A ONE-POT SYNTHESIS OF 4-METHYLPYRANO[3,2-*C*]QUINOLIN-2,5[6*H*]-DIONES

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Abstract: 4-hydroxy-2-quinolone being endowed with both nucleophilic and electrophilic properties furnishes the dimeric quinoline in a base catalyzed self-condensation process. A one step synthesis, starting from 4-hydroxy-2-quinolone with ethyl acetoacetate and pyridine proceeded through the Michael addition, which was followed by cyclization, gave an angular isomer 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione. The reaction was then extended to synthesize further derivatives of angular pyrano quinolones. Structures of all the products have been established by spectral and elemental analysis data.

Keywords: One pot synthesis, 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-diones.

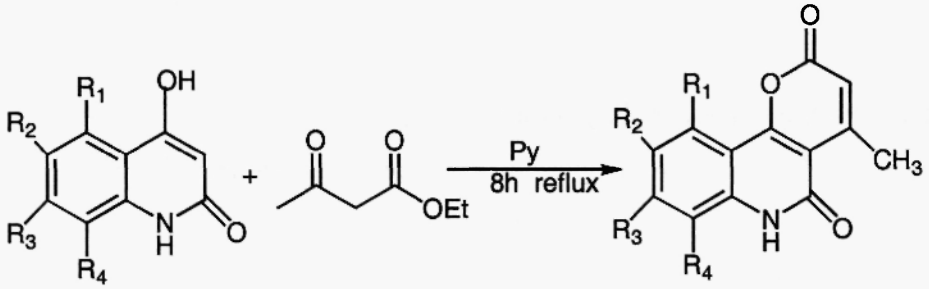
Introduction: Pyranoquinolines constitute the parent ring structure of pyranoquinoline alkaloids, which occur in the plant family Rutaceae. We have recently reported[1,2,3] the synthesis of a series of 3,5-disubstituted pyrano[2,3-*b*]quinolin-2-ones starting from 2-chloro-3-formyl quinolines and 2-chloro-3-formyl-4-phenyl/methyl quinolines respectively. In continuation of our studies and in view of the pharmacological activities[4,5] of pyranoquinolines, we herewith report the synthesis of new unreported derivatives of 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione and its derivatives (Scheme 1).

Experimental: Melting points were determined on a Boetius Microheating table and are uncorrected. IR spectra were recorded on a perkin-Elmer-597 Infrared spectrophotometer as KBr Pellets. ^{1}H NMR spectra were recorded on a AMX 400 spectrometer in $CDCl_3$.

The coupling constants (J) were expressed in Hz. Mass spectra were recorded on a Jeol D 300 mass spectrometer. Carlo Erba 106 and Perkin-Elmer model 240B CHN analyzer performed elemental analyses and the values are within the permissible limits (± 0.5%).

4-hydroxy-2-quinolones have been prepared by known procedures[6]. The hitherto unknown derivatives of 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione synthesized were reported in Table 1.

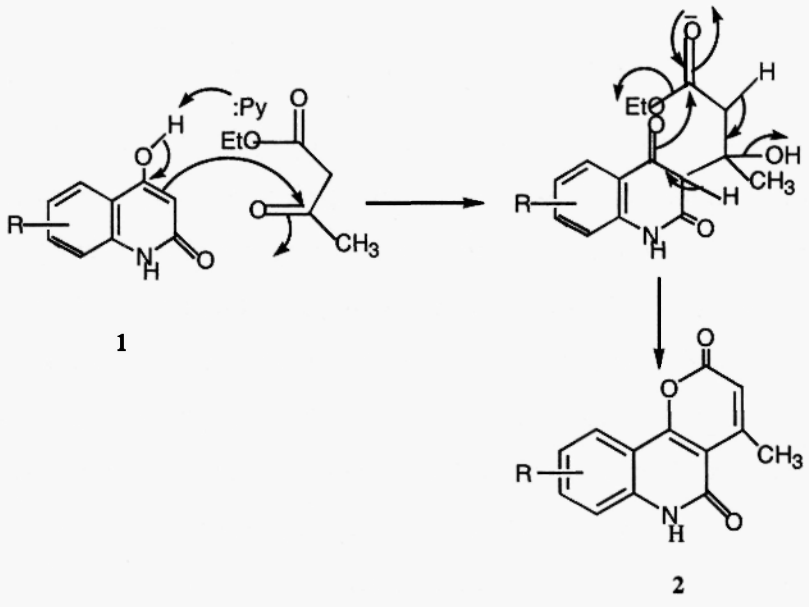
Scheme 1:



1(a-g) **2(a-g)**

(a) $R_1=R_2=R_3=R_4=H$
(b) $R_1=R_2=R_4=H$; $R_3=CH_3$
(c) $R_1=R_2=R_3=H$; $R_4=CH_3$
(d) $R_1=R_3=R_4=H$; $R_2=OCH_3$
(e) $R_1=R_2=R_4=H$; $R_3=OCH_3$
(f) $R_1=R_2=R_3=H$; $R_4=OCH_3$
(g) $R_1=R_4=OCH_3$; $R_2=R_3=H$

Mechanism : Scheme 2 : Probable pathway for the formation of 2



General Procedure: Synthesis of 4-methylpyrano[3,2-c]quinolin-2,5[6*H*]-diones (2a-g): A mixture of 4-hydroxy-2-quinolone (0.004 M) along with ethyl acetoacetate (0.004 M) and pyridine (6-8 drops) was refluxed for 8 h in an oil bath at 120-130^{0}C. Excess of ethyl acetoacetate and pyridine was removed by distillation. The reaction mixture was cooled, added to ice-cooled water (50 ml) and acidified with HCl when 4-methylpyrano[3,2-c]quinolin-2,5[6*H*]-dione separated as yellow precipitate. The precipitated product was then filtered, washed with water, dried, and chromatographed over silica gel. The petrol-ethyl acetate (4:1) elute fractions furnished the pure compound, which was further recrystallized from petrol-chloroform mixture (Table 1). M.p., yield, ir and analytical data of (**2a-g**) are given in Table 1.

Results and Discussion: The OH group at 4th-position in the 4-hydroxy-2-quinolone activates the nucleophilic carbon at C-3 in the presence of a base and prompts it to react with a Michael type acceptor. Thus 4-hydroxy-2-quinolone[6] (**1a**) upon refluxing with active methylene compound ethyl acetoacetate in the presence of pyridine for 8 h gave a product in 80 % yield, which melts at 246-248°C. Its IR spectra showed very sharp peaks. The peak at 1715cm^{-1}, was assigned to the pyrone ring. It possesses stronger absorption at 1666cm^{-1}(corresponds to an angular isomer) in the carbonyl region, which is attributable to amide-carbonyl stretching. 2-quinolones possess stronger carbonyl absorption at higher wavelength than 4-quinolones[7,8]. The PMR spectra showed very sharp signals. The protons at C-7 and C-10 appear as a doublet at δ7.40 and δ7.67 of value J=7.9 Hz and J=8 Hz respectively (Indicates an angular isomer. The C-7 and C-10 protons of linear isomer would appear much downfield than the angular isomer)[7,8]. The protons at C-8 and C-9 appear as a multiplet at δ7.31-7.36. The proton at position C-3 appears as a singlet at δ6.59. The signal due to methyl protons appears as a singlet at δ2.75. A broad singlet is obtained at δ12.01, which correspond to NH. The Mass spectra also showed intense molecular ion peak at m/e 227. Thus from the above spectral studies the product was confirmed as 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione (**2a**) an angular isomer. The reaction sequence leading to **2a** was then extended to synthesize compounds (**2b-g**) and similar results were obtained.

Table – 1. Physical and Spectroscopic data of (2a–g) [a] :

Compd.	M.p. ^{0}C (Yield %)	Elemental analyses		IR[b]	^{1}H NMR[C] (δ) ppm	MS *m/z* 70ev (m+)
		Calcul. (%)	Found (%)	νmax (cm^{-1})		
2a	246-248 (80)	C 68.72 H 3.99 N 6.16	C 68.70 H 3.97 N 6.14	1715 1666	δ2.75 (s, 3H,C_4-CH_3); δ6.59(s, 1H,C_3-H); δ7.40(d,IH,J=7.9,C_7-H); δ7.67(d,IH,J=8,C_{10}-H); δ7.31-7.36(m, 2H,C_8-H & C_9-H); δ12.01(bs,1H,NH)	227
2b	236-238 (70)	C 69.79 H 4.60 N 6.14	C 69.68 H 4.59 N 5.80	1716 1666	δ2.72(s,3H,C_8-CH_3); δ2.75(s,3H,C_4-CH_3); δ6.58(s,1H,C_3-H); δ7.38(s,1H,C_7-H); δ7.66(d,1H,J=7.8,C_{10}-H); δ7.25(d,1H,J=8,C_9-H); δ11.72(bs,1H,NH)	241
2c	227-229 (70)	C 69.70 H 4.60 N 5.81	C 69.67 H 4.58 N 5.80	1718 1658	δ2.72(s,3H,C_7-CH_3); δ2.76(s,3H,C_4-CH_3); δ6.61(s,1H,C_3-H); δ7.68(d,1H,J=7.2,C_{10}-H); δ7.29-7.33(m,2H,C_8-H & C_9-H); δ11.72(bs,1H,NH)	241
2d	247-249 (75)	C 65.37 H 4.31 N 5.45	C 65.36 H 4.30 N 5.44	1725 1667	δ2.74(s,3H,C_4-CH_3); δ3.78(s,3H,C_9-OCH_3); δ6.58(s,1H,C_3-H); δ7.47(d,1H,J=7.4,C_7-H); δ7.71(s,1H,C_{10}-H); δ7.40(d,1H,J=7.9,C_8-H); δ11.75(bs,1H,NH)	257

2e	263-265 (75)	C 65.37 H 4.31 N 5.45	C 65.36 H 4.29 N 5.43	1722 1665	δ2.75(s,3H,C_4-CH_3); δ3.77(s,3H,C_8-OCH_3); δ6.59(s,1H,C_3-H); δ7.49(s,1H, C_7-H); δ7.68(d,1H,J=7.7,C_{10}-H); δ7.41(d,1H,J=7.9,C_9-H); δ11.76(bs,1H,NH)	257
2f	258-260 (70)	C 65.37 H 4.31 N 5.45	C 65.36 H 4.30 N 5.43	1725 1665	δ2.77(s,3H,C_4-CH_3); δ3.77(s,3H,C_7-OCH_3); δ6.59(s,1H,C_3-H); δ7.69(d,1H,J=8.2,C_{10}-H); δ7.32-7.38(m, 2H,C_8-H & C_9-H); δ11.72(bs,1H,NH)	257
2g	251-253 (70)	C 62.72 H 4.56 N 4.88	C 62.70 H 4.53 N 4.87	1717 1665	δ2.76(s,3H,C_4-CH_3); δ3.76(s,3H,C_7-OCH_3); δ3.92(s,3H,C_{10}-OCH_3); δ6.58(s,1H,C_3-H); δ7.38-7.43(m, 2H,C_8-H &C_9-H); δ11.74(bs,1H,NH)	287

a) recrystallized from Petrol-Chloroform mixture b) as KBr pellets
c) as $CDCl_3$ solvent

The plausible mechanism has been proposed for the formation of 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione(**2**) in **Scheme-2**. The expected Michael addition was followed by cyclization, involving the nucleophilic oxygen at C-4 and electrophilic carboxyl carbon in the side chain afforded the product **2**, which was isolated after chromatographic purification.

Conclusion: In conclusion, we have demonstrated the synthesis of newer derivatives of angular[3,2-*c*]pyranoquinolones in one pot method through Michael addition.

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