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Studies on Metal Chelates of 8-Hydroxy-5-quinolyl Ketone Oxime, *O*-Carbamoyl and *O*-Thiocarbamoyl Derivatives as Bactericides

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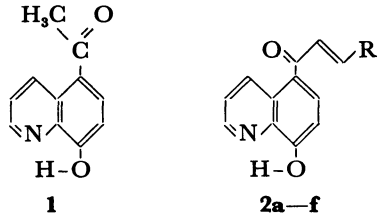
The reaction of 5-acetyl-8-quinolinol (**1**) and corresponding chalcone derivatives **2a—f** with hydroxylamine hydrochloride in boiling pyridine gave the corresponding oximes **3** and **4a—f** respectively in almost quantitative yields. Further interaction of **3** and **4a—e** with phenyl isocyanate and/or thiocyanate the corresponding carbamate and/or thiocarbamate (**5a,b**) and (**6a—e, 7a—e**) were achieved. Metal chelates of **1, 3,** and **4e,f** with bivalent metal cations like Fe(II), Cu(II), and Zn(II) have been synthesized and characterized by elemental and IR-spectral analysis. The synthesized compounds were biologically screened to study the structure activity relationship, (SAR) and the effect of complexation and type of metal cation on the potency of the more biologically active compounds.

The biological activity of oximes, carbamates, and thiocarbamates is of interest. Acetophenone *O*-methylcarbamoyl oxime and esters of dithiocarbamic acids, have clearly been established as insecticides,[1] leading anthelmintic[2-4] and herbicidal[5] agents. It has been observed recently that some drugs have increased activity when administered as metal complexes more so their metal chelates.[6,7]

In this work SAR has been done to evaluate the bactericidal activity of the oxime, carbamate, thiocarbamate derived from 5-acetyl-8-quinolinol and/or its chalcone derivatives. Effect of complexation and type of metal cation on the potency of the more effective compounds was considered.

Results and Discussion

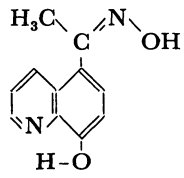
Interaction of **1** and the chalones **2a—f** with hydroxylamine hydrochloride gave the corresponding oximes **3** and **4a—f** respectively.



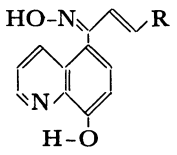
1

2a—f

a, R = C_6H_5
b, R = *p*-$CH_3OC_6H_4$
c, R = *p*-ClC_6H_4
d, R = 
e, R = *n*-C_3H_7
f, R = *n*-C_6H_{13}



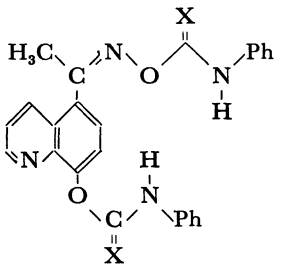
3



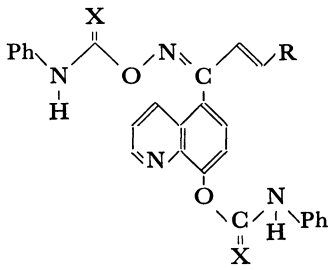
4a—f

The IR spectra of compound **3** and **4a—f** showed a broad band at 3200—2800 cm^{-1} characteristic to the oxime hydroxyl group in addition to ν C=N at 1600 cm^{-1} with the lack of ν C=O group. The NMR (DMSO) of compound **3** revealed signals at δ 2.3 (s, 1H, OH), 2.8—3.2 (s, 3H, CH_3), and 6.75—7.4 (m, 5H, aromatic), the proton of Q-OH was appeared at δ 7.2 confusing with the aromatic protons.

Phenyl isocyanate and phenyl isothiocyanate react readily with the oximes **3** and **4a—e** in boiling dry benzene in presence of triethylamine to afford the corresponding carbamates and thiocarbamates **5a,b**; **6a—e** and **7a—e** in good yields.



5a, X=O
b, X=S

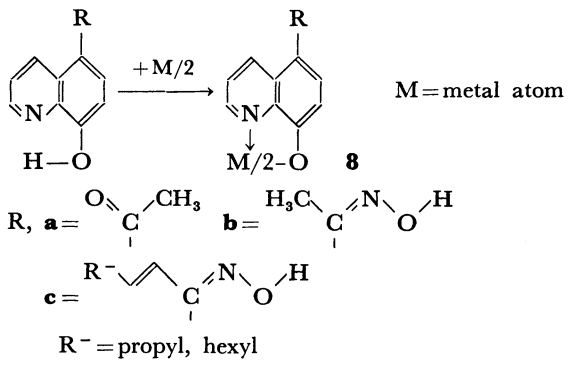


6a—e, X=O
7a—e, X=S

The structure of the carbamates **6a—e** and thiocarbamates **7a—e** was assigned on both analytical and spectral data. The IR spectra of carbamates showed the lack of (ν OH) and presence of (ν NH) as a single band in the 3200 cm^{-1} region and (ν C=O) in the region 1700 cm^{-1}. The NMR (DMSO) spectra of **5b** showed signals at δ 3.25 (s, 3H, CH_3), 7.5—8.5 (m, 10H, aromatics), and 8.7 (s, 1H, NH); **6b** δ 2.8 (s, 3H, CH_3), 6.5—7.0 (m, 15H, aromatics), and 8.2 (s, 1H, NH).

Interaction of compounds **1, 3, 4e,f** with the appropriate amounts of metal salt solution gave the corresponding complex. The IR spectra showed a broad distinct band at 3200—3100 cm^{-1} in the ligands were found due to hydrogen bonding.[8,9] On this basis the intramolecular hydrogen bonded chelate structures (-O-H-N-) have been proposed for the ligands. A critical examination of the spectra of metal chelates indicates that the bands at 3100 cm^{-1} present in the ligands is shifted to higher values (3600—3300 cm^{-1}) in the chelates. Thus on metal chelate formation, the bands between 3600—3300 cm^{-1} which appear in all chelates are not present in the original ligands.[10,11] The disappearance of hydrogen-bonded -OH in the

ligands and its reappearance in the metal chelates are suggestive of O–M–N bond formation, where M is a metal atom. The bands of medium intensity around 1600 cm^{-1} in the spectra of ligands due to (ν C=N–) is shifted to lower values with weak intensity in the spectra of chelates. It is due to M←N bond formation. The bands between 1600—1490 cm^{-1} are due to aromatic rings. The overall study and the analytical data show that the ligands form chelates of the type ML_2 where L=ligand. The reaction may be written as follows:



The structure of the metal chelate is in good agreement with previous work.[12,13]

Screening for Antimicrobial Activity: The bacteriostatic properties of the oxime, carbamates, and metal chelate complexes were studied by the usual cupplate agar diffusion technique[12] against some selected Gram positive: *Bacillus cereus, Staphylococcus aureus,* and *Micrococcus luteus*; and Gram negative bacteria: *Serratia* sp., *E. coli,* and *Pseudomonas aeruginosa.*

A final concentration of 100 ppm of the tested compounds in ethylene glycol was used.

5-[1-(Hydroxyimino)ethyl]-8-quinolinol (**3**) is effective only against the tested Gram positive bacteria. Substituting the methyl group by a styryl Ph–CH=CH (**4a**) abolishes its potency, while further substitution by an electron releasing or activating group at the phenyl neucleus (**4b,c**) restore this activity towards *Bacillus cereus* and *Staph. aureus.* The same observation was noticed also on using furfurylidene instead of benzylidene Ph–CH= derivative (**4d**). On the other hand, substitution by a 1-pentenyl or 1-octenyl group (**4e** and **f**) enhances similarly the bactericidal activity and is also extends towards other tested *Gram negative* bacteria.

Converting the oxime **3** to its carbamate **5a** or thiocarbamate derivative **5b** removes its activity while the carbamate or thiocarbamate **6** or **7** have no effect on *micrococcus luteus,* and their activity either abolishes or have no changes on the other *Gram positive* bacterial species. It is worthy to mention that the thiocarbamate is less effective than the carbamate derivative (cf. **6e**, **7e**).

Metal chelation of the more effective bactericidal compounds **3**, **4e,f** with bivalent metal cations e.g. Cu^{2+}, Zn^{2+}, Fe^{2+} has different effect depending on the type of substituent at the 5-position within 8-quinolinol nucleus and the type of metal cation. Complexing with zinc increases largely its potency towards both *Gram positive* and *Gram negative* bacteria and is not significantly affected by the type of substitution at the 5-position of 8-quinolinol while complexing with Cu has different effect depending on the type of 5-substituent. The larger effect was noticed on increasing the alkyl side chain length within the 5-substituent relative to unsubstituted 5-acetyloxime, cf. $[\mathbf{3}]_2Cu$, $[\mathbf{4e}]_2Cu$, and $[\mathbf{4f}]_2Cu$; and 5-[1-(hydroxyimino)ethyl] complex $[\mathbf{3}]_2Cu$ is less effective than its precursor 5-acetyl $[\mathbf{1}]_2Cu$. On the other hand complexing with Fe^{3+} has different effect. It decreases sharply or abolishes the potency after complexation especially on enlarging alkyl side chain with the 5-substituent, (cf. $[\mathbf{4e}]_2Fe$, $[\mathbf{4f}]_2Fe$).

Conclusion

5-Acetyl-8-quinolinol is more effective as bactericides than its oxime, while the chalcone oxime derivatives **4a—f** have variable effect depending on the type of the substituent R. Conversion of the oxime to carbamate or thiocarbamate decreases or abolishes this activity and the carbamates are more effective than corresponding thiocarbamates.

On complexation of the ligands it increases and extends the activity towards *Gram negative* bacteria depending on the type of metal cation used. The more effective complexes are those containing Zn metal independing on the 5-substituent which is not the case of Cu.

Experimental

All the melting points are uncorrected. IR spectra were recorded on a Perkin-Elemer infrared 137B spectrophotometer. NMR spectra in DMSO were measured on a Varian, 90 MHz. The time allowed for the completion of the reaction and the purity of the prepared compounds were monitored by TLC.

Reaction of 5-Acetyl-8-quinolinol (1) and Its Chalcone Derivatives 2a—f with Hydroxylamine Hydrochloride: A solution of 5-acetyl-8-quinolinol (**1**) and/or corresponding chalcones **2a—f** (0.01 mol) and hydroxylamine hydrochloride (0.015 mol) in dry pyridine[14] (20 ml) was heated under reflux for 3 h. The reaction mixture was poured onto crushed ice and the precipitated solid was filtered off and crystallized from the suitable solvent to give the corresponding oximes **3** and **4a—f** respectively. The results are given in Table 1.

Reaction of Oximes 3 and 4a—f with Phenyl Isocyanate and Phenyl Isothiocyanate: A solution of the oximes **3**, **4a—e** (0.01 mol), phenyl isocyanate or phenyl isothiocyanate (0.01 mol) in dry benzene 25 ml containing triethylamine (0.5 ml) was heated under reflux for 4 h. The

Table 1a. Physical and Analytical Data of Oximes **3**, **4a—p**, *O*-Phenylcarbamoyl Oximes **5a**, **6a—e**, and *O*-Phenylthiocarbamoyl Oximes **5b**, **7a—e**

Compd	Yield	Mp θ_m/°C	Molecular formula	Analysis (%)[a] Found N	Found Cl	Found S	Calcd N	Calcd Cl	Calcd S
3	96	193	$C_{11}H_{10}O_2N_2$	14.05			13.86		
4a	75	240	$C_{18}H_{14}O_2N_2$	9.99			9.65		
b	85	330	$C_{19}H_{16}O_3N_2$	8.90			8.75		
c	70	310	$C_{18}H_{13}O_2N_2Cl$	8.88	10.69		8.63	10.94	
d	72	340(decomp)	$C_{16}H_{12}O_3N_2$	10.29			10.00		
e	65	310—312	$C_{15}H_{16}O_2N_2$	11.20			10.94		
f	60	327—329	$C_{18}H_{22}O_2N_2$	9.72			9.40		
5a	75	225	$C_{25}H_{20}O_4N_4$	12.95			12.73		
b	71	235	$C_{25}H_{20}O_2N_4S_2$	12.00		13.35	11.86		13.56
6a	65	328—330	$C_{32}H_{24}O_4N_4$	10.88			10.61		
b	68	260—262	$C_{33}H_{26}O_5N_4$	10.30			10.03		
c	53	235—237	$C_{32}H_{23}O_4N_4Cl$	10.12	6.52		9.95	6.31	
d	60	288—290	$C_{30}H_{22}O_5N_4$	11.08			10.81		
e	46	250(decomp)	$C_{29}H_{26}O_4N_4$	11.65			11.34		
7a	62	293—295	$C_{32}H_{24}O_2N_4S_2$	10.18	11.68		10.00		11.43
b	64	>340	$C_{33}H_{26}O_3N_4S_2$	9.62	11.03		9.49		10.85
c	49	>340	$C_{32}H_{23}O_2N_4S_2Cl$	9.60	10.98		9.42		10.76
d	56	248—250	$C_{30}H_{22}O_3S_2$	10.50	11.83		10.18		11.64
e	43	340	$C_{32}N_{32}O_2N_4$	9.97	11.49		9.86		11.27

a) All C, H analysis gave satisfactory results.

Table 1b. Physical and Analytical Data of Metal Chelate Complexes of **1**, **3**, **4e**, and **6f**

Compd	Mp θ_m/°C	Molecular formula	Analysis (%)[a] Found/Calcd N	Found/Calcd Metal	UV spectra[b] λ_{max}/nm
1$_2$Cu	335—337 (decomp)	$[C_{11}H_8O_2N]_2Cu$	6.55 6.43	14.76 14.59	255, 283, 378
1$_2$Zn	350	$[C_{11}H_8O_2N]_2Zn$	6.63 6.40	15.19 14.95	258, 288, 385
1$_2$Fe	350	$[C_{11}H_8O_2N]_2Fe$	6.82 6.50	13.29 13.05	247, 278, 368, 430(sh)
3$_2$Cu	350	$[C_{11}H_9O_2N_2]_2Cu$	12.28 12.03	13.90 13.65	250(sh), 310(sh), 358
3$_2$Zn	296—298	$[C_{11}H_9O_2N_2]_2Zn$	12.10 11.98	14.15 13.99	260, 338, 383
3$_2$Fe	>350	$[C_{11}H_9O_2N_2]_2Fe$	12.50 12.23	12.45 12.20	250, 290(sh), 350
4e$_2$Cu	>350	$[C_{15}H_{15}O_2N_2]_2Cu$	9.99 9.76	11.25 11.08	240, 280(sh), 370(sh)
4e$_2$Zn	>350	$[C_{15}H_{15}O_2N_2]_2Zn$	9.90 9.73	11.53 11.36	260, 284(sh), 350
4e$_2$Fe	>350	$[C_{15}H_{15}O_2N_2]_2Fe$	10.05 9.89	10.10 9.87	
6f$_2$Cu	>350	$[C_{18}H_{21}O_2N_2]_2Cu$	8.88 8.51	9.95 9.66	258 285, 330, 390
4f$_2$Zn	>350	$[C_{18}H_{21}O_2N_2]_2Zn$	8.70 8.49	10.15 9.91	255, 283, 355, 400(sh)
4f$_2$Fe	>350	$[C_{18}H_{21}O_2N_2]_2Fe$	8.85 8.62	8.80 8.59	

a) All C, H analysis gave satisfactory results. b) Saturated solution in methanol (1:5 dilution).

separated crystalline solid was filtered off, washed with ether and recrystallized from dioxane to give the corresponding carbamate or thiocarbamate derivatives **5a,b**; **6a—e** and **7a—e** respectively. The results are given in Table 1a.

Chelation of 1 and Oximes 3, 4e,f with Bivalent Metal Cation, e.g. Fe(II), Cu(II), and Zn(II): The complexes were prepared by dissolving the ligands **1**, **3**, and **4e,f** in warm aqueous ethanol and treated with an appropriate amount of

Table 2. Bactericidal Screening of Compounds **3**—**7** and Some of Their Complexes

Compd No.	Gram positive (inhibition zones in mm)			Gram negative (inhibition zones in mm)		
	Becillus cereus	*Staphylococcus aureus*	*Micrococcus luteus*	*Serratia* sp.	*E. coli*	*Pseudom. aeruginose*
3	10	10	10	—	—	—
4a	—	—	—	—	—	—
b	10	10	—	—	—	—
c	12	11	—	—	—	—
d	10	12	—	—	—	—
e	18	16	10	10	9	8
f	18	16	10	10	8	9
5a	—	—	—	—	—	—
b	—	—	—	—	—	—
6a	—	—	—	—	—	—
b	—	—	—	—	—	—
c	10	10	—	—	—	—
d	—	—	—	—	—	—
e	10	10	—	—	—	—
f	10	10	—	—	—	—
7a	—	—	—	—	—	—
b	—	—	—	—	—	—
c	10	10	—	—	—	—
d	10	12	—	—	—	—
e	—	—	—	—	—	—
f	—	—	—	—	—	—
[**1**]$_2$Cu	15	18	16	7	6	7
[**1**]$_2$Zn	25	25	18	20	25	10
[**1**]$_2$Fe	12	14	12	13	8	12
[**3**]$_2$Cu	7	—	—	—	—	—
[**3**]$_2$Zn	20	22	18	20	15	10
[**3**]$_2$Fe	10	8	—	8	—	—
[**4e**]$_2$Cu	12	15	14	10	8	7
[**4e**]$_2$Zn	22	22	20	20	22	10
[**4e**]$_2$Fe	8	10	—	10	—	—
[**4f**]$_2$Cu	37	38	22	10	11	—
[**4f**]$_2$Zn	22	22	18	15	20	10
[**4f**]$_2$Fe	8	7	—	7	—	—

metal salt solution in aqueous ethanol. The mixture was heated under reflux on a water bath for 1 h. The resulting precipitates of the complexes were filtered off, washed well with hot water and dried. The physical and analytical data are recorded in Table 1b.

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