SYNTHESIS AND BIOLOGICAL ACTIVITIES OF [6,8-DIBROMO-3-ARYL-3,4-DIHYDRO-4-OXO-2-QUINAZOLINYL]METHYL N-SUBSTITUTED DITHIOCARBAMATES

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ABSTRACT

Twentyfour new [6,8-dibromo-3-aryl-3,4-dihydro-4-oxo-2-quinazolinyl]methyl N-substituted dithiocarbamates have been synthesized from 6,8-dibromo-2-chloromethyl-3-aryl-4(3H)-quinazolinones and the ammonium salts of N-substituted dithiocarbamic acids obtained from different primary/secondary amines. These compounds have been screened for their antifungal and insecticidal activities and most of them have been found to be potential insecticides.

INTRODUCTION

QUINAZOLINONES have been reported to possess a wide range of biological activities such as antifungal[1], herbicidal[2] and insecticidal[3], Dithiocarbamates are also associated with antifungal[4] and insecticidal[5] actvities. Therefore in view of their importance and in continuation of our work on 4(3H)-quinazolinones[6-8], we report the synthesis, antifungal and insecticidal activities of some new [6,8-dibromo-3-aryl-3,4-dihydro-4-oxo-2-quinazolinyl]methyl N-substituted dithiocarbamates in this communication.

The present compounds were synthesized by the reaction of 6,8-dibromo-2-chloromethyl-3-aryl-4(3H)-quinazolinones with various ammonium salts of N-substituted dithiocarbamic acids. These compounds were screened for their antifungal and insecticidal activities.

MATERIALS AND METHODS

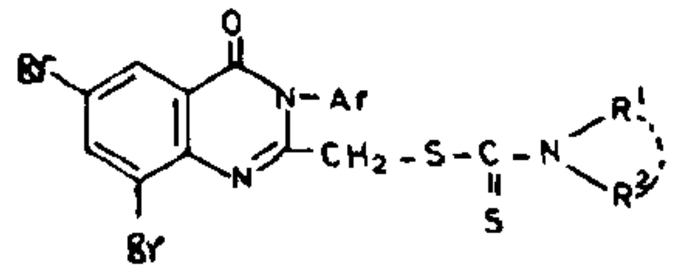
The purity of the compounds was checked by TLC. Melting points were determined in open capillaries using Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer infracord 283 spectrophotometer in nujol. The PMR spectra were recorded on Varian EM 360 60 MHz spectrophotometer using TMS as the internal reference.

The ammonium salts of N-substituted dithiocarbamic acids required were prepared from various primary/secondary amines adopting standard procedure[9].

6,8-Dibromo-2-chloromethyl-3(o-chlorophenyl)-4(3H)-quinazolinone.

A mixture of N-chloroacetyl-3,5-dibromoanthranilic acid (37.1 g; 0.1 mol), o-chloroaniline (12.7 g; 0.1 mol) and phosphorous trichloride (13.5 g; 0.1 mol) in toluene (150 ml) was refluxed at 130–140° for 3 hr. The cooled reaction mixture was decomposed with cold water and subsequently steam-distilled to remove toluene. The product was filtered, washed first with 10% sodium bicarbonate solution and then with cold water and recrystallized from benzene to get colourless needles (33.3 g; 72%), m.p. 145°. [Found: C, 38.75; H, 1.61; N, 5.95; $C_{15}H_8N_2OCl_2Br_2$ requires C, 38.96; H, 1.73; N, 6.06%]. IR: 1670 (O=C–N–), 1600 (C=N), and 1580 (aromatic C=C); PMR (in $CDCl_3$) δ 4.3 (*s*, 2H, $-CH_2-$); 7.52–7.80 (*m*, 5H, Ar-H) and 8.14 (*d*, 1H, Ar-C_5–H).

Similarly 6,8-dibromo-2-chloromethyl-3-(o-anisyl)-4(3H)-quinazolinone was prepared.



[6,8-Dibromo-3-(o-chlorophenyl)-3,4-dihydro-4-oxo-2-quinazolinyl]-methyl-piperidinedithiocarbamate (IX).

To a solution of 6,8-dibromo-2-chloromethyl-3-(o-chlorophenyl)-4(3H)-quinazolinone (4.74 g; 0.01 mol) in acetone (30 ml), ammonium salt of piperidinodithiocarbomate (1.78 g; 0.01 mol) was added and the mixture was stirred for 30 min. The reaction mixture was then refluxed for 3 hr on a water-bath. Acetone was removed and the residue was washed with small portions of cold water. The crude product was recrystallized from alcohol to get a pure, colourless crystalline solid (2.1 g; 72%), m.p. 135°. [Found: C, 42.90; H, 3.00; N, 7.11; $C_{21}H_{18}N_3OS_2ClBr_2$ requires

Table 1 *Physical, Analytical and Biological data of the* [6,8-*Dibromo*-3-*aryl*-3,4-*dihydro*-4-*oxo*-2-*quinazolinyl*]*methyl*-*N*-*substituted dithiocarbamates.*

Compd.	Ar	NR^1R^2	m. p. °C	% of Nitrogen		Fungicidal Activity				Insecticidal activity (% mortality)	
						C. lunata		*D. halodis*			
				Obs.	Calc.	log ED_{50}	Relative toxicity	log ED_{50}	Relative toxicity	24 hr	48 hr
I	*o*-chlorophenyl	Anilino	90	7.00	7.05	1.90	1.55	1.95	1.54	80	90
II		*p*-Toluidino	95	6.81	6.89	1.85	1.59	1.80	1.60	80	–
III		*p*-Phenetidino	95	6.71	6.74	1.85	1.59	1.60	1.87	60	80
IV		*p*-Anisidino	115	6.68	6.72	1.80	1.64	1.70	1.76	60	–
V		Benzylamino	90	6.85	6.89	1.70	1.73	1.35	2.22	–	–
VI		Cyclohexyl amino	115	6.95	6.98	2.00	1.47	1.35	2.22	45	60
VII		(Dimethyl amino)-propylamino	135	9.24	9.27	1.35	2.18	1.30	2.30	60	–
VIII		Pyrrolidino	170	7.29	7.32	2.10	1.40	1.90	1.58	60	–
IX		Piperidino	135	7.11	7.15	1.80	1.64	1.70	1.76	38	50
X		Morpholino	120	7.10	7.13	1.85	1.59	1.60	1.87	–	20
XI		4′-Phenylpiperizino	190	8.40	8.43	1.70	1.73	1.55	1.25	50	60
XII		Dicyclohexylamino	165	6.11	6.14	1.90	1.55	1.60	1.87	40	–
XIII	*o*-Anisyl	Anilino	107	7.07	7.10	2.65	1.11	2.60	1.15	65	75
XIV		*p*-Toluidino	110	6.90	6.94	2.55	1.15	2.40	1.25	68	75
XV		*p*-Phenetidino	112	6.74	6.78	2.65	1.11	2.60	1.15	40	80
XVI		*p*-Anisidino	122	6.72	6.76	2.45	1.20	2.55	1.17	50	–
XVII		Benzylamino	97	6.90	6.94	2.35	1.25	2.45	1.22	–	–
XVIII		Cyclohexylamino	125	7.00	7.03	2.95	1.00	3.00	1.00	40	60
XIX		(Dimethylamino)-propylamino	140	9.30	9.33	2.05	1.44	2.15	1.39	50	60
XX		Pyrrolidino	175	7.34	7.38	2.60	1.13	2.55	1.17	40	50
XXI		Piperidino	145	7.16	7.20	2.75	1.07	2.80	1.07	40	40
XXII		Morpholino	127	7.14	7.17	2.35	1.25	2.45	1.22	–	20
XXIII		4′-Phenylpiperizino	185	8.44	8.48	2.55	1.15	2.40	1.25	40	60
XXIV		Dicyclohexylamino	162	6.14	6.18	2.95	1.00	3.00	1.00	20	40
	Calixin	–	–	–	–	1.15	2.56	1.10	2.73	–	–
	Fenitrothion	–	–	–	–	–	–	–	–	80	–

C, 42.93; H, 3.06; N, 7.15 %]. IR: 1690 (O=C–N–), 1600 (C=N); 1230 (C=S) and 720 (C–Cl). PMR: (in $CDCl_3$) δ 1.50 (*m*, 6H, $-(CH_2)_3$ cyclic); 2.52 (*m*, 4H, $-CH_2-N-CH_2-$ cyclic); 4.60 (*s*, 2H, $-CH_2$); 7.50–7.80 (*m*, 5H, Ar–H) and 8.20 (*d*, 1H, Ar–C_5 H).

The analytical and physical data of the rest of the compounds which were prepared in a similar way, are presented in table 1.

Biological Studies

The antifungal activity of the compounds synthesized was determined by a standard method[10] at different concentrations, *viz* 30, 60, 120 and 160 μg/ml. Relative toxicities are calculated from log ED_{50} values and the results are presented in table 1. The fungi employed were: *Curvularia lunata* and *Drechslaria halodis*. Calixin, a commercial fungicide has been employed as a standard. The insecticidal activity has been evaluated against *Periplanata americana* at 50 μg/ml concentration, adopting the procedure of Menusan[11]. The mortality of the insect was recorded at the end of 24 and 48 hr and the percentage was calculated. Fenitrothion was employed as a standard for the insecticidal activity. The results are presented in table 1.

RESULTS AND DISCUSSION

Among the twentyfour quinazolinone dithiocarbamates tested for their fungicidal activity, compounds with 3-*p*-chlorophenyl group proved to be quite superior over the compounds with 3-*o*-anisyl group. Compound VII was more efficient in its fungicidal action against both the fungi employed while compounds V and VI were selective in their action as they could inhibit the growth of *D. halodis* at 30 μg/ml concentration. Least efficient were the compounds with cyclohexylamino and dicyclohexyl amino groups (XVIII and XXIV) as they failed to cause even 50% inhibition at the higher concentration also. The rest of all could cause 100% inhibition atleast at a concentration of 360 μg/ml.

The results on insecticidal activity of the compounds also revealed that the compounds with 3-*p*-chlorophenyl group, are more potential insecticides over the compounds with 3-o-anisyl group. Compounds I, II and III exhibited the insecticidal activity on a par with that of the standard (Fenitrothion) employed. Except compound XXIV, all other compounds of the series could exhibit a moderate insecticidal activity.

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