66. *Reactions of Certain Thiazoles and Glyoxalines with Picryl Chloride and 2 : 4-Dinitrochlorobenzene.*

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The object of this investigation was to prepare quaternary thiazolium and glyoxalinium salts containing *N*-picryl or *N*-2 : 4-dinitrophenyl groups.

OWING to difficulties experienced in repeating earlier preparations of simple thiazoles and glyoxalines, it was decided to survey the methods available. New methods of preparing thiazole, 4-methylthiazole and 1 : 4-dimethylthiazole were adopted, and a synthesis of 5-methylthiazole carried out.

The only account found of an attempt to prepare the desired quaternary salts is given by Tomlinson (J., 1936, 1607), who obtained a compound, apparently 2-hydroxy-3-picryl-4-methyl-2 : 3-dihydrothiazole, when 4-methylthiazole and picryl chloride interacted with access to atmospheric moisture. It

was considered that the unstable quaternary salt was first formed, but that the chlorine passed to the 2-position, from which it was rapidly hydrolysed.

Tomlinson's experimental findings have been confirmed and the above compound was also obtained when either picryl chloride or picryl iodide reacted with 4-methylthiazole in cold acetone solution.

The reactions between picryl chloride (and in some cases 2 : 4-dinitrochlorobenzene) and thiazole, 2-methylthiazole, 5-methylthiazole, 2 : 4-dimethylthiazole, 2 : 5-dimethylthiazole, 1 : 4-dimethylglyoxaline and 1 : 5-dimethylglyoxaline, alone and/or in acetone solution, have been studied.

From thiazole and picryl chloride, *thiazole hydrochloride* and a *picrylthiazole* of undetermined orientation were formed, presumably according to the substitutive reaction :

$$2C_3H_3NS + C_6H_2(NO_2)_3Cl = C_3H_2NS{\cdot}C_6H_2(NO_2)_3 + C_3H_3NS,HCl$$

The reaction between 2-methylthiazole and picryl chloride alone or in acetone solution provided the only instance of quaternary salt formation in the thiazoles investigated. The desired *N-picryl-2-methylthiazolium chloride* was obtained, but decomposed in hot alcoholic solution, forming either a picryl-2-methylthiazole or 2-methylthiazole picrate.

In acetone solution, 5-methylthiazole, like thiazole itself, readily yielded the *hydrochloride* of the base and a *picryl-5-methylthiazole* by substitution.

2 : 4-Dimethylthiazole reacted with picryl chloride (and 2 : 4-dinitrochlorobenzene) only at relatively high temperatures and not at all in acetone solution, and the only identifiable product isolated was the *hydrochloride* of the base.

2 : 5-Dimethylthiazole and picryl chloride in acetone solution yielded a highly coloured product which may be an acetone addition compound formed from the picryl-2 : 5-dimethylthiazole at first produced.

The recorded melting points of certain thiazole picrates were found to be incorrect and new values were determined.

N-*Picryl*-1 : 4-*dimethylglyoxalinium chloride*, N-(2 : 4-*dinitrophenyl*)-1 : 4-*dimethylglyoxalinium chloride* and N-(2 : 4-*dinitrophenyl*)-1 : 5-*dimethylglyoxalinium chloride* were readily obtained from the appropriate glyoxalines in acetone solution.

As it would be very difficult to determine experimentally the orientation of the picryl groups in the substituted thiazoles obtained, the authors make the following tentative suggestions :

In view of the conversion of *N*-picryl-2-methylthiazolium chloride into picryl-2-methylthiazole by heat, it seems likely that in the other cases where substitution occurs it is preceded by the formation of unstable quaternary salts as is postulated by Tomlinson in the case of the reaction between 4-methylthiazole and picryl chloride.

Occupation of the C_2-position by a methyl radical appears to disfavour substitution by a picryl group in the cases of 2-methylthiazole and 2 : 4-dimethylthiazole, but when this position is unoccupied, as in thiazole, 4- and 5-methylthiazoles, substitution is rapid. Tomlinson adduces no evidence for ascribing the C_2- and the N_3-position to the hydroxyl and the picryl group respectively rather than the converse, in the product from 4-methylthiazole.

If the postulation that quaternary salt formation precedes picryl substitution is correct, these points favour the view that the C_2-position is the most reactive towards picryl chloride as a substitutive reagent, and lead to the suggestion that the products obtained from thiazole and 5-methylthiazole are 2-*picrylthiazole* and 2-*picryl*-5-*methylthiazole* respectively.

The inactivity of 2 : 4-dimethylthiazole and reactivity of 2 : 5-dimethylthiazole would suggest that of the other two points at which substitution in the ring may occur, the C_4-position is the more probable, it being inferred that when 2 : 5-dimethylthiazole reacts with picryl chloride in acetone solution the product is an acetone derivative of 4-picryl-2 : 5-dimethylthiazole. For a similar reason, it is probable that the product of decomposition of *N*-picryl-2-methylthiazolium chloride is 4-*picryl*-2-*methylthiazole*.

Experimental.

Thiazole.—Popp (*Annalen*, 1889, **250**, 273) prepared thiazole by diazotising aminothiazole with ethyl nitrite in alcohol. The authors were unable to repeat this and attempted alternative methods of preparation.

(1) An attempted preparation from thioformamide and αβ-dichlorodiethyl ether was unsuccessful.

(2) Willstätter and Wirth (*Ber.*, 1909, **42**, 1918) describe the preparation of thiazole from thioformamide and chloroacetaldehyde hydrate; the yield, however, is poor.

(3) It was decided to concentrate on methods employing 2-aminothiazole as starting material, as this is easily obtained from thiourea and αβ-dichlorodiethyl ether. Diazotisation of aminothiazole (23 g.) with nitrous acid, followed by reduction with sodium hypophosphite, gave a poor yield of thiazole (2·5 g.). When reduction was carried out with sodium formate, the yield was even poorer. The method finally adopted was to convert 2-aminothiazole into 2-chlorothiazole, followed by reduction with zinc dust and acetic acid. Schatzmann (*Annalen*, 1891, **261**, 10) prepared 2-chlorothiazole by boiling diazotised 2-aminothiazole with concentrated

hydrochloric acid. Finding this unsatisfactory, the authors adopted the following procedure : 2-Aminothiazole (24 g.) was dissolved in 140 ml. of 5N-hydrochloric acid and cooled to − 5°, and sodium nitrite (16 g.) added in concentrated solution. The cold diazo-solution was added to an ice-cold hydrochloric acid solution of cuprous chloride (prepared from 18 g. of copper carbonate, copper, and hydrochloric acid) and kept overnight. The mixture was then heated to remove a little ether which had been added to prevent frothing, made alkaline, and steam-distilled. The separated 2-chlorothiazole (6 g.) was dried with potassium carbonate; b. p. 138—142°.

A solution of 2-chlorothiazole (13 g.) in glacial acetic acid (50 ml.) was heated almost to boiling, and zinc dust (15 g.) added in small quantities. The solution was refluxed for 2 hours, made alkaline and steam-distilled, all the thiazole coming over with the first 20 ml. of distillate. The thiazole was salted out with potassium carbonate and dried over potassium hydroxide; yield 8·5 g., b. p. 117°. Thiazole picrate, prepared by mixing alcoholic or glacial acetic acid solutions of thiazole and picric acid and recrystallised from alcohol, had m. p. 159—160° (Popp, *Annalen*, 1889, **250**, 275, records m. p. 151°).

Reaction between Thiazole and Picryl Chloride.—Thiazole (0·85 g.) and picryl chloride (2·5 g.) were warmed together for a few moments to aid mixing. The mixture, which set to a hard red mass on cooling, was extracted with boiling acetone (40 ml.). The colourless hygroscopic crystals of *thiazole hydrochloride* which separated on cooling, after being washed with small quantities of acetone, had m. p. 139—140° (Found : Cl, 29·5. C_3H_3NS,HCl requires Cl, 29·2%). The red acetone mother-liquor on concentration yielded further crops of the hydrochloride and then a yellow crystalline solid insoluble in water. Recrystallised from acetone–water (decolourising carbon), this *picrylthiazole* formed bright yellow prisms, m. p. 172° [Found : N, 18·9. $C_3H_2NS{\cdot}C_6H_2(NO_2)_3$ requires N, 18·9%].

The presence of acetone made little difference to the result.

Thiazole and 2 : 4-dinitrochlorobenzene also interacted to form thiazole hydrochloride on heating (confirmed by analysis), but no other product could be isolated.

2-Methylthiazole.—2-Methylthiazole cannot be prepared from thioacetamide and αβ-dichlorodiethyl ether, as the hydrogen chloride liberated decomposes the thioacetamide. Hantzsch's method (*Annalen*, 1889, **250**, 270) was adopted, thioacetamide and chloroacetal being used. 2-Methylthiazole picrate, formed by mixing alcoholic solutions of the base and picric acid, crystallised from hot alcohol in yellow needles, m. p. 153°. Hantzsch records m. p. 145—146°.

Reaction between 2-Methylthiazole and Picryl Chloride.—No reaction took place between 2-methylthiazole and 2 : 4-dinitrochlorobenzene either alone or in acetone solution. A mixture of 2-methylthiazole (1 g.) and picryl chloride (2·5 g.) turned deep purple after a short time and set to a semi-solid crystalline mass; the quaternary salt could not be isolated.

A solution of 2-methylthiazole (5·5 g.) and picryl chloride (13·7 g.) in acetone (40 ml.) became deep purple after 4 days. The *N-picryl-2-methylthiazolium chloride* which separated was collected, washed several times with acetone (yield, 8·2 g.), and recrystallised from boiling alcohol, forming colourless elongated prisms, m. p. 126°, readily soluble in water (Found : Cl, 10·3. $[C_4H_5NS{\cdot}C_6H_2(NO_2)_3]Cl$ requires Cl, 10·3%). From the alcoholic mother-liquor, a small quantity of yellow *picryl-2-methylthiazole*, m. p. 150° (after recrystn. from alcohol), was isolated [Found : N, 18·2. $C_4H_4NS{\cdot}C_6H_2(NO_2)_3$ requires N, 18·1%].

As it was suspected that the picryl substitution product had been formed through decomposition of the quaternary salt by boiling in alcohol, the following experiment was performed : A solution of the quaternary salt (2 g.) in alcohol (40 ml.) was refluxed for 12 hours. On cooling, orange-red clusters separated from the deep red solution. After recrystallisation from alcohol (decolourising carbon), yellow needles, m. p. 153°, were obtained which depressed the m. p. of the picryl-2-methylthiazole, m. p. 150°, described above, but not that of 2-methylthiazole picrate [Found : N, 17·2. Calc. for $C_4H_5NS,C_6H_2(NO_2)_3{\cdot}OH$: N, 17·1%].

4-Methylthiazole.—The preparation of 4-methylthiazole by distilling 2-hydroxy-4-methylthiazole with zinc dust (Arapides, *Annalen*, 1888, **249**, 23) and from 2-amino-4-methylthiazole hydrochloride by diazotisation and reduction being unsatisfactory, it was obtained by reduction of 2-chloro-4-methylthiazole (Tscherniac, J., 1919, **115**, 1072) with zinc and glacial acetic acid (see preparation of thiazole from 2-chlorothiazole above). 4-Methylthiazole was salted out from the steam-distillate with potassium carbonate, dried over potassium hydroxide, and distilled (yield, 12 g. from 23 g. of 2-chloro-4-methylthiazole). The picrate, prepared from the base and picric acid in glacial acetic acid or alcohol and recrystallised from alcohol, had m. p. 182° (Popp, *Annalen*, 1889, **250**, 277, records 174°).

Reaction between 4-Methylthiazole and Picryl Chloride.—No identifiable products were obtained by heating mixtures of 4-methylthiazole and 2 : 4-dinitrochlorobenzene. After confirmation of Tomlinson's finding (*loc. cit.*) that a yellow crystalline compound [m. p. 181° (decomp.)] giving the required analysis for 2-hydroxy-3-picryl-4-methyl-2 : 3-dihydrothiazole (Found : C, 36·7; H, 2·5; N, 16·9; S, 10·0. Calc. for $C_{10}H_8O_7N_4S$: C, 36·6; H, 2·4; N, 17·1; S, 9·8%) was obtained when 4-methylthiazole was warmed with picryl chloride, the experiment was repeated in acetone solution : a solution of 4-methylthiazole (2·0 g.) and picryl chloride (2·5 g.) in acetone (20 ml.) was kept for 3 days at room temperature. The fine yellow needles were separated from the deep red liquor and washed with acetone (yield, 1·7 g.). They melted at 181° (decomp.), alone or mixed with the product obtained by Tomlinson's method. The same compound was also obtained from 4-methylthiazole (1 g.) and picryl iodide (3·4 g.) in acetone (15 ml.) after 3 months. To make certain that the compounds described above were not simply 4-methylthiazole picrate (m. p. 182°, and isomeric with the hydroxypicrylmethyldihydrothiazole), mixed m. p.'s were determined and marked depressions noted in all cases.

5-*Methylthiazole*.—Bromopropaldehyde hydrate (40 g.) and thiourea (20 g.) were heated together on the water-bath for 1 hour, filtered from a small amount of sulphur, and cooled, and potassium hydroxide solution (50%) added. The potassium salts were removed and on the addition of more potassium hydroxide an oil separated which solidified. The solid was collected and dissolved in ether to remove unchanged thiourea; evaporation of the ether yielded 2-amino-5-methylthiazole (20 g.). This was dissolved in 140 ml. of 5N-hydrochloric acid and diazotised at — 10° with sodium nitrite (16 g.); the diazo-solution was added to an ice-cold solution of cuprous chloride in hydrochloric acid, left overnight, made alkaline, and steam-distilled, yielding 2-chloro-5-methylthiazole (14 g.), b. p. 163—165°. Reduction was carried out as described under thiazole, and 5-methylthiazole (10 g.) obtained, b. p. 141—142°. 5-*Methylthiazole picrate*, prepared from the base and picric acid in alcoholic solution, had m. p. 170° [Found : N, 17·2. $C_4H_5NS,C_6H_2(NO_2)_3{\cdot}OH$ requires N, 17·1%].

Reaction between 5-*Methylthiazole and Picryl Chloride*.—5-Methylthiazole (1 g.) and picryl chloride (1·25 g.) were dissolved in acetone (15 ml.). After 24 hours, a colourless crystalline solid had separated from the red solution. After decantation and washing with acetone, this had m. p. 81° and proved to be 5-*methylthiazole hydrochloride* (Found : Cl, 27·6. C_4H_5NS,HCl requires Cl, 26·9%). Dilution of the mother-liquor with water gave a dull yellow solid. Recrystallised from acetone–water (decolourising carbon), this formed bright yellow prisms, m. p. 111°, of a *picryl-5-methylthiazole* [Found : C, 38·5; H, 2·6; N, 17·6. $C_4H_4NS{\cdot}C_6H_2(NO_2)_3$ requires C, 38·7; H, 1·9; N, 18·1%].

2 : 4-*Dimethylthiazole*.—By Hantzsch's method (*Annalen*, 1889, **250**, 265) 25 g. of thioacetamide yielded 15 g. of the thiazole. Prepared by mixing alcoholic solutions of the base and picric acid, and recrystallised from alcohol, 2 : 4-dimethylthiazole picrate was obtained in yellow plates, m. p. 140—141° (Hantzsch records 137—138°).

Reaction between 2 : 4-*Dimethylthiazole and Picryl Chloride*.—Preliminary attempts to obtain a quaternary salt by heating 2 : 4-dimethylthiazole with 2 : 4-dinitrochlorobenzene or picryl chloride at about 180° resulted only in the isolation of the hydrochloride of the base as a sublimate in the reaction flask.

2 : 4-Dimethylthiazole (1·2 g.) and picryl chloride (2·5 g.) were refluxed at 120—130°. After 30 minutes a pale yellow, feathery sublimate formed. This, after resublimation, was colourless, very hygroscopic, and melted at 189°. Analysis proved it to be 2 : 4-*dimethylthiazole hydrochloride* (Found : Cl, 23·6. C_5H_7NS,HCl requires Cl, 23·7%). Further yields of the hydrochloride were obtained by prolonging the heating, but no other product could be isolated from the tarry reaction mixture. Attempts to bring about quaternary salt formation by using acetone and benzyl alcohol as solvents for the reagents were fruitless. There was apparently no reaction in acetone.

2 : 5-*Dimethylthiazole*.—Hubacher's method (*Annalen*, 1890, **259**, 240) gave trifling yields, and Gabriel's method (*Ber.*, 1910, **43**, 1287) was preferred, though the yield was poor.

Prepared by mixing alcoholic solutions of the base and picric acid, and recrystallised from alcohol, 2 : 5-dimethylthiazole picrate was obtained in yellow leaflets, m. p. 172—173° (Hubacher records 166—167°).

Reaction between 2 : 5-*Dimethylthiazole and Picryl Chloride*.—A solution of 2 : 5-dimethylthiazole (1·5 g.) and picryl chloride (3·5 g.) in acetone (20 ml.) became deep purple after 4 hours. After 10 days at room temperature, deep red nacreous plates, m. p. 172° (decomp.) (after washing with hot alcohol), separated. Analysis indicates that this may be an acetone addition *compound* of picryl-2 : 5-dimethylthiazole [Found : S, 8·3; N, 13·6. $C_5H_6NS{\cdot}C_6H_2(NO_2)_3,C_3H_6O$ requires S, 8·4; N, 14·7%].

1 : 4-*Dimethylglyoxaline*.—The base was prepared by the following adaptation of Weidenhagen's method for the preparation of other glyoxalines (*Ber.*, 1935, **68**, 1960) : Copper acetate (60 g.) was dissolved in 20% aqueous ammonia (200 ml.), and formalin (25 ml.) added, followed by methylamine hydrochloride (40 g.) and acetol acetate (20 g.). The mixture was heated at 100° for 15 minutes, cooled, and extracted with chloroform. Separation of a copper salt of a glyoxaline did not take place, hence the N_1-position in the iminazole ring had apparently been methylated. The chloroform extract yielded **1** : 4-dimethylglyoxaline (3·5 g.), b. p. 195—197°, on distillation; this was identified by the formation of the picrate, m. p. 167—168° (Pyman, J., 1910, **97**, 1820).

Reaction between 1 : 4-*Dimethylglyoxaline and Picryl Chloride*.—N-*Picryl*-1 : 4-*dimethylglyoxalinium chloride* separated when solutions of molecular quantities of the reactants were mixed in acetone; it formed pale yellow prisms (after washing with acetone), m. p. 179° [Found : Cl, 10·3. $C_5H_8N_2,C_6H_2(NO_2)_3Cl$ requires Cl, 10·3%].

N-(2 : 4-*Dinitrophenyl*)-1 : 4-*dimethylglyoxalinium chloride*, similarly obtained from 1 : 4-dimethylglyoxaline and 2 : 4-dinitrochlorobenzene, formed orange prisms (after washing with acetone), m. p. 227° [Found : Cl, 12·0. $C_5H_8N_2,C_6H_3(NO_2)_2Cl$ requires Cl, 11·8%].

1 : 5-*Dimethylglyoxaline*.—This base was prepared, along with the 1 : 4-isomer, by Pyman's method (J., 1910, **97**, 1820). The isomers were separated by fractional distillation.

Reaction between 1 : 5-*Dimethylglyoxaline and* 2 : 4-*Dinitrochlorobenzene*.—N-(2 : 4-*Dinitrophenyl*)-1 : 5-*dimethylglyoxalinium chloride* separated when acetone solutions of molecular quantities of the reactants were mixed; it formed yellow prisms (after washing with acetone), m. p. 253° [Found : Cl, 11·5. $C_5H_8N_2,C_6H_3(NO_2)_2Cl$ requires Cl, 11·8%].

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