# Intermediates in the Halogenation of Some 2-Aminothiazoles

By **Luciano Forlani** * and **Alessandro Medici**, Istituto di Chimica Organica, Viale Risorgimento 4, 40136 Bologna, Italy

Halogenation of 2-aminothiazoles in various solvents to produce 2-amino-5-halogenothiazoles proceeds *via* an addition–elimination mechanism. The addition products ($\Delta^2$-thiazolines) have been isolated and characterized by their n.m.r. spectral properties. The high regiospecificity and stereospecificity of the addition step are discussed. In these reactions, the behaviour of the C(4)–C(5) double bond in 2-aminothiazoles is similar to that of the double bond in ethylenes.

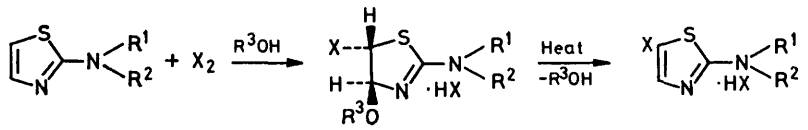
HALOGENATION of 2-aminothiazoles occurs at the 5-position, and is considered to be an aromatic electrophilic substitution, activated by the amino-group. English [1] reported the isolation of an aminothiazole ' bromide–perbromide ' in the bromination of 2-aminothiazole in water in the presence of hydrogen bromide. Garreau [2] isolated a partially saturated bromothiazole derivative in the bromination of 2-amino-4,5-dimethylthiazole. We report here the isolation of the $\Delta^2$-thiazoline intermediates (2) in the halogenation (bromination and chlorination) of the 2-aminothiazoles (1).

## RESULTS AND DISCUSSION

When methanolic bromine is added dropwise to a methanolic solution of 2-aminothiazole (1) at 0 °C, the bromine solution is instantaneously decolourized. The immediate disappearance of the u.v. absorption maximum (in methanol) due to the 2-aminothiazole ($\lambda_{max.}$ 257 nm; $\varepsilon$ 9.05 × $10^4$) is not accompanied by the appearance of the maximum due to the expected 2-amino-5-bromothiazole (3a; X = Br) ($\lambda_{max.}$ 268 nm; $\varepsilon$ 8.01 × $10^4$) which appears only after heating. In preparative runs, a white compound, soluble only in polar solvents (alcohols, water, or dimethyl sulphoxide), was obtained on removing the solvent under reduced pressure. Attempts to purify the crude solid by column chromatography or crystallization failed. The solid did not give free iodine from aqueous potassium iodide. The purity of this compound could be improved by adding 1 equiv. of methanolic hydrogen bromide to the reaction mixture initially.

We have assigned the $\Delta^2$-thiazoline hydrobromide structure (2a; X = Br, $R^3$ = Me) to the white product, arising from addition of the nucleophilic part of the solvent ($R^3O$) to (1a) during the bromination. 2-Aminothiazole and 2-amino-5-bromothiazole do not react with methanol, even in the presence of large amounts of hydrogen bromide. 2-Amino-5-bromothiazole (3a) is obtained in reasonable yield by heating the hydrobromide (2a; X = Br, $R^3$ = Me) (as a solid or in solution), and reduction of this hydrobromide with zinc in acetic acid yields the starting thiazole (1a).

Other adducts (2b—e; X = Br, $R^3$ = Me) have been obtained similarly [Scheme 1; see Table for yields, physical properties, and $^1$H n.m.r. spectra for the starting aminothiazoles (1) and the adducts (2)]. The signals due to the thiazoline ring protons in (2) are shifted to higher field compared with the starting aminothiazoles (1).




SCHEME 1

a; $R^1$ = $R^2$ = H
b; $R^1$ = $R^2$ = Me
c; $R^1$ = H, $R^2$ = $Bu^i$
d; $R^1$ = H, $R^2$ = $PhCH_2$

$R^3$ = Me, Et, H, or $HO{\cdot}CH_2{\cdot}CH_2$; X = Br or Cl

$^{13}$C N.m.r. data (in $CD_3OD$) confirm structure (2): compound (2a), $\delta$ 173.09 (s, C-2), 99.06 (d, C-4), and 52.90 (d, C-5) p.p.m.; compound (2b), $\delta$ 171.66 (s, C-2), 99.93 (d, C-4), and 53.00 (d, C-5) p.p.m., values in agreement with those for other $\Delta^2$-thiazoline derivatives.[3]

The reaction giving compounds (2) is stereospecific; no isomers were detectable. Experiments carried out in $CD_3OD$ (see later) show that C(4)H and C(5)H do not undergo exchange during the bromination. No coupling is observed between these protons; the dihedral angle between these bonds in (2) is probably *ca.* 90°, the protons being bonded to $sp^3$ carbon atoms in a *trans*-arrangement.

Bromination of 2-acetylaminothiazole in methanol also yields (2a; X = Br, $R^3$ = Me), deacetylation occurring during the bromination.

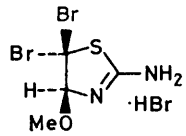
[1] J. P. English, D. J. Clark, D. Seeger, R. H. Ebel, and J. W. Clapp, *J. Amer. Chem. Soc.*, 1946, **68**, 453.

[2] Y. Garreau, *Compt. rend.*, 1954, 564.

[3] L. Forlani, A. Medici, M. Ricci, and P. E. Todesco, *Synthesis*, 1977, 320.

We have been able to obtain the free $\Delta^2$-thiazoline from the hydrobromide (unstable and difficult to purify) only in the case of compound (2a; X = Br, $R^3$ = Me), by neutralization with $NaHCO_3$: m.p. 73—75 °C, n.m.r. (in $CD_3OD$; int. ref. $Me_4Si$), δ 5.95 (1 H, s, 4-H), 5.64 (1 H, s, 5-H), and 3.42 (3 H, s, OMe); *m/e* 210 ($M^+$); picrate, m.p. 183—185 °C.

Bromination of 2-aminothiazole occurs similarly in ethanol and ethylene glycol to give the adducts (2a; X = Br; $R^3$ = Et and $HOCH_2CH_2$), respectively (Table). We have also obtained an adduct arising from addition of bromine and methanol to the C(4)–C(5) double bond on bromination of 2-amino-3-methyl shifted to higher field than in the starting 2-amino-5-bromothiazole (δ 7.43), as would be expected on change of




(4)

hybridization (from $sp^2$ to $sp^3$) of C-4. We have assigned structure (4) to the product isolated from this further bromination, and this assignment is confirmed by $^{13}C$ n.m.r. results: δ($CD_3OD$) 179.49 (s, C-2), 100.08 (d,

2-Alkylaminothiazoles (1) and intermediates (2) in their halogenation in $R^3OH$ at 0 °C; yields and n.m.r. data

| | | | | | N.m.r. in $CD_3OD$ (int. ref. $Me_4Si$) | | | |
|---|---|---|---|---|---|---|---|---|
| Compound | $R^3$ | X | Yield (%) | M.p./°C | δ(5-H) [a] | δ(4-H) [a] | δ(alkyl) | δ($OR^3$) |
| (1a) | | | [b] | 93—94 | 6.47 [c] | 6.93 [c] | | |
| (1b) | | | 95 | 83—85 [d] | 6.49 [c] | 7.06 [c] | 3.03 (6 H, s) | |
| (1c) | | | [e] | 72—73 | 6.46 [c] | 6.95 [c] | 0.9—1.7 (8 H, m), 3.6 (1 H, m) | |
| (1d) | | | [e] | 131—132 | 6.49 [c] | 6.98 [c] | 4.46 (2 H, s), 7.36 (5 H, s) | |
| (2a) | Me | Br | 90 | 126—127 | 5.69 | 6.11 | | 3.52 (3 H, s) |
| (2b) | Me | Br | 85 | 166—168 | 5.73 | 6.16 | 3.44 (6 H, s) | 3.47 (3 H, s) |
| (2c) | Me | Br | 85 | 122—124 | 5.73 | 6.13 | 0.9—2 (9 H, m) | 3.53 (3 H, s) |
| (2d) | Me | Br | 90 | 116—118 | 5.77 | 6.16 | 4.81 (2 H, s), 7.30 (5 H, s) | 3.50 (3 H, s) |
| (2a) | Et | Br | 95 | 102—104 | 5.71 | 6.06 | | 1.20 (3 H, t), 3.53 (2 H, q) |
| (2a) | $HO{\cdot}CH_2{\cdot}CH_2$ | Br | 80 | 130—132 | 5.76 | 6.05 | | 3.5—3.8 (4 H, m) |
| (2a) | H | Br | 90 | 118—121 | 5.90 | 5.97 | | |
| | | | | | 5.80 [f] | 6.00 [f] | | |
| (2a) | H | Cl | 95 | 109—111 | 5.75 | 5.87 | | |
| (2a) [g] | Me | Br | 95 | 105—107 | 5.84 | 6.23 | 3.70 (3 H, s) | 3.53 (3 H, s) |
| | | | | | 5.83 [f] | 6.33 [f] | 3.59 (3 H, s) [f] | 3.53 (3 H, s) [f] |

[a] 1 H, s, except where noted. [b] By recrystallization of commercial product (E.G.A.). [c] 1 H, d, $J_{4,5}$ 4.2 Hz. [d] B.p. at 15 mmHg. [e] See ref. 3. [f] In $(CD_3)_2SO$. [g] *N*-Methylthiazolium nitrate derivative.

thiazolium nitrate (Table), but attempts to obtain the 2-amino-5-bromo-3-methylthiazolium nitrate by heating failed.

Bromination or chlorination of 2-aminothiazole in water (in the presence or absence of HBr or HCl) also gives white crystals of the adducts (2a; $R^3$ = H, X = Br or Cl) (Table). Iodine is not liberated from aqueous potassium iodide, showing the absence of free halogen.

Bromination of 2-aminothiazole in acetic acid (the most commonly used solvent in such halogenations [4]) at 15 °C leads to immediate decolourization of the bromine solution, but 2-amino-5-bromothiazole is not observed. Addition of light petroleum to the reaction mixture causes precipitation of an unstable solid. It was possible to record only its n.m.r. spectrum (in $CD_3OD$) which was analogous to that for compound (2a; X = Br, $R^3$ = Me). Similar behaviour is observed in the bromination of 2-aminothiazole in tetrahydrofuran at −20 °C.

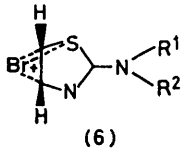
Methanolic bromine is rapidly decolourized by a methanolic solution of the 2-amino-5-bromothiazole, and a white solid is obtained on removal of the solvent under reduced pressure; m.p. 117—118 °C, n.m.r. ($CD_3OD$; int. ref. $Me_4Si$) δ 5.82 (1 H, s, 4-H), and 3.88 (3 H, s, OMe). The (4)H signal is C-4), and 56.20 (s, C-5) p.p.m. N.m.r. analysis of solutions of the adducts (2) in $CD_3OD$ shows that exchange between $OCH_3$ and $OCD_3$ groups occurs for the few minutes at room temperature, although it does not occur for the free thiazolidine obtained from compound (2a; X = Br, $R^3$ = Me) or for (2b) and for the 3-methylthiazolidinium nitrate analogue of (2a), even after long reaction times. In all cases deuterium exchange for C(4)H and C(5)H is not observed. Furthermore, compound (2a; X = Br, $R^3$ = H) is converted (in 2 days at room temperature) into compound (2a; X = Br, $R^3$ = $CD_3O$) simply by dissolution in $CD_3OD$. These exchanges probably occur by some acid-catalysed tautomeric equilibrium, which is possible only when $R^2$ = H and the ring nitrogen atom is not methylated. Scheme 2 represents a reasonable pathway for this reaction. The $^1H$ n.m.r. signals of the thiazolidine ring protons are not affected by the exchange; stereospecific addition of the nucleophilic part of the solvent probably occurs to the positively charged species (5).

In conclusion the halogenation of 2-aminothiazoles occurs by an addition–elimination pathway, the first

[4] H. Erlenmeyer and H. Kiefler, *Helv. Chim. Acta*, 1945, **28**, 985; H. C. Beyerman, P. H. Berben, and J. S. Bontekoe, *Rec. Trav. chim.*, 1954, **73**, 325.

step of which is attack by halogen on the C(4)–C(5) double bond, followed by stereospecific addition of the nucleophile. The fact that 2-(*NN*-dimethylamino)-thiazole (1b) reacts readily is evidence against the possibility that the reaction occurs on the imino-form of the thiazoles (arising from a tautomeric equilibrium [5]).

The regioselectivity of the present reactions (halogenation only at the 5-position) is in agreement with direct conjugation between the 5-position and the 2-amino group,[6] and by the presence of the sulphur atom which probably plays an important role in stabilizing a bromonium ion intermediate [7] such as (6) and promoting the stereospecificity of the reactions. However, the formation of the adducts (2) emphasizes the lack of aromaticity of the thiazoles (1), and indicates that the



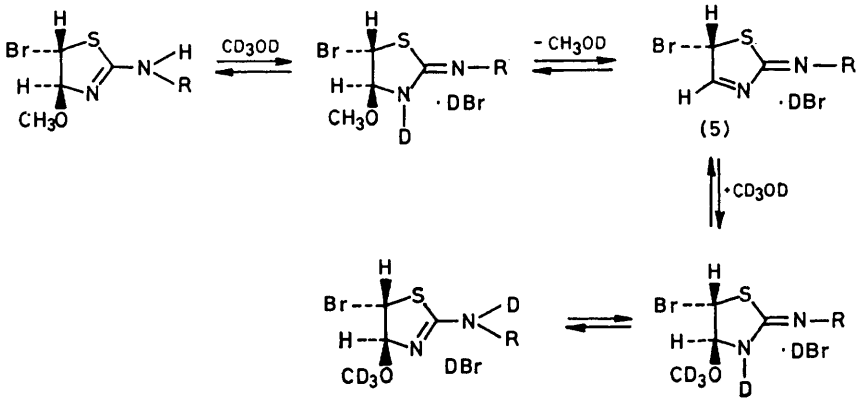
(6)

behaviour of the C(4)–C(5) double bond is similar to that usually observed for ethylene derivatives.

## EXPERIMENTAL

2-*N*-Alkylaminothiazoles (1) were obtained by the cyclization (in the presence of bromine) between substituted thioureas and α-bromoacetaldehyde.[8] 2-*N*-Alkylamino-5-bromothiazoles [3,4] obtained from (1a), (1c), and (1d) and 2-amino-5-chlorothiazole have already been described. 5-Bromo-2-(*NN*-dimethylamino)thiazole hydrobromide was also prepared by bromination of 2(*NN*-dimethylamino)thiazole in acetic acid [4] in 70% yield; m.p. 35—36 °C; n.m.r. ($CDCl_3$; int. ref. $Me_4Si$): δ 7.05 (1 H, s, 4-H) and 3.04 (6 H, s, Me).

M.p.s and b.p.s are uncorrected. $^1H$ and $^{13}C$ n.m.r., and u.v. spectra were recorded respectively with JEOL (60 MHz), JEOL MS-D 100, and Perkin-Elmer (257) instruments. Solvents were purified by the usual procedures.[9] Deuteriated solvents (Merck) were used without purification.



SCHEME 2

Halogenations were carried out at 0 °C, in an ice–water bath, with equimolecular solutions of reagents in the selected solvent. The same compounds were obtained from runs carried out at room temperature, but the purity of the materials is better at 0 °C. The hydrobromides (2) were obtained by removing the solvent *in vacuo* or by precipitation (in water). 2-Amino-5-halogenothiazole hydrohalides (3) were obtained by heating the reaction mixtures at *ca.* 70 °C for several hours. Neutralization with sodium hydrogen carbonate yields the free 2-amino-5-halogenothiazoles which are identical to those obtained by halogenation of 2-aminothiazoles in acetic acid at 70 °C.[3]

We thank Dr. D. Macciantelli (C.N.R. Ozzano) for recording the $^{13}C$ n.m.r. spectra. This work was carried out with financial assistance from C.N.R. (Roma).

[7/1917 *Received*, 2nd *November*, 1977]

[5] M. Sélim, M. Sélim, O. Tétu, G. Drillen, and P. Rumpf, *Bull. Soc. chim. France*, 1965, **3**, 3527; J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, ' The Tautomerism of Heterocycles,' Academic Press, New York, 1976; L. Forlani, A. Medici, and P. E. Todesco, *Tetrahedron Letters*, 1976, 201.

[6] L. Forlani, A. Medici, and L. Lunazzi, *Tetrahedron Letters*, 1977, 4525.

[7] G. Bellucci, G. Berti, R. Bianchini, G. Ingrosso, and E. Mastrorilli, *Gazzetta*, 1976, **106**, 955.

[8] R. H. Wiley, D. C. England, and L. C. Behr, *Org. Reactions*, 1951, **6**, 367.

[9] A. Weissberger, ' Techniques of Organic Chemistry,' Interscience, New York, vol. VIII, 1955.