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AN UNEXPECTED REARRANGEMENT OF 4-BROMO-2(3*H*)-BENZOTHIAZOLONES

Michael MELLOR* and Susan E. OSBOURN

Schering Agrochemicals Limited, Chesterford Park Research Station,
Saffron Walden, Essex CB10 1XL

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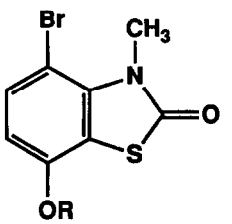
ABSTRACT: The rearrangement of 4-bromo-2(3*H*)-benzothiazolones to the corresponding 6-bromo-2(3*H*)-benzothiazolones has been shown to occur in high yield in refluxing 48% hydrobromic acid.

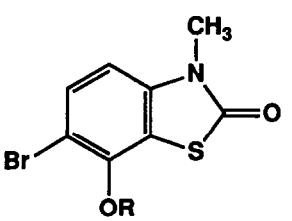
Recently we discovered that the known fungicidal activity of 3,4-disubstituted-2(3*H*)-benzothiazolones[1] is enhanced by the introduction of an alkoxy group at the 7-position[2]. In order to explore further this discovery, we wished to prepare the novel compound 4-bromo-7-hydroxy-3-methyl-2(3*H*)-benzothiazolone(1). It was envisaged that (1) could be obtained by dealkylation of a corresponding 4-bromo-7-alkoxy-2(3*H*)-benzothiazolone employing refluxing 48% hydrobromic acid, a strategy which had worked well for the analogous 4-chloro-7-alkoxy-2(3*H*)-benzothiazolones[2].



(1) R = H

(2) R = Et

Treatment of 4-bromo-7-ethoxy-3-methyl-2(3*H*)- benzothiazolone (2)[2,3] with refluxing 48% hydrobromic acid for 10 hours gave a high yield of a de-ethylated product as expected. However, on further investigation it became clear that the desired compound (1) had not been produced, but rather, an isomeric compound which we postulated as being 6-bromo-7-hydroxy-3-methyl-2(3*H*)-benzothiazolone (3) on the basis of the following experiment.



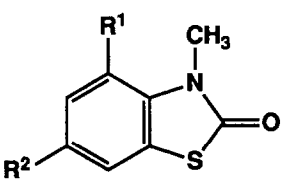
(3) R = H

(4) R = Et

Re-alkylation of compound (3) with bromoethane in the presence of potassium carbonate did not regenerate (2) but gave instead a new compound, the properties of which were consistent with it having the structure (4) ($^m/_e$287,289 (M+); δ1.44 t (CH_3), 3.42 s (CH_3), 4.17 q (CH_2), 6.68 d (J = 9 Hz, 4-H), 7.47 d (J = 9Hz, 5-H)).

The precise configuration of compound (4) was secured by 1D-difference N.O.E. measurements. Irradiation of the N-methyl singlet (δ 3.42) resulted in an enhancement of the δ 6.68 signal indicating that a proton occupies the 4-position. Irradiation of the methylene quartet (δ 4.17) produced no N.O.E. indicating the absence of a proton *ortho* to the ethoxy group. By contrast, irradiation of the equivalent methylene quartet in compound (2) did result in enhancement of the 6-H signal as expected. These data are consistent only with the configuration depicted in structure (4).

In order to understand the above rearrangement more fully, the importance of the 7-oxygen-substituent was investigated. On subjecting the desoxy-analogue, 4-bromo-3-methyl-2(3*H*)-benzothiazolone (5)[3,4] to the same reaction conditions, rearrangement was again observed, the known compound 6-bromo-3-methyl-2(3*H*)-benzothiazolone (6)[5] being isolated in 82% yield. Clearly the 7-oxygen-substituent is not required for the rearrangement to take place. The ^{1}H NMR spectrum of (6) displays an N-methyl singlet at δ 3.40 which, on irra-



(5) $R^1 = Br$; $R^2 = H$

(6) $R^1 = H$; $R^2 = Br$

(7) $R^1 = R^2 = Br$

(8) $R^1 = R^2 = H$

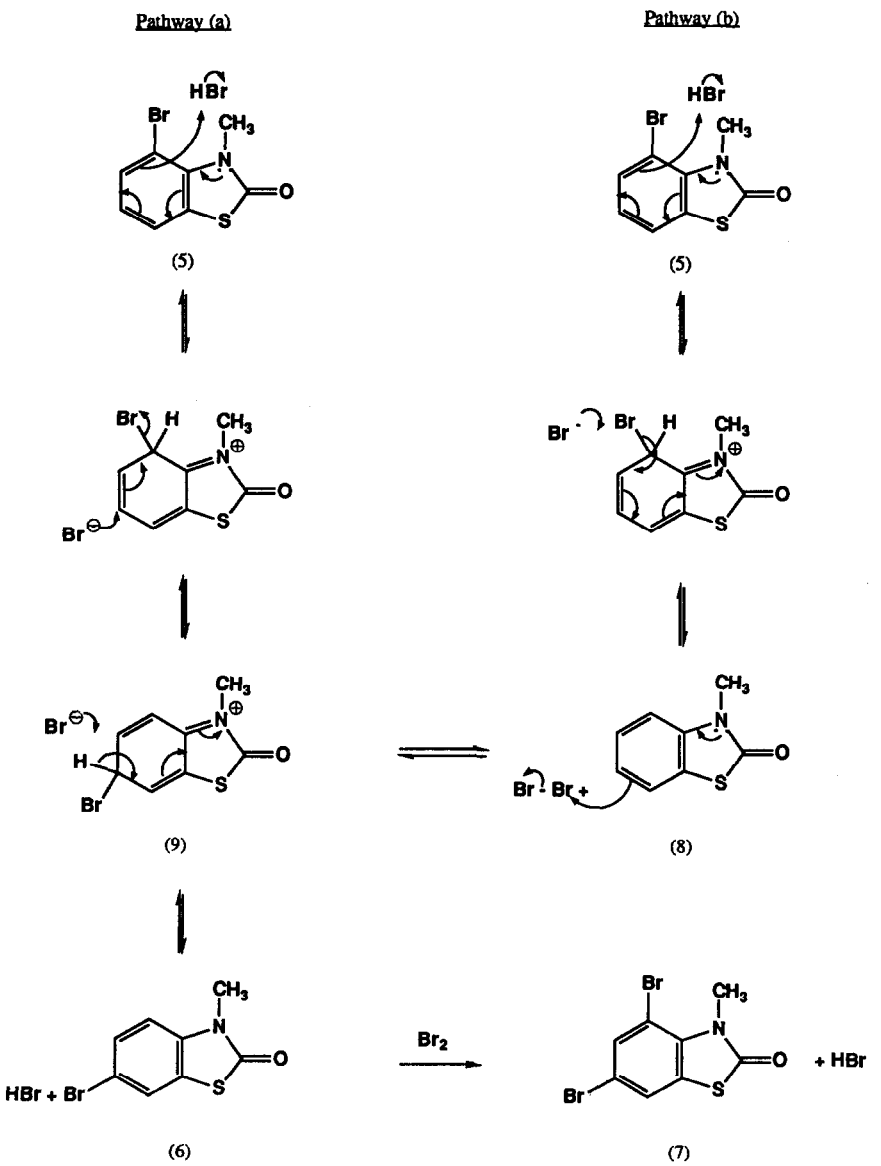
diation, gives an N.O.E. for the aromatic signal at δ 6.89. In addition, the coupling constant for the δ 6.89 signal is 9 Hz indicating that it is *ortho* coupled. These observations confirmed the identity of (6) and ruled out 5-bromo-3-methyl-2(3*H*)-benzothiazolone as an alternative structure for the product.

More detailed examination, by moving-belt L.C.M.S. analysis, of the crude product obtained from the hydrobromic acid treatment of (5), revealed that not only was compound (6) produced (83.5%), but also the previously unreported 4,6-dibromo-3-methyl-2(3*H*)-benzothiazolone (7) (11%) and 3-methyl-2(3*H*)-benzothiazolone (8)[3,5] (2.5%). The identities of (7) and (8) were confirmed by independent synthesis (see Experimental Section).

Two alternative mechanisms accounting for the rearrangement, including the formation of the minor products, are proposed in Scheme 1. Both proceed through the common intermediate (9).

Following protonation at the 4-position, S_N2' displacement of the 4-bromo-substituent by bromide ion (pathway (a)) would lead directly to the intermediate (9)[6].

Scheme 1



Alternatively, direct attack of bromide ion on the 4-bromo-substituent would afford compound (8) and molecular bromine (pathway (b)). Subsequent electrophilic bromination of (8) at the preferred 6-position[5] would also lead to the intermediate (9). Finally, deprotonation of (9) would afford the major product (6), further bromination of which, by residual traces of bromine[7], would then generate the minor product (7).

To ascertain the preferred pathway, the reaction was repeated in the presence of excess phenol as a bromine scavenger. If pathway (b) is favoured, then removal of bromine from the reaction medium should result in the accumulation of compound (8). If pathway (a) is favoured, the presence of phenol should have little effect on the product distribution.

H.P.L.C. analysis of the product mixture, following removal of all phenolic materials, showed compounds (6) and (8) accounting for 16% and 77% of the mixture respectively. Whilst this result does not completely rule out pathway (a), the evidence indicates that rearrangement occurs primarily *via* pathway (b).

The above observations suggest that care should be taken when subjecting other bromo-substituted, electron-rich heteroaromatic systems to refluxing hydrobromic acid if analogous rearrangements are to be avoided.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded on either a Perkin-Elmer R32 instrument operating at 90 MHz or a Bruker AC 300 instrument operating at 300 MHz. E.I. mass spectra were recorded on a VG Trio 2 Quadrupole mass spectrometer at 70 eV. Moving-belt L.C.M.S. was carried out using a VG 7070E mass spectrometer at 70 eV equipped with an L.C.M.S interface. H.P.L.C. was performed using columns and eluants detailed in the text. Elemental analyses were performed on a Carlo-Erba 1106 instrument.

4-Bromo-7-ethoxy-3-methyl-2(3*H*)-benzothiazolone (2)

4-Bromo-7-ethoxy-2(3*H*)-benzothiazolone[3] (4.09g; 15 mmol) and anhydrous potassium carbonate (2.08g; 15 mmol) in 2-butanone (75 ml) were stirred at reflux for 1 hour. Iodomethane (6.39g; 45 mmol) was then added and the reaction mixture stirred at reflux for a further 4 hours. After cooling, the mixture was filtered and the filtrate was evaporated to give the crude product as a brown solid (4.74g). Recrystallisation from ethanol gave the desired compound (2) as a cream solid (2.62g; 61%). M.pt. 109-111° C. A second recrystallisation gave an analytically pure sample, M.pt. 117.5-118.5° C.

^{1}H NMR ($CDCl_3$) : δ 1.42t (J = 7 Hz, CH_3); 3.82 s (CH_3); 4.11 q (J = 7Hz, CH_2); 6.50 d (J = 9 Hz, 6 - H); 7.37 d (J = 9 Hz, 5 - H).

M.S. : $^m/_e$ 287, 289 (M^+)

$C_{10}H_{10}BrNO_2S$: Theory : C 41.68; H 3.50; N 4.86 Found : C 41.85; H 3.44; N 4.84

Compounds (5) and (8) were prepared in a similar manner :

4-Bromo-3-methyl-2(3*H*)-benzothiazolone (5)

Methylation of 4-bromo-2(3*H*)-benzothiazolone[3,4] gave compound (5) in 81% yield. M.pt. 133.5 - 134.5° C (Di-isopropyl ether). (Lit.[4] M.pt. 139 -140° C).

^{1}H NMR ($CDCl_3$) : δ 3.92 s (CH_3); 6.92 dd (6 - H); 7.32 d (J = 12 Hz, 5 - H or 7 - H); 7.41 d (J = 12 Hz, 5 - H or 7 - H).

M.S. : $^m/_e$ 243, 245 (M+)

C_8H_6BrNOS : Theory : C 39.36; H 2.48; N 5.74 Found : C 39.09; H 2.03; N 5.34

3-Methyl-2(3*H*)-benzothiazolone (8)

Methylation of 2(3*H*)-benzothiazolone[3,5] gave compound (8) in 94% yield. M.pt. 73-74° C (Lit.[5] M.pt. 74° C).

^{1}H NMR ($CDCl_3$) : δ 3.35 s (CH_3); 6.89 - 7.45 m (4H).

Reaction of 4-bromo-7-ethoxy-3-methyl-2(3*H*)- benzothiazolone (2) with refluxing 48% hydrobromic acid

A mixture of 4-bromo-7-ethoxy-3-methyl-2(3*H*)-benzothiazolone (2) (3g; 10.4 mmol) and 48% hydrobromic acid (63 ml) was stirred at reflux for 10 hours. On cooling, a yellow solid separated which was collected by filtration, washed with water and dried *in vacuo* to give crude 6-bromo-7-hydroxy-3-methyl-2(3*H*)-benzothiazolone (3) (2.57 g; 95%). M.pt. 235-237° C (dec.) A suitable recrystallisation solvent was not found for this material. Therefore it was used without further purification.

^{1}H NMR (DMSO-D_6) : δ3.31 s (CH_3); 6.80 d (J = 9 Hz, 4 - H); 7.49 d (J = 9 Hz, 5 - H); 10.37 bs (D_2O-exchangeable) (OH).

M.S. : $^m/_e$ 259, 261 (M+)

6-Bromo-7-ethoxy-3-methyl-2(3*H*)-benzothiazolone (4)

Crude 4-bromo-7-hydroxy-3-methyl-2(3*H*)-benzothiazolone(3) (0.13 g; 0.5 mmol), from the above experiment, was stirred in refluxing 2-butanone (10 ml) with anhydrous potassium carbonate (0.07 g; 0.5 mmol) for 1.5 hours. Bromoethane (0.16 g; 1.5 mmol) was then added and the mixture was stirred at reflux for a further 16 hours. Filtration of the reaction mixture, followed by evaporation of the filtrate gave the crude title compound (4). Purification by column chromatography on silica gel (eluant : dichloromethane) gave compound (4) (0.12 g; 83%). M.pt. 75.8-76.5° C.

^{1}H NMR ($CDCl_3$) :	δ 1.44 t (J = 7 Hz, CH_3); 3.42 s (CH_3); 4.17 q (J = 7 Hz, CH_2); 6.68 d (J = 9 Hz, 4 - H); 7.47 d (J = 9 Hz, 5 - H).	
M.S. :	$^m/_e$ 287, 289 (M^+)	
$C_{10}H_{10}BrNO_2S$:	Theory : C 41.68; H 3.50; N 4.86	Found: C 41.83; H 3.44; N 4.53

Reaction of 4-bromo-3-methyl-2(3*H*)-benzothiazolone (5) with refluxing 48% hydrobromic acid

i) 4-Bromo-3-methyl-2(3*H*)-benzothiazolone (5) (0.5 g; 2.05 mmol) and 48% hydrobromic acid (15 ml) were stirred together at reflux for 6 hours. On cooling, a yellow solid was precipitated which was collected by filtration, washed with water and dried to give 0.51 g crude product. Purification by column chromatography on silica gel (eluant : dichloromethane) gave the major product as a white solid (0.41g; 82%) which was identified as 6-bromo-3-methyl-2(3*H*)-benzothiazolone (6). Recrystallisation from methanol gave an analytically pure sample. M.pt. 124-125° C (Lit.[5] M.pt. 126-127° C).

^{1}H NMR ($CDCl_3$) :	δ 3.40 s (CH_3); 6.89 d (J = 9 Hz, 4 - H); 7.43 dd (J = 9 Hz, 2 Hz, 5 - H); 7.53 d (J = 2 Hz, 7 - H)	
C_8H_6BrNOS :	Theory : C 39.36; H 2.48; N 5.74	Found : C 39.16; H 2.11; N 5.37

ii) The reaction of part (i) was repeated but, on cooling, the mixture was diluted with water and extracted twice with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give a yellow solid (0.45 g). H.P.L.C. analysis (Dynamax-60A-Si 8μm column; dichloromethane) of this material indicated that three significant components[8] were present. By comparison of retention times with authentic samples and with additional confirmation of product assignment by means of the moving-belt L.C.M.S. technique, the three major products were identified as 6-bromo-3-methyl-2(3*H*)-benzothiazolone (6) (83.5%), 4,6-dibromo-3-methyl-2(3*H*)-benzothiazolone (7) (11%) (*vide infra*) and 3-methyl-2(3*H*)- benzothiazolone (8) (2.5%).

Reaction of 4-bromo-3-methyl-2(3*H*) -benzothiazolone (5) with refluxing 48% hydrobromic acid in the presence of excess phenol

4-Bromo-3-methyl-2(3*H*)-benzothiazolone (5) (92 mg; 0.38 mmol) and phenol (75.5 mg; 0.8 mmol) were stirred together in refluxing 48% hydrobromic acid (3.7 ml) for 5.5 hours. On cooling, the reaction mixture was diluted with water and extracted twice with dichloromethane. The combined extracts were washed thoroughly with 5% sodium carbonate solution, dried ($MgSO_4$) and evaporated to give a yellow oil (57.2 mg). H.P.L.C. analysis (Dynamax-60A-Si 8μm column: dichloromethane), with compound identification by comparison of retention

times with those of authentic samples, showed two significant components[8] viz. 3-methyl-2(3*H*)-benzothiazolone (8) (77%) and 6-bromo-3-methyl-2(3*H*)-benzothiazolone (6) (16%).

4,6-Dibromo-3-methyl-2(3*H*)-benzothiazolone (7)

Bromine (4 g; 25 mmol) in glacial acetic acid (5 ml) was added dropwise over 30 min. to a stirred solution of 3-methyl-2(3*H*)-benzothiazolone (8) (1.92 g; 11.6 mmol) in glacial acetic acid (20 ml) at room temperature. The mixture was stirred at reflux for 22 hours before adding a further quantity of bromine (3.1 g; 10.4 mmol) in acetic acid (5 ml) over a 20 min. period. After stirring at reflux for an additional 20 hours, the acetic acid was evaporated. The residue was dissolved in dichloromethane, washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to give the crude product as a fawn solid (3.64 g). Purification by column chromatography on silica gel (eluant: dichloromethane), followed by preparative H.P.L.C. (Dynamax-60A-Si 8μm column: dichloromethane: n-hexane, 1:1) gave the title compound (7) as a white solid (1.21 g; 32%). Recrystallisation from propan-2-ol gave an analytically pure sample. M.pt. 158-160° C.

^{1}H NMR ($CDCl_3$):	δ 3.78 s (CH_3); 7.41 d (J = 2 Hz, 1 H); 7.57 d (J = 2 Hz, 1 H)	
M.S.:	$^m/_e$ 321, 323, 325 (M^+)	
$C_8H_5Br_2NOS$:	Theory: C 29.74; H 1.56; N 4.34	Found: C 29.33; H 1.09; N 4.00

References and Footnotes

1. Uematsu, T.; Inoue, S.; Yamashita, N. (Sumitomo Chemical Co., Ltd.), Ger. Offen. 2,801,868 (1978) (*Chem. Abs.* **89** 179989s).

2. Mellor, M.; Steele, C.R. (Schering Agrochemicals Limited). Eur. Pat. Appl. EP 245, 991 (1987) (*Chem. Abs.* **108** 112436b).

3. For a review of synthetic approaches to 2(3*H*)-benzothiazolones, see J. M. Sprague and A.H. Laud, in Heterocyclic Compounds, Vol.5, R.C. Elderfield, ed., John Wiley and Sons, Inc., New York (1957), p. 484. Compounds (2), (5) and (8) were all synthesised by the well-established sequence : 1) Condensation of an appropriately substituted aniline with thiocyanate ion to give the corresponding phenylthiourea, 2) Oxidative cyclisation to the 2-aminobenzothiazole (employing Br_2 or $SOCl_2$[9]), 3) Conversion to the 2-chlorobenzothiazole by diazotisation, 4) Acid hydrolysis to the 2(3*H*)-benzothiazolone, and 5) N-alkylation. For a typical experimental procedure see reference 2.

4. Inoue, S.; Uematsu, T.; Kato, T.; Ueda, K. *Pestic. Sci.* **1985**, *16*, 589.

5. Hunter, R.F. *J.Chem.Soc.* **1930**, 125.

6. The driving force for a S_N2' reaction might arise through the release of steric compression between the 3- and 4-substituents.

7. Arising either *via* pathway (b) or through hydrobromic acid decomposition.

8. Peaks in the H.P.L.C. chromatogram integrating for > 1.5% of the total chromatogram are considered to correspond to significant components.

9. Papenfuhs,T. *Angew. Chem. Suppl.* **1982**, 1155-1166.