poured into water and the crystals were precipitated. Recrystallization from EtOH–H_2O afforded 2 g of XIV as colorless plates, mp 132°. *Anal.* Calcd. for $C_{14}H_{19}O_2N$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.27; H, 7.93; N, 5.85. UV λ_{max}^{EtOH}: 277 mμ (log ε 3.43).

1,2,3,4-Tetrahydro-4,6-dihydroxy-1-spirocyclohexanoisoquinoline (VI)——Fusion of 1.5 g of XIV at 150° for 3 hr afforded a solid, which was recrystallized from EtOH to give 1.2 g of VI as colorless prisms, mp 178—180°, whose IR spectrum was identical with an authentic sample.[4] UV λ_{max}^{EtOH}: 282 mμ (log ε 3.34).

N-benzoyl-[β-(benzoyloxy)-β-(3-benzoyloxyphenyl)]ethylamine (XVI)——a) Benzoylation of XIV: A solution of 25 mg of XIV in $CHCl_3$ was benzoylated with 5 ml of benzoyl chloride in the presence of 10% NaOH aq. solution by Schotten–Baumann reaction. The $CHCl_3$ layer was separated, washed with 10% HCl aq. solution and dried on K_2CO_3. Evaporation of the solvent gave a solid which was recrystallized from benzene–cyclohexane to give 30 mg of colorless needles, mp 128—131°, whose IR spectrum was identical with that of the tribenzoyl compound (XVI) described below, and this compound also showed no depression of melting point on admixture with the tribenzoyl compound (XVI) described later.

b) Benzoylation of I: A solution of 40 mg of I in $CHCl_3$ was benzoylated with 5 ml of benzoyl chloride in the presence of 10% NaOH aq. solution by Schotten–Baumann reaction. The solvent layer was separated, washed with 10% HCl aq. solution and dried on K_2CO_3. Evaporation of the solvent gave a solid which was recrystallized from benzene–cyclohexane to give 48 mg of colorless needles, mp 128—131°. *Anal.* Calcd. for $C_{29}H_{23}O_5N$: C, 74.82; H, 4.98; N, 3.01. Found: C, 74.30; H, 5.05; N, 2.99. IR cm^{-1} (KBr): $\nu_{C=O}$ 1720 (ester): $\nu_{C=O}$ 1630 (amide).

Acknowledgement We thank President A. Yanagisawa and Director O. Takagi of the Grelan Pharmaceutical Co. Ltd. for their encouragement, Miss R. Kobayashi and Mrs. R. Shibuya for microanalyses, and Miss Y. Tadano for NMR spectral determination.

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Synthesis of Mercaptoquinazolinone Derivatives as Potential Antimalarials[1]

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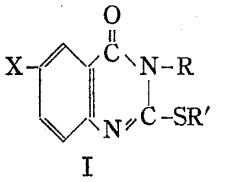
Many quinazolines possessing a wide variety of biological activities are known. The antimalarial activity of febrifugine,[3,4] an alkaloid having 3-substituted 4(3*H*)quinazolinone structure, spurred the preparation and testing of a number of quinazolines[5] and quinazolinones[6] and several patent claims have been made on quinazolinones as intermediates for potential antimalarials.[7] Wolf[8] has reported that 2- and 4-sulphanilamidoquinazolines are

1) The major part of the paper was presented before the 55th session of the Indian Science Congress held at B.H.U., Varanasi-5 (India) in January, 1968.
2) Location: *Varanasi-5, India.*
3) J.B. Koepfli, J.F. Mead and J.A. Brockman, *J. Am. Chem. Soc.*, **69**, 1837 (1947); **71**, 1048 (1949); **72**, 3323 (1950).
4) B.R. Baker, F.J. McEvoy, R.E. Schaub, J.P. Joseph and J.H. Williams, *J. Org. Chem.*, **18**, 178 (1953).
5) F.W. Wiselogle, "Survey of Antimalarial Drugs 1941—1945," Edward Bros., Ann. Arbor, Michigan (U.S.A.), 1946.
6) B.R. Baker, R.E. Schaub, J.P. Joseph, F.J. McEvoy and J.H. Williams, *J. Org. Chem.*, **17**, 164 (1952).
7) B.R. Baker and M.V. Querry, U.S. Patent 2796417 (1957); *C.A.*, **52**, 459 (1958); B.R. Baker, U.S. Patent 2811524 (1957); *C.A.*, **52**, 5488 (1958).
8) F.J. Wolf, U.S. Patent 2473931 (1949); *C.A.*, **43**, 7042 (1949).

antimalarials exhibiting schizonticidal activity. The compounds having the side chain $-CH_2COCH_2R$ (where R=ω-N-morpholylpropyl or ω-N-piperidyl-*n*-butyl) at position-3 of the 4(3*H*)-quinazolinone nucleus were shown to have significant antimalarial activity.[9]

Several 2,3-disubstituted 4(3*H*)-quinazolinones were active against *Plasmodium gallinaceum*[10,11] and showed antiinflammatory action on experimental edemes in animals.[12] Also, the screening of several quinazolinone derivatives against *p. gallinaceum* in chicks by Sengupta, Bami and Sharma[13] showed that 2-mercapto-3-allyl 4(3*H*)-quinazolinone and its 6-methyl isomer were active at 4 quinine equivalent of dosage.

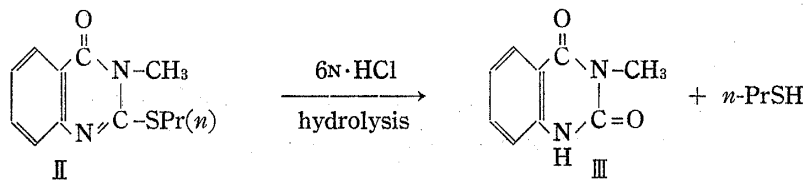
In view of these facts and that the biological activity of compounds is influenced by various substituents and their positions, a number of 2-alkyl (or aryl) thio-3-substituted 4(3*H*)-quinazolinones and 6-bromo-2-(N-piperidinocarboxamidomethylthio)-3-substituted 4(3*H*)-quinazolinones having the general structure (I) have been synthesized for testing their antimalarial activity.



I

where X=H or Br
R=alkyl or aryl
R′=H, *n*-Pr, iso-Pr, *n*-C_5H_{11}, iso-C_5H_{11}, $-CH_2C_6H_4NO_2-$ or $-CH_2CON$ 

The simplest synthetic route to these products proved to be the alkylation with the appropriate alkyl halides of the sodium salt of the corresponding 2-mercapto-3-substituted 4(3*H*)-quinazolinones prepared by the method of Bhargava, *et al.*[14]



II III

That the alkylation occurred at the sulphur rather than the nitrogen atom was proved for a representative member II of the series by acid hydrolysis to the corresponding mercaptan and sulphur free hydroxy compound (III).

The pharmacological testing of these compounds as antimalarials against *P. gallinaceum* infection in chicks is in progress and will be reported at a future date.

Experimental

2-Mercapto-3-methyl-4(3*H*)-quinazolinone——It was prepared by condensing anthranilic acid (13.0 g) with methyl isothiocyanate (7.3 g) by the method of Bhargava, *et al.*[14] in 60% yield, mp 257—258° (EtOH). Butler, *et al.*[15] reports mp 260—261° (AcOH). (Found: N, 14.51%. $C_9H_8N_2OS$ requires N, 14.58%).

Similarly other 2-mercapto-3-aryl-4(3*H*)-quinazolinones were prepared in more than 60% yields.[14,16]

6-Bromo-2-mercapto-3-substituted 4(3*H*)-quinazolinones——These were prepared as described in an earlier paper.[17]

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15) K. Butler and M.W. Partridge, *J. Chem. Soc.*, **1959**, 1519.
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17) P.N. Bhargava and R. Lakhan, *Current Sci.* (India), **36**, 575 (1967).

3-Methyl-2-*n*-propylmercapto-4(3*H*)-quinazolinone——To a solution of 4.0 g of sodium hydroxide in 80 ml of 50% aqueous ethanol, 6.1 g of 2-mercapto-3-methyl-4(3*H*)-quinazolinone was added and the resulting mixture was stirred until the solution was clear. *n*-Propyl bromide (4.8 g) was then added and the solution stirred for an hour at 24—25°. After cooling of the resulting mixture to 0°, the product was filtered, washed with water, ethanol and air dried. It was then crystallised from ethanol into colorless crystals.

Similarly, other 2-alkylthio-3-substituted-4(3*H*)-quinazolinones were prepared. Their yields, melting points and analytical data are listed in Tables I to IV.

2-*o*-Nitrobenzylthio-3-phenyl-4(3*H*)-quinazolinone——2-Mercapto-3-phenyl-4(3*H*)-quinazolinone (2.5 g) was dissolved in minimum quantity of approx. 10% alcoholic sodium hydroxide solution with constant stirring until the solution was complete. *o*-Nitrobenzyl chloride (1.7 g) dissolved in 95% ethanol (15 ml) was then added and the reaction mixture was allowed to stand for half an hour at room temperature with

Table I. 2-*n*-Propylthio-3-substituted 4(3*H*)-Quinazolinones

S.No.	3-Substituent	Yield, %	mp °C	Molecular formula	Nitrogen, % Found	Nitrogen, % Calcd.	Sulphur, % Found	Sulphur, % Calcd.
1.	Methyl-	60	84	$C_{12}H_{14}ON_2S$	12.12	11.97	13.64	13.68
2.	*o*-Tolyl-	69	69	$C_{18}H_{18}ON_2S$	9.11	9.03	10.30	10.32
3.	*m*-Tolyl-	83	92	$C_{18}H_{18}ON_2S$	8.95	9.03	10.39	10.32
4.	*p*-Tolyl-	85	103	$C_{18}H_{18}ON_2S$	9.01	9.03	10.48	10.32
5.	*m*-Chlorophenyl-	55	141	$C_{17}H_{15}ON_2ClS$	8.40	8.47	9.78	9.68
6.	*p*-Chlorophenyl-	65	127	$C_{17}H_{15}ON_2ClS$	8.35	8.47	9.61	9.68
7.	*o*-Methoxyphenyl-	56	151	$C_{18}H_{18}O_2N_2S$	8.59	8.59	9.80	9.81
8.	*p*-Methoxyphenyl-	70	158	$C_{18}H_{18}O_2N_2S$	8.67	8.59	9.89	9.81
9.	*p*-Ethoxyphenyl-	86	152	$C_{19}H_{20}O_2N_2S$	8.11	8.23	9.45	9.41
10.	α-Naphthyl-	80	122	$C_{21}H_{18}ON_2S$	8.00	8.09	9.19	9.25
11.	Benzyl-	75	109	$C_{18}H_{18}ON_2S$	9.12	9.03	10.37	10.32

Table II. 2-Isopropylthio-3-substituted 4(3*H*)-Quinazolinones

S. No.	3-Substituent	Yield, %	mp °C	Molecular formula	Nitrogen, % Found	Nitrogen, % Calcd.	Sulphur, % Found	Sulphur, % Calcd.
1.	*o*-Tolyl-	52	98	$C_{18}H_{18}ON_2S$	9.00	9.03	10.39	10.32
2.	*m*-Tolyl-	60	132	$C_{18}H_{18}ON_2S$	8.91	9.03	10.52	10.32
3.	*p*-Tolyl-	67	130	$C_{18}H_{18}ON_2S$	8.97	9.03	10.30	10.32
4.	*o*-Methoxyphenyl-	48	159	$C_{18}H_{18}O_2N_2S$	8.67	8.59	9.73	9.81
5.	*p*-Methoxyphenyl-	72	196	$C_{18}H_{18}O_2N_2S$	8.45	8.59	9.86	9.81
6.	*p*-Ethoxyphenyl-	70	162	$C_{19}H_{20}O_2N_2S$	8.19	8.23	9.45	9.41
7.	α-Naphthyl-	76	193	$C_{21}H_{18}ON_2S$	8.16	8.09	9.38	9.25
8.	Benzyl-	60	125	$C_{18}H_{18}ON_2S$	9.19	9.03	10.25	10.32

Table III. 2-*n*-Amylthio-3-substituted 4(3*H*)-Quinazolinones

S. No.	3-Substituent	Yield, %	mp °C	Molecular formula	Nitrogen, % Found	Nitrogen, % Calcd.	Sulphur, % Found	Sulphur, % Calcd.
1.	Methyl-	48	55	$C_{14}H_{18}ON_2S$	10.49	10.69	12.00	12.21
2.	Phenyl-	78	96	$C_{19}H_{20}ON_2S$	8.60	8.64	9.99	9.88
3.	*o*-Tolyl-	85	85	$C_{20}H_{22}ON_2S$	8.13	8.29	9.50	9.47
4.	*m*-Tolyl-	72	90	$C_{20}H_{22}ON_2S$	8.23	8.29	9.56	9.47
5.	*p*-Tolyl-	62	97	$C_{20}H_{22}ON_2S$	8.37	8.29	9.60	9.47
6.	*m*-Chlorophenyl-	56	80	$C_{19}H_{19}ON_2ClS$	7.75	7.80	8.99	8.92
7.	*o*-Methoxyphenyl-	55	130	$C_{20}H_{22}O_2N_2S$	8.01	7.91	9.03	9.04
8.	*p*-Methoxyphenyl-	60	134	$C_{20}H_{22}O_2N_2S$	7.85	7.91	9.17	9.04
9.	*p*-Ethoxyphenyl-	90	131	$C_{21}H_{24}O_2N_2S$	7.56	7.61	8.78	8.70
10.	α-Naphthyl-	65	107	$C_{23}H_{22}ON_2S$	7.44	7.49	8.65	8.56
11.	Benzyl-	51	68	$C_{20}H_{22}ON_2S$	8.30	8.29	9.41	9.47

Table IV. 2-Isoamylthio-3-substituted 4(3*H*)-Quinazolinones

S. No.	3-Substituent	Yield, %	mp °C	Molecular formula	Nitrogen, % Found	Nitrogen, % Calcd.	Sulphur, % Found	Sulphur, % Calcd.
1.	Methyl-	55	82	$C_{14}H_{18}ON_2S$	10.62	10.69	12.12	12.21
2.	Phenyl-	63	111	$C_{19}H_{20}ON_2S$	8.66	8.64	9.95	9.88
3.	*o*-Tolyl-	71	84	$C_{20}H_{22}ON_2S$	8.21	8.29	9.34	9.47
4.	*m*-Tolyl-	85	89	$C_{20}H_{22}ON_2S$	8.30	8.29	9.57	9.47
5.	*p*-Tolyl-	50	106	$C_{20}H_{22}ON_2S$	8.15	8.29	9.48	9.47
6.	*m*-Chlorophenyl-	65	120	$C_{19}H_{19}ON_2ClS$	7.78	7.80	8.98	8.92
7.	*p*-Chlorophenyl-	68	126	$C_{19}H_{19}ON_2ClS$	7.97	7.80	8.89	8.92
8.	*o*-Methoxyphenyl-	60	145	$C_{20}H_{22}O_2N_2S$	7.86	7.91	9.03	9.04
9.	*p*-Methoxyphenyl-	57	150	$C_{20}H_{22}O_2N_2S$	7.95	7.91	9.16	9.04
10.	*p*-Ethoxyphenyl-	90	147	$C_{21}H_{24}O_2N_2S$	7.53	7.61	8.78	8.70
11.	α-Naphthyl-	52	103	$C_{23}H_{22}ON_2S$	7.41	7.49	8.66	8.56
12.	Benzyl-	50	89	$C_{20}H_{22}ON_2S$	8.14	8.29	9.59	9.47

occasional stirring when a crystalline product was obtained. It was removed by filtration, washed with water and finally with ethanol, and dried. Recrystallization of the product from acetone and ethanol mixture (1:1) gave pale yellow long needles.

Similarly, various 2-*o*-nitrobenzylmercapto-3-substituted-4(3*H*)quinazolinones have been prepared (Table V).

6-Bromo-3-ethyl-2-(N-piperidylcarboxamidomethylthio)-4(3*H*)-quinazolinone——It was prepared as described above by treating the sodium salt of 6-bromo-3-ethyl-2-mercapto-4(3*H*)quinazolinone with N-chloroacetylpiperidine in ethanol in 55% yield, mp 162° (Found: N, 10.04; S, 7.89; Br, 19.44. $C_{17}H_{20}BrN_3O_2S$ requires N, 10.24; S, 7.80; Br, 19.51%).

Similarly other compounds in this series were prepared as recorded in Table VI.

Table V. 2-*o*-Nitrobenzylthio-3-substituted 4(3*H*)-Quinazolinones

S. No.	3-Substituent	Yield, %	mp °C	Molecular formula	Nitrogen, % Found	Nitrogen, % Calcd.	Sulphur, % Found	Sulphur, % Calcd.
1.	Methyl-	55	152	$C_{16}H_{13}O_3N_3S$	12.71	12.84	9.89	9.79
2.	Phenyl-	70	206	$C_{21}H_{15}O_3N_3S$	10.64	10.80	8.13	8.22
3.	*o*-Tolyl-	55	161	$C_{22}H_{17}O_3N_3S$	10.30	10.42	7.98	7.93
4.	*m*-Tolyl-	65	156	$C_{22}H_{17}O_3N_3S$	10.45	10.42	8.01	7.93
5.	*p*-Tolyl-	68	226	$C_{22}H_{17}O_3N_3S$	10.58	10.42	8.00	7.93
6.	*m*-Chlorophenyl-	75	177	$C_{21}H_{14}O_3N_3ClS$	9.98	9.91	7.69	7.55
7.	*p*-Chlorophenyl-	62	229	$C_{21}H_{14}O_3N_3ClS$	9.85	9.91	7.65	7.55
8.	*o*-Methoxyphenyl-	50	189	$C_{22}H_{17}O_4N_3S$	10.00	10.02	7.72	7.63
9.	*p*-Methoxyphenyl-	62	181	$C_{22}H_{17}O_4N_3S$	10.25	10.02	7.60	7.63
10.	*p*-Ethoxyphenyl-	65	200	$C_{23}H_{19}O_4N_3S$	9.60	9.69	7.33	7.39
11.	α-Naphthyl-	66	203	$C_{25}H_{17}O_3N_3S$	9.39	9.57	7.26	7.29
12.	Benzyl-	60	160	$C_{22}H_{17}O_3N_3S$	10.27	10.42	7.99	7.93

Table VI. 6-Bromo-2-(N-piperidinylcarboxamidomethylthio)-3-substituted 4(3*H*)-Quinazolinones

S. No.	3-Substituent	Yield, %	mp °C	Molecular formula	Nitrogen, % Found	Nitrogen, % Calcd.	Bromine, % Found	Bromine, % Calcd.
1.	Methyl-	42	118	$C_{16}H_{18}O_2N_3BrS$	10.47	10.60	20.28	20.20
2.	*o*-Tolyl-	62	166	$C_{22}H_{22}O_2N_3BrS$	8.95	8.90	17.09	16.95
3.	*p*-Tolyl-	75	165	$C_{22}H_{22}O_2N_3BrS$	9.06	8.90	16.92	16.95
4.	*m*-Chlorophenyl-	60	150	$C_{21}H_{19}O_2N_3BrCl$	8.52	8.53	16.34	16.25
5.	*p*-Chlorophenyl-	60	176	$C_{21}H_{19}O_2N_3BrClS$	8.61	8.53	16.39	16.25
6.	*o*-Methoxyphenyl-	68	198	$C_{22}H_{22}O_3N_3BrS$	8.56	8.61	16.40	16.40
7.	*p*-Methoxyphenyl-	90	191	$C_{22}H_{22}O_3N_3BrS$	8.80	8.61	16.29	16.40
8.	*p*-Ethoxyphenyl-	50	155	$C_{23}H_{24}O_3N_3BrS$	8.34	8.37	16.00	15.93
9.	Benzyl-	65	172	$C_{22}H_{22}O_2N_3BrS$	8.83	8.90	16.96	16.95

Hydrolysis of 3-Methyl-2-*n*-propylthio-4(3*H*)-quinazolinone (II)——6N Hydrochloric acid (15 ml) was added to a solution of 3-methyl-2-*n*-propylthio-4(3*H*)-quinazolinone (2.34 g) in absolute ethanol (30 ml) and the resulting solution was heated under reflux for 4 hr. Distilled off ethanol and poured the reaction mixture into ice-cold water. White needles separated which were filtered and dried. Recrystallization of this from ethanol gave 1.5 g of pure 3-methyl-2,4-(1*H*,3*H*)-quinazolindione (III), mp 244° (Found: C, 61.32; H, 4.49; N, 15.80. $C_9H_8N_2O_2$ requires: C, 61.37; H, 4.54; N, 15.92%).

The above filtrate gave characteristic reactions of the mercaptans and the mercaptan was identified to be *n*-propyl mercaptan as usual.

Acknowledgement Thanks are due to Dr. P. N. Bhargava for his valuable suggestions and guidance, to the authorities of Banaras Hindu University for providing the necessary facilities and to the Council of Scientific and Industrial Research, New Delhi (India) for the award of a Junior Research Fellowship to me.

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UDC 615.33.011.5

Studies on Cerulenin. VI.[1] Some Spectroscopic Features of Cerulenin

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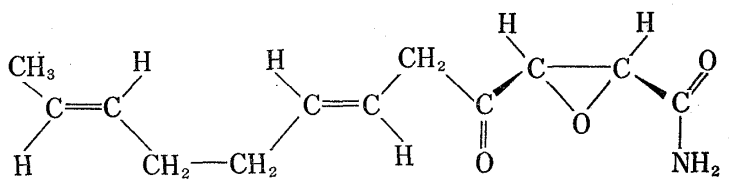
(Received December 21, 1968)

The structure of antifungal antibiotic, cerulenin[3] has been reported in the previous paper[1] as (2***S***) (3***R***)-2,3-epoxy-4-oxo-6,10-dodecadienoyl amide (see Fig. 1).



(2***S***) (3***R***) 2,3-epoxy-4-oxo-6,10-dodecadienoylamide

Fig. 1. Cerulenin

However, the configurations of the two double bonds in the structure were not completely determined. It became clear that, of the two double bonds in cerulenin, one had a *trans* configuration from the strong absorption (–CH out-of-plane bending)[4] at 967 cm^{-1}, which disappeared when cerulenin was converted into the tetrahydride.[1] In general, when the chemical shifts for two protons in the olefinic region in the nuclear magnetic resonance (NMR) spectrum are different, the *cis* and *trans* configuration can be distinguishable by the coupling constant values between the two protons. In cerulenin, the coupling constant values and the configuration of olefinic proton could not be determined because four olefinic protons were equal magnetically. Later, from the results of investigation of NMR spectra of cerulenin and related compounds it has been found that

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