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Studies on Synthesis of 6-Bromo-2,3-disubstituted 4(3*H*)-Quinazolinones and Their Thiones

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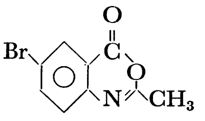
Synthesis of some 2,3-disubstituted 6-bromo-4(3*H*)-quinazolinones is described. Treatment of some 4-quinazolinones with phosphorus pentasulfide gave the corresponding 4-quinazolinethiones. The reaction of 6-bromo-2-methyl-3,1-benzoxazin-4-one with hydroxylamine hydrochloride gave 6-bromo-3-hydroxy-2-methyl-4(3*H*)-quinazolinone which on treatment with alkyl halides, acyl chlorides and sulfonyl chlorides gave the corresponding ethers, esters, and sulfonates respectively. 2-Styryl-4(3*H*)-quinazolinone derivatives are obtained by condensation of aromatic aldehydes and corresponding 3-substituted-6-bromo-2-methyl-4(3*H*)-quinazolinones. Their antibacterial affinities are of considerable efficiency.

4(3*H*)-Quinazolinones have become of increasing importance in recent years owing to their interesting pharmacological properties,1) and their use as analgesics,2) potential anticonvalsant,3) muscle relaxant,4) and long-acting sedatives.5)

6-Bromo-2-methyl-3,1-benzoxazin-4-ones (**1**) are known to react with amines to give the corresponding 4-quinazolinones,6—8) which were condensed7,9) with aromatic aldehydes to afford the corresponding 6-bromo-2-(2-arylvinyl)-4(3*H*)-quinazolinones (**2b**—**f**) (*cf.* Table 1).

Reaction of 6-bromo-4-quinazolinones (**2a**,**c**—**e**) with phosphorus pentasulfide in boiling pyridine gave the corresponding 4-quinazolinethiones10—12) (**3a**,**c**—**e**) (*cf.* Table 1). The structures of **3** were established by their elemental and spectral analyses. Their IR spectra showed the stretching vibration bands of C=S (1230—1250 cm^{-1}) and C=N (1615—1630 cm^{-1}).



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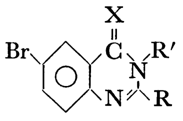


2; X=O
3; X=S

	R	R′
a;	$-CH_3$	$-C_6H_4CH_3$-*p*
b;	$-CH=CHC_6H_4OCH_3$-*p*	$-C_6H_5$
c;	$-CH=CHC_6H_4Cl$-*m*	$-C_6H_4CH_3$-*p*
d;	$-CH=CHC_6H_4Cl$-*p*	$-C_6H_4CH_3$-*p*
e;	$-CH=CHC_6H_4NO_2$-*P*	$-C_6H_4CH_3$-*P*
f;	$-CH=CHC_6H_5$	$-C_6H_4CH_3$-*p*
g;	$-CH_3$	2-C_5H_4N
h;	$-CH_3$	2-C_5H_4N

These compounds were reconverted to **2** by boiling with dilute hydrochloric acid. Also, condensation of **1** with heterocyclic amines,13—15) namely, 2- and 3-aminopyridines, 2-aminothiazoles, 2-aminobenzoxazole and 2-aminobenzothiazole in dry pyridine gave the corresponding 6-bromo-4-quinazolinones (**2h**, **i**, **4**, and **5a**,**b**) (*cf.* Tables 1 and 2).

TABLE 1. 6-BROMO-2-(2-ARYLVINYL)-4-QUINAZOLINONES (**2**) AND 4-THIONES (**3**)

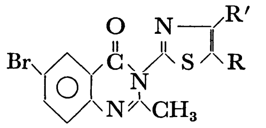
No.	Mp / °C	Molecular formula	Calcd (Found) (%) C	H	N	S	Br
2b	264—265	$C_{23}H_{17}N_2O_2Br$	63.74 (63.26)	3.92 (3.71)	6.46 (6.36)	— —	18.47 (18.21)
2c	203—204	$C_{23}H_{16}N_2OClBr$	61.13 (60.91)	3.54 (3.21)	6.20 (6.42)	— —	
2d	228—229	$C_{23}H_{16}N_2OClBr$	61.13 (61.61)	3.54 (3.45)	6.20 (6.22)	— —	
2ea)	301—302	$C_{23}H_{16}N_3O_3Br$	59.74 (59.64)	3.46 (3.56)	9.09 (9.22)	— —	17.31 (16.76)
2f	216—217	$C_{23}H_{17}N_2OBr$	66.18 (66.23)	4.07 (4.09)	6.71 (6.81)	— —	19.18 (19.68)
2g	205	$C_{14}H_{10}N_3OBr$	53.16 (53.61)	3.16 (3.22)	13.29 (13.33)	— —	25.31 (25.61)
2h	190	$C_{14}H_{10}N_3OBr$	53.16 (53.16)	3.16 (3.36)	13.29 (13.21)	— —	25.31 (25.91)
3a	190—191	$C_{16}H_{13}N_2SBr$	52.33 (52.21)	4.04 (4.31)	8.72 (8.64)	9.96 (9.71)	24.92 (24.10)
3c	146	$C_{23}H_{16}N_2SClBr$	59.03 (58.61)	3.42 (3.31)	5.98 (5.81)	6.84 (6.61)	— —
3d	256—257	$C_{23}H_{16}N_2SClBr$	59.03 (58.61)	3.42 (3.41)	5.98 (5.81)	6.84 (6.61)	— —
3ea)	320	$C_{23}H_{16}N_3O_2SBr$	57.74 (57.61)	3.34 (3.12)	8.78 (8.61)	6.69 (8.61)	16.73 (16.66)

a) Crystallized from pyridine.

Table 2. 3-Substituted-6-bromo-2-methyl-4-quinazolinones (4 and 5)

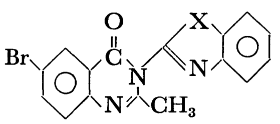
No.	Mp/°C	Molecular formula	Calcd (Found) (%) C	H	N	S	Br
4a	174—176	$C_{18}H_{12}N_3OSBr$	54.27 (53.68)	3.01 (3.20)	10.55 (10.21)	8.04 (8.21)	20.10 (20.40)
4b	221	$C_{18}H_{14}N_3OSBr$	55.33 (55.61)	3.30 (3.21)	10.19 (10.14)	7.76 (7.41)	19.41 (19.31)
4c	191—192	$C_{19}H_{14}N_3O_2SBr$	53.27 (53.11)	3.27 (3.11)	9.81 (9.81)	7.47 (7.63)	18.69 (18.41)
4d	195—196	$C_{16}H_{14}N_3O_3SBr$	47.05 (47.12)	3.43 (3.33)	10.29 (10.21)	7.84 (7.61)	19.60 (19.41)
4e	241	$C_{24}H_{16}N_3SBr$	62.88 (62.41)	3.49 (3.52)	9.17 (8.81)	6.99 (6.60)	17.46 (17.14)
5a	222	$C_{16}H_{10}N_3O_2Br$	53.93 (53.42)	2.80 (2.61)	11.79 (11.61)	— —	22.47 (22.11)
5b[a)]	241	$C_{16}H_{10}N_3OSBr$	51.61 (51.41)	2.68 (2.61)	11.29 (11.41)	8.60 (8.41)	21.50 (21.46)

a) Crystallized from acetic acid.



4

	R	R′
4a;	H	$-C_6H_5$
b;	H	$-C_6H_4CH_3$-*p*
c;	H	$-C_6H_4OCH_3$-*p*
d;	$-COOC_2H_5$	$-CH_3$
e;	$-C_6H_5$	$-C_6H_5$

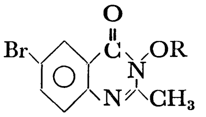


5

5a; X=O

Their structures were established by elemental and spectral analyses. Their IR spectra showed the stretching vibration bands of C=O (1720—1680 cm^{-1}) and C=N (1630—1615 cm^{-1}).

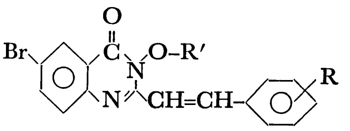
On the other hand, treating 6-bromo-2-methyl-3,1-benzoxazin-4-ones (**1**) with hydroxylamine hydrochloride in presence of potassium hydroxide gave the corresponding 6-bromo-2-methyl-3-hydroxy-4(3*H*)-quinazolinones[16—17] (**6a**). Reactions of 6-bromo-4-quinazolinone (**6a**) with alkyl halides, acyl chlorides and sulfonyl chlorides gave the corresponding ethers (**6b**—**e**), esters (**6f**—**e**), and sulfonates (**6j**,**k**) respectively. (*cf*. Table 3).



6

	R		R
a;	H	**g**;	$-COC_6H_4NO_2$-*p*
b;	*n*-C_4H_9	**h**;	$-COC_6H_4Cl$-*p*
c;	$-CH_2C_6H_5$	**i**;	$-COCH_2C_6H_5$
d;	$-CH_2C_6H_4NO_2$-*p*	**j**;	$-SO_2C_6H_5$
e;	$-CH_2C_{10}H_7$-α	**k**;	$-SO_2C_6H_4CH_3$-*p*
f;	$-COC_6H_5$		

On the other hand, when **6a** was condensed with aromatic aldehydes,[9)] it gave the corresponding 6-bromo-2-(2-arylvinyl)-3-hydroxy-4-quinazolinones (**7a**—**d**), which reacted with alkyl halides, sulfonyl chlorides to give the corresponding ethers (**8a**—**e**), and sulfonates (**8f**—**g**) respectively (*cf*. Table 4). Moreover



	R	R′		R	R′
7a;	H	H	**8a**;	*m*-Cl	$-CH_2C_6H_5$
b;	*p*-OCH_3	H	**b**;	*p*-OCH_3	$-CH_3$
c;	*p*-Cl	H	**c**;	*p*-OCH_3	*n*-C_4H_9
d;	*m*-Cl	H	**d**;	*p*-OCH_3	$-CH_2C_6H_5$
			e;	*p*-OCH_3	$-CH_2C_{10}H_7$-α
			f;	*p*-OCH_3	$-SO_2C_6H_4CH_3$-*p*
			g;	*p*-Cl	$-SO_2C_6H_4CH_3$-*p*

(**8a**,**e**—**g**) were also obtained by condensing (**6c**,**e**,**d**) with the corresponding aromatic aldehydes.

The IR spectra of **6a** and **7a**—**d** showed stretching vibration bands of OH (3360—3340 cm^{-1}), C=O (1720—1680 cm^{-1}), and C=N (1650—1620 cm^{-1}). However, the IR spectra of **6b**—**k** and **8a**—**h** did not show stretching vibration bands of OH groups.

The UV spectra of **2a**,**b**, **3a**, **4c**, **5a**,**b**, and **8d** in ethanol are similar to those of 2,3-disubstituted 4(3*H*)-quinazolinones,[9)] showing two main bands in the region 280—288 and 325—350 nm, (*cf*. Table 5).

Table 5. UV spectral data of 2,3-disubstituted 4(3*H*)-quinazolinones

Compound	λ_{max} nm (ε)			
2a	285 (7000)	325 (3000)	—	—
2b	282 (9000)	350 (10000)	—	—
3a	287 (5000)	353 (4000)	370 (5000)	383 (3000)
4c	287 (7000)	340 (5000)	—	—
5a	287 (9000)	335 (4000)	—	—
5b	282 (8000)	340 (11000)	—	—
8d	287 (27000)	350 (41000)	—	—

The higher red shifts of the electronic absorption bands for the compound (**3a**) compared with that of the corresponding compound (**2a**) become understandable in view of the higher energy level of nonbonding electrons in sulfur compared to oxygen.[18)] The band at 370 nm presumably arises from π-π* and n-π* transitions in the C=S group.[18)]

Biological screening results: The antimicrobial activities of the prepared compounds against a variaty of microbes were determined.[19] These microorganisms include Gram-positive and Gram-negative bacteria.

The bacteria used are: *Bacillus subtilis*, *Staphylcoccus aureus*, *Escherichia coli*, *Pesudomonas aeruginosa*, *Mycobacterium pheli*, *Proteus morganii*, *Serratia* and *Bacillus megaterium*.

The results showed that most of the prepared compounds (**3a**, **4a**—**c**,**e**, **5b**, and **6c**,**g**,**h**,**k**) show from a little to a strong activity on the Gram-positive and Gram-negative bacteria. The activity expressed in percent range 40—70% inhibition was found at concentration 10^{-3} M. The more strong active compounds against *Staphylcoccus aureus* are **6c**,**g**,**h**, that against *Pesudomonas aeruginosa*, *Mycobacterium pheli* and *Escherichia coli* is **6h** and those against *Eschericha coli* are **4a**—**c** and **6k** and those against *Serratia*, *Bacillus megaterium* and *Staphylcoccus aureus* are **3a**, **4a**—**c**,**e**, and **5b**, respectively.

TABLE 3. 6-BROMO-2-METHYL-3-HYDROXY-4-QUINAZOLINONES AND THEIR ETHERS AND ESTERS (**6**)

No.	Mp/C°	Molecular formula	Calcd (Found) (%) C	H	N	S	Br
6a	249—250	$C_9H_7N_2O_2Br$	42.35 (42.41)	2.74 (2.61)	10.98 (10.18)	— —	31.37 (31.21)
6b	146—147	$C_{13}H_{15}N_2O_2Br$	50.16 (50.61)	4.82 (4.61)	9.00 (9.61)	— —	25.72 (25.11)
6c	174—175	$C_{16}H_{13}N_2O_2Br$	55.65 (55.41)	3.76 (3.16)	8.11 (8.12)	— —	23.18 (23.22)
6d	215—216	$C_{16}H_{12}N_3O_4Br$	49.23 (49.16)	3.07 (3.41)	10.76 (10.44)	— —	20.51 (20.91)
6e	190—191	$C_{20}H_{15}N_2O_2Br$	60.75 (60.11)	3.79 (3.88)	7.08 (7.11)	— —	20.25 (20.46)
6f	162—163	$C_{16}H_{11}N_2O_3Br$	53.48 (53.11)	3.06 (3.21)	7.79 (7.61)	— —	22.28 (22.11)
6g	227—228	$C_{16}H_{10}N_3O_5Br$	47.52 (47.41)	2.47 (2.61)	10.39 (10.61)	— —	19.80 (19.66)
6h	175—176	$C_{16}H_{10}N_2O_3ClBr$	48.79 (48.11)	2.54 (2.61)	7.11 (7.14)	— —	— —
6i	144—145	$C_{17}H_{13}N_2O_3Br$	57.14 (56.91)	3.64 (3.41)	7.84 (7.61)	— —	22.40 (22.11)
6j	162—163	$C_{15}H_{11}N_2O_4SBr$	45.56 (45.41)	2.78 (2.61)	7.08 (7.21)	8.10 (8.61)	20.22 (20.91)
6k	165—166	$C_{16}H_{13}N_2O_4SBr$	46.94 (46.71)	3.17 (3.11)	6.84 (6.16)	7.82 (7.11)	19.55 (19.41)

TABLE 4. 6-BROMO-2-(2-ARYLVINYL)-3-HYDROXY-4-QUINAZOLINONES AND THEIR ETHERS AND ESTERS (**7** and **8**)

No.	Mp/°C	Molecular formula	Calcd (Found) (%) C	H	N
7a	221—222	$C_{16}H_{11}N_2O_2Br$	55.97 (55.61)	3.20 (3.30)	8.16 (8.11)
7b	261	$C_{17}H_{13}N_2OBr$	54.66 (54.16)	3.48 (3.12)	7.50 (6.87)
7c	300	$C_{16}H_{10}N_2O_2ClBr$	50.86 (51.06)	2.64 (2.81)	6.87 (7.74)
7d	259	$C_{16}H_{10}N_2O_2ClBr$	50.86 (51.12)	2.64 (2.81)	7.41 (7.18)
8a	186—187	$C_{23}H_{16}N_2O_2ClBr$	59.03 (59.21)	3.42 (3.31)	5.98 (5.81)
8b	208—209	$C_{18}H_{15}N_2O_3Br$	55.81 (55.61)	3.87 (3.61)	7.23 (7.41)
8c	169—170	$C_{21}H_{21}N_2O_3Br$	58.74 (58.31)	4.89 (4.61)	6.52 (6.23)
8d	184	$C_{24}H_{19}N_2O_3Br$	62.20 (61.91)	4.10 (4.31)	6.00 (6.21)
8e	216—217	$C_{28}H_{21}N_2O_2Br$	67.60 (67.21)	4.22 (4.66)	5.63 (5.41)
8f	170—171	$C_{24}H_{19}N_2O_5SBr$	54.64 (54.81)	3.60 (3.41)	5.31 (5.11)
8g	243	$C_{23}H_{16}N_2O_4SBr$	55.64 (55.81)	3.22 (3.61)	5.64 (5.68)

Experimental

Melting points reported are uncorrected. Elemental analysis was carried out on a Colman C, H, and N analyser. IR spectra were recorded on a Perkin-Elmer infracord. The biological screening was carried out at the Microbiological Laboratory, Department of Botany, Assiut University.

6-Bromo-2-methyl-3,1-benzoxazin-4-one (1).[7] Pale yellow needles from carbon tetrachloride, mp 130—131 °C.

6-Bromo-2-methyl-3-p-tolyl-4(3H)-quinazolinone (2a).[8] Colourless needles from ethanol, mp 131—132 °C.

3-Substituted 6-Bromo-2-(2-arylvinyl)-4(3H)-quinazolinones (2c—f and 7, 8): 3-Substituted 6-bromo-2-methyl-4(3*H*)-quinazolinone (**2a**, **b**, or **6a**) was refluxed with corresponding aldehydes for 10 min. The cooled reaction mixtures gave precipitates on adding ethanol, which were filtered and crystallized from ethanol. The yield was about 80—90%. The results are listed in Table 1.

2,3-Disubstituted 6-Bromo-4(3H)-quinazolinethiones (3): A mixture of **2a**—**f** (0.01 mol) and phosphorus pentasulfide (0.01 mol) in 100 ml pyridine was refluxed for 5 h. The reaction mixture was cooled and poured into dilute acetic acid. The crude product was filtered, washed with water and recrystallized from the proper solvent. The results are listed in Table 1.

Reaction of 1 with Heterocyclic Amines (2h, i, 4, and 5): A mixture of 1 (0.01 mol) and corresponding heterocyclic amines (0.013 mol) in 100 ml dry pyridine was refluxed for 5 h. The solvent was evaporated to dryness, and the residue was washed with dilute acetic acid followed by water. The crude product was filtered, dried and recrystallized from the proper solvent. The results are listed in Tables 1 and 2.

6-Bromo-2-methyl-3-hydroxy-4(3H)-quinazolinone (7a). To a mixture of 1 (0.01 mol) and hydroxylamine hydrochloride (0.03 mol), a dilute solution of potassium hydroxide (0.05 mol) was slowly added with vigorous shaking. The reaction mixture was heated on a water bath for 30 min and then acidified with dilute acetic acid. The crude product was filtered, dried and crystallized from ethanol–benzene mixture as white needles, mp 245 °C (sublimed).

Reaction of 6a and 7 with Alkyl Halides, Acyl Chlorides, and Sulfonyl Chlorides (6b—k and 8). To a suspension of **6a** or **7a**—**d** (0.01 mol) in dry acetone (50 ml), was added 0.011 mol of anhydrous potassium carbonate and 0.011 mol of alkyl halides, acyl chloride, or sulfonyl chlorides. The mixture was heated on a steam bath for 3 h. After filtration acetone was evaporated. The crude product was recrystallized from the proper solvent, yield being about 80%. The results are listed in Tables 3 and 4.

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