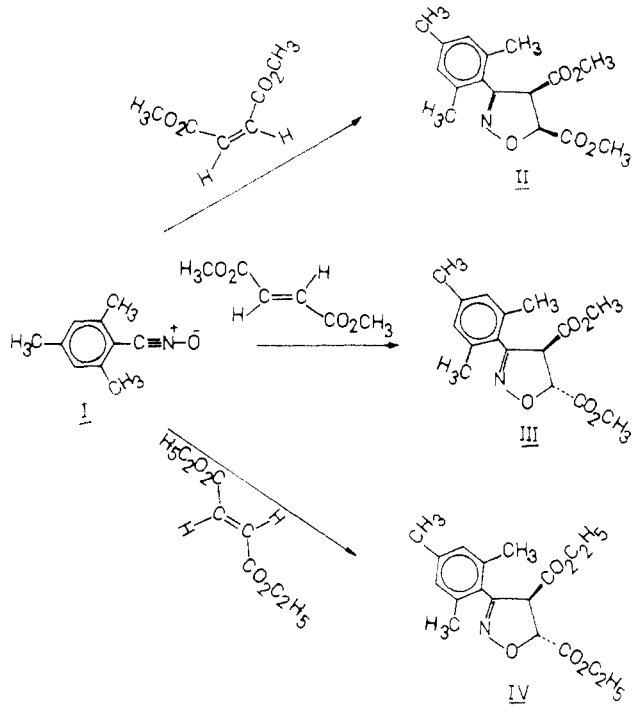
Scheme I



petroleum ether to yield 11.9 g (78%) of the product: mp 125–126.5 °C; NMR ($CDCl_3$) δ 6.88 (2 H, s), 5.57 (1 H, d, J = 6.5 Hz), 4.71 (1 H, d, J = 6.5 Hz), 3.85 (3 H, s), 3.60 (3 H, s), 2.28 (3 H, s), 2.19 (6 H, s).

***trans*-Diethyl-3-(2,4,6-trimethylphenyl)-4,5-dihydro-4,5-isoxazoledicarboxylate (IV).** To a solution of 6.44 g (40 mmol) of freshly prepared 2,4,6-trimethylbenzonitrile oxide in 50 mL of tetrahydrofuran was added 7.2 g (42 mmol) of diethyl fumarate. The resulting mixture was heated under reflux for 8 h. Tetrahydrofuran was removed on a rotary evaporator at diminished pressure. Distillation of the oily residue yielded 11.1 g (83%) of the product, bp 145–149 °C/0.005 mmHg; NMR ($CDCl_3$) δ 6.85 (2 H, s), 5.52 (1 H, d, J = 7 Hz), 4.67 (1 H, d, J = 7 Hz), 4.28 (2 H, q, J = 7.2 Hz), 4.01 (2 H, q, J = 7.2 Hz), 2.25 (3 H, s), 2.18 (6 H, s), 1.32 (3 H, t, J = 7.2 Hz), 0.97 (3 H, t, J = 7.2 Hz).

Elemental analyses (C, H, N) for compounds II–IV in agreement with theoretical values were obtained and submitted for review.

***Elemental Analyses*.** The results are shown as follows.

***Compound II*.** Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.73; H, 6.39; N, 4.65.

***Compound III*.** Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.66; H, 6.41; N, 4.56.

***Compound IV*.** Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.55; H, 7.17; N, 4.29.

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Registry No. I, 2904-57-6; II, 108295-19-8; III, 100854-03-3; IV, 108295-20-1; dimethyl maleate, 624-48-6; dimethyl fumarate, 624-49-7; diethyl fumarate, 623-91-6.

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Synthesis and Antibacterial Activity of 2-[[ω-(Dialkylamino)alkyl]thio]-3-aryl(or alkyl)-6,8-disubstituted-4(3*H*)-quinazolinones

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Synthesis of 47 new 2-[[ω-(dialkylamino)alkyl]thio]-3-aryl(or alkyl)-6,8-disubstituted-4(3*H*)-quinazolinones, 2–6, from the corresponding 2-thio-4(3*H*)-quinazolinones, 1, has been described. Fifteen of them were screened for their antibacterial activity by the Rideal Walker drop serial dilution method against two common bacteria, *Staphylococcus aureus* and *Escherichia coli*.

A number of quinazolin-4-one derivatives (*1–4*) have been found to exhibit high activity against a variety of microbes parasitizing animals and plants. Tregubenko et al. (*5*) have synthesized several 2-(N,N-disubstituted aminoethylthio)-3-aryl-4(3*H*)-quinazolinones and -thiones and evaluated them as radioprotective agents. Furthermore, 2-((N-substituted aminoethyl)thio)-3-aryl-6-iodo-4(3*H*)-quinazolinones have been reported (*6*) to be either CNS stimulants or depressants on mice.

In view of our continuing interest (*1*) in the syntheses and biological activities of 4(3*H*)-quinazolinones, we report here the synthesis of a series of 2-[[ω-(dialkylamino)alkyl]thio]-3-aryl(or alkyl)-6,8-disubstituted-4(3*H*)-quinazolinones (**2–6**).

The title compounds **2–6** were prepared (Scheme I) by heating an appropriately substituted anthranilic acid with an isothiocyanate to give 2-thio-3-aryl(or alkyl)-6,8-disubstituted-4-(3*H*)-quinazolinone (**1**) and subsequent treatment with suitable dialkylaminoalkyl bromide hydrobromide salts. The reaction proceeds to completion within a few minutes probably due to

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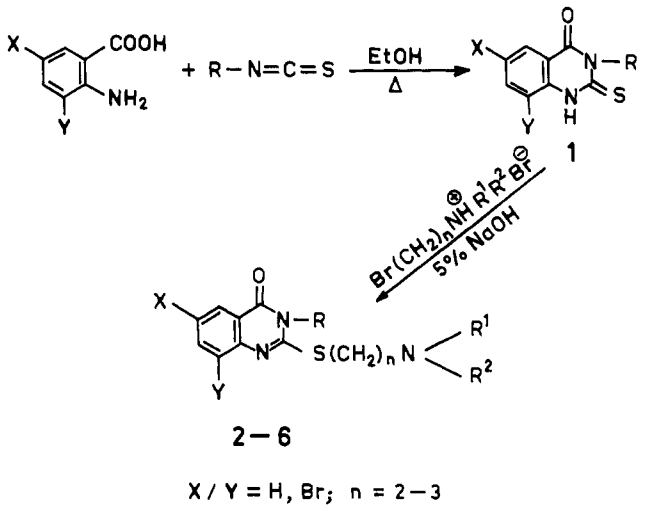
Scheme I



enhanced reactivity of the halide by participation of the neighboring β- or γ-amino group.

The structures of the compounds were confirmed by elemental analyses and IR and NMR spectra. In a typical case, the NMR spectrum (90 MHz) of 2-[[β-(diethylamino)ethyl]-thio]-3-(*m*-tolyl)-6,8-dibromo-4(3*H*)-quinazolinone (**5m**) in $CDCl_3$ shows a doublet for the C-5 aromatic proton of the quinazolinone ring at δ 8.50 ppm (J = 3 Hz) and a multiplet of 5 H intensity at δ 7.27–8.00 ppm for the remaining aromatic protons. A pair of multiplets appear at δ 3.22–3.40 ppm (2 H intensity) and at δ 2.81–3.21 ppm (2 H intensity) for methylene groups attached to the sulfur and nitrogen atoms (S–CH_2CH_2–N<). A quartet of 4 H intensity is observed at δ 2.68 ppm (J = 8 Hz) for methylene groups attached to nitrogen atom (–N(CH_2)$_2$). A singlet of 3 H intensity is observed at δ 2.50 ppm for the methyl substituent of the phenyl ring and a triplet of 6 H intensity (J = 8 Hz) at δ 1.13 ppm for the two methyl groups [–N(CH_2–CH_3)$_2$]. The IR spectrum (Nujol) of above compound lacks any absorption in the N–H stretching region, which is characteristic of the starting material. However, it shows absorption bands at 1710 (s) and 1610 (m) cm^{-1} for the endocyclic carbonyl group and C=N stretchings.

A general feature in the IR spectra of the 4(3*H*)-quinazolinones **2–6** in Nujol is the appearance of one to two variable intensity bands in the 3300–3100-cm^{-1} region due to N–H stretching where a primary or secondary amino group is present in the side chain, a medium to strong C=O absorption in the 1740–1700-cm^{-1} region, and a strong C=N stretching band around 1650 cm^{-1}. In addition, skeletal C=C vibrations of aromatic rings give rise to a series of two–three bands in the 1600–1500-cm^{-1} region.

Fifteen of the synthetic compounds were tested for their antibacterial activity against *S. aureus* and *E. coli* by the Rideal Walker drop serial dilution method at concentrations of 12.5, 25, and 100 μg/mL. From the results (Table I) it is inferred that the substituted 4(3*H*)-quinazolinones are more active against gram-positive bacterium (*S. aureus*) than the gram-negative one (*E. coli*). Among these the compounds **4** having β-diisopropylaminoethyl substituent at position 2 are markedly active at higher concentration (100 μg/mL) against *S. aureus* while none of the tested compounds exhibit any detectable activity against *E. coli* at low concentrations (12.5 μg/mL).

Table I. Antibacterial Activity[a] of 2-[[ω-(Dialkylamino)alkyl]thio]-3-aryl(or alkyl)-6,8-disubstituted-4(3*H*)-quinazolinones (2–6)

	bacterial growth at given concn in μg/mL					
	Escherichia coli			*Staphylococcus aureus*		
compd no.	12.5	25	100	12.5	25	100
2b	–	–	+	–	++	++
2g	–	+	+	–	+	+
2j	–	–	–	–	–	+
2k	–	+	+	–	–	–
2o	–	+	+	–	–	+
3b	–	–	–	–	–	+
3f	–	–	–	–	–	–
3p	–	–	+	–	–	–
4d	–	–	+	–	+	++
4g	–	–	–	–	+	++
4i	–	–	+	+	+	++
4o	–	+	++	+	+	++
5i	–	–	+	–	+	+
5m	–	+	+	+	+	++
6i	–	+	+	–	–	–

[a] The activity is indicated as inactive (–), slight (+), or marked (++).

Experimental Section

Melting points were determined in an open capillary on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 257 and 720 spectrophotometers and NMR spectra on a Jeol FX 90Q spectrometer at 90 MHz at the probe temperature of 27 °C with Me_4Si as an internal reference. Elemental analyses were carried out on a Coleman analyser. Purity of compounds was checked by TLC using silica gel G (E. Merck).

The 5-bromo- and 3,5-dibromoanthranilic acids were prepared by known methods (*7*). 3-Bromopropylamine hydrobromide was purchased from Ega-chemie, Steinheim, West Germany. *N*-substituted and *N*,*N*-disubstituted 2-bromoethylamine hydrobromides, the required intermediates, were obtained from the corresponding 2-aminoethanols by reaction with 48% hydrobromic acid as described earlier (*6*, *8*). In this manner *N*,*N*-diisopropyl-2-bromoethylamine hydrobromide, mp 140–142 °C was also prepared. It gave satisfactory elemental analyses (C, H, Br) and they were submitted for review.

***2-Thio-3-(3′-chloro-2′-methylphenyl)-6,8-dibromo-4-(3H)-quinazolinone* (*1*, *X* = *Y* = *Br*).** Equimolar quantities of 3,5-dibromoanthranilic acid (14.7 g) and 3-chloro-2-methylphenyl isothiocyanate (9.0 g) in 50 mL of absolute ethanol were refluxed on a water bath for 6 h. After cooling, the solid product was filtered and washed with 5% sodium hydrogen carbonate solution followed by a little of aqueous ethanol. The solid product was dissolved in 10% alcoholic sodium hydroxide solution, filtered, and reprecipitated by the addition of dilute hydrochloric acid. The product was finally washed with water and crystallized from ethanol, yield 70%, mp 210 °C. It gave elemental analyses (N, S) within ±0.3% of the theoretical values. IR (Nujol) 3450, m; 3350, m (overtone); 1660, s; 1610, m; 1260, w, cm^{-1}.

***2-Thio-3-(5′-chloro-2′-methylphenyl)-6,8-dibromo-4-(3H)-quinazolinone* (*1*, *X* = *Y* = *Br*).** This compound was prepared by the interaction of 3,5-dibromoanthranilic acid with 5-chloro-2-methylphenyl isothiocyanate under the conditions described above. The product was crystallized from ethanol, yield 72%, mp 195 °C. It gave satisfactory microanalytical results (C, H, Br). IR (Nujol) 3450, m; 3350, m (overtone); 1680, s; 1610, m; 1240, s, cm^{-1}.

Other 2-thio-3-aryl(or alkyl)-4(3*H*)-quinazolinones (*9*), 2-thio-3-aryl-6-bromo-4(3*H*)-quinazolinones (*10*), and 2-thio-3-aryl-6,8-dibromo-4(3*H*)-quinazolinones (*11*) were prepared according to the procedures published from this laboratory.

***2-(β-Aminoethylthio)-3-(p-tolyl)-6,8-dibromo-4(3H)-quinazolinone* (*2n*).** 2-Thio-3-(*p*-tolyl)-6,8-dibromo-4(3*H*)-quinazolinone (4.2 g) was dissolved in a just sufficient amount of 5% ethanolic sodium hydroxide solution and treated with 2-bromoethylamine hydrobromide (2.2 g) in 15 mL of absolute

Table II. 2-(β-Aminoethylthio)-3-aryl(or alkyl)-6,8-disubstituted-4(3*H*)-quinazolinones (2)

compd no.	substituents R	X	Y	yield, %	mp, °C
2a	*m*-$CH_3C_6H_4$	H	H	70	272
2b	*p*-$CH_3C_6H_4$	H	H	68	267
2c	*m*-ClC_6H_4	H	H	80	277
2d	*p*-ClC_6H_4	H	H	78	295
2e	*p*-$CH_3OC_6H_4$	H	H	75	282
2f	*p*-$C_2H_5OC_6H_4$	H	H	68	285
2g	C_2H_5	H	H	62	240
2h	*o*-$CH_3C_6H_4$	Br	H	65	276
2i	*m*-$CH_3C_6H_4$	Br	H	68	>340
2j	*p*-$CH_3C_6H_4$	Br	H	62	312
2k	*o*-$CH_3OC_6H_4$	Br	H	65	285
2l	*p*-$C_2H_5OC_6H_4$	Br	H	70	313
2n	*p*-$CH_3C_6H_4$	Br	Br	55	165
2o	*p*-ClC_6H_4	Br	Br	57	125

Table III. 2-(γ-Aminopropylthio)-3-aryl(or alkyl)-6,8-disubstituted-4(3*H*)-quinazolinones (3)

compd no.	substituents R	X	Y	yield, %	mp, °C
3a	*m*-$CH_3C_6H_4$	H	H	76	270
3b	*p*-$CH_3C_6H_4$	H	H	77	273
3c	*m*-ClC_6H_4	H	H	78	278
3d	*p*-ClC_6H_4	H	H	72	303
3e	*p*-$CH_3OC_6H_4$	H	H	80	248
3f	*p*-$C_2H_5OC_6H_4$	H	H	75	295
3g	C_2H_5	H	H	65	170
3h	*o*-$CH_3C_6H_4$	Br	H	70	300
3i	*m*-$CH_3C_6H_4$	Br	H	68	288
3j	*p*-$CH_3C_6H_4$	Br	H	70	285
3k	*o*-$CH_3OC_6H_4$	Br	H	67	288
3l	*p*-$C_2H_5OC_6H_4$	Br	H	72	305
3m	*m*-$CH_3C_6H_4$	Br	Br	63	190
3n	*p*-$CH_3C_6H_4$	Br	Br	62	85
3p	3′-Cl-2′-$CH_3C_6H_3$	Br	Br	55	77
3q	5′-Cl-2′-$CH_3C_6H_3$	Br	Br	65	90

Table IV. 2-[[β-(Diisopropylamino)ethyl]thio]-3-aryl(or alkyl)-6,8-disubstituted-4(3*H*)-quinazolinones (4)

compd no.	substituents R	X	Y	yield, %	mp, °C
4a	*m*-$CH_3C_6H_4$	H	H	71	265
4b	*p*-$CH_3C_6H_4$	H	H	74	230
4c	*m*-ClC_6H_4	H	H	74	237
4d	*p*-ClC_6H_4	H	H	70	103
4e	*p*-$CH_3OC_6H_4$	H	H	78	123
4f	*p*-$C_2H_5OC_6H_4$	H	H	76	125
4g	C_2H_5	H	H	63	235
4h	*o*-$CH_3C_6H_4$	Br	H	68	87
4i	*m*-$CH_3C_6H_4$	Br	H	74	178
4j	*p*-$CH_3C_6H_4$	Br	H	70	93
4l	*p*-$C_2H_5OC_6H_4$	Br	H	72	110
4o	*p*-ClC_6H_4	Br	Br	64	91

ethanol at room temperature. The mixture was stirred and allowed to stand for 1 h. The product was filtered and washed several times with water followed by a little ethanol. It was crystallized from ethanol–benzene (1:1) to form white crystals, yield 55%, mp 165 °C. The structure of the compound was confirmed by the spectral data: IR (Nujol) 3240, w; 3100, m (N–H stretchings); 1720, m (C=O str); 1660, s; 1610, m; 1505, m, cm^{-1}. NMR (Me_2SO-d_6) δ 2.40 (s, 3 H, CH_3), 2.53–3.30 (m, 4 H, $-CH_2CH_2-$), 7.06–8.00 (m, 6 H, Ar-*H*), 12.86–13.13 (broad, 2 H, $-NH_2$).

Table V. 2-[[β-(Diethylamino)ethyl]thio]- and 2-[[β-(Isopropylamino)ethyl]thio]-3-aryl-6,8-disubstituted-4-(3*H*)-quinazolinones (5 and 6)

compd no.	substituents R	X	Y	yield, %	mp, °C
5i	*m*-$CH_3C_6H_4$	Br	H	71	>360
5l	*p*-$C_2H_5OC_6H_4$	Br	H	68	101
5m	*m*-$CH_3C_6H_4$	Br	Br	69	110
6h	*o*-$CH_3C_6H_4$	Br	H	74	296
6j	*p*-$CH_3C_6H_4$	Br	H	77	305

Following this procedure the title compounds **2–6** were prepared by the interaction of 2-thio-3-aryl(or alkyl)-6,8-disubstituted-4(3*H*)-quinazolinones (**1**) with different N-substituted and N,N-disubstituted 2-bromoethylamine or 3-bromopropylamine hydrobromide salts. Their yields and melting points are reported in Tables II–V. All these compounds gave elemental analyses for C, H, and N within ±0.4% of the calculated values.

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Registry No. **1a**, 37641-49-9; **1b**, 37641-50-2; **1c**, 1028-38-2; **1d**, 1028-40-6; **1e**, 1031-88-5; **1f**, 1035-51-4; **1g**, 13906-08-6; **1h**, 18009-08-0; **1i**, 18009-09-1; **1j**, 18009-10-4; **1k**, 18009-13-7; **1l**, 18009-14-8; **1m**, 18730-29-5; **1n**, 18730-30-8; **1o**, 18730-32-0; **1p**, 108534-45-8; **1q**, 108534-46-9; **2a**, 108534-15-2; **2b**, 108534-02-7; **2c**, 108534-16-3; **2d**, 108534-17-4; **2e**, 108534-18-5; **2f**, 108534-19-6; **2g**, 108534-03-8; **2h**, 108534-20-9; **2i**, 108534-21-0; **2l**, 108534-22-1; **2n**, 108534-23-2; **2o**, 108534-04-9; **3a**, 108534-24-3; **3b**, 108534-05-0; **3c**, 108534-25-4; **3d**, 108534-26-5; **3e**, 108534-27-6; **3f**, 108534-06-1; **3g**, 108534-28-7; **3h**, 108534-29-8; **3i**, 108534-30-1; **3j**, 108534-31-2; **3k**, 108534-32-3; **3l**, 108534-33-4; **3m**, 108534-34-5; **3n**, 108534-35-6; **3p**, 108534-07-2; **3q**, 108534-36-7; **4a**, 108534-37-8; **4b**, 108534-38-9; **4c**, 108534-39-0; **4d**, 108534-08-3; **4e**, 108534-40-3; **4f**, 108534-41-4; **4g**, 108534-09-4; **4h**, 108534-42-5; **4i**, 108534-10-7; **4j**, 108534-43-6; **4l**, 108534-44-7; **4o**, 108534-11-8; **5i**, 108534-12-9; **5l**, 58126-07-1; **5m**, 108534-13-0; **6h**, 108534-14-1; **6j**, 58126-01-5; *m*-$MeC_6H_4N{=}C{=}S$, 621-30-7; *p*-$MeC_6H_4N{=}C{=}S$, 622-59-3; *m*-$ClC_6H_4N{=}C{=}S$, 2392-68-9; *p*-$ClC_6H_4N{=}C{=}S$, 2131-55-7; *p*-$MeOC_6H_4N{=}C{=}S$, 2284-20-0; *p*-$EtOC_6H_4N{=}C{=}S$, 3460-49-9; $EtN{=}C{=}S$, 542-85-8; *o*-$MeC_6H_4N{=}C{=}S$, 614-69-7; *o*-$MeOC_6H_4N{=}C{=}S$, 3288-04-8; 3-Cl-2-$MeC_6H_3N{=}C{=}S$, 19241-35-1; 5-Cl-2-$MeC_6H_3N{=}C{=}S$, 19241-36-2; $Br(CH_2)_2NH_2{\cdot}HBr$, 2576-47-8; $Br(CH_2)_3NH_2{\cdot}HBr$, 5003-71-4; $Br(CH_2)_2N(Pr\text{-}i)_2{\cdot}HBr$, 90221-87-7; $Br(CH_2)_2N(Et)_2{\cdot}HBr$, 1069-72-3; $Br(CH_2)_2NHPr\text{-}i{\cdot}HBr$, 96400-94-1; anthranilic acid, 118-92-3; 5-bromoanthranilic acid, 5794-88-7; 3,5-dibromoanthranilic acid, 609-85-8.

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