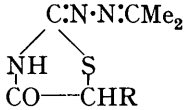
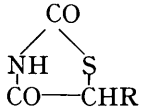
123. *Thiazole and Thiadiazine Formation from Thiosemicarbazones.*

By John McLean and Forsyth James Wilson.

It was found by Wilson and Burns (J., 1922, **121**, 870; 1923, **123**, 799) and by Wilson and Stephen (J., 1926, 2531) that thiosemicarbazones in presence of sodium ethoxide reacted with esters of α-halogenated acids to give thiazole derivatives; *e.g.*, $CMe_2{:}N{\cdot}N{:}C(SNa){\cdot}NH_2 + CHRBr{\cdot}CO_2Et \longrightarrow$ (I) + EtOH + NaBr. Hydrolysis of this thiazole derivative with concentrated hydrochloric acid removed acetone and hydrazine, giving a 2 : 4-diketotetrahydrothiazole (II); 2*N*-hydrochloric acid, however, removed acetone only and the intermediate hydrazone (III) was isolated as the hydrochloride.


(I.)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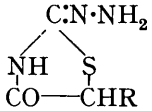
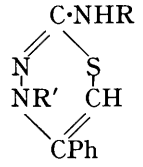
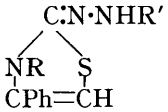

(III.)

Bose and his co-workers (*J. Indian Chem. Soc.*, 1924, **1**, 51; 1925, **2**, 95) have described the reaction of ω-bromoacetophenone with thiosemicarbazide and 4-substituted thiosemicarbazides. From thiosemicarbazide, 2-amino-5-phenyl-1 : 3 : 4-thiadiazine (IV; R = R′ = H) and 2-keto-4-phenyl-2 : 3-dihydro-1 : 3-thiazole-2-hydrazone (V; R = R′ = H) were formed, and substituted thiosemicarbazides produced derivatives of these substances: $NHR{\cdot}CS{\cdot}NH{\cdot}NHR' + CH_2Br{\cdot}COPh \longrightarrow NHR{\cdot}C(S{\cdot}CH_2{\cdot}COPh){:}N{\cdot}NHR' \xrightarrow{-H_2O}$ (IV) and (V).

(IV.) 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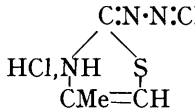
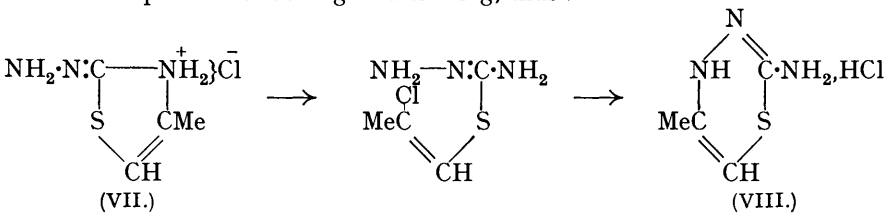

(VI.)

The reactions between chloroacetone and acetonethiosemicarbazone, benzaldehydethiosemicarbazone, and acetophenonethiosemicarbazone, which we have now investigated, conform to the general scheme $CRR'{:}N{\cdot}N{:}C(SH){\cdot}NH_2 + CH_2Cl{\cdot}COMe \xrightarrow{-H_2O}$ (VI), with formation of 2 : 3-dihydrothiazole derivatives. In order to fix the labile hydrogen atom present in the thiosemicarbazone, the sodium derivative was employed and the reactions took a similar course; *e.g.*, with the sodium derivative of acetophenonethiosemicarbazone the reaction produced *2-keto-4-methyl-2 : 3-dihydrothiazole-2-α-phenylethylidenehydrazone.*

Hydrolysis of these 2 : 3-dihydrothiazole derivatives with *N*/10-hydrochloric acid gave the hydrochloride of 2-keto-4-methyl-2 : 3-dihydrothiazole-2-hydrazone (VII), which was exceedingly deliquescent and was identified as the *picrate.* An aqueous solution of the hydrochloride readily formed the corresponding benzylidene and acetophenone derivatives and reduced Fehling's solution immediately in the cold.

Hydrolysis with concentrated hydrochloric acid, however, resulted in the formation of a six-membered ring, the *hydrochloride* of *2-amino-5-methyl-1 : 3 : 4-thiadiazine* (VIII)

being formed in each case. This enlargement of a five- to a six-membered ring is rather remarkable; we suggest that it may proceed by an opening of the five-ring, followed by reclosure in a new position so as to give a six-ring, thus :



(VII.) (VIII.)

Attempts to prepare the above 1 : 3 : 4-thiadiazine by Bose's method from thiosemicarbazide and chloroacetone in alcoholic solution were not successful, probably because a complex mixture was formed. In concentrated hydrochloric acid solution, however, an excellent yield of 2-amino-5-methyl-1 : 3 : 4-thiadiazine hydrochloride was obtained. Bose (second reference) suggests that thiazole formation from thiosemicarbazides depends on the basic character of the 4-amino-group present in the thiosemicarbazide but that this is not the only factor. The fact that no thiazole is produced when the reaction between thiosemicarbazide and chloroacetone takes place in strongly acid solution would suggest that hydrogen-ion concentration influences the reaction and determines the nature of the product, namely, whether thiazole or thiadiazine will be formed. Some derivatives of 2-amino-5-methyl-1 : 3 : 4-thiadiazine are described.

Chloroacetaldehyde appears to react with thiosemicarbazones in a similar manner to chloroacetone. Reactions were carried out with the thiosemicarbazones of benzaldehyde and acetone, but owing to the small quantity of chloroacetaldehyde available the reaction products were obtained in small quantity and hydrolysis was not attempted.

Experimental.

Chloroacetone and Benzaldehydethiosemicarbazone. Formation of 2-Keto-4-methyl-2 : 3-dihydrothiazole-2-benzylidenehydrazone (VI; R = H, R′ = Ph).—(a) The thiosemicarbazone (8 g.) was dissolved in 100 c.c. of absolute alcohol, 4·5 g. of chloroacetone added, and the mixture refluxed for 15 minutes; a reddish colour developed. After removal of the alcohol under reduced pressure the residue was dissolved in water, and sodium carbonate added. The dark yellow powder which separated was dissolved in dilute hydrochloric acid and reprecipitated with sodium carbonate; the light yellow powder obtained had m. p. 190° after darkening at 185° (Found : N, 19·4; S, 14·7. $C_{11}H_{11}N_3S$ requires N, 19·3; S, 14·7%). The *hydrochloride*, prepared by evaporating a solution of the *substance* in a little *N*/10-hydrochloric acid to dryness under reduced pressure, separated as an almost colourless powder, m. p. 131°, on addition of light petroleum to a chloroform solution (Found : N, 16·6. $C_{11}H_{11}N_3S$,HCl requires N, 16·7%).

(b) The sodium derivative of benzaldehydethiosemicarbazone separated in theoretical yield when a concentrated absolute-alcoholic solution of the thiosemicarbazone to which sodium (1 atom) had been added was refluxed for ½ hour and then cooled. 10 G. were suspended in chloroform, 5 g. of chloroacetone added, and the liquid refluxed for 10 minutes, filtered from sodium chloride, and concentrated; a substance, m.p. 190°, identical with that described in (a) was obtained.

Chloroacetone and Acetonethiosemicarbazone. Formation of 2-Keto-4-methyl-2 : 3-dihydrothiazole-2-isopropylidenehydrazone (VI; R = R′ = Me).—A suspension of the thiosemicarbazone (9·8 g.) in about 60 c.c. of chloroform containing 6·9 g. of chloroacetone was refluxed for 10—15 minutes; solution was soon effected. The cold filtered solution was extracted several times with small quantities of water, and neutralisation of the aqueous extract with sodium carbonate precipitated the *substance* as a light yellow powder readily soluble in organic solvents but best purified by solution in acid and precipitation with alkali; it melted at 90° (quickly heated) or 115° (very slowly heated) (Found : N, 25·0; S, 19·0. $C_7H_{11}N_3S$ requires N, 24·8; S, 18·9%).

Chloroacetone and Acetophenonethiosemicarbazone. Formation of 2-Keto-4-methyl-2 : 3-dihydrothiazole-2-α-phenylethylidenehydrazone (VI; R = Ph, R′ = Me).—A hot solution of the thiosemicarbazone (9·6 g.) in benzene was refluxed with 4·6 g. of chloroacetone for 15 minutes. The *hydrochloride* of the substance, which separated during the heating, was recrystallised from

a small quantity of absolute alcohol; it was sparingly soluble in water and melted at 154° (Found : N, 15·6; S, 11·7. $C_{12}H_{13}N_3S$,HCl requires N, 15·7; S, 11·9%). A warm aqueous solution of the hydrochloride deposited the *substance* itself on addition of sodium carbonate as a cream-coloured powder, which crystallised from aqueous alcohol in colourless prisms, m. p. 134° (Found : N, 18·3. $C_{12}H_{13}N_3S$ requires N, 18·2%).

Formation of 2-Keto-4-methyl-2 : 3-dihydrothiazole-2-α-phenylethylidenehydrazone from Chloroacetone and the Sodium Derivative of Acetophenonethiosemicarbazone.—This sodium derivative was prepared by adding the thiosemicarbazone (1 mol.) to a concentrated solution of sodium ethoxide (1 mol.); solution occurred and after 10 minutes' warming the sodium derivative separated; a further quantity was obtained on addition of light petroleum. It was suspended (9·2 g.) in chloroform, chloroacetone (4 g.) added, and the mixture refluxed for ½ hour. After filtration from sodium chloride, the solution was shaken with a little dilute hydrochloric acid; a hydrochloride identical with the one previously obtained was deposited.

Hydrolysis of the above 2 : 3-Dihydrothiazoles.—In all cases when hydrolysis was effected by boiling with 5*N*-hydrochloric acid two products were obtained, a hygroscopic hydrochloride which could not be obtained pure but could be isolated as the picrate of 2-keto-4-methyl-2 : 3-dihydrothiazole-2-hydrazone, and a hydrochloride identified as the hydrochloride of 2-amino-5-methyl-1 : 3 : 4-thiadiazine. The process may be illustrated by the hydrolysis of 2-keto-4-methyl-2 : 3-dihydrothiazole-2-α-phenylethylidenehydrazone hydrochloride with (a) *N*/10-hydrochloric acid, (b) concentrated hydrochloric acid. (a) The substance (9 g.) with 40 c.c. of acid was steam-distilled till no more acetophenone passed over (¾ hour). The residual solution on evaporation under reduced pressure gave a deliquescent hydrochloride. Addition of picric acid to the aqueous solution gave *2-keto-4-methyl-2 : 3-dihydrothiazole-2-hydrazone picrate*, which separated from boiling water as a yellow microcrystalline powder, m. p. 192° (Found : N, 23·6. $C_4H_7N_3S,C_6H_3O_7N_3$ requires N, 23·4%).

(b) The liquid obtained by heating the substance with acid for 10 minutes under reflux was steam-distilled to remove acetophenone and evaporated to dryness under reduced pressure. The residual *2-amino-5-methyl-1 : 3 : 4-thiadiazine hydrochloride* was washed with cold absolute alcohol; it crystallised, though with difficulty, from this boiling solvent in colourless prisms, m. p. 228° (Found : N, 25·6. $C_4H_7N_3S$,HCl requires N, 25·4%). It did not reduce Fehling's solution in the cold and did not react with benzaldehyde (absence of hydrazino-group). The *picrolonate* of the base, deposited on addition of aqueous-alcoholic picrolonic acid to an aqueous solution of the hydrochloride, crystallised from dilute alcohol in golden-yellow needles, m. p. 235° (Found : N, 25·0. $C_4H_7N_3S,C_{10}H_8O_5N_4$ requires N, 24·9%).

2-Amino-5-methyl-1 : 3 : 4-thiadiazine was synthesised by heating on the water-bath a suspension of thiosemicarbazide (4 g.) in about 40 c.c. of concentrated hydrochloric acid with chloroacetone (4·3 g.). On standing over-night, colourless prisms of a hydrochloride, m. p. 228°, identical with the previous specimen, were deposited (picrolonate, m. p. 235°); a further quantity was obtained by concentration. An aqueous solution of the salt to which the requisite quantity of potassium hydroxide had been added was evaporated to dryness, and the residue extracted with hot benzene (charcoal), from which, on cooling, the base separated in cream-coloured prisms, m. p. 109° (Found : N, 32·7. $C_4H_7N_3S$ requires N, 32·7%). It was not stable, undergoing rapid oxidation in the air. The base dissolved in acetic anhydride with evolution of heat; on standing, the *triacetyl* derivative was deposited in plates, which could be recrystallised from benzene–light petroleum; m. p. 167° (Found : C, 47·1; H, 5·1; N, 16·4. $C_{10}H_{13}O_3N_3S$ requires C, 47·1; H, 5·1; N, 16·5%). The *dibenzoyl* derivative was obtained by treating the base with benzoyl chloride and after some time shaking the resultant oil with sodium carbonate; the crystals so obtained could be purified from alcohol and melted at 201—202° (Found : N, 12·5. $C_{18}H_{15}O_2N_3S$ requires N, 12·5%).

Owing to the presence of the amino-group the base reacted with carbon disulphide and with phenylthiocarbimide as described below.

2-Amino-5-methyl-1 : 3 : 4-thiadiazine 5-methyl-1 : 3 : 4-thiadiazine-2-dithiocarbamate, $C_4H_7N_3S,HS{\cdot}CS{\cdot}NH{\cdot}C\begin{matrix}N{\cdot}NH\\S{-}CH\end{matrix}CMe$, was prepared by warming 4 g. of the thiadiazine base in alcoholic solution containing about 2 g. of potassium hydroxide and 6 g. of carbon disulphide. The liquid soon solidified to a mass of yellow crystals which, after washing with water and alcohol, decomposed at 142° (Found : N, 25·3. $C_4H_7N_3S,C_5H_7N_3S_2$ requires N, 25·4%).

2-Anilinothioformamido-5-methyl-1 : 3 : 4-thiadiazine was prepared by adding 4·1 g. of phenylthiocarbimide to a suspension of 3·8 g. of the thiadiazine base in about 30 c.c. of benzene; the suspension became warm and soon solidified. After collection and washing with benzene the

thiourea crystallised from absolute alcohol in minute colourless needles, m. p. 200° (decomp.) (Found : N, 21·2. $C_{11}H_{12}N_4S_2$ requires N, 21·2%).

Chloroacetaldehyde and Acetonethiosemicarbazone. Formation of 2-*Keto*-2 : 3-*dihydrothiazole*-2-iso*propylidenehydrazone* (VI; R = R′ = Me, Me at 4 = H).—A solution of the thiosemicarbazone (2 g.) in 20 c.c. of absolute alcohol containing 1 g. of chloroacetaldehyde was refluxed for 10 minutes, cooled, diluted to 100 c.c. with water, and treated with dilute sodium carbonate solution till just alkaline. The yellow precipitate, dissolved in dilute hydrochloric acid and reprecipitated with sodium carbonate, gave a cream-coloured powder, m. p. 140° (Found : N, 27·1. $C_6H_6N_3S$ requires N, 27·1%), readily soluble in organic solvents and crystallisable from aqueous alcohol.

Chloroacetaldehyde and Benzaldehydethiosemicarbazone. Formation of 2-*Keto*-2 : 3-*dihydrothiazole*-2-*benzylidenehydrazone* (VI; R = H, R′ = Ph, Me at 4 = H). The thiosemicarbazone (1·8 g.) with 0·8 g. of chloroacetaldehyde in absolute alcohol was refluxed for ½ hour, and the solution concentrated to small bulk, considerably diluted with water, and neutralised with sodium carbonate. The solid deposited after standing and scratching was dissolved in dilute hydrochloric acid, reprecipitated with sodium carbonate, and obtained as a cream-coloured powder, m. p. 169° (Found : N, 20·6. $C_{10}H_9N_3S$ requires N, 20·7%).

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"Freeland" Chemical Laboratories,
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