

Synthesis and Comparison of the Biological Activities of Derivatives of 3,5-Diphenyl-2H-pyrano[2,3-b] Quinolin-2-one

N. VENKATESH KUMAR, N. SAMPATH KUMAR and S.P. RAJENDRAN*

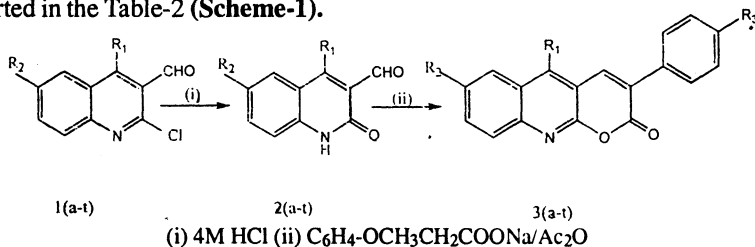
Department of Chemistry, Bharathiar University, Coimbatore-641 046, India

Synthesis of a series of title compounds (3) and its unknown derivatives is reported by the condensation of sodium salt of methoxy phenylacetic acid with 3-formyl-4-phenyl-2-quinolones (2). The compounds (2) in turn were obtained from their respective chloroquinolines (1). Structures of all the products have been established by spectral and elemental analysis data. Biocidal activities have been tested *in vitro*.

Key Words: Synthesis, 3,5-Diphenyl-2H-pyrano[2,3-b]quinolin-2-ones, Derivatives, Biological activities.

INTRODUCTION

The pyranoquinoline alkaloids have been reported to be associated with interesting pharmacological activities¹ like anticoagulant², coronary constricting³, optically brightening⁴ and biological activity⁵. Synthesis of title compound and its derivatives which are expected to be pharmacologically active is reported herewith. Our main objective is to synthesise hitherto unknown derivatives of 3,5-diphenyl-2H-pyrano(2,3-b)quinolin-2-ones and compare their biocidal activities. We have recently reported the synthesis of 3,5-diphenyl-2H-pyrano(2,3-b)quinolin-2-ones (3a–h) from 2-chloro-3-formyl-4-phenylquinolines⁶ (1a–h) by the condensation with sodium phenyl acetate. Now, we report herewith the synthesis of the methoxy derivatives of 3,5-diphenyl-2H-pyrano(2,3-b)quinolin-2-ones (3i–o) from 3-formyl-4-phenyl-2-quinolones in Table-1. The antibacterial activities of all the new derivatives of pyrano(2,3-b)quinolines (3i–o) as well as that of known (3a–h) is reported in the Table-2 (Scheme-1).



- | | |
|---|---|
| (a) R ₁ =C ₆ H ₅ ; R ₂ =R ₃ =H | (i) R ₁ =C ₆ H ₅ ; R ₂ =H; R ₃ =OCH ₃ |
| (b) R ₁ =C ₆ H ₄ -CH ₃ ; R ₂ =R ₃ =H | (j) R ₁ =C ₆ H ₄ -CH ₃ ; R ₂ =H; R ₃ =OCH ₃ |
| (c) R ₁ =C ₆ H ₄ -OCH ₃ ; R ₂ =R ₃ =H | (k) R ₁ =C ₆ H ₄ -OCH ₃ ; R ₂ =H; R ₃ =OCH ₃ |
| (d) R ₁ =C ₆ H ₅ ; R ₂ =Cl; R ₃ =H | (l) R ₁ =C ₆ H ₅ ; R ₂ =Cl; R ₃ =OCH ₃ |
| (e) R ₁ =C ₆ H ₅ ; R ₂ =CH ₃ ; R ₃ =H | (m) R ₁ =C ₆ H ₅ ; R ₂ =CH ₃ ; R ₃ =OCH ₃ |
| (f) R ₁ =C ₆ H ₄ -Cl; R ₂ =R ₃ =H | (n) R ₁ =C ₆ H ₄ -Cl; R ₂ =H; R ₃ =OCH ₃ |
| (g) R ₁ =C ₆ H ₄ -Br; R ₂ =R ₃ =H | (o) R ₁ =C ₆ H ₄ -Br; R ₂ =H; R ₃ =OCH ₃ |
| (h) R ₁ =CH ₃ ; R ₂ =R ₃ =H | |

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. ^1H NMR spectra were recorded on an AMX-400 spectrometer in CDCl_3 . Mass spectra were recorded on a Jeol D-300 mass spectrometer. Elemental analyses were performed by Perkin-Elmer model 240 B CHN analyser. For all the compounds satisfactory microanalysis values were obtained (C, H, N \pm 0.5%). The 3-formyl-4-phenyl-2-quinolones (**3a-h**) have been prepared from 2-chloro-3-formyl-4-phenylquinoline by treating⁶ with 4 M HCl. The known pyrano compounds (**3a-h**) have also been prepared by the method already reported by us⁶ from 3-formyl-4-phenyl-2-quinolone by refluxing with sodium salt of phenylacetic acid.

Typical Procedure: Synthesis of 3(4'-methoxy)phenyl-5-phenyl-2H-pyrano(2,3-b)quinolin-2-ones^{7,8} (3i-o): A mixture of **2** (0.001 mol), freshly fused sodium methoxyphenyl acetate (0.0616 mol), acetic anhydride (0.05 mol) was heated under reflux for 8 h at 170–180°C in an oil bath. The reaction mixture was then poured into crushed ice (*ca.* 100 g) with stirring and kept aside for 4–5 h. The resulting solid was filtered, dried and recrystallised from acetic acid to yield (**3i-o**) (Table-1).

TABLE-1
PHYSICAL AND SPECTROSCOPIC DATA OF (**3i-o**)^a

Compd.	m.p. (°C) (Yield %)	IR ^b (cm^{-1})	^1H NMR ^c (δ) ppm	ms m/z (m^+)
3i	265–266 (68)	1745 1655	δ 3.64 (s, 3H, $\text{C}_3\text{—C}_4\text{—OCH}_3$); δ 7.27–7.68 (m, 13H, C_3 & $\text{C}_5\text{—Ar—H}$, $\text{C}_4\text{—H}$, $\text{C}_6\text{—H}$, $\text{C}_7\text{—H}$ & $\text{C}_8\text{—H}$); δ 8.22 (d, 1H, $\text{C}_9\text{—H}$)	379
3j	273–274 (70)	1750 1648	δ 2.51 (s, 3H, $\text{C}_5\text{—C}_4\text{—CH}_3$); δ 3.62 (s, 3H, $\text{C}_3\text{—C}_4\text{—OCH}_3$); δ 7.23–7.70 (m, 12H, C_3 & $\text{C}_5\text{—Ar—H}$, $\text{C}_6\text{—H}$, $\text{C}_7\text{—H}$ & $\text{C}_8\text{—H}$); δ 8.20 (d, 1H, $\text{C}_9\text{—H}$)	393
3k	251–252 (71)	1749 1660	δ 3.64 (s, 3H, $\text{C}_3\text{—C}_4\text{—OCH}_3$); δ 3.72 (s, 3H, $\text{C}_5\text{—C}_4\text{—OCH}_3$); δ 7.20–7.72 (m, 12H, C_3 & $\text{C}_5\text{—Ar—H}$, $\text{C}_4\text{—H}$, $\text{C}_6\text{—H}$, $\text{C}_7\text{—H}$ & $\text{C}_8\text{—H}$); δ 8.19 (d, 1H, $\text{C}_9\text{—H}$)	409
3l	278–279 (70)	1740 1650	δ 3.81 (s, 3H, $\text{C}_3\text{—C}_4\text{—OCH}_3$); δ 7.25–7.82 (m, 13H, C_3 & $\text{C}_5\text{—Ar—H}$, $\text{C}_4\text{—H}$, $\text{C}_6\text{—H}$, $\text{C}_8\text{—H}$ & $\text{C}_9\text{—H}$)	414 416
3m	260–261 (69)	1748 1652	δ 2.53 (s, 3H, $\text{C}_7\text{—CH}_3$); δ 3.65 (s, 3H, $\text{C}_3\text{—C}_4\text{—OCH}_3$); δ 7.28–7.86 (m, 12H, C_3 & $\text{C}_5\text{—Ar—H}$, $\text{C}_4\text{—H}$, $\text{C}_6\text{—H}$ & $\text{C}_8\text{—H}$); δ 8.26 (d, 1H, $\text{C}_9\text{—H}$)	393
3n	280–281 (64)	1762 1660	δ 3.62 (s, 3H, $\text{C}_3\text{—C}_4\text{—OCH}_3$); δ 7.20–7.86 (m, 13H, C_3 & $\text{C}_5\text{—Ar—H}$, $\text{C}_4\text{—H}$, $\text{C}_6\text{—H}$, $\text{C}_8\text{—H}$ & $\text{C}_9\text{—H}$)	414 416
3o	276 (d) (62)	1750 1650	δ 3.66 (s, 3H, $\text{C}_3\text{—C}_4\text{—OCH}_3$); δ 7.21–7.88 (m, 13H, C_3 & $\text{C}_5\text{—Ar—H}$, $\text{C}_4\text{—H}$, $\text{C}_6\text{—H}$, $\text{C}_8\text{—H}$ & $\text{C}_9\text{—H}$)	458 460

(a) recrystallised from acetic acid

(b) as KBr pellets

(c) CDCl_3 solvent

Antibacterial activity⁹: The compounds (3a–o) were screened for their antibacterial activities against *Escherichia coli*, *Bacillus subtilis* and *Aeromonas hydrophilla* were determined by agar diffusion technique^{9,10}. 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 H₂O) 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°C for 24 h. The zones of inhibition around the discs were measured after 24 h. Streptomycin was used as a standard to compare the antibacterial activity of the compounds (3a–o) (Table-2).

TABLE-2
ANTIBACTERIAL ACTIVITY DATA (3a–o)^a

Compound	Organisms—Diameter of inhibition zone in mm								
	<i>Aeromonas hydrophilla</i>			<i>Bacillus subtilis</i>			<i>Escherichia coli</i>		
	1%	2%	4%	1%	2%	4%	1%	2%	4%
3a	—	5.2	7.9	5.0	6.0	5.5	3.0	3.5	5.0
3b	3.0	4.0	6.0	5.2	5.6	6.0	4.0	4.2	5.1
3c	4.0	6.0	10.0	5.0	6.5	7.0	4.5	5.0	6.0
3d	—	—	—	4.0	4.2	5.0	—	4.1	5.1
3e	3.1	3.8	5.9	5.2	5.4	6.1	4.1	4.4	4.9
3f	—	—	1.0	3.0	4.0	4.8	1.0	3.9	4.8
3g	—	—	1.0	4.0	5.3	6.1	2.0	3.8	5.2
3h	—	—	—	—	—	—	—	—	—
3i	1.0	5.1	7.7	4.9	6.1	5.4	3.1	3.7	4.9
3j	4.0	6.2	8.1	5.4	6.6	8.1	4.4	8.2	15.2
3k	6.0	7.0	14.2	5.2	6.7	7.2	5.1	6.0	6.4
3l	—	1.0	2.0	4.0	5.4	13.1	2.0	4.4	5.5
3m	3.2	3.9	6.0	5.1	5.6	6.2	4.2	4.7	5.1
3n	1.0	—	2.1	3.2	4.3	5.3	2.0	4.1	4.8
3o	2.0	1.0	3.0	4.1	5.5	6.2	2.0	3.9	5.3
Streptomycin (standard)	8.0	12.0	19.0	8.0	10.0	18.0	7.0	10.0	18.0

(a) The mean of three replicate values

RESULTS AND DISCUSSION

The 3-formyl-4-phenyl-7-chloro-2-quinolone (**2l**) so obtained was prepared and then subjected to Perkin type condensation with sodium methoxyphenyl acetate and acetic anhydride to give a compound (**3l**) in 70% yield, which melts at 278–279°C. Its IR spectrum showed peaks at 1740 and 1650 cm^{-1} which are assigned to the pyrone system. The ^1H NMR showed very sharp signals. The signals due to methoxy protons appear as a singlet at δ 3.81. The signals due to aromatic protons appear as a multiplet in the region δ 7.25– δ 7.82 (m, 13H, C_3 and C_5 —Ar—H, C_4 —H, C_6 —H, C_8 —H and C_9 —H). Its mass spectrum gave intense molecular ion peak at 414 and 416 as M and M + 2 peak respectively. Thus the compound (**3l**) was identified as 3(4'-methoxy)phenyl-5-phenyl-7-chloro-2H-pyrano(2,3-b)quinolin-2-one. The reaction sequence leading to (**3l**) was then extended to synthesize further derivatives.

Antibacterial Activity: The antibacterial activities of all the derivatives of pyranoquinolines were checked by agar diffusion method. *Escherichia coli*, *Bacillus subtilis* and *Aeromonas hydrophilla* were used as test organisms. All the compounds were screened at 1, 2 and 4% disc solutions in chloroform and were used for the studies.

The parent 3,5-diphenylpyranoquinoline showed almost same antibacterial activity when compared to the 3(4'-methoxy)phenyl-5-phenylpyranoquinoline against the test organisms *Escherichia coli*, *Bacillus subtilis* and *Aeromonas hydrophilla* at three different concentrations like 1, 2 and 4%. The methyl derivatives like 3-phenyl-5(4'-methyl)phenyl and 7-methyl-3,5-diphenylpyranoquinoline showed low inhibition activity when compared to the 3(4'-methoxy)phenyl-5(4'-methyl)phenyl and 7-methyl-3(4'-methoxy)phenyl-5-phenyl-pyranoquinolines. While the compound 3(4'-methoxy)phenyl-5(4'-methyl)phenylpyranoquinoline showed very good antibacterial activity against the test organism *E. coli*. The methoxy derivatives like 3-phenyl-5(4'-methoxy)phenylpyranoquinoline showed moderate activity while 3(4'-methoxy)phenyl-5(4'-methoxy)phenylpyranoquinoline showed very good activity especially against *A. hydrophilla*. The chloro and bromo derivatives like 3-phenyl-5(4'-chloro)phenyl, 3,5-diphenyl-7-chloropyranoquinoline and 3-phenyl-5(4'-bromo)phenylpyranoquinoline showed almost no activity against *A. hydrophilla* and showed moderate activity against *B. subtilis* and *E. coli*, while their respective methoxy derivatives showed moderate activity against all the three test organisms.

According to the observation, the toxicity increases with the increase in concentration of the test solution containing new compounds. Generally the derivatives of 3(4'-methoxy)phenyl-5(4'-methoxy)phenylpyranoquinolines showed higher antibacterial activity than the derivatives of 3,5-diphenylpyranoquinolines. This may be due to the presence of methoxy group. The overall results showed that the derivatives of 3,5-diphenylpyranoquinolines are active against the bacterial species. But it could not reach the effectiveness of the conventional bactericide, streptomycin.

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Contact:

CCS, ETH Zurich-Technopark, Techno-parkstrasse.1

CH-8005 Zurich, Switzerland

E-mail: info@chemsens.pharma.ethz.ch

<http://www.chemsens.ethz.ch>