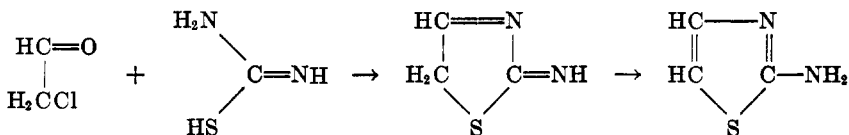


THE PREPARATION OF 2-AMINOTHIAZOLE FROM
CYCLIC ACETALS

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The synthesis of 2-aminothiazole involves basically a reaction between chloroacetaldehyde and thiourea.

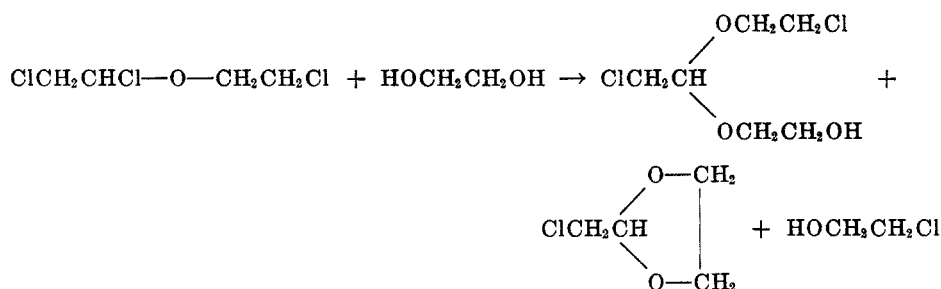


Chloroacetaldehyde is obtainable as a 40 per cent aqueous solution and is converted to a trimer as the water is removed. Since chloroacetaldehyde shows this tendency to polymerize and can not be obtained pure, several preparations of 2-aminothiazole have been described in the literature which avoid its use but employ instead compounds which may be the equivalent as far as the reaction is concerned. Thus, diethylchloroacetal has been converted to aminothiazole (3, 5) by reaction with thiourea. Postovskii prepared the diethylchloroacetal by the direct chlorination of diethyl acetal (5) while Magidson and Sokalora (2) chlorinated an equimolar mixture of acetaldehyde and ethanol. Markees, Kellerhals, and Erlenmeyer (3) prepared 2-aminothiazole from 1,2-dichlorodiethyl ether and Britton and Harding (1) used *bis*-(1,2-dichloroethyl) ether. In the latter cases, the α -chloroethers were easily hydrolyzed to the hemiacetals of chloroacetaldehyde and thus into chloroacetaldehyde itself.

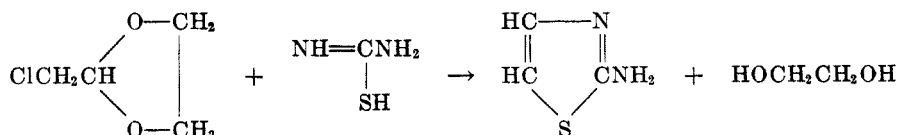
The isolation of 2-aminothiazole in all of the processes above was accomplished in much the same way. This involved treating the product mixture with activated carbon, neutralizing the clear filtrate with a concentrated solution of NaOH (30–40 per cent), and extracting the free base with ether. After the ether was removed, the solid product was recrystallized from ethanol. The reported yields varied from about 50 to more than 90 per cent of the theoretical, based on the thiourea.

The process presented in this paper describes the preparation of 2-aminothiazole from cyclic acetals, which were readily formed by the action of glycols on α -chloroethers. Two such ethers, α,β,β' -trichlorodiethyl ether and bis-(α,β -dichloroethyl) ether, were used for this purpose. These ethers were easily prepared by chlorinating β,β' -dichlorodiethyl ether at 30°. The α,β,β' -trichlorodiethyl ether formed first in almost quantitative yield. Further chlorination of this substance produced excellent yields of the bis-(α,β -dichloroethyl) ether.

Ethylene glycol reacts with α,β,β' -trichlorodiethyl ether to give 2-chloromethyl dioxolane and ethylene chlorohydrin

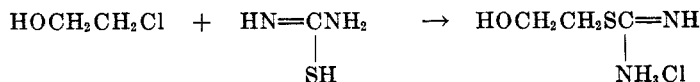


The formation of ethylene chlorohydrin is desirable especially if it can be recovered in the anhydrous condition. This has been accomplished, and the chloromethyl dioxolane can be converted to 2-aminothiazole in excellent yield.



Reaction of the trichloroether with diethylene glycol gives the cyclic acetal, 2-chloromethyl trioxocane with 8 atoms in the ring, which may also be converted to 2-aminothiazole.

α, β, β' -Trichlorodiethyl ether reacts with thiourea directly to give 2-aminothiazole. However, in this case, an equimolar amount of ethylene chlorohydrin is formed which also reacts with thiourea so that a molar excess of thiourea is required. (4)



An efficient method has been devised by which 2-aminothiazole can be recovered from the product mixture in the form of its hydrochloride. In this process acetone was added to the product mixture; the system was refrigerated, and the 2-aminothiazole hydrochloride was collected as a clean, white precipitate. This product was obtained as an essentially pure product without any treatment with activated carbon or recrystallization.

EXPERIMENTAL

Preparation of chloromethyl dioxolane from α, β, β' -trichlorodiethyl ether. A mixture of 31 g. (0.5 mole) of ethylene glycol and 89 g. (0.5 mole) of α, β, β' -trichlorodiethyl ether was refluxed under a pressure of 200 mm. of mercury. Anhydrous ethylene chlorohydrin was removed at the same rate as it was formed until a vapor temperature of 95° was reached. Further distillation gave 107 g. of chloromethyl dioxolane, representing a conversion of 87%.

If toluene is added along with the other reactants ethylene chlorohydrin may be recovered at normal pressure as the toluene azeotrope.

Preparation of 2-aminothiazole hydrochloride from 2-chloromethyl dioxolane. 2-Chloromethyl-1,3-dioxolane (30.5 g., 0.25 mole), 19.0 g. of thiourea (0.25 mole), 9 ml. of concen-

trated HCl solution, and 100 ml. of acetone were refluxed for four hours and allowed to cool. This mixture was cooled in a Dewar flask containing Dry Ice. The product settled out of the mixture in the form of a semiplastic mass, which changed to a white granular precipitate when it was thoroughly dispersed. This precipitate formed a cake which was broken up and dispersed several times. The mixture was filtered while cold and the filter cake was washed with cold acetone. This process gave 31.0 g. of 2-aminothiazole hydrochloride, representing a conversion of 91%.

DISCUSSION OF RESULTS

2-Aminothiazole can be prepared in excellent yield from 2-chloromethyl dioxolane. This permits the successful preparation of 2-aminothiazole from α, β, β' -trichlorodiethyl ether which is in turn very easily prepared from β, β' -dichlorodiethyl ether.

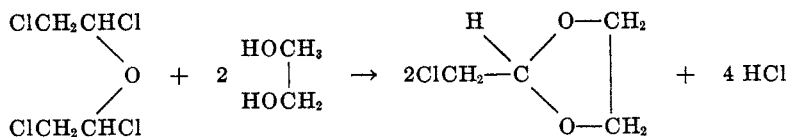
The conversion of α, β, β' -trichlorodiethyl ether to chloromethyl dioxolane permits the recovery of anhydrous ethylene chlorohydrin as a by-product which is of considerable value. Attempts to remove the ethylene chlorohydrin by distillation at atmospheric pressure were not successful in that no constant-boiling fraction was obtained. This might have been possible with a more efficient column. The ethylene chlorohydrin was readily removed as a toluene azeotrope, but some difficulty was encountered in separating the two components. Anhydrous ethylene chlorohydrin was easily obtained when the reaction was carried out at reduced pressure (200 mm. of Hg) and removed as fast as formed. This may be the best method of carrying out the reaction if the recovery of the chlorohydrin is important.

Over-all yields of 2-aminothiazole, using chloromethyl dioxolane as an intermediate, were about 90 per cent, and the product was recovered as the hydrochloride in one operation by adding acetone and cooling the reaction mixture.

The presence of appreciable amounts of water is not necessary in order to obtain good yields of product; and, in fact, very much water is detrimental to the separation of 2-aminothiazole as the hydrochloride by the method described. No neutralization, treatment with activated carbon, or extraction with ether was necessary as reported in the other processes.

The acetone can be readily recovered by distillation. The glycol can also be recovered by distillation, or it can be used without purification for reaction with more of the trichlorodiethyl ether to form chloromethyl dioxolane.

2-Chloromethyl-1,3-dioxolane has been prepared from bis-(α, β -dichloroethyl) ether as well as from α, β, β' -trichlorodiethyl ether. When the bis-(α, β -dichloroethyl) ether is used, the only by-product which is formed, theoretically, is HCl. Thus, one mole of this ether can produce two moles of chloroacetaldehyde and four moles of HCl. This is illustrated:



2-Aminothiazole has also been prepared from 2-chloromethyl-1,3,6-trioxocane by using exactly the same process as has been described. The trioxocane may be used in place of the dioxolane, and the only real difference in the two methods is the formation of diethylene glycol as a by-product in place of ethylene glycol. Since the trioxocane is more difficult to prepare than the dioxolane, the route through the dioxolane is preferred.

The use of acetone to decrease the solubility of the 2-aminothiazole hydrochloride in the reaction product and to cause its separation at low temperatures was particularly effective. The acetone was either added initially as a solvent for the reaction or to the reaction mixture after the reaction was complete. In either case 2-aminothiazole was separated as an essentially pure product when the reaction mixture was cooled to about -20° . The optimum amount of acetone was a volume equal to or a little greater than the volume of the reactants. A small amount of water did not interfere with this method of isolation of the product, but large volumes of water must be avoided. Other solvents such as methyl alcohol, ethyl alcohol, and isopropyl alcohol were used, but they were not as effective as acetone.

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SUMMARY

2-Aminothiazole has been prepared from the cyclic acetals, 2-chloromethyl-1,3-dioxolane and 2-chloromethyl-1,3,6-trioxocane by reaction with thiourea in the presence of small amounts of HCl.

When acetone is used as a solvent or added to the reaction mixture at the end of the run, 2-aminothiazole hydrochloride separates as a white crystalline compound if the temperature is lowered to -20 to -40° with Dry Ice. This very simple process gives an essentially pure product.

2-Chloromethyl dioxolane and 2-chloromethyl trioxocane can be prepared from α,β,β' -trichlorodiethyl ether and *bis*-(α,β -dichloroethyl) ether by treatment with ethylene glycol and diethylene glycol, respectively.

The formation of 2-chloromethyl dioxolane from α,β,β' -trichlorodiethyl ether gives ethylene chlorohydrin which may be recovered as an anhydrous product.

The preparation of 2-aminothiazole from these cyclic acetals may be considered as one step in an over-all process starting with β,β' -dichlorodiethyl ether.

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