

CHEMISTRY OF THE THIAZOLES

IV. Bromination and Nitration of Some Monosubstituted Thiazoles

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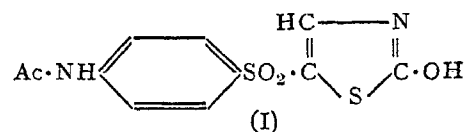
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CERTAIN gaps at present exist in the data on the orientation of the incoming group on substitution in the case of some monosubstituted thiazoles. To fill this up, we have attempted the bromination and nitration of the three isomeric methylthiazoles, 2-hydroxythiazole, 2-methoxythiazole and 5-acetamidothiazole. The results obtained are presented here. The significance of these in the light of our present knowledge would be discussed in the succeeding paper.

2-Methylthiazole does not undergo substitution with ease. On bromination, it furnished a bromo compound, presumably 2-methyl-5-bromothiazole. Babo and Prijs¹ nitrated 2-methylthiazole at 330° C. and obtained 2-methyl-5-nitrothiazole in about 4 per cent. yield. We had obtained the same nitro compound in about the same yield by carrying out the nitration at 110° C. 4-Methylthiazole could not be brominated at all even on heating the reactants at 110° C. for 12 hours. Ochiai² first reported that 4-methylthiazole could not be nitrated but Nagasawa³ has obtained a mononitro compound, m.p., 57.5° C., the yields not being stated. We have nitrated 4-methylthiazole at 100° C. (12 hours) to obtain the same nitro compound in about 30 per cent. yields, which has been proved to be 4-methyl-5-nitrothiazole by Erlenmeyer *et al.*⁴ since it is different from 4-methyl-2-nitrothiazole (m.p., 36-8°) prepared by them from 2-amino-4-methylthiazole. 5-Methylthiazole on bromination furnished 2-bromo-5-methylthiazole in good yields. The structure of this has been confirmed by the fact that on treatment with sulphanilamide it furnishes 2-sulphanilamido-5-methylthiazole. On nitration, 5-methylthiazole furnished a mononitro compound, m.p. 110° C., which should be 5-methyl-4-nitrothiazole because it is different from 5-methyl-2-nitrothiazole reported by Erlenmeyer *et al.*⁴

2-Hydroxythiazole was prepared by the action of ammonium thiocarbamate on chloroacetaldehyde and this compound is identical with that obtained by Ganapathi and Venkataraman⁵ as a byproduct in the preparation of 2-halogenothiazole from 2-aminothiazole by diazotisation and Sandmeyer's reaction. On bromination it furnished a monobromo compound, m.p.

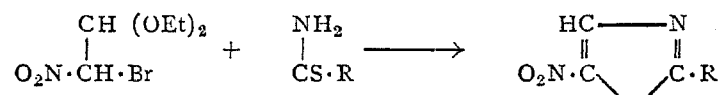
67° C., which we consider to be 2-hydroxy-5-bromothiazole; it furnished with potassium acetamido phenylsulphinat, the corresponding sulphone (I).



Since the 4-bromothiazoles do not react, we assign the structure of 2-hydroxy-5-bromothiazole for the bromination product. On nitration, 2-hydroxythiazole easily furnishes a nitrothiazole, m.p. 146–7° C., which is identical with that obtained by Ganapathi and Venkataraman⁶ by the hydrolysis of 2-bromo-5-nitrothiazole. On treatment with acetic anhydride, 2-hydroxythiazole yields an acetyl derivative; since this dissolves in alkali, this is not an O-acetyl compound. We assign it the structure of 2-hydroxy-5-acetylthiazole. This compound also reacts very vigorously with phosphorus oxychloride indicating the presence of the hydroxy group. All the above-mentioned 2-hydroxythiazoles are not stable. They do not keep on standing but undergo polymerisation or decomposition and turn dark, as is expected.

Treatment of 2-bromothiazole with sodium methoxide furnished 2-methoxythiazole, b.p. 142–6° C. in good yields. It gets nitrated easily with a mixture of nitric acid and sulphuric acid at the room temperature, furnishing a compound, m.p. 59°, which we take to be 2-methoxy-5-nitrothiazole. On bromination of 2-methoxythiazole, we also obtain a bromo compound which we consider to be 2-methoxy-5-bromothiazole.

Attempts to synthesise 5-nitro-2-hydroxythiazole and 5-nitro-2-methylthiazole by the action of α : α' -bromonitroacetal on ammonium thiocarbamate and thioacetamide respectively as follows:

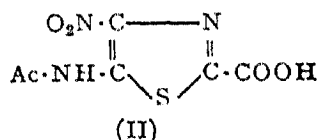


were not successful. We expected to fix up the orientation of the nitrated products by the above synthesis.

After our work on the nitration and bromination of 5-acetamidothiazole was completed, the paper by Prijs, Mengisen Fallab and Erlenmeyer⁷ appeared. As reported by Prijs *et al.*,⁷ we also find that bromination of 5-acetamidothiazole always leads to the dibromo derivative. Using even less than one molecular equivalent of bromine did not furnish the mono bromo derivative. To prepare the mono bromo derivative, we brominated 5-acetamidothiazole-2-carboxylic acid and obtained surprisingly enough only 5-acetamido-2:4-dibromothiazole. So, just as it happens in the thiophene derivatives, there was decarboxylation and bromination. Prijs *et al.*⁷ have however been

successful in preparing the mono bromo derivative by the use of N-bromo-succinimide.

Nitration of 5-acetamidothiazole furnished in our hands a nitro derivative, m.p. 197–8° C., which Prijs *et al.*⁷ describe as a dinitro derivative. But we find it to be only a mono nitro compound, with the structure 5-acetamido-4-nitrothiazole. Conclusive proof was obtained by nitrating 5-acetamidothiazole-2-carboxylic acid to 5-acetamido-4-nitrothiazole-2-carboxylic acid (II), m.p. 155–6°, and decarboxylating it to a compound identical with the nitration product of 5-acetamidothiazole.



Two things are of interest to note in this connection. While the bromination of 5-acetamidothiazole-2-carboxylic acid leads to decarboxylation, nitration does not effect this. While 5-acetamidothiazole-2-carboxylic acid is easily nitrated and brominated, Ganapathi and Venkataraman⁸ could not nitrate 2-acetamidothiazole-4-carboxylic acid and 2-acetamidothiazole-5-carboxylic acid, in spite of the fact that the position 5 in the first compound was free.

The significance of the findings presented here are discussed in the succeeding paper.

EXPERIMENTAL

2-Methyl-5-nitrothiazole.—2-Methylthiazole (15.0 g.) was gradually added to a cooled mixture of fuming sulphuric acid (50 c.c.) and fuming nitric acid (40 c.c.), the mixture kept overnight, heated on the steam-bath for 10 hours and then at 120° C. in an oil-bath for 4 hours. The liquid after cooling was poured on ice when a white solid was thrown down. The aqueous mixture was extracted with ether, and the solvent removed from the extract whereby 2-methyl-5-nitrothiazole was obtained (yield, 0.78 g.). It crystallised from petroleum-ether and had m.p. 129–31° C. (Found: N, 19.1; C₄H₄O₂N₂S requires N, 19.4 per cent.).

2-Methyl-5-bromothiazole.—2-Methylthiazole (5 g.) in acetic acid (10 c.c.) was treated with bromine (8 g.). The mixture was allowed to stand overnight, heated on the steam-bath for 10 minutes, poured on ice water, the mixture made alkaline with sodium bicarbonate and extracted with ether. After removal of the solvent, the bromothiazole was distilled. It passed over at 148–56° (yield, 3.45 g.) (Found: N, 7.78; C₄H₄NSBr requires N, 7.86 per cent.). The bromo compound did not form a picrate.

4-Methyl-5-nitrothiazole.—4-Methylthiazole (6.0 g.) was added gradually to fuming sulphuric acid (15 c.c.) followed by potassium nitrate (6.0 g.), maintaining the temperature between 20–30° C. The mixture was kept overnight at room temperature, heated on the steam-bath for 24 hours, cooled and poured on ice. The mixture was neutralised with sodium carbonate and then extracted with ether. After removal of the solvent a crystalline solid was obtained (3.0 g.) which on recrystallisation from petroleum-ether had m.p. 58–9° C. (Found: N, 19.24; $C_4H_4O_2N_2S$ requires N, 19.44 per cent.). The nitro compound dissolves in dilute sodium hydroxide solution to give a yellow solution which readily turns deep red. It did not yield a picrate.

5-Methyl-4-nitrothiazole.—5-Methylthiazole (4.0 g.) was added slowly to fuming sulphuric acid (15 c.c.) followed by potassium nitrate (4.0 g.) maintaining the temperature between 20° and 30° C. by cooling. After keeping overnight, it was heated on the steam-bath for 12 hours, cooled and poured on ice. The mixture was neutralised with sodium carbonate and then extracted with ether. After removal of the solvent, a crystalline solid resulted (2.5 g.) which crystallised from petroleum-ether in shining plates and had m.p. 110° C. (Found: N, 19.12; $C_4H_4O_2N_2S$ requires N, 19.44 per cent.). The product dissolves in dilute sodium hydroxide with a red colour which darkens on keeping. It did not form a picrate.

2-Bromo-5-methylthiazole.—To 5-methylthiazole (5.0 g.) taken up in acetic acid (10 c.c.), bromine (8.2 g.) was added slowly with good cooling, the mixture allowed to stand overnight, poured on ice water, made alkaline with sodium carbonate and then extracted with ether. After dehydrating the ethereal solution (sodium sulphate), the solvent was removed. The residual 2-bromo-5-methylthiazole distilled at 192–200° C. (yield, 5 g.) and appears to be identical with that prepared by Ganapathi and Venkataraman⁵ from 2-amino-5-methylthiazole.

2-p-Aminobenzenesulphonamido-5-methylthiazole.—The foregoing bromo-compound (4 g.), sulphanilamide (4 g.), anhyd. potassium carbonate (2 g.) and copper bronze (0.5 g.) were intimately mixed and heated in the oil-bath at 120° C. for one hour. The dark coloured fused mass was triturated with sodium hydroxide filtered, and the filtrate neutralised with hydrochloric acid. The precipitate obtained was collected and crystallised from alcohol (yield, 2.5 g.), m.p. 245–47° (Found: N, 15.51; $C_{10}H_{11}N_3O_2S_2$ requires N, 15.61 per cent.). This product was identical with an authentic sample obtained by the hydrolysis of 2-acetsulphanilamido-5-methylthiazole in turn prepared by the condensation of 2-amino-5-methylthiazole and acetsulphanilyl chloride in pyridine.

2-Hydroxythiazole.—Freshly prepared ammonium thiocarbamate (23 g.) was dissolved in water (15 c.c.) and freshly distilled chloroacetaldehyde (19 g.) was added gradually with cooling and stirring. The reaction mixture was then kept in the refrigerator overnight. 2-Hydroxythiazole separated as a brown solid was collected (3 g.) and crystallised from alcohol; m.p. 69–70° (Found: N, 14.1; C_3H_3ONS requires N, 13.86 per cent.). 2-Hydroxythiazole on keeping darkens and probably polymerises. It forms a red dye when coupled with diazotised *p*-toluidine.

2-Hydroxy-5-bromothiazole.—2-Hydroxythiazole (2 g.) was dissolved in chloroform (10 c.c.) and bromine (3.2 g.) was added to it gradually with good shaking and under external cooling. The reaction mixture was then kept in the ice-box for 3 to 4 hours when a yellowish solid (1.5 g.) with deep penetrating odour separated. It was separated and purified by dissolving it in alcohol and adding water; m.p. 67° (dec.) (Found: N, 7.3; C_3H_2ONBr requires N, 7.7 per cent.). The bromo compound is not very stable and decomposes on standing.

4-Acetamidophenyl-(2'-hydroxy) thiazolyl (5)-sulphone.—An intimate mixture of the foregoing bromo compound (3 g.), potassium *p*-acetamidobenzene sulphinate (4 g.), copper bronze (0.1 g.), trace of iodine and propylene glycol (15 c.c.) was maintained at 100° C. for about 6 hours and then poured on ice. A solid separated along with some tar. The solid matter was separated, washed with water and crystallised from dilute alcohol (0.8 g.); m.p. 263–64.5° (dec.). The product was soluble in alkali (Found: N, 8.9; $C_{11}H_{10}O_4N_2S_2$ requires N, 9.3 per cent.).

2-Hydroxy-5-nitrothiazole.—To a cooled mixture of con. sulphuric acid (10 c.c.) and con. nitric acid (4 c.c.) was added 2-hydroxythiazole (4 g.) in small portions under external cooling. After completion of addition, the mixture was kept in the ice-chest for 3 hours and then at room temperature for 1 hour. On pouring it on ice, a yellowish brown precipitate was thrown out, which was filtered and crystallised from dilute alcohol; 2-hydroxy-5-nitrothiazole separated in yellowish needles, m.p. 146–7° C. (yield, 1.5 g.) (Found: N, 19.0; $C_3H_2O_3N_2S$ requires N, 19.1 per cent.). It is identical with the product prepared by Ganapathi and Venkataraman by boiling 2-bromo-5-nitrothiazole with dilute sulphuric acid. It dissolves in alkali with red coloration.

2-Hydroxy-5-acetylthiazole.—2-Hydroxythiazole (3 g.) was dissolved in pyridine (5 c.c.) and acetic anhydride (10 c.c.) was added to it, the reaction mixture kept overnight and next day heated on the steam-bath for 3 hours. The excess of acetic anhydride and pyridine were removed under vacuum

by distillation and the residual pasty mass treated with ice. The solid that separated was filtered, washed and crystallised from alcohol (yield, 0.8 g.); m.p. 195–7° C. (Found: N, 9.4; $C_5H_5O_2NS$ requires N, 9.8 per cent.). It dissolves in alkali and reacts with phosphorus oxychloride.

2-Methoxythiazole.—2-Bromothiazole (18 g.) was added gradually to sodium methoxide (prepared from sodium, 2.5 g., and methyl alcohol, 70 c.c.) and refluxed for 20 hours on the steam-bath. The reaction mixture was diluted with ether, the separated sodium bromide filtered off, and the solvent removed from the filtrate. The residual 2-methoxythiazole on distillation passed over at 142–46° C. (yield, 12 g.) It gave a picrate, m.p. 90° C. (Found: N, 16.1; $C_{10}H_8O_8N_4S$ requires N, 16.2 per cent.).

2-Methoxy-5-nitrothiazole.—2-methoxythiazole (7.5 g.) was added gradually to a cooled mixture of con. sulphuric acid (30 c.c.) and con. nitric acid (8 c.c.) and the reaction mixture allowed to stand overnight. On pouring on ice the nitro compound was thrown out which crystallised from petroleum-ether (3.5 g.), m.p. 59° (Found: N, 17.67; $C_4H_4O_3N_2S$ requires N, 17.5 per cent.). The nitro compound gives a yellow coloration in dilute sodium hydroxide.

5-Acetamido-4-nitrothiazole.—5-Acetamidothiazole (0.5 g.) was slowly added to concentrated sulphuric acid (4 c.c.) under cooling; to this con. nitric acid (2 c.c.) was gradually added and the reaction mixture allowed to stand overnight. On pouring the clear solution on ice, the nitro compound separated, which was filtered off, washed (0.25 g.) and crystallised from alcohol; m.p. 197–8° (Found: N, 22.1; $C_5H_5O_3N_3S$ (mono nitro derivative) requires N, 22.4 per cent.; $C_5H_4O_5N_4S$ (dinitro compound) requires N, 24.1 per cent.). This nitro compound dissolved in sodium hydroxide solution with a red colour.

(ii) 5-Acetamido-4-nitrothiazole-2-carboxylic acid (prepared as described below, 1 g.) was maintained at 160–70° C. till there was no more evolution of carbon dioxide. On crystallising the residual mass from acetone was obtained the nitro compound (0.3 g.) as a crystalline powder, m.p. 197–8° (Found: N, 22.0; $C_5H_5O_3N_3S$ requires N, 22.4 per cent.). This compound is identical with that described above and obtained by the nitration of 5-acetamidothiazole.

5-Acetamido-4-nitrothiazole-2-carboxylic acid.—5-Acetamidothiazole-2-carboxylic acid (1 g.) was added in portions to con. sulphuric acid (8 c.c.) followed by con. nitric acid (2 c.c.) and the reaction mixture was allowed to stand overnight. On pouring the solution on ice, a solid separated which was filtered, dissolved in dilute sodium bicarbonate solution and precipitated

by acid (0.5 g.). On crystallisation from alcohol the nitro compound had m.p. 155–56° (dec.), solidified and again melted at 189–92° (Found: N, 17.8; $C_6H_5O_5N_3S$ requires N, 18.1 per cent.).

5-Acetamido: 2:4-dibromothiazole.—5-Acetamidothiazole (1 g.) was dissolved in acetic acid (6 c.c.) and to this was added bromine (1.3 g.). The mixture was allowed to stand overnight, poured on ice, and the mixture neutralised with sodium bicarbonate, when the bromo compound separated as a dark brown mass. On crystallisation from alcohol (0.8 g.), the dibromo compound had m.p. 148–49° (Found: N, 9.3; $C_5H_4ON_2SBr_2$ requires N, 9.3 per cent.). Even by using less than half the amount of bromine the same dibromo compound was obtained.

(ii) To 5-acetamidothiazole-2-carboxylic acid suspended in chloroform (20 c.c.) was added bromine (1.2) with external cooling in ice water, the reaction mixture allowed to stand overnight. The excess of bromine was removed with sodium sulphite, the chloroform solution separated, and the solvent removed. The residual brown solid mass was triturated with dilute sodium bicarbonate solution, which was found to extract the unreacted starting material. The product that did not dissolve in bicarbonate (0.8 g.) on crystallisation from acetone had m.p. 148–49° (Found: N, 9.3; $C_5H_4ON_2SBr_2$ requires N, 9.3 per cent.) and was found to be identical with 5-acetamido: 2:4-dibromothiazole described above.

We thank Mr. M. H. Shah, Microanalyst, for carrying out the analyses reported in this paper.

SUMMARY

In connection with the study of the orienting influences in the thiazole nucleus, 2-methylthiazole, 4-methylthiazole, 5-methylthiazole, 2-hydroxythiazole, 2-methoxythiazole, 5-acetamidothiazole and 5-acetamidothiazole-2-carboxylic acid have been nitrated and brominated and the results obtained have been presented. The significance of the results is discussed in the next part.

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