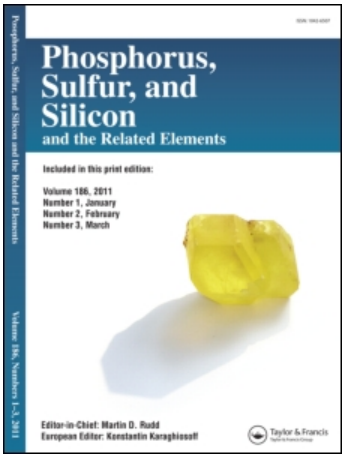

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW 8-HYDROXYQUINOLINE SULPHONAMIDE DERIVATIVES

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW 8-HYDROXYQUINOLINE SULPHONAMIDE DERIVATIVES

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Some new derivatives containing both 8-hydroxyquinoline and sulphonylamino β-lactams and thiazolidinones have been prepared. These compounds were synthesized from the corresponding 8-hydroxyquinoline sulphonylhydrazide (1) by converting it to hydrazones (2). The latter hydrazones (2) were easily transformed to β-lactams (3) and thiazolidinones (4) by cyclocondensation reaction with chloroacetyl chloride and/or mercaptoacetic acid. Some metal chelates with Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Cd^{2+} have been prepared for some of the compounds and screened in vitro for their biological activity.

INTRODUCTION

A literature survey has revealed that the chemistry of quinoline incorporated with *p*-toluene sulphonamide have attracted special attention because of their therapeutic activity.[1,2] Chivers *et al.*[3] reported that, some quinoline-8-sulphonyl derivatives have been interesting as potential pesticides. Also, some of the known sulphonamides were found to be biologically versatile compounds of anticancer,[4] antimalaria,[5] antitubercular[6] and other diverse activities.[7,8] So, since the introduction of the sulpha drugs into clinical practice, a continuous problem has been the emergence of drug-resistant strains of bacteria. However, synthesis of new sulphonamides with a modified microbiological spectrum, is important to keep pace with the appearance of resistant bacterial strains.

RESULTS AND DISCUSSION

Recently, there is much growing interest in the chemistry and chemotherapy of the activity of some drugs when administer as metal complexes, more so their metal chelates,[9,10] in the therapy of numerous bacterial infections. A similar indication was also found in a paper of Tiwari *et al.*[11] Thus, the present investigation was carried out as an extension of studies[12] on the chemistry of 8-hydroxyquinoline sulphonamides. The prepared compounds possess both the features of 8-hydroxyquinoline and aminosulphonamide moieties. So, synthesis of the hitherto unreported compounds involves the preparation of 8-

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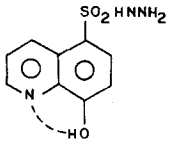
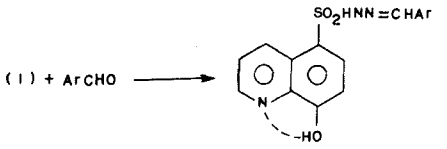
hydroxyquinoline sulphonic acid which is converted to sulphonylchloride. The latter reacted easily with hydrazine giving a quantitative yield of the hydrazide (HQSH) (1).



(1)

A series of sulphonylhydrazones (2) has prepared by condensation of (1) with some aromatic aldehydes. The reaction was conducted in ethanol in the presence of a catalytic amount of base.

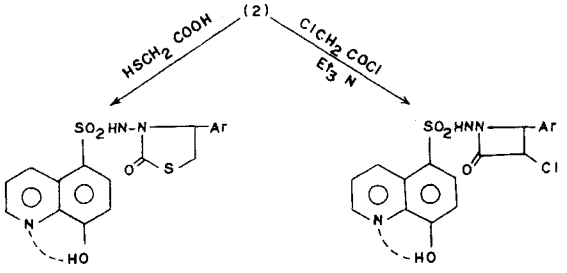


(2)

Ar, $a = C_6H_5$— $d = C_6H_4$—OH (p)
$b = C_6H_4$—OCH_3 $e = C_6H_4$—NO_2 (p)
$c = C_6H_4$—Cl (p)

The structure of compounds (2) was confirmed on the basis of the correct microanalytical data and IR-spectroscopic evidence of (2) showed bands at 1620–1600 cm^{-1} ν(C=N); 3100 cm^{-1} ν(NH); 1370 cm^{-1} ν(—SO_2NH) and a broad distinct band at 3140–3050 cm^{-1} due to hydrogen bonding.[13] On this basis the intramolecular hydrogen bonded chelate structure (—O—H···N—) has been proposed for the compounds (1)–(4).

Cyclocondensation reactions of the hydrazones (2) with chloroacetyl chloride and/or mercaptoacetic acid were achieved according to literature methods.[14,15] The products are the cyclic β-lactams (3) and thiazolidinones (4).

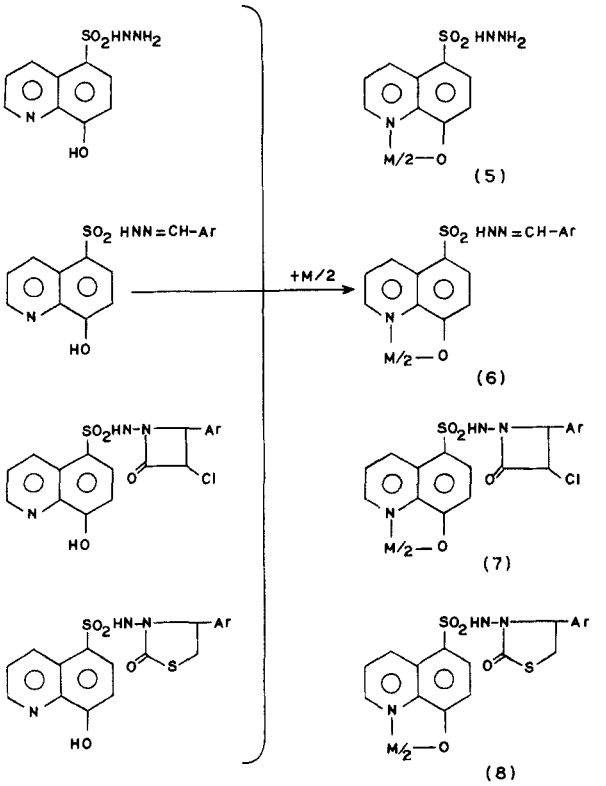


(4) (3)

The structure of the compounds was deduced from the correct analytical data, and spectroscopic evidence. Besides the principal bands described in case of compounds (2), there are bands at 1770–1750 cm^1 $\nu[\rangle C{=}O$ mono cyclic β-lactam for compounds (3)][16] and at 1700–1695 cm^{-1} $\nu[\rangle C{=}O$ cyclic thiazolidinones for compounds (4)].[16]

From the spectral analysis, it must be pointed out that, under the experimental condition the —OH group in compounds (3) did not undergo chloroacetylation. This may be due to the strong intramolecular hydrogen bonding.

Complexation of the ligands (1), (2), (3) and (4) was carried out by mixing a molar proportions of the ligands in alcohol with metal salts in distilled water at 50–60°C. The resulting precipitate of the chelates were digested on a water bath for 30 minutes giving (5), (6), (7) and (8).



The overall study and the analytical data given in Table I shows that all compounds form chelates of the type ML_2 where L = ligand. A critical examination of the IR spectra of ligands indicates the presence of bands at 3100 cm^{-1} and 3140–3050 cm^{-1}. Instead, these bands are located at range 3500–3300 cm^{-1} in the corresponding chelates. This is an indication of the involvement of —OH group of quinoline in chelate formation.[16,18] The bands of medium intensity around 1600 cm^{-1} in the spectra of ligands due to $\nu(\rangle C{=}N—)$ shift to lower values with weak intensity in the spectra of chelates. It is due to M←N bond formation. Other groups absorbs at almost the same frequency as in the ligands.

TABLE I

Physical and analytical data of Hydrazones (2), β-Lactams (3) and Thiazolidinones (4)

Compound	m.p. (°C)	Yield %	Formula	Calcd. C	H	Cl	S	Found C	H	Cl	S
2a	310 dec.	70	$C_{16}H_{13}N_3O_3S$	58.71	3.97	—	9.78	58.09	3.72	—	9.25
b	180-1	65	$C_{17}H_{15}N_3O_4S$	57.14	4.20	—	8.96	57.08	4.01	—	9.01
c	300 dec.	72	$C_{16}H_{12}ClN_3O_3S$	53.11	3.31	9.82	8.85	53.56	3.21	9.99	8.52
d	240-1	78	$C_{16}H_{13}N_3O_4S$	55.97	3.79	—	9.32	55.90	3.13	—	9.00
e	280 dec.	63	$C_{16}H_{12}N_4O_5S$	51.61	3.22	—	8.60	51.98	3.09	—	8.51
3a	88-9	40	$C_{18}H_{14}ClN_3O_4S$	53.53	3.46	8.79	7.93	53.92	3.31	8.09	7.81
b	140-1	30	$C_{19}H_{16}ClN_3O_5S$	52.59	3.69	8.18	7.38	52.09	4.01	8 51	7.08
c	210-1	35	$C_{18}H_{15}Cl_2N_3O_4S$	49.31	3.42	16.21	7.30	49.90	3.52	16.61	7.09
d	190-1	39	$C_{18}H_{14}ClN_3O_5S$	51.48	3.33	8.46	7.62	51.59	3.66	8.81	7.79
e	176-7	45	$C_{18}H_{13}ClN_4O_6S$	48.16	2.89	7.91	7.13	48.71	3.01	8.09	7.52
4a	170-1	50	$C_{18}H_{15}N_3O_4S_2$	53.86	3.74	—	15.96	53.99	3.91	—	16.02
b	220-2	55	$C_{19}H_{17}N_3O_5S$	52.90	3.94	—	14.84	53.01	4.12	—	15.09
c	310 dec.	60	$C_{18}H_{14}ClN_3O_4S_2$	49.59	3.21	8.15	14.69	50.12	3.51	8.71	15.00
d	298-9	40	$C_{18}H_{14}N_3O_5S_2$	51.92	3.36	—	15.38	52.01	3.49	—	15.41
e	295 dec.	45	$C_{18}H_{14}N_4O_6S_2$	48.43	3.13	—	14.34	48.34	3.09	—	14.49

EXPERIMENTAL

All melting points were determined on a kofler melting point apparatus and are uncorrected. The exact melting points of the chelates could not be determined but were more than 300°C. IR spectra were obtained using a Pye-Unicam SP-200 G spectrophotometer.

(a) *Preparation of 8-hydroxyquinoline sulphonylhydrazide* (**1**): This compound was prepared according to the literature method.[3]

(b) *Preparation of 8-hydroxyquinoline-5-arylidenesulphonamides* (**2a–e**): These compounds were prepared according to the literature method[3] cited for this type of condensation reaction.

(c) *Preparation of 3-chloro-4-substituted-1-(5-sulphonamide-8-hydroxyquinolinyl)azetidin-2-ones* (**3a–e**): These compounds were prepared according to the method of Bose *et al.*[14] for the β-lactam synthesis.

(d) *Preparation of 2-substituted-3-[5-sulphonamide-8-hydroxyquinolinyl] thiazolidin-4-ones* (**4a–c**): These compounds were prepared according to Surry *et al.*[15] for the thiazolidinone synthesis.

(e) *Complexes:* The ligands (0.1 M) in ethyl alcohol was treated with (0.1 M aqueous solution of the metal salt at 50–60°C. The resulting precipitate of the chelate were digested on a water bath for 30 min., filtered and washed with hot distilled water and dried. The physical and analytical data are depicted in Table II.

BIOLOGICAL SCREENING

The biological properties of ligands and their metal chelates were studied by the usual cup-plate agar diffusion technique[17] against, Staphloccus aureus, Micrococcus luteus, serratia sp., Asperigillus flavus, Mucor, Pusillus and Trichophyton longifusus. 1.0% (W/V) solutions of the compounds were prepared. The starting material HQSH (1) showed no antimicrobial activity against all the bacteria and fungi used. Transformation of (1) to (2), (3) and (4) showed a scattered activity against some of the bacteria and fungi used. However, transformation of ligands (1), (2), (3) and (4) to chelates (5), (6), (7) and (8) exerted predominant activity against the majority of the bacteria and fungi used. In spite of the predominant potency of the chelates, the more potent complexes are that with Ni^{2+} and

TABLE II

Biological screening of compounds 1–4 and their metal complexes 5–8 (inhibition zones in mm)

Compound	Composition*	Staphylococcus aureus	Micrococcus lueus	Serratia sp.	Asperigillus flavus	Mucro-pusillus	Trichophyton longifusus
1	(HQSH)	−ve	−ve	−ve	−ve	−ve	−ve
5a	$(HQSH)_2FeNO_3$	15	14	17	−ve	−ve	−ve
b	$(HQSH)_2Co$	−ve	−ve	15	−ve	−ve	−ve
c	$(HQSH)_2Ni$	−ve	20	22	18	25	15
d	$(HQSH)_2Cu$	15	16	18	−ve	−ve	−ve
e	$(HQSH)_2Cd$	30	20	27	30	40	42
2a		−ve	−ve	−ve	−ve	10	−ve
b		−ve	−ve	13	−ve	−ve	−ve
c		−ve	15	−ve	20	−ve	−ve
d		15	−ve	−ve	−ve	15	−ve
e		20	−ve	−ve	−ve	−ve	−ve
6a	$(C_{16}H_{13}N_3O_3S)_2FeNO_3$	15	−ve	−ve	10	8	10
b	$(C_{17}H_{15}N_3O_4S)_2Co$	−ve	−ve	10	−ve	15	−ve
c	$(C_{16}H_{12}ClN_3O_3S)_2Ni$	15	25	15	30	−ve	10
d	$(C_{16}H_{13}N_3O_4S)_2Cu$	−ve	13	−ve	15	−ve	13
e	$(C_{16}H_{12}N_4O_5S)_2Cd$	20	20	10	25	−ve	15
3a		−ve	−ve	−ve	−ve	−ve	−ve
b		−ve	−ve	−ve	−ve	15	−ve
c		−ve	16	−ve	20	−ve	−ve
d		−ve	−ve	17	−ve	−ve	−ve
e		−ve	−ve	−ve	−ve	−ve	15

(*Continued*)

TABLE II. (Cont.)

Compound	Composition*	Staphylococcus aureus	Micrococcus lueus	Serratia sp.	Asperigillus flavus	Mucro-pusillus	Trichophyton longifusus
7a	$(C_{18}H_{14}ClN_3O_4S)_2FeNO_3$	15	20	−ve	−ve	20	24
b	$(C_{19}H_{16}ClN_3O_5S)_2Co$	−ve	−ve	15	−ve	−ve	8
c	$(C_{18}H_{15}Cl_2N_3O_4S)_2Ni$	20	24	33	25	30	25
d	$(C_{18}H_{14}ClN_3O_5S)_2Cu$	−ve	15	−ve	−ve	16	−ve
e	$(C_{18}H_{13}ClN_4O_6S)_2Cd$	35	40	33	36	14	45
4a		−ve	−ve	−ve	15	−ve	−ve
b		−ve	15	18	−ve	20	−ve
c		15	−ve	−ve	−ve	−ve	15
d		−ve	−ve	−ve	−ve	−ve	18
e		20	−ve	−ve	−ve	18	−ve
8a	$(C_{18}H_{15}N_3O_4S_2)_2FeNO_3$	−ve	10	−ve	15	−ve	10
b	$(C_{19}H_{17}N_3O_5S_2)_2Co$	−ve	15	23	20	15	−ve
c	$(C_{18}H_{14}ClN_3O_4S_2)_2Ni$	15	20	−ve	18	20	30
d	$(C_{18}H_{14}N_3O_5S_2)_2Cu$	10	15	13	−ve	30	20
e	$(C_{18}H_{14}N_4O_6S_2)_2Cd$	30	13	15	−ve	20	20

* All the complexes gave correct analysis for S, N and metal.

Cd^{2+}. We can thus say that antimicrobial activity of the hitherto prepared compounds in this investigation is enhanced on complexation with metals.

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