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CYCLIZATION OF 1,3-BIS-(β-CHLOROETHYL)-UREA*

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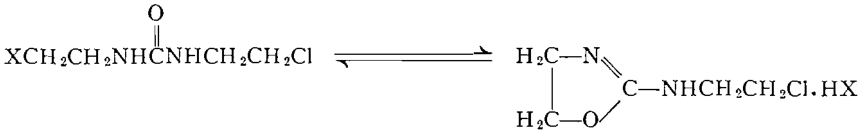
It was found that the double melting point property of 2-(β-chloroethylamino)-2-oxazoline hydrochloride (II*a*) is associated with its conversion in the molten state into 1,3-bis-(β-chloroethyl)-urea (I*a*). Although 2-(β-chloroethylamino)-2-oxazoline hydrobromide (II*b*) does not exhibit a double melting point, it also rearranges in the molten state to the corresponding urea (I*b*).



I*a*, X = Cl
b, X = Br

II*a*, X = Cl
b, X = Br

1-(β-Bromoethyl)-3-(β-chloroethyl)-urea and 1,3-bis-(β-chloroethyl)-urea on heating in water cyclized respectively to the hydrobromide and hydrochloride salts of 2-(β-chloroethylamino)-2-oxazoline. The conversion of 1-(β-bromoethyl)-3-(β-chloroethyl)-urea into the hydrobromide salt II*b* rather than the hydrochloride salt of 2-(β-bromoethylamino)-2-oxazoline can be attributed to the lower bond energy of the C–Br linkage in comparison with the C–Cl linkage.

EXPERIMENTAL†

1,3-Bis-(β-chloroethyl)-urea

1,3-Bis-(β-chloroethyl)-urea (m.p. 126.5–128° C) was prepared in 61.2% yield by the method of Bestian (1). A mixture melting point determination with a known (2) sample of 1,3-bis-(β-chloroethyl)-urea gave no depression.

2-(β-Chloroethylamino)-2-oxazoline Hydrochloride

1,3-Bis-(β-chloroethyl)-urea (20 g, 0.1 mole) in water (50 ml) was heated under reflux for 1 hour. After the clear solution was evaporated to dryness *in vacuo*, crystals were obtained, yield 20 g (100%). These crystals melted at 103–104° C, resolidified and remelted at 121–123° C. Three crystallizations from absolute ethanol–ether (1 : 1) solution raised the melting points to 107–109° C and 125–127° C. Anal. Calc. for $C_5H_{10}Cl_2N_2O$:

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†*All melting points are uncorrected. The microanalyses were determined by Micro-Tech Laboratories, Skokie, Ill., and Schwartzkopf Microanalytical Laboratory, Woodside, N.Y.*

C, 32.45; H, 5.45; Cl, 38.32; N, 15.14%. Found: C, 32.77; H, 5.37; Cl, 37.86; N, 14.96%.

A picrate (m.p. 192–194° C) was formed in the usual manner from water. The product was identified by a mixture melting point determination with a known (2) sample of 2-(β-chloroethylamino)-2-oxazoline picrate (m.p. 193–194° C).

A sample of 2-(β-chloroethylamino)-2-oxazoline hydrochloride (m.p. 107–109° C and 125–127° C) was held in the molten state for 1 minute. The molten mass crystallized immediately on cooling and the crystals melted sharply at 125–127° C. These crystals no longer gave a picrate and they did not depress the melting point of a known sample of 1,3-bis-(β-chloroethyl)-urea.

2-(β-Chloroethylamino)-2-oxazoline hydrochloride (9.25 g, 0.05 mole) in absolute methanol (180 ml) was passed through a column of Amberlite IRA-400 resin (150 ml in the hydroxyl form). The column was washed with the same volume of methanol and the eluate and washings were evaporated to dryness *in vacuo* under nitrogen. The residual crystalline mass melted at 81–84° C, yield 7.43 g (100%). These crystals of 2-(β-chloroethylamino)-2-oxazoline were very soluble in water, alcohol, and acetone. Three crystallizations from acetone–hexane solution raised the melting point to 84–86° C. Anal. Calc. for $C_5H_9ClN_2O$: C, 40.40; H, 6.10; Cl, 23.85; N, 18.85%. Found: C, 39.78; H, 6.35; Cl, 23.50; N, 18.52%.

2-(β-Chloroethylamino)-2-oxazoline Hydrobromide

Gaseous hydrogen bromide was passed into a solution of 2-(β-chloroethylamino)-2-oxazoline (841 mg, 0.005 mole) in water (10 ml) until a pH of 3 was obtained. The solution was evaporated *in vacuo* at 45° C and the resulting oil crystallized on standing in a vacuum desiccator overnight, yield 1.3 g (100%). Crystallization from ethanol–ether solution gave a constant melting point of 118.5–119.5° C. Anal. Calc. for $C_5H_{10}BrClN_2O$: C, 26.17; H, 4.39; halogen, 50.27; N, 12.21%. Found: C, 26.41; H, 4.26; halogen, 49.88; N, 11.77%.

A sample of 2-(β-chloroethylamino)-2-oxazoline hydrobromide in water was converted into its picrate (m.p. 193–194° C) in 95% yield in the usual manner.

1-(β-Bromoethyl)-3-(β-chloroethyl)-urea

1-(β-Chloroethylamino)-2-oxazoline hydrobromide (76 mg, 0.00033 mole) was heated for 15 minutes in dry *o*-xylene (3 ml) to 130–140° C (temperature of the oil bath). The mixture upon cooling deposited crystals, which were collected by filtration; yield, 42 mg (55.3%). Crystallization from warm (50° C) ethanol–ether solution raised the melting point from 108.5–110° C to 109–111° C. Anal. Calc. for $C_5H_{10}BrClN_2O$: C, 26.17; H, 4.39; halogen, 50.27; N, 12.21%. Found: C, 26.02; H, 4.35; halogen, 50.30; N, 12.01%.

Cyclization of 1-(β-Bromoethyl)-3-(β-chloroethyl)-urea

1-(β-Bromoethyl)-3-(β-chloroethyl)-urea (80 mg) in water (2 ml) was heated for approximately 1 hour at 70–80° C until a clear solution was obtained. The clear solution on treatment with aqueous picric acid solution gave a 93.5% yield of 2-(β-chloroethylamino)-2-oxazoline picrate (193–194° C) which was identified by a mixed melting point determination.

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