Acetylene Chemistry. Part 28 [1]. New C-2 Substituted Furo[2,3-*b*]quinolines *via* Pd-catalyzed Reaction

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Four new C-2 substituted furo[2,3-*b*]quinolines have been synthesized *via* Pd-catalyzed reaction. The present study was to provide furo[2,3-*b*]quinolines for biological studies on the influence of the side chain length and its polarity of the biological activity particularly against phytopathogenic bacteria and fungi.

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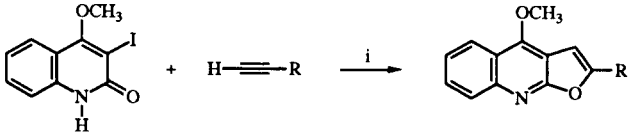
The rutaceae alkaloid dictamnine and related C-2 substituted furo[2,3-*b*]quinolines show antibiotic activity in a wide range [4-8]. Detailed bioassays so far were not possible, due to lengthy synthesis and poor yields of pure products [9].

The palladium catalyzed reaction between 3-iodo-4-methoxy-2(1*H*)-quinolinone and alkynes with terminal hydrogen led to the isolation of 2-substituted furo[2,3-*b*]quinoline derivatives exclusively under the prescribed conditions (see Experimental). The earlier work on the synthesis of these substances afforded a complex reaction mixture containing an alkyne dimer, 3-alkynyl-2(1*H*)-quinolinone derivatives along with the desired furo[2,3-*b*]quinoline derivatives [9].

It is apparent that the amount of the catalyst plays a major role in this synthesis. When the catalyst is present in twofold excess in comparison to the previous work [9] the reaction affords the furo[2,3-*b*]quinolines as the only product [2].

Scheme



1 2 3

i: TEA, $[Pd(PPh_3)_2]Cl_2$/CuI, N_2, reflux

2,3 (R=); a: b: OH c: OH d: OH

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were recorded as potassium bromide disks on a Pye Unicam SP3-200 spectrophotometer. The uv spectra were obtained in methanol on a Shimadzu 160-UV Spectrophotometer. The ^1H nmr and ^{13}C nmr spectra were recorded with tetramethylsilane as internal standard on a Varian Gemini 200 spectrometer. Mass spectra were obtained on a Varian MAT 44S spectrometer at 70 eV. Merck silica gel 60 F_{254} and Merck silica gel 60 (70-230 mesh) were used for preparative tlc and column chromatography respectively. The catalyst is prepared by mixing $[Pd(PPh_3)_2]Cl_2$ and CuI 1:1 (w/w) and making to a fine powder.

General Procedure for the Reaction of 3-Iodo-4-methoxy-2(1*H*)-quinolinone (**1**) with Alkynes.

All of these reactions were carried out under a nitrogen atmosphere.

To a solution of 3-iodo-4-methoxy-2(1*H*)-quinolinone (**1**) (200 mg, 0.66 mmole) and triethylamine (30 ml) alkyne (1.65 mmoles) in small portions and the catalyst $[Pd(PPh_3)_2]Cl_2$/CuI (14.4 mg, 0.016 mmole) were added. The reaction mixture was heated under reflux for about 6 hours, diluted with ethyl acetate (50 ml) and filtered through celite. The filtrate was evaporated *in vacuo* to give an oily residue which was separated by column chromatography (dichloromethane-ethyl acetate 95:5) to give the furo-[2,3-*b*]quinoline derivative.

2-Hexyl-4-methoxyfuro[2,3-*b*]quinoline (**3a**).

This compound was obtained in 29% (55 mg) yield, mp 84°; ir: ν 2955 (CH), 2850 (OCH_3), 1580 (C=C) cm^{-1}; uv: λ max 240 nm (ϵ 56623), 266 (ϵ 3723), 314 (ϵ 14190), 322 (ϵ 10616), 328 (ϵ 11668); ^1H nmr (deuteriochloroform): δ 0.90 (t, J = 6.8 Hz, 3H, 6-H), 1.39 (m, 6H, 2'-H, 3'-H, 4'-H), 1.77 (m, 2H, 5'-H), 2.75 (m, 2H, 1'-H), 4.38 (s, 3H, OCH_3), 6.64 (s, 1H, 3-H), 7.41 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H, 7-H), 7.63 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H, 6-H), 7.98 (dd, J = 1.5, 8.4 Hz, 1H, 8-H), 8.27 (dd, J = 1.5, 8.4 Hz, 1H, 5-H); ^{13}C nmr (deuteriochloroform): δ 14.04 (C-6'), 22.53 (C-5'), 27.15 (C-4'), 28.6 (C-3'), 28.86 (C-2'), 31.54 (C-1'), 58.88 (OCH_3), 99.52 (C-3), 105.34 (C-4a), 119.05 (C-3a), 122.19 (C-5), 123.52 (C-6), 127.79 (C-8), 128.96 (C-7), 145.04 (C-8a), 155.24 (C-2), 158.53 (C-4), 163.97 (C-9a); ms: m/z 283 (M^+), 268 (M^+-CH_3), 240 (268-CO), 226 (M^+-C_4H_9), 212 (M^+-C_5H_{11}), 198, 197, 183, 155, 127, 76.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.20; H, 7.46; N, 4.90. Found: C, 76.12; H, 7.14; N, 5.08.

4-Methoxyfuro[2,3-*b*]quinoline-2-propanol (**3b**).

This compound was obtained in 27% (45 mg) yield, mp 171°; ir: ν 3400 (OH), 2945 (CH), 2880 (OCH_3), 1580 (C=C) cm^{-1}; uv: λ max 241.1 nm (ϵ 51286), 266 (ϵ 3326), 314 (ϵ 12705), 321 (ϵ 9418), 329 (ϵ 10399); ^1H nmr (deuteriochloroform): δ 2.06 (m, 2H, 2'-H), 2.92 (t, J = 7.4 Hz, 2H, 1'-H), 3.78 (m, 2H, 3'-H), 4.41 (s, 3H, OCH_3), 7.43 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H, 7-H), 7.65 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H, 6-H), 7.97 (dd, J = 0.6, 8.4 Hz, 1H, 8-H), 8.24 (dd, J = 0.6, 8.4 Hz, 1H, 5-H); ^{13}C nmr (deuteriochloroform): δ 25.01 (C-2'), 29.71 (C-1'), 58.91 (OCH_3), 61.77 (C-3'), 100.07 (C-3), 105.16 (C-4a), 119.02 (C-3a), 122.22 (C-5), 123.63 (C-6), 127.73 (C-8), 129.12 (C-7), 145.05 (C-8a), 155.45 (C-2), 157.54 (C-4), 162.31

(C-9a); ms: m/z 257 (M^+), 239 (M^+-H_2O), 226 (M^+-OCH_3), 212, 198, 197, 183, 155, 127, 101, 76, 69, 55.

Anal. Calcd. for $C_{15}H_{15}NO_3$·0.5 H_2O: C, 68.43; H, 5.99; N, 5.32. Found: C, 68.25; H, 5.78; N, 5.05.

4-Methoxyfuro[2,3-*b*]quinoline-2-butanol (**3c**).

This compound was obtained in 35% (60.3 mg) yield, mp 163.5°; ir: ν 3390 (OH), 2935 (CH), 2850 (OCH_3), 1581 (C=C) cm^{-1}; uv: λ max 241 nm (ϵ 54075), 265 (ϵ 3507), 314 (ϵ 13397), 322 (ϵ 9908), 328 (ϵ 10939); ^1H nmr (methanol-d_4): δ 1.70 (m, 2H, 2'-H), 1.88 (m, 2H, 3'-H), 2.83 (t, J = 7.2 Hz, 2H, 1'-H), 3.65 (t, J = 6.3 Hz, 2H, 4'-H), 4.43 (s, 3H, OCH_3), 6.79 (s, 1H, 3-H), 7.43 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H, 7-H), 7.66 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H, 6-H), 7.87 (dd, J = 0.6, 8.5 Hz, 1H, 8-H), 8.24 (dd, J = 0.6, 8.4 Hz, 1H, 5-H); ^{13}C nmr (methanol-d_4): δ 23.15 (C-2'), 27.73 (C-3'), 31.46 (C-1'), 58.51 (OCH_3), 60.83 (C-4'), 99.62 (C-3), 104.89 (C-4a), 118.52 (C-3a), 122.00 (C-5), 123.31 (C-6), 126.14 (C-8), 129.13 (C-7), 143.96 (C-8a), 155.61 (C-2), 157.71 (C-4), 163.48 (C-9a); ms: m/z 271 (M^+), 256 (M^+-CH_3), 238 (M^+-H_2O), 226 (M^+-CH_3O), 198, 197, 183, 155, 140, 127, 101, 76, 55.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 7.46; N, 5.16. Found: C, 70.86; H, 6.66; N, 5.32.

4-Methoxyfuro[2,3-*b*]quinoline-2-nonanol (**3d**).

This compound was obtained in 25% (55.8 mg) yield, mp 148°; ir: ν 3400 (OH), 2920 (CH), 2850 (OCH_3), 1583 (C=C) cm^{-1}; uv: λ max 240 nm (ϵ 44668), 268 (ϵ 4808), 313 (ϵ 11376), 323 (ϵ 8790), 328 (ϵ 9419); ^1H nmr (deuteriochloroform): δ 1.50 (m, 14H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H, 7'-H, 8'-H), 2.78 (t, J = 7.1 Hz, 2H, 1'-H), 3.64 (t, J = 6.4 Hz, 2H, 9'-H), 4.42 (s, 3H, OCH_3), 6.68 (s, 1H, 3-H), 7.43 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H, 7-H), 7.65 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H, 6-H), 7.98 (dd, J = 0.6, 8.4 Hz, 1H, 8-H), 8.24 (dd, J = 0.6, 8.4 Hz, 1H, 5-H); ^{13}C nmr (deuteriochloroform): δ 25.69 (C-5'), 27.16 (C-4'), 28.60 (C-6), 28.06 (C-3'), 29.17 (C-7'), 29.30 (C-2'), 29.71 (C-8'), 32.78 (C-1'), 58.92 (OCH_3), 63.01 (C-9'), 99.59 (C-3), 105.61 (C-4a), 119.02 (C-3a), 122.12 (C-5), 123.55 (C-6), 127.76 (C-8), 129.31 (C-7), 145.01 (C-8a), 155.27 (C-2), 158.47 (C-4), 163.97 (C-9); ms: m/z 341 (M^+), 310 (M^+-OCH_3), 240, 226, 212 (M^+-$C_8H_{17}O$), 198, 197, 189, 183, 174, 155, 101, 76, 55.

Anal. Calcd. for $C_{21}H_{27}NO_3$·0.5 H_2O: C, 71.97; H, 8.05; N, 3.99. Found: C, 71.79; H, 8.37; N, 3.75.

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