Synthesis and Biological Evaluation of 5-Oxo-imidazolines and Aryl Amides

R. C. Khunt, N. J. Datta and A. R. Parikh*
Department of Chemistry, Saurashtra University, Rajkot–360 005.

Accepted 6 December 2001
Revised 10 November 2001
Received 3 August 2000

2-Chloro-7-methoxy-quinoline-3-carboxaldehyde I on reaction with hydrazine hydrate, yield N-amino- 2-chloro-7-methoxy quinolin-3-yl azomethine II, which on reaction with acid chloride and 5-oxazolinone derivatives furnished arylamide IIIa-o and 5-oxo imidazoline IVa-o respectively. All the products were screened for antimicrobial activity against several microbes.

Among a wide variety of aryl amide[1-3], 5-oxo imidazoline[4-6] have played an important role in medicinal chemistry. Some of them have received considerable attention as potential antimicrobial agents. Moreover, quinoline derivatives are associated with various pharmacological activities[7-9] . These observations led to prepare arylamides and 5-oxo imidazoline derivatives bearing quinoline nucleus.

The starting compound, 2-chloro-7-methoxy-quinoline-3-carboxaldehyde I was prepared by Vilsmier-Haack chloroformylation of m-methoxy acetanilide which on reaction with hydrazine hydrate yielded N-amino-2-chloro-7-methoxy-quinolin-3-yl azomethine 10 II. This on reaction with acid chloride and 5-oxazolone gave arylamides IIIa-o and 5-oxo-imidazolines IVa-o respectively.

The characterization of all the products was established by elemental analyses, IR and PMR spectral study. All the products were screened for their antimicrobial activity against different strains of bacteria and fungi. The melting points are uncorrected. Infrared spectra (KBr) were recorded on a Nicolet Magna IR 550 Series II and ^{1}H NMR spectra on a Hitachi NMR-1200 (60 MHz) using TMS as an internal standard.

Preparation of N-aroylamino-(2'-chloro-7'-methoxy-quinolin-3'-yl)-azomethines (IIIa-o) was carried out by refluxing a mixture of p-chloro benzoic acid (1.56, 0.01 mol) and thionyl chloride (5 ml) for 6 h. Excess of thionyl chloride was removed by distillation. The acid chloride obtained was cooled to 0° and N-amino-2-chloro-7- methoxy quinolin-3-yl-azomethines (2.32, 0.01 mol) in chloroform was added. The reaction mixture was refluxed for 5 hr in presence of pyridine. The product was isolated and crystallised from DMF. IIIe Yield 68%, m.p. 182-85°. Anal. calcd. for $C_{18}H_{13}O_2N_3Cl_2$, C, 57.75; H, 3.47; N, 7.48%. Found, C, 57.78; H, 3.45; N, 7.38%. TLC: ethylacetate : hexane (5:5). R_f (0.38) cm IR (υ max): 1657 (C=O), 1621 (C=C), 745 (C-Cl str.) in cm^{-1}. Similarly other aromatic acid chlorides are condensed. The physical constants along with NMR spectral data are given in Table 1.

Preparation of N-(2'-Phenyl-4'-arylidene-5'-oxo-imidazolin-1'-yl)-2-chloro-7-methoxy-quinolin-3-yl-azomethine (IVa-o) was brought about by refluxing a mixture of N-amino-2-chloro-7-methoxy-quinolin-3-yl-azomethine (2.35, 0.01 mol) and 4-arylidene-2-phenyl-5-oxazolinone[11] (0.02 mol) in 20 ml of dry pyridine for 6-8 h. The excess of solvent was removed under reduced pressure and the reaction mixture was poured into crushed ice. The product was isolated and crystallised from ethanol and DMF. IVa, yield 68%, m.p. 195-98°. Anal. calcd. for $C_{27}H_{19}O_2N_4Cl$ C, 70.97; H, 4.16; N, 12.26%. Found C, 70.90; H, 4.18; N, 12.15%. TLC Solvent System: Acetone: Benzene (4:6). R_f (0.63) IR (υ max): 1673 (C=O), 1617 (C=C), 732 (C-Cl str.). Similarly other azlactones were condensed. The physical constants along with NMR spectral data are given in Table 1.

The antimicrobial activity was assayed by using cup-plate method[12] by measuring the inhibition zones in mm. All the compounds were screened *in vitro* for antimicrobial activity against a variety of bacterial strains such as *Bacillus megaterium, Escherichia coli, Staphylococcus aureus, Sal-*

*For correspondence

TABLE 1: PHYSICAL CONSTANTS AND SPECTRAL DATA OF THE COMPOUNDS IIIa-o AND IVa-o.

Compd. No.	R	M.P. (0)	Rf value	X	-OCH_3	Ar-H + =CH	-NH
IIIa	C_6H_5-	175-77	0.46	-	4.05(3H,s)	7.4 to 9.2(m,10H)	9.3(s,H)
IIIa	3-NH_2-C_6H_4-	175-77	0.37	-	4.01(3H,s)	7.4 to 9.2(m, 9H)	9.28(s,H)
IIIc	2-Cl-C_6H_4-	215-18	0.46	-	4.07(3H,s)	7.5 to 9.25(m, 9H)	9.3(s,H)
IIId	3-Cl-C_6H_4-	170-73	0.67	-	4.05(3H,s)	7.4 to 9.2(m, 9H)	9.25(s,H)
IIIe	4-Cl-C_6H_4-	182-85	0.38	-	4.01(3H,s)	7.0 to 8.2(m, 9H)	9.2(s,H)
IIIf	2,4-$(OH)_2$-C_6H_3-	>275-77	0.48	-	4.03(3H,s)	7.5 to 9.3(m, 8H)	9.32(s,H)
IIIg	2-OH-C_6H_4-	180-83	0.37	-	4.01(3H,s)	7.5 to 9.0(m, 9H)	9.2(s,H)
IIIh	4-OH-C_6H_4-	225-27	0.45	-	4.01(3H,s)	7.5 to 9.1(m, 9H)	9.23(s,H)
IIIi	2-OCH_3-C_6H_4-	217-19	0.64	-	4.01(3H,s)	7.4 to 9.2(m, 9H)	9.25(s,H)
IIIj	3-OCH_3-C_6H_4-	220-23	0.46	-	4.01(3H,s)	7.5 to 9.2(m, 9H)	9.25(s,H)
IIIk	4-CH_3-C_6H_4-	125-27	0.58	2.5(3H,s)	4.01(3H,s)	7.5 to 9.2(m, 9H)	9.25(s,H)
IIIl	2-C_5H_4N-	158-60	0.35	-	4.06(3H,s)	7.5 to 9.1(m, 9H+CH=CH)	9.2(s,H)
IIIm	3-C_5H_4N-	225-27	0.45	-	4.0(3H,s)	7.9 to 9.1(m, 9H)	9.25(s,H)
IIIn	α-Ch=CH-C_6H_4-	99-102	0.40	-	4.0(3H,s)	7.5 to 9.1(m, 9H)	9.2(s,H)
IIIo	3,4,5-$(OH)_3$-C_6H_2-	140-43	0.37	-	4.01(3H,s)	7.5 to 9.1(m, 7H)	9.21(s,H)
IVa	C_6H_5-	195-97	0.63	-	4.01(3H,s)	7.02 to 9.2 (m, 15H)	
IVb	3-Br-C_6H_4-	208-10	0.73	-	4.01(3H,s)	7.02 to 9.2 (m, 14H)	
IVc	3-Cl-C_6H_4-	120-23	0.68	-	4.01(3H,s)	7.1 to 9.1(m, 14H)	
IVd	4-Cl-C_6H_4-	194-97	0.65	-	4.01(3H,s)	7.1 to 9.1(m, 14H)	
IVe	2,4-$(Cl)_2$-C_6H_3-	182-85	0.64	-	3.99(3H,s)	7.36 to 9.3(m, 13H)	
IVf	N,N-$(CH_3)_2$-C_6H_4-	213-15	0.55	3.8(s,6H)	4.0(3H,s)	7.05 to 9.2(m, 14H)	
IVg	2-C_4H_3O-	188-91	0.72	-	4.09(3H,s)	6.5 to 8.9(m, 13H)	
IVh	3-OH-4-OCH_3-C_6H_3-	170-73	0.66	-	4.0(3H,s)	7.1 to 9.06(m, 14H)	
IVi	2-OH-C_6H_4-	214-17	0.56	-	3.99(3H,s)	7.3 to 9.3(m, 14H)	
IVj	4-OH-C_6H_4-	220-23	0.63	-	4.0(6H,s)	7.2 to 9.6(m, 13H)	
IVk	2-OCH_3-C_6H_4-	212-15	0.64	-	4.01(6H,s)	7.5 to 9.6(m, 14H)	
IVl	4-OCH_3-C_6H_4-	165-67	0.63	-	4.09(6H,s)	7.6 to 9.24(m, 14H)	
IVm	4-SCH_3-C_6H_4-	220-23	0.60	2.5(s, 3H)	4.0(3H,s)	7.5 to 9.3(m, 14H)	
IVn	2-NO_2-C_6H_4-	150-53	0.81	-	4.0(3H,s)	7.2 to 9.4(m, 14H)	
IVo	4-NO_2-C_6H_4-	180-83	0.70	-	3.9(3H,s)	7.2 to 9.2(m, 14H)	

TABLE 2: ANTIMICROBIAL ACTIVITY OF THE COMPOUNDS IIIa-o, IVa-o.

Compd. No.	R	Antimicrobial activitiy Zones of inhibition (mm)			Antifungal activity zone of inhibition (mm)	
		B. megaterium	*S. typhosa*	*S. aureus*	*E. coli*	*A. niger*
IIIa	C_6H_5-	14	9	13	20	18
IIIb	3-NH_2-C_6H_4-	16	10	20	21	15
IIIc	2-Cl-C_6H_4-	14	9	13	22	19
IIId	3-Cl-C_6H_4-	15	10	14	22	17
IIIe	4-Cl-C_6H_4-	16	9	12	17	20
IIIf	2,4-$(OH)_2$-C_6H_3-	14	13	15	18	12
IIIg	2-OH-C_6H_4-	14	10	17	17	10
IIIh	4-OH-C_6H_4-	12	11	13	15	19
IIIi	2-OCH_3-C_6H_4-	16	12	12	18	15
IIIj	3-OCH_3-C_6H_4-	16	9	13	15	15
IIIk	4-CH_3-C_6H_4-	16	10	13	19	19
IIIl	2-C_5-H_4N-	14	10	16	12	17
IIIm	3-C_5H_4N-	12	9	14	15	19
IIIn	α-Ch=CH-C_6H_4-	15	12	15	13	16
IIIo	3,4,5-$(OH)_3$-C_6H_2-	14	10	18	15	20
IVa	C_6H_5-	15	11	18	19	20
IVb	3-Br-C_6H_4-	13	10	22	20	19
IVc	3-Cl-C_6H_4-	17	12	22	23	16
IVd	4-Cl-C_6H_4-	11	10	24	24	15
IVe	2,4-$(Cl)_2$-C_6H_3-	13	12	20	19	20
IVf	N,N-$(CH_3)_2$-C_6H_4-	15	11	16	22	15
IVg	2-C_4-H_3O-	14	11	14	19	18
IVh	3-OH-4-OCH_3-C_6H_3-	16	11	18	20	22
IVi	2-OH-C_6H_4-	15	9	16	21	20
IVj	4-OH-C_6H_4-	15	14	15	18	15
IVk	2-OCH_3-C_6H_4-	14	10	17	20	12
IVl	4-OCH_3-C_6H_4-	13	10	17	20	15
IVm	4-SCH_3-C_6H_4-	15	12	16	17	17
IVn	2-NO_2-C_6H_4-	16	13	19	22	19
IVo	4-NO_2-C_6H_4-	18	12	16	22	18

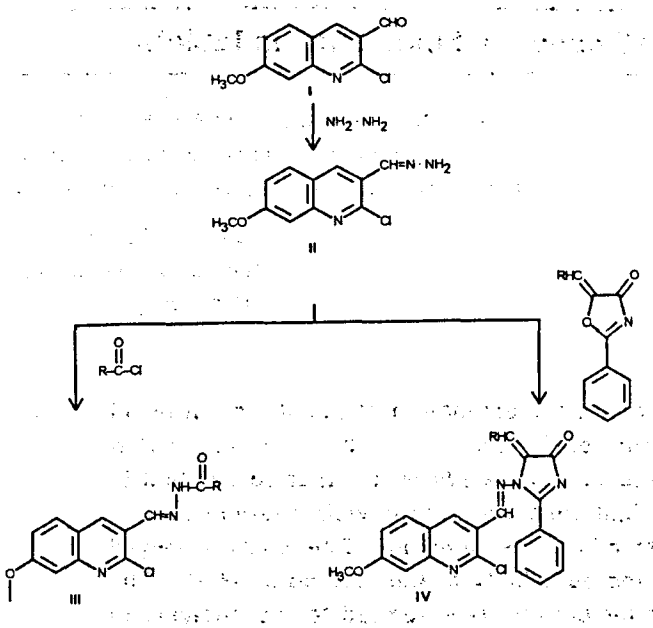

Fig. 1: Synthesis of compound IIIa-o and IVa-o.

monella typhosa and fungi such as *Aspergillus niger* at a concentration of 40 µg. Known antibiotics like chloramphenicol, ampicillin, penicillin and greseofulvin were used for comparison purpose.

All compounds reported in Table 2 were tested *in vitro* for antimicrobial activity against various microbes. Under identical conditions, the reference antibiotics showed the following zones of inhibition ampicillin,15-28 mm, chloramphenicol,12-22 mm, penicillin,15-23 mm against bacterial strains and griseofulvin showed zone of inhibition of 20 mm against *Aspergillus niger.* It can be concluded from Table 2, that compounds IIIb, IIIe, IIIi, IIIj, IIIk, IVa, IVc, IVi, IVj, IVm and IVo were found active against *Bacillus megaterium.* The compounds IIIb, IIIg, IIIo, IVa, IVb, IVc, IVd and IVn exhibited siginificant activity against *Staphylococaus aureus.* The compounds IIIa, IIIb, IIIc, IIId, IIIk, IVb, IVc, IVd, IVh and IVo showed maximum activity against *Escherichia coli.* No compounds are active against *Salmonella typhosa,* while compound IIIc, IIIe, IIIg, IIIk, IIIm, IIIo, IVa, IVe, IVh and IVi exhibited highest activity against *Aspergillus niger.*

REFERENCES

1. Oza, H., Joshi, D. and Parekh, H., **Heterocycl. Commun.,** 1997, 9, 563.
2. Joshi, N., Korgaokar, S. and Parekh, H., **Indian J. Heterocycl. Chem.,** 1996, 5, 241.
3. Shah, B.R. and Desai, N.C., **Indian J. Chem.,** 1995, 34B, 201.
4. Upadhyay, P.S., Joshi, S.N., Baxi, A.J. and Parikh, A.R., **Indian J. Heterocycl Chem.,** 1991, 1, 71.
5. Trivedi, B. and Shah, V.H., **J. Indian Chem. Soc.,** 1993, 70, 645.
6. Vishnu, K. and Dingra, V., **Indian J. Heterocycl. Chem.,** 1994, 4, 69.
7. Misra, V.S., Gupta, P.N., Pandey, R.N. and Gupta, G.P., **Chem. Abstr.,** 1981, 94, 1032839.
8. Kumar, P., Dhawan, K. N., Urat, S., Bhargawa, K. P. and Kishore, K., **Arch. Pharm.,** 1983, 316, 759.
9. Gujral, M.L., Saxena, P.N. and Tiwari, R.S., **Indian J. Med. Res.,** 1955, 43, 637.
10. Meth-Cohn, O., Tarnowski, B., Narine, B., Hayes, R., Kezad, A., Rhouti, S. and Robinson, A., **Chem. Abstr.,** 1982, 96, 19930g.
11. Vogel, A.I., In; Practical Chemistry, English Language Book Society a longmann group Ltd., 1971, 909.
12. Barry, A.L., **Biol. Abstr.,** 1977, 64, 25183.