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Synthesis and Antimicrobial Activity of 2-Aryl-1-Methyl-3H-1,4-Oxazino(5,6-C)Quinolines

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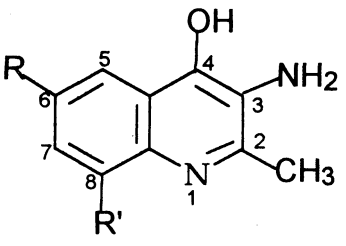
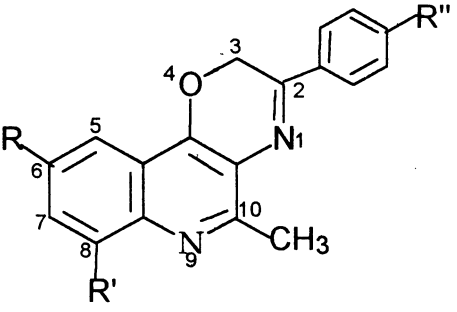
It describes the synthesis of 2-aryl-10-methyl-1,4-oxazino(5,6-c) quinolines (V, VI, VII, VIII) by the condensation of their corresponding amino hydroxy quinolines (I, II, III, IV) with different ω-bromoacetophenones in dry acetone in presence of anhydrous potassium carbonate. The products are characterised by their elemental and spectral analyses. A few selected compounds are also screened for their antimicrobial properties.

INTRODUCTION

It is found in literature that many of 1,4-benzoxazine derivatives are associated with a wide variety of biological and pharmacological properties[1–4]. A few are also reported to possess antiulcer[5], antiinflammatory[6] and anthelmintic[7] activities. As a continuation of our previous work on nitrogen heterocycles[8–10], we now report the synthesis of hitherto unknown 2-aryl-10-methyl-3H-1,4-oxazino-(5,6-c)quinoline derivatives (V, VI, VII, VIII) from their corresponding aminohydroxy quinolines[11, 12] (I, II, III, IV) in the presence of anhydrous potassium carbonate in dry acetone. The compounds synthesised were characterised by their elemental and spectral analyses.





I, R = R' = H
II, R = H, R' = CH_3
III, R = CH_3, R' = H
IV, R = H, R' = OCH_3

V, R = R' = H
VI, R = H, R' = CH_3
VII, R = CH_3, R' = H
VIII, R = H, R' = OCH_3

R" = H, Cl, Br, NO_2, CH_3, OCH_3.

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EXPERIMENTAL

A mixture of I, II, III or IV (10 mmol), anhydrous potassium carbonate (35 mmol) was stirred rapidly at 25°C for 1 h. The ω-bromoacetophenone (12 mmol) was added to the above mixture and refluxed for 6 h. The excess solvent was removed by distillation under vacuum and the residue was washed with ice cold water (150 mL). The precipitate was recrystallised from the suitable solvent (Table-1). **Vb**: PMR ($CDCl_3$, δ ppm): 2.45 (s, 3H, 10-CH_3), 4.6 (s, 2H, —CH_2—), 6.9–8.2 (m, 8H, Ar—H). Mass (m/Z): 308 ($M^{+\cdot}$, 30), 306 (M—H_2, 80), 271 (306–Cl, 10), 198 (M—C_6H_4Cl, 15), 155 (306-C_8H_4OCl, 100), 138 (C_7H_5NCl, 100). **VIb**: PMR ($CDCl_3$, δ ppm): 1.25 (s, 3H, 8-CH_3, 2.8 (s, 3H, 10-CH_3), 4.7 (s, 2H, —CH_2—), 6.9–8.2 (m, 7H, Ar—H). Mass (m/Z): 322 (M^+, 70), 320 (M—H_2, 100), 285 (320-Cl, 8), 186 (M—C_8H_5Cl, 5), 184 (M—C_7H_5NCl, 22), 130 (C_9H_8N,62). **VIIb**: PMR ($CDCl_3$, δ ppm): 2.9 (s, 3H, 10-CH_3), 2.2 (s, 3H, 6-CH_3), 5.3 (s, 2H, —CH_2—), 7.3–8.2 (m, 7H, Ar—H). Mass (m/Z): 322 (M^+, 8), 320 (M—H_2, 5), 211 (M—C_6H_4Cl, 15), 183 (211-CO, 21), 139 (C_7H_6NCl, 100), 111 (139-H_2CN, 27). **VIIIb**: (PMR, $CDCl_3$, δ ppm): 2.6 (s, 3H, 10-CH_3), 3.9 (s, 3H, —OCH_3), 5.45 (s, 2H, —CH_2—), 6.9–8.1 (m, 7H, Ar—H). Mass (m/Z): 338 (M^+, 42), 336 (M—H_2, 5), 310 (M—CO, 17), 139 (C_7H_6NCl, 100), 111 (139-H_2CN, 35).

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF OXAZINOQUINOLINES

Comp. No.	—R	Yield (%)	m.p. (°C)	Mol. formula	Elemental analyses %, Found (Calcd.)		
					C	H	N
Va	—H	40	135–36	$C_{18}H_{14}N_2O$	78.83 (78.81)	5.11 (5.09)	10.22 (10.20)
b	—Cl	73	190–91	$C_{18}H_{13}N_2OCl$	70.12 (70.11)	4.22 (4.20)	9.09 (9.08)
c	—Br	68	180–83	$C_{18}H_{13}N_2OBr$	61.19 (61.17)	3.68 (3.67)	7.93 (7.91)
d	—NO_2	65	128–29	$C_{18}H_{13}N_3O_3$	67.71 (67.69)	4.07 (4.06)	13.16 (13.14)
e	—CH_3	52	164–65	$C_{19}H_{16}N_2O$	79.19 (79.15)	5.55 (5.53)	9.72 (9.70)
f	—OCH_3	45	148–49	$C_{19}H_{16}N_2O_2$	75.00 (74.98)	5.26 (5.25)	9.21 (9.20)
VIa	—H	43	132–33	$C_{19}H_{16}N_2O$	79.17 (79.15)	5.55 (5.53)	9.72 (9.70)
b	—Cl	70	135–36	$C_{19}H_{15}N_2OCl$	70.80 (70.78)	4.66 (4.64)	8.69 (8.68)
c	—Br	65	146–47	$C_{19}H_{15}N_2OBr$	62.12 (62.10)	4.09 (4.08)	7.63 (7.61)
d	—NO_2	62	169–70	$C_{19}H_{15}N_3O_3$	68.47 (68.45)	4.50 (4.48)	12.61 (12.60)
e	—CH_3	49	172–73	$C_{20}H_{18}N_2O$	79.47 (79.46)	5.96 (5.94)	9.27 (9.26)

Comp. No.	—R	Yield (%)	m.p. (°C)	Mol. formula	Elemental analyses %, Found (Calcd.)		
					C	H	N
f	$-OCH_3$	44	153–54	$C_{20}H_{18}N_2O_2$	75.47 (75.46)	5.66 (5.64)	8.80 (8.78)
VIIa	—H	43	109–11	$C_{19}H_{16}N_2O$	79.16 (79.10)	5.55 (5.52)	9.72 (9.70)
b	—Cl	70	115–16	$C_{19}H_{15}N_2OCl$	70.80 (70.71)	4.65 (4.62)	8.69 (8.65)
c	—Br	60	121–22	$C_{19}H_{15}N_2OBr$	62.12 (62.01)	4.08 (4.06)	7.62 (7.59)
d	$-NO_2$	60	215–16	$C_{19}H_{15}N_3O_3$	68.46 (68.40)	4.50 (4.47)	12.60 (12.57)
e	$-CH_3$	50	95–97	$C_{20}H_{18}N_2O$	79.47 (79.45)	5.96 (5.93)	9.27 (9.26)
f	$-OCH_3$	44	90–92	$C_{20}H_{18}N_2O_2$	74.47 (74.49)	5.66 (5.64)	8.80 (8.79)
VIIIa	—H	46	105–06	$C_{19}H_{16}N_2O_2$	75.00 (74.96)	5.26 (5.24)	9.25 (9.19)
b	—Cl	65	145–46	$C_{19}H_{15}N_2O_2Cl$	67.45 (67.35)	4.43 (4.41)	8.28 (8.22)
c	—Br	60	137–39	$C_{19}H_{15}N_2O_2Br$	59.50 (59.45)	3.91 (3.90)	7.31 (7.28)
d	$-NO_2$	60	127–28	$C_{19}H_{15}N_3O_4$	65.32 (65.37)	4.29 (4.32)	12.03 (12.01)
e	$-CH_3$	50	174–75	$C_{20}H_{18}N_2O_2$	75.47 (75.40)	5.66 (5.62)	8.80 (8.82)
f	$-OCH_3$	46	114–16	$C_{20}H_{18}N_2O_3$	71.85 (71.81)	5.38 (5.35)	8.38 (8.39)

Satisfactory elemental analyses for halogens were also obtained. Compounds V and VI were purified from aq. methanol, and VII and VIII from ethanol.

RESULTS AND DISCUSSION

The absence of the absorption of N—H and O—H stretching in the IR spectra of these compounds confirms the cyclisation. Absorption bands due to C=N stretching vibrations are found in the region 1620–1590 cm^{-1}. The symmetric and antisymmetric stretching vibrations of aliphatic and aromatic ether systems are observed around 1365–1260 and 1160–1070 cm^{-1} respectively. The aliphatic C—H stretching vibrations are also observed around 2950–2800 cm^{-1}. The PMR spectra of these compounds display a three proton singlet around δ 2.6–3.0 due to the C-10 methyl group. The methylene group of oxazine ring appears as a singlet at δ 4.7–5.5. The aromatic protons resonate around δ 6.9–8.1. The substituents also display their peaks at their respective positions. The mass spectra of these compounds show a moderately intense molecular ion peak. The loss of hydrogen molecule is a common feature in all these compounds. In some cases M-2 peak appears as the base peak. The loss of aryl group from the oxazine ring is also a common feature in these compounds.

All the compounds of the type, V, VI and VIIa, c, d, e and VIIIa, c, d, e were screened for their biological activities.

Antibacterial activity: These compounds were tested against *Bacillus subtilus, Bacillus polymixa* (gram +ve), *Escherichia coli* and *Klebsiella pneumonia* (gram –ve) at the dose levels of 120, 360, and 600 μg/mL by filter paper disc method[13]. The compounds Vb, VIb, VIIb and VIIIb are found to be more toxic towards all the bacteria at 600 μg/mL. The relatively high toxicity of these compounds may be due to the presence of *p*-chlorophenyl moiety. Rest of the compounds are ineffective towards all the bacteria employed at all the dose levels.

Antifungal activity: Antibacterial activity was determined by the food poisoning method[14] against *Curvularia lunata* and *Fusarium oxysporum* at the dose levels of 120, 360 and 600 μg/mL. The compounds Vb, VIIa, b, d and VIIIa, b registered maximum activity against both the fungi even at the dose level of 360 μg/mL. The rest of the compounds registered lowest activity against *F. oxysporum* and are found to be ineffective towards *C. lunata*.

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