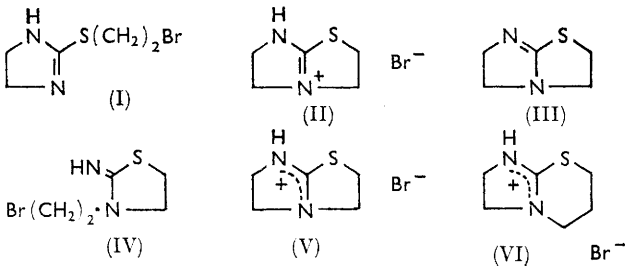
2,3,6,7-Tetrahydroimidazo[2,1-*b*]thiazolium Bromide and Some 2-Iminothiazolidine Precursors

By L. A. Cort

A new preparation of 2,3,6,7-tetrahydroimidazo[2,1-*b*]thiazolium bromide, and some of its chemistry, is described. The compound previously accepted as 2-imino-3-(2-bromoethyl)thiazolidine is shown to be 2-imino-3-(2-thiocyanatoethyl)thiazolidine hydrobromide; a similar state of affairs exists with the chlorine analogue.

It has been shown [1] that attempted liberation of the free base from the hydrobromide of 2-(2-bromoethylthio)imidazol-2-ine (I) leads to 2,3,6,7-tetrahydro-



[5*H*]imidazo[2,1-*b*]thiazolium bromide (II). Formulation of the product as the quaternary ammonium salt rather than as the hydrobromide of 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole (III) rests on the positive Liebermann nitroso-test obtained, and on the inability to isolate a free base after treatment with alkali. Further, it is recognised [2] that Bredt's rule applies to heterocyclic as well as to alicyclic rings, and that (III) might not be capable of existence.

However, it has now been found that attempted liberation of the free base from the hydrobromide of 3-(2-bromoethyl)-2-iminothiazolidine (IV) also gives the bicyclic product previously described. Re-examination of the Liebermann nitroso-reaction shows that the positive result is due not to the formation of an *N*-nitroso-compound but to the formation (by ring opening) of a thionitrite; this suggests that the structure of the bicyclic product is better represented as the amidinium salt (V) (as put forward [3] for the 7-substituted compounds), although there is strong infrared absorption [1] attributable to C=N.

The instability of the thionitrite renders structure determination difficult (see Experimental section), but it is probably *N*-(2-thionitroethyl)imidazol-2-one; there is a certain amount of spectroscopic evidence for this. Decomposition, by effective hydrolysis at the thionitrite group, probably leads to a disulphide through dimerisation. In view of the fact that thiazolidines undergo normal *N*-nitrosation,[4] the opening of the sulphur-containing ring with nitrous acid is unexpected. Furthermore, with mercuric chloride or bromide no evidence of ring-opening was forthcoming; there was

[1] L. A. Cort, *J. Chem. Soc.*, 1965, 3456.
[2] F. S. Fawcett, *Chem. Reviews*, 1950, **47**, 219.
[3] H. Dorn, (*a*) *Chem. Ber.*, 1964, 3246; (*b*) *Angew. Chem.*, 1964, **76**, 301.
[4] R. L. Peck and K. Folkers, "Chemistry of Penicillin," ed. H. Clarke *et al.*, Princeton Univ. Press, 1949, 144.

simply formation of a 1 : 1 double salt, a reaction found [5] with *S*-benzylthiouronium salts.

The tetrahydroimidazothiazolium bromide failed to react with alkyl halides, or with benzoyl chloride in pyridine, but with benzoyl chloride in alkali a dibenzoate ($C_{19}H_{18}N_2O_3$) was obtained. It is to be expected that alkali would open the sulphur-containing ring (cf. the hydrolysis of *S*-alkylthiouronium salts), and that the resulting hydroxyimidazoline would tautomerise; dibenzoylation could then give *N*-benzoyl-*N'*-(2-benzoylthioethyl)imidazolidin-2-one. This structure is supported by the strong infrared absorption shown at 1650, 1658, and 1728 cm.$^{-1}$ (covering C=O absorption in three different environments). The bromide was unaffected by potassium borohydride in aqueous methanol (neutral or alkaline) (cf. borohydride reduction [6] of monocyclic thiazolium salts).

1,2,3,5,6,7-Hexahydroimidazo[2,1-*b*][1,3]thiazinium bromide (VI) is the 1,3-thiazinium analogue of the bromide (V). This also gave an unstable thionitrite with nitrous acid, and it similarly failed to react with potassium borohydride in methanol. With mercuric bromide it gave a 1 : 1 double salt.

In the present work, 2-amino-2-thiazoline and 2-bromoethanol were used to give the hydroxyethyl compound from which the 3-(2-bromoethyl)-2-iminothiazolidine (IV) hydrobromide was prepared. This product has been previously described; [7] it results from di-(2-bromoethyl)amine hydrobromide and potassium thiocyanate in ethanol. However, it is reported [7] that the product (m. p. 148°) dissociates during crystallisation to give the free base (m. p. 207°) which, of course, now appears to be unlikely. In our hands the latter preparation gave only the higher-melting material, analysis and infrared absorption (cf. ref. 8) of which indicate it to be 3-(2-thiocyanatoethyl)-2-iminothiazolidine hydrobromide. Authentic 3-(2-bromoethyl)-2-iminothiazolidine hydrobromide was found to be stable on crystallisation; heated in water with potassium thiocyanate it gave the thiocyanato-derivative.

It is similarly reported [7] that 3-(2-chloroethyl)-2-iminothiazolidine hydrochloride yields on crystallisation the free base (m. p. 188°). By the reaction described, we have obtained two products (m. p. 145° and 184°) which are, respectively, 3-(2-chloroethyl)-2-iminothiazolidine hydrochloride and the 2-thiocyanatoethyl derivative. (These give picrates with the same m. p., 146°.) It is unfortunate that in the earlier work analyses for nitrogen only were obtained; it is also probable that isolation of the "free bases" was accomplished, not by crystallisation of the pure 2-halogenoethyl compounds, but from original mother-liquors or from impure samples (both thiocyanato-derivatives are less soluble than their precursors).

Since both syntheses of the bromide (V) are lengthy, an alternative preparation was sought. It is known [9] that 2-amino-2-thiazoline and an excess of alkyl halide give only the mono-(3)-substituted 2-iminothiazolidines. 1,2-Dibromoethane and 2-amino-2-thiazoline underwent an exothermic reaction on heating; always some dibromoethane was recovered, and from the residue only the hydrobromide of the starting base could be isolated. The same reaction occurred when solvent was used; in one experiment only was it possible to isolate 1,2-di-(2-iminothiazolidin-3-yl)ethane (as dipicrate); this could not be repeated. On heating together 2-amino-2-thiazoline and 3-(2-bromoethyl)-2-iminothiazolidine hydrobromide, with or without solvent, only starting materials were recovered.

EXPERIMENTAL

Melting points are corrected.

3-(2-*Bromoethyl*)-2-*iminothiazolidine Hydrobromide*.—2-Aminothiazol-2-ine (34·2 g.) was boiled in acetone (100 ml.) with ethylene bromohydrin (42·0 g.) for 2 hr. The solid which separated (26·2 g.) crystallised from methanol–water as hexagonal prisms, m. p. 169—171°, of 3-(2-*hydroxyethyl*)-2-*iminothiazolidine hydrobromide*, mixed with 2-aminothiazol-2-ine hydrobromide (m. p. 171°), m. p. 145—158° (Found: C, 26·4; H, 4·8; Br^-, 35·0; N, 12·1; S, 14·2. $C_5H_{10}N_2OS,HBr$ requires C, 26·4; H, 4·9; Br^-, 35·2; N, 12·3; S, 14·1%). The *picrate* separated from methanol–water as yellow prisms, m. p. 130—132° (Found: C, 35·0; H, 3·6; N, 18·4; S, 8·7. $C_{11}H_{13}N_5O_8S$ requires C, 35·2; H, 3·5; N, 18·7; S, 8·5%). With benzoyl chloride and 2N-sodium hydroxide the hydrobromide afforded the *dibenzoate* of the free base, m. p. 76° (plates from methanol–water) (Found: C, 64·7; H, 5·1; N, 7·9; S, 8·9. $C_{19}H_{18}N_2O_3S$ requires C, 64·4; H, 5·1; N, 7·9; S, 9·05%).

The foregoing hydrobromide (22·7 g.) was heated on the steam-bath with phosphorus tribromide (20 ml.) for 1 hr. with occasional shaking. Liquid was decanted from the cooled product and the residue treated at 0° dropwise with methanol (20 ml.). The crystalline solid obtained (23·1 g., m. p. 135—140°) gave the bromo-hydrobromide as prisms, m. p. 146—147° (lit.,[7] 148°), from methanol (Found: C, 20·8; H, 3·5; Br, 55·1; Br^-, 27·7; N, 9·5; S, 11·1. Calc. for $C_5H_9BrN_2S,HBr$: C, 20·7; H, 3·5; Br, 55·1; Br^-, 27·55; N, 9·7; S, 11·05%). The picrate separated as yellow prisms from methanol, then acetone–benzene, m. p. 142° (lit.,[7] 144—145°) (Found: C, 30·5; H, 2·9; Br, 18·4; N, 15·8; S, 7·1. Calc. for $C_{11}H_{12}BrN_5O_7S$: C, 30·1; H, 2·8; Br, 18·2; N, 16·0; S, 7·3%).

2,3,6,7-*Tetrahydroimidazo*[2,1-b]*thiazolium Bromide*.—The bromohydrobromide (16·0 g.) above was dissolved in the minimum of water and cooled to 0°. A cooled solution of 2N-potassium hydroxide was added until there was no further precipitate and the solid was immediately isolated and washed with a little ice–water. Crystallisation from methanol–acetone gave the tetrahydroimidazothiazolium bromide (2·5 g.) as prisms, m. p. 176—177° (Found: C, 29·1; H, 4·5; Br^-, 38·4; N, 13·3; S, 15·5. Calc. for $(C_5H_9N_2S)^+Br^-$: C, 28·7; H, 4·3; Br^-, 38·2; N, 13·4;

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[6] G. M. Clarke and P. Sykes, *Chem. Comm.*, 1965, 370.
[7] V. Prelog, G. Driza, and V. Hanousek, *Coll. Czech. Chem. Comm.*, 1931, **3**, 578.
[8] G. L. Caldow and H. W. Thompson, *Spectrochim. Acta*, 1958, **13**, 212.
[9] K. K. Kuz'mina, N. G. Ostroumova, Yu. V. Markova, and M. N. Shchukina, *Zhur. obshchei Khim.*, 1962, **32**, 3215.

S, 15·3%). The compound was identical (mixed m. p. and infrared absorption spectrum) with the salt prepared [1] *via* 2-(2-bromoethylthio)imidazol-2-ine hydrobromide. It did not yield a 3,5-dinitrobenzoate, but gave a picrate, yellow prisms, m. p. and mixed m. p. 173—174°, from methanol–acetone–water [Found: C, 37·1; H, 3·2; N, 19·5; S, 8·7. Calc. for $(C_5H_9N_2)^+(C_6H_2N_3O_7)^-$: C, 37·0; H, 3·1; N, 19·6; S, 9·0%].

The bromide was recovered (m. p. and mixed m. p.) after attempted reactions with n-butyl bromide in boiling ethanol, with phenacyl bromide in boiling methanol, or with bromine water at 90°; with benzoyl chloride and pyridine, benzoic anhydride (m. p. and mixed m. p. 41°) only was isolated. There was no colour reaction between the bromide and sodium nitroprusside in dilute ammonia.

To a solution of the bromide (2·1 g.) and sodium nitrite (0·69 g.) in water (5 ml.) at 0° was added dropwise glacial acetic acid (1 ml.) during 15 min. *N*-(2-Thionitrotoethyl)-imidazol-2-one separated as a pink solid (1·0 g., m. p. ~70°) which was washed with water and then ether. Examined immediately it had log ε 3·9, 2·8, and 1·0 at $\lambda_{max.}$ 206, 335, and 548 mμ (infl. 510 mμ) in ethanol; the corresponding absorption shown [10] by t-butyl thionitrite has log ε 4·02, 2·99, and 1·18 at $\lambda_{max.}$ 229, 339, and 599 mμ in heptane. A solution in acetone was dried (Na_2SO_4) and evaporated directly on to rock-salt plates, whereupon selective infrared absorption was found at 3390 (m) (NH), 1730 (s) (C=O), and 1200 cm.$^{-1}$ (s) (C–O). The same thionitrite was obtained using hydrochloric acid; it was soluble only in polar organic solvents and resisted crystallisation. It could not be made to yield a picrate, and decomposed in solution or in the solid state within 24 hr. with liberation of oxides of nitrogen. The pale yellow gummy product could not be crystallised; it showed none of the original ultraviolet absorption above 205 mμ, but there was new (weak) absorption at 255 mμ (R·S·S·R); the infrared absorption previously noted was still exhibited.

From attempted reduction of the bromide (2·5 g.) with potassium borohydride in methanol there was finally obtained the picrate (1·0 g.) of the starting material, m. p. and mixed m. p. 172—173°. With benzoyl chloride and 2N-sodium hydroxide there was obtained N-*benzoyl*-N′-(2-*benzoylthioethyl*)*imidazolidin*-2-*one*, m. p. 117°, leaflets from carbon tetrachloride (Found: C, 64·8; H, 5·2; N, 7·9; S, 8·8. $C_{19}H_{18}N_2O_3S$ requires C, 64·4; H, 5·1; N, 7·9; S, 9·05%). With mercuric bromide in 96% ethanol, the bromide (V) gave the *double salt*, m. p. 140—143°, leaflets from ethanol (Found: C, 10·8; H, 1·4; N, 5·0; S, 5·6. $C_7H_9BrN_2S,HgBr_2$ requires C, 10·5; H, 1·6; N, 4·9; S, 5·6%); log ε 4·19 at $\lambda_{max.}$ 213 mμ (ethanol).

1,2,3,5,6,7-Hexahydroimidazo[2,1-*b*][1,3]thiazinium bromide (VI) similarly gave a *double salt*, m. p. 105—107°, plates from ethanol (Found: C, 12·5; H, 2·1; N, 4·7; S, 5·5. $C_6H_{11}BrN_2S,HgBr_2$ requires C, 12·3; H, 1·9; N, 4·8; S, 5·5%); log ε 4·18 at $\lambda_{max.}$ 227 mμ (ethanol).

(With D. R. Robson) *Reaction between Di-*(2-*halogenoethyl*)*amine Salts and Potassium Thiocyanate*.—The chloroamine hydrochloride (53 g.) and the thiocyanate (29·4 g.) were boiled in water (50 ml.) for 6 hr. Potassium chloride was removed from the cold mixture, and the solution evaporated to dryness at 80°. The residue was treated with hot methanol (4 × 25 ml.) and acetone (200 ml.) was added. The solid (4·2 g.) which separated at 0° had m. p. 171—176°; crystallisation from methanol–acetone, then water, gave 3-(2-*thiocyanatoethyl*)-2-*iminothiazolidine hydrochloride* as rhombs, m. p. 184—185° (Found: C, 32·0; H, 4·6; Cl$^-$, 15·7; N, 18·6; S, 28·8. $C_6H_9N_3S_2,HCl$ requires C, 32·2; H, 4·5; Cl$^-$, 15·8; N, 18·8; S, 28·5%), showing $\nu_{max.}$ at 2150 cm.$^{-1}$ (Nujol). The *picrate*, yellow prisms from acetone–water, had m. p. 145—146° (Found: C, 34·3; H, 3·0; N, 20·05; S, 15·4. $C_{12}H_{12}N_6O_7S$ requires C, 34·6; H, 2·9; N, 20·2; S, 15·4%).

The mother-liquor above was further diluted with acetone (200 ml.) to give a precipitate (6·0 g.), m. p. 138—143°. Crystallisation from methanol–acetone gave rhombs of 3-(2-*chloroethyl*)-2-*iminothiazolidine hydrochloride*, m. p. 145—146° (Found: C, 29·9; H, 5·3; Cl, 34·9; Cl$^-$, 17·4; N, 13·65; S, 16·0. $C_5H_9ClN_2S,HCl$ requires C, 29·9; H, 5·0; Cl, 35·3; Cl$^-$, 17·6; N, 13·9; S, 15·9%. The picrate, yellow plates from acetone–water, had m. p. 146—147° (lit.,[7] 143—144°) (Found: C, 33·8; H, 3·2; Cl, 8·8; N, 17·3; S, 8·0. Calc. for $C_{11}H_{12}ClN_5O_7S$: C, 33·55; H, 3·1; Cl, 9·0; N, 17·8; S, 8·1%).

Di-(2-bromoethyl)amine hydrobromide (12·0 g.) and potassium thiocyanate (7·6 g.) were boiled in water (25 ml.) for 3 hr. Cooling to 0° gave crystals (7·0 g.) of 3-(2-*thiocyanatoethyl*)-2-*iminothiazolidine hydrobromide*, m. p. 206—208° (decomp.) (plates from water) (Found: C, 26·8; H, 3·7; Br$^-$, 29·7; N, 15·5; S, 23·9. $C_5H_9N_3S_2,HBr$ requires C, 26·9; H, 3·8; Br$^-$, 29·8; N, 15·7; S, 23·9%), showing $\nu_{max.}$ at 2150 cm.$^{-1}$ (Nujol). Use of twice the quantity of bromoamine hydrobromide gave the same product only.

3-(2-Bromoethyl)-2-iminothiazolidine hydrobromide (0·58 g.) and potassium thiocyanate (0·20 g.) were boiled in 96% ethanol (5 ml.) for 6 hr. After evaporation to dryness the residue on crystallisation from water gave 3-(2-thiocyanatoethyl)-2-iminothiazolidine hydrobromide (0·42 g.), m. p. and mixed m. p. 206—208° (decomp.). The picrate had m. p. and mixed m. p. 145—146°; mixed with 3-(2-bromoethyl)-2-iminothiazolidine picrate (m. p. 142°), m. p. 120—134°.

1,2-*Di*-(2-*iminothiazolidin*-3-*yl*)*ethane*.—1,2-Dibromoethane (9·4 g.) and 2-aminothiazol-2-ine (5·1 g.) were boiled in n-propanol (20 ml.) for 2 hr. On cooling a little 2-aminothiazol-2-ine hydrobromide separated (m. p. and mixed m. p. 169—171°). To the cooled mother-liquor was added just sufficient 2N-sodium hydroxide to render the mixture alkaline; the material extracted into ether was treated with picric acid in n-propanol to yield yellow prisms of the *dipicrate* of 1,2-(2-iminothiazolidin-3-yl)ethane, m. p. 232° (decomp.) [mixed with 2-aminothiazol-2-ine picrate (m. p. 242°, decomp.), m. p. 220—227° (decomp.)] (Found: C, 34·45; H, 3·0; N, 20·2; S, 9·2. $C_{20}H_{20}N_{10}O_{14}S_2$ requires C, 34·9; H, 3·0; N, 20·3; S, 9·3%). When the experiment was carried out in methanol or in acetone the final product isolated was 2-aminothiazol-2-ine picrate, m. p. and mixed m. p. 238—240° (decomp.).

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