

CHEMISTRY OF THE THIAZOLES

Part II. Synthesis of 4-Aminothiazole Derivatives

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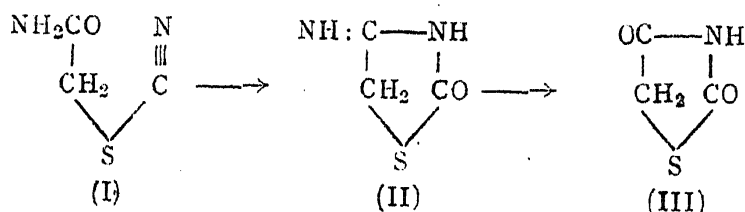
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Received July 28, 1945

(Communicated by Lt.-Col. S. S. Sokhey, M.A., M.D., F.A.S.C., I.M.S.)

IN Part I of this series,¹ a number of methods for the synthesis of 5-aminothiazole derivatives were described. This paper deals with the attempts made to synthesise 4-aminothiazole and derivatives.

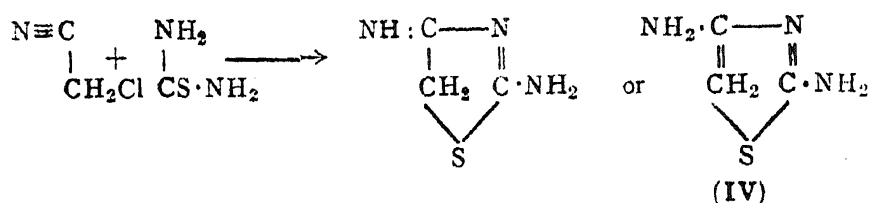
By the action of dilute sulphuric acid on thiocynoacetamide (I) Miolati² obtained a compound described as "isothiohydantoin" (II) the reaction proceeding as follows:



We have confirmed the preparation of this compound but our attempts to convert it into 4-acetaminothiazole or 2:4-diacetaminothiazole were unsuccessful. This compound is very feebly basic and could be extracted from dilute sulphuric acid solution with ether. It did not react with acetic anhydride to yield the acetyl derivative. It is very unstable to dilute acid or alkali. With dilute hydrochloric acid or sulphuric acid it is converted into 2:4-diketothiazolidine (III).

We next attempted to synthesise 4-aminothiazoles from the corresponding thiazole-4-carboxylic esters. Ethyl 2-methylthiazole-4-carboxylate prepared by the action of thioacetamide on bromopyruvic ester, could not be converted into 2-methyl-4-acetaminothiazole by the Curtius method. But ethyl 2-aminothiazole-4-carboxylate³ was converted into 2:4-diacetaminothiazole by the Curtius method.

While we were investigating the above method for the synthesis of 4-aminothiazoles, an abstract of a German Patent⁴ came to our notice wherein the fusion of thiourea with chloracetonitrile is claimed to produce 2:4-diaminothiazole hydrochloride (IV), the reaction proceeding obviously as follows:



We have now found that this reaction proceeds with surprising ease in alcoholic solution to furnish in quantitative yields the hydrochloride of 2:4-diaminotiazole (IV). The free base could not be isolated and in this respect it resembles 4-aminoglyoxaline.⁵ On acetylation a diacetamino derivative was obtained which was found to be identical with 2:4-diacetaminotiazole prepared from ethyl 2-aminotiazole-4-carboxylate as described above. This new reaction was further investigated using in the place of thiourea other representative thioamides; but these did not yield the required 4-aminothiazole derivatives. The 4-amino group in these cases appears to split off by hydrolysis. Thioformamide and thioacetamide when condensed individually with chloracetonitrile produced about one molecular equivalent of ammonium chloride and an oil which has not so far been characterised. Ammonium thiocarbamate when treated similarly produced one molecular equivalent of ammonium chloride and in addition ammonia also evolved from the reaction mixture. Ethyl thio-oxamate ($\text{NH}_2\cdot\text{CS}\cdot\text{COOEt}$) condensed with chloracetonitrile to yield a product, m.p. 140, which appears to be 4-ketothioazoline-2-carboxylate. Full details of these results will be published shortly.

EXPERIMENTAL

Ethyl 2-methylthiazole-4-carboxylate.—Pyruvic ester (8 g.) was brominated with bromine (11 g.) in carbon disulphide (80 c.c.) according to Erlenmeyer.³ After removing the hydrogen bromide with solid barium carbonate, the crude ester obtained was treated with thioacetamide (3 g.) in alcoholic solution and the product worked up as usual. The thiazole ester obtained (1 g.) crystallised in colourless elongated plates and had m.p. 64–65°. (Found: N, 7.75; $\text{C}_7\text{H}_9\text{O}_2\text{NS}$ requires N, 8.18%.)

2:4-Diaminotiazole hydrochloride.—Thiourea (8.9 g.) in hot alcohol (50 c.c. of 50%) was treated with chloracetonitrile (8.9 g.). The clear solution was refluxed for 15 minutes when it set to a crystalline mass. It was cooled, filtered, washed with a little alcohol and dried. The first crop (14 g.) separated in bunches of thick rectangular plates. The mother liquor on evaporation to dryness yielded 3.9 g. more of the product. On crystallisation from 75% alcohol the compound obtained turns brownish at 170° and does not melt below 275°. (Found: N, 27.52; Cl, 23.18; $\text{C}_3\text{H}_6\text{N}_3\text{SCl}$ requires N, 27.72; Cl, 23.40%.) It yielded a picrate which, after

crystallisation from boiling water, darkens at 210° and melts with decomposition above 290°.

2 : 4-Diacetaminothiazole.—(i) The foregoing amino compound (2 g.) was refluxed with acetic anhydride (5 c.c.) and pyridine (5 c.c.) for 45 minutes, diluted with water and the solid that separated (2.4 g.) crystallised from boiling water. The diacetamino compound separated in thick rhombic plates melting at 239–41°. (Found: N, 20.99; C₇H₉N₃O₂S requires N, 21.10%.)

(ii) Ethyl 2-aminothiazole-4-carboxylate (4 g.) in rectified spirits (10 c.c.) and hydrazine hydrate (3 c.c. of 84%) were refluxed for 6 hours. The residue obtained after distilling off the solvent was dissolved in boiling water (charcoal) and evaporated to dryness (yield of the hydrazide, 3.5 g.). On crystallisation from boiling water the hydrazide melted at 183–94°. The crude hydrazide (2 g.) in water (15 c.c.) and acetic acid (3 c.c.) was cooled to 0° and carefully treated with sodium nitrite (1 g.) in water (6 c.c.). The azide which precipitated as a brown solid was washed with ice-water and dried (yield 1.8 g.). The crude azide was decomposed by warming with a mixture of acetic anhydride (3 c.c.) and acetic acid (5 c.c.). On working up as usual, 2 : 4-diacetaminothiazole was obtained which crystallised in white shining plates and had m.p. 234–36°. This did not depress the melting point of the previously described sample on admixture.

We thank Lt.-Col. S. S. Sokhey, Director, for his kind interest in these investigations and the Lady Tata Memorial Trust for the award of a scholarship to one of us (A.V.).

SUMMARY

That chloracetonitrile condenses with thiourea to yield 2:4-diaminothiazole hydrochloride has been confirmed. The diacetamino compound prepared from this by acetylation has been found to be identical with that prepared from ethyl 2-aminothiazole-4-carboxylate by the Curtius method. Chloracetonitrile reacted with other thioamide compounds but the products are found to be not 4-aminothiazole derivatives.

Ethyl 2-methylthiazole-4-carboxylate could not be converted into 2-methyl-acetaminothiazole.

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