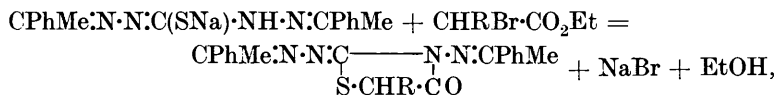


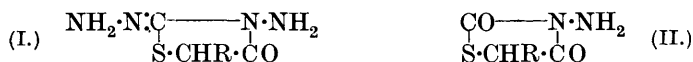
CLXXXV.—*Some Thiazole Derivatives. Part II.*

By HERBERT WILLIAM STEPHEN and FORSYTH JAMES WILSON.

IN continuation of Part I (J., 1926, 2531), we have found that diacetophenonethiocarbohydrazone reacts in alcoholic solution in presence of sodium ethoxide with ethyl α -bromopropionate, ethyl α -bromo-*n*-butyrate and ethyl phenylbromoacetate thus,



yielding 3-phenylmethylmethyleamino-2:4-diketo-5-methyl (or ethyl, or phenyl)tetrahydrothiazole-2-phenylmethylmethylenehydrazone (R = Me, Et, Ph respectively). Unlike the parent compound (R = H), these substances could not be satisfactorily hydrolysed by dilute or concentrated hydrochloric acid and it was not possible to obtain hydrochlorides of the bases (I) or (II), mixtures containing the acids CHR(SH)\cdot\text{CO}_2\text{H invariably resulting.

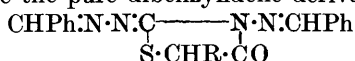


Attempts to prepare the bases (I) by reaction between thiocarbohydrazone, sodium ethoxide and the foregoing esters or ethyl chloroacetate * in alcoholic solution



* By the interaction of thiocarbohydrazone, ethyl chloroacetate and potassium hydroxide Guha and De (*J. Ind. Chem. Soc.*, 1925, 1, 141) obtained a substance quite different from that obtained by us.

did not give pure products; these, however, on treatment with benzaldehyde gave the pure dibenzylidene derivatives

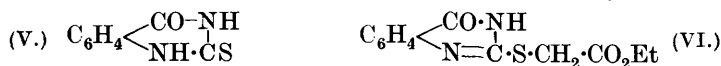


3-Amino-2 : 4-diketo-5-methyltetrahydrothiazole-2-hydrazone was obtained in the pure condition.

Further experiments were undertaken, but without success, to synthesise compounds containing a thiazole ring fused to another ring structure, two examples of which were given in Part I. *o*-Phenylenethiocarbamide in alcoholic solution in presence of sodium ethoxide reacted with ethyl α -bromopropionate and ethyl α -bromo-*n*-butyrate to give *ethyl benziminazolyl-2- α -thiolpropionate* and *ethyl benziminazolyl-2- α -thiol-*n*-butyrate*, respectively (III; R = Me and Et). Ring closure of these compounds in benzene solution by means of sodium wire or powder could not, however, be effected. *Benziminazolyl-2- α -thiolpropionic acid* and *benziminazolyl-2- α -thiol-*n*-butyric acid* have been prepared. *o*-Phenylenethiocarbamide and chloroacetic acid in boiling aqueous solution gave *benziminazole-2-thioglycollic acid* (formula as III; R = H).

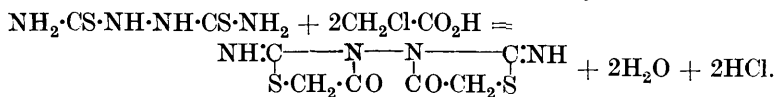


Methylenethiocarbamide failed to react with ethyl chloroacetate in presence of sodium ethoxide or pyridine. Trimethylenethiocarbamide reacted with ethyl chloroacetate in hot pyridine solution, giving *ethyl 1 : 4 : 5 : 6-tetrahydropyrimidine-2-thioglycollate* (IV); this decomposed on heating and was insoluble in benzene, the usual method of effecting ring closure thus being precluded. *o*-Benzoylenethiocarbamide (V) reacted with ethyl chloroacetate in alcoholic solution in presence of sodium ethoxide to give an oil which appeared to be a complex mixture; fractional distillation in a high vacuum failed to effect a separation, but from one of the fractions a small quantity of *ethyl 4-keto-3 : 4-dihydroquinazoline-2-thioglycollate* (VI)



was obtained.

Frerichs and Förster (*Annalen*, 1909, **371**, 257) and Frerichs and Höller (*ibid.*, 1913, **398**, 256) found that hydrazodithiocarbamic acid and chloroacetic acid gave in aqueous solution a compound which they regarded as 3 : 3-bis-*p*-thiohydantoin :



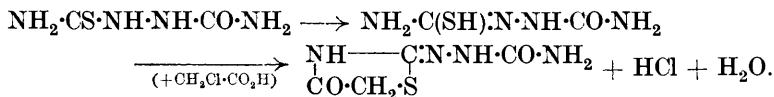
We obtained the same compound by heating hydrazodithiocarbonamide with ethyl chloroacetate in alcoholic solution in presence of sodium ethoxide. As noted by these authors, this compound, although insoluble in all the usual solvents, dissolved in sodium hydroxide solution and was precipitated on acidification; we found in addition that if the alkaline solution was boiled for a short time and then acidified, no precipitate formed, the solution containing thioglycollic acid as shown by Andreasch's test, rupture of the ring having occurred; this test proves the presence of the group C·S·C. Boiling with concentrated hydrochloric acid gradually dissolved the substance, hydrolysis occurring, the products being hydrazine hydrochloride and 2 : 4-diketotetrahydrothiazole. For this reason we ascribe to the compound the structure (VII) of 2 : 4-diketotetrahydrothiazole-2-ketazine in preference to that given by Frerichs, the hydrolysis taking place thus :



it is difficult to see how a compound of the alternative structure could undergo hydrolysis in this manner. The formation of the substance would then be represented thus :



Hydrazothiodicarbonamide, $\text{NH}_2 \cdot \text{CS} \cdot \text{NH} \cdot \text{NH} \cdot \text{CO} \cdot \text{NH}_2$, did not dissolve in alcoholic sodium ethoxide or pyridine. When it was boiled in aqueous solution with chloroacetic acid, a white precipitate, insoluble in solvents, soon appeared. This was 2 : 4-diketotetrahydrothiazole-2-semicarbazone, formed thus :



The yield was rather poor, and the mother-liquor contained 2 : 4-diketotetrahydrothiazole and semicarbazide hydrochloride, evidently produced by hydrolysis of a portion of the substance. Boiling with sodium hydroxide solution gave thioglycollic acid, showing the presence of the group C·S·C. The structure of the compound was proved by boiling with dilute hydrochloric acid, which effected hydrolysis into 2 : 4-diketotetrahydrothiazole and semicarbazide hydrochloride.

In continuation of investigations on the thermal decomposition of carbohydrazones (J., 1927, 107), the decomposition of some thiocarbohydrazones, thiosemicarbazones, and δ -phenylthiosemi-

carbazones on heating was studied, but without very definite results. Diacetophenonethiocarbohydrazone and bis-dibenzyl ketone thiocarbohydrazone were unaffected by prolonged boiling in alcoholic solution; at their melting points they gave ketazines as the only recognisable products. Acetone- and acetophenone-thiosemicarbazones and δ -phenylthiosemicarbazones when heated at or above their melting points yielded the ketazines as the only recognisable products together with ammonia or aniline and hydrogen sulphide.

EXPERIMENTAL.

Reactions with Diacetophenonethiocarbohydrazone.—A suspension of this substance in alcohol containing sodium ethoxide (1 mol.) was boiled for 10 minutes, ethyl α -bromopropionate (slightly more than 1 mol.) was then added, and the boiling continued for $\frac{1}{2}$ hour. The liquid was filtered hot from sodium bromide and on cooling deposited 3-phenylmethylmethyleneamino-2:4-diketo-5-methyltetrahydrothiazole-2-phenylmethylmethylenehydrazone, which crystallised from alcohol in prismatic needles, m. p. 150°; yield, 90% (Found: N, 15.5; S, 8.7. $C_{20}H_{20}ON_4S$ requires N, 15.4; S, 8.8%). 3-Phenylmethylmethyleneamino-2:4-diketo-5-ethyltetrahydrothiazole-2-phenylmethylmethylenehydrazone (needles from alcohol, m. p. 110°) was prepared in the same way from ethyl α -bromo-*n*-butyrate; yield, 90% (Found: N, 15.0; S, 8.4. $C_{21}H_{22}ON_4S$ requires N, 14.8; S, 8.5%). 3-Phenylmethylmethyleneamino-2:4-diketo-5-phenyltetrahydrothiazole-2-phenylmethylmethylenehydrazone, prepared in the same way from ethyl phenylbromoacetate, crystallised from alcohol in prismatic needles, m. p. 165°; yield, 80% (Found: N, 13.2; S, 7.4. $C_{25}H_{22}ON_4S$ requires N, 13.1; S, 7.4%). The three compounds are soluble in alcohol, ether, benzene and chloroform, and insoluble in light petroleum.

In a similar way there was produced from thiocarbohydrazone and ethyl chloroacetate a white solid, which was very soluble in alcohol, pyridine, and water and insoluble in other organic solvents and crystallised from alcohol in prismatic needles, m. p. 119–120°. It was apparently impure 3-amino-2:4-diketotetrahydrothiazole-2-hydrazone (I; R = H) (Found: N, 39.5; S, 23.1. $C_3H_6ON_4S$ requires N, 38.4; S, 21.9%), but repeated crystallisation with change of solvent failed to improve the analytical values. This substance gave a dibenzylidene derivative (m. p. 138°) identical with that previously prepared from the dihydrochloride (Part I, *loc. cit.*). 3-Amino-2:4-diketo-5-methyltetrahydrothiazole-2-hydrazone (I; R = Me) was prepared in a similar manner from ethyl α -bromopropionate with addition of a little dry benzene; after removal of sodium bromide in the heat and of a little unaltered thiocarbo-

hydrazide which separated on cooling, the solution was concentrated in an evacuated desiccator. The solid obtained crystallised from alcohol–light petroleum in rhombic plates, m. p. 100–101°, soluble in water and alcohol, insoluble in light petroleum; the yield was small (Found: S, 20.0. $C_4H_8ON_4S$ requires S, 20.0%). The *dibenzylidene* derivative (small prisms from aqueous alcohol, m. p. 114°) was prepared by heating the base with benzaldehyde in alcoholic solution (Found: N, 16.7. $C_{18}H_{16}ON_4S$ requires N, 16.7%). 3-Amino-2:4-diketo-5-ethyltetrahydrothiazole-2-hydrazone was obtained in poor yield by the preceding method from ethyl α -bromo-*n*-butyrate, crystallised from alcohol–light petroleum in glistening plates, m. p. 92–93°, and could not be obtained pure (Found: S, 16.1. $C_5H_{10}ON_4S$ requires S, 18.4%). It is very soluble in water and alcohol and insoluble in light petroleum. The *dibenzylidene* derivative forms prismatic needles, m. p. 106°, from alcohol (Found: N, 16.0. $C_{19}H_{18}ON_4S$ requires N, 16.0%).

Reactions with o-Phenylenethiocarbamide.—An absolute-alcoholic solution was boiled with sodium ethoxide (1 mol.) for 10 minutes, ethyl α -bromopropionate (1 mol.) was then added, and the boiling continued for $\frac{1}{2}$ hour. The solution after removal of sodium bromide was concentrated considerably and then made turbid by addition of water. The *ethyl benziminazolyl-2- α -thiolpropionate* (III; R = Me) which separated on standing crystallised from ether–light petroleum in prismatic plates, very soluble in ether, alcohol, and chloroform and insoluble in water and light petroleum. Like the corresponding 2-thioglycollate (Part I), this substance appeared to exhibit dimorphism; the stable variety melted at 100° (yield, 90%) (Found: N, 11.3; S, 12.8. $C_{12}H_{14}O_2N_2S$ requires N, 11.2; S, 12.8%). No blackening was produced on long heating and standing with alkaline lead acetate solution, the absence of the group C:S being thus indicated. Hydrolysis with concentrated hydrochloric acid appeared to give impure benziminazolyl-2- α -thiolpropionic acid, which was subsequently obtained pure by another reaction (p. 1420). *Ethyl benziminazolyl-2- α -thiol-*n*-butyrate* (III; R = Et), prepared in the same way from ethyl α -bromo-*n*-butyrate, showed a similar solubility and also appeared to exhibit dimorphism; the stable variety (long, prismatic needles from ether–light petroleum) melted at 108–109° (yield, 90%) (Found: N, 10.6; S, 12.3. $C_{13}H_{16}O_2N_2S$ requires N, 10.6; S, 12.1%). Hydrolysis with concentrated hydrochloric acid gave *benziminazolyl-2- α -thiol-*n*-butyric acid* [glistening plates from water, m. p. 176° (decomp.)], which had an acid reaction and was soluble in alcohol and insoluble in benzene and chloroform (Found: N, 11.9; S, 13.7. $C_{11}H_{12}O_2N_2S$ requires N, 11.9; S, 13.6%).

Ring closure was attempted with both esters. With the thiol-

propionate sodium wire appeared to give promising results. The ester was heated in dry benzene solution with an excess of the metal; gas was slowly evolved and a yellowish solid appeared, which was occasionally detached from the surface of the metal. After $1\frac{1}{2}$ hours' heating, the benzene, which contained very little dissolved matter, was decanted, and the solid was dried in a desiccator and, after a mechanical removal of most of the sodium, dissolved in absolute alcohol. The warm solution was neutralised with a few drops of concentrated hydrochloric acid and, after removal of sodium chloride, concentrated in an evacuated desiccator. The solid obtained crystallised from absolute alcohol–light petroleum, melted at 179° (decomp.), and was *benziminazolyl-2- α -thiolpropionic acid* (Found: N, 12.5; S, 14.5. $C_{10}H_{10}O_2N_2S$ requires N, 12.6; S, 14.4%).

Since it was thought that this acid had been formed by hydration of a dicyclic structure, the above procedure was modified by neutralising the alcoholic solution with dry gaseous hydrogen chloride instead of the aqueous acid; this was attended, even on ice-cooling, with the production of a very disagreeable odour resembling that of mercaptan. After removal of sodium chloride and concentration in a desiccator a yellow gum remained, a hot acetone solution of which deposited, on cooling, a white, amorphous powder, m. p. $118-119^\circ$ (Found: N, 10.3%); this was very soluble in water and the solution had an acid reaction. The substance was not the dicyclic compound and was not identified. The experiment was repeated with the thiol-*n*-butyrate; this gave an amorphous powder (from acetone; m. p. 120°) acidic in reaction (Found: N, 9.7; S, 10.2%), which was not the dicyclic compound.

Benziminazole-2-thioglycollic acid was obtained by boiling under reflux for 3 hours *o*-phenylenethiocarbamide and chloroacetic acid (1 mol.) in aqueous solution. The crystals deposited on cooling melted indefinitely. The first crop obtained by recrystallisation from water consisted of needles, m. p. 215° , of the acid; subsequent crops still melted over a range of temperature (Found: N, 13.5. $C_9H_8O_2N_2S$ requires N, 13.5%).

Reaction with Trimethylenethiocarbamide (Schacht, *Arch. Pharm.*, 1897, **235**, 461).—This substance did not react with ethyl chloroacetate in alcoholic solution containing sodium ethoxide; it reacted, however, with this ester (1 mol.) in boiling pyridine solution. After $\frac{1}{2}$ hour's boiling, the dark solution on cooling deposited a brownish solid which crystallised from absolute alcohol in small needles consisting of *ethyl 1 : 4 : 5 : 6-tetrahydropyrimidine-2-thioglycollate* (IV) (Found: N, 13.8; S, 15.8. $C_8H_{14}O_2N_2S$ requires N, 13.9; S, 15.8%). It was insoluble in the usual solvents except water and alcohol and

melted at 256°, decomposing from 200° upwards. Boiling with sodium hydroxide gave thioglycollic acid, which was detected in the usual way.

Reaction with Benzoylenethiocarbamide (Rupe, *Ber.*, 1897, **30**, 1089).—To a boiling absolute-alcoholic solution of the substance, sodium ethoxide (1 mol.) in alcohol was added, and after 10 minutes ethyl chloroacetate (1 mol.). After boiling for $\frac{1}{2}$ hour, the solution was filtered from sodium chloride and evaporated in a vacuum; a mobile oil remained. This was fractionally distilled under very low pressure, but the temperature rose throughout without any indication that a true fractionation was being effected, and analyses of various fractions gave no definite information. Air was bubbled for a short time through one of the higher-boiling fractions; a small quantity of solid consisting of *ethyl 4-keto-3 : 4-dihydroquinazoline-2-thioglycollate* (VI) (fine needles from absolute alcohol, m. p. 149°) was deposited (Found : S, 12.1. $C_{12}H_{12}O_3N_2S$ requires S, 12.1%). A benzene solution of the oil, on being heated with sodium wire, slowly evolved gas with formation of tar.

Reaction with Hydrazodithiodicarbonamide (Freund and Wischewiansky, *Ber.*, 1893, **26**, 2877).—To a hot absolute-alcoholic solution, sodium ethoxide (2 mols.) in alcohol was added, and after 10 minutes ethyl chloroacetate (rather more than 2 mols.). After $\frac{1}{2}$ hour's heating, the bulky white precipitate was collected and, being insoluble in solvents, was washed with water (Found : N, 24.1; S, 27.6. $C_6H_6O_2N_4S_2$ requires N, 24.3; S, 27.8%). The yield was theoretical. This substance, identical with that obtained by Frerichs (*loc. cit.*), decomposed at a high temperature without melting and is regarded by us as 2 : 4-diketotetrahydrothiazole-2-ketazine (VII). It gradually dissolved in boiling concentrated hydrochloric acid, and evaporation then gave a solid, from which hot chloroform extracted 2 : 4-diketotetrahydrothiazole, which was identified by comparison with an authentic specimen; the residue was hydrazine hydrochloride, which was identified by conversion into benzylideneazine. The compound prepared by Frerichs gave the same products when boiled with concentrated hydrochloric acid.

Reaction with Hydrazothiodicarbonamide (Freund and Schander, *Ber.*, 1896, **29**, 2508).—This substance was boiled for a few minutes in aqueous solution with chloroacetic acid (1 mol.); a crystalline precipitate rapidly formed and was filtered off when cold. This was 2 : 4-diketotetrahydrothiazole-2-semicarbazone and was insoluble in organic solvents and only sparingly soluble in hot water, from which it separated in small, glistening plates, m. p. 221—222° (complete decomp.) after becoming brown at 210° (yield, 35%) (Found : N, 32.0; S, 18.5. $C_4H_6O_2N_4S$ requires N, 32.2; S, 18.4%). Hydro-

lysis with sodium hydroxide gave thioglycollic acid, which was recognised in the usual way. The substance was boiled with dilute hydrochloric acid, and the residue obtained on evaporation was extracted with hot chloroform, which dissolved 2:4-diketotetrahydrothiazole, leaving semicarbazide hydrochloride.

Acetophenone- δ -phenylthiosemicarbazone, $\text{CPhMe:N}\cdot\text{NH}\cdot\text{CS}\cdot\text{NHPh}$ (fine, pale yellow, prismatic needles from alcohol-benzene, m. p. 195°) was prepared by boiling the two components in alcoholic solution for $\frac{1}{2}$ hour and was deposited in 95% yield on cooling (Found: N, 15.6; S, 11.9. $\text{C}_{15}\text{H}_{15}\text{N}_3\text{S}$ requires N, 15.6; S, 11.9%).

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