The Synthesis of Some *S*-Substituted-2-mercapto-3-aryl-4-quinazolones

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Several 4-quinazolone derivatives and 2- or 4-sulphanilamido-quinazolines have been reported to be therapeutically active.[1,2] Several potential antimalarials belonging to substituted quinazolones and quinazolines have been screened against blood-induced *P. gallinaceum* infection in 7-day-old chicks. Gujral et al. observed the hypnotic activity of 2-alkyl-3-aryl-4(3*H*)-quinazolones in rats.[3]

The above findings have led the authors to prepare *S*-substituted-2-mercapto-3-aryl-4-quinazolones[4,5] as possible antimalarials. In the present investigation, the synthesis of *S*-substituted-2-mercapto-3-aryl-4-quinazolones from anthranilic acid, arylisothiocyanates and alkyl halides has been studied.

Experimental

2-Mercapto-3-*m*-chlorophenyl-4-quinazolone.—A mixture of *m*-chlorophenylisothiocyanate (15 g.), *o*-aminobenzoic acid (15 g.) and absolute ethanol (150 ml.) was refluxed on a water bath for about 2 hr. The product was washed with ethanol, dissolved in 10% sodium hydroxide, precipitated with dilute hydrochloric acid, filtered, and after washing with water, dried.

Similarly, various 2-mercapto-3-aryl-4-quinazolones were prepared from the corresponding arylisothiocyanates and *o*-aminobenzoic acid. Their yields, melting points, and analytical data are listed in Table I.

2-Ethylthio-3-*m*-chlorophenyl-4-quinazolone.—To a solution of sodium hydroxide (5 g.) in (85 ml.) of 50% aqueous ethanol, 2-mercapto-3-*m*-chlorophenyl-4-quinazolone (7.5 g.) was added. The solution was then stirred, filtered and treated with ethyl iodide (4 ml.); after being stirred again for an hour, the solution gave a crystalline product which was washed first with water and then with ethanol. Long needles were obtained on crystallization form ethanol.

Similarly, various *S*-substituted-2-mercapto-3-aryl-4-quinazolones have been prepared. Their yields,

TABLE I. 2-THIO-3-ARYL-4-QUINAZOLONES

Aryl group	Yield %	M. p. °C	Molec. formula	N, %		S, %	
				Found	Calcd.	Found	Calcd.
m-Chlorophenyl-	90	292	$C_{14}H_9N_2OSCl$	9.66	9.70	11.21	11.09
p-Chlorophenyl-	90	320	$C_{14}H_9N_2OSCl$	9.73	9.70	11.14	11.09
p-Bromophenyl-	90	320	$C_{14}H_9N_2OSBr$	8.52	8.41	9.86	9.61
o-Methoxyphenyl-	75	265	$C_{15}H_{12}N_2O_2S$	9.73	9.86	11.40	11.27
p-Methoxyphenyl-	80	275	$C_{15}H_{12}N_2O_2S$	9.75	9.86	11.32	11.27
p-Ethoxyphenyl-	90	335	$C_{16}H_{14}N_2O_2S$	9.28	9.39	10.82	10.74
Benzyl-	75	248	$C_{15}H_{12}N_2OS$	10.51	10.45	12.01	11.94
α-Naphthyl-	70	266	$C_{18}H_{12}N_2OS$	9.33	9.21	10.61	10.52

TABLE II. *S*-SUBSTITUTED-2-MERCAPTO-3-*m*-CHLOROPHENYL-4-QUINAZOLONES

2-Substituent	Yield %	M. p. °C	Molec. formula	N, %		S, %	
				Found	Calcd.	Found	Calcd.
2-Methylthio-	86	156	$C_{15}H_{11}N_2OSCl$	9.33	9.25	10.70	10.58
2-Ethylthio-	70	124	$C_{16}H_{13}N_2OSCl$	8.81	8.84	10.31	10.11
2-Butylthio-	70	88	$C_{18}H_{17}N_2OSCl$	8.20	8.12	9.50	9.28
2-Allylthio-	75	178	$C_{17}H_{13}N_2OSCl$	8.47	8.52	9.87	9.73
2-α-Methylallylthio-	60	94	$C_{18}H_{15}N_2OSCl$	8.21	8.17	9.42	9.34
2-Benzylthio-	80	106	$C_{21}H_{15}N_2OSCl$	7.28	7.39	8.57	8.45
2-*p*-Nitrobenzylthio-	70	162	$C_{21}H_{14}N_3O_3SCl$	9.87	9.91	7.63	7.55
2-Carboxymethylthio-	75	180	$C_{16}H_{11}N_2O_3SCl$	8.20	8.08	9.41	9.23

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2) B. R. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph and J. H. Williams, *J. Org. Chem.*, **18**, 178 (1953).
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5) T. N. Ghosh, *J. Indian Chem. Soc.*, **7**, 981 (1390).

TABLE III. *S*-SUBSTITUTED-2-MERCAPTO-3-*p*-CHLOROPHENYL-4-QUINAZOLONES

2-Substituent	Yield %	M. p. °C	Molec. formula	N, %		S, %	
				Found	Calcd.	Found	Calcd.
2-Methylthio-	90	178	$C_{15}H_{11}N_2OSCl$	9.21	9.25	10.65	10.58
2-Ethylthio-	80	150	$C_{16}H_{13}N_2OSCl$	8.78	8.84	10.24	10.11
2-Isopropylthio-	85	152	$C_{17}H_{15}N_2OSCl$	8.16	8.47	9.90	9.68
2-Butylthio-	85	113	$C_{18}H_{17}N_2OSCl$	8.11	8.12	9.32	9.28
2-Allylthio-	80	137	$C_{17}H_{13}N_2OSCl$	8.45	8.52	9.69	9.73
2-α-Methylallylthio-	85	134	$C_{18}H_{15}N_2OSCl$	8.10	8.17	9.39	9.34
2-Benzylthio-	95	183	$C_{21}H_{15}N_2OSCl$	7.32	7.39	8.63	8.45
2-*p*-Nitrobenzylthio-	75	218	$C_{21}H_{14}N_3O_3SCl$	9.79	9.91	7.48	7.55
2-Carboxymethylthio-	80	218	$C_{16}H_{11}N_2O_3SCl$	8.19	8.08	9.46	9.23
2-Amylthio-	75	102	$C_{19}H_{19}N_2OSCl$	7.76	7.80	9.31	8.92

TABLE IV. *S*-SUBSTITUTED-2-MERCAPTO-3-*p*-BROMOPHENYL-4-QUINAZOLONES

2-Substituent	Yield %	M. p. °C	Molec. formula	N, %		S, %	
				Found	Calcd.	Found	Calcd.
2-Methylthio-	90	208	$C_{15}H_{11}N_2OSBr$	8.00	8.07	9.51	9.22
2-Ethylthio-	85	146	$C_{16}H_{13}N_2OSBr$	7.69	7.75	8.91	8.86
2-Butylthio-	85	121	$C_{18}H_{17}N_2OSBr$	7.30	7.20	8.33	8.22
2-Allylthio-	85	148	$C_{17}H_{13}N_2OSBr$	7.43	7.50	8.63	8.57
2-α-Methylallylthio-	80	131	$C_{18}H_{15}N_2OSBr$	7.33	7.23	8.43	8.26
2-Benzylthio-	95	182	$C_{21}H_{15}N_2OSBr$	6.58	6.62	7.81	7.56
2-*p*-Nitrobenzylthio-	75	230	$C_{21}H_{14}N_3O_3SBr$	8.82	8.97	6.57	6.83
2-Carboxymethylthio-	80	214	$C_{16}H_{11}N_2O_3SBr$	7.23	8.19	9.50	9.35

TABLE V. *S*-SUBSTITUTED-2-MERCAPTO-3-*o*-METHOXYPHENYL- AND *S*-SUBSTITUTED-2-MERCAPTO-3-BENZYL-4-QUINAZOLONES

Compound	Yield %	M. p. °C	Molec. formula	N, %		S, %	
				Found	Calcd.	Found	Calcd.
2-Methylthio-3-*o*-methoxyphenyl-4-quinazolone	88	134	$C_{16}H_{14}N_2O_2S$	9.32	9.39	10.69	10.74
2-Ethylthio-3-*o*-methoxyphenyl-4-quinazolone	72	114	$C_{17}H_{16}N_2O_2S$	8.79	8.97	10.32	10.28
2-Butylthio-3-*o*-methoxyphenyl-4-quinazolone	70	141	$C_{19}H_{20}N_2O_2S$	8.31	8.23	9.67	9.41
2-Allylthio-3-*o*-methoxyphenyl-4-quinazolone	60	98	$C_{18}H_{16}N_2O_2S$	8.58	8.64	9.99	9.87
2-Methylthio-3-benzyl-4-quinazolone	75	94	$C_{16}H_{14}N_2OS$	9.88	9.93	11.52	11.34
2-Ethylthio-3-benzyl-4-quinazolone	70	83	$C_{17}H_{16}N_2OS$	9.56	9.46	10.94	10.81
2-Allylthio-3-benzyl-4-quinazolone	70	93	$C_{18}H_{16}N_2OS$	9.12	9.09	10.64	10.39

TABLE VI. *S*-SUBSTITUTED-2-MERCAPTO-3-*p*-METHOXYPHENYL-4-QUINAZOLONES

2-Substituent	Yield %	M. p. °C	Molec. formula	N, %		S, %	
				Found	Calcd.	Found	Calcd.
2-Methylthio-	84	148	$C_{16}H_{14}N_2O_2S$	9.41	9.39	10.62	10.74
2-Ethylthio-	75	170	$C_{17}H_{16}N_2O_2S$	8.81	8.97	10.34	10.28
2-Butylthio-	75	122	$C_{19}H_{20}N_2O_2S$	8.40	8.23	9.53	9.41
2-Allylthio-	70	160	$C_{18}H_{16}N_2O_2S$	8.56	8.64	9.78	9.87
2-α-Methylallylthio-	50	113	$C_{19}H_{18}N_2O_2S$	8.32	8.28	9.56	9.46
2-Benzylthio-	80	153	$C_{22}H_{18}N_2O_2S$	7.63	7.48	8.80	8.55
2-*p*-Nitrobenzylthio-	70	188	$C_{22}H_{17}N_3O_4S$	10.10	10.02	7.81	7.61
2-Carboxymethylthio-	80	182	$C_{17}H_{14}N_2O_4S$	8.23	8.19	9.50	9.35

TABLE VII. *S*-SUBSTITUTED-2-MERCAPTO-3-*p*-ETHOXYPHENYL-4-QUINAZOLONES

2-Substituent	Yield %	M. p. °C	Molec. formula	N, %		S, %	
				Found	Calcd.	Found	Calcd.
2-Methylthio-	90	158	$C_{17}H_{16}N_2O_2S$	8.98	9.00	10.11	10.29
2-Ethylthio-	85	139	$C_{18}H_{18}N_2O_2S$	8.48	8.59	9.99	9.81
2-Butylthio-	80	140	$C_{20}H_{22}N_2O_2S$	8.01	7.91	9.20	9.03
2-Allylthio-	80	152	$C_{19}H_{18}N_2O_2S$	8.17	8.28	9.39	9.46
2-α-Methylallylthio-	65	134	$C_{20}H_{20}N_2O_2S$	7.88	7.95	9.00	9.09
2-Benzylthio-	85	241	$C_{23}H_{20}N_2O_2S$	7.13	7.21	8.38	8.24
2-*p*-Nitrobenzylthio-	70	186	$C_{23}H_{19}N_3O_4S$	9.57	9.69	7.44	7.39
2-Carboxymethylthio-	80	202	$C_{18}H_{16}N_2O_4S$	7.77	7.82	9.01	8.99

melting points, and analytical data are recorded in Tables II to VII.

2-Carboxymethylthio-3-*m*-chlorophenyl-4-quinazolone.—An equimolecular quantity of sodium monochloroacetate was added to an alkaline solution of 2-mercapto-3-*m*-chlorophenyl-4-quinazolone, and the mixture was shaken for 6 hr. It was then acidified with dilute hydrochloric acid, and the precipitate obtained was dissolved in sodium bicarbonate solution and reprecipitated with diluted hydrochloric acid. The product was crystallized from ethanol.

Similarly, other 2-carboxymethylthio derivatives of -3-*p*-chlorophenyl-, -3-*p*-bromophenyl-, -3-*p*-methoxyphenyl- and -3-*p*-ethoxyphenyl-4-quinazolones were prepared. Their yields, melting points, and analytical data are also recorded in Tables II, III, IV, VI, and VII.

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