

**624.** *Attempted Ring-closures of 2-(2-Bromoethylthio)-2-imidazoline and the Propyl Homologue*

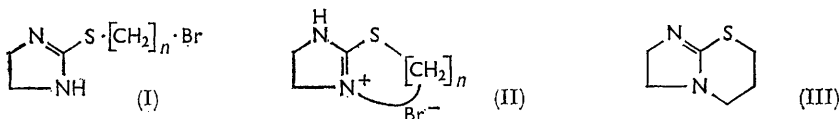
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When heated, the hydrobromides of the bases named in the title disproportionate to give the two di(imidazolinythio)alkanes; the free bases undergo ring-closure to give bicyclic quaternary ammonium salts with nitrogen at a bridgehead.

WHEN heated above its melting point, the hydrobromide of 2-(3-bromopropylthio)-2-imidazoline (I;  $n = 3$ ) underwent disproportionation into 1,3-di-(2-imidazolin-2-ylthio)propane dihydrobromide and 1,3-dibromopropane, presumably through intermolecular sulphonium salt formation. A by-product was 1,2-dibromopropane, which probably arises from an alternative decomposition of the sulphonium salt, giving allyl bromide and hydrogen bromide.

The free base, 2-(3-bromopropylthio)-2-imidazoline (I;  $n = 3$ ), was liberated with aqueous sodium hydroxide, but within minutes of being prepared, at room temperature, it

formed the intramolecular quarternary ammonium salt (II;  $n = 3$ ). This product could not be made to yield a free base that could be isolated from aqueous solution, and with nitrous acid a substance was obtained which gave a positive Liebermann nitroso reaction; these reactions indicate that it is not the hydrobromide of compound (III).



The apparent molecular weight of the product, determined from the depression of the freezing point of water, was 110; the expected apparent molecular weight of the bromide (II;  $n = 3$ ) is 111.5. This result also precludes the possibility that the product is an intermolecular di(quaternary ammonium) or disulphonium salt. It is unlikely that the product is 1-(2-imidazolin-2-yl) thietanium bromide since both 2-(3-bromo-propylthio)-2-imidazoline hydrobromide and picrate are stable, and there is no tendency for the former to disproportionate when heated (through intramolecular sulphonium salt formation) to give thietan.

Similar reactions occurred with the hydrobromide of 2-(2-bromoethylthio)-2-imidazoline (I;  $n = 2$ ). On being held above its melting point this salt gave 1,2-di-(2-imidazolin-2-ylthio)ethane dihydrobromide. [It is interesting to note that S-(2-hydroxyethyl)-thiuronium bromide yields<sup>1</sup> 1,4-dithian when heated.] Attempted preparation of the free base (I;  $n = 2$ ) gave a product which changed rapidly into the bromide (II;  $n = 2$ ). The apparent molecular weight was found to be 102; the expected value is 104.5.

In similar reactions involving 2-(2-hydroxyethyl)-4,5-benzothiazole similar conclusions are reached<sup>2</sup> that ring-closure is intramolecular on nitrogen, but no proof is advanced. By use of an entirely different route, 2,3,5,6-tetrahydro-7-phenylimidazo[2,1-b]thiazolium chloride has been prepared.<sup>3</sup>

Both quaternary ammonium salts had ultraviolet spectra expected<sup>4</sup> of 2-imidazolinium salts, and strong C=N infrared absorption.

## EXPERIMENTAL

Melting points are corrected.

2-(2-Hydroxyethylthio)-2-imidazoline hydrobromide was obtained only as a glass. The *picrate*, prisms and needles from acetone-water, had m. p. 221–223° (decomp.) (lit.,<sup>5</sup> 143–145°) (Found: C, 35.1; H, 3.0; N, 18.8; S, 8.7.  $C_{11}H_{13}N_5O_8S$  requires C, 35.2; H, 3.5; N, 18.7; S, 8.5%). After a mixture of the hydrobromide (20 g.) and phosphorus tribromide (14 ml.) had ceased to evolve hydrogen bromide on a steam-bath, cautious addition of methanol to the cooled product gave a solid (19.1 g.) which furnished, from methanol-acetone, rhombs of 2-(2-bromoethylthio)-2-imidazoline hydrobromide, m. p. 174–180° (Found: C, 20.6; H, 3.5; Br, 55.2; Br<sup>-</sup>, 27.8; N, 9.5; S, 11.1.  $C_5H_9BrN_2S \cdot HBr$  requires C, 20.7; H, 3.5; Br, 55.1; Br<sup>-</sup>, 27.55; N, 9.7; S, 11.05%). The *picrate*, feathery needles from acetone-water, had m. p. 117° (Found: C, 30.3; H, 2.7; Br, 18.5; N, 16.1; S, 7.5.  $C_{11}H_{12}BrN_5O_7S$  requires C, 30.15; H, 2.8; Br, 18.2; N, 16.0; S, 7.3%); it could not be titrated.<sup>1</sup>

The foregoing bromo-hydrobromide (5.0 g.) was inserted in a bath at 190°, and the temperature was raised to 210° during 6 min.; with effervescence the liquid resolidified. The residue was taken up in the minimum of hot water and the solution treated with an equal volume of methanol, to yield crystals (1.9 g.) of 1,2-di-(2-imidazolin-2-ylthio)ethane dihydrobromide, m. p. and mixed m. p. 285–286° (decomp.) after recrystallisation [lit.,<sup>5</sup> 278–280° (decomp.)] (Found: C, 24.6; H, 4.1; Br<sup>-</sup>, 40.8; N, 14.5; S, 16.1. Calc. for  $C_8H_{14}N_4S_2 \cdot 2HBr$ : C, 24.6; H, 4.1;

<sup>1</sup> L. A. Cort, *J.*, 1961, 5191.

<sup>2</sup> T. Takahashi, S. Nishigaki, and H. Taniyama, *J. Pharm. Soc. Japan*, 1944, **64**, 237; A. Bawley, *U.S.P.* 2,418,748/1947.

<sup>3</sup> H. Dorn and M. Schütt, *Chem. Ber.*, 1964, 3246; H. Dorn, *Angew. Chem.*, 1964, **76**, 301.

<sup>4</sup> R. J. Ferm, J. L. Riebsomer, E. L. Martin, and G. H. Daub, *J. Org. Chem.*, 1953, **18**, 643.

<sup>5</sup> R. N. Boyd and M. Meadow, *Analyt. Chem.*, 1960, **32**, 551.

Br<sup>-</sup>, 40.6; N, 14.3; S, 16.4%). This yielded the corresponding dipicrate as prisms from acetone-water, m. p. and mixed m. p. 223—228° (decomp.), equiv. by titration<sup>1</sup> 328. The free base, liberated from the di-hydrobromide with sodium hydroxide, separated as plates from methanol. The crystals almost melted and immediately resolidified at 156°, and finally melted at 212° (lit.,<sup>5</sup> m. p. 202—204°) (Found: C, 41.9; H, 6.1; N, 24.3; S, 27.7. C<sub>8</sub>H<sub>14</sub>N<sub>4</sub>S<sub>2</sub> requires C, 41.7; H, 6.1; N, 24.3; S, 27.8%).

*2,3,6,7-Tetrahydro-5H-imidazo[2,1-b]thiazolium Bromide.*—This bromide was prepared from 2-(2-bromoethylthio)-2-imidazoline hydrobromide, as described below for the hexahydroimidazothiazinium bromide. It formed prisms, m. p. 176.5—177.5° (from methanol-acetone) [Found: C, 28.8; H, 4.5; Br<sup>-</sup>, 38.1; N, 13.3; S, 15.4. (C<sub>5</sub>H<sub>9</sub>N<sub>2</sub>S)<sup>+</sup>Br<sup>-</sup> requires C, 28.7; H, 4.3; Br<sup>-</sup>, 38.2; N, 13.4; S, 15.3%. Apparent *M* (depression of freezing point of water; *c* 0.72), 102. (C<sub>5</sub>H<sub>9</sub>N<sub>2</sub>S)<sup>+</sup>Br<sup>-</sup> requires apparent *M*, 104.5]; log  $\epsilon$  4.05 at  $\lambda_{\max}$ . 213  $\mu$ ;  $\nu_{\max}$ . (Nujol) at 3090m, 2710m, 1600s, 1535s, 1330m, 1311w, 1276s, 1262sh, 1210s, 1190sh, 1160w 1100w, 1028w, 1000m, 950m, 867m, 797w, and 697mb cm.<sup>-1</sup>. The picrate formed prisms, m. p. 173.5—174.5° (from acetone-water) [Found: C, 37.2; H, 2.8; N, 19.5; S, 9.2. (C<sub>5</sub>H<sub>9</sub>N<sub>2</sub>S)<sup>+</sup>(C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>)<sup>-</sup> requires C, 37.0; H, 3.1; N, 19.6; S, 9.0%]; it could not be titrated.<sup>1</sup>

*Experiments Starting with the Bromopropanol.*—Gas chromatography showed that the 3-bromopropanol used (Eastman) contained 5—10% of 1,3-dibromopropane.

The bromopropanol (50 g.) and 2-imidazoline-2-thiol (40 g.) were boiled in methanol (50 ml.) for 1 hr.; the solution was then diluted with acetone (100 ml.) and stood overnight in the ice-chest. The solid (7.3 g.), m. p. 205—210°, was recrystallised from methanol-acetone to give prisms, m. p. 225°, of 1,3-di-(2-imidazolin-2-ylthio)propane dihydrobromide (lit.,<sup>5</sup> m. p. 225°) (Found: C, 26.8; H, 4.4; Br<sup>-</sup>, 39.4; N, 13.7; S, 15.9. Calc. for C<sub>8</sub>H<sub>16</sub>N<sub>4</sub>S<sub>2</sub>·2HBr: C, 26.6; H, 4.5; Br<sup>-</sup>, 39.35; N, 13.8; S, 15.8%). The original filtrate was held at 80°/20 mm. for 1 hr.; the 2-(3-hydroxypropylthio)-2-imidazoline hydrobromide was obtained only as a glass. It was maintained at 25—30° and treated portionwise with phosphorus tribromide (35 ml.) until reaction had apparently ceased. The mixture was then warmed on a steam-bath for 20 min., cooled in ice, and the excess of tribromide destroyed with methanol. When reaction had ceased the mixture was held at 80°/20 mm. for 20 min., and the cold residue triturated with ether and acetone to give a crystalline solid (77 g.), m. p. 90—98°. Recrystallisation from methanol-acetone gave 2-(3-bromopropylthio)-2-imidazoline hydrobromide as prisms, m. p. 125° (Found: C, 23.65; H, 4.1; Br, 52.6; N, 9.2; S, 10.3. C<sub>8</sub>H<sub>11</sub>BrN<sub>2</sub>S·HBr requires C, 23.7; H, 4.0; Br, 52.6; N, 9.2; S, 10.55%). The corresponding picrate separated from methanol-acetone-water as plates, m. p. 105° (Found: C, 31.9; H, 3.0; Br, 17.6; N, 15.35; S, 7.1. C<sub>12</sub>H<sub>14</sub>BrN<sub>5</sub>O<sub>7</sub>S requires C, 31.9; H, 3.1; Br, 17.7; N, 15.5; S, 7.1%).

The foregoing hydrobromide (1.0 g.) was inserted for 6 min. in a bath at 200°, and the cooled total product extracted with cyclohexane. The solid residue had m. p. 216—221° (0.35 g.) (from methanol-acetone) raised to 225° on further crystallisation; this gave, on mixing with 1,3-di-(2-imidazolin-2-ylthio)propane dihydrobromide, no depression of m. p.

Gas chromatography of the cyclohexane solution (4 mm.  $\times$  91 cm. column; 20% dinonyl phthalate on Celite; 112°; N<sub>2</sub> 68 ml./min.) showed it to contain two substances; the less volatile had the same retention time as authentic 1,3-dibromopropane, and the more volatile (<10% of the mixture; relative retention time to authentic 1,3-dibromopropane, 0.47) had the same retention time as authentic 1,2-dibromopropane. Under the same conditions, the relative retention times of thietan<sup>6</sup> and allyl bromide were 0.17 and 0.079, respectively, and the authentic dibromopropanes each gave separately only one peak. On a 4 mm.  $\times$  126 cm. column of 10% Carbowax on Celite at 123°, with argon (flow rate 45 ml./min.) as the carrier gas, the retention times of the two dissolved reaction products were again the same as those for authentic 1,3- and 1,2-dibromopropane.

In control experiments in which 1,3-dibromopropane (2 ml.) was heated with ammonium bromide (1 g.), and with 2-iminothiazolidine hydrobromide (1 g.), at 200° for 6 min., the cyclohexane extract of the cold mixture was found by gas chromatography to contain 1,3-dibromopropane only.

*1,2,3,5,6,7-Hexahydroimidazo[2,1-b][1,3]thiazinium Bromide.*—2-(3-Bromopropylthio)-2-imidazoline hydrobromide (10 g.) was dissolved in the minimum volume of water and cooled to 0°. A cooled solution of 2*N*-sodium hydroxide (16.5 ml.) was added and the precipitated solid immediately isolated and washed with a little ice-water. It (3.5 g.) partially melted

<sup>6</sup> G. M. Bennett and A. L. Hock, *J.*, 1927, 2496.

at  $\sim 65^\circ$  and had completely melted at  $190^\circ$ ; it was completely soluble in cold dry acetone, and within minutes the solution deposited needles (m. p.  $178\text{--}186^\circ$ ) of the *hexahydroimidazothiazinium bromide*, m. p.  $200\text{--}201^\circ$  (from methanol-acetone) [Found: C, 32.5; H, 5.0; Br<sup>-</sup>, 35.95; N, 12.5; S, 14.35.  $(\text{C}_6\text{H}_{11}\text{N}_2\text{S})^+\text{Br}^-$  requires C, 32.3; H, 5.0; Br<sup>-</sup>, 35.8; N, 12.6; S, 14.4%. Apparent  $M$  (depression of the freezing point of water;  $c$  0.85), 110.  $(\text{C}_6\text{H}_{11}\text{N}_2\text{S})^+\text{Br}^-$  requires apparent  $M$ , 111.5];  $\log \epsilon$  4.05 at  $\lambda_{\text{max}}$  225  $\text{m}\mu$ ;  $\nu_{\text{max}}$  (Nujol) 3090m, 2730m, 1600s, 1535s, 1325sh, 1310s, 1284s, 1262s, 1215w, 1220m, 1200s, 1060w, 1042m, 1018m, 968m, 920m, 901m, 863w, 795mb, and 687mb  $\text{cm}^{-1}$ . (On several occasions the free base underwent quaternisation on the filter, the heat of reaction being sufficient to cause liquefaction.) The *picrate* formed needles, m. p.  $185\text{--}186^\circ$  (from water-methanol)-acetone [Found: C, 39.0; H, 3.5; N, 18.9; S, 8.6.  $(\text{C}_6\text{H}_{11}\text{N}_2\text{S})^+(\text{C}_6\text{H}_2\text{N}_3\text{O}_7)^-$  requires C, 38.8; H, 3.5; N, 18.9; S, 8.6%]; it could not be titrated.<sup>1</sup>

The bromide (1.0 g.) was dissolved in 45% hydrobromic acid (2 ml.) and allowed to stand over sodium hydroxide for 24 hr., after which acetone was added to the ice-cold solution; the bromide (0.35 g.) was precipitated, m. p. and mixed m. p.  $195\text{--}200^\circ$ . When an aqueous solution of the bromide was treated with one equivalent of sodium acetate or of sodium hydroxide, nothing could be extracted from the clear solution into ether. The bromide, after treatment with acetic acid and sodium nitrite, gave a strongly positive reaction in a Liebermann nitroso test. This test was equally positive starting with the tetrahydroimidazothiazolium bromide, and with diethylamine hydrobromide, but only very weakly positive starting with ammonium bromide, under the same conditions.

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