BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 1444—1446 (1969)

# Studies on 6-Bromo-2-mercapto-3-substituted 4-(3*H*)-Quinazolinones

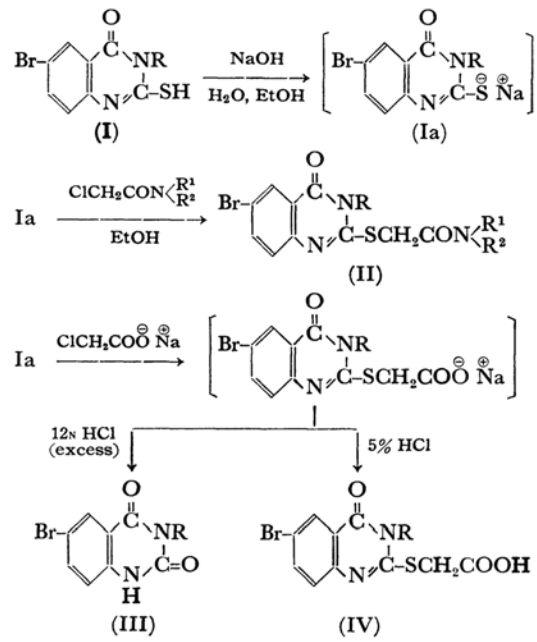
P. N. Bhargava and R. Lakhan

*The Chemistry Department, Faculty of Science, Banaras Hindu University, Varanasi-5, India*

(Received July 26, 1968)

In continuation of our earlier work on heterocyclic sulphur compounds of interest as antimalarials and ataractic agents,[1] we have extended the alkylation of the sodium salts of 6-bromo-2-mercapto-3-aryl(or alkyl)-4(3*H*)-quinazolinones in alcoholic alkali solution with typical halogen compounds (prepared by the interaction of chloroacetyl chloride and secondary amines in benzene) and also with monochloroacetic acid.

In the present communication, for example, when 6-bromo-2-mercapto-3-substituted 4(3*H*)-quinazolinone (I) was treated with aqueous alcoholic alkali, the sodium salt (Ia) was formed (soluble in aqueous ethanol) which without isolation was converted to the *S*-substituted derivative (II) by reaction with *N,N*-disubstituted chloroacetamides as shown in the reaction scheme.




An interesting point was observed when the sodium salt (Ia) was treated in cold with sodium monochloroacetate and the precipitate obtained was kept in contact with excess of concentrated hydrochloric acid. The product was then found to be the corresponding 2-hydroxyquinazolinone (III) and not the expected 2-carboxymethylthio derivative (IV). The structure of the 2,4-diketo derivative (III) was confirmed by preparing it from 5-bromoanthranilic acid and the corresponding urea.[2]

However, the 2-carboxymethylthio derivative (IV) was obtained by a modified procedure. The solution of the sodium salt (Ia) on treatment with sodium monochloroacetate and subsequent acidification with 5% hydrochloric acid gave the desired product (IV).

## Experimental

**6-Bromo-2-mercapto-3-substituted 4-(3*H*)-Quinazolinones (I).** These were prepared by the condensation of 5-bromoanthranilic acid and various isothiocyanates as described earlier.[1]

**6-Bromo-2-(*N,N*-diethylcarbamoyl)methylthio-3-phenyl-4-(3*H*)-quinazolinone (II).** 6-Bromo-2-mercapto-3-phenyl-4-(3*H*)-quinazolinone (I,R = $C_6H_5$ 6.66 g) was dissolved in minimum amount of 10% sodium hydroxide solution (prepared in 50% ethanol). The solution was filtered and treated with 3.3 g of *N,N*-diethylchloroacetamide dissolved in 10 m*l* of ethanol. The reaction mixture was stirred at room temperature for about 4 hr when a precipitate was obtained. It was filtered, washed with water, ethanol and recrystallized from ethanol into colourless crystals.

Following the same procedure other 6-bromo-2-(*N,N*-disubstituted carbamoyl)methylthio-3-substituted 4-(3*H*)-quinazolinones have been prepared. Their yields, melting points and analytical data are recorded in Tables 1—4.

**6-Bromo-3-phenyl-2,4-(1*H*, 3*H*)-quinazolindione (III).** 6-Bromo-2-mercapto-3-phenyl-4-(3*H*)-quinazolinone (0.01 mol) was dissolved in 2.1 equivalents of 1N sodium hydroxide solution (in 50% ethanol) and the resulting solution was treated in cold with monochloroacetic acid (0.011 mol). The reaction mixture was stirred for 4—6 hr when a precipitate was obtained. It was filtered and the residue was kept in contact with excess of 12N hydrochloric acid at room temperature for 2 hr. The reaction mixture was then filtered and washed several times with water to remove the acid and dried. It was crystallized from acetone-ethanol mixture (1 : 1) into colourless needles to give 68% yield of 6-bromo-3-phenyl-2,4-(1*H*,3*H*)-quinazolindione.

1) P. N. Bhargava and R. Lakhan, *Current Sci. (India)*, **36**, 575 (1967), and references cited therein.

2) G. R. Dave, G. S. Mewada and G. C. Amin, *Acta Chim. Acad. Sci. Hung.*, **34**, 101 (1962).

Table 1. 6-Bromo-2-(*N*,*N*-diethylcarbamoyl)methylthio-3-substituted 4-(3*H*)-quinazolinones (II)

| No. | R | Yield % | Mp °C | Formula | % Nitrogen | | % Sulphur | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Found | Calcd | Found | Calcd |
| 1 | $C_6H_5$ | 80 | 201 | $C_{20}H_{20}BrN_3O_2S$ | 9.30 | 9.42 | 7.11 | 7.17 |
| 2 | *o*-$CH_3\cdot C_6H_4$ | 57 | 169 | $C_{21}H_{22}BrN_3O_2S$ | 9.05 | 9.13 | 7.09 | 6.95 |
| 3 | *m*-$CH_3\cdot C_6H_4$ | 43 | 224 | $C_{21}H_{22}BrN_3O_2S$ | 9.26 | 9.13 | 6.82 | 6.95 |
| 4 | *p*-$CH_3\cdot C_6H_4$ | 85 | 192 | $C_{21}H_{22}BrN_3O_2S$ | 9.18 | 9.13 | 6.78 | 6.95 |
| 5 | *m*-$Cl\cdot C_6H_4$ | 45 | 157 | $C_{20}H_{19}BrClN_3O_2S$ | 8.78 | 8.74 | 6.51 | 6.66 |
| 6 | *p*-$Cl\cdot C_6H_4$ | 72 | 181 | $C_{20}H_{19}BrClN_3O_2S$ | 8.89 | 8.74 | 6.45 | 6.66 |
| 7 | *o*-$CH_3O\cdot C_6H_4$ | 49 | 163 | $C_{21}H_{22}BrN_3O_3S$ | 8.65 | 8.82 | 6.62 | 6.72 |
| 8 | *p*-$CH_3O\cdot C_6H_4$ | 75 | 171 | $C_{21}H_{22}BrN_3O_3S$ | 8.78 | 8.82 | 6.72 | 6.72 |
| 9 | *p*-$C_2H_5O\cdot C_6H_4$ | 82 | 165 | $C_{22}H_{24}BrN_3O_3S$ | 8.40 | 8.57 | 6.49 | 6.53 |
| 10 | $CH_3$ | 40 | 120 | $C_{15}H_{18}BrN_3O_2S$ | 11.05 | 10.93 | 8.27 | 8.33 |
| 11 | $C_2H_5$ | 50 | 135 | $C_{16}H_{20}BrN_3O_2S$ | 10.37 | 10.55 | 7.93 | 8.04 |
| 12 | $C_6H_5\cdot CH_2$ | 78 | 143 | $C_{21}H_{22}BrN_3O_2S$ | 9.02 | 9.13 | 6.99 | 6.95 |

Table 2. 6-Bromo-2-(*N*-methyl-*N*-phenylcarbamoyl)methylthio-3-substituted 4-(3*H*)-quinazolinones

| No. | R | Yield % | Mp °C | Formula | % Nitrogen | | % Sulphur | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Found | Calcd | Found | Calcd |
| 1 | $C_6H_5$ | 50 | 242 | $C_{23}H_{18}BrN_3O_2S$ | 8.91 | 8.75 | 6.76 | 6.67 |
| 2 | *o*-$CH_3\cdot C_6H_4$ | 70 | 209 | $C_{24}H_{20}BrN_3O_2S$ | 8.37 | 8.50 | 6.59 | 6.48 |
| 3 | *m*-$CH_3\cdot C_6H_4$ | 78 | 204 | $C_{24}H_{20}BrN_3O_2S$ | 8.52 | 8.50 | 6.47 | 6.48 |
| 4 | *p*-$CH_3\cdot C_6H_4$ | 65 | 188 | $C_{24}H_{20}BrN_3O_2S$ | 8.49 | 8.50 | 6.65 | 6.48 |
| 5 | *p*-$Cl\cdot C_6H_4$ | 52 | 237 | $C_{23}H_{17}BrClN_3O_2S$ | 8.04 | 8.16 | 6.07 | 6.22 |
| 6 | *o*-$CH_3O\cdot C_6H_4$ | 55 | 214 | $C_{24}H_{20}BrN_3O_3S$ | 8.11 | 8.23 | 6.14 | 6.27 |
| 7 | *p*-$CH_3O\cdot C_6H_4$ | 47 | 106 | $C_{24}H_{20}BrN_3O_3S$ | 8.26 | 8.23 | 6.38 | 6.27 |
| 8 | *p*-$C_2H_5O\cdot C_6H_4$ | 50 | 234 | $C_{25}H_{22}BrN_2O_3S$ | 7.98 | 8.02 | 6.29 | 6.10 |
| 9 | $CH_3$ | 30 | 115 | $C_{18}H_{16}BrN_3O_2S$ | 10.00 | 10.05 | 7.85 | 7.65 |
| 10 | $C_2H_5$ | 68 | 128 | $C_{19}H_{18}BrN_3O_2S$ | 9.58 | 9.72 | 7.53 | 7.41 |
| 11 | $C_6H_5\cdot CH_2$ | 60 | 142 | $C_{24}H_{20}BrN_3O_2S$ | 8.35 | 8.50 | 6.53 | 6.48 |

Table 3. 6-Bromo-2-(*N*-ethyl-*N*-phenylcarbamoyl)methylthio-3-substituted 4-(3*H*)-quinazolinones

| No. | R | Yield % | Mp °C | Formula | % Nitrogen | | % Bromine | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Found | Calcd | Found | Calcd |
| 1 | $C_6H_5$ | 62 | 183 | $C_{24}H_{20}BrN_3O_2S$ | 8.59 | 8.50 | 16.06 | 16.19 |
| 2 | *o*-$CH_3\cdot C_6H_4$ | 85 | 192 | $C_{25}H_{22}BrN_3O_2S$ | 8.10 | 8.27 | 15.89 | 15.75 |
| 3 | *m*-$CH_3\cdot C_6H_4$ | 90 | 206 | $C_{25}H_{22}BrN_3O_2S$ | 8.50 | 8.27 | 15.78 | 15.75 |
| 4 | *p*-$CH_3\cdot C_6H_4$ | 87 | 200 | $C_{25}H_{22}BrN_3O_2S$ | 8.35 | 8.27 | 15.61 | 15.75 |
| 5 | *m*-$Cl\cdot C_6H_4$ | 66 | 232 | $C_{24}H_{19}BrClN_3O_2S$ | 8.13 | 7.95 | 15.00 | 15.14 |
| 6 | *p*-$Cl\cdot C_6H_4$ | 43 | 116 | $C_{24}H_{19}BrClN_3O_2S$ | 8.11 | 7.95 | 15.17 | 15.14 |
| 7 | *o*-$CH_3O\cdot C_6H_4$ | 55 | 220 | $C_{25}H_{22}BrN_3O_3S$ | 8.06 | 8.02 | 15.18 | 15.27 |
| 8 | *p*-$CH_3O\cdot C_6H_4$ | 50 | 160 | $C_{25}H_{22}BrN_3O_3S$ | 7.94 | 8.02 | 15.05 | 15.27 |
| 9 | $CH_3$ | 52 | 146 | $C_{19}H_{18}BrN_3O_2S$ | 9.95 | 9.72 | 18.64 | 18.52 |
| 10 | $C_2H_5$ | 58 | 145 | $C_{20}H_{20}BrN_3O_2S$ | 9.60 | 9.42 | 18.02 | 17.94 |
| 11 | $C_6H_5\cdot CH_2$ | 55 | 173 | $C_{25}H_{22}BrN_3O_2S$ | 8.22 | 8.27 | 15.53 | 15.75 |

TABLE 4. 6-BROMO-2-(*N*-BENZYL-*N*-PHENYLCARBAMOYL)METHYLTHIO-3-SUBSTITUTED 4-(3*H*)-QUINAZOLINONES

| No. | R | Yield % | Mp °C | Formula | % Nitrogen | | % Bromine | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Found | Calcd | Found | Calcd |
| 1 | $C_6H_5$ | 51 | 203 | $C_{29}H_{22}BrN_3O_2S$ | 7.47 | 7.55 | 14.30 | 14.39 |
| 2 | *o*-$CH_3 \cdot C_6H_4$ | 65 | 215 | $C_{30}H_{24}BrN_3O_2S$ | 7.25 | 7.37 | 14.09 | 14.04 |
| 3 | *m*-$CH_3 \cdot C_6H_4$ | 48 | 195 | $C_{30}H_{24}BrN_3O_2S$ | 7.16 | 7.37 | 13.81 | 14.04 |
| 4 | *p*-$CH_3 \cdot C_6H_4$ | 60 | 244 | $C_{30}H_{24}BrN_3O_2S$ | 7.33 | 7.37 | 14.25 | 14.04 |
| 5 | *m*-$Cl \cdot C_6H_4$ | 62 | 206 | $C_{29}H_{21}BrClN_3O_2S$ | 7.02 | 7.11 | 13.38 | 13.55 |
| 6 | *p*-$Cl \cdot C_6H_4$ | 55 | 205 | $C_{29}H_{21}BrClN_3O_2S$ | 7.18 | 7.11 | 13.41 | 13.55 |
| 7 | *o*-$CH_3O \cdot C_6H_4$ | 76 | 237 | $C_{30}H_{24}BrN_3O_3S$ | 7.11 | 7.17 | 13.56 | 13.66 |
| 8 | *p*-$CH_3O \cdot C_6H_4$ | 45 | 235 | $C_{30}H_{24}BrN_3O_3S$ | 7.32 | 7.17 | 13.78 | 13.66 |
| 9 | *p*-$C_2H_5O \cdot C_6H_4$ | 57 | 214 | $C_{31}H_{26}BrN_3O_3S$ | 6.84 | 7.00 | 13.27 | 13.33 |
| 10 | $CH_3$ | 35 | 187 | $C_{24}H_{20}BrN_3O_2S$ | 8.59 | 8.50 | 16.02 | 16.19 |
| 11 | $C_2H_5$ | 50 | 190 | $C_{25}H_{22}BrN_3O_2S$ | 8.30 | 8.27 | 16.00 | 15.75 |
| 12 | $C_6H_5 \cdot CH_2$ | 53 | 185 | $C_{30}H_{24}BrN_3O_2S$ | 7.45 | 7.37 | 13.84 | 14.04 |

TABLE 5. 6-BROMO-3-SUBSTITUTED-2,4-(1*H*,3*H*)-QUINAZOLINDIONES

| No. | R | Crystallization solvent | Yield % | Mp °C | Formula | % Nitrogen | | % Bromine | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Found | Calcd | Found | Calcd |
| 1 | $C_6H_5$ | a | 68 | 314 | $C_{14}H_9BrN_2O_2$ | 8.67 | 8.83 | 25.12 | 25.23 |
| 2 | *o*-$CH_3 \cdot C_6H_4$ | a | 50 | 259 | $C_{15}H_{11}BrN_2O_2$ | 8.35 | 8.46 | 24.11 | 24.17 |
| 3 | *m*-$CH_3 \cdot C_6H_4$ | a | 70 | 321 | $C_{15}H_{11}BrN_2O_2$ | 8.41 | 8.46 | 24.00 | 24.17 |
| 4 | *p*-$CH_3 \cdot C_6H_4$ | a | 75 | 230* | $C_{15}H_{11}BrN_2O_2$ | 8.39 | 8.46 | 23.91 | 24.17 |
| 5 | *m*-$Cl \cdot C_6H_4$ | b | 68 | 233[d] | $C_{14}H_8BrClN_2O_2$ | 7.84 | 7.97 | 23.05 | 22.76 |
| 6 | *p*-$Cl \cdot C_6H_4$ | c | 55 | 216[d] | $C_{14}H_8BrClN_2O_2$ | 8.12 | 7.97 | 22.79 | 22.76 |
| 7 | *o*-$CH_3O \cdot C_6H_4$ | a | 60 | 310 | $C_{15}H_{11}BrN_2O_3$ | 8.02 | 8.07 | 22.85 | 23.05 |
| 8 | *p*-$CH_3O \cdot C_6H_4$ | c | 62 | 288 | $C_{15}H_{11}BrN_2O_3$ | 7.93 | 8.07 | 23.01 | 23.05 |
| 9 | *p*-$C_2H_5O \cdot C_6H_4$ | c | 90 | 290 | $C_{16}H_{13}BrN_2O_3$ | 7.58 | 7.76 | 22.03 | 22.16 |
| 10 | $CH_3$ | a | 55 | 291 | $C_9H_7BrN_2O_2$ | 11.06 | 10.98 | 31.16 | 31.37 |
| 11 | $C_6H_5 \cdot CH_2$ | a | 65 | 264 | $C_{15}H_{11}BrN_2O_2$ | 8.40 | 8.46 | 24.29 | 24.17 |

a Acetone and ethanol (1 : 1), b Ethanol and ethyl acetate (2 : 1),
c Acetone, ethanol and ethyl acetate mixture (1 : 2 : 1).
* Decomposition without melting, d Melting with decomposition.

Similarly, other 6-bromo-3-substituted-2,4-(1*H*,3*H*)-quinazolindiones were obtained. Their properties and analytical data are given in Table 5. The identity of these compounds was confirmed by direct comparison with authentic samples of diketoquinazolines prepared by the method of Dave *et al.*[2]

**6-Bromo-2-carboxymethylthio-3-phenyl-4-(3*H*)-quinazolinone (IV).** An equimolar quantity of sodium monochloroacetate was added to an alkaline solution of 6-bromo-2-mercapto-3-phenyl-4-(3*H*)-quinazolinone, and the mixture was stirred for six hours. It was then acidified with 5% hydrochloric acid to Congo red, and the precipitate obtained was dissolved in sodium bicarbonate solution and filtered. The filtrate on reprecipitation with 5% hydrochloric acid gave the required product in 50% yield. It was crystallized from 95% ethanol, mp 190°C. (Found: C, 48.92; H, 2.75; S, 8.35%. Calcd for $C_{16}H_{11}BrN_2O_3S$: C, 49.10; H, 2.81; S, 8.18%).

Authors thank the authorities of Banaras Hindu University for providing the facilities and the Council of Scientific and Industrial Research, New Delhi, India, for the award of a Junior Research Fellowship to one of them (R.L.).