CCCXXXII.—*Some Thiazole Derivatives. Part I.*

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It was shown by Wilson and Burns (J., 1922, **121**, 870; 1923, **123**, 799) that the sodium derivative of acetonethiosemicarbazone reacted with esters of α-halogeno-acids to produce thiazole derivatives. This work has now been extended.

Acetone-δ-phenylthiosemicarbazone was treated in alcoholic solution with esters of α-halogeno-acids in presence of sodium ethoxide; the reaction proceeded smoothly as in previous cases,

giving in excellent yield the 2-*iso*propylidenehydrazone of a 2 : 4-diketotetrahydrothiazole.

$$CMe_2{:}N{\cdot}N{:}C(SNa){\cdot}NHPh + CHRBr{\cdot}CO_2Et =$$
$$NaBr + EtOH + CMe_2{:}N{\cdot}N{:}C\begin{array}{l}NPh{\cdot}CO\\ S\text{——}CHR\end{array} \quad (I.)$$

The esters employed were ethyl chloroacetate, ethyl α-bromo-*n*-butyrate, and ethyl phenylbromoacetate. By analogy with previous work, it was expected that dilute or concentrated acids would effect hydrolysis as shown by (*a*) or (*b*) respectively :

$$NH_2{\cdot}N{:}C\begin{array}{l}NPh{\cdot}CO\\ S\text{——}CHR\end{array},HCl \quad (II.) \xleftarrow{(a)} (I.) \xrightarrow{(b)} OC\begin{array}{l}NPh{\cdot}CO\\ S\text{——}CHR\end{array} \quad (III.)$$
$$+Me_2CO \qquad\qquad +Me_2CO + N_2H_4,2HCl$$

In previous cases these two stages were sharply distinguished, but in the present instances the hydrolysis could not be arrested at the first stage; it was therefore carried to completion with concentrated acid, but the yields of 2 : 4-diketo-3-phenyl-5-R-tetrahydrothiazole (III) were small, considerable decomposition taking place.

In the expectation of obtaining a compound with a thiazole ring fused on to another ring structure, experiments were carried out with ethylenethiocarbamide. This substance gave a sodium derivative with sodium ethoxide, but it was not necessary to isolate it, for it reacted *in situ* with ethyl (or methyl) chloroacetate in hot alcoholic solution, giving in good yield *ethyl* (or *methyl*) 4 : 5-*dihydroiminazole*-2-*thioglycollate* (IV).

$$\begin{array}{l}CH_2{\cdot}NH\\ CH_2\text{—}N\end{array}\!\!>C{\cdot}SNa + CH_2Cl{\cdot}CO_2Et = NaCl + \begin{array}{l}CH_2{\cdot}NH\\ CH_2\text{—}N\end{array}\!\!>C{\cdot}S{\cdot}CH_2{\cdot}CO_2Et. \quad (IV.)$$

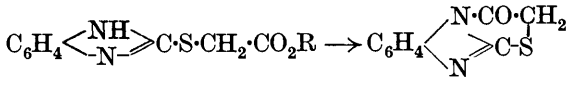
Efforts to effect ring closure with this compound so as to produce 4 : 5-*dihydroiminazole*-2-*thioglycollo*-1-*lactam* (V), were unsuccessful. It was found, however, that this substance could be formed in small yield by heating ethylenethiocarbamide with either ethyl or *n*-butyl chloroacetate in pyridine solution :

$$\begin{array}{l}CH_2{\cdot}NH\\ CH_2\text{—}N\end{array}\!\!>C{\cdot}SH + CH_2Cl{\cdot}CO_2R + C_5H_5N =$$
$$ROH + C_5H_5N,HCl + \begin{array}{l}CH_2{\cdot}N{\cdot}CO{\cdot}CH_2\\ CH_2{\cdot}N\end{array}\!\!>C{\cdot}S \quad (V.)$$

Experiments in which *o*-phenylenethiocarbamide was substituted for ethylenethiocarbamide gave much more definite results. The *sodium* derivative of this thiocarbamide was isolated in a pure state, but, as in previous cases, an alcoholic solution of the thiocarbamide to which 1 mol. of sodium ethoxide had been added was used.

This solution when heated for a short time with ethyl chloroacetate gave *ethyl benziminazole-2-thioglycollate* (VI); the *methyl* ester was prepared in the same way.

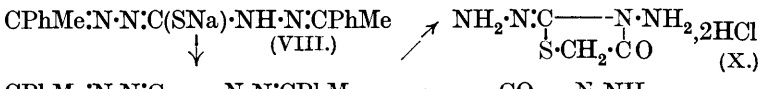
Ring-closure with these esters was effected by heating in benzene solution with sodium powder, the same substance, *benziminazole-2-thioglycollo-1-lactam* (VII), being produced from either ester.



(VI.) (VII.)

The yield was, however, only 25% and could not be improved.

The production of thiazoles from thiocarbohydrazones was next investigated. We had intended to make a general study of aldehydic and ketonic thiocarbohydrazones, but while this work was in progress a paper by Guha and Dey (*J. Indian Chem. Soc.*, 1925, **2**, 225) appeared, in which a number of thiocarbohydrazones were described. We have therefore modified our programme and have dealt with the application of these compounds in thiazole formation. A few thiocarbohydrazones which we had prepared are described in the experimental part. Diacetophenonethiocarbohydrazone, the *sodium* derivative (VIII) of which we prepared, was found to be the most suitable for use. It reacted in alcoholic solution with ethyl chloroacetate in presence of sodium ethoxide in the usual manner, giving 3-*phenylmethylmethyleneamino*-2 : 4-*diketotetrahydrothiazole*-2-*phenylmethylmethylenehydrazone* (IX) in excellent yield. This compound on hydrolysis with dilute hydrochloric acid gave



(VIII.) (X.) (IX.) (XI.)

acetophenone and 3-*amino*-2 : 4-*diketotetrahydrothiazole*-2-*hydrazone dihydrochloride* (X), an extremely deliquescent solid giving a *dibenzylidene* derivative. On the other hand, hydrolysis with concentrated hydrochloric acid yielded acetophenone, hydrazine hydrochloride, and 3-*amino*-2 : 4-*diketotetrahydrothiazole hydrochloride* (XI), also a very deliquescent solid which gave a *benzylidene* derivative. Both hydrochlorides were obtained in good yield, but attempts to prepare the pure bases from them were unsuccessful.

It is believed that the dicyclic systems described are new. This work will be continued.

Experimental.

Experiments with Acetone-δ-phenylthiosemicarbazone.

This substance was prepared by adding a slight excess of acetone to a boiling saturated alcoholic solution of the thiosemicarbazide and continuing the boiling for 15 minutes. It separated on cooling and was recrystallised from alcohol as glistening plates, m. p. 130°, soluble in alcohol, ether, and benzene; yield 90% (Found: N, 20·4, 20·3. $C_{10}H_{13}N_3S$ requires N, 20·3%). The sodium derivative could not be obtained in a pure state.

With Ethyl Chloroacetate.—The necessary quantity of sodium ethoxide in alcohol was added to a boiling saturated alcoholic solution of the δ-phenylthiosemicarbazone; after heating this solution for 5 minutes, the ester (1 mol.) was added. A vigorous reaction occurred with separation of a flocculent, yellow solid. After heating for ½ hour and cooling, the solid was collected, washed with warm water, and recrystallised from alcohol (charcoal). Fine, almost colourless needles of 2 : 4-*diketo*-3-*phenyltetrahydrothiazole*-2-iso*propylidenehydrazone* (I, R = H), m. p. 200°, were deposited; yield 70% (Found: N, 17·0, 16·9. $C_{12}H_{13}ON_3S$ requires N, 17·0%). The substance was hydrolysed by boiling for 3 hours with concentrated hydrochloric acid; the solution was then evaporated to dryness and the residue, after standing in a vacuum over soda-lime and concentrated sulphuric acid and then being washed with cold water to remove hydrazine hydrochloride, was recrystallised from water. The needles, m. p. 143°, were identical with 2 : 4-diketo-3-phenyltetrahydrothiazole (III, R = H), described by Evers (*Ber.*, 1888, **21**, 975) and by Lange (*ibid.*, 1879, **12**, 597); yield, small (Found: N, 7·3. Calc.: N, 7·3%).

With Ethyl α-Bromo-n-butyrate.—The reaction was carried out as before, the sodium bromide which separated in the heat being filtered off and washed with a little absolute alcohol; the filtrate and washings on cooling deposited 2 : 4-*diketo*-3-*phenyl*-5-*ethyltetrahydrothiazole*-2-iso*propylidenehydrazone* (I, R = Et), fine needles from alcohol, m. p. 131°, yield 75% (Found: N, 15·2, 15·3. $C_{14}H_{17}ON_3S$ requires N, 15·3%). Boiling with concentrated hydrochloric acid (3 hours) gave on cooling 2 : 4-*diketo*-3-*phenyl*-5-*ethyltetrahydrothiazole* (III, R = Et), feathery needles from water, m. p. 98°; yield small, extensive decomposition having occurred (Found: N, 6·5. $C_{11}H_{11}O_2NS$ requires N, 6·3%).

With Ethyl Phenylbromoacetate.—The reaction, carried out as in the first case, gave a flocculent precipitate which was collected after ¼ hour's heating, and washed with warm water. Recrystallisation from acetone gave 2 : 4-*diketo*-3 : 5-*diphenyltetrahydrothiazole*-

2-iso*propylidenehydrazone* (I, R = Ph), hair-like needles, m. p. 189°, yield 75%, insoluble in water and ether, sparingly soluble in alcohol (Found : N, 13·0, 13·0. $C_{18}H_{17}ON_3S$ requires N, 13·0%). Hydrolysis of this substance with concentrated hydrochloric acid did not lead to a definite result.

Experiments with Ethylenethiocarbamide.

This substance was prepared by Hofmann's method (*Ber.*, 1872, **5**, 242) and melted at 196° (Hofmann gives 194°) (Found : N, 27·5. Calc. : N, 27·5%). The sodium derivative was obtained in an impure state only.

An absolute alcoholic solution of the thiocarbamide was boiled for 10 minutes with sodium ethoxide (1 mol.); ethyl chloroacetate (1 mol.) was then added and the boiling continued for ½ hour. The solution, after being filtered while hot from sodium chloride, deposited on cooling *ethyl* 4 : 5-*dihydroiminazole*-2-*thioglycollate* (IV), needles from absolute alcohol, which began to decompose at about 160°, turning pink, and melted at 190° to a dark red liquid. It was very soluble in water and alcohol, insoluble in ether, light petroleum, and benzene. The best yield was obtained by using the minimum quantity of alcohol, as concentration of the mother-liquors caused decomposition (Found : N, 15·0; S, 17·2. $C_7H_{12}O_2N_2S$ requires N, 15·0; S, 17·0%). The formation of thioglycollic acid (recognised by Andreasch's test) and ethyl alcohol on hydrolysis with sodium hydroxide proved the presence of the group $\cdot S\cdot CH_2\cdot CO_2Et$ in this compound. The *methyl* ester (needles from absolute alcohol), prepared in the same way from methyl chloroacetate, showed a similar solubility; it began to decompose at about 170° and melted at 190° (Found : N, 16·0; S, 18·6. $C_6H_{10}O_2N_2S$ requires N, 16·1; S, 18·4%); best yield about 80%. Attempts in various ways to effect ring-closure with these esters were unsuccessful.

Ethyl chloroacetate was added to a hot pyridine solution of ethylenethiocarbamide (1 mol.) and the whole was boiled for ½ hour. The dark-coloured solution was evaporated to dryness under reduced pressure and the gummy residue dissolved in hot absolute alcohol. The crystals deposited on cooling gave, on recrystallisation from absolute alcohol, colourless plates of 4 : 5-*dihydroiminazole*-2-*thioglycollo*-1-*lactam* (V), m. p. 159°, yield 10—20% (Found : N, 19·7. $C_5H_6ON_2S$ requires N, 19·7%). It was readily soluble in water and alcohol, but insoluble in other common solvents, and showed Andreasch's test for thioglycollic acid after heating with alkali. The same substance was obtained by substituting *n*-butyl chloroacetate for the ethyl ester in the above method of preparation, the identity being established by a mixed m. p. determination. The

compound, in spite of repeated experiments, was obtained on these two occasions only; further attempts led apparently to complex mixtures.

Experiments with o-*Phenylenethiocarbamide.*

The *sodium* derivative, prepared by mixing a hot absolute alcoholic solution with sodium ethoxide (1 mol.) in alcohol, heating for 10 minutes, and then concentrating, was an almost white powder giving an alkaline reaction (Found: Na, 13·4. $C_7H_5N_2SNa$ requires Na, 13·3%).

An absolute alcoholic solution of the thiocarbamide was boiled with sodium ethoxide (1 mol.); ethyl chloroacetate was then added and the heating continued for ½ hour. After filtration from sodium chloride, the solution did not crystallise even on concentration; addition of a little water, however, caused turbidity and crystals separated on standing, more being deposited on further dilution. This substance, *ethyl benziminazole-2-thioglycollate* (VI), when freshly recrystallised from ether–light petroleum or dilute alcohol, melted at 73°, but in a very few minutes a change occurred and it then melted sharply at 97°, this modification, rhombic prisms, being quite stable; this may be a case of dimorphism, but the change was too rapid for investigation. Yield 85% (Found: N, 11·9; S, 13·7. $C_{11}H_{12}O_2N_2S$ requires N, 11·9; S, 13·6%). The *methyl* ester (yield 80%), prepared in the same way using methyl chloroacetate, showed a similar solubility and the same peculiarity as regards m. p. (metastable form at 72°; stable form, rhombic prisms, at 83°) (Found: N, 12·6; S, 14·4. $C_{10}H_{10}O_2N_2S$ requires N, 12·6; S, 14·4%). Neither ester developed any noticeable blackening on heating with very concentrated sodium hydroxide solution and subsequent addition of a lead salt, whilst *o*-phenylenethiocarbamide itself produced strong blackening under these conditions; this is in conformity with the presence of the group C–S–C in these esters.

Sodium powder (excess) was added to a hot benzene solution of the ethyl ester and the heating was continued for ½ hour under reflux on the water-bath. A deep yellow colour developed and a yellow solid was deposited; the benzene solution after decantation, filtration and evaporation to dryness left a residue which on recrystallisation from alcohol gave *benziminazole-2-thioglycollo-1-lactam* (VII), prismatic needles, m. p. 181°, yield 25% (Found: N, 14·7; S, 17·0; *M*, ebullioscopic in benzene, 187. $C_9H_6ON_2S$ requires N, 14·7; S, 16·8%; *M*, 190). There was a considerable amount of unchanged ester, and by carrying out the reaction on the water-bath the formation of the yellow compound was minimised. The methyl ester gave the same result.

Experiments with Thiocarbohydrazones.

Thiocarbohydrazide was prepared by the method of Stollé and Bowles (*Ber.*, 1908, **41**, 1099).

Diacetonethiocarbohydrazone, $(CMe_2{:}N{\cdot}NH)_2CS$, obtained by heating under reflux thiocarbohydrazide with excess of dry acetone for several hours and concentration of the solution, crystallised from alcohol–light petroleum in prismatic plates, m. p. 192° (decomp.), very soluble in alcohol and acetone; yield 90% (Found: N, 30·3. Calc. for $C_7H_{14}N_4S$: N, 30·1%).

Diacetophenonethiocarbohydrazone, $(CMePh{:}N{\cdot}NH)_2CS$, was deposited with production of a yellow colour by boiling the components (ketone in slight excess) in alcoholic solution for 1 hour. It crystallised from alcohol–chloroform in very pale yellow, fine, prismatic needles, m. p. 199° with darkening in colour from 175° upwards; very soluble in chloroform, soluble in benzene, sparingly soluble in alcohol, ether, and light petroleum, yield 90—95% (Found: N, 18·1; S, 10·3. Calc. for $C_{17}H_{18}N_4S$: N, 18·1; S, 10·3%).

These two substances have been prepared by Guha and Dey (*loc. cit.*) by methods differing in detail from ours. We found that in making the diacetone derivative prolonged boiling was necessary before the correct analytical results could be obtained, the nitrogen values otherwise being high. Guha and Dey give the m. p.'s of the diacetone and diacetophenone derivatives as 195° and 185°, respectively.

Bis-dibenzyl ketone thiocarbohydrazone, $[C(CH_2Ph)_2{:}N{\cdot}NH]_2CS$, was prepared by heating the components (ketone in slight excess) in alcoholic solution until a clear yellow solution resulted. The solid which separated on cooling crystallised from alcohol in fine, colourless needles, m. p. 143°, soluble in the usual solvents except light petroleum, yield 90% (Found: N, 11·4; S, 6·4. $C_{31}H_{30}N_4S$ requires N, 11·4; S, 6·5%).

Reactions with Diacetophenonethiocarbohydrazone.—The *sodium* derivative was obtained as a yellow powder by adding sodium ethoxide (1 mol.) to an absolute alcoholic suspension of the thiocarbohydrazone, heating for 10 minutes, and then precipitating the cooled yellow solution with ether. It was washed with ether and dried over sulphuric acid; it gave an alkaline aqueous solution (Found: Na, 6·9. $C_{17}H_{17}N_4SNa$ requires Na, 6·9%).

To a boiling alcoholic solution of the sodium derivative ethyl chloroacetate was added in very slight excess and the boiling continued for ½ hour. Sodium chloride was filtered off in the heat, and on cooling 3-*phenylmethylmethyleneamino*-2 : 4-*diketotetrahydrothiazole*-2-*phenylmethylmethylenehydrazone* (IX) was deposited; colourless needles from alcohol–benzene, m. p. 175°, insoluble in

water and light petroleum, soluble in alcohol, benzene, and chloroform; yield 85% (Found : N, 16·0; S, 9·3. $C_{19}H_{18}ON_4S$ requires N, 16·0; S, 9·1%). This compound was boiled under reflux for about 10 minutes with a slight excess of *N*-hydrochloric acid, the acetophenone was removed by decantation and ether-extraction, and the aqueous solution was evaporated to small bulk under reduced pressure and finally to dryness in a vacuum over sulphuric acid and soda-lime. The residue, *3-amino-2 : 4-diketotetrahydrothiazole-2-hydrazone dihydrochloride* (X), was a crystalline, extremely deliquescent solid which had to be manipulated in a dry atmosphere (Found : S, 14·5. $C_3H_6ON_4S,2HCl$ requires S, 14·6%). The *dibenzylidene* derivative, glistening plates from alcohol, melted at 138° (Found : N, 17·5. $C_{17}H_{14}ON_4S$ requires N, 17·4%).

The hydrolysis of the compound of m. p. 175° was carried a stage further by boiling in an open vessel with concentrated hydrochloric acid for about ½ hour. After removal of the acetophenone by ether, the aqueous solution was evaporated to dryness on the water-bath and finally in a vacuum over sulphuric acid and soda-lime. The residue after washing with dry ether was extracted with a little hot absolute alcohol, hydrazine hydrochloride remaining undissolved; the extract on evaporation in a vacuum over sulphuric acid gave a highly deliquescent solid, which was dried for several days in a vacuum over phosphoric anhydride. It was *3-amino-2 : 4-diketotetrahydrothiazole hydrochloride* (XI) (Found : S, 19·0, 19·1. $C_3H_4O_2N_2S,HCl$ requires S, 19·0%). The *benzylidene* derivative crystallised from alcohol in fine, colourless needles, m. p. 158° (Found : S, 14·6. $C_{10}H_8O_2N_2S$ requires S, 14·5%).

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