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A one Step Synthesis of 4-Methyl-3,4-Dihydro-2H,5H-Pyrano[3,2-C]Quinolin-2,5[6H]-Diones and Their Biological Activities

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***Abstract*—A novel one step methodology for the synthesis of pyranoquinolines has been developed from 4-hydroxy-2(1H)-quinolone being endowed with both nucleophilic and electrophilic properties. Michael addition followed by cyclization gave an angular isomer 4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]quinolin-2,5[6H]-diones starting from 4-hydroxy-2(1H)-quinolone with crotonic acid and pyridine. The reaction was then extended to synthesize further derivatives of angular pyranoquinolones. Structures of all the products have been established by spectral and elemental analysis data.**

Key words*— *One step synthesis, Michael addition, 4-hydroxy-2(1H)-quinolone, 4-methyl-3,4-dihydro-2H,5H pyrano[3,2c] quinolin-2,5[6H]-diones, Biological activity.

I. INTRODUCTION

The synthesis of pyranoquinolines have gained more interest in recent years as they constitute the parent ring structure of pyranoquinoline alkaloids, which occur in the plant family rutaceae[1]. They have interesting pharmacological activities[1], like anticoagulant[2], coronary constricting[3], optically brightening[4] and biological activity[5]. 4-hydroxy-2(1H)-quinolone is a versatile and convenient precursor for the synthesis of a wide variety of heterocyclic compounds[6-1]. We have reported[13-16] the synthesis of a series of 3,5-di substituted pyrano[2,3-b]quinolin-2-ones starting from 2-chloro-3-formylquinolines and 2-chloro-3-formyl-4-phenyl/ methylquinolones respectively as well as the angular pyrano quinolines starting from 4-hydroxy-2(1H)-quinolone. In continuation of our studies and in view of pharmacological activities of pyranoquinolines we herewith report the synthesis of new unreported derivatives of 4-methyl-3,4-dihydro-2H,5H -pyrano[3,2-c]quinolin-2,5[6H]-diones [Scheme I]

II. MATERIALS AND METHODS

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 analyser performed elemental analysis and the values are within the permissible limits (± 0.5 %).

4-hydroxy-2(1H)-quinolone have been prepared by known procedures[17]. The hitherto unknown derivatives of 4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]quinolin-2,5[6H]-diones synthesized were reported in Table I and their biological activities in Table II.

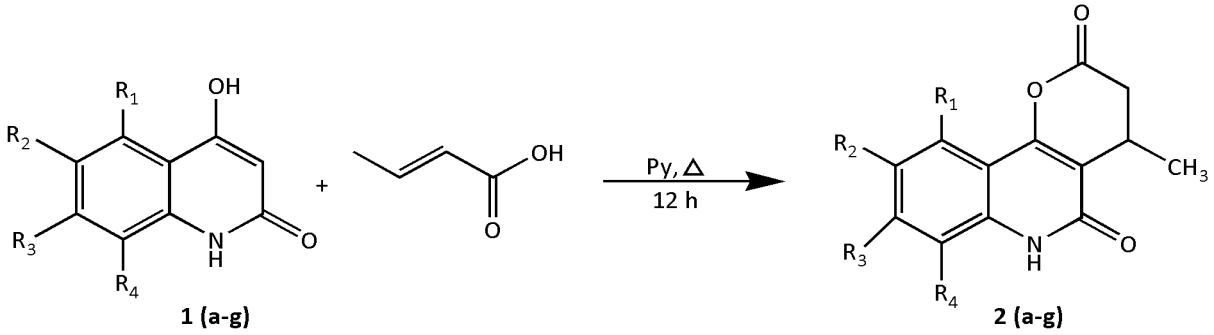
ANTIBACTERIAL ACTIVITY[18]

The compounds (2a-g) were screened for their antibacterial activities against *Escherichia coli, Bacillus subtilis and Aeromonas hydrophilla* were determined by agar diffusion technique[18,19]. The bacteria were cultured in nutrient agar medium and used as inoculum for the study. Bacterial cells were swabbed onto nutrient agar medium (prepared from NaCl 5.0 g, peptone 10.0 g, beef extract 10.0 g and distilled water) in petri plates. The compounds to be tested were dissolved in chloroform to a final concentration of 1, 2 and 4 % and soaked in filter paper discs. These discs were placed on the already seeded plates and incubated at 37±2^{0}C for 24 h. The zones of inhibition around the discs were measured after 24 h. Streptomycin was used as standards to compare the antibacterial activity of the compounds (2a-g) (Table II).

General Procedure: Synthesis of 4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]quinolin-2,5[6H]-diones (2a-g):

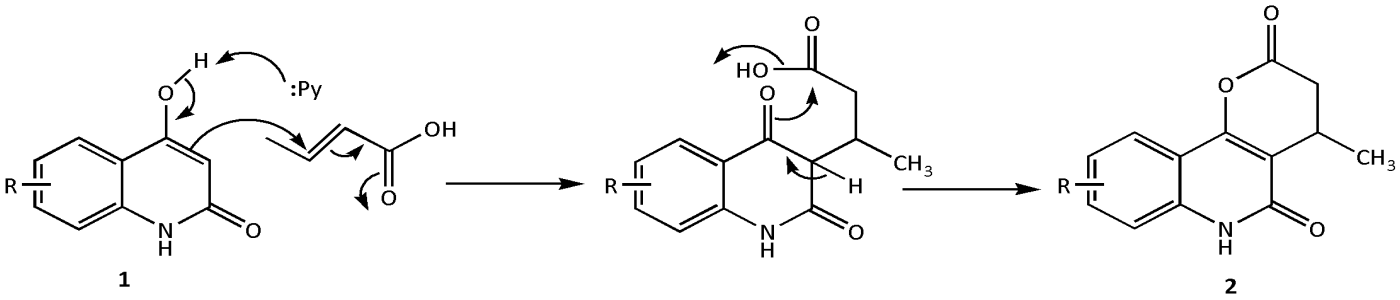
A mixture of 4-hydroxy-2(1H)-quinolone (1 g), crotonic acid (1 g), and pyridine (1 ml) was refluxed for 12 hours in an oil bath at 120^0 – 130^{0}C. Excess of crotonic acid and pyridine was removed by distillation. The reaction mixture was cooled, added to ice-cooled water (50 ml) and acidified with HCl when 4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]quinolin-2,5 [6H]-diones separated as yellow precipitate. The precipitated product was then filtered, washed with water, dried and chromatographed over silica gel. The petrol-ethyl acetate (20:1) elute fractions furnished the pure compound, which on crystallization from petrol-acetone mixture afforded 2(a-g). M.P., Yield, IR and analytical data of 2(a-g) are given in Table I.

Scheme I:



(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 II: Probable pathway for the formation of 2



III. Results and Discussion

The presence of hydroxyl group at C-4 in 4-hydroxy-2(1H)-quinolone activates the nucleophilic carbon at C-3 which prompts to react with a Michael type acceptor giving the expected product 4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c] quinolin-2,5[6H]-diones, 2a in 60 % yield which melts at 252-254^{0}C. The IR spectra showed very sharp peaks. The peak at 1720 cm^{-1} was assigned to the pyrone ring. It possesses stronger absorption at 1665 cm^{-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[20,21]. The ^{1}H NMR spectra showed very sharp signals in which the proton at position C-4 appeared as sextet at δ3.62 of value J=7 Hz. The hydrogen at position C-3 observed as doublet of doublet at δ2.68 of value J=8.0 and 7.5Hz respectively. The signal due to methyl protons at C-4 showed a singlet at δ1.24. The hydrogen's at C-7 and C-10 showed a doublet at δ7.50 and δ7.78 of value J=7.9Hz and J=8.0Hz respectively. We observed a triplet for C_8-H and C_9-H at δ7.32 of value J=8.1Hz. A broad singlet was obtained at δ12.01 corresponds to NH. The mass spectra also showed intense molecular ion peak at m/e 229. The plausible mechanism has been proposed for the formation of 4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]quinolin-2,5[6H]-diones, an angular isomer in Scheme II. The reaction sequence leading to 2a was then extended to synthesize compounds 2(b-g) and similar results were obtained.

ANTIBACTERIAL ACTIVITY

The antibacterial activity of the test solution containing new compounds with their inhibition zone furnished in Table II and the antibiotic streptomycin was used as a standard. According to the observation, the toxicity increases with the increase in concentration of the test solution containing new compounds. Among the different synthetic compounds, 2f and 2g seem to be very much active against the pathogens under study and it is evidenced by their inhibitory zone. Generally the methoxy derivatives are much active against the bacterial species than compared with other derivatives. 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 metabolism[18].

Table I. Physical and Spectroscopic data of (2a-g)[a]:

Compd.	M.p. ^{0}C (Yield %)	Elemental analyses Calcul. (%)	Found (%)	IR[b] νmax (cm^{-1})	^{1}H NMR[c] (δ) ppm	MS *m/z* 70ev (m+)
2a	252-254 (60)	C 68.65 H 3.89 N 6.06	C 68.60 H 3.85 N 6.05	1720 1665	δ6.57 (s, 1H, C4-H); δ2.68 (dd, 2H, J=8, 7.5, C3-H); δ1.24 (s, 3H, C4-CH3); δ7.50 (d, 1H, J=7.9, C7-H); δ7.78 (d, 1H, J=8, C10-H); δ7.32 (t, 2H, J=8.1, C8-H & C9-H); δ12.01 (bs, 1H, NH)	229
2b	243-245 (55)	C 69.70 H 4.60 N 5.81	C 69.68 H 4.59 N 5.80	1718 1658	δ2.70 (s, 3H, C8-CH3); δ6.65 (s, 1H, C4-H); δ2.65 (dd, 2H, J=8, 7.5, C3-H); δ1.30 (s, 3H, C4-CH3); δ7.40 (d, 1H, J=8, C7-H); δ7.80 (d, 1H, J=8, C10-H); δ7.35 (d, 1H, J=8.1, C9-H); δ12.10 (bs, 1H, NH)	243
2c	231-233 (55)	C 69.79 H 4.60 N 6.14	C 69.67 H 4.58 N 5.80	1716 1658	δ2.72 (s, 3H, C7-CH3); δ6.60 (s, 1H, C4-H); δ2.70 (dd, 2H, J=8.2, 7.6, C3-H); δ1.35 (s, 3H, C4-CH3); δ7.75 (d, 1H, J=8.1, C10-H); δ7.30- δ7.35 (m, 2H, C8-H & C9-H); δ12.12 (bs, 1H, NH)	243
2d	255-257 (55)	C 65.37 H 4.31 N 5.45	C 65.36 H 4.30 N 5.44	1722 1665	δ3.75 (s, 3H, C9-OCH3); δ6.70 (s, 1H, C4-H); δ2.82 (dd, 2H, J=7.9, 7.4, C3-H); δ1.40 (s, 3H, C4-CH3); δ7.50 (d, 1H, J=7.6, C7-H); δ7.75 (d, 1H, J=7.8, C10-H); δ7.45 (d, 1H, J=8, C8-H); δ11.75 (bs, 1H, NH)	259
2e	268-270 (55)	C 65.36 H 4.30 N 5.44	C 65.37 H 4.31 N 5.45	1725 1670	δ3.75 (s, 3H, C8-OCH3); δ6.65 (s, 1H, C4-H); δ2.70 (dd, 2H, J=8.2, 7.7, C3-H); δ1.40 (s, 3H, C4-CH3); δ7.50 (d, 1H, J=8.1, C7-H); δ7.70 (d, 1H, J=7.9, C10-H); δ7.45 (d, 1H, J=7.9, C9-H); δ11.85 (bs, 1H, NH)	259
2f	262-264 (55)	C 62.70 H 4.53 N 4.87	C 62.72 H 4.56 N 4.88	1725 1665	δ3.78 (s, 3H, C7-OCH3); δ6.60 (s, 1H, C4-H); δ2.70 (dd, 2H, J=8.1, 7.6, C3-H); δ1.35 (s, 3H, C4-CH3); δ7.65 (d, 1H, J=8.2, C10-H); δ7.35- δ7.40 (m, 2H, C8-H & C9-H); δ11.90 (bs, 1H, NH)	259
2g	257-259 (55)	C 65.36 H 4.30 N 5.43	C 65.37 H 4.31 N 5.45	1715 1660	δ3.75 (s, 3H, C7-OCH3); δ3.95 (s, 3H, C10-OCH3); δ6.55 (s, 1H, C4-H); δ2.75 (dd, 2H, J=8.1, 7.6, C3-H); δ1.45 (s, 3H, C4-CH3); δ7.40- δ7.45 (m, 2H, C8-H & C9-H); δ11.95 (bs, 1H, NH)	289

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

Table II. Antibacterial activity data of (2a-g)[a]:

Compd	Organisms – Diameter of inhibition zone in mm								
	Aeromonas hydrophilla			Bacillus subtilis			Escherichia coli		
	1 %	2 %	4 %	1 %	2 %	4 %	1 %	2 %	4 %
2a	-	4.0	6.0	3.0	4.0	4.8	3.0	3.5	5.0
2b	4.0	6.0	6.0	3.5	4.0	4.5	4.0	4.2	5.1
2c	-	-	-	4.1	4.5	5.0	4.5	5.0	6.0
2d	1.0	5.1	7.7	5.5	6.6	7.5	5.1	6.2	6.8
2e	3.1	3.8	5.9	5.2	6.7	8.3	4.0	6.0	8.1
2f	4.0	6.0	8.1	4.5	7.2	9.2	5.0	7.1	13.6
2g	6.0	7.0	14.2	4.0	6.0	13.1	4.4	8.2	15.2

a) The mean of three replicate values

IV. Conclusion

We have demonstrated that 4-hydroxy-2(1H)-quinolone is successfully used to synthesize newer derivatives of angular pyranoquinolones in one step method through Michael addition. The expected Michael addition was followed by cyclization, involving the nucleophilic oxygen at C-4 and electrophilic carbonyl carbon in the side chain afforded the product 2(a-g), which was carefully isolated after chromatographic purification. The overall results showed that the derivatives of angular pyranoquinolones are active against the bacterial species. But it could not reach the effectiveness of the conventional bactericide, streptomycin.

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