

One-pot Synthesis and the Biological Activities of 4-Methylpyrano[3,2-*C*]-quinolin-2,5-[6*H*]-diones

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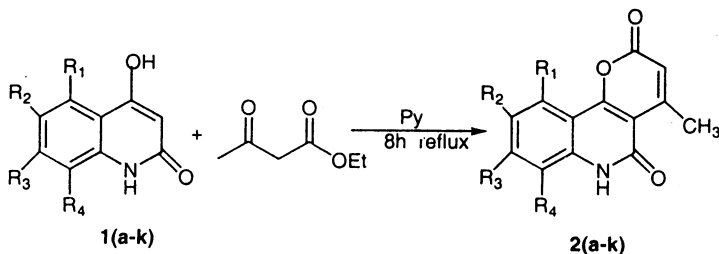
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One step synthesis, starting from 4-hydroxy-2-quinolone with ethyl acetoacetate and pyridine proceeded through the Michael addition, gave an angular isomer 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione. The reaction sequence was then extended to synthesize further derivatives of angular pyrano quinolones. Structures of all the products have been established by spectral and elemental analysis data. The antibacterial activity against various bacterial strains like *Escherichia coli*, *Bacillus subtilis*, *Aeromonas hydrophilla*, *Staphylococcus aureus* and *Klebsiella pneumoniae* have also been investigated.

Key Words: One pot synthesis, 4-Methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-diones, Biological activities.

The synthesis of pyranoquinolines has gained momentum in recent years as they constitute the parent ring structure of pyranoquinoline alkaloids which have been reported to be associated with interesting pharmacological activities¹ like anticoagulant², coronary constricting³, optically brightening⁴ and biological activity⁵. 4-Hydroxy-2-quinolones⁶ (1a–g) and 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-diones (2a–g) have been reported earlier⁷. We herewith report the synthesis of new derivatives of 4-methylpyrano[3,2-*c*]quinolin-2,5[6*H*]-dione (Scheme-1) and illustrate their antibacterial activities.



Scheme-1

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. ¹H NMR spectra were recorded on an AMX-400 spectrometer in CDCl₃. The coupling constants (*J*) were expressed in Hz. Mass

spectra were recorded on a Jeol D300 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%).

TABLE-1
PHYSICAL AND SPECTROSCOPIC DATA OF (2h-k)^a

Compd.	m.p. (°C) (Yield, %)	(% Elemental analyses)		IR ^b ν_{\max} (cm ⁻¹)	¹ H NMR ^c (δ) ppm	MS m/z 70 ev (m ⁺)
		Calcd.	Found			
2h	241–242 (80)	C 65.37 H 4.31 N 5.45	C 65.36 H 4.30 N 5.44	1725 1660	δ 2.74 (s, 3H, C ₄ -CH ₃); δ 2.84 (s, 3H, C ₉ -CH ₃); δ 6.58 (s, 1H, C ₃ -H); δ 7.47 (d, 1H, J = 7.4, C ₇ -H); δ 7.68 (s, 1H, C ₁₀ -H); δ 7.40 (d, 1H, J = 7.9, C ₈ -H); δ 11.75 (bs, 1H, NH)	241
2i	269–271 (73)	C 59.67 H 3.08 N 5.35	C 59.67 H 3.07 N 5.34	1725 1660	δ 2.74 (s, 3H, C ₄ -CH ₃); δ 6.59 (s, 1H, C ₃ -H); δ 7.56–7.74 (m, 3H, C ₇ -H, C ₈ -H & C ₁₀ -H); δ 11.74 (bs, 1H, NH)	262 264
2j	250–252 (74)	C 73.91 H 3.65 N 5.07	C 73.90 H 3.64 N 5.06	1720 1660	δ 2.72 (s, 3H, C ₄ -CH ₃); δ 6.60 (s, 1H, C ₃ -H); δ 7.44–7.65 (m, 6H, Ar-H); δ 11.78 (bs, 1H, NH)	277
2k	259–261 (74)	C 73.91 H 3.65 N 5.06	C 73.89 H 3.63 N 5.06	1720 1662	δ 2.73 (s, 3H, C ₄ -CH ₃); δ 6.61 (s, 1H, C ₃ -H); δ 7.43–7.67 (m, 6H, Ar-H); δ 11.76 (bs, 1H, NH)	277

^a recrystallized from petrol-chloroform mixture, ^b as KBr pellets, ^c as CDCl₃ solvent.

General Procedure: Synthesis of 4-methylpyrano[3,2-c]quinolin-2,5[6H]-diones (2a-k): 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°C. The reaction mixture was poured in ice and acidified with HCl when 4-methylpyrano[3,2-c]quinolin-2,5[6H]-dione separated as yellow precipitate. It was then filtered, dried and recrystallized from petrol-chloroform mixture. M.p., yield, ir and analytical data of (2a–j) are given in Table-1.

Antibacterial Studies: Antibacterial screening for the *in-vitro* growth inhibitory activity against *Escherichia coli*, *Bacillus subtilis*, *Aeromonas hydrophilla*, *Staphylococcus aureus* and *Klebsiella pneumoniae* were determined for the compounds (2a–k) by disc diffusion technique. The bacteria were cultured in nutrient agar medium and used as inoculum for the study. Bacterial cells were swabbed on to nutrient agar medium [prepared from NaCl (5.0 g), peptone (5.0

g), agar (20.0 g), beef extract powder (3.0 g), yeast extract powder (3.0 g), agar (20.0 g) in 100 mL distilled water; pH = 7.5 ± 0.2] in petri plates. The compounds to be tested were dissolved in chloroform to final concentrations of 500 µgm/disc and soaked in filter paper discs of 5 mm diameter and 1 mm thickness. These discs were placed on the already seeded plates and incubated at 35°C for 24 h. The inhibition zone around each disc was measured after 24 h. Streptomycin was used as standard to compare the antibacterial activity of the compounds (2a–k) (Table-2).

TABLE-2
ANTIBACTERIAL ACTIVITY DATA (2a–k)^a

Compound	Microorganisms employed at 500 µgm/disc				
	<i>Escherichia coli</i>	<i>Bacillus subtilis</i>	<i>Aeromonas hydrophilla</i>	<i>Staphylococcus aureus</i>	<i>Klebsiella pneumoniae</i>
2a	–	–	+	–	+
2b	+	+	–	–	++
2c	–	+	–	–	–
2d	+	+	+	–	–
2e	+	+	+	–	++
2f	+	+	+	+	++
2g	+	+	+	+	++
2h	+	+	+	–	++
2i	+	+	+	+	++
2j	+	+	+	+	++
2k	+	+	+	+	++

^a The mean of three replicate values (+) = presence of antibacterial activity.
(–) = Absence of antibacterial activity.

RESULTS AND DISCUSSION

The 4-hydroxy-2-quinolone (1h) upon refluxing with ethyl acetoacetate in the presence of pyridine for 8 h gave a product in 80% yield, which melts at 241–242°C. The peak at 1725 cm⁻¹ was assigned to the pyrone ring. It possesses stronger absorption at 1660 cm⁻¹ (corresponding 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^{9, 10}. The PMR spectra showed very sharp signals. The signal due to methyl protons appears as a singlet at δ 2.74 and δ 2.84 respectively. The proton at position C-3 and C-10 appears as a singlet at δ 6.58 and δ 7.68 respectively. The protons at C-7 and C-8 appear as a doublet at δ 7.47 and δ 7.40 of value J = 7.4 Hz and 7.9 Hz respectively (indicates an angular isomer). A broad singlet is obtained at δ 11.75, which correspond to NH. The mass spectra also showed intense

molecular ion peak at m/e 241. Thus from the above spectral studies the product was confirmed as 4,9-dimethylpyrano[3,2-*C*]quinolin-2,5[6*H*]-dione (**2h**), an angular isomer. The reaction sequence leading to **2h** was then extended to synthesize compounds (**2h-k**) and similar results were obtained.

Antibacterial Studies: The antibacterial activity of the test solution containing new compounds at 500 $\mu\text{g}/\text{disc}$ is furnished in Table-2 and the antibiotic streptomycin was used as a standard. Among the different synthetic compounds, **2i** and **2j** seem to be very much active against the pathogens under study, and it is evidenced by their inhibitory zone. Even though, all the compounds are active against various pathogens, but their effectiveness did not reach the conventional bacteriostatic streptomycin. This may be due to cellular integrity of the microbes and/or non-effectiveness of these compounds against microbial metabolism¹¹.

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REFERENCES

1. H.T. Openshaw, in: R.H.F. Manske (Ed.), *The Alkaloids*, Academic Press, New York, Vol. IX, p. 223 (1967).
2. L.H. Singer and N.P. Kong, *J. Am. Chem. Soc.*, **88**, 5213 (1960).
3. I.C. Bathwar and K.J. Venkataraman, *J. Chem. Soc.*, 2420 (1932).
4. N.S. Narasimhan, R.S. Mali and M.V. Barve., *Synthesis*, 906 (1979).
5. M. Dean, in: L. Zchmeister (Ed.), *Progress in the Chemistry of Natural Products*, Verlag Chemic, Weinheim, Vol. 9, p. 235 (1952).
6. C. Balasubramaniam, Ph.D Dissertation, Bharathiar University, Coimbatore, India.
7. N. Venkatesh Kumar and S.P. Rajendran, *Heterocyclic Comm.* (in press).
8. P.G. Lawrence, P.L. Harold and O.G. Francis, *Antibiot. Chemother.*, 1597 (1980).
9. E.A. Clarke and M.F. Grundon, *J. Chem. Soc.*, 4190 (1964).
10. Witcop, Patrick and Rosenblum, *J. Am. Chem. Soc.*, **73**, 2641 (1951).
11. C.H. Collins and P.M. Lyne, *Microbial Methods*, University Park Press. Batlimore (1970).

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