

A SYNTHESIS OF ORIXIARINE

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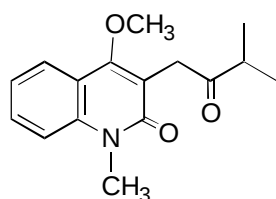
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Abstract – A synthesis of the quinoline alkaloid, orixiarine was achieved starting from *N*-methylaniline and isopropyl methyl ketone.

A hemiterpenoid quinoline alkaloid, named orixiarine was recently isolated in 1998 from *Skimmia laureola* (Rutaceae), which is an aromatic gregarious evergreen shrub found in Western Himalayas and Kashmir.^{1,2} The plant is used for the treatment of smallpox.³



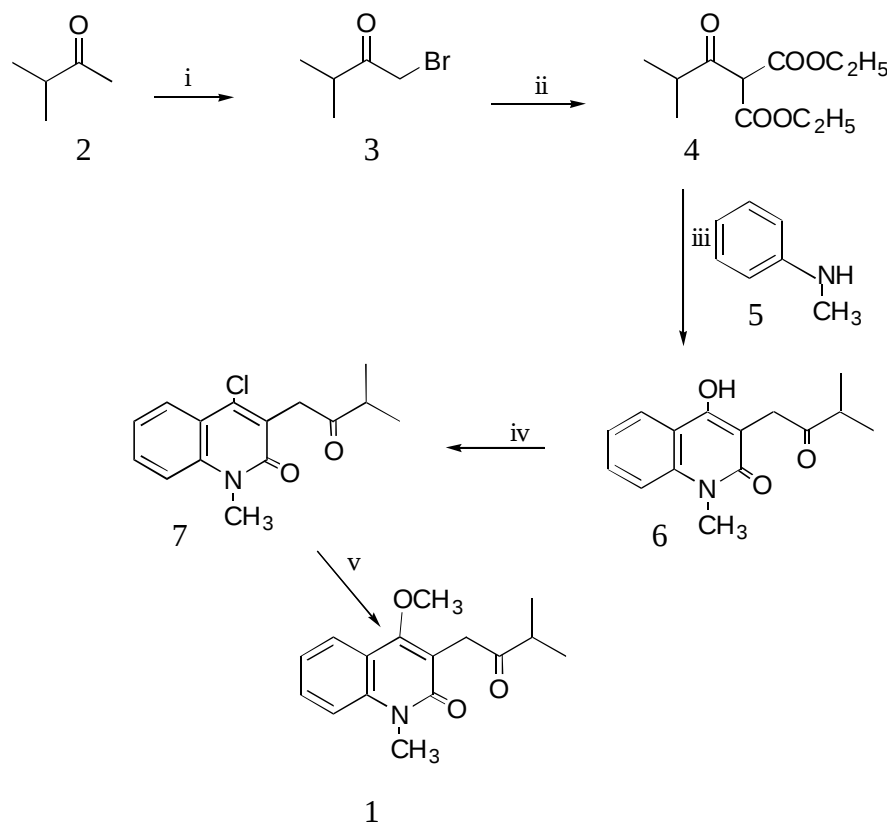
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Herein we report our approach resulting in a synthesis of orixiarine (**1**). As shown in the Scheme 1, the synthesis of **1** was realized through, a five-step procedure based on condensation reactions.

As the first step, 1-bromo-3-methyl-2-butanone (**3**) was obtained by bromination of isopropyl methyl ketone (**2**) and on further treatment with sodium methoxide and diethyl malonate, the bromo compound was converted to diethyl 2'-oxoisopentylmalonate (**4**) in moderate yields.⁴

Adapting the general method of the synthesis of 2,4-dihydroxyquinoline⁵ the compound (**4**) was reacted with *N*-methyl substituted anilines. Ring closure⁶ by thermal cyclization of the resulting dianilide compound (**5**) in refluxing diphenyl ether for 1 h gave 1-methyl-3-(3-methyl-2-oxobutyl)-4-hydroxy-2-quinolinone (**6**). Reaction of **6** with phosphorous oxychloride under reflux conditions^{7,8} for 3 h led to conversion of **6** to its chloro derivative (**7**) in 90% yield. Finally on treatment with sodium methoxide and after analysis the ¹H-NMR and ¹³C-NMR spectra of the methoxy product (**1**) have been found identical with that isolated from *Skimmia laureola*.¹

Scheme 1



(i) Br_2 , CH_3OH , rt, stirring, 61 % (ii) $\text{CH}_2(\text{COOC}_2\text{H}_5)_2$, Na, CH_3OH , 80°C , 3 h, 70 %
 (iii) Ph_2O , NMA, reflux, 1 h, 65 % (iv) POCl_3 , reflux, 3 h, 90 % (v) Na, CH_3OH ,
 reflux, 2.5 h, 80 %.

Thus, we have developed a facile route for the synthesis of the terpenoid quinoline alkaloid, orixiarine in good yield, which could pave a path for its biological evaluation.

EXPERIMENTAL

TLC was used to access the reactions and purity of products. mps were determined on a Boetius Microheating Table and Mettler-FP5 Melting apparatus and were uncorrected. IR spectra were recorded in Shimadzu – 8201-FT instrument in KBr pellets and only noteworthy absorption levels (reciprocal centimeter) are listed. ^1H -NMR spectra were recorded in a AMX-400 MHz spectrometer in CDCl_3 solution; chemical shifts are expressed in ppm (δ) relative TMS, coupling constants (J) in Hz. Satisfactory microanalyses were obtained on Carlo Erba 1106 and Perkin Elmer models 240 CHN analyzer. Mass spectra were recorded on a Jeol – 300 mass spectrometer.

Diethyl 2'-oxoisopentylmalonate (4): Sodium methoxide, prepared from sodium (1.15 g, 0.05 mol) and 20 mL of dry methanol was added to diethyl malonate (7.6 mL, 0.05 mol) during 30 min with continuous stirring. After all diethyl malonate had been introduced, the mixture was heated on a water bath for 15 min and allowed to cool. 1-Bromo-3-methyl-2-butanone (3) (5.6 mL, 0.05 mol) was then added over a period of 10 min and kept on a water bath for 3 h for the completion of the reaction. Besides distilling off the methanol, the residue was diluted with water and extracted with ether. The ether extract dried over

anhydrous sodium sulfate was filtered and concentrated to give diethyl 2'-oxoisopentylmalonate (**4**) (yield (3.9 mL, 70 %)). bp 175-178 °C. IR (KBr, $\gamma_{\max}$) 2980, 1760, 1270 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 1.10 – 1.45 (m, 12H, 4 CH_3), δ 2.67 (m, 1H, $-\text{CH}-(\text{CH}_3)_2$), δ 3.15 (d, 2H, $-\text{CH}_2-\text{CH}$, $J = 7.58$ Hz), δ 3.39 (t, 1H, $\text{CH}-\text{CH}_2$), δ 4.28 (m, 4H, 2-O- CH_2-CH_3). MS [70 eV, m/z (M^+)] 244. *Anal.* Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_5$: C, 59.05; H, 8.16. Found: C, 59.01; H, 8.19.

1-Methyl-3-(3-methyl-2-oxobutyl)-4-hydroxy-2-quinolinone (6): A solution of *N*-methylaniline (**5**) (1.10 mL, 0.01 mol) and diethyl 2'-oxoisopentylmalonate (**4**) (2.3 mL, 0.01 mol) in 10 mL of diphenyl ether was refluxed at 200 °C for 1 h. The reaction mixture was cooled gradually and washed several times with petroleum ether. The gummy residue was further washed three times with benzene (3x 50 mL) to give a colorless powder (**6**). It was then recrystallized with CHCl_3 . mp >300 °C; yield 65 %; IR (KBr, $\gamma_{\max}$) 1680, 1643, 3350 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 1.15 (s, 3H, CH_3), δ 1.21 (s, 3H, CH_3), δ 2.89 (h, 1H, $-\text{CH}-(\text{CH}_3)_2$, $J = 7.56$ Hz), δ 3.80 (s, 3H, $-\text{N-CH}_3$), δ 4.05 (s, 2H, CH_2), δ 7.30 (t, 1H, $\text{C}_7\text{-H}$, $J = 7.48$ Hz), δ 7.40 (d, 1H, $\text{C}_8\text{-H}$, $J = 8.44$ Hz), δ 7.60 (t, 1H, $\text{C}_6\text{-H}$, $J = 7.62$ Hz), δ 8.20 (d, 1H, $\text{C}_5\text{-H}$, $J = 7.84$ Hz), δ 12.50 (s, 1H, $-\text{OH}$). MS [70 eV, m/z (M^+)] 259. *Anal.* Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_3$: C, 69.46; H, 6.61; N, 5.41 Found: C, 69.41; H, 6.55; N, 5.34.

1-Methyl-3-(3-methyl-2-oxobutyl)-4-chloro-2-quinolinone (7): 1-Methyl-3-(3-methyl-2-oxobutyl)-4-hydroxy-2-quinolinone (**6**) (0.26 g, 0.001 mol) was directly refluxed in phosphorous oxychloride (3 mL, 0.02 mol) for 3 h. After cooling, it was poured in to crushed ice and allowed to stand overnight. The mixture was then extracted using ethyl acetate and the extract was dried over anhydrous sodium sulfate. Purification with silica gel column chromatography with petroleum ether-ethyl acetate yielded the product (**7**) at (98:2). mp 215 °C (CHCl_3). IR (KBr, $\gamma_{\max}$) 1705, 1665. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 1.25 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.97 (h, 1H, $\text{CH}-(\text{CH}_3)_2$, $J = 8.04$ Hz), 3.95 (s, 3H, N-CH_3), 4.20 (s, 2H, CH_2), 7.40-8.35 (m, 4H, Ar-H). MS [70 eV, m/z (M^+)] 278.

1-Methyl-3-(3-methyl-2-oxobutyl)-4-methoxy-2-quinolinone (orixiarine) (1): A solution of 1-Methyl-3-(3-methyl-2-oxobutyl)-4-chloro-2-quinolinone (**7**) (0.56 g, 0.002 mol) and sodium methoxide (0.0515 g, 0.0025 mol) in 20 mL of dry methanol was refluxed for 2.5 h. Upon cooling, the solid separated was filtered and recrystallized with methanol, to furnish **1** (Yield 80 %). The $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectrum of the product was essentially identical to the corresponding spectra that have been reported¹ previously for authentic. mp 173-178 °C. IR (KBr, $\gamma_{\max}$) 1665, 1630. MS [70 eV, m/z (M^+)] 273. *Anal.* Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3$: C, 70.31; H, 7.01; N, 5.13 Found: C, 70.18; H, 6.89; N, 5.21.

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