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Synthesis of Derivatives of 3-Phenyl-2H-Pyrano[2,3-b] Quinoline-2-Ones and Comparision of Their Biological Activities

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Synthesis of a series of title compounds including several hitherto unknown derivatives of 3-phenyl-2H-pyrano (2,3-b) quinoline-2-ones (3) is reported by the Perkin type reaction of 3-formyl-2-quinolones (2) with sodium salt of phenylacetic acid. The 3-formyl-2-quinolones inturn were obtained from 2-chloro-3-formylquinolines (1). Structures of all the products have been established by spectral and elemental analysis data. Biocidial activities have been tested *in vitro*.

Key Words: Synthesis, Derivatives, 3-Phenyl-2H-pyrano[2,3-b] quinoline-2-ones, Biological activities.

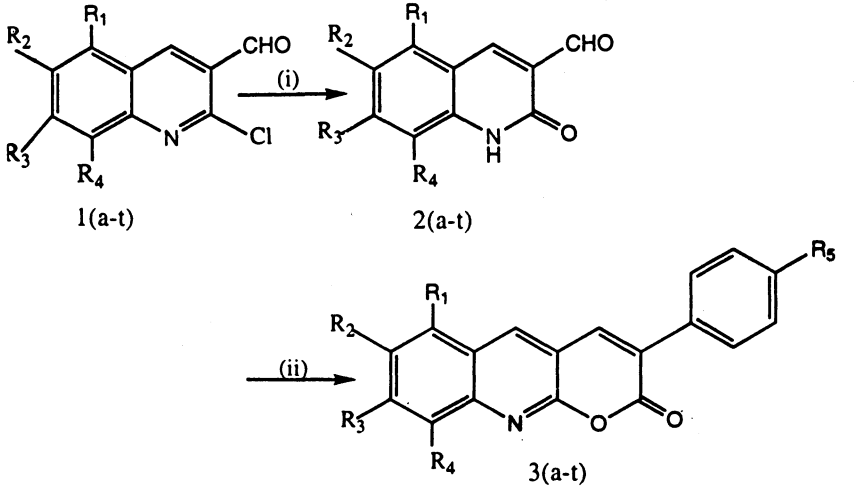
INTRODUCTION

The synthesis of pyranoquinolines have gained more interest in recent years as they constitute the parent ring structure of pyranoquinoline alkaloids which have been reported to be associated with interesting pharmacological activities[1] like anticoagulant[2] coronary constricting[3], optically brightening[4] and biological activity[5]. Synthesis of title compound and its derivatives is reported by the condensation of 3-formyl-2-quinolones with sodium salt of phenylacetic acid. One of our main objectives is to compare the biocidal activities of all the derivatives of pyranoquinolines **(Scheme-1).**

EXPERIMENTAL

Melting points were determined using Raaga melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer-597 infrared spectrophotometer as KBr pellets. ^{1}H 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 and the values are within the permissible limits (± 0.5). 2-Chloro-3-formylquinolines[6] have been prepared by known procedures. 3-Formyl-2-quinolones[7] **(2a–f)** and 3-phenyl-2H-pyrano (2,3-b) quinoline-2-ones[8] **(3a–f)** have been reported earlier. But the hitherto unknown derivatives of 3-formyl-2-quinolones **(2g–j)** and 3-(4′-methoxy)-phenyl-2H-pyrano-(2,3-b)- quinoline-2-ones **(3g–t)** is reported in Tables 1 and 2. The biocidal activities of all the derivatives of pyranoquinolines **(3a–t)** have been reported in Table-3.

Scheme-1



(i) 4M HCl (ii) $C_6H_5CH_2COONa/(CH_3CO)_2O$

(a) $R_1 = R_2 = R_3 = R_4 = R_5 = H$

(b) $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = CH_3$

(c) $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = CH_3$

(d) $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = CH_3$

(e) $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = OCH_3$

(f) $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OCH_3$

(g) $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = OCH_3$

(h) $R_1 = R_3 = R_5 = H$; $R_2 = R_4 = CH_3$

(i) $R_1 = R_2 = R_5 = H$;
$R_3 = R_4 =$ —CH=CH—CH=CH—

(j) $R_1 = R_2 =$ —CH=CH—CH=CH—;
$R_3 = R_4 = R_5 = H$

(k) $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = OCH_3$

(l) $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$; $R_5 = OCH_3$

(m) $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$; $R_5 = OCH_3$

(n) $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$; $R_5 = OCH_3$

(o) $R_1 = R_3 = R_4 = H$; $R_2 = R_5 = OCH_3$

(p) $R_1 = R_2 = R_4 = H$; $R_3 = R_5 = OCH_3$

(q) $R_1 = R_2 = R_3 = H$; $R_4 = R_5 = OCH_3$

(r) $R_1 = R_3 = H$; $R_2 = R_4 = CH_3$; $R_5 = OCH_3$

(s) $R_1 = R_2 = H$;
$R_3 = R_4 =$ —CH=CH—CH=CH—;
$R_5 = OCH_3$

(t) $R_1 = R_2 =$ —CH=CH—CH=CH—;
$R_3 = R_4 = H$; $R_5 = OCH_3$

Synthesis of 3-formyl-2-quinolones[7] (2a–t): A mixture of **1** (0.0104 mole) and aqueous hydrochloric acid (35 mL, 4 M) was heated under reflux for 8 h in an oil bath at 120–130°C and then allowed to cool at room temperature. After 1 h the reaction mixture was poured into crushed ice, when the product was separated as a yellow solid. It was filtered, washed with water, dried and recrystallised from aqueous acetic acid (Table-1).

Synthesis of 3-phenyl/methoxy phenyl-2H-pyrano (2,3-b) quinoline-2-ones[8] (3a–t): A mixture of **2** (0.001 mole), freshly fused sodium phenyl/methoxyphenyl acetate (0.0016 mole), acetic anhydride (0.05 mole) was heated under reflux for 8 h at 170–180°C in an oil bath. The reaction mixture was then poured into crushed ice (≈ 100 g) with stirring and kept aside for 4–5 h. The resulting solid was filtered, dried and recrystallised from acetic acid to yield **(3a–t)** (Table-2).

TABLE-1
PHYSICAL AND SPECTROSCOPIC DATA OF (2g–j)[a]

Compd.	m.p. (°C)	Yield (%)	IR[b] γ_{max} (cm^{-1})	MS m/z (m+)
2g	260–262	64	1685, 1640	203
2h	289–290	86	1680, 1640	201
2i	286–287	85	1690, 1650	223
2j	291–292	85	1680, 1640	223

[a] Recrystallised from aq. acetic acid. [b] As KBr pellets.

Antibacterial activity[9]: Antibacterial activity of the compounds **(3a–t)** was determined by agar diffusion technique. 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 DMF to a final concentration of 500 μg/disc 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. Amoxycillin was used as a standard to compare the antibacterial activity of the compounds **(3a–t)** (Table-3).

RESULTS AND DISCUSSION

The chloroaldehyde **(1h)** was converted to oxo compound **(2h)** by refluxing with aqueous 4 M HCl followed by usual work up to give a product in 86% yield which melts at 289–290°C. Its IR spectrum showed peaks at 1680 cm^{-1} (—CHO) and 1640 cm^{-1} (—NHC=O). The 3-formyl-2-quinolone **(2h)** so obtained was then subjected to Perkin type condensation with sodium phenyl acetate and acetic anhydride to give a compound **(3h)** in 74% yield, which melts at 252–254°C. Its IR spectrum showed peaks at 1720 and 1660 cm^{-1} which are assigned to the pyrone system. The PMR spectra showed very sharp signals. The protons at positions 4 and 5 appear as a singlet at δ 7.89 and δ 8.26 respectively. The signals due to aromatic protons appears as a multiplet in the region δ 7.31–7.80 (m, 7H, C_3-Ar-H, C_6-H & C_8-H). The signals due to methyl protons appear as a singlet at δ 2.50 and δ 2.76 respectively. The mass spectra also showed intense molecular ion peak at m/e 301. Thus the compound **(3h)** was identified as 6,8-dimethyl-3-phenyl-2H-pyrano-(2,3-b)-quinolin-2-one. The reaction sequence leading to **(3h)** was then extended to synthesise compounds **(3i–t)**.

Antibacterial Activity: The antibacterial activity of all the derivatives of pyranoquinolines was checked by agar diffusion method. *Staphylococcus aureus, Escherichia coli* and *Klebsiella pneumoniae* were used as test organisms. All the compounds were screened at 500 μg/disc solution in DMF and were used for the studies.

TABLE-2
PHYSICAL AND SPECTROSCOPIC DATA OF (3g–t)[a]

Compd.	m.p. (°C) Yield (%)	IR[b] (cm^{-1})	^1H NMR[c] (δ) ppm	MS m/z (m^+)
3g	277–279 (60)	1725 1675	δ 3.82 (s, 3H, C_9-OCH_3); δ 7.95 (s, 1H, C_4-H); δ 8.20 (s, 1H, C_5-H; δ 7.32–7.92 (m, 8H, C_3-Ar-H, C_6-H, C_7-H & C_8-H	303
3h	252–254 (74)	1720 1660	δ 2.50 (s, 3H, C_7-CH_3); δ 2.76 (s, 3H, C_9-CH_3); δ 7.89 (s, 1H, C_4-H); δ 8.26 (s, 1H, C_5-H); δ 7.31–7.80 (m, 7H, C_3-Ar-H, C_6-H & C_8-H)	301
3i	302–304 (73)	1720 1670	δ 7.20–8.11 (m, 13H, C_3-Ar-H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_9-H, C_{10}-H & C_{11}-H).	323
3j	266–268 (73)	1726 1680	δ 7.33–8.60 (m, 13H, C_3-Ar-H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_9-H, C_{10}-H &C_{11}-H)	323
3k	242–244 (73)	1720 1680	δ 3.85 (s, 3H, C_5-C_4'-OCH_3); δ 7.98 (s, 1H, C_4-H); δ 8.38 (s, 1H, C_5-H); δ 7.20–7.95 (m, 8H, C_3-Ar-H, C_6-H, C_7-H, C_8-H & C_9-H)	303
3l	230–231 (73)	1735 1682	δ 2.55 (s, 3H, C_7-CH_3); δ 3.86 (s, 3H, C_3-C_4'-OCH_3) δ 7.92 (s, 1H, C_4-H); δ 8.28 (s, 1H, C_5-H); δ 6.95–7.90 (m, 7H, C_3-Ar-H, C_6-H, C_8-H & C_9-H)	317
3m	233–235 (73)	1720 1670	δ 2.57 (s, 3H, C_8-CH_3); δ 3.85 (s, 3H, C_3-C_4'-OCH_3); δ 7.94 (s, 1H, C_4-H); δ 8.29 (s, 1H, C_5-H); δ 7.10–7.92 (m, 7H, C_3-Ar-H, C_6-H, C_7-H & C_9-H)	317
3n	225–227 (60)	1725 1676	δ 2.78 (s, 3H, C_9-CH_3); δ 3.85 (s, 3H, C_3-C_4'-OCH_3); δ 7.96 (s, 1H, C_4-H); δ 8.33 (s, 1H, C_5-H); δ 7.16–7.94 (m, 7H, C_3-Ar-H, C_6-H, C_7-H & C_8-H).	317
3o	245–246 (75)	1736 1680	δ 3.86 (s, 3H, C_3-C_4'-OCH_3); δ 3.95 (s, 3H, C_7-OCH_3); δ 7.95 (s, 1H, C_4-H); δ 8.23 (s, 1H, C_5-H); δ 6.90–7.89 (m, 7H, C_3-Ar-H, C_6-H, C_8-H & C_9-H)	333
3p	262–264 (75)	1740 1685	δ 3.82 (s, 3H, C_3-C_4'-OCH_3); δ 3.94 (s, 3H, C_8-OCH_3); δ 7.98 (s, 1H, C_4-H); δ 8.33 (s, 1H, C_5-H); δ 7.10–7.95 (m, 7H, C_3-Ar-H, C_6-H, C_7-H & C_9-H)	333
3q	257–259 (60)	1718 1670	δ 3.86 (s, 3H, C_3-C_4'-OCH_3); δ 3.96 (s, 3H, C_9-OCH_3); δ 7.99 (s, 1H, C_4-H); δ 8.36 (s, 1H, C_5-H); δ 7.12–7.96 (m, 7H, C_3-Ar-H, C_6-H, C_7-H & C_8-H)	333
3r	222–224 (74)	1720 1680	δ 2.49 (s, 3H, C_7-CH_3); δ 2.75 (s, 3H, C_9-CH_3); δ 3.85 (s, 3H, C_3-C_4'-OCH_3); δ 7.82 (s, 1H, C_4-H); δ 8.23 (s, 1H, C_5-H); δ 7.15–7.74 (m, 6H, C_3-Ar-H, C_6-H & C_8-H)	331
3s	248–249 (73)	1735 1685	δ 3.84 (s, 3H, C_3-C_4'-OCH_3); δ 7.22–8.14 (m, 12H, C_3-Ar-H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_9-H, C_{10}-H & C_{11}-H).	353
3t	256–258 (73)	1730 1680	δ 3.86 (s, 3H, C_3-C_4'-OCH_3); δ 7.21–8.15 (m, 12H,C_3-Ar-H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_9-H, C_{10}-H & C_{11}-H).	353

[a] Recrystallised from acetic acid. [b] As KBr pellets. [c] $CDCl_3$ solvent.

TABLE-3
ANTIBACTERIAL ACTIVITY DATA (**3a–t**)

Compound	Organisms		
	Diameter of inhibition Zone (mm) at 500 μgm/disc		
	Staphylococcus aureus	*Escherichia coli*	*Klebsiella pneumoniae*
3a	1	1	–
3b	–	–	–
3c	2	1	–
3d	–	–	–
3e	1	1	–
3f	1	–	–
3g	1	2	–
3h	7	5	–
3i	8	8	–
3j	2	5	–
3k	2	2	–
3l	1	2	–
3m	8	9	–
3n	–	2	–
3o	2	3	–
3p	2	1	–
3q	2	1	–
3r	–	4	–
3s	14	6	14
3t	3	6	–
Amoxycillin (Standard)	16	21	18

The parent 3-phenylpyranoquinoline showed almost the same antibacterial effect when compared to the 3-phenyl-(4′-methoxy)-pyranoquinoline against the test organisms *S. aureus* and *E. coli* at 500 μg/disc. The methyl derivatives like 7-methyl-3-phenylpyranoquinoline showed low inhibition activity when compared to the 7-methyl-3-(4′-methoxy)-phenylpyranoquinoline. The 6 and 8-methyl derivatives of 3-phenylpyranoquinolines showed no activity; while 6 and 8 methyl derivatives of 3-(4′-methoxy)-phenylpyranoquinolines showed very little inhibition activity against *S. aureus* and *E. coli.* All the methoxy derivatives of 3-phenylpyranqouinolines showed low inhibition activity when compared to the methoxy derivatives of 3-(4′-methoxy)-phenylpyranoquinolines. The compound 6,8-dimethyl-3-phenylpyranoquinoline showed moderate antibacterial effect while the compound 6,8-dimethyl-3-(4′-methoxy)-phenyl pyranoquinoline showed no activity against *S. aureus* and less activity against *E. coli.* The benzo(h)-3-phenylpyranoquinoline was found to be moderately active against *S. aureus* and *E. coli*, while the benzo(h)-3-(4′-methoxy)-phenylpyranoquinoline

was found to be more active against *S. aureus* and *K. pneumoniae.* The benzo(f)-3-phenyl and benzo(f)-3-(4′-methoxy)-phenylpyranoquinoline were found to show almost same antibacterial effect. The benzo(h)-3-(4′-methoxy)-phenylpyranoquinoline was the only compound which showed very good antibacterial activity against *S. aureus* and *K. pneumoniae,* while all the other derivatives showed no activity against *K. pneumoniae* and moderate activity against *S. aureus* and *E. coli.*

Generally the derivatives of 3-(4′-methoxy)-phenylpyranoquinolines showed higher antibacterial activity than the derivatives of 3-phenylpyranoquinolines. This is mainly due to the presence of methoxy group. The overall results showed that the derivatives of 3-phenylpyranoquinolines are active against the bacterial species. But it could not reach the effectiveness of the conventional bactericide, amoxycillin.

REFERENCES

1. H.T. Openshaw, in: R.H.F. Manske (Ed.), The Alkaloids, Vol, IX, Academic Press, New York, 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, Vol. 9, Verlag Chemie, Weinhein, p. 235 (1952).
6. O.M. Cohn, B. Narine and B. Tarnouski, *J. Chem. Soc., Perkin Trans. (I)*, 1520 (1981).
7. T. Tilakaraj and Sarvottam Y. Ambekar, *J. Indian Chem. Soc.*, **62**, 251 (1985).
8. ———— , *J. Indian Chem. Soc.*, **63**, 981 (1986).
9. A.W. Bauer, W.M.M. Kirby. J.C. Sherris and M. Truck., *Amer. J. Chin. Pathol.*, **45**, 493 (1966).

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