CHEMISTRY OF THE THIAZOLES

Part I. Synthesis of 5-Aminothiazole Derivatives

By K. Ganapathi and (Mrs.) Alamela Venkataraman

(From the Department of Chemotherapy, Haffkine Institute, Parel, Bombay)

Received July 28, 1945

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

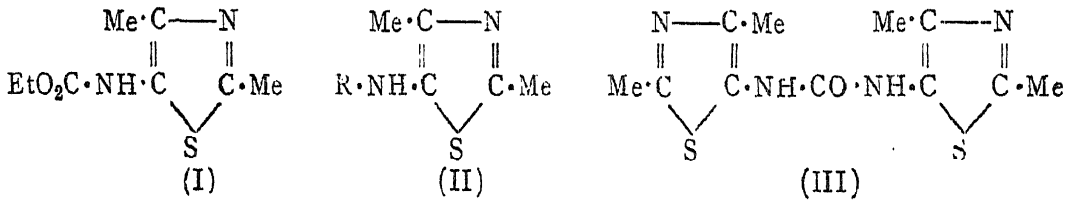
1. Introduction: Previous Work

For the synthesis of the 4- and 5-sulphanilamido derivatives of thiazole, we required 4-aminothiazole, 5-aminothiazole and their various substitution products. Though 2-aminothiazole has been synthesised as early as 1889, the isomeric 4-amino and 5-aminothiazoles are not known so far. However a number of derivatives have been described in literature whose structures have not been established beyond doubt. Wallach[1] obtained a compound called "chrysean" by passing hydrogen sulphide into a concentrated solution of sodium cyanide. Later on, Hellsing[2, 3] investigated this compound and suggested it to be probably 2-thioamido-5-amino-thiazole; on degrading this, he obtained an acetamino compound, m.p. 162°, which he has suggested to be 5-acetaminothiazole. Another series of compounds have been prepared by Weidel and Niemilowicz[4] by the degradation of "ethylenethiouramil"; as the final degradation product he obtained a compound described as 2-methyl-5-aminothiazole, which being obtained in very small quantities was not further investigated. Apart from these, there is on record no other attempt made to synthesise 5-aminothiazole or its derivatives. Our preliminary studies led us to realise that the synthesis of these compounds requires a thorough investigation and so all the methods theoretically possible were tried in suitable cases. In this paper is presented some of the results obtained and ready for publication.

2. Conversion of Thiazole-5-carboxylic Esters into 5-Aminothiazole Derivatives

The conversion of the thiazole carboxylic esters into the aminothiazoles was first tried because all the starting esters required are known and can be prepared comparatively easily; they are all of unequivocal constitution and so the structures of aminothiazole and derivatives prepared from them will be definite and could be used as reference compounds for further studies. The three methods known for the conversion of the ester into the

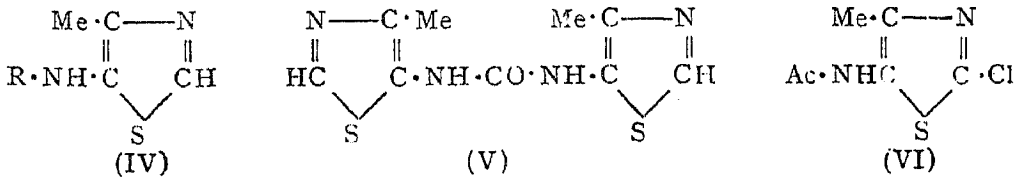
amino grouping, *viz.*, the Hofmann, the Curtius and the Schmidt's reactions were tried with the easily accessible ethyl 2:4-dimethylthiazole-5-carboxylate. The amide of the thiazole ester could not be converted into the amino compound by using sodium hypochlorite or sodium hypobromite under a variety of conditions; the use of alkali caused decomposition of the starting product and about 50 per cent. of the amide was also hydrolysed to the acid. Hydrazoic acid failed to react with 2:4-dimethylthiazole-5-carboxylic acid or its ester. (Similarly, 2-amino-4-methylthiazole-5-carboxylate and 2-sulphanilamido-4-methylthiazole-5-carboxylic acid failed to react with hydrazoic acid.) The Curtius reaction yielded the amino compound under a particular set of conditions. The hydrazide obtained from the ester on treatment with nitrous acid furnished in good yields the liquid azide which reacted with alcohol to yield the urethane (I). This could not successfully be converted into the amine; it resisted hydrolysis with 48 per cent. hydrobromic acid, concentrated hydrochloric acid and 50 per cent. sulphuric acid but was completely decomposed with 10 per cent. sodium hydroxide. The stability of this urethane to acids and its instability to alkali is characteristic of the thiazoles. The decomposition of the azide with various other reagents was studied. While the treatment with 50 per cent. acetic acid (Lindeman)[7] produced a high melting product difficult to purify, dilute hydrochloric acid furnished a small quantity of the required 2:4-dimethyl-5-aminothiazole (II, R=H). With dioxane,[8] the azide decomposed to yield the urea derivative (III) along with a liquid product not identical with the amine. Treat-



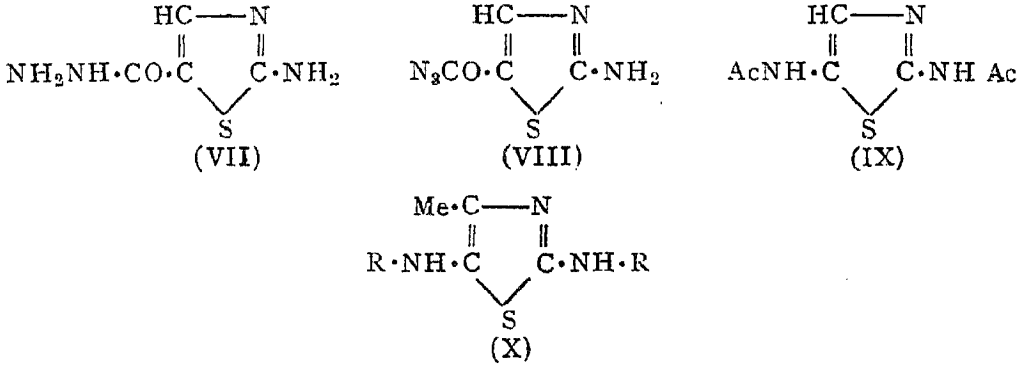
ment of the azide with acetone did not lead to its decomposition. When the *dry* azide was treated with a mixture of acetic acid and acetic anhydride, 2:4-dimethyl-5-acetaminothiazole (II, R=Ac) was obtained in practically quantitative yields, the urea derivative being absent. It appears that in this case as the amine is being formed it is fixed up immediately as the acetyl derivative so that the intermediate isocyanate is not given a chance to react with it to form the urea derivative. The acetamino compound under the conditions described in the experimental part underwent hydrolysis to furnish 2:4-dimethyl-5-aminothiazole.

Ethyl 4-methylthiazole-5-carboxylate was next chosen for study and the behaviour of this compound was not quite similar to that of the 2:4-dimethyl analogue. Though the corresponding amide,[9] with sodium hypochlorite or sodium hypobromite, under the usual conditions, underwent

composition, under a set of conditions[10] yielded the required 4-methyl-aminothiazole (IV, R=H), isolated, after acetylation, as the acetyl derivative (IV, R=Ac). The decomposition of the corresponding azide with various reagents was also tried. The urea derivative (V) could readily be obtained by treating the azide with water. With dilute hydrochloric acid the amine could be isolated. With acetic acid and acetic anhydride, the azide furnished 4-methyl-5-acetaminothiazole (IV, R=Ac) in good yields. The hydrolysis of this to the amino compound could not successfully be effected. While under the usual conditions the product remained unaffected, under drastic conditions it underwent extensive decomposition.



To study the influence of the various groupings in position 2 of the thiazole ring on the nature of the decomposition of the azide, some more thiazole derivatives were investigated. Ethyl thiazole-5-carboxylate could not successfully be converted into 5-acetaminothiazole so far. Starting from ethyl 2-chloro-4-methylthiazole-5-carboxylate we could obtain 2-chloro-4-methyl-5-acetaminothiazole (VI) though in the decomposition of the azide with acetic acid and acetic anhydride the yield of the acetamino compound is not so good in this case. Ethyl 2-bromothiazole-5-carboxylate could not be converted into 2-bromo-5-acetaminothiazole; the decomposition of the azide was not at all smooth as usually observed. The hydrazide (VII) obtained from ethyl 2-aminothiazole-5-carboxylate was treated with nitrous acid. Since in this compound the 2-amino group does not undergo diazotization under the conditions employed, the azide (VIII) was produced in good yields; this with acetic acid and acetic anhydride yielded 2:5-diacetamino thiazole (IX) which is required as a reference compound in connection with studies on orientation in the thiazole series. Starting from ethyl 2-amino-



-methylthiazole-5-carboxylate, we obtained 2 : 5-diacetamino-4-methylthiazole (X, R=Ac); in this case, however, the treatment of the azide with dilute

hydrochloric acid furnished in good yields a product whose nitrogen value was much lower than that of the expected amine (X, R = H).

3. Conversion of 5–Acetylthiazoles into 5–Acetaminothizoles

In the benzene and other polycyclic series, the conversion of the acetyl into the acetamino group by the Beckmann transformation of the oxime has been achieved with notable success. So we tried this reaction on the oximes of the two 5-acetyl derivatives of thiazole known and prepared without difficulty. On treating the oxime of 4-methyl-5-acetylthiazole[12] with phosphorous pentachloride in benzene we were able to obtain in about 30 per cent. yields 4-methyl-5-acetaminothiazole, m.p. 86–87°, which was identical with the product obtained from ethyl 4-methylthiazole-5-carboxylate. On the other hand, treatment of the oxime with hydrogen chloride and acetic anhydride, a condition very often employed, led to the production of not the acetamino compound but a crystalline product, m.p. 73°, which was found to be the acetyl derivative of the oxime. This acetyl derivative on hydrolysis yielded the original oxime. The oxime of 2 : 4-dimethyl-5-acetylthiazole[11] on treatment with phosphorous pentachloride furnished in about 10 per cent. yields 2 : 4-dimethyl-5-acetaminothiazole. Treatment of this oxime with hydrogen chloride and acetic anhydride yielded an oil which on hydrolysis yielded back the oxime; this oily product is therefore the acetyl derivative of the oxime.

4. Synthesis of 5–Nitrothiazoles and Their Reduction to 5–Aminothiazoles

The synthesis of 5-aminothiazole derivatives by the reduction of the corresponding nitrothiazoles was then investigated. It is indeed strange that upto 1938, no nitrothiazole compound was known. Ochiai[13] first prepared 2-hydroxy-4-methyl-5-nitrothiazole and 2–nitroamino–4–methyl–5–nitrothiazole by nitrating 2-hydroxy-4-methylthiazole and 2-amino-4-methylthiazole respectively. He could not reduce the two nitrothiazoles to the corresponding amino compounds. Nagasawa[14] has subsequently prepared 2 : 4-dimethyl-5-nitrothiazole and 2-acetamino-4-nitro-5-methylthiazole by nitration. The original papers of these authors are not available and the abstract of these contain very little details of the experiments. To prepare 4- or 5-nitrothiazole we planned to start with a 2-halogeno, amino or acetaminothiazole (2-hydroxythiazole is as yet unknown), nitrate and then convert the halogeno or the amino group into the hydrogen atom. Our attempts to nitrate 2-chloro and 2-bromothiazole (even at 100° with excess of nitric acid and sulphuric acid) ended in failure, the starting compound being

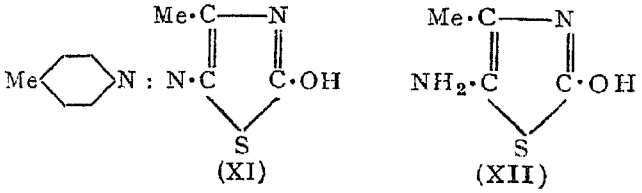
recovered unchanged. This is not unexpected because thiazole itself undergoes bromination only in the vapour phase[15] and the speed of substitution by kationoid reagents in the case of chlorothiazole is far slower than in the case of thiazole because of the "inductive effect (I)" of the halogen atom.[16] 2-Acetaminothiazole on the other hand, as was expected, easily underwent nitration to yield a mono nitration product. Ochiai and Nagasawa[17] have concluded from their studies that a substituent as hydroxy, methyl and amino at the position 2 of the thiazole ring directs the incoming substituent (in kationoid substitution) to the position 5. Their conclusion is unwarranted because in all cases studied by them there is already a methyl group blocking the position 4. Erlenmeyer, Bloch and Kiefer[18] have mentioned that the sulphonation of 2-aminothiazole leads to 2-aminothiazole-5-sulphonic acid; the proof for this structure they had promised in a subsequent paper which has not so far appeared. Bogert and Cherbcoff[19] obtained a dye by coupling diazotised *para* nitraniline (and also sulphanilic acid) with 2-aminothiazole in which they have assumed, without giving any proof, that the azo group is linked to the position 5 of thiazole nucleus. Though in substitution by kationoid reagents, it is very likely that a group in position 2 will direct the incoming substituent to the position 5 if it is unoccupied (and to position 4 if position 5 is occupied), a definite proof for this is lacking. Our attempts to obtain this so far are unsuccessful. We are thus tentatively assigning the structure of 2-acetamino-5-nitrothiazole to the compound obtained by nitrating 2-acetaminothiazole. Hydrolysis of this furnished 2-amino-5-nitrothiazole which could also be prepared directly from 2-aminothiazole by nitration and rearrangement as in the case of 2-aminopyridine. All attempts to convert the 5-nitro-2-amino and nitro-acetamino compounds into the diacetaminothiazole by reduction and acetylation ended in failure. Though the reduction of the nitro compound proceeded on with a number of reducing agents, the isolation of the diacetamino compound (which we have synthesised independently by other method for comparison) was not possible. The only slender evidence we can advance at present to show that the nitro group occupies the position 5 is that the picrate of the reduction product from 2-amino-nitrothiazole is not identical with the picrate of 2 : 4-diaminothiazole.[20] By an alternative method, an attempt was made to synthesise 2-amino-5-nitrothiazole and 2-amino-4-nitrothiazole for reference by nitrating 2-acetaminothiazole-4-carboxylate and 2-acetaminothiazole-5-carboxylate respectively, hydrolysing and then decarboxylating the products obtained. But the nitration of the two compounds did not at all proceed on, the starting material being recovered unchanged.

2 : 4-Dimethylthiazole furnished on nitration 2 : 4-dimethyl-5-nitrothiazole in good yields. Though the reduction of this nitro compound with

all the usual reducing agents undoubtedly proceed on, the isolation of the reduction product once again presented difficulties. Under the conditions described in the experimental part, by using iron, we could isolate, after acetylation, 2:4-dimethyl-5-acetaminothiazole in about 25 per cent. yield. We have got on hand the reductions of some nitrothiazole derivatives.

5. Synthesis of 5–Azothiazoles and Their Reduction to 5–Aminothiazoles

The preparation of the amino compound by the reduction of the corresponding azo compound was successful in one case attempted but this method is only of limited applicability. 2:4-Dimethylthiazole or 2-amino-4-methylthiazole did not couple with diazotised *para* toluidine. 2-Hydroxy-4-methyl thiazole could not be nitrosoated but it underwent coupling with diazotised *para* toluidine yielding the azo dye (XI). While this decomposed on treatment with tin or stannous chloride and hydrochloric acid, sodium hydrosulphite smoothly reduced it to 2-hydroxy-4-methyl-5-aminothiazole (XII) which, as is to be expected, is feebly basic.



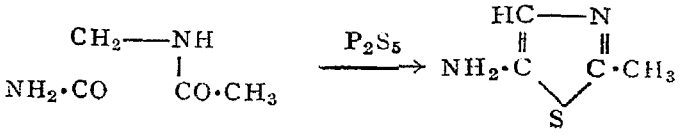
(XI) (XII)

6. Some Unsuccessful Attempts

The bromine atom in position 2 of thiazole is very reactive and could be converted into amino and substituted amino groups. But the bromine atom at the position 5 exhibits the properties of that attached to the benzene ring. 2:4-Dimethyl-5-bromothiazole was not at all reactive towards potassium phthalimide, urotropin and sulphanilamide. It did not form the Grignard reagent under the standard conditions, though it was debrominated by zinc dust and acetic acid. Huntress and Pfister[21] have also found the chlorine atom in 2-phenyl-5-chloro-4-hydroxymethyl thiazole to be very unreactive.

2:4-Dimethylthiazole did not react with hydrazoic acid to form 2:4-dimethyl-5-aminothiazole.

An attempt to synthesise 2-methyl-5-aminothiazole by the Gabriel's method[22] by treating acetylglycineamide with phosphorous pentasulphide as shown below was not successful. Acetylglyceniamide appears to decompose



into acetamide, the smell of which is very predominant, under the conditions of the reaction.

7. Experimental

Ethyl 2 : 4-dimethylthiazole-5-carboxylate.—By reacting thioacetamide (25 g.) with ethyl α-chloroacetoacetate (55 g.), 50 g. (82% yield) of the thiazole carboxylic ester was obtained. The following method does not require the isolation of thioacetamide and is very rapid: A mixture of acetamide (59 g.) and phosphorous pentasulphide (45 g.) in benzene (50 c.c.) was gently warmed on the steam-bath and treated gradually with a solution of ethyl α-chloroacetoacetate (33 g.) in benzene (50 c.c.), heating being discontinued during the addition of the ester. After refluxing the mixture for 3 hours more, it was cooled, the gummy mass dissolved in water and acidified with hydrochloric acid (50 c.c.). The acidic aqueous layer was separated, extracted with ether, neutralised with solid sodium carbonate and the oily layer obtained steam-distilled. The distillate furnished 25 g. of the crystalline ester. This was further purified by dissolving it in dilute hydrochloric acid, extracting the solution with ether and then reprecipitating with sodium carbonate (charcoal). The product thus obtained was very pure; m.p. 50–51°. The original benzene layer yielded a little more of the ester.

2 : 4-*Dimethylthiazole-5-amide.*—Ethyl 2 : 4-dimethylthiazole-5-carboxylic ester (14 g.) was shaken with excess of liquor ammomia (350 c.c.) and allowed to stand overnight when most of the solid went into solution. A small quantity of the undissolved ester was filtered off and the clear solution evaporated to a small volume when the amide separated. It was filtered and crystallised from a small quantity of water (yield, 6·6 g.), m.p. 73–74° (Found: N, 17·77; $C_6H_8O_4N_2S$ requires N, 17·64%). The mother-liquor on evaporation to dryness furnished the acid, m.p. 227° (3 g.) produced by the hydrolysis of the ester.

2: 4-*Dimethyl-5-acetaminothiazole* (*II, R=Ac*).—A mixture of 2:4-dimethylthiazole-5-carboxylate (18·5 g.), hydrazine hydrate (22 c.c. of 40%) and alcohol (15 c.c.) was refluxed for 3 to 4 hours on the steam-bath. The alcohol was distilled off under reduced pressure, the residue dissloved in ice-water, the aqueous solution extracetd with ether to remove any unchanged ester and evaporated to dryness (yield of the hydrazide, 16 g.). On crystallisation from excess of boiling benzene it had m.p. 139–40°. The crude hydrazide (8·5 g.) as obtained above dissolved in dilute acetic acid (75 c.c. of 1:3) was treated with a solution of sodium nitrite (4·5 g.) in water (15 c.c.) at 0° C. The azide, which was crystalline at low temperature, was taken up in ether and dried over anhydrous sodium sulphate. The ethereal solution was added to a mixture of acetic acid (10 c.c.) and acetic anhydride

(15 c.c.). After removing the ether, the residue was gently warmed until the evolution of nitrogen was complete. It was then concentrated to a small volume by distillation and the residue dissolved in a small quantity of ice-water (50–75 c.c.). The decolourised solution was carefully neutralised with solid sodium carbonate when the acetamino compound separated in a crystalline form. This was filtered, washed with a little water and dried; yield, 8·4 g. (99%). On crystallisation from benzene or a small volume of water it separated in thick plates and had m.p. 64–65° (Found : N, 16·70; $C_7H_{10}ON_2S$ requires N, 16·46%). The acetamino compound yields a picrate, m.p. 210°.

The above described acetamino compound (10 g.) was refluxed with alcohol (25 c.c.), concentrated hydrochloric acid (10 c.c.) and water (2 c.c.) for 10 hours. More alcohol (25 c.c.) was added and the solution concentrated to a small bulk under reduced pressure. The residue was diluted with a few bits of ice, covered with ether and basified with 40% caustic soda. The free amino compound was recovered through ether extraction. This yielded 6·8 g. (theory 7·4 g.) of the crude 2 : 4-dimethyl-5-aminothiazole; b.p. 130–150°/3–5 mm. The amino compound yielded a picrate, m.p. 189–91°.

Urea derivative (*III*).—On crystallisation from alcohol it separated in plates and had m.p. 246–48° (Found: N, 20·38; $C_{11}H_{14}N_4OS_2$ requires N, 19·85%).

2 : 4-*Dimethylthiazole-5-urethane* (*I*).—The ethereal solution of the azide described above obtained from the hydrazide (4·0 g.) was refluxed with absolute alcohol (25 c.c.) for 1 hour. On distilling off the solvent, the urethane was obtained as a colourless mass (yield, 3·3 g.). On crystallisation from benzene it melted at 96–97° (Found: N, 14·34; $C_8H_{12}O_2N_2S$ requires N, 13·99%). The picrate of the urethane melted at 184–85°.

4-*Methyl-5-acetaminothiazole* (*IV, R=Ac.*).—(i) 4-Methylthiazole-5-carboxylic hydrazide[23] (3·5 g.) dissolved in dilute hydrochloric acid (8·5 c.c. of concentrated acid diluted with 25 c.c. water) was treated with a solution of sodium nitrite (1·8 g.). The azide separated immediately as a crystalline mass, which was filtered, washed with a little ice-cold water and air-dried (yield, 3 g.). It crystallised from ether in fibrous prismatic needles, m.p. 83°. The azide was dissolved in a mixture of acetic acid (3 c.c.) and acetic anhydride (5 c.c.) and gently warmed till the evolution of nitrogen ceased. The reaction mixture was concentrated and diluted with cold water when the acetamino compound separated as a crystalline solid (yield, 3·2 g.): it crystallised from boiling water or benzene in fine needles and had m.p. 87° (Found: N, 17·78; $C_6H_8N_2OS$ requires N, 17·94%).

(ii) 4-Methylthiazole-5-carboxylamide (2·6 g.) was treated with potassium hydroxide (40 c.c. of 2·5 N) to which had been added under ice-cooling bromine (1 c.c.). The mixture was allowed to stand at the room temperature for 2 days and then extracted with ether. The ethereal extract, which showed fluorescence, was evaporated to dryness and treated with a few drops of acetic anhydride. The acetyl derivative thus obtained (0·6 g.) crystallised from water in silky needles and had m.p. 87° causing no depression with the specimen reported above. The picrate of this acetamino compound, crystallised from hot methanol, had m.p. 198°.

Urea derivative (*V*).—The azide obtained as described above under (i) was gently boiled with water for 3 hours; the solid that separated was filtered and crystallised from boiling alcohol; m.p. 244–47° (Found: N, 21·61; $C_9H_{10}ON_4S_2$ requires N, 22·02%). The urea derivative is also obtained in good yields by boiling the azide with benzene moistened with a few drops of water.

2-*Chloro-4-methyl-5-acetaminothiazole* (*VI*).—A mixture of ethyl 2-chloro-4-methylthiazole-5-carboxylate[12] (6·0 g.), hydrazine hydrate (6 c.c. of 42%) and alcohol (10 c.c.) was refluxed for 4 hours. More alcohol was added to dissolve the crystals, the solution filtered hot and cooled. The yellow crystals were separated and dried; m.p. 184° (yield, 4·7 g.). The above crystalline hydrazide (3·1 g.) dissolved in water (25 c.c.), acidified with concentrated hydrochloric acid (5 c.c.) and treated with a solution of sodium nitrite (1·3 g.). The azide that formed was quickly filtered, washed and air-dried (yield, 1·8 g.); m.p. about 115°. This was dissolved in acetic acid (5 c.c.) and acetic anhydride (3 c.c.), gently warmed and then heated on the steam-bath for 1 hour. On working up as usual, the acetamino compound was obtained (yield, 0·6 g.). On crystallisation from alcohol (charcoal) it had m.p. 196–97° (Found: N, 14·54; $C_6H_7N_2OS$ Clrequires N, 14·70%).

2 : 5-*Diacetaminothiazole* (*IX*).—Ethyl 2-aminothiazole-5-carboxylate (3 g.) was converted into the hydrazide (m.p. 205°) (2·5 g.) as usual. It was taken up in dilute acetic acid and converted into the azide (2·3 g.) which on treatment with acetic acid and acetic anhydride yielded the acetamino compound, (2·1 g.). From glacial acetic acid it was obtained as an amorphous powder not melting below 285° (Found: N, 20·93; $C_7H_9N_3O_2S$ requires N, 21·09%).

4-*Methyl*-2:5-*diacetaminothiazole* (*X*, *R*=*Ac*).—Ethyl 2-amino-4-methylthiazole-5-carboxylate (4·2 g.) in alcohol (15 c.c.) was refluxed with hydrazine hydrate (15 c.c. of 42%) for 14 hours. The hydrazide that precipitated

was filtered off, washed with alcohol and recrystallised from boiling water; m.p. 211–13° (yield, 2·2 g.). From the alcoholic filtrate the unchanged ester could be recovered. The hydrazide (2·1 g.) was converted into the acetamino compound through the azide as described above and crystallised from boiling water (charcoal); it separated in thick rhombic plates and did not melt below 240° (yield, 2·1 g.) (Found: N, 19·68; $C_8H_{11}O_2N_3S$ requires N, 19·71%).

Urea derivative.—The azide prepared as described above was refluxed with water for 2 hours and the product obtained crystallised from dilute acetic acid; m.p. 240–45°. (Found: N, 28·89; $C_9H_{12}N_6OS_2$ requires N, 29·56).

2-*Acetamino*-4-*methyl*-5-*urethanylthiazole.*—The azide as described above was refluxed with alcohol and the urethane obtained (m.p. 150–55°) was acetylated by treating with acetic anhydride. On crystallisation from dilute alcohol, the acetyl derivative of the urethane melted at 203° (Found: N, 17·26; $C_9H_{13}N_3O_3S$ requires N, 17·28%). The picrate of the urethane on crystallisation from hot water had m.p. 208°.

Oxime of 4-*methyl*-5-*acetylthiazole.*—A mixture of 4-methyl-5-acetylthiazole[12] (5 g.) in alcohol (10 c.c.), hydroxylamine hydrochloride (4 g.) and sodium acetate (8 g.) in water (10 c.c.) was refluxed for 3 hours. The oxime crystallised out on cooling in thick glistening rhombic prisms. The mixture was diluted with ice-water, the crystals filtered, washed and dried (yield, 5·4 g.). On crystallisation from hot alcohol or excess boiling benzene it separated in thick plates and had m.p. 145°. (Found: N, 17·65; $C_6H_8ON_2S$ requires N, 17·94%). On using pyridine in the place of sodium acetate and alcohol, the same oxime was obtained in about the same yield. The picrate of the oxime, crystallised from boiling alcohol, had m.p. 166°.

Action of phosphorous pentachloride on the oxime.—The above described oxime (finely powdered, 1 g.) suspended in dry benzene (30 c.c.) was treated with powdered phosphorous pentachloride (1 g.). The mixture was vigorously refluxed for 30 minutes and the solvent removed completely under reduced pressure. The residue was dissolved in ice-water (charcoal), filtered and neutralised with sodium carbonate. The acetamino compound separated as a crystalline solid which was filtered, dried and extracted with benzene to free it from the inorganic material. The benzene extract yielded 0·3 g. of the compound (m.p. 86–87°) (picrate m.p. 198°) found to be identical with 4-methyl-5-acetaminothiazole.

Action of acetic anhydride and hydrogen chloride on the oxime.—The oxime described above (3 g.) in acetic anhydride (30 c.c.) was saturated with dry hydrogen chloride and allowed to stand overnight. Most of the acetic

anhydride was distilled off and the residue dissolved in a small volume of water. On neutralising the clear solution with sodium carbonate, a crystalline white solid separated which was separated and crystallised from ether (yield, 2·8 g.). On recrystallisation from ligroin it separated in thick rectangular blocks and had m.p. 73° [Found: N, 13·86; $C_8H_{10}O_2N_2S$ (acetyl derivative of the oxime) requires N, 14·14%]. This was found to be the acetyl derivative of the oxime and on hydrolysis with dilute hydrochloric acid yielded back the original oxime, m.p. 145°.

2:4-*Dimethyl-5-acetylthiazole.*—This compound has been obtained by Smith and Sapiro[11] in poor yields. But we could prepare it in good yields by the following two methods:

(i) A solution of chloracetylacetone (9·0 g.) in alcohol (10 c.c.) was treated with thioacetamide (5 g.) under cooling in ice-bath; it was then allowed to stand at the room temperature for 15 minutes and then heated on the steam-bath for 15 minutes more. On cooling, crystals of 2:4-dimethyl-5-acetylthiazole hydrochloride separated which on working up yielded the free base, b.p. 228–30° (yield, 10 g.).

(ii) A mixture of acetamide (30 g.) and phosphorous pentasulphide (22·5 g.) was gently warmed on the water-bath and treated with chloroacetylacetone (13·5 g.) in small quantities. The mixture was carefully warmed for 15 to 20 minutes. The reaction product was dissolved in water (120 c.c.), acidified with concentrated hydrochloric acid (25 c.c.), extracted with ether and the acidic solution after basification was thoroughly extracted with ether. From the ether extract 2 : 4-dimethyl-5-acetylthiazole was obtained, b.p. 230° (yield, 10 g.).

Oxime.—By treating the foregoing acetylthiazole derivative with hydroxylamine hydrochloride and sodium acetate in alcohol the oxime was obtained which on crystallisation from dilute alcohol or boiling benzene had m.p. 131°. (Found: N, 16·72; $C_7H_{10}N_2OS$ requires N, 16·46%). The oxime yielded a picrate, m.p. 184–85°.

Treatment of the oxime with phosphorous pentachloride.—The oxime (1 g.) suspended in dry benzene (25 c.c.) was treated with phosphorous pentachloride (1 g.) and working up as usual, 0·15 g. of 2: 4-dimethyl-5-acetaminothiazole (m.p. 62–64°) was obtained.

Action of acetic anhydride and hydrogen chloride on the oxime.—On treating the foregoing oxime with acetic anhydride and hydrogen chloride and working up as usual, an oily product (picrate, m.p. 122–24°) was obtained which on hydrolysis with dilute hydrochloric acid, yielded back the original oxime, identified as such and also as the picrate.

2-Acetamino-5-nitrothiazole.—2-Acetaminothiazole (50 g.) in concentrated sulphuric acid (150 c.c.) was treated with fuming nitric acid (15 c.c.) below 10°; the mixture was heated on the steam-bath for about 15 minutes (or allowed to stand overnight) and poured into crushed ice. The copious precipitate formed was filtered, washed thoroughly with ice-water and dried at 100° (yield, 54–58 g.). On crystallising from acetic acid or alcohol, it was obtained in long plates and had m.p. 265° (Found: N, 22·20; $C_5H_5O_3N_3S$ requires N, 22·46%). The nitro compound dissolves in alkali and ammonia with a deep orange colour.

2-Amino-5-nitrothiazole.—The foregoing acetyl compound (54 g.) was hydrolysed by boiling with hydrochloric acid (500 c.c. of 4 N) until solution was complete. The red solution was diluted with an equal volume of water, boiled with charcoal (10 minutes) and the amino compound precipitated from the clear solution by adding crystalline sodium acetate. The crystalline yellow precipitate was filtered, washed with water and dried (yield, 34 g.). It crystallised from alcohol or boiling water in groups of deep yellow needles, m.p. 203° (Found: N, 28·83; $C_3H_3O_2N_3S$ requires N, 28·96%). It yielded a picrate, m.p. 190–91°.

This compound can also be prepared directly from 2-aminothiazole as follows: Crystalline 2-aminothiazole (20 g.) was added to concentrated sulphuric acid (50 c.c.) below 15° C. followed by fuming nitric acid (10 c.c.). The reaction mixture was left aside without external cooling when the temperature rose to 45°. After allowing to stand overnight it was poured into crushed ice (about 500 g.), filtered from dark impurity and the clear filtrate neutralised with solid sodium carbonate. The nitro compound separated as a crystalline solid (yield, 20–21 g.). On crystallisation from boiling water (charcoal) it yielded 18·5 g. of 2-amino-5-nitrothiazole, m.p. 200–01°.

2-Acetamino-4-methyl-5-nitrothiazole. —2-Acetamino-4-methylthiazole (10·4 g.) in concentrated sulphuric acid (30 c.c.) was treated with fuming nitric acid (3 c.c.) below 10°. The reaction mixture after allowing to stand at the room temperature overnight was poured into ice and worked up as described above. The nitro compound (13 g.) on crystallisation from dilute acetic acid separated in pale yellow elongated rods, m.p. 228° (Found: N, 20·64. $C_6H_7O_3N_3S$ requires N, 20·89%).

2-Amino-4-methyl-5-nitrothiazole.—The foregoing acetamino compound was hydrolysed as described in the previous experiment. The amino compound obtained on crystallisation from alcohol had m.p. 220° (Found: N, 26·15; $C_4H_5O_2N_3S$ requires N, 26·40%). Picrate of this crystallised from hot alcohol and had m.p. 180°.

2: 4-*Dimethyl-5-nitrothiazole.*—This compound has been described by Nagasawa[14] but no details of the preparation are available. The following condition has been found to furnish it in practically quantitative yields: 2: 4-dimethylthiazole (22·6 g.) was added with cooling to a mixture of concentrated sulphuric acid (50 c.c.) and fuming nitric acid (40 c.c.). The reaction mixture was warmed at 60–70° for 3 hours and finally on the boiling water-bath until the evolution of fumes stopped (10 hours). After cooling, the mixture was poured into powdered ice (300 g.) when part of the nitro compound separated as crystalline solid. Sodium acetate was added to the mixture until no more of the nitro compound separated. It was taken up in ether, the extract dried and the solvent removed. On fractionation of the residue (30 g.), 2: 4-dimethyl-5-nitrothiazole passed over at 170–80°/6 mm. or 100–01° at 1·5 mm. (yield, 22–25 g.). Nagasawa gives b.p. 65°/0·07 mm.

2: 4-*Dimethyl-5-acetaminothiazole.*—2 : 4-Dimethyl-5-nitrothiazole (5 g.) in benzene (150 c.c.) was refluxed with activated iron (50 g.)[24] for 7 hours, about 15 c.c. of water being added gradually during this period. The benzene layer was decanted off, the residue washed with boiling benzene (30 c.c.) and the solvent distilled off. The residue (3·6 g.) was boiled with acetic anhydride (3 c.c.), diluted with 10 c.c. of water and extracted with ether to remove the unreduced nitro compound. The aqueous solution on neutralising with sodium carbonate furnished about 1·5 g. of 2: 4-dimethyl-5-acetaminothiazole identified by comparing with the specimen prepared previously by the Curtius reaction.

The reduction could also be carried out by iron dust in acidified alcohol.

2: 4-*Dimethylthiazole.*—As a result of a number of experiments, the following has been found to be the best and most rapid method for the preparation of this compound in quantity : Acetamide (100 g.) and phosphorous pentasulphide (75 g.) covered with a layer of benzene (100 c.c.) was gently warmed on the water-bath and to the melt chloracetone (35 c.c.) in benzene (35 c.c.) was added in the course of about 30 minutes. When the addition was over, the mixture was refluxed for 1 hour more, poured into ice and made acidic with hydrochloric acid. The solution was steam-distilled to remove benzene and unreacted chloracetone. 2: 4-Dimethylthiazole was recovered by basifying the solution and steam-distilling; yield, 35–40 c.c.

2: 4-*Dimethyl-5-bromothiazole.*—2: 4-Dimethylthiazole (38 g.) in chloroform (100 c.c.) was treated with bromine (54 g.) in chloroform (50 c.c.) in the cold. The reaction mixture was allowed to stand at room temperature for one hour and the solvent removed. The orange red crystalline perbromide obtained was washed with ether (yield, 85–90 g.), suspended in

ice-water (150 g.), made alkaline, the heavy oil separated, dried over potash and the residue (50 g.) fractionated. The bromo compound distilled at 85–90°/10 mm. (yield, 45 g.). By passing dry hydrogen chloride into the ethereal solution of the bromo compound the hydrochloride was obtained (Found: Cl, 14·99; $C_5H_7NSBrCl$ requires Cl, 15·52%).

The bromo compound did not react with urotropin, potassium phthalimide, or acetylsulphanilamide and copper powder. It did not form the Grignard reagent with magnesium under the usual conditions. By heating 11 g. of the bromo compound with zinc dust (15 g.) and acetic acid (50 c.c.) for 16 hours, the compound was debrominated and 2:4-dimethylthiazole was obtained in quantitative yields.

2-Hydroxy-4-methyl-5-(p-tolueneazo) thiazole (*XI*).—A solution of *p*-toluidine (5·5 g.) in water (40 c.c.) and concentrated hydrochloric acid (15 c.c.) was diazotised with a solution of sodium nitrite (4·4 g.) and the diazo solution poured into a cold solution of 2-hydroxy-4-methylthiazole (5·7) in sodium hydroxide (50 c.c. of about 4%). The bright yellow azo-compound that separated immediately was filtered off, washed with water and dried (yield, 9·5 g.). On crystallising from benzene or acetic acid it was obtained in yellow needles which darkened at 180° and decomposed completely above 190° (Found: N, 17·62; $C_{11}H_{11}N_3OS$ requires N, 18·0%).

2-Hydroxy-4-methyl-5-aminothiazole (*XII*).—The foregoing freshly prepared azo compound (9·5 g.) was dissolved in dilute sodium hydroxide (100 c.c. of 4%) and treated with sodium hydrosulphite (36 g.). After warming at 60° C. for 1 hour, the pale yellow solution was cooled and extracted with ether. On acidifying the alkaline solution with 50% acetic acid a granular solid separated which was collected, washed with water and dried (yield, 5 g.). It crystallised from alcohol and had m.p. 153–55° (Found: N, 21·21; $C_4H_6ON_2S$ requires N, 21·53%). It was not soluble in dilute mineral acids and on drying at 100° turned brownish. With acetsulphanilyl chloride it yielded an acetsulphanilamido derivative thus establishing the presence of the amino group in the compound.

We thank Lt.-Col. S. S. Sokhey, Director, for his kind interest in these investigations and also the Lady Tata Memorial Trust for the award of a scholarship to one of us (A.V.). We are indebted to Mr. C. V. Deliwala and Mr. R. A. Bellary who prepared and supplied ethyl 2-aminothiazole-5-carboxylate and acetylglycineamide respectively used in these investigations.

8. Summary

Synthesis of 5-aminothiazole derivatives has been investigated by various methods. Conditions have been worked out to convert the 5-carboxylic

ester into the 5-acetamino grouping. Accordingly, 4-methyl-5-acetaminothiazole, 2:4-dimethyl-5-acetaminothiazole, 2-chloro-4-methyl-5-acetaminothiazole, 2:5-diacetaminothiazole and 2:5-diacetamino-4-methylthiazole have been synthesised starting from the corresponding esters by the Curtius reaction. The reaction failed to yield the 5-acetamino compounds from ethyl thiazole-5-carboxylate and ethyl 2-bromothiazole-5-carboxylate. 2:4-Dimethyl-5-acetaminothiazole was hydrolysed to the amino compound while this was not successful in the case of 4-methyl-5-acetaminothiazole.

The oxime of 4-methyl-5-acetylthiazole on treatment with phosphorous pentachloride yielded by Beckman transformation 4-methyl-4-acetaminothiazole while with acetic anhydride and hydrogen chloride the acetate of the oxime was obtained. Similarly the oxime of 2:4-dimethyl-5-acetylthiazole with phosphorous pentachloride furnished in about 10% yields 2:4-dimethyl-5-acetaminothiazole and with acetic anhydride and hydrogen chloride the acetate of the oxime.

Nitration of 2-acetaminothiazole yielded a nitration product which is provisionally considered as 2-acetamino-5-nitrothiazole; hydrolysis of this yielded 2-amino-5-nitrothiazole which could be prepared directly also from 2-aminothiazole. These two nitro compounds underwent reduction with all the usual reducing agents but the reduction products as such or after acetylation could not be isolated. 2:4-Dimethyl-5-nitrothiazole could be reduced with iron to the amino compound which on acetylation yielded 2:4-dimethyl-5-acetaminothiazole.

2-Hydroxy-4-methylthiazole underwent coupling with diazotised *p*-toluidine to yield an azo dye which on reduction furnished 2-hydroxy-4-methyl-5-aminothiazole.

The bromine atom in 2:4-dimethyl-5-bromothiazole could not be converted into the amino or substituted amino groupings; the bromo compound did not form the Grignard reagent but was easily debrominated by zinc dust. 2:4-Dimethylthiazole did not react with hydrazoic acid to furnish 2:4-dimethyl-5-aminothiazole. Acetylglycineamide did not react with phosphorous pentasulphide to furnish 2-methyl-5-aminothiazole by the Gabriel's reaction.

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