

# CHEMISTRY OF THE THIAZOLES

### Part III. Synthesis of Thiazole Derivatives Unsubstituted in Position 2: An Evaluation of Various Possible Methods

BY K. GANAPATHI AND (MRS.) ALAMELA VENKATARAMAN

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

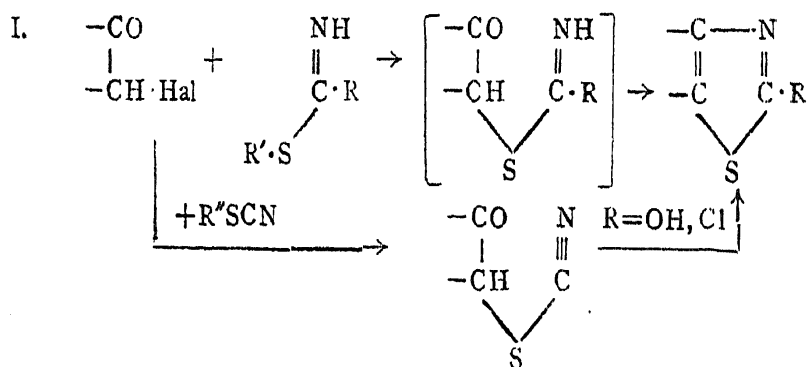
Received July 28, 1945

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

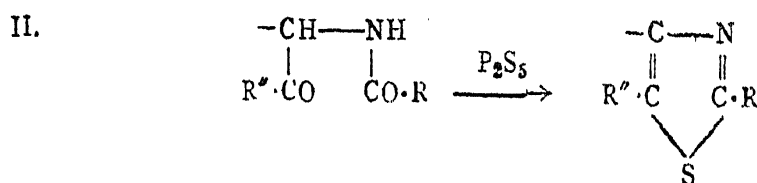
## INTRODUCTION

A NUMBER of thiazole derivatives unsubstituted in position 2 of the thiazole ring were required in connection with some other work and we are also interested in the manufacture of 4-methyl-5- $\beta$ -hydroxyethylthiazole which is required as an intermediate in the synthesis of thiamine chloride. Though a number of methods have been mentioned in literature, most of them are covered up in patents, the abstracts of which available do not disclose details adequate enough for reproducing the results claimed. We, therefore, undertook to study and compare all possible methods of synthesis of these compounds. The results obtained and the conclusions drawn so far are presented in this paper. An account of the various efforts made to prepare 4-methyl-5- $\beta$ -hydroxyethylthiazole will appear in a separate communication.

For the synthesis of the thiazole compounds, several methods are available which can be classified into the following two groups:



where :  $R'=H, R=H, Me, COOEt, ^1NH_2, OMe, OEt.$

$$R' = \text{NH}_4, R = \text{OH}, \text{SiH}^2.$$
$$R'' = \text{Na, K, Ba, NH}_4.$$


where R and R' are alkyl, aryl, or aralkyl groups.<sup>3</sup>

In both these methods, the reactions that are of interest to us at present are those in which R is hydrogen or where it is otherwise, it should be capable of subsequent conversion into hydrogen. Thus, seven methods are theoretically possible of which three are examined here. The preparation of 2-mercaptothiazole derivatives<sup>2</sup> and their oxidation to the thiazoles<sup>5</sup> have been previously investigated in some cases by others.

#### METHOD 1

The only method which yields directly the 2 unsubstituted thiazole derivative involves the condensation of the  $\alpha$ -chloroketone or aldehyde with thioformamide. This method has been employed fairly frequently to synthesise a number of thiazoles. Though *prima facie* this appears to be the best method, the drawbacks are that the yield in the preparation of thioformamide, especially on a large scale, is unsatisfactory, it is not very stable, particularly under acidic conditions, and the yields in the condensations are not uniformly good. The condensation of the  $\alpha$ -chloroketone with a mixture of formamide and phosphorus pentasulphide without the isolation of thioformamide<sup>4</sup> was tried in a variety of solvents and of these only ether gave satisfactory results. In the case of the  $\alpha$ -chloroketones which are stable, the treatment of the mixture without any solvent yielded the best results; the total time taken for the reaction was very much shortened and the isolation of the thiazole derivative formed presented no difficulties. Thus, four representative compounds have been prepared by this method. By reacting a mixture of phosphorous pentasulphide, formamide and ethyl  $\alpha$ -chloroacetoacetate, ethyl 4-methylthiazole-5-carboxylate has been prepared in quantity; this method appears to be the best so far worked out for the large-scale preparation of this compound. Similarly, 4-methylthiazole, 4:5-dimethylthiazole and 4-methyl-5-acetylthiazole have been prepared in good yields and these methods replace the older ones described in literature for their preparation in quantity. We find that this method can be used in other cases also wherein the chloroketone is fairly stable under the experimental conditions. But the parent compound thiazole could not be prepared by treating chloroacetal with a mixture of formamide and phosphorous pentasulphide; so also, ethyl thiazole-4-carboxylate was not obtained from bromopyruvic ester.

#### METHOD 2

Of all the methods described for the synthesis of the thiazole compounds, the one which is easily the best involves the condensation of thiourea with  $\alpha$ -halogenoketones or aldehydes to yield the corresponding 2-aminothiazoles. Thiourea is a very cheap material, the condensation could be carried out

even in distinctly acidic media, an advantage not shared by other methods, and the yields are comparatively very good. The conversion of the 2-aminothiazole derivatives into those unsubstituted in position 2 was tried by the two methods available involving the Sandmeyer's reaction, viz., the conversion of the amino group into the halogen atom which is subsequently reduced to the hydrogen atom and the direct replacement of the diazonium group by the hydrogen atom.

The conversion of the halogen atom into hydrogen either by means of zinc dust in acetic acid or catalytically with palladium, proceeds in very good yields. But the preparation of the 2-halogenothiazoles as reported in literature was far from satisfactory. The diazotisation of 2-aminothiazole and some derivatives has been reported,<sup>6</sup> but we could not repeat these experiments even in moderate yields. McLean and Muir<sup>7</sup> have also recently recorded their inability to repeat many of the experiments of the earlier investigators; these authors after many trials could prepare 2-chlorothiazole in not more than about 20 per cent. yields by diazotising 2-aminothiazole in hydrochloric acid and treating the diazonium solution with cuprous chloride. Erlenmeyer and Morel<sup>8</sup> have recently converted ethyl 2-aminothiazole-4-carboxylate into ethyl 2-bromothiazole-4-carboxylate in about 70 per cent. yields by diazotising the aminothiazole derivative in a mixture of phosphoric acid and nitric acid and treating the diazonium solution with a large excess of hydrobromic acid and copper powder. Since it is imperative that the amine should be in the ammonium form to undergo diazotisation,<sup>9</sup> we tried the condition for the diazotisation of the weakly basic amines with notable success. The diazotisation of 2-aminothiazole by the addition of the amine dissolved in acetic acid to nitrosyl sulphuric acid did not proceed on in as good yields as when the amine was dissolved in sulphuric acid and added to nitrosyl sulphuric acid.<sup>11</sup> In a mixture of phosphoric acid (70 to 85 per cent.) and concentrated nitric acid, the diazotisation proceeded on well as also the 'inverted diazotisation' of Walker and Hodgson<sup>10</sup> using sulphuric acid and glacial acetic acid. Morgan and Morrow<sup>11</sup> have diazotised 2-aminothiazole both in perchloric acid and dilute sulphuric acid (20 per cent.). We have found that the best yields are obtained by using about 40 to 50 per cent. sulphuric acid. The results of trying various conditions are presented in Table I.

The decomposition of the diazonium salt was carefully investigated and herein a good improvement was effected. Heating the diazonium solution with concentrated hydrochloric acid<sup>6</sup> gave only traces of the chlorothiazole; with concentrated hydrochloric acid and copper powder the yield was 20 per cent.; cuprous chloride increased the yield to about 34 per cent.

and the best yield of 70 per cent. was obtained when a mixture of copper sulphate and sodium chloride was used in aqueous medium.<sup>12</sup> While we were trying the effects of various metallic chlorides in the place of sodium chloride, the paper of Hodgson, Birtell and Walker<sup>13</sup> came to our notice. These authors have found that ferric chloride gives good results but is not superior to sodium chloride. By using a mixture of sodium bromide and copper sulphate for the decomposition of the diazo solution 2-bromothiazole is obtained in good yields. The advantage in this method is that only one molecular equivalent of sodium bromide is used while Erlenmeyer and Morel<sup>8</sup> use a large excess of hydrobromic acid. It is worthwhile mentioning here that 2-halogenothiazole is an intermediate in the manufacture of the drug sulphathiazole according to a patented process and the only factor that prevented the commercial exploitation of this method was the bad yield in which the 2-halogenothiazoles were obtained till now.

A number of 2-aminothiazole derivatives were subjected to the reaction to study the effects of the various substituents on the ease of diazotisation and decomposition of the diazonium salts. As was expected, the various substituents in the positions 4 and/or 5 of the thiazole ring in the 2-aminothiazole derivatives showed some significant and striking effects in the above reactions. Thus 2-chloro-5-methylthiazole could be prepared in about 76 per cent. yields and 2-chloro-5-ethylthiazole in 70 per cent. yields from the corresponding 2-aminothiazole derivatives.<sup>27</sup> The diazotisation of the higher homologues did not proceed on well because the basicity of these products decreased very much and no stable ammonium salt could be obtained. As a striking contrast to the case of 2-amino-5-methylthiazole, the 4-methyl isomer yielded 2-chloro-4-methylthiazole in poor yields. 2-Amino-4:5-dimethylthiazole yielded the corresponding 2-chloroderivative in about 50 per cent. yields. Ethyl 2-aminothiazole-5-carboxylate furnished the 2-chloro derivative in very poor yields but the 2-bromo compound could be prepared in about 60 per cent. yields under a set of conditions. In the case of 2-amino-4-methylthiazole-5-carboxylate the chloroderivative was obtained in about 45 per cent. yields, a red dye accompanying this product. 2-Amino-4-carbethoxymethylthiazole and 2-amino-4-methyl-5-carbethoxymethylthiazole could not be smoothly diazotised, the diazonium salt rapidly undergoing decomposition. 2-Amino-5-nitrothiazole<sup>28</sup> could not be diazotised smoothly without spontaneous decomposition and formation of highly coloured products under all conditions. However, the 2-chloro- and 2-bromo-compounds required by us for many purposes, was prepared in good yields by diazotising 2-amino-5-nitrothiazole in sulphuric acid in the presence of sodium halide and copper sulphate. This new modification

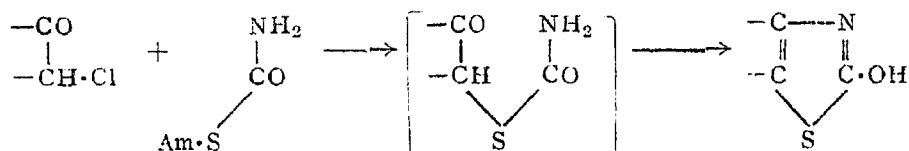
was tried in a number of cases in this Laboratory and as a result of the experiments we conclude that to obtain good yields by this method it is necessary that the diazotisation of the amine should proceed on very fast and the diazonium salt should also decompose very rapidly. When tried in the case of 2-aminothiazole and 2-aminothiazole-5-carboxylate this modified method gives lower yields than the usual method. The results presented above indicate that the preparation of the 2-halogenothiazoles from the 2-aminothiazole derivatives is not of universal applicability.

The conversion of 2-aminothiazole into thiazole by the Sandmeyer's reaction according to Popp<sup>14</sup> is not at all satisfactory.<sup>7</sup> 2-Aminothiazole was diazotised with sodium nitrite solution in a mixture of phosphoric acid and nitric acid or 40 per cent. sulphuric acid and the diazonium solution was treated with (a) methyl alcohol containing a suspension of copper suboxide,<sup>15</sup> (b) methyl alcohol containing a suspension of copper bronze, (c) an aqueous suspension of calcium hypophosphite<sup>16,17</sup> and (d) alkaline formaldehyde.<sup>18</sup> The yields of thiazole in the four experiments were respectively 32 per cent., 28 per cent., 36 per cent., and traces. The use of hypophosphorus acid in the place of calcium hypophosphite gave slightly lower yields. By using the method of Hodgson,<sup>15</sup> diazotisation (inverted) with nitrosylsulphuric acid in sulphuric acid and treating the diazo product with cuprous oxide in methyl alcohol, thiazole was obtained in 30 per cent. yields. The reduction with calcium hypophosphite is the best and most convenient method for the actual working. Starting from 2-amino-5-methylthiazole, 5-methylthiazole was obtained in 60 per cent. yield by using calcium hypophosphite and in 40 per cent. yield by using cuprous oxide in methyl alcohol. 5-Ethylthiazole could similarly be obtained in 56 per cent. yield. The other 2-aminothiazole derivatives gave very unsatisfactory yields with these reagents. Thus the direct conversion of the 2-amino group into the hydrogen is advantageous only to prepare 5-methyl and 5-ethylthiazoles. In the other cases it is advantageous to prepare the 2-chloro or 2-bromo compounds and then reduce them.

### METHOD 3

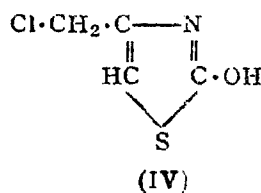
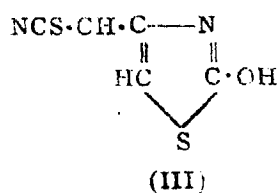
The third method of preparing thiazole derivatives unsubstituted in position 2 consists in synthesising 2-hydroxythiazole derivatives and then converting the hydroxyl group into the hydrogen atom. The method of replacing the hydroxyl by hydrogen by distilling with zinc dust<sup>19</sup> proceeds in bad yield and therefore it is preferable to convert the hydroxyl group into the chlorine atom and then reduce it to hydrogen. There are two methods available for the synthesis of the 2-hydroxythiazole derivatives from the  $\alpha$ -halogenoketones. The first is the conversion of the  $\alpha$ -halogenoketone

into  $\alpha$ -thiocyanoketone by treatment with ammonium, potassium or better barium thiocyanate and then isomerising the thiocyanoketone. This method has been employed by Andersag and Westphal<sup>20</sup> for the synthesis of 4-methyl-5- $\beta$ -hydroxyethylthiazole but they have not stated the yields obtained in the various stages. The other less known method is due to Marchesini<sup>21</sup> which consists in the condensation of the  $\alpha$ -halogenoketone with ammonium thiocarbonate as follows:



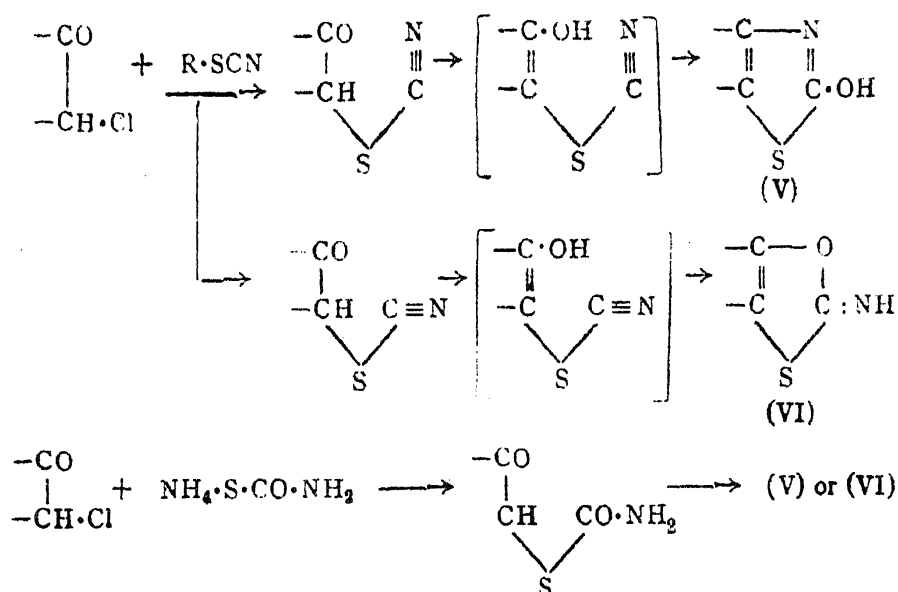
These methods have not been studied in detail.

Our attempts to prepare the hitherto unknown parent compound 2-hydroxythiazole, required by us for more than one purpose, by condensing dichlorether or chloroacetal with the thiocyanates or ammonium thiocarbamate were unsuccessful. The condensation of chloroacetone with the thiocyanates as also with ammonium thiocarbamate to yield 2-hydroxy-4-methylthiazole has previously been studied by Hantzsch<sup>22</sup> and by Tcherniac.<sup>23,2</sup> After comparing these two methods we find that the condensation of chloroacetone with ammonium thiocarbamate furnishes 2-hydroxy-4-methylthiazole in distinctly better yields (90 per cent.). Though thiocyanoacetone could be obtained in good yields the isomerisation could not be effected quantitatively, tarry and resinous products being also produced, the nature of which has not been investigated. The reaction of  $\alpha$ -chloromethylethylketone with ammonium thiocarbamate led to the production of 2-hydroxy-4:5-dimethyl thiazole in about 25 per cent. yields, there being formed an oily side product. By treating the chloroketone with barium thiocyanate, the thiocyano compound could be obtained in good yields; on isomerising this with hydrochloric acid the hydroxythiazole derivative was obtained in about 20 per cent. yields, while with concentrated sulphuric acid in glacial acetic acid the yield increased to 40 per cent., an oily by-product being produced in both cases. *Sym.* Dichloroacetone condensed with two molecular equivalents of ammonium thiocyanate or potassium thiocyanate to furnish in good yields 2-hydroxy-4-thiocyanomethylthiazole (III); ammonium thiocarbamate, on the other hand, furnished in about 25 per cent. yields



2-hydroxy-4-chloromethylthiazole (IV), along with a by-product which could not be purified. When ethyl  $\alpha$ -chloroacetoacetate was treated with ammonium thiocyanate or potassium thiocyanate, a product, m.p.  $128^\circ$ , was obtained in poor yields; treatment of ethyl  $\alpha$ -thiocyanoacetoacetate with acids also yielded the same product. This compound is described in literature<sup>26</sup> as ethyl 2-hydroxy-4-methylthiazole-5-carboxylate. On the other hand, treatment of ethyl  $\alpha$ -chloroacetoacetate with ammonium thiocarbamate furnished in very good yields a product, m.p.  $175^\circ$ , whose properties agree with that of structure ethyl 2-hydroxy-4-methylthiazole-5-carboxylate. We first surmised that these two compounds might be dimeric just like the " $\alpha$ - and  $\beta$ -rhodim" of Tcherniac.<sup>24,25</sup> But on treatment with phosphorous oxychloride, the product, m.p.  $175^\circ$ , yielded ethyl 2-chloro-4-methylthiazole-5-carboxylate while the lower melting product did not yield this chloro compound. Thus while we are sure that the higher melting product (m.p.  $175^\circ$ ) is ethyl 2-hydroxy-4-methylthiazole-5-carboxylate, the structure assigned to the lower melting product appears to be doubtful. In the case of chloroacetylacetone a similar result was obtained. On treating this with ammonium thiocarbamate a crystalline product (m.p.  $210-12^\circ$ ) was obtained in good yields and it is identical with 2-hydroxy-4-methyl-5-acetylthiazole obtained by Nagasawa<sup>31</sup> from 2-hydroxy-4-methylthiazole by acetylation and also by the action of acetylchloride and aluminium chloride. The action of barium thiocyanate on chloroacetylacetone furnished not the above-mentioned product but one of m.p.  $228^\circ$ , the structure of which we have not fixed up. Thus we find that the chloro derivatives of the  $\beta$ -ketonic ester or  $\beta$ -diketone do not yield the same product on treatment with ammoniumthiocarbamate and with barium or any alkali metal thiocyanate. While the product obtained with ammoniumthiocarbamate has been definitely established here to be the expected 2-hydroxythiazole derivative, that obtained with the thiocyanates is of doubtful structure.

In the condensation of thiourea with  $\alpha$ -halogenoketones or aldehydes, the 2-aminothiazole derivatives are formed usually in good yields with no by-products. But in the isomerisation of the  $\alpha$ -thiocyanoketones or in the condensation of ammonium thiocarbamate with  $\alpha$ -chloroketones, in addition to the hydroxythiazole derivatives (which themselves in many cases are formed in poor yields) other products are also formed, the nature of which has not been investigated so far. The reason appears to be that in the case of thiourea, because of the symmetry in structure of the reagent, there is only one way in which the reaction can proceed on. But in the other cases the reaction can take at least two courses as follows:



There are grounds to suggest that in many of the reactions, compounds of structure (VI) might also be produced in addition to the 2-hydroxythiazole derivatives.

Phosphorous oxychloride appears to be a reliable reagent for the conversion of the 2-hydroxythiazole into 2-chlorothiazole derivatives. We have found that 2-hydroxy-4:5-dimethylthiazole and ethyl 2-hydroxy-4-methylthiazole-5-carboxylate (m.p. 175°) give the corresponding 2-chlorothiazole derivatives in theoretical yields on treatment with phosphorous oxychloride.

Another possible and cheap method of preparing the 2-chlorothiazole derivatives is to treat the  $\alpha$ -thiocyanoketone derivatives with dry hydrogen chloride. By this method Tcherniac<sup>24</sup> has obtained a mixture of 2-hydroxy-4-methylthiazole and 2-chloro-4-methylthiazole from thiocyanacetone. The thiocyanoketone obtained from  $\alpha$ -chloromethylethylketone on saturation with dry hydrogen chloride furnished in good yields 2-chloro-4:5-dimethylthiazole; no hydroxy compound was formed in this case. Also, the action of phosphorous oxychloride on the thiocyanoketone yielded the same chloro compound along with a small amount of a crystalline product. The thiocyanoketone prepared from  $\alpha$ -chloroacetoacetate when treated with dry hydrogen chloride yielded an oil which on allowing to stand for many weeks deposited crystals of the chloro compound.

#### EXPERIMENTAL

*Ethyl 4-methylthiazole-5-carboxylate.*—This has been prepared by many workers<sup>29</sup> by the action of thioformamide on  $\alpha$ -chloro (or bromo) acetoacetate. After many trials, varying the quantities of the reactants, the following method has been found to be the best.



A mixture of phosphorous pentasulphide (13.2 g.), formamide (13.5 g.) and ethyl  $\alpha$ -chloroacetoacetate (33 g.) was allowed to react, first cooled in ice-water, then at room temperature and finally by heating under reflux. The mixture was diluted with water, acidified with hydrochloric acid, extracted with ether, the acid product made just basic and steam-distilled (or extracted with ether). The thiazole ester obtained passed over at 230–36° (most of it at 233°); yield, 26 c.c.

*4-Methylthiazole*.—McLean and Muir<sup>7</sup> who required this compound in quantity have prepared it by reducing 2-chloro-4-methylthiazole in turn obtained from thiocynoacetone according to Tcherniac.<sup>24</sup> This is very conveniently prepared by reacting monochloroacetone (18.5 g.), formamide (13.5 g.) and phosphorous pentasulphide (13.2 g.) and working up as described in the previous preparation. One thus obtains 6–7 c.c. of 4-methylthiazole.

*4:5-Dimethylthiazole*.—This compound has been prepared by Buchman, Reims and Sargent<sup>5</sup> by the oxidation of 2-mercapto-4:5-dimethylthiazole. By reacting  $\alpha$ -chloromethylethylketone (21 g.) with a mixture of formamide (13.5 g.) and finely powdered phosphorous pentasulphide (13.2 g.) and working up as usual, 11.5 g. of 4:5-dimethylthiazole was obtained, b.p. 158°; picrate m.p. 186–87°. Buchman, *et al.*<sup>5</sup> record b.p. 81–83°/59 mm. for 4:5-dimethylthiazole and m.p. 186–87° for its picrate.

*4-Methyl-5-acetylthiazole*.—The preparation of this compound has very recently been reported by Baumgarten, *et al.*<sup>30</sup> by the action of thioformamide on chloroacetylacetone and also from ethyl 4-methylthiazole-5-carboxylate by a more involved process and in lower yields. Treating a mixture of formamide (20 g.) and phosphorous pentasulphide (12 g.) with chloroacetylacetone (13.5 g.) and working up as usual, 9.5 g. of 4-methyl-5-acetylthiazole was obtained, b. p. 226°; picrate, m.p. 106–07. Baumgarten, *et al.* record b.p. 107–08°/13 mm. for 4-methyl-5-acetylthiazole and m.p. 108° for the picrate. The ketone is water-soluble and could not be steam-distilled.

*2-Chlorothiazole*.—A typical experiment is as follows:—2-Aminothiazole (30 g. of the distilled product) was dissolved in phosphoric acid (120 c.c. of 80 per cent.), the solution cooled to 5° C. and then concentrated nitric acid (60 c.c.) was slowly run in and stirred well. When the temperature of the mixture was 0° to – 5° C. it was diazotised with a solution of sodium nitrite (24 g.) the solution being allowed to flow under the surface of the liquid through a drawn out pipette or separating funnel. After all the nitrite was added, stirring was continued for 30 minutes more and then the diazonium solution was added to a solution of copper sulphate (50 g.) and

sodium chloride (50 g.) in 200 c.c. water kept cooled in ice-water. The evolution of nitrogen was immediate and ceased in about 10 minutes. The mixture was allowed to stand at the room temperature for about 30 minutes more, the acid partly neutralised and steam-distilled; the chlorothiazole rapidly passed over in the distillate. The results obtained in the various experiments under different conditions are given in Table I.

TABLE I

Exp. No.	Amino-thiazole taken	Medium of diazotisation	Sodium nitrite added	Agent used for decomposition	% Yield of chloro-thiazole
1	10 g.	HCl	7.5 g.	CuCl	20 <sup>a</sup>
2	"	H <sub>3</sub> PO <sub>4</sub> , 50 c.c., HNO <sub>3</sub> , 20 c.c.	"	Con. HCl	5-10 <sup>b</sup>
3	"	" "	"	Cu, 8 g.; HCl,	34
4	"	" "	"	CuCl, 15 g.; HCl, 75 c.c.	34
5	30 g.	H <sub>3</sub> PO <sub>4</sub> , 120 c.c., HNO <sub>3</sub> , 60 c.c.	24 g.	CuSO <sub>4</sub> , 50 g.; NaCl, 50 g.	70 <sup>c</sup>
6	"	" "	"	CuSO <sub>4</sub> , 25 g.; NaCl, 50 g.	50
7	"	" "	"	CuSO <sub>4</sub> , 100 g.; NaCl 100 g.	70
8	24 g.	AcOH, 75 c.c.	18 g. in H <sub>2</sub> SO <sub>4</sub>	CuCl, 20 g.; HCl, 80 c.c.	15 <sup>c</sup>
9	10 g.	H <sub>2</sub> SO <sub>4</sub> , 20 c.c.	7.5 g. H <sub>2</sub> SO <sub>4</sub>	CuSO <sub>4</sub> , 16 g., NaCl, 16 g.	42 <sup>d</sup>
10	"	H <sub>2</sub> SO <sub>4</sub> , 16 c.c., H <sub>2</sub> O, 60 c.c.	7.0 g.	CuSO <sub>4</sub> , 20 g.; NaCl, 18 g.	35
11	"	H <sub>2</sub> SO <sub>4</sub> , 16 c.c., H <sub>2</sub> O, 30 c.c.	"	" "	50
12	"	H <sub>2</sub> SO <sub>4</sub> , 50 c.c. (1:1) CuSO <sub>4</sub> , 25 g., NaCl, 11.7 g., H <sub>2</sub> O, 50 c.c.	8.4 g.	Nil	30

<sup>a</sup> Condition of McLean and Muir.<sup>7</sup>

<sup>b</sup> Decomposition according to Schatzmann.<sup>6</sup>

<sup>c</sup> The amine is diazotised with nitrosylsulphuric acid.

<sup>d</sup> Inverted diazotisation; after the amine was added to nitrosylsulphuric acid, glacial acetic acid (75 c.c.) was added below 5° C.

<sup>e</sup> In a number of experiments, along with 2-chlorothiazole, a small quantity of a crystalline solid, m.p. 70°-71°, also passed over; this slowly dissolved in alkali and the quantity obtained was not enough for further examination.

**2-Chloro-5-nitrothiazole.**—A mixture of 2-amino-5-nitrothiazole<sup>28</sup> (2.9 g.) in dilute sulphuric acid (20 c.c. of 1:1), copper sulphate (10 g.) and sodium chloride (4.7 g.) in water (25 c.c.) was cooled to 10° C. and treated carefully with sodium nitrite (1.55 g.) in water (5 c.c.) with rapid stirring. The evolution of nitrogen was steady and was complete in about 10 to 15 minutes. The chloro compound which had separated as a crystalline white solid was extracted with ether and purified by steam-distillation (yield, 1.5 g.). It crystallised from ether in hexagonal plates, m.p. 61°. (Found: N, 16.76; C<sub>3</sub>H<sub>3</sub>O<sub>2</sub>N<sub>2</sub>SCl requires N, 17.02 per cent.)

**2-Bromo-5-nitrothiazole.**—(i) This was prepared as above by treating a mixture of 2-amino-5-nitrothiazole (7.25 g.) in dilute sulphuric acid

(25 c.c. con. acid + 50 c.c. water), copper sulphate (25 g.) and sodium bromide (10.3 g.) with sodium nitrite (4 g.) in water (10 c.c.). The yield of crude 2-bromo-5-nitrothiazole was 8.5 to 10.5 g. which on steam-distillation yielded a purer product (8–10 g.). On crystallisation from alcohol, ether or benzene, it separated in thick colourless plates, m.p. 91–92°. (Found: N, 13.47;  $C_3H_3O_2N_2SBr$  requires N, 13.41 per cent.)

(ii) The same bromo compound could be prepared very easily directly from 2-aminothiazole as follows:

2-Aminothiazole (10 g.) was dissolved in concentrated sulphuric acid (30 c.c.) below 15° C. Fuming nitric acid (5 c.c.) (or a mixture of con. nitric acid, 10 c.c. and sulphuric acid, 10 c.c.) was then added with stirring at 10° C. Cooling was then discontinued when the temperature of the reaction mixture rose to 45° C. After allowing it to stand overnight at 30° the mixture was poured into a cold solution of copper sulphate (37.5 g.) and sodium bromide (31.8 g.) in water (125 c.c.) at 15°. This mixture was diazotised as above described with sodium nitrite (8.4 g.). The crude 2-bromo-5-nitrothiazole obtained weighed 14.5 g. which on steam-distillation yielded 13 g. of the pure product in colourless crystals.

TABLE II  
4-and/or 5-Substituted 2-Halogenothiazoles

Exp. No.	2-Halogenothiazole prepared	Medium of diazotisation	b.p.	% Yield	N. percentage	
					Found	Required
1	2-Bromo ..	$H_3PO_4 + HNO_3$	171–74°	75	..	..
2	2-Chloro 5-methyl ..	"	174–76°	65	..	..
3	" ..	$H_2SO_4$	"	76	..	..
4	" ..	"	"	60 <sup>a</sup>	..	..
5	2-Bromo-5-methyl- ..	"	192–200°	70	8.30	7.87
6	2-Chloro-5-ethyl- ..	"	192–93°	70	9.39	9.47
7	2-Bromo-5-ethyl- ..	"	215°	50	6.88	7.30
8	2-Chloro-4:5 dimethyl- ..	"	190–92°	50	9.57	9.47
9	2-Chloro-4-methyl- ..	"	"	Trace	..	..
10	2-Chloro-4-methyl-5-carbethoxy- ..	"	M.p. 50–51°	40	..	..
11	2-Bromo-5-carbethoxy- ..	"	192– 94/5 mm.	60 <sup>b</sup>	6.09	5.93

The diazotisation was carried out in a mixture of phosphoric acid and nitric acid as given in Table I or in dilute sulphuric acid. The decomposition of the diazonium solution was effected by using about 1.2 molecular equivalents each of copper sulphate and sodium halide at about 0° C.

<sup>a</sup> In this case the diazonium solution was treated with cuprous chloride (15 g.) and con hydrochloric acid (60 c.c.).

<sup>b</sup> This yield is obtained only if the diazotisation is carried out very rapidly and the solution added to the copper salt immediately. The chloro compound is formed in poor yields.

*Preparation of thiazole and alkylthiazoles.*—The 2-aminothiazoles were diazotised in a mixture of phosphoric acid and nitric acid or dilute sulphuric acid and the diazonium solution treated with the reagents mentioned. After the evolution of nitrogen ceased, the solutions were allowed to stand at the room temperature for about one hour and then steam-distilled after making them alkaline. Steam-distillation was continued till the distillate did not yield any perceptible amount of picrate with a solution of picric acid. The distillate was acidified with concentrated hydrochloric (sufficient to fix all the basic material) and the solution concentrated to a small bulk. The solution was saturated with soda and extracted with ether repeatedly. From this extract the thiazole derivative was recovered. 5-Ethylthiazole is very sparingly soluble in water and so can be separated from the distillate as such. Some of the typical experiments carried out are given in Table III.

TABLE III

Expt. No.	Thiazole prepared	Amine taken	Medium of diazotism	Diazonium solution treated with	Percentage yield
1	Thiazole	10 g.	H <sub>3</sub> PO <sub>4</sub> + HNO <sub>3</sub>	Cu <sub>2</sub> O, 20 g. MeOH, 200 c.c.	34
2	"	"	"	Cu, 20 g. MeOH, 200 c.c.	30
3	"	"	H <sub>2</sub> SO <sub>4</sub> , AcOH	Cu <sub>2</sub> O, 20 g. MeOH, 200 c.c.	28 <sup>a</sup>
4	"	"	H <sub>3</sub> PO <sub>4</sub> + HNO <sub>3</sub>	CaHP, 40 g. Water, 120 c.c.	36
5	"	"	H <sub>2</sub> SO <sub>4</sub>	"	30
6	"	"	"	Formalin, 30 c.c. NaOH, 50 g.; H <sub>2</sub> O, 250 c.c.	5
7	5-Methylthiazole	11.5 g.	"	CaHP, 33 g. Water 120 c.c.	60
8	"	"	"	Cu <sub>2</sub> O, 15 g. MeOH, 150 c.c.	40
9	5-Ethylthiazole	6.2 g.	"	CaHP, 25 g. Water, 60 c.c.	56 <sup>b</sup>
10	"	"	"	HP Acid, 80 c.c. (33%)	42
11	4-Methylthiazole-5-carboxylate	9.3 g.	"	CaHP, 30 g.	16
12	"	"	"	Cu <sub>2</sub> O, 30 g.	15

CaHP : Calcium hypophosphite ; HP Acid : Hypophosphorus acid.

<sup>a</sup> Condition of Hodgson and Turner.<sup>15</sup>

<sup>b</sup> Found : N, 12.03 ; C<sub>5</sub>H<sub>7</sub>NS requires N, 12.38%.

*Ammonium thiocarbamate.*—The preparation of this compound has been briefly mentioned by Tcherniac<sup>24</sup> but not described in detail. As a result of a number of experiments, the following was found to be the best method :

A cold saturated solution of ammonium thiocyanate (40 g. in 30 c.c. water) was gradually added to dilute sulphuric acid (290 c.c. of concentrated

acid diluted with 400 c.c. water) at about 25 ° C. and the liberated carbonyl sulphide passed into a saturated solution of alcoholic ammonia (250 c.c.) maintained at about 10°. The white crystalline solid that separated during 2 to 3 hours was filtered, pressed well, washed with ether and used directly. Yield, 20-25 g.

*2-Hydroxy-4 : 5-dimethylthiazole.*—(i) Ammonium thiocarbamate (13 g.) in water (15 c.c.) was gradually treated with  $\alpha$ -chloromethylethylketone (10 g.) under cooling. On allowing the solution to stand overnight, some crystals and a colourless oil separated. The crystalline product was filtered and washed free from the adhering oil; yield, 1 g.; m.p. 146°. The oily product on extraction with alkali furnished a little more of the crystalline product. On crystallisation from benzene, alcohol or ligroin it separated in big rhombic plates or prisms; m.p. 147°. (Found: N, 11.25;  $C_5H_7ONS$  requires N, 10.85 per cent.)

(ii)  $\alpha$ -Chloromethylethylketone (21 g.) in alcohol (15 c.c.) was treated with barium thiocyanate (33 g.). The mixture was shaken at intervals and allowed to stand overnight. The mixture was diluted with water and the turbid solution extracted with ether (5  $\times$  20 c.c.). The ether extract yielded the thiocyanoketone as an oil (24 g.) The oil was boiled with concentrated sulphuric acid (2.5 c.c.) in glacial acetic acid (25 c.c.). The resulting dark solution was poured into water (150 c.c.), the pinkish crystals obtained were filtered, washed with water and dried (yield, 9.2 g. or 40 per cent. of theory); m.p. 146°. The mother-liquor on extraction with ether furnished 13.2 g. of the oily product which on allowing to stand for a number of weeks, furnished some more of the crystalline product.

On treating the thiocyanoketone obtained as above described with dilute hydrochloric acid (120 c.c. of 2 N) instead of a mixture of sulphuric acid and glacial acetic acid, only 4.8 g. (or 20 per cent.) of the hydroxy compound was obtained.

*Ethyl 2-hydroxy-4-methylthiazole-5-carboxylate.*—Ammonium thiocarbamate (13 g.) dissolved in water (10 c.c.) was gradually treated with ethyl  $\alpha$ -chloroacetoacetate (18 c.c. 21.5 g.) adding pieces of ice to the mixture, which was then allowed to stand overnight. The crystalline product that had separated was filtered, washed with ice-water free from the adhering oily product (yield, 13 g.) This on crystallisation from boiling alcohol separated in glistening plates; m.p. 175°. (Found: N, 7.50, 7.82;  $C_7H_9O_3NS$  requires N, 7.48 per cent.) This compound is soluble in dilute ammonia, alkali and carbonate. It was recovered unchanged after boiling for 2 hours with dilute alkali and alcoholic potash.<sup>26</sup> On heating with

phosphorous oxychloride it furnished ethyl 2-chloro-4-methylthiazole-5-carboxylate (*vide infra*).

*Ethyl 2-hydroxy-4-methylthiazole-5-carboxylate* (?), *m.p.* 128°.—The preparation of this compound is not given in detail in literature.<sup>26</sup> It was prepared by the following method:

Ammonium thiocyanate (6 g.) in alcohol (15 c.c.) was treated with ethyl  $\alpha$ -chloroacetoacetate (6.9 g.) in the cold and the mixture allowed to stand overnight at room temperature. After refluxing for 15 minutes it was diluted with water (60 c.c.), the sticky solid that had separated filtered off, washed with water and dried. On shaking with ether a crystalline product was extracted which melted at 128° after recrystallisation from a mixture of benzene and ligroin (yield 1 g.).

Use of barium thiocyanate in the place of ammonium thiocyanate did not improve the yield of the product. This compound, *m.p.* 128°, on treatment with phosphorus oxychloride did not yield ethyl 2-chloro-4-methylthiazole-5-carboxylate.

*2-Hydroxy-4-methyl-5-acetylthiazole*.—Chloracetylacetone (13.5 g. of *b.p.* 150–59°) was added in small portions to a cold solution of freshly prepared ammonium thiocarbamate (9.4 g.) in water (10 c.c.). The reaction was spontaneous with much effervescence and ice bits were added to control the reaction. After setting aside overnight, the crystalline solid that had separated was filtered, washed with ice-water and finally with ether to free from traces of the chloroketone and oily impurities. The dried solid (7.5 g.) on crystallisation from boiling water separated in colourless elongated rods melting at 210–12°. (Found: N, 8.99;  $C_6H_7O_2NS$  requires N, 8.92 per cent.). The acetyl derivative yielded a semicarbazone, *m.p.* 240–44°. Nagasawa<sup>31</sup> gives the *m.p.* 210.5° for 2-hydroxy-4-methyl-5-acetylthiazole (prepared from 2-hydroxy-4-methylthiazole by Friedel-Craft's reaction) and *m.p.* 244° for the semicarbazone.

*Action of Barium thiocyanate on Chloracetylacetone*.—Barium thiocyanate (7.7 g.) in alcohol (10 c.c.) was mixed with chloracetylacetone (6.75 g.). The reaction was imminent and the mixture set to a thick mass. After adding some more alcohol (15 c.c.) the mixture was allowed to stand for one hour. The brownish mass was diluted with water, filtered, washed with water and dried (yield, 5 g.) On crystallisation from excess of alcohol the product decomposed at 228° (sintering from 200°). Mixed *m.p.* with the 2-hydroxy-4-methyl-5-acetylthiazole, 150–160°. (Found: N, 9.07  $C_6H_7O_2NS$  requires N, 8.92 per cent.) On boiling with dilute hydrochloric acid, the substance appears to undergo some change but no tangible product could be isolated.

*2-Hydroxy-4-thiocyanomethylthiazole*.—Ammonium thiocyanate (5 g.) in alcohol (10 c.c.) was treated with  $\alpha$ : $\gamma$ -dichloroacetone (5 g.) under cooling. After adding a few bits of ice, the mixture was allowed to stand overnight. The crystalline product that had separated was filtered off, washed, dried, and extracted with hot benzene. The benzene extract yielded a crystalline product (4 g.), m.p.  $95^{\circ}$ . On crystallising from alcohol, it separated in rectangular plates and had m.p.  $98.5^{\circ}$ . (Found: N, 16.22;  $C_5H_4N_2OS_2$  requires N, 16.28 per cent.) By using 7 g. of potassium thiocyanate and 4.3 g. of dichloroacetone a purer product weighing 5.6 g. was obtained.

*2-Hydroxy-4-chloromethylthiazole (IV)*.—Ammonium thiocarbamate (8.5 g.) suspended in alcohol (15 c.c.) was reacted with  $\alpha$ : $\gamma$ -dichloroacetone (12 g.) under cooling. The dark brownish product that separated on allowing to stand overnight was filtered, washed with water and dried (yield, 12 g.). Hot benzene extracted from the above a colourless crystalline product (3 g.) m.p.  $151-52^{\circ}$ , turning brownish at  $110^{\circ}$ . (Found: N, 9.68; 9.30;  $C_4H_4ONSCl$  requires N, 9.37 per cent.) It dissolves in dilute alkali. The residue after the separation of this product was a dark resinous mass, m.p.  $75-90^{\circ}$  difficult to purify.

*2-Chloro-4 : 5-dimethylthiazole*.—(i) *2-Hydroxy-4 : 5-dimethylthiazole* (10 g.) was gently refluxed with phosphorous oxychloride (30 c.c.) for about 2 hours, the excess of phosphorous oxychloride distilled off (15 c.c.) and the residue after decomposition with ice water was steam distilled; 9 c.c. (11.2 g.) of a colourless oil passed over which was separated, dried and distilled; b.p.  $190-92^{\circ}$ . (Found: N, 9.57;  $C_5H_5NSCl$  requires N, 9.49 per cent.).

(ii) Dry hydrogen chloride was passed into an ethereal solution of  $\alpha$ -thiocyanomethylethylketone (9.5 g. prepared as described before) for about 4 hours. The white crystalline product that separated gradually filled the flask. After removing the ether and the acid fumes, the contents were diluted with water and the oily layer taken up in ether. After a thorough extraction with alkali (100 c.c. of N NaOH), the ethereal solution was dried and the solvent removed. The residue (6 g.) distilled at  $185-90^{\circ}$  and was found to be 2-chloro-4:5-dimethylthiazole.

The same chlorothiazole compound was obtained by treating  $\alpha$ -thiocyanomethylethylketone with phosphorous oxychloride for 2 hours under reflux.

*Ethyl 2-chloro-4-methylthiazole-5-carboxylate*.—Ethyl 2-hydroxy-4-methylthiazole-5-carboxylate (10 g., m.p.  $175^{\circ}$ ) was gently refluxed with phosphorous oxychloride (25 c.c.) for 3 hours. Part of the excess of the oxy-

chloride was distilled off and the residue decomposed with water. The solid was taken up in ether (charcoal) and from the extract 9 g. of 2-chloro-4-methylthiazole-5-carboxylate, m.p. 48–51°, was obtained.

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.).

#### SUMMARY

Three methods of synthesising thiazole derivatives unsubstituted in position 2 of the thiazole ring have been investigated to ascertain their scope. The reactions involving the condensation of thioformamide with  $\alpha$ -halogenoketones are best effected by treating the halogenoketones with a mixture of formamide and phosphorous pentasulphide; syntheses of 4-methylthiazole, 4:5-dimethylthiazole, 4-methyl-5-acetylthiazole and ethyl 4-methylthiazole-5-carboxylate are described as examples. By this method thiazole and ethyl thiazole-4-carboxylate could not be prepared.

2-Aminothiazole, the 5-methyl and 5-ethyl derivatives have been converted into the corresponding 2-chloro and 2-bromo derivatives in good yields by diazotising the aminothiazoles in a mixture of phosphoric acid and nitric acid or about 45 per cent. sulphuric acid and treating the diazonium products with an aqueous solution of copper sulphate and sodium halide. Treatment of the diazonium solutions with cuprous oxide in alcohol or calcium hypophosphite yielded the deaminated products, the latter giving better yields than the former reagent. These reactions are not of universal applicability and their scope has been ascertained by studying them in a number of cases. 2-Chloro-5-nitrothiazole and 2-bromo-5-nitrothiazole have been prepared by diazotising 2-amino-5-nitrothiazole in dilute sulphuric acid containing copper-sulphate and the sodium halide.

The preparation of 2-hydroxythiazole derivatives by condensing  $\alpha$ -halogenoketone with either the thiocyanates or ammonium thiocarbamate has been studied using chloracetone, dichloracetone,  $\alpha$ -chloromethyl-ethylketone, chloracetylacetone and ethyl  $\alpha$ -chloroacetoacetate. In the case of the chloroderivatives of  $\beta$ -ketonic ester and  $\beta$ -diketone, ammonium thiocarbamate yields the expected 2-hydroxy thiazole derivative while the product obtained using the thiocyanates is of doubtful constitution. The 2-hydroxythiazol compounds could be converted into the 2-chlorothiazole in good yields by treating with phosphorous oxychloride. Saturation of  $\alpha$ -thiocyanomethylethylketone with hydrogen chloride furnished 2-chloro-4:5-dimethylthiazole.



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