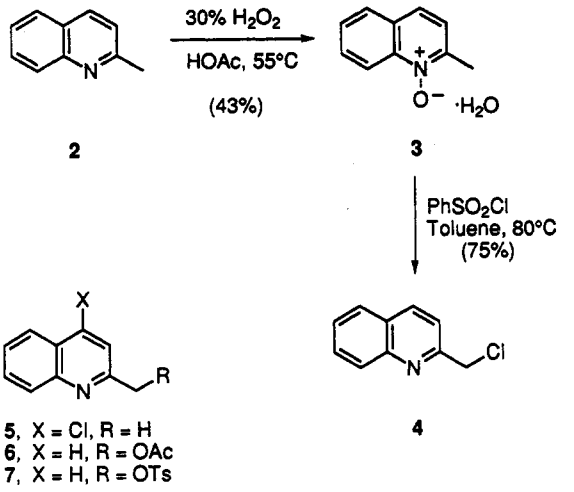
synthesis by peritoneal mast cells.[3] Its involvement in the pathophysiology of a variety of allergic and inflammatory conditions is under active investigation.[4] As a potentially interesting therapeutic agent **1** presents an opportune target for synthetic development, and herein we describe a convergent approach in which 2-(chloromethyl)quinoline (**4**) and the substituted phenol **12** are coupled in the final step. The latter is obtained by an aldol condensation of the dianion of *m*-hydroxyacetophenone with *n*-butyraldehyde.

2-(Chloromethyl)quinoline (**4**) was conveniently prepared from quinaldine (**2**) by first converting this substance to its *N*-oxide monohydrate **3** with H_2O_2 in acetic acid.[5] Attempts to convert **3** or its less stable anhydrous form to **4** with phosphorus oxytrichloride[6] led to the nuclear chlorinated product **5** and **4** in approximately equal amounts. Exposure of **3** to acetyl chloride in the presence of excess LiCl was also unsatisfactory, furnishing acetate **6** as the major product, while similar treatment of **3** with *p*-toluenesulfonyl chloride gave a 1:1 mixture of **4** and **7**. Finally, modification of a procedure due to Vozza,[7] in which **3** was reacted with benzenesulfonyl chloride, afforded **4** of high purity in 75% yield.

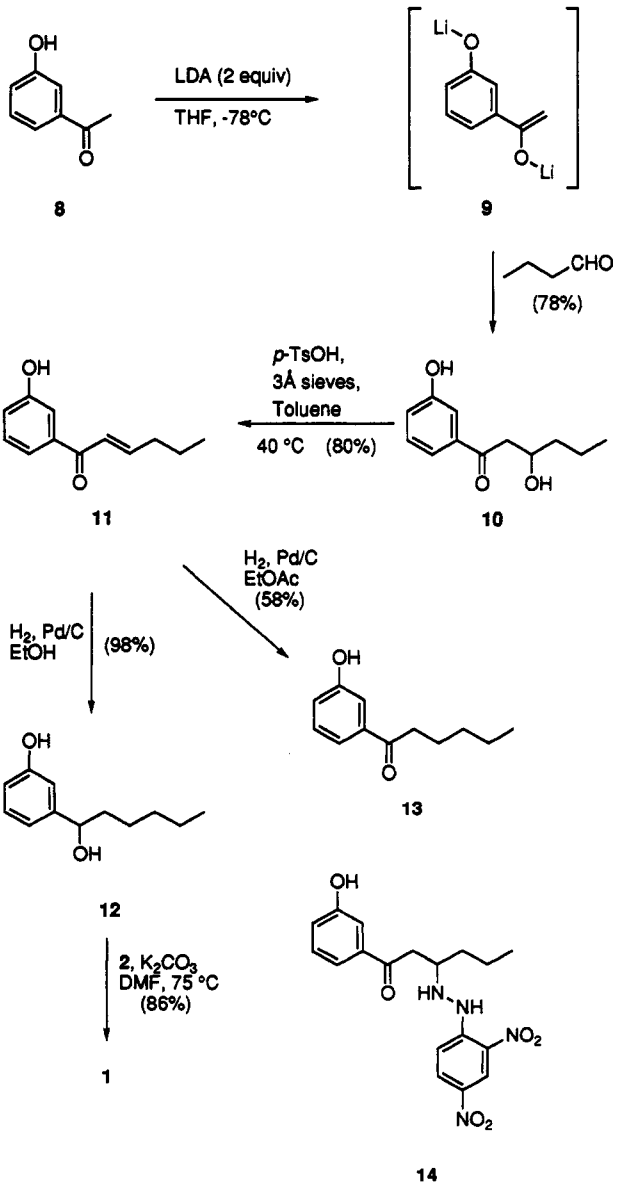
Synthesis of the phenol derivative **12** began from *m*-hydroxyacetophenone (**8**) and was based on the premise that the dilithio dianion **9** would undergo kinetically controlled condensation with *n*-butyraldehyde to give the crossed aldol product **10**. Although **9** is a highly insoluble species, this heterogeneous aldol condensation afforded



2 **3** **4**

5, X = Cl, R = H
6, X = H, R = OAc
7, X = H, R = OTs

β-hydroxy ketone **10** in excellent yield. Dehydration of **10** was carried out under acidic catalysis in the presence of molecular sieves to give α,β-unsaturated ketone **11** which was characterized as the conjugate addition product **14** obtained with 2,4-dinitrophenylhdyrazine. Hydrogenation



8 **9** **10** **11** **12** **13** **1** **14**

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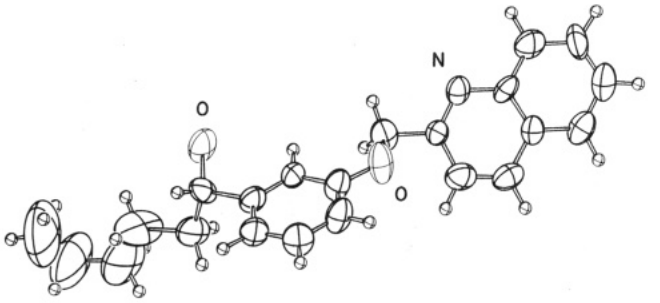

Figure 1. ORTEP drawing of 1 with heteroatoms labeled. Thermal ellipsoids are drawn at the 50% probability level.

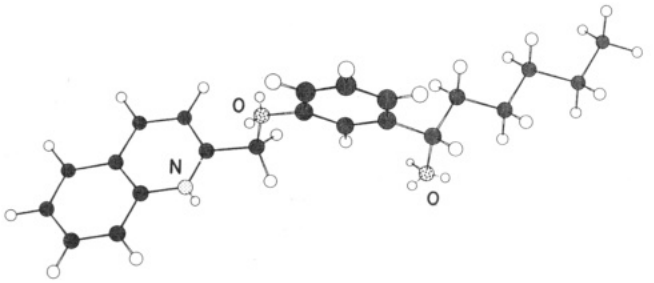

Figure 2. Conformation of 1 calculated by MM2.

of **11** over palladium-on-carbon in ethyl acetate gave the aryl ketone **13**. However, when ethanol was employed as solvent, both the double bond and carbonyl group of **11** were reduced, leading in a single operation and in quantitative yield to **12**. Interestingly, no hydrogenolysis of the benzylic alcohol of **12** was observed under these conditions.

The final coupling of **12** with **4** was carried out in DMF with anhydrous potassium carbonate as base and produced **1** in high yield after chromatographic purification. An X-ray crystallographic analysis of **1** fully confirmed its structure (Figure 1) and also revealed a conformation in the solid state which closely parallels that predicted from a molecular mechanics computation (Figure 2).[9] In both the calculated (MM2) and observed (X-ray) structures the quinoline and benzenoid rings of **1** are virtually perpendicular. The secondary alcohol oxygen and the methylene carbon connecting the quinoline to the phenoxy group lie slightly below the plane of the benzene ring and occupy a syn relationship. The alcohol oxygen deviates from the plane of the benzene ring by 29° in the calculated structure and 18° in the observed structure, while the linking methylene group is 19° (calculated) and 8° (observed) out of the plane of the benzene ring. The conformation of **1** as revealed by its X-ray crystal structure appears to be at variance with a rationale for the design of 5-lipoxygenase inhibitors based on an isosteric fit with 15-HETE.[1]

Experimental Section

Solvents were purified and dried prior to use by distillation from an appropriate drying agent. Diethyl ether, tetrahydrofuran, and toluene were distilled from sodium benzophenone ketyl under an argon atmosphere. Methylene chloride, dimethyl sulfoxide, pyridine, diisopropylamine, and triethylamine were distilled from calcium hydride under an argon atmosphere. Bulk solvents for chromatography and workup of reactions were distilled through glass prior to use. Starting materials were obtained from commercial sources and, unless stated otherwise, used without further purification.

Solvents were removed at water aspirator pressure by rotary evaporation, and residual solvent was removed by vacuum pump at less than 1.0 Torr. Glassware and syringes were dried in an oven at 165 °C overnight and cooled in a dessicator over $CaSO_4$ prior to use. Flasks were flame-dried under a stream of argon.

Analytical thin-layer chromatography (TLC) was performed on precoated TLC plates (Silica Gel 60 F-254, layer thickness 0.2 mm). Flash chromatography was performed with Silica Gel 60 (230–400 mesh ASTM). Radial chromatography was carried out on individually prepared rotors with layer thicknesses of 1, 2, or 4 mm.

Melting points were determined using a capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a 5DXB FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained on a 300-MHz or 400-MHz spectrometer, and chemical shifts are expressed as ppm downfield from tetramethylsilane. Mass spectra (MS) were obtained at an ionization potential of 70 eV. High resolution mass spectra (HRMS) were determined by the peak match method.

3-(3-Hydroxyhexanoyl)phenol (10). To dry THF (1.3 mL) and freshly distilled diisopropylamine (156 mg, 1.54 mmol) at 0 °C (ice bath) under Ar was added a 1.6 M solution of *n*-butyllithium in hexane (0.97 mL, 1.54 mmol) dropwise over 0.5 h and the resulting mixture was stirred at 0 °C for 1.25 h. The mixture was cooled to −78 °C and a solution of 3-hydroxyacetophenone (**8**) (100 mg, 0.73 mmol) in dry THF (0.7 mL) was added slowly via cannula. The pale yellow suspension was stirred for 1 h at −78 °C and then treated with a solution of freshly distilled (from $CaSO_4$) *n*-butyraldehyde (58 mg, 0.81 mmol) in THF (0.4 mL) during 10 min. After stirring for 0.3 h, the mixture was quenched by addition of glacial HOAc (93 μL, 1.62 mmol) in dry Et_2O (0.5 mL) followed by additional Et_2O (10 mL), and the cooling bath was removed. To the cold mixture was added chilled saturated aqueous NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (5 × 10 mL), and the combined organic extracts were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na_2SO_4. Removal of solvent yielded 183 mg of an amber oil which was purified by flash chromatography (30 g of Silica Gel 60, 2.5% MeOH–$CHCl_3$) to give 118 mg (78%) of **10** as a colorless oil: IR (neat) 3349, 2957, 1673, 1586, 1450, 1277, 998, 886, 786 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.42 (m, 2H), 7.27 (t, J = 8 Hz, 1H), 7.05 (dt, J = 8, 2 Hz, 1H), 4.28 (m, 1H), 3.91 (d, J = 4 Hz, 1H, exchanged with D_2O), 3.09 (m, 2H), 1.50 (m, 4H), 0.92 (t, J = 7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 201.2, 156.5, 137.9, 129.9, 121.1, 120.3, 114.5, 68.0, 44.9, 38.5, 18.7, 13.9; MS m/z 208 (M^+), 190 (6), 165 (7), 121 (100); HRMS m/z 208.10990 (M^+), calcd for $C_{12}H_{16}O_3$ 208.10990.

***trans*-3-(3-Hex-2-enoyl)phenol (11).** A solution of **10** (102 mg, 0.50 mmol) in dry toluene (5 mL) was degassed by passing a vigorous stream of Ar through the mixture for 10 min, and *p*-toluenesulfonic acid monohydrate (56 mg, 0.30 mmol) and powdered 3-Å molecular sieves (102 mg) were added. The mixture was warmed to 40 °C for 22 h with rapid stirring and then was cooled and filtered through Celite. The filter pad was washed with EtOAc, and the combined organic solutions were washed with 0.05 M aqueous $NaHCO_3$ (2 × 1 mL) and saturated aqueous NaCl (1 mL) and dried over anhydrous Na_2SO_4. Filtration and concentration of the solution gave 104 mg of an amber oil which was purified by radial chromatography (2-mm rotor, 30% EtOAc–hexane) to afford 76 mg (80%) of **11** as a pale pink oil: IR (neat) 3342, 2964, 1662, 1657, 1450, 1304, 978, 878, 786 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 (t, J = 2 Hz, 1H), 7.47 (dt, J = 8, 1 Hz, 1H), 7.33 (t, J = 8 Hz, 1H), 7.10 (m, 3H), 6.85 (dt, J = 16, 1 Hz, 1H), 2.28 (dt, J = 7, 1 Hz, 2H), 1.51 (m, J = 7 Hz, 2H), 0.96 (t, J = 7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.6, 156.5, 151.0, 139.1, 129.7, 125.9, 120.9, 120.4, 115.3, 34.9, 21.3, 13.7; MS m/z 190 (M^+, 85), 147 (45), 121 (100): HRMS m/z 190.09934 (M^+), calcd for $C_{12}H_{14}O_2$ 190.09937.

A mixture of **11** (17.5 mg, 0.092 mmol), 2,4-dinitrophenylhydrazine (20 mg, 0.101 mmol), and glacial HOAc (1 drop) in absolute EtOH (0.5 mL) was warmed at 70 °C for 20 h. The mixture was

(8) Tanida, H. *Yakugaku Zashi* **1958**, *78*, 611. (*Chem. Abstr.* **1958**, *52*, 18420.)

(9) Molecular mechanics calculations were performed using the Chem 3D Plus program. Structures were minimized to an RMS of 0.01.

concentrated and purified by radial chromatography (1-mm rotor, 30% EtOAc–hexane) to give 14.8 mg (42%) of **14** as a yellow solid: mp (hexane–CH_2Cl_2) 153 °C dec; IR (KBr) 3389, 2957, 1669, 1623, 1589, 1334 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 9.05 (d, J = 2 Hz, 1H), 8.22 (dd, J = 2, 10 Hz, 1H), 7.77 (d, J = 10 Hz, 1H), 7.48 (dd, J = 8, 1 Hz, 1H), 7.38 (m, 1H), 7.34 (t, J = 8 Hz, 1H), 7.07 (m, 1H), 5.00 (s, 1H), 4.43 (s, 1H), 3.59 (m, 1H), 3.12 (m, 2H), 1.61 (m, 1H), 1.48 (m, 3H), 0.95 (t, J = 7 Hz, 3H).

3-(1-Hydroxyhexyl)phenol (12). A mixture of **11** (76 mg, 0.40 mmol) and 10% palladium on charcoal (15.5 mg) in absolute EtOH (4 mL) was stirred under H_2 (1 atm) at 25 °C for 1 h. The solution was thoroughly degassed (aspirator pressure) and the catalyst was removed by filtration and washed with EtOAc (10 mL). Concentration of the filtrate gave 75.7 mg (98%) of pure **12** as a white solid: mp (hexane–$CHCl_3$) 99 °C; IR (KBr) 3382, 2934, 1591, 1483, 1403, 1277, 1025, 912, 785, 699 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19 (t, J = 8 Hz, 1H), 6.86 (m, 2H), 6.74 (dt, J = 8, 1 Hz, 1H), 5.58 (bs, 1H), 4.62 (t, J = 6 Hz, 1H), 2.14 (bs, 1H), 1.70 (m, 2H), 1.27 (m, 6H), 0.86 (t, J = 7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.0, 146.4, 129.6, 118.3, 114.7, 112.7, 74.7, 38.7, 31.6, 25.4, 22.5, 14.0; MS m/z 194 (M^+), 123 (100), 95 (43); HRMS m/z 194.13070 (M^+), calcd for $C_{12}H_{18}O_2$ 194.13067. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.31; H, 9.38.

Quinaldine *N*-Oxide Monohydrate (3). To distilled quinaldine (**2**) (25.0 g, 170.0 mmol) was added 30% H_2O_2 (27.7 g, 240.0 mmol) and glacial HOAc (76 mL, 1.33 mol). The mixture was warmed at 55 °C for 20 h, cooled to 0 °C (ice bath), and then treated with a solution of KOH (98 g, 1.75 mol) in water (122 mL) during 2 h. The resulting solid was filtered and the filtrate was washed with $CHCl_3$ (35 mL). The solid and the concentrated $CHCl_3$ extract were added to benzene, and the mixture was distilled until water no longer azeotroped (~220 mL benzene). The hot, yellow benzene solution was decanted from dark brown, insoluble material and cooled to 0 °C (ice bath). The chilled solution was treated dropwise with water (6 mL) resulting in precipitation of a nearly colorless solid which was collected by filtration and air-dried to give 13.2 g (43%) of **5**: mp 76 °C (lit. mp 77–78 °C).[5]

2-(Chloromethyl)quinoline (4). A solution of **3** (8.8 g, 49.8 mmol) in dry toluene (0.11 L) was warmed to 80 °C under Ar while a solution of benzenesulfonyl chloride (18.5 g, 104.5 mmol) in dry toluene (24 mL) was introduced during 0.25 h. After 2 h at 80 °C, a red oil separated from the solution. The mixture was cooled to 0 °C (ice bath) and treated with 5% aqueous HCl (120 mL). The red, aqueous layer was washed with toluene (120 mL), and the toluene solutions were discarded. The mixture was diluted with $CHCl_3$ (0.6 L) and ice-cold 10% aqueous NaOH (120 mL). The layers were separated, and the yellow aqueous solution was extracted with $CHCl_3$ (2 × 0.5 L). The combined organic extracts were washed with water (2 × 0.25 L) and dried over anhydrous Na_2SO_4. Filtration and concentration afforded (after vacuum drying) 6.6 g (76%) of **4** as a yellow solid: mp (hexane) 55 °C (lit. mp 54–55.5 °C).[8]

2-[[3-(1-Hydroxyhexyl)phenoxy]methyl]quinoline (1). A mixture of **12** (16 mg, 0.08 mmol), dry DMF (0.15 mL), and powdered anhydrous K_2CO_3 (26 mg, 0.18 mmol) under Ar was warmed at 75 °C for 1.5 h, cooled to rt, and then treated with a solution of 2-(chloromethyl)quinoline (**4**) (18 mg, 0.10 mmol) in dry DMF (0.10 mL). Heating was resumed at 75 °C and after 20 h the mixture was concentrated under reduced pressure. The residue was dissolved in water (1 mL) and EtOAc (1 mL). The aqueous layer was extracted with EtOAc (5 × 1 mL). The combined organic extracts were washed with water (3 × 1 mL) and concentrated. The crude residue was dissolved in Et_2O (8 mL), and the solution was washed with 10% aqueous NaOH (3 × 1 mL) and saturated aqueous NaCl (2 × 1 mL). The solution was concentrated to give 27 mg of yellow oil. Purification of the oil by radial chromatography (1-mm rotor, 30–50% EtOAc–hexane) afforded 23 mg (86%) of **1** as a white solid: mp (hexane) 69 °C; IR (neat) 3350, 2930, 1586, 1485, 1429, 1263, 1080, 826, 783 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 7.80 (dd, J = 8, 1 Hz, 1H), 7.72 (m, 1H), 7.65 (d, J = 8 Hz, 1H), 7.53 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.05 (t, J = 2 Hz, 1H), 6.91 (m, 2H), 5.35 (s, 2H), 4.62 (t, J = 7 Hz, 1H), 2.19 (bs, 1H), 1.69 (m, 2H), 1.38 (m, 1H), 1.24 (m, 5H), 0.85 (t, J = 7 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.8, 157.9, 147.5, 146.9, 136.9, 129.7, 129.5, 128.9, 127.7, 126.6, 126.5, 119.1, 118.7, 113.6, 112.6, 74.4, 71.2, 39.0, 31.7, 25.4, 22.5, 14.0; MS m/z 335 (M^+), 264 (55), 143 (62), 142 (100); HRMS m/z 335.18850 (M^+), calcd for $C_{22}H_{25}NO_2$ 335.18850. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.99; H, 7.64; N, 4.11.

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Supplementary Material Available: Full details of the X-ray crystallographic analysis and calculated MM2 internal coordinates for **1** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.