SYNTHESIS OF NEW QUINOLINE ALKALOIDS OF CHIOCOCCA ALBA

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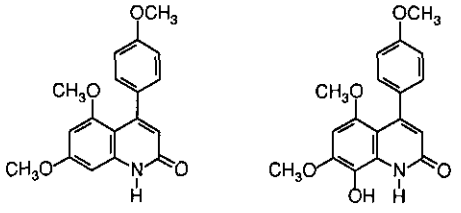
Abstract———Two new quinoline alkaloids, 5,7-dimethoxy-4-(4-methoxyphenyl)-2(1H)-quinolinone (1) and 8-hydroxy-5,7-dimethoxy-4-(4-methoxyphenyl)-2(1H)-quinolinone (2) were synthesized.

During past ten years many quinoline alkaloids related to 2(1H)-quinolinone have been isolated from natural resources, and synthesized.[1] These quinolinones usually possess an oxygen function at C-4 position on the quinoline ring. Recently, two new alkaloids were isolated from Chiococca alba L. (Rubiaceae), a tropical and subtropical shrub of the American continent.[2] The structure of the alkaloids was established by ir, uv, ms, and nmr spectra as 5,7-dimethoxy-4-(4-methoxyphenyl)-2(1H)-quinolinone (1) and 8-hydroxy-5,7-dimethoxy-4-(4-methoxyphenyl)-2(1H)-quinolinone (2), bearing a phenyl group instead of an oxygen function at C-4 position on the quinoline ring. Now, we report here the synthesis of the quinolinones.

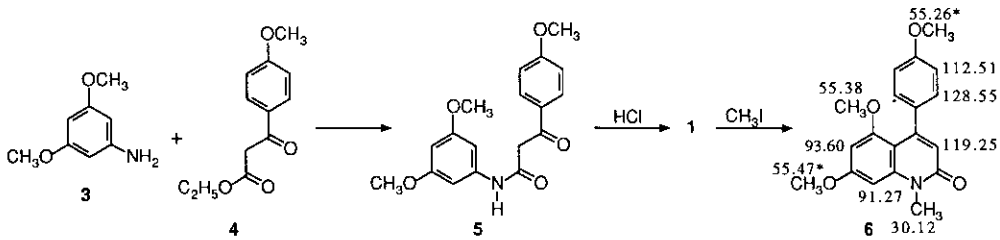


1 2

Scheme 1

The amide (5), prepared by reaction of 3,5-dimethoxyaniline (3) with ethyl 4-methoxybenzoylacetate[3] (4), was treated in concentrated hydrochloric acid-dioxane (1:5) at 25℃ to give the desired 5,7-dimethoxy-4-(4-methoxyphenyl)-2(1H)-quinolinone (1) in 72% yield. However, purification of the quinolinone (1) was difficult due to low solubility in organic solvents.

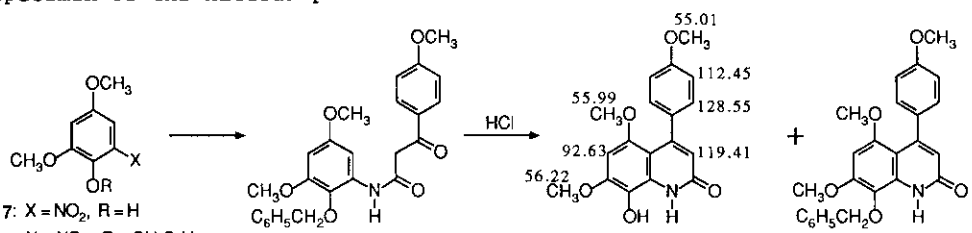
Methylation of 1 with sodium hydride followed by methyl iodide afforded the corresponding N-methyl-2(1H)-quinolinone (6) in 85% yield.



Scheme 2

Next, we synthesized 8-hydroxy-2(1H)-quinolinone (2). Benzylation of 2,4-dimethoxy-6-nitrophenol[4] (7) gave the corresponding benzyl ether (8), which was reduced to 2-benzyloxy-3,5-dimethoxyaniline (9) by sodium dithionite.[5] The amine (9) was treated with ethyl 4-methoxybenzoylacetate (4) to give the amide (10) in 86% yield. Cyclization of 10 in concentrated hydrochloric acid-dioxane (1:5) at 100 ℃ for 1 h afforded the corresponding 8-benzyloxy-2(1H)-quinolinone (11)(12% yield) and the desired 8-hydroxy-2(1H)-quinolinone (2)(65% yield). The isolated 8-benzyloxy-2(1H)-quinolinone (11) was treated in concentrated hydrochloric acid-dioxane(1:5) at 100 ℃ for 1 h to give 2 in 44% yield.

In the ^{1}H-nmr spectrum of quinolinones (1, 2, 6 and 11), the resonance for OCH_3 (3.38– 3.47 ppm) at C-5 position was shielded by 0.5 ppm compared to the resonance for other OCH_3 (3.86– 3.98ppm) due to magnetic anisotropy of benzene ring at C-4 position. Assignment of CH_3 and CH carbons of quinolinones (6 and 2) was achieved by DEPT spectra and a heteronuclear 2D-COSY run, as shown in Scheme 2 and Scheme 3, respectively. However, we could not prove that the synthesized 2(1H)-quinolinones (1, 2) are identical with the corresponding natural products, because spectral data or the specimen of the natural products were not available.



Scheme 3

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H- and ^{13}C-nmr spectra were recorded at 270.05 and 67.5 MHz, respectively, with tetramethylsilane as an internal standard, unless otherwise noted. All reactions were run with magnetic stirring. Anhydrous sodium sulfate was used for drying extracts, and the solvent was removed with a rotary evaporator and finally under high vacuum. Column chromatography was performed with E. Merck silica gel 60 (230-400 mesh). Uv spectra were recorded in methanol.

N-(3,5-Dimethoxyphenyl)-3-(4-methoxyphenyl)-3-oxopropionamide (5) A solution of 3,5-dimethoxyaniline (3, 500 mg, 3.3 mmol) and ethyl 4-methoxybenzoylacetate (4, 730 mg, 3.3 mmol) in toluene (6 ml) containing pyridine (2 drops) was refluxed for 20 h. The reaction mixture was evaporated, and dissolved in CH_2Cl_2 (20 ml). The solution was washed with 10% HCl (3× 20 ml) and water (20 ml), dried, and evaporated. The residue was chromatographed on a silica gel column using ethyl acetate as the eluent to afford 5 (740 mg, 69%). The substance was purified by recrystallization from CH_2Cl_2-hexane (630 mg, 59%), mp 113-115 ℃. Ms m/z(%): 329(M^+, 73), 150 (100), 135 (88). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.55; H, 5.80; N, 4.22. Ir(KBr): 1680, 1658 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ : 3.79(6H, s, 2 × OCH_3), 3.90(3H, s, OCH_3), 4.04(2H, s, CH_2), 6.25(1H, d, J=2Hz, C_4-H), 6.82(2H, d, J=2Hz, C_2-H and C_6-H), 6.98 and 8.02 (each 2H, d, J=9Hz, CH_3O-$C_6\underline{H}_4$), 9.34(1H, br, NH).

5,7-Dimethoxy-4-(4-methoxyphenyl)-2(1H)-quinolinone (1) Concentrated HCl (4 ml) was added to a solution of the amide (5, 50 mg, 0.15 mmol) in dioxane (20 ml). After the solution was left at 25 ℃ for 1 h, and poured into water (100 ml), the resulting mixture was neutralized with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (4 × 50 ml). The extract was washed with brine, dried and evaporated to afford the quinolinone(1, 34mg, 72%), mp >300 ℃. Ms m/z(%): 311(M^+, 100), 296(10). Ir (KBr): 1660(C=O), 1632, 1602, 1434, 1392, 1382, 1246, 1210, 1142 cm^{-1}. Uv λ_{max} nm (log ε): 218(4.41), 262(4.06), 321(3.89) and λ_{min} nm(log ε): 249(3.96), 272(3.69). ^{1}H-Nmr (DMSO-$\underline{d}_6$) δ : 3.39(3H, s, C_5-OCH_3), 3.78(3H, s, OCH_3), 3.79 (3H, s, OCH_3), 5.89(1H, s, C_3-H), 6.25(1H, d, J=2Hz, C_6-H), 6.52(1H, d, J=2Hz, C_8-H), 6.90 and 7.15(each 2H, d, J=9Hz, CH_3O-$C_6\underline{H}_4$-), 11.60(1H, br, NH).

5,7-Dimethoxy-4-(4-methoxyphenyl)-1-methyl-2(1H)-quinolinone (6) Sodium hydride (13.5 mg, 0.56 mmol) was added to a solution of 1 (35 mg, 0.11 mmol) in DMF (10 ml). The mixture was kept at 25 ℃ for 1 h, and methyl iodide (0.1 ml, excess) was added. After the whole was left at 25 ℃ for 1 h and poured into water (50 ml), the resulting aqueous solution was extracted with ether (4 × 50 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed on a silica gel column using CH_2Cl_2-methanol (20:1) as the eluent to afford the N-methyl compound (6, 31 mg, 85%). The substance was recrystallized from hexane (26mg, 71%), mp 169-171℃ . Ms m/z(%): 325(M^+, 100), 295(9). Anal. Calcd for $C_{19}H_{19}NO_4 \cdot 1/4H_2O$: C, 69.18; H, 5.96; N,4.25. Found: C, 69.15; H, 5.87; N, 4.20. Ir (KBr): 1646(C=O), 1610, 1512, 1368, 1244, 1214, 1168, 1052 cm^{-1}. Uv λ_{max} nm (log ε): 219(4.55), 262(4.25), 324(4.13) and λ_{min} nm (log ε): 249 (4.16), 273(3.76). ^{1}H-Nmr ($CDCl_3$) δ : 3.45(3H, s, C_5-OCH_3), 3.72(3H, s, N-CH_3), 3.86(3H, s, OCH_3), 3.92(3H, s, OCH_3), 6.25(1H, d, J=2Hz, C_6-H), 6.34 (1H, s, C_3-H), 6.48(1H, d, J=2Hz, C_8-H), 6.88 and 7.18(each 2H, d, J=9Hz, CH_3O-C_6H_4-). ^{13}C-Nmr ($CDCl_3$) δ : 30.12, 55.26, 55.38, 55.47 (CH_3); 91.27, 93.60, 112.51, 119.25, 128.55(CH); 105.46, 134.50, 143.29, 149.83, 158.69, 159.08, 162.16, 162.28(C).

2-Benzyloxy-1,5-dimethoxy-3-nitrobenzene (8) A mixture of 2,4-dimethoxy-6-nitrophenol (7, 200 mg, 1 mmol), benzyl bromide (0.18 ml, 1.5 mmol), K_2CO_3 (206 mg, 1.5 mmol) in acetone (4 ml) was refluxed for 2 h. The reaction mixture was evaporated, and water (30 ml) was added. The resulting mixture was extracted with CH_2Cl_2 (3× 30 ml). The extract was washed with 5% NaOH (3× 40 ml) and water (40 ml), dried and evaporated. The residue was chromatographed on a silica gel column using ethyl acetate-hexane (2:8) as the eluent to afford 8 (276 mg, 95%) as an oil. Ms m/z(%): 289(M^+, 18), 243(13), 198(7), 91(100). High-resolution ms Calcd for $C_{15}H_{15}NO_5$: 289.0950. Found: 289.0958. ^{1}H-Nmr ($CDCl_3$) δ : 3.82(3H, s, OCH_3), 3.90(3H, s, OCH_3), 5.09(2H, s, CH_2), 6.69(1H, d, J=3Hz, C_6-H), 6.82(1H, d, J=3Hz, C_4-H), 7.3-7.6(5H, m, C_6H_5).

2-Benzyloxy-3,5-dimethoxyaniline (9) Sodium dithionite (697 mg, 4 mmol) was added in portions during 10 min to a boiling solution of 8 (232 mg, 0.8 mmol) in ethanol-water(2:1, 10.8 ml). After most of ethanol was evaporated under reduced pressure, the residual oily emulsion was rendered al-

kaline by addition of 3N-NaOH (20 ml), and extracted with CH_2Cl_2 (3× 20ml). The extract was washed with 3N-NaOH (20 ml) and water (20 ml), dried and evaporated. The residue was chromatographed on a silica gel column using ethy acetate as the eluent to afford 9 (98 mg, 47%) as an oil. Ms m/z(%): 259(M^+, 10), 168(100). High-resolution ms Calcd for $C_{15}H_{17}NO_3$: 259.1208. Found: 259.1222. ^{1}H-Nmr ($CDCl_3$) δ : 3.73(3H, s, OCH_3), 3.83(3H, s, OCH_3), 4.93(2H, s, CH_2), 5.97(1H, d, J=3Hz, Ar-H), 6.00(1H, d, J=3Hz, Ar-H), 7.3-7.6(5H, m, C_6H_5).

N-(2-Benzyloxy-3,5-dimethoxyphenyl)-3-(4-methoxyphenyl)-3-oxopropionamide (10) A solution of amine (9, 84 mg, 0.32 mmol) and ethyl 4-methoxybenzoylacetate (4, 108 mg, 0.48 mmol) in toluene (2 ml) containing pyridine (1 drop) was refluxed for 20 h. The reaction mixture was evaporated, and the oily residue was dissolved in CH_2Cl_2 (10 ml). The resulting solution was washed with 10% HCl (3× 10ml) and water (10 ml), dried and evaporated. The residue was chromatographed on a silica gel column using ethyl acetate-hexane (4:6) as the eluent to afford 10 (122 mg, 86%). The substance was recrystallized from CH_2Cl_2-hexane (109 mg, 77%), mp 176-177 ℃. Ms m/z(%): 435(M^+, 6), 344(74), 168(100), 135(43). Anal. Calcd for $C_{25}H_{25}NO_6 \cdot 1/10H_2O$: C, 68.67; H, 5.81; N, 3.20. Found: C, 68.54; H, 5.75; N, 3.18. Ir (KBr): 1680, 1660 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ : 3.78(3H, s, OCH_3), 3.87(3H, s, OCH_3), 3.88(2H, s, $COCH_2CO$), 3.89(3H, s, OCH_3), 4.99 (2H, s, CH_2-C_6H_5), 6.29(1H, d, J=3Hz, C_4-H), 7.60(1H, d, J=3Hz, C_6-H), 6.96 and 7.83(each 2H, d, J=9Hz, CH_3O-C_6H_4-), 7.3-7.6(5H, m, C_6H_5), 9.26(1H, br, NH).

Cyclization of 10 Concentrated HCl (2 ml) was added to a solution of the amide (10, 45 mg) in dioxane (10 ml). After the solution was heated at 100 ℃ for 1 h, and poured into water (30 ml), the resulting mixture was extracted with CH_2Cl_2 (3× 20 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed on a silica gel column. Elution with ethyl acetate-hexane (3:7) afforded a less polar 8-benzyloxy-2(1H)-quinolinone(11, 5.2 mg, 12%) and further elution with ethyl acetate-hexane (7:3) afforded a more polar 8-hydroxy-2(1H)-quinolinone (2, 22 mg, 65%). The quinolinones (11 and 2) thus obtained were recrystallized to afford 4.0 mg and 18 mg of colorless crystals, respectively.

8-Benzyloxy-5,7-dimethoxy-4-(4-methoxyphenyl)-2(1H)-quinolinone (11): mp 173-174 ℃ (recrystallized from ethyl acetate-hexane). Ms m/z(%): 417(M^+,

25), 326(100). High-resolution ms Calcd for $C_{25}H_{23}NO_5$: 417.1576. Found: 417.1605. Ir (KBr): 1658(C=O), 1612, 1516, 1464, 1444, 1414, 1378, 1354, 1292, 1246, 1230, 1208, 1178, 1142, 1064, 1006, 834 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 3.47(3H, s, C_5-OCH_3), 3.86(3H, s, OCH_3), 3.98(3H, s, OCH_3), 5.09(2H, s, CH_2), 6.22 and 6.26(each 1H, s, C_3-H and C_6-H), 6.89 and 7.19(each 2H, d, J=9Hz, CH_3O-$C_6\underline{H}_4$-), 7.3-7.6(5H, m, C_6H_5), 9.07(1H, br, NH).

8-Hydroxy-5,7-dimethoxy-4-(4-methoxyphenyl)-2(1H)-quinolinone (2): mp 237-239 ℃ (recrystallized from CH_2Cl_2-ethyl acetate). Ms m/z(%): 327(M^+, 100), 312(90). Anal. Calcd for $C_{18}H_{17}NO_5 \cdot 2/5H_2O$: C, 64.63; H, 5.36; N, 4.19. Found: C, 64.60; H, 5.12; N, 4.25. Ir (KBr): 3348(OH), 1660(C=O), 1628, 1610, 1516, 1456, 1422, 1358, 1288, 1244, 1210, 1172, 1122, 1056, 1004, 834, 758cm^{-1}. Uv λ_{max} nm (log ε): 219(4.15), 276(4.08), 321(3.58) and λ_{min} nm (log ε): 250(3.37), 293(3.49). ^{1}H-Nmr (400 MHz, DMSO-d_6) δ : 3.38 (3H, s, C_5-OCH_3), 3.80(3H, s, CH_3O-C_6H_4-), 3.89(3H, s, C_7-OCH_3), 5.93(1H, s, C_3-H), 6.48(1H, s, C_6-H), 6.92 and 7.18(each 2H, d, J=9Hz, CH_3O-$C_6\underline{H}_4$-), 8.96(1H, br, OH), 9.95(1H, br, NH). ^{13}C-Nmr(100 MHz, DMSO-d_6) δ : 55.01, 55.99, 56.22(CH_3); 92.63, 112,45, 119.41, 128.55(CH); 103.73, 125.26, 130.53, 133.59, 148.72, 150.61, 151.00, 158.41, 160.43(C).

Debenzylation of 11 Concentrated HCl (0.4 ml) was added to a solution of 11 (10.0 mg) in dioxane (2 ml). After the solution was heated at 100 ℃ for 1 h, and poured into water (10ml), the resulting mixture was extracted with CH_2Cl_2 (3× 10 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed on a silica gel column using ethyl acetate-hexane (7:3) as the eluent to afford 2 (3.4 mg, 44%).

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