DERIVATIVES OF THIAZOLE

BY

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This Research was carried out in The Royal Technical College, GLASGOW.

To the Governors of that College and to the Department of Scientific and Industrial Research the Author tenders his sincere thanks for Scholarships, during the tenure of which, the investigation was made.

He also wishes to record his great gratitude to Professor Forsyth J. Wilson, the Director and Supervisor of the Research, for the interest he has shown and for his kindly advice throughout the course of the work.

INDEX

ABBREVIATIONS

Amer. Chem. J.	American Chemical Journal.
Ann.	Justus Liebig's Annalen der Chemie.
Arch. Pharm.	Archiv der Pharmazie.
Ber.	Berichte der Deutschen chemischen Gesellschaften.
Bull. Soc. chim.	Bulletin de la Société chimique de France.
J. Amer. Chem. Soc.	Journal of the American Chemical Society.
J. Chem. Soc.	Journal of the Chemical Society.
J. Indian Chem. Soc.	Journal of the Indian Chemical Society.
Monatsh.	Monatshefte für Chemie und verwandte Thiele anderer Wissenschaften.

SUMMARY

THE investigation described in this thesis forms one portion of an extensive programme of research being carried on in the Department of Organic Chemistry of The Royal Technical College, Glasgow. The work is under the general supervision of Professor Forsyth J. Wilson, and includes the reactions of the following classes of compounds:-

Semicarbazones, $\begin{matrix}R\\R'\end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2$

Thiosemicarbazones, $\begin{matrix}R\\R'\end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2$

Semioxamazones, $\begin{matrix}R\\R'\end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}NH_2$

Carbohydrazones, $\begin{matrix}R\\R'\end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}N{:}C\!<\!\begin{matrix}R\\R'\end{matrix}$

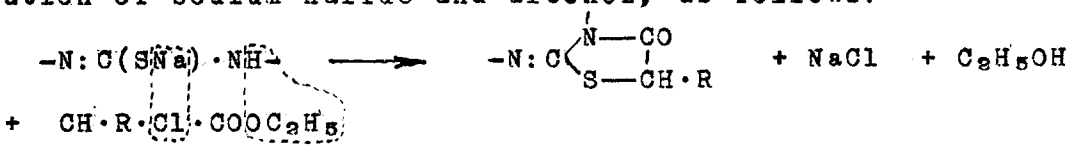
Thiocarbohydrazones, $\begin{matrix}R\\R'\end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}N{:}C\!<\!\begin{matrix}R\\R'\end{matrix}$

The Author has dealt exclusively with those classes containing sulphur, - thiosemicarbazones, thiocarbohydrazones, and other closely related compounds which may be generally called THIOCARBAMIDES; i.e. compounds containing the group NH·CS·NH. The particular aim of the research has been the application of such compounds to THIAZOLE - formation.

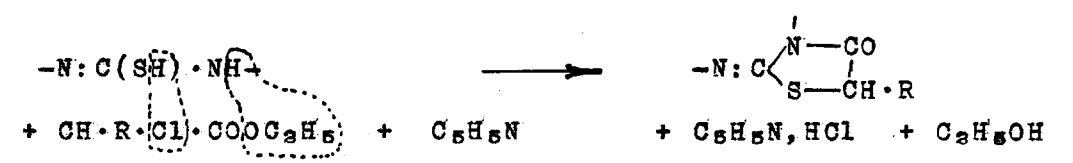
By virtue of the group NH·CS·NH, these thiocarbamides are capable of reacting with sodium ethoxide to form

sodium derivatives in which the metal is apparently attached to sulphur, $-N:C(SNa)\cdot NH-$.

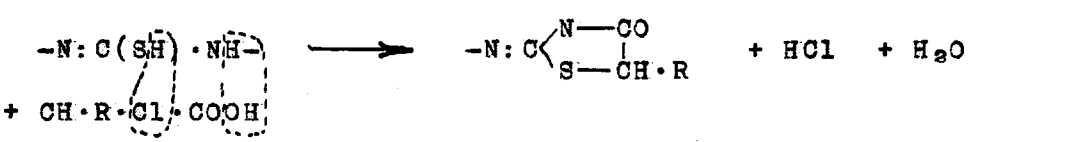
When this group reacts with ESTERS of α-HALOGENO-ACIDS, ring-closure has been found to take place in certain cases by elimination of sodium halide and alcohol, as follows:-

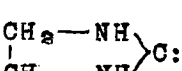


In some cases, sodium halide only was eliminated in the reaction, and ring-closure of the resulting open-chain compound was effected by subsequent treatment in benzene solution with sodium; or, by carrying out the original reaction in presence of pyridine instead of sodium ethoxide, thus:-



With other thiocarbamides, reactions have taken place directly with α-HALOGENO-ACIDS in aqueous solution, to form the open-chain compound through loss of hydrogen halide only, or the thiazole by elimination of both hydrogen halide and water, thus:-



The reactions with certain cyclic thiocarbamides such as ethylenethiocarbamide,  and

ortho-phenylenethiocarbamide, $C_6H_4\langle^{NH}_{NH}\rangle C:S$ have given rise to dicyclic systems in which there is a thiazole-ring fused on to another ring-structure: such dicyclic systems are believed to be new.

As an interesting side-line, an investigation of the thermal decomposition of thiosemicarbazones and thiocarbohydrazones has been made.

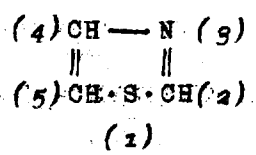
NOTE. In the Theoretical and Experimental sections, *italics* type has been used for the names of new compounds.

NOMENCLATURE

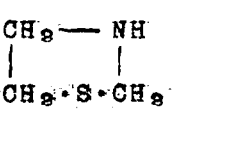
The Nitrogen-atoms in Thiosemicarbazide are distinguished by letters, as follows:-

$$\underset{\delta}{NH_2}\cdot\underset{\gamma}{NH}\cdot CS\cdot\underset{\alpha}{NH_2}$$

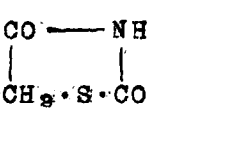
Most of the compounds prepared in the course of the work can be conveniently regarded as derived from Thiazole, and named accordingly; the conventional system of numbering has been adopted, and the following scheme shows the relation of 2:4-diketotetrahydrothiazole to thiazole:-



Thiazole



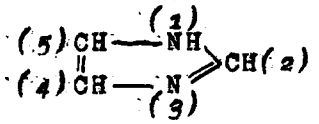
2:3:4:5-tetrahydrothiazole



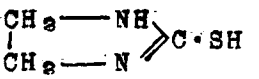
2:4-diketotetrahydrothiazole

Several of the thiocarbamides used, however, are more conveniently regarded as derivatives of the parent substances Iminazole, Pyrimidine, Benziminazole and Quinazoline. The new compounds now prepared have been named in this manner and the following scheme shows the system of numbering for each of these classes:-

(a)

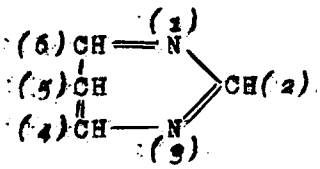


Iminazole

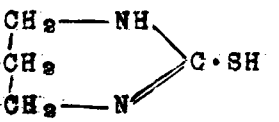


2-Mercapto-4:5-dihydro-iminazole
(Ethylenethiocarbamide)

(b)

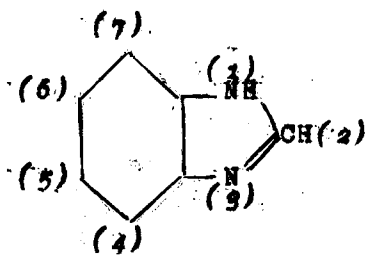


Pyrimidine

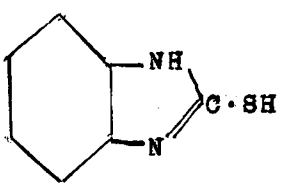


2-Mercapto-1:4:4:6-tetra-hydropyrimidine
(Trimethylenethiocarbamide)

(c)

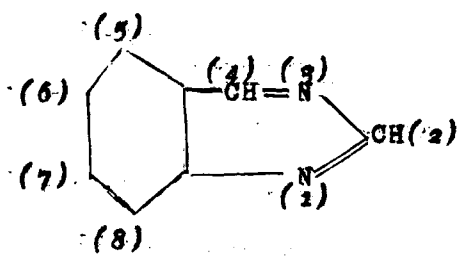


Benziminazole

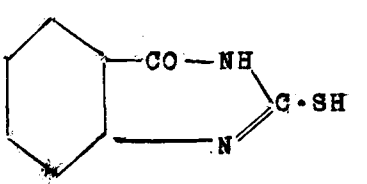


2-Mercaptobenziminazole
(o-Phenylenethiocarbamide)

(d)



Quinazoline



2-Mercapto-4-keto-3:4-dihydroquinazoline
(o-Benzoylenethiocarbamide)

THEORETICAL

THIOSEMICARBAZONES of numerous aldehydes and ketones have been prepared chiefly by Neuberg and Neimann (*Ber.*, 1902, **35**, 2409) and also by Freund and Schander (*ibid.*, 2602).

These thiosemicarbazones yield metallic derivatives in which the metal is apparently attached to sulphur,

$$\begin{matrix}R\\R'\end{matrix}\!\!>\!C{:}N\cdot NH\cdot C(SM)\cdot NH \qquad \text{or} \qquad \begin{matrix}R\\R'\end{matrix}\!\!>\!C{:}N\cdot N{:}C(SM)\cdot NH_2$$

Wilson and Burns (*J. Chem. Soc.*, 1922, **121**, 870) prepared the sodium derivative of acetonethiosemicarbazone and investigated the action of halogen-compounds on it.

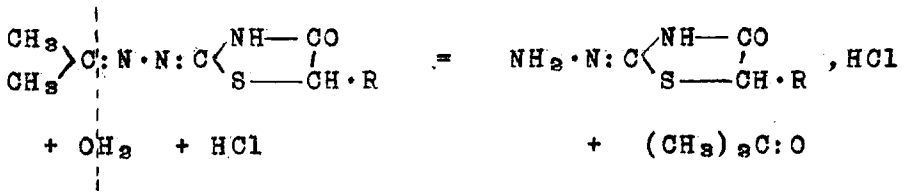
In a later paper (*J. Chem. Soc.*, 1923, **123**, 799) the action of esters of α-halogeno-acids on the sodium derivative of acetonethiosemicarbazone was described; such esters yielded ψ-thiohydantoin derivatives of a new type, thus:-

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{:}N\cdot N{:}C(SNa)\cdot NHH + CH\cdot R\cdot Br\cdot CO\cdot OC_2H_5 = \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{:}N\cdot N{:}C\begin{matrix}NH-CO\\S-CH\cdot R\end{matrix} + NaBr + C_2H_5OH$$

Hydrolysis of these compounds by boiling with concentrated hydrochloric acid removed acetone and hydrazine, and gave derivatives of 2:4-diketotetrahydrothiazole, thus:-

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{:}N\cdot N{:}C\begin{matrix}NH-CO\\S-CH\cdot R\end{matrix} + OH_2 + H_2O + 2HCl = OC\begin{matrix}NH-CO\\S-CH\cdot R\end{matrix} + (CH_3)_2C{:}O + NH_2\cdot NH_2, 2HCl$$

Hydrolysis for a much shorter time with 2-N hydrochloric acid removed acetone only, and the intermediate hydrazone was obtained as the hydrochloride:-



The Author has extended the reaction with esters of α-halogeno-acids in the first instance to the *sodium* derivative of *acetone-δ-phenylthiosemicarbazone*, and then to various other thiocarbamides.

In those cases where a two-stage hydrolysis on the lines indicated has been theoretically possible, this has been attempted.

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1. δ-PHENYLTHIOSEMICARBAZIDE, $NH_2 \cdot NH \cdot CS \cdot NHC_6H_5$

δ-Phenylthiosemicarbazones are prepared directly from δ-phenylthiosemicarbazide by heating in alcoholic solution with the required aldehyde or ketone,

$$\begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}O + NH_2 \cdot NH \cdot CS \cdot NHC_6H_5 = \begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}N \cdot NH \cdot CS \cdot NHC_6H_5 + H_2O$$

Benzaldehyde-δ-phenylthiosemicarbazone which is described by Pulvermacher (*Ber.*, 1884, 27, 615) was prepared. Investigation showed that the sodium derivative of this substance did not readily react with ethyl chloroacetate. Accordingly, *acetone-δ-phenylthiosemicarbazone* and *acetophenone-δ-phenylthiosemicarbazone*, which have not been previously described were prepared in good yield; the former was used for the reactions with the various esters.

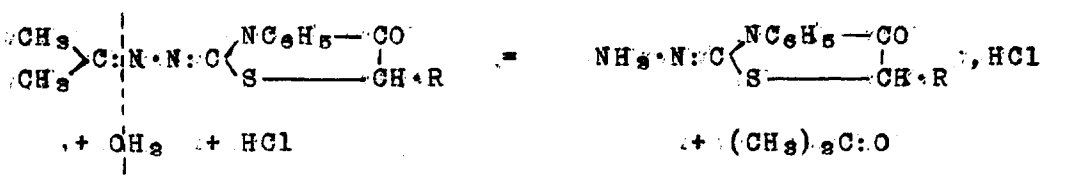
The *sodium* derivative of acetone-δ-phenylthiosemicarbazone was formed in solution by heating acetone-δ-phenylthiosemicarbazone with sodium ethoxide (1 mol.) in alcohol. The derivative could not be isolated in a pure state, but in alcoholic solution it reacted with esters of α-halogeno-acids, giving in excellent yield the 2-*iso*propylidenehydrazone of a 2:4-diketotetrahydrothiazole.

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C{:}N \cdot N{:}C(SNa) \cdot NHC_6H_5 + CH \cdot R \cdot Br \cdot COOC_2H_5 = \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C{:}N \cdot N{:}C\!<\!\begin{matrix} NC_6H_5 - CO \\ | \quad\quad | \\ S \quad\quad CH \cdot R \end{matrix} + NaBr + C_2H_5OH$$

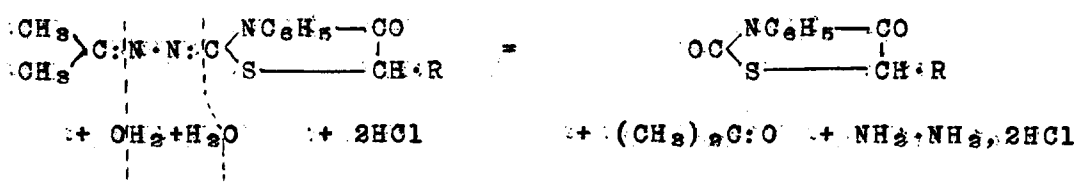
The esters used were ethyl chloroacetate, ethyl α-bromo-*n*-butyrate and ethyl phenylbromoacetate, giving *2:4-diketo-3-phenyl-5-R-tetrahydrothiazole-2-isopropylidenehydrazone*, where *R*=H, C_2H_5, and C_6H_5 respectively.

By analogy with the work of Wilson and Burns (*loc. cit.*), it was expected that these compounds would be hydrolysed in two stages:

(1) with 2-N hydrochloric acid



(2) with concentrated hydrochloric acid



In the present instances, however, the two stages of hydrolysis were less sharply distinguished.

Boiling with 2-N hydrochloric acid removed acetone which was proved in each case by the nitroprusside and iodoform tests. The other product of the hydrolysis appeared to be a mixture in each case, and none of the hydrochlorides of the intermediate hydrazones were isolated.

Hydrolysis with concentrated hydrochloric acid gave more definite results; each of the *iso*propylidene derivatives gave a small yield of the corresponding 2:4-diketo-3-phenyl-

5-R-tetrahydrothiazole, $OC\langle^{NC_6H_5-CO}_{S-CH\cdot R}$.

The yield of these products could not be improved, as the hydrolysis was evidently accompanied by extensive decomposition; aniline hydrochloride, $C_6H_5NH_2,HCl$, was identified, and the presence of this substance indicated rupture of the thiazole-ring.

2: 4-Diketo-3-phenyl-5-ethyltetrahydrothiazole, $OC\langle^{NC_6H_5-CO}_{S-CH\cdot C_2H_5}$ has not been previously described, but the 5=H and the 5=C_6H_5 compounds have been previously prepared by other methods.

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2. α-PHENYLTHIOSEMICARBAZIDE, $NHC_6H_5\cdot NH\cdot CS\cdot NH_2$

Having no free $NH_2\cdot NH$ group, this compound does not react with aldehydes or ketones to form phenylthiosemicarbazones. Accordingly, attempts to apply it to thiazole-formation were made directly.

An alcoholic solution of the sodium derivative was prepared in the usual method, by treating α-phenylthiosemicarbazide with sodium ethoxide(1 mol.) in alcoholic solution. The addition of ethyl chloroacetate merely caused a reaction with the sodium ethoxide; sodium chloride was precipitated and unaltered α-phenylthiosemicarbazide was recovered from the solution.

The other general methods of thiazole-formation were

likewise unsuccessful. Heating with ethyl chloroacetate in pyridine solution did not bring about a reaction, the thiosemicarbazide being recovered unchanged.

No reaction took place on boiling with chloracetic acid in aqueous solution.

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8. METHYLENETHIOCARBAMIDE, $CH_2\langle^{NH}_{NH}\rangle C:S$

Owing to its extreme insolubility, it was exceedingly doubtful if this substance could be applied to thiazole-formation. Experiment confirmed this doubt; the substance failed to dissolve or undergo any change even on prolonged boiling in alcoholic sodium ethoxide, pyridine with ethyl chloroacetate, or an aqueous solution of chloracetic acid.

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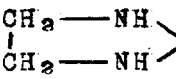
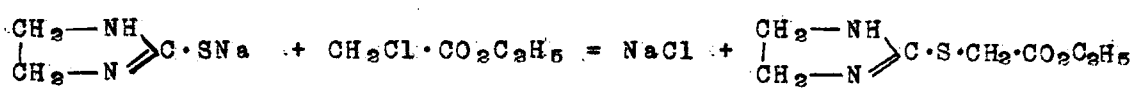
4. ETHYLENETHIOCARBAMIDE, 

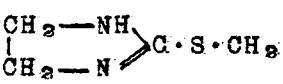
Being an easily soluble compound, ethylenethiocarbamide was investigated with respect to thiazole-formation in the hope of obtaining a dicyclic compound in which there was a thiazole-ring fused on to another ring structure.

An alcoholic solution of the sodium derivative of ethylenethiocarbamide was prepared in the usual manner, but attempts to isolate this derivative by precipitation resulted in unaltered thiocarbamide.

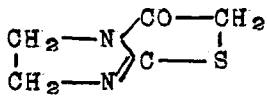
No further attempts were made to obtain the sodium derivative, as it was found to react in alcoholic solution with ethyl chloroacetate, giving in good yield *ethyl 4:5-dihydroiminazole-2-mercaptoacetate*, sodium chloride only being eliminated:

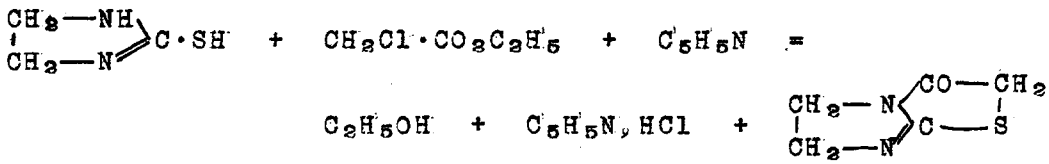


The reaction with methyl chloroacetate took place in a similar manner, giving the corresponding *methyl* ester.

Attempts were made to hydrolyse with sodium hydroxide in order to obtain the free acid  from the esters, but such treatment ruptured the molecule and the formation of mercaptoacetic acid, $CH_2(SH)\cdot CO_2H$ was proved; this, however, afforded proof of the presence of the group $\cdot S\cdot CH_2\cdot CO_2C_2H_5$ (or CH_3) in the compounds.

Since the reactions with the esters of chloroacetic acid had resulted in the formation of open-chain compounds, attempts were made to effect ring-closure by heating ethyl (or methyl) 4:5-dihydroiminazole-2-mercaptoacetate in presence of toluene, amyl alcohol or solvent naphtha. The esters did not dissolve, and except for partial decomposition, were unaltered. Owing to their insolubility in benzene, a method of effecting ring-closure by heating in benzene solution with sodium (later used with success in the case of other open-chain compounds, compare pages 18 and 61) was not available.

The dicyclic compound *4:5-dihydroiminazole-2-mercaptoacetate-1-lactam*,  was obtained by a modification of the original reaction. Ethylenethiocarbamide and ethyl chloroacetate were heated together (in molecular proportions) in pyridine solution, when the following reaction took place:-



The yield was small and the compound was obtained pure on one occasion only; subsequent experiments gave rise to mixtures from which no pure substance could be isolated.

Hydrolysis with sodium hydroxide solution gave, as in the case of the open-chain esters, mercaptoacetic acid.

The constitution of the lactam compound was definitely

established by preparing it from ethylenethiocarbamide and a different ester of chloracetic acid. Methyl chloroacetate and *l*-menthyl chloroacetate failed to react with ethylenethiocarbamide in pyridine solution, but *n*-butyl chloroacetate gave a small yield of the same dicyclic compound, thus proving that ring-closure had taken place by the elimination of ethyl or *n*-butyl alcohol.

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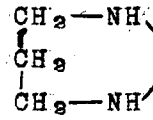
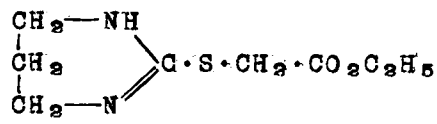
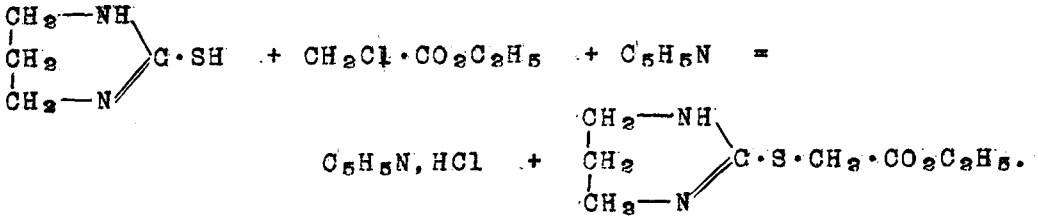
5. TRIMETHYLENETHIOCARBAMIDE, 

Owing to the difficulty of preparation of trimethylenediamine from which this thiocarbamide is prepared, only a small amount was obtainable. Its reactions showed, however, that the increase from two to three methylene groups caused it to be less reactive than ethylenethiocarbamide; a reaction with ethyl chloroacetate took place only in pyridine solution, and even under these conditions, the open-chain, and not the dicyclic compound was formed.

In the usual reaction in presence of sodium ethoxide, ethyl chloroacetate merely reacted with the ethoxide, and trimethylenethiocarbamide was recovered unchanged from the solution. In pyridine solution, trimethylenethiocarbamide and ethyl chloroacetate reacted to give *ethyl 1:4:5:6-tetrahydropyrimidine-2-mercaptoacetate*, 



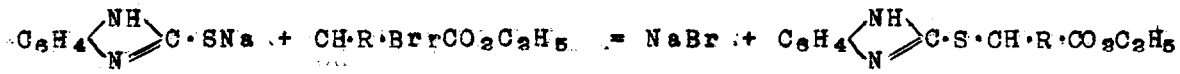
The formation of mercaptoacetic acid on hydrolysis with sodium hydroxide solution proved, as before, the presence of the group $\cdot S \cdot CH_2 \cdot CO_2C_2H_5$.
Owing to the insolubility of the ester in benzene, the use of sodium to bring about ring-closure was again precluded.

---

6. *ortho*-PHENYLENETHIOCARBAMIDE, $C_6H_4\langle NH \rangle C:S$

This thiocarbamide reacted with sodium ethoxide in alcoholic solution in the usual manner to form the *sodium* derivative, $C_6H_4\langle N \rangle C \cdot SNa$. This derivative was isolated in a pure state.

It reacted in alcoholic solution with esters of α-halogeno-acids in a similar manner to the sodium derivative of ethylenethiocarbamide; sodium halide only was eliminated, resulting in monocyclic compounds.



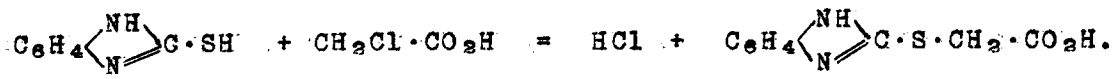
The esters employed were ethyl chloroacetate, methyl chloroacetate, ethyl α-bromopropionate and ethyl α-bromo-*n*-butyrate. It was found with the series of compounds formed, and also

later in studying the reactions of thiocarbohydrazones, that the products derived from the esters of chloracetic acid differed considerably in reactions from those derived from esters of the higher halogeno-acids. For this reason it is convenient to consider separately the compounds from ethyl and methyl chloroacetates.

By the foregoing reaction ethyl or methyl chloroacetate gave in 80 to 85% yield *ethyl(or methyl) benziminazole-2-mercaptoacetate*, $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH_2\cdot CO_2C_2H_5$(or CH_3). Both compounds melted below 100°, and exhibited a phenomenon which may be a case of dimorphism; when freshly crystallised (irrespective of the solvent employed) the melting-point was 10 to 20° lower than the stable melting-point. The change to the stable form took place in a very few minutes and was too rapid to permit of investigation by ordinary methods.

Hydrolysis of the compounds with sodium hydroxide solution or hydrochloric acid did not rupture the molecule and cause the formation of mercaptoacetic acid as in the case of the corresponding compounds from ethylene- and trimethylene-thiocarbamides. Both esters appeared to be hydrolysed to *benziminazole-2-mercaptoacetic acid*, $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH_2\cdot CO_2H$. Formed in this manner, the acid was very impure and could not be completely purified by crystallisation; it was

subsequently prepared pure, however, by the interaction of *o*-phenylenethiocarbamide and chloracetic acid in aqueous solution:-



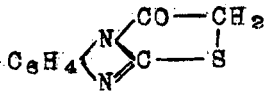
In consequence of the great stability of this acid, positive evidence of the presence of the group C·S·C in the esters could not be obtained; comparative experiments with *o*-phenylenethiocarbamide, however, indicated that the group C:S was not present in the esters. Neither ester developed any noticeable blackening on heating with very concentrated sodium hydroxide solution and the subsequent addition of a lead salt, whilst *o*-phenylenethiocarbamide itself produced strong blackening under these conditions.

By analogy with the reactions of ethylenethiocarbamide, attempts were made to form the dicyclic compound by heating *o*-phenylenethiocarbamide and ethyl chloroacetate in pyridine solution; no reaction took place, the thiocarbamide being recovered unchanged.

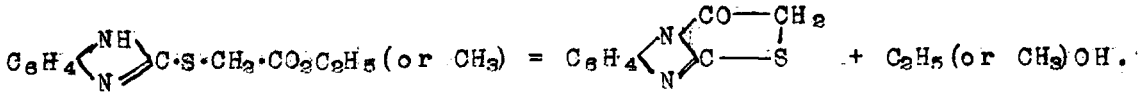
Attention was then directed to the possibility of removing 1 molecule of alcohol from the open-chain esters, thereby causing ring-closure. For this purpose, the method using sodium(previously referred to) was successful.

Ethyl(or methyl) benziminazole-2-mercaptoacetate was heated in benzene solution with excess of sodium powder; the same

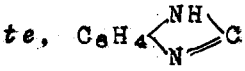
substance, *benziminazole-2-mercaptoaceto-1-lactam*,



was produced from both esters, definitely proving ring-closure by elimination of ethyl(or methyl) alcohol:-



The yield of the dicyclic compound was only 25% in each case, and could not be improved; a considerable amount of the ester was recovered unchanged at the end of the experiment.

Ethyl α-bromopropionate and ethyl α-bromo-*n*-butyrate reacted with the sodium derivative of *o*-phenylenethiocarbamide giving in 90% yield *ethyl benziminazole-2-α-mercaptopropionate*,  and *ethyl benziminazole-2-α-mercapto-n-butyrate*,  respectively. In variation of melting-point, both these compounds exhibited the same phenomenon as was observed with the previous members of the series.

Hydrolysis with sodium hydroxide solution or concentrated hydrochloric acid again failed to decompose the esters to the corresponding mercapto-acid, but as in the former cases, experimental evidence favoured the C·S·C structure rather than the alternative C:S.

Hydrolysis with concentrated hydrochloric acid gave with each ester the corresponding free acid, but only one of them,

benziminazole-2-α-mercapto-n-butyric acid,

$C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH(C_2H_5)\cdot CO_2H$, was obtained pure by this method. The free acid corresponding to the other ester was, however, isolated in the course of a different reaction (compare below and page 65).

Attempts to obtain the dicyclic compound by treatment with sodium did not succeed in the case of these two esters. The products of the reactions were insoluble in benzene and could not be easily removed from the excess of sodium powder. A modification of the method was also used, sodium wire being substituted for the powder; the most of the sodium could then be removed mechanically and final traces decomposed in alcoholic solution with hydrochloric acid. The reactions, which are fully described in the experimental section (compare page 64 *et seq.*), appeared to be very complicated. In no case was the dicyclic compound formed, but one reaction with ethyl benziminazole-2-α-mercaptopropionate gave *benziminazole-2-α-mercapto-propionic acid,* $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH(CH_3)\cdot CO_2H$, which was obtained impure by the hydrolysis of its ethyl ester.

While the main products of the reactions with both esters were isolated and analysed, they were not identified; they were totally different from the dicyclic compounds expected.

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7. *ortho*-BENZOYLENETHIOCARBAMIDE, $C_6H_4\langle^{CO—NH}_{NH—C:S}$

In presence of sodium ethoxide, *o*-benzoylenethiocarbamide reacted with ethyl chloroacetate to give a product which was a mobile oil. Distillation of the oil under the high vacuum of the mercury pump gave fractions differing in boiling-point by only one or two degrees, but the analysis of these fractions gave widely differing results. Redistillation of the fractions did not improve the results, and a repitition of the whole experiment gave fractions of still different analytical values. The oil was obviously a mixture which could not be separated into its components by distillation. This view was supported by the fact that from one of the fractions there ultimately separated on standing a small amount of a solid which was found to be *ethyl 4-keto-3:4-dihydroquinazoline-2-mercapto-acetate*, $C_6H_4\langle^{CO—NH}_{N=}\rangle C\cdot S\cdot CH_2\cdot CO_2C_2H_5$; no further quantities of this substance were obtained.

The reaction may be formulated in the usual manner:-

$$C_6H_4\langle^{CO—NH}_{N=}\rangle C\cdot SNa + CH_2Cl\cdot CO_2C_2H_5 = NaCl + C_6H_4\langle^{CO—NH}_{N=}\rangle C\cdot S\cdot CH_2\cdot CO_2C_2H_5.$$

Treatment of the oil in benzene solution with sodium, in the hope of obtaining the dicyclic compound, was quite unsuccessful. Likewise, an attempted reaction between *o*-benzoylenethiocarbamide and ethyl chloroacetate in pyridine gave no positive results.

8. THIOCARBOHYDRAZIDE, $NH_2 \cdot NH \cdot CS \cdot NH \cdot NH_2$

Thiocarbohydrazide is insoluble in organic solvents, but thiocarbohydrazones may be generally prepared by heating thiocarbohydrazide in alcoholic suspension with the required aldehyde or ketone. Mono- or di-thiocarbohydrazones can be formed, depending on whether one or two molecules of the aldehyde or ketone are employed.

$$\begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}O + NH_2 \cdot NH \cdot CS \cdot NH \cdot NH_2 + O{:}C\!<\!\!\begin{matrix} R \\ R' \end{matrix} =$$

$$2H_2O + \begin{matrix} R \\ R' \end{matrix}\!\!>\!C{:}N \cdot NH \cdot CS \cdot NH \cdot N{:}C\!<\!\!\begin{matrix} R \\ R' \end{matrix}$$

Several thiocarbohydrazones have been prepared by Stollé and Bowles(*Ber.*, 1908, 41, 1099), and by Guha and Dé(*J. Indian Chem. Soc.*, 1925, 2, 225).

The Author has prepared diacetonethiocarbohydrazone and diacetophenonethiocarbohydrazone by methods differing in detail from those used by Guha and Dé(*loc. cit.*), and different melting-points for the substances were observed.

The following, which have also been prepared, have not been previously described:-

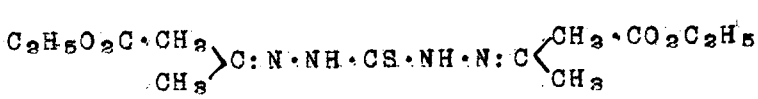
Bis-dibenzyl ketone thiocarbohydrazone,

$$\begin{matrix} C_6H_5 \cdot CH_2 \\ C_6H_5 \cdot CH_2 \end{matrix}\!\!>\!C{:}N \cdot NH \cdot CS \cdot NH \cdot N{:}C\!<\!\!\begin{matrix} CH_2 \cdot C_6H_5 \\ CH_2 \cdot C_6H_5 \end{matrix}$$

Mono(ethyl acetoacetate)thiocarbohydrazone,

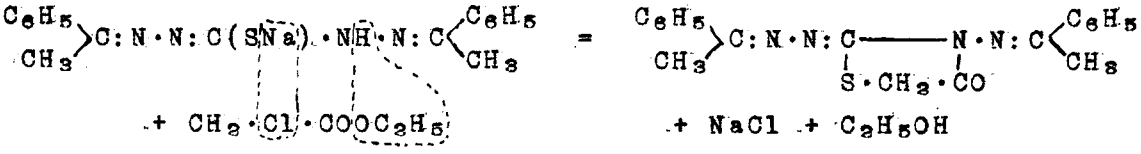
$$\begin{matrix} C_2H_5O_2C \cdot CH_2 \\ CH_3 \end{matrix}\!\!>\!C{:}N \cdot NH \cdot CS \cdot NH \cdot NH_2$$

Di(ethyl acetoacetate)thiocarbohydrazone,

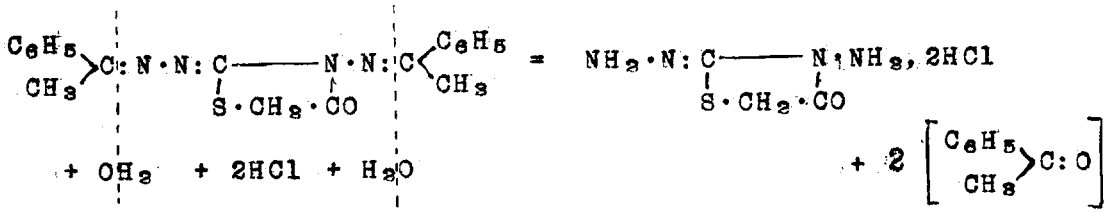


Preliminary investigation showed, that of the foregoing thiocarbohydrazones, diacetophenonethiocarbohydrazone was the most favourable for a reaction in presence of sodium ethoxide with ethyl chloroacetate; accordingly, it has been employed throughout the series of reactions with esters of α-halogeno-acids.

The *sodium* derivative of diacetophenonethiocarbohydrazone was obtained pure, but, as in previous cases, it was not found necessary to isolate it. In alcoholic solution it reacted with ethyl chloroacetate to form in 85% yield *3-phenylmethylmethyleneamino-2:4-diketotetrahydrothiazole-2-phenylmethylmethylenehydrazone*, by elimination of sodium chloride and ethyl alcohol, thus:-

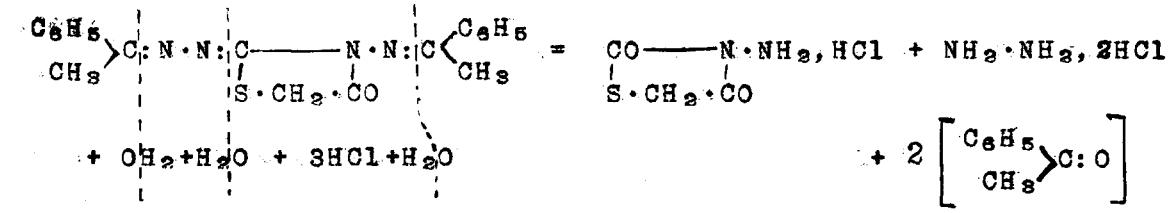


The compound could be hydrolysed in two stages, corresponding to those observed by Wilson and Burns(*loc.cit.*) in the case of the thiazoles derived from acetonethiosemicarbazone. Boiling for a very short time with N-hydrochloric acid removed acetophenone, and the intermediate *3-amino-2:4-diketotetrahydrothiazole-2-hydrazone* was obtained as the *dihydrochloride* :-



The dihydrochloride was an extremely deliquescent solid which had to be manipulated in a dry atmosphere. With benzaldehyde, it gave a *dibenzylidene* derivative.

Hydrolysis with concentrated hydrochloric acid, on the other hand, removed both acetophenone and hydrazine, and gave *3-amino-2:4-diketotetrahydrothiazole hydrochloride*, also a deliquescent solid which gave a *benzylidene* derivative.



Both hydrochlorides were obtained in good yield, but attempts to liberate the free bases in a pure state by treatment of the hydrochlorides with sodium carbonate did not succeed.

Ethyl α-bromopropionate, ethyl α-bromo-*n*-butyrate and ethyl phenylbromoacetate reacted with the sodium derivative of diacetophenonethiocarbohydrazone in a similar manner to ethyl chloroacetate, giving in 80 to 90% yield *3-phenylmethylmethylenamino-2:4-diketo-5-R-tetrahydrothiazole-2-phenylmethylmethylenehydrazone*, where *R*= CH_3, C_2H_5 and C_6H_5 respectively.

Hydrolysis of these compounds did not lead to very definite results; the two stages corresponding to dilute and concentrated hydrochloric acid found in the case of the previous compound were not sharply distinguished.

Treatment with very dilute hydrochloric acid removed acetophenone and gave a mixture in which hydrazine hydrochloride was always present; this indicated that the stage of formation of the intermediate hydrochloride had been passed. The deliquescent solids obtained after removal of the hydrazine hydrochloride were mixtures of the two possible hydrochlorides, and analytical results varied with each experiment. Owing to their highly deliquescent nature, no separation of these two hydrochlorides could be effected.

Hydrolysis with concentrated hydrochloric acid did not give the 3-amino-2:4-diketo-5-R-tetrahydrothiazole hydrochloride; complete rupture of the thiazole-ring took place giving the corresponding mercapto-acid. These acids were identified by their colour reactions.

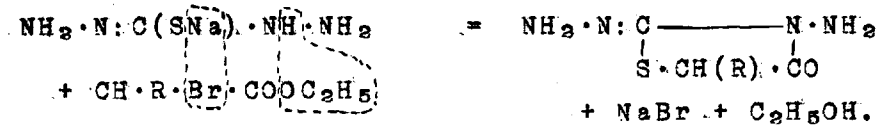
$$\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C{:}N\cdot N{:}\,C\!\!<\!\!\begin{matrix} S\cdot CH(R)\cdot CO \\ \text{———} \\ N\cdot N{:}\,C\!<\!\begin{matrix} C_6H_5 \\ CH_3 \end{matrix} \end{matrix} = CH\cdot R(SH)\cdot CO_2H + 2(NH_2\cdot NH_2,2HCl)$$

$$+ \; 4HCl \; + \; 5H_2O \qquad + \; 2\left[\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C{:}O\right] \; + \; CO_2$$

With a view to obviating this hydrolysis, the production of the 3-amino-2:4-diketo-5-R-tetrahydrothiazole-2-hydrazone bases was attempted by a reaction between thiocarbohydrazide

in presence of sodium ethoxide, and the esters of the α-halogeno-acids.

Thiocarbohydrazide readily dissolved when warmed with sodium ethoxide(1 mol.) in alcohol. The solution of the *sodium* derivative thus formed reacted with ethyl chloroacetate, ethyl α-bromopropionate and ethyl α-bromo-*n*-butyrate to give in satisfactory yield the bases *3-amino-2:4-diketo-5-R-tetrahydrothiazole-2-hydrazone*, where *R*= H, CH_3 and C_2H_5 respectively.



Formed in this manner, the bases were very impure.

Correct analytical results were obtained only in the case of *3-amino-2:4-diketo-5-methyltetrahydrothiazole-2-hydrazone* (the product from ethyl α-bromopropionate).

Repeated crystallisation of the other two bases failed to improve the analyses.

The 5-H compound, however, on treatment with benzaldehyde yielded the same dibenzylidene derivative as was previously prepared from the dihydrochloride of the base.(compare page 24).

The other bases gave *dibenzylidene* derivatives whose analyses agreed with the theoretical values.

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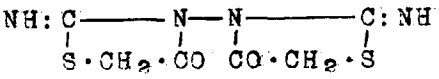
9. HYDRAZODICARBONTHIOAMIDE, $NH_2 \cdot CS \cdot NH \cdot NH \cdot CS \cdot NH_2$

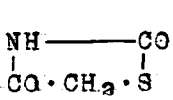
Frerichs and Förster(*Ann.*, 1909, 371, 257) and Frerichs and Höller(*Ann.*, 1913, 398, 256) found that hydrazodicarbonthioamide reacted with chloroacetic acid in aqueous solution to give a compound which they regarded as bis-thiohydantoin,



It has now been found that hydrazodicarbonthioamide, in alcoholic solution in presence of sodium ethoxide, reacts with ethyl chloroacetate to give the identical compound in theoretical yield.

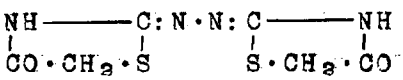
As noted by the above-named authors, this substance, although insoluble in water and organic solvents, dissolved in sodium hydroxide solution and was reprecipitated on acidification; but it was further found that if the alkaline solution was boiled for a few minutes, acidification no longer caused precipitation, the solution then containing mercaptoacetic acid, as shown by Andreasch's test. This shows rupture of the ring, but proves the presence of the group C·S·C in the compound.

Hydrolysis with concentrated hydrochloric acid gradually dissolved the substance; the solution was concentrated and finally taken to dryness. The products of hydrolysis were hydrazine hydrochloride, $NH_2 \cdot NH_2, 2HCl$ and 2:4-diketotetra-

hydrothiazole, 

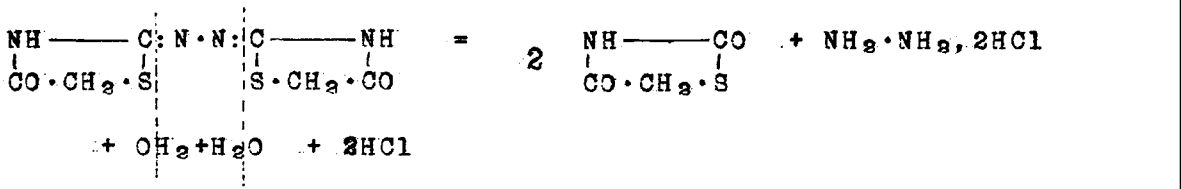
Prepared by Frerichs'method, the compound gave the same hydrolysis products.

On this evidence it must be concluded that the correct structure of the compound is *2: 4-diketotetrahydrothiazole-2-ketazine*,



and not that given by Frerichs.

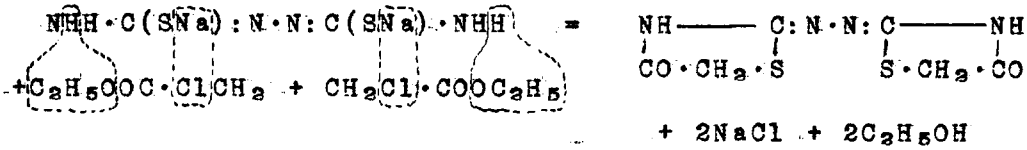
The course of the hydrolysis can then be easily formulated thus:-



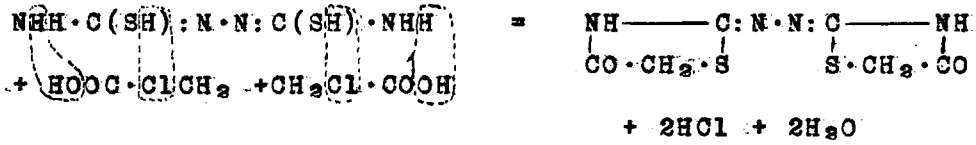
It is difficult to account for such a hydrolysis from a compound of the alternative structure.

The formation of the substance can then be represented in the usual manner:-

(1) through the sodium derivative, with ethyl chloroacetate



(2) with chloroacetic acid



Frerichs and Höller also investigated the reaction between hydrazodicarbonthioamide and

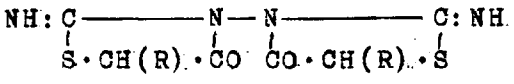
(1) ∝-bromopropionic acid

(2) ∝-bromo-*n*-butyric acid

and by similar reactions to that with chloroacetic acid, obtained compounds to which they gave the structures

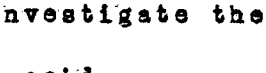
(1) C,C'-Dimethyl-bis-thiohydantoin, and

(2) C,C'-Diethyl-bis-thiohydantoin,



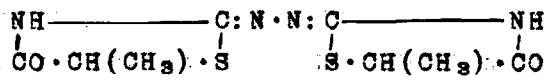
where R=CH_3 and C_2H_5 respectively.

Since it was probable that both these compounds should have the ketazine structure as in the case of that derived from chloroacetic acid, it was decided to prepare these compounds by Frerichs' method and to investigate their behaviour on hydrolysis with hydrochloric acid.

The so-called C,C'-dimethyl-bis-thiohydantoin was hydrolysed with concentrated hydrochloric acid in the usual manner; the only products were hydrazine hydrochloride and 2:4-diketo-5-methyltetrahydrothiazole,  .

This proves that the correct structure of the compound is

2:4-diketo-5-methyltetrahydrothiazole-2-ketazine,



Similarly, the "C,C'-Dimethyl-bis-thiohydantoin" on hydrolysis

with concentrated hydrochloric acid, gave hydrazine hydrochloride and 2:4-diketo-5-ethyltetrahydrothiazole, $\begin{matrix}NH\text{———}CO,\\ CO\cdot CH(C_2H_5)\cdot S\end{matrix}$

thus proving the compound to be *2:4-diketo-5-ethyltetrahydrothiazole-2-ketazine*, $\begin{matrix}NH\text{———}C{:}N\cdot N{:}C\text{———}NH\\ CO\cdot CH(C_2H_5)\cdot S\quad\quad S\cdot CH(C_2H_5)\cdot CO\end{matrix}$.

Frerichs and Höller found, correctly, that the foregoing compounds were more acidic than basic; this appeared somewhat surprising since thiohydantoin itself, $\begin{matrix}NH{:}C\text{———}NH\\ S\cdot CH_2\cdot CO\end{matrix}$ is more basic than acidic.

On the structure now given, their acidic nature is easily explained; 2:4-diketotetrahydrothiazole is an acid ("senfolessigsaure") as are also its 5-methyl and 5-ethyl derivatives. It would be expected that the ketazines derived from these acids would also be acidic in nature.

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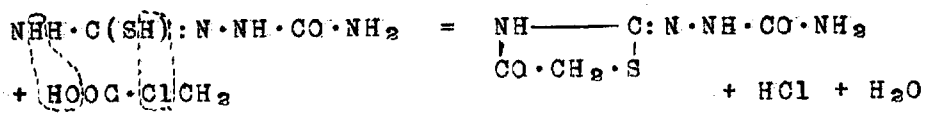
10. HYDRAZOTHIODICARBONAMIDE, $NH_2\cdot CS\cdot NH\cdot NH\cdot CO\cdot NH_2$

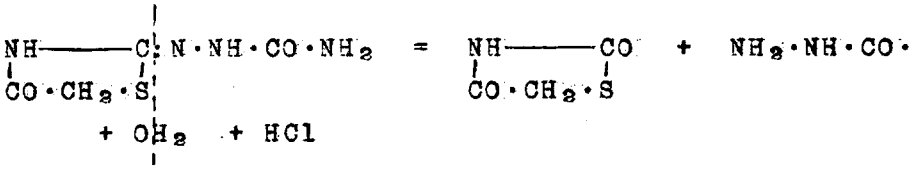
Since this thiocarbamide did not dissolve in alcoholic sodium ethoxide, nor in pyridine, the usual methods of thiazole-formation were precluded.

It reacted with chloroacetic acid in aqueous solution to form *2:4-diketotetrahydrothiazole-2-semicarbazone*, by elimination of hydrochloric acid and water, thus:-



As in the case of the corresponding compound from hydrazodicarbonthioamide, boiling of this substance with sodium hydroxide solution caused rupture of the ring; mercaptoacetic acid was formed, proving the presence of the group C·S·C.

The structure of the compound was proved by hydrolysing with N-hydrochloric acid; the products were semicarbazide hydrochloride, $NH_2 \cdot NH \cdot CO \cdot NH_2, HCl$ and 2:4-diketotetrahydrothiazole:-



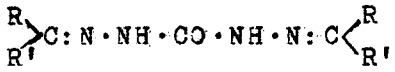
In the reaction between the thiocarbamide and chloroacetic acid, the yield of 2:4-diketotetrahydrothiazole-2-semicarbazone was only 35% of theory, and examination of the mother-liquors of the reaction revealed the presence of semicarbazide hydrochloride and 2:4-diketotetrahydrothiazole. Evidently the hydrochloric acid eliminated during the reaction had caused a partial hydrolysis of the semicarbazone.

The formation of a semicarbazone by the foregoing reaction is analagous to the formation of ketazines from hydrazdicarbonthioamide, and affords further proof that the ketazine structure is the correct one.

THERMAL DECOMPOSITION of

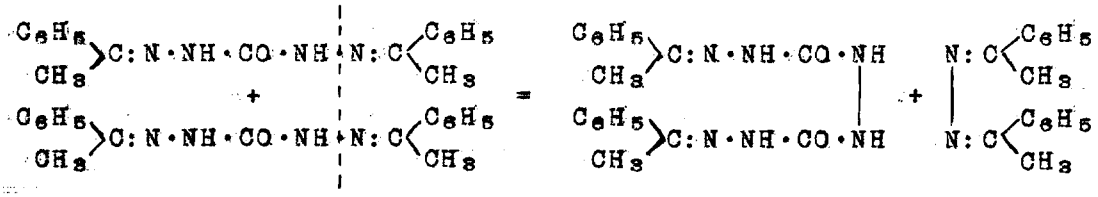
1. Thiosemicarbazones.
2. δ-Phenylthiosemicarbazones.
3. Thiocarbohydrazones.

The thermal decomposition of carbohydrazones,

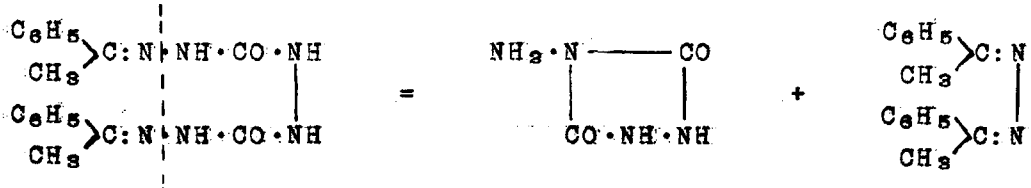


has been investigated by Brown, Pickering and Wilson (*J. Chem. Soc.*, **1927**, **131**, 107). They found that diacetophenonecarbohydrazone decomposed in two stages:

(1) in boiling alcoholic solution, giving diacetophenonehydrazidicarbohydrazone and methylphenylketazine, thus:-



(2) when heated at its melting-point, giving 4-aminourazole and methylphenylketazine, the intermediate diacetophenonehydrazidicarbohydrazone evidently decomposing in this way:-



Dibenzaldehydecarbohydrazone was found to decompose in an exactly similar manner.

The compounds investigated by the Author were

1. Acetonethiosemicarbazone,

   Acetophenonethiosemicarbazone,

2. Acetone-δ-phenylthiosemicarbazone,

   Acetophenone-δ-phenylthiosemicarbazone,

3. Diacetophenonethiocarbohydrazone,

   Bis-dibenzyl ketone thiocarbohydrazone.

All the above-mentioned compounds were found to be much more stable than the carbohydrazones; in no case was there any evidence of decomposition in alcoholic solution, even on prolonged boiling.

1. When acetonethiosemicarbazone was distilled at its melting-point (182°), an oil collected which was identified as dimethyl-ketazine. This was probably formed along with hydrazodicarbon-thioamide as follows:-

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C\!:\!N\cdot NH\cdot CS\cdot NH_2 \;+\; \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C\!:\!N\cdot NH\cdot CS\cdot NH_2 \;=\; \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C\!:\!N \;-\; \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C\!:\!N \;+\; NH_2\cdot CS\cdot NH\cdot NH\cdot CS\cdot NH_2.$$

No hydrazodicarbonthioamide was isolated, the residue after heating being dark and tarry. During the distillation there was abundant evolution of ammonia and hydrogen sulphide, indicating decomposition of the hydrazodicarbonthioamide.

Acetophenonethiosemicarbazone did not decompose when heated

at its melting-point(108°),but when the temperature was raised to 165° ammonia and hydrogen sulphide were evolved and thereafter the decomposition proceeded freely. From the residue after cooling there was extracted methylphenylketazine, but there was no trace of any hydrazodicarbonthioamide.
When the decomposition was attempted at temperatures below 165°, the product consisted of unaltered acetophenonethiosemicarbazone along with varying amounts of the ketazine

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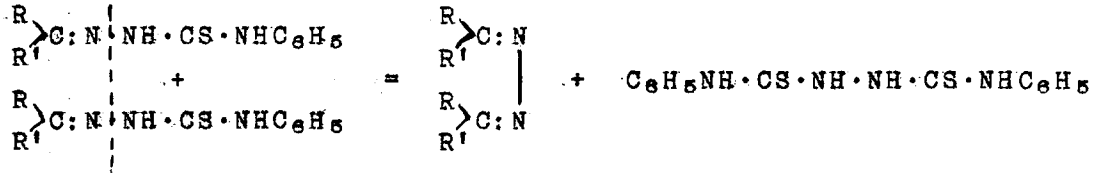
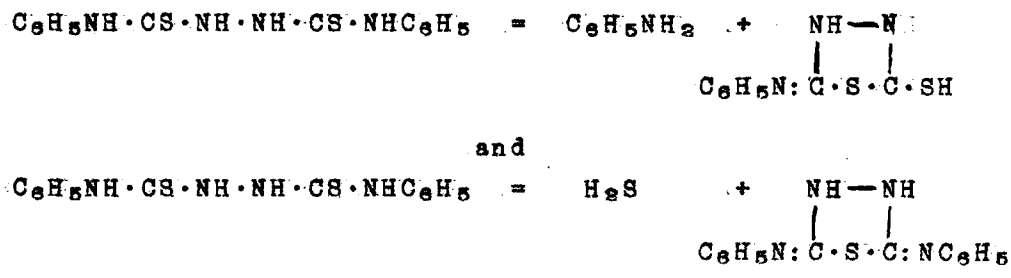
2. Acetone-δ-phenylthiosemicarbazone and acetophenone-δ-phenylthiosemicarbazone decomposed in a similar manner when heated at their melting-points.

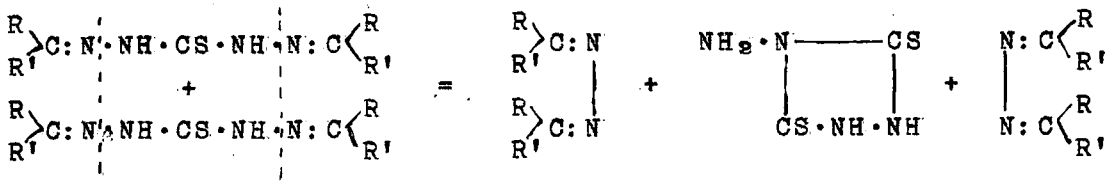


The ketazine was obtained in each case, but the only other products were aniline and hydrogen sulphide. It thus appeared that the hydrazodicarbonthiophenylamide first formed decomposed in two directions as described by Busch and Schmidt(*Ber.*, 1913, **46**, 2243).



Neither of these solid products were isolated pure.

3. Diacetophenonethiocarbohydrazone and bis-dibenzyl ketone thiocarbohydrazone when heated at their melting-points decomposed in a similar manner to the carbohydrazones:-



The ketazine was isolated in each case, but the 4-aminodithiourazole appeared to be completely decomposed, no other solid product being obtained. Ammonia and hydrogen sulphide were abundantly evolved during the heating.

The foregoing reactions were carried out at several different temperatures, in the dry state and also in presence of a solvent, but the results were not more successful.
In view of this, the investigation was not carried further.

EXPERIMENTAL

1. Experiments with δ-PHENYLTHIOSEMICARBAZIDE, $NH_2 \cdot NH \cdot CS \cdot NHC_6H_5$.

δ-Phenylthiosemicarbazide was prepared by the method of Pulvermacher(*Ber.*, 1894, 27, 615).

Acetone-δ-phenylthiosemicarbazone, $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:N \cdot NH \cdot CS \cdot NHC_6H_5$.

δ-Phenylthiosemicarbazide dissolved in the minimum quantity of hot alcohol was treated with acetone(slightly more than 1 mol.), and the solution boiled under reflux for fifteen minutes. The solid which separated on cooling crystallised from alcohol in glistening plates, m.p. 130°. It was soluble in alcohol, ether, benzene and chloroform, but insoluble in water and light petroleum. Only a small amount was obtained by concentration of the mother-liquors of the reaction, the initial separation being almost complete. Yield 90%.

Found: N, 20·36, 20·29%

$C_{10}H_{13}N_3S$ requires N, 20·29%.

Acetophenone-δ-phenylthiosemicarbazone, $\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C:N \cdot NH \cdot CS \cdot NHC_6H_5$.

δ-Phenylthiosemicarbazide was boiled in alcoholic solution with acetophenone(slightly more than 1 mol.) for half-an-hour under reflux. The thiosemicarbazone crystallised from the yellow solution on cooling, and a further crop was obtained by concentration of the mother-liquors.

Recrystallisation from alcohol-benzene gave the compound as pale yellow, fine, prismatic needles, m.p. 195°. It was soluble in alcohol, benzene and chloroform, sparingly soluble in ether, and insoluble in water and light petroleum. Yield 95%.

Found: N, 15·60; S, 11·91%

$C_{15}H_{15}N_3S$ requires N, 15·61; S, 11·90%

Sodium derivative of acetone-δ-phenylthiosemicarbazone,

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C{:}N{\cdot}N{:}C(SNa){\cdot}NHC_6H_5.$$

To acetone-δ-phenylthiosemicarbazone dissolved in hot absolute alcohol was added sodium ethoxide (1 mol.) in alcohol. A yellowish-brown solution was formed and after ten minutes' heating it was cooled, when it became still darker in colour. Attempts to isolate the derivative in a pure state, by precipitating with ether or light petroleum were unsuccessful. A white powder was obtained which dissolved in water forming an alkaline solution.

Found: Na, 7·7·0%

$C_{10}H_{12}N_3SNa$ requires Na, 10·0%

It was found that the alcoholic solution sufficed for the desired reactions of this substance; accordingly, no further attempts were made to isolate it in a pure state.

Action of Esters of α-Halogeno-acids on the Sodium derivative of Acetone-δ-phenylthiosemicarbazone.

1. Ethyl Chloroacetate, $CH_2Cl \cdot CO_2C_2H_5$.

2:4-Diketo-3-phenyltetrahydrothiazole-2-isopropylidenehydrazone,

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:N\cdot N:C\!<\!\begin{matrix} NC_6H_5 - CO \\ S \quad\quad\quad CH_2 \end{matrix}$$

Acetone-δ-phenylthiosemicarbazone was heated for five minutes with sodium ethoxide(1 mol.) in absolute alcohol. Ethyl chloroacetate(slightly more than 1 mol.) was then added. A vigorous reaction at once occurred, with the separation of a flocculent yellow solid. Heating was continued for half-an-hour, and after cooling, the solid was filtered off and washed with warm water until free from sodium chloride(which was formed and precipitated in the course of the reaction). Recrystallisation from a large quantity of alcohol, using charcoal to remove colour, gave the compound as fine, almost colourless needles, m.p.200°. It was soluble in alcohol, ether, benzene and chloroform, and insoluble in water and light petroleum. Yield 70%.

Found: N, 16·97, 16·93%

$C_{12}H_{13}N_3S$ requires N, 17·00%

2:4-Diketo-3-phenyltetrahydrothiazole, $OC\!<\!\begin{matrix} NC_6H_5 - CO \\ S \quad\quad\quad CH_2 \end{matrix}$

The above *iso*propylidene derivative was boiled under reflux for three hours with concentrated hydrochloric acid; the

solution was evaporated to dryness on the water-bath and finally in an evacuated desiccator containing soda-lime over sulphuric acid. Treatment of the dry residue with cold water removed hydrazine hydrochloride, which was identified by conversion into benzalazine on treatment with benzaldehyde. The residue, which was small, crystallised from hot water in needles, m.p. 143°. It was soluble in alcohol and ether. From its properties it is evidently identical with the substance previously described by Evers(*Ber.*, 1888, 21, 975) and by Lange(*Ber.*, 1879, 12, 597). Lange gives the m.p. 148°, but Evers gives 143° and points out that the substance exists in two crystalline forms, needles and plates.

Found: N, 7·33%

Calculated for $C_9H_7O_2NS$: N, 7·25%

The yield was small and could not be improved; extensive decomposition appeared to take place during the hydrolysis, as aniline hydrochloride was also found present in the residue. This showed that rupture of the thiazole-ring had taken place.

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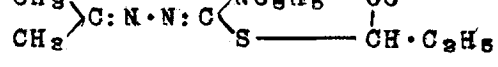
2. Ethyl α-Bromo-*n*-butyrate, $CH_3 \cdot CH_2 \cdot CHBr \cdot CO_2C_2H_5$.

2:4-Diketo-3-phenyl-5-ethyltetrahydrothiazole-2-isopropylidene-hydrazone,

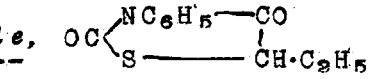


Acetone-δ-phenylthiosemicarbazone was treated with sodium ethoxide as before, and ethyl α-bromo-*n*-butyrate (slightly more

than 1 mol.) added. Sodium bromide was precipitated immediately, and after heating under reflux for half-an-hour, was filtered hot and washed with a little hot absolute alcohol. The solid, which deposited from the filtrate and washings on cooling, recrystallised from alcohol in fine needles, m.p. 131°. It was soluble in alcohol, ether, benzene and chloroform, but insoluble in water and light petroleum. Yield 75%.

Found: N, 15·23, 15·38%

$C_{14}H_{17}ON_3S$ requires N, 15·27%

2:4-Diketo-3-phenyl-5-ethyltetrahydrothiazole, 

The *iso*propylidene derivative was boiled under reflux for three hours with concentrated hydrochloric acid. On cooling, the acid solution deposited a small amount of a solid which crystallised from hot water in feathery needles, m.p. 98°.

Found: N, 6·46%

$C_{11}H_{11}O_2NS$ requires N, 6·34%

This compound has not been previously described.

On evaporation to dryness, the acid-liquor gave a residue which consisted of hydrazine hydrochloride (proved by conversion into benzalazine) together with some aniline hydrochloride. As in the previous case, the small yield of the thiazole could not be improved; the presence of the aniline hydrochloride indicated rupture of the thiazole-ring.

When the *iso*propylidene derivative was heated along with the

theoretical amount of hydrochloric acid in a sealed tube at 150°, there was high gaseous pressure indicating extensive decomposition.

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3. Ethyl Phenylbromoacetate, $CH(C_6H_5)Br \cdot CO_2C_2H_5$.

2:4-Diketo-3:5-diphenyltetrahydrothiazole-2-isopropylidene-hydrazone, $(CH_3)_2C{:}N \cdot N{:}C\langle^{NC_6H_5-CO}_{S-CH \cdot C_6H_5}$

This reaction, carried out exactly as in the case of ethyl chloroacetate, gave a flocculent precipitate which was collected after fifteen minutes' heating, and washed with warm water until free from sodium bromide. Recrystallisation from acetone gave the compound as hair-like needles, m.p. 189°. It was soluble in ether, benzene, chloroform and acetone, sparingly soluble in alcohol, and insoluble in water and light petroleum. Yield 75%.

Found: N, 12·95, 12·97%

$C_{18}H_{17}ON_3S$ requires N, 13·00%

2:4-Diketo-3:5-diphenyltetrahydrothiazole, $OC\langle^{NC_6H_5-CO}_{S-CH \cdot C_6H_5}$

The *iso*propylidene derivative was hydrolysed as before, by boiling with concentrated hydrochloric acid. After twenty minutes' heating, there commenced to be deposited a precipitate of gelatinous appearance. The quantity gradually increased, and at the end of three hours, the solid was collected by

filtering the cooled solution. Repeated crystallisation was necessary to obtain the compound pure; from alcohol, it was in the form of needles, m.p.173°, and was evidently identical with the substance described by Wheeler and Johnson (*J. Amer. Chem. Soc.*, 1902, 24, 690) who prepared it by a different method.

As in the previous cases, hydrazine hydrochloride was obtained by evaporation of the acid filtrate, and was identified in the usual manner.

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2. Experiments with α-PHENYLTHIOSEMICARBAZIDE, $NHC_6H_5 \cdot NH \cdot CS \cdot NH_2$

α-Phenylthiosemicarbazide was prepared by the method of Fischer and Besthorn (*Ann.*, 1882, 212, 324).

Having no $NH_2 \cdot NH$ group, this substance does not form aldehydic or ketonic derivatives; it was therefore used directly for the reactions with ethyl chloroacetate.

Reaction with Ethyl Chloroacetate:

(a) in presence of sodium ethoxide.

α-Phenylthiosemicarbazide in hot absolute alcoholic solution was treated with sodium ethoxide (1 mol.) in alcohol. A reddish-coloured solution was formed and after ten minutes' heating, ethyl chloroacetate (slightly more than 1 mol.) was added. Sodium chloride was immediately precipitated, and the solution became still darker in colour. After half-an-hour the solution was filtered hot; the filtrate deposited no solid on cooling, even after concentration, and when all the solvent had been removed under reduced pressure, the residue was a dark, tarry mass. This was redissolved in the minimum quantity of hot absolute alcohol, and on cooling, a brownish-coloured solid separated. Recrystallisation from alcohol gave colourless prisms, m.p. 200° (decomp.). These were identified by mixed m.p. test as unaltered α-phenylthiosemicarbazide.

(b) in pyridine solution.

In the hope of obtaining a reaction between α-phenylthiosemicarbazide and ethyl chloroacetate, these substances (in molecular proportions) were heated together for half-an-hour in pyridine solution. The solution became very dark in colour, and no solid was deposited on cooling. Removal of the pyridine under reduced pressure gave a dark tarry residue.
Repeated crystallisation of this residue from absolute alcohol gave colourless prisms, again identified as unaltered α-phenylthiosemicarbazide.

Reaction with Chloroacetic Acid in aqueous solution.

α- Phenylthiosemicarbazide and chloroacetic acid (1 mol.) were boiled together in aqueous solution for about two hours. The solution, which was yellow in colour, deposited a solid on cooling, and as in the previous experiments, this was found to be unaltered α-phenylthiosemicarbazide.

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3. Experiments with

METHYLENETHIOCARBAMIDE, $CH_2\langle^{NH}_{NH}\rangle C:S$.

Hemmelmayr (*Monatsh.*, 1931, 12, 90).

Owing to its extreme insolubility, methylenethiocarbamide could not be applied to thiazole-formation.

Attempts were made to form the sodium derivative in the usual manner, but the substance did not dissolve even on prolonged boiling with alcoholic sodium ethoxide.

It was also found to be insoluble in pyridine, and the addition of ethyl chloroacetate to the suspension, did not cause any reaction.

Likewise, the thiocarbamide failed to react with chloroacetic acid in aqueous solution, even on prolonged boiling.

4. Experiments with ETHYLENETHIOCARBAMIDE, $\begin{matrix}CH_2—NH\\ |\\ CH_2—NH\end{matrix}\!\!>C:S$

Ethylenethiocarbamide was prepared by the method of Hofmann (*Ber.*, 1872, 5, 242). The m.p. of the substance was found to be 196°. (Hofmann gives 194°.)

Found: N, 27·45%

Calculated for $C_3H_6N_2S$: N, 27·45%

Sodium derivative of ethylenethiocarbamide, $\begin{matrix}CH_2—NH\\ |\\ CH_2—N\end{matrix}\!\!>C\cdot SNa$.

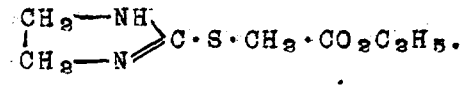
To ethylenethiocarbamide dissolved in hot absolute alcohol was added sodium ethoxide (1 mol.) in alcohol. There was no change in the colour of the solution, and after ten minutes' heating, the solution was cooled and attempts made to isolate the sodium derivative. Concentration of the solution, or precipitation with ether or light petroleum gave unaltered ethylenethiocarbamide.

It was found, however, that the alcoholic solution reacted with ethyl chloroacetate as though it contained this sodium derivative; accordingly, no further attempts were made to isolate it.

Action of Esters of Chloroacetic acid on the Sodium derivative of Ethylenethiocarbamide.

1. Ethyl Chloroacetate.

Ethyl 4:5-Dihydroiminazole-2-mercaptoacetate,



An absolute alcoholic solution of ethylenethiocarbamide was boiled for ten minutes with sodium ethoxide (1 mol.); ethyl chloroacetate (1 mol.) was then added, and boiling under reflux continued for half-an-hour. The solution, after having been filtered from sodium chloride while hot, deposited a solid on cooling. This solid crystallised from absolute alcohol in fine needles. It commenced to decompose, turning pink, at temperatures of 160° or over (depending on the rate of heating), and melted at 190° to a dark red liquid.

The substance was very soluble in water and alcohol, but insoluble in ether, benzene and light petroleum. The best yield (60%) was obtained by using the minimum quantity of alcohol in the reaction, as concentration of the mother-liquors caused a partial decomposition. The addition of light petroleum to the mother-liquors caused the separation of a further small amount of the compound.

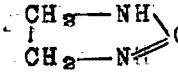
Found: N, 14·98; S, 17·18%

$C_7H_{12}O_2N_2S$ requires N, 14·98; S, 17·02%

The foregoing ester was boiled for two hours under reflux with sodium hydroxide solution. A portion of the liquid was then distilled, and ethyl alcohol was detected in the distillate by the formation of iodoform. On acidifying the main portion of the solution, hydrogen sulphide was evolved, and the presence of mercaptoacetic acid, $CH_2(SH)\cdot CO_2H$ was proved by Andreasch's test, as follows:-

> A portion of the solution was boiled until free from hydrogen sulphide, cooled, and a very dilute solution of ferric chloride added. Ammonium hydroxide was then added, and a deep reddish-coloured solution was produced, the colour becoming still more intense on shaking with air.

The presence of mercaptoacetic acid showed that the sodium hydroxide, in addition to hydrolysing the ester to the free acid by removal of alcohol, had ruptured the molecule. It proved, however, the attachment of sulphur to carbon in the acetic acid residue, i.e. the presence of the group $\cdot S\cdot CH_2\cdot CO_2C_2H_5$ in the compound.

Unsuccessful attempts were made to obtain the free acid  by a milder form of hydrolysis. Boiling with water failed to hydrolyse the ester, whilst the addition of the theoretical amount of sodium hydroxide in very dilute solution caused the formation of mercaptoacetic acid as before.

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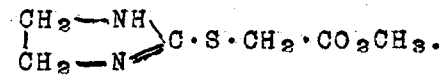
2. Methyl Chloroacetate, $CH_2Cl \cdot CO_2CH_3$.

Methyl 4:5-Dihydroiminazole-2-mercaptoacetate,



This substance was prepared in exactly the same manner as the ethyl ester, using methyl chloroacetate. It crystallised from absolute alcohol in fine needles, and showed a similar solubility to the previous compound. It commenced to decompose, turning pink, at about 170°, and melted at 190° to a red liquid. As before, there was a tendency for decomposition to occur during concentration of the mother-liquors, and the best yield (80%) was obtained by employing the minimum quantity of alcohol, the small second crop being precipitated by the addition of light petroleum.

Found: N, 15·95; S, 18·55%

$C_6H_{10}O_2N_2S$ requires N, 16·10; S, 18·40%

On hydrolysis with sodium hydroxide solution, this ester behaved in a similar manner to the ethyl ester; methyl alcohol and mercaptoacetic acid were formed, proving the structure assigned to the compound to be correct.

Since the foregoing reactions did not result in the formation of the desired dicyclic compound, various attempts were made to bring about ring-closure of these esters by elimination of alcohol.

The substances were heated with toluene, amyl alcohol or solvent naphtha (b.p.165-175°), but this treatment effected no change except a partial decomposition of the esters when a temperature of 160-170° was reached.

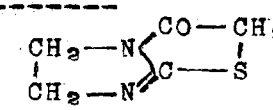
Owing to their insolubility in benzene, a method of effecting ring-closure by heating in benzene solution with sodium (later used with success in the case of other compounds, compare page 61) was not available.

Reaction of Esters of Chloroacetic Acid on Ethylenethiocarbamide in Pyridine solution.

With a view to obtaining the dicyclic compound, it was decided to attempt a modification of the usual reaction, using ethylenethiocarbamide directly, with pyridine to absorb the hydrochloric acid eliminated in the reaction.

1. Ethyl Chloroacetate.

4:5-Dihydroiminazole-2-mercaptoaceto-1-lactam,



Ethylenethiocarbamide was dissolved in pure pyridine, and ethyl chloroacetate (1 mol.) was added. The solution was boiled under reflux for half-an-hour, the condenser being attached to the reaction flask by a ground-glass joint. During the heating the solution became dark in colour. No solid was deposited on cooling, and the pyridine was removed by distillation under

reduced pressure. The residue, which was a reddish-brown gum, was dissolved in a small quantity of hot absolute alcohol, and on cooling, crystals deposited. Recrystallisation from absolute alcohol gave the dicyclic substance as plates, m.p. 159°. It was very soluble in water and alcohol, but insoluble in other common solvents.

Found: N, 19·75%

$C_5H_6ON_2S$ requires N, 19·72%

The yield was only about 10%, most of the product being recovered from the alcoholic mother-liquors as a resin, either by concentration or the addition of light petroleum. This resin would not solidify even on cooling in a freezing-mixture of solid carbon dioxide and ether. Distillation of the resin under the high vacuum of the mercury pump (less than 1mm.) resulted in extensive decomposition, and from the tarry residue in the flask, only pyridine hydrochloride was isolated.

A small quantity of the compound of m.p. 159° was hydrolysed with sodium hydroxide, and the presence of mercaptoacetic acid was proved by the usual test.

Having obtained the dicyclic compound, attempts were then made to establish its constitution definitely by preparing it from ethylenethiocarbamide and a different ester of chloroacetic acid, by elimination of the corresponding alcohol.

2. Methyl Chloroacetate.

The reaction in pyridine solution was repeated, using methyl chloroacetate (1 mol.), but after a few minutes' heating, the solution became almost black. The resulting product after removal of the pyridine was a tarry mass from which no solid was isolated.

It was found that methyl chloroacetate forms an additive compound with pyridine much more rapidly than ethyl chloroacetate, and the preferential formation of this additive compound probably accounted partly for the failure of the desired reaction with ethylenethiocarbamide.

Modifications of the method in which alcohol-pyridine mixtures were used as the solvent, gave no definite results; the substitution of quinoline for pyridine in the original reaction resulted in a similar dark tarry residue.

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3. *l*-Menthyl Chloroacetate, $CH_2Cl \cdot CO_2C_{10}H_{19}$

The reaction with this ester proceeded to all appearances in a similar manner to that with ethyl chloroacetate. On removal of the pyridine a gummy residue was obtained, but this, on recrystallisation from alcohol, gave unaltered ethylenethiocarbamide.

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4. *n*-Butyl Chloroacetate, $CH_2Cl \cdot CO_2C_4H_9$

The reaction with *n*-butyl chloroacetate, carried out in

exactly the same manner, gave a very small yield of the dicyclic compound, and identity was established by means of a mixed m.p. determination, when no depression was shown.

In spite of repeated experiments using ethyl chloroacetate or *n*-butyl chloroacetate, the lactam was obtained pure on two occasions only. Further attempts to prepare it led apparently to the formation of complex mixtures from which none of the compound of m.p.159° could be isolated.

The great similarity in the solubilities of this substance and ethylenethiocarbamide practically rendered a separation from unaltered ethylenethiocarbamide impossible.

With solutions of metallic salts, such as mercuric chloride, both the dicyclic compound and ethylenethiocarbamide gave insoluble salts.

The formation of the dicyclic compound on these two occasions, however, proved that alcohol had been eliminated in the course of the reaction, causing ring-closure.

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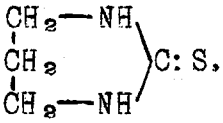
5. Experiments with

TRIMETHYLENETHIOCARBAMIDE, 

Trimethylenethiocarbamide was prepared by the method of Schacht (*Arch. Pharm.*, 1887, 225, 461).

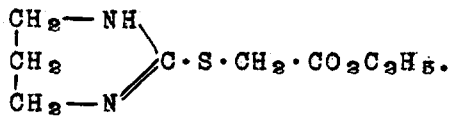
Reaction with Ethyl Chloroacetate:

(a) in presence of sodium ethoxide.

Trimethylenethiocarbamide in hot absolute alcoholic solution was treated with sodium ethoxide (1 mol.) in alcohol. After ten minutes' heating, ethyl chloroacetate (1 mol.) was added. Sodium chloride was immediately precipitated, and after half-an-hour, the solution was filtered hot. The solid which deposited from the filtrate on cooling, was recrystallised from alcohol; it melted at 207°, and was identified by mixed m.p. test, as unaltered trimethylenethiocarbamide.
Evidently the ethyl chloroacetate reacted with the sodium ethoxide alone, and not with the sodium derivative of the thiocarbamide.

(b) in pyridine solution.

Ethyl 1:4:5:6-Tetrahydropyrimidine-2-mercaptoacetate,



Trimethylenethiocarbamide and ethyl chloroacetate (1 mol.) were heated together in pyridine solution for half-an-hour.

On cooling, the dark-coloured solution deposited brownish-coloured crystals. Recrystallisation from absolute alcohol gave small colourless needles, which commenced to decompose about 200°, turning brown, and melted with complete decomposition at 256°. The compound was soluble in water and alcohol, but insoluble in ether, benzene, chloroform, acetone and light petroleum. Yield 70%.

Found: N, 13·77; S, 15·75%

$C_8H_{14}O_2N_2S$ requires N, 13·87; S, 15·89%.

Hydrolysis of the compound by heating with sodium hydroxide solution gave ethyl alcohol and mercaptoacetic acid (by Andreasch's test), again showing rupture of the molecule in addition to the simple hydrolysis, but proving the presence of the group C·S·C.

Owing to the insolubility of the compound in benzene, the method of effecting ring-closure by heating in benzene solution with sodium was again precluded.

In the hope of obtaining the dicyclic compound, the reaction in pyridine solution was repeated, heating being continued for two hours; the same open-chain compound was, however, obtained. as the only product.

6. Experiments with *ortho*-PHENYLENETHIOCARBAMIDE, $C_6H_4\langle^{NH}_{NH}\rangle C:S$

ortho-Phenylenethiocarbamide was prepared by the method of Lellmann (*Ann.*, 1883, 221, 9).

Sodium derivative of o-phenylenethiocarbamide, $C_6H_4\langle^{NH}_{N}\rangle C\cdot SNa$

o-Phenylenethiocarbamide dissolved in hot absolute alcohol was treated with sodium ethoxide (1 mol.) in alcohol. A slight darkening in colour took place, and after heating for ten minutes, the solution was cooled. The addition of ether or light petroleum did not precipitate any solid, but concentration of the solution in an evacuated desiccator gave an almost white powder. It was washed with a little ether, and dried in a desiccator over sulphuric acid. It was completely soluble in cold water, forming an alkaline solution.

Found: Na, 13·37%

$C_7H_5N_2SNa$ requires Na, 13·27%

Action of Esters of ∝-Halogeno-acids on the Sodium derivative of *o*-Phenylenethiocarbamide.

1. Ethyl Chloroacetate.

Ethyl Benziminazole-2-mercaptoacetate, $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH_2\cdot CO_2C_2H_5$.

o-Phenylenethiocarbamide dissolved in hot absolute alcohol was boiled for ten minutes with sodium ethoxide (1 mol.) in alcohol; ethyl chloroacetate (1 mol.) was then added.

Sodium chloride was immediately precipitated, and after heating for half-an-hour, the hot solution was filtered. The filtrate did not crystallise even after concentration, but the addition of a small quantity of water when the solution was at a moderate temperature caused turbidity, and on standing, crystals separated. Further quantities of the solid were then precipitated by the addition of more water.

When freshly crystallised from ether-light petroleum or aqueous alcohol, the substance melted at 78°, but almost immediately a change occurred, and the m.p. was indefinite. After a very few minutes, however, the m.p.was again sharp at 97°, and this modification of the compound, rhombic prisms, was quite stable. This may be a case of dimorphism, but the change was too rapid to permit of investigation.

The substance was very soluble in alcohol, ether, benzene, chloroform and acetone, very sparingly soluble in light petroleum, and insoluble in water.

Found: N, 11·88, S, 13·72%

$C_{11}H_{12}O_2N_2S$ requires N, 11·86; S, 13·56%

As in the case of the corresponding compound from ethylenethiocarbamide, the best yield (85%) was obtained by using the minimum quantity of alcohol for the reaction, as during concentration of the aqueous-alcoholic mother-liquors, a hydrolysis appeared to take place. (compare page 59).

2. Methyl Chloroacetate.

Methyl Benziminazole-2-mercaptoacetate, $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH_2\cdot CO_2CH_3$.

This reaction was carried out in exactly the same manner, using methyl chloroacetate (1 mol.). As before, the product crystallised on diluting the alcoholic solution with water. The compound showed a similar solubility to the ethyl ester, and a similar peculiarity of m.p. When freshly crystallised from ether+light petroleum or aqueous alcohol, it melted at 72°, and in a very few minutes, changed to the stable form, rhombic prisms, m.p.83°. Yield 80%.

Found: N, 12·56; S, 14·38%

$C_{10}H_{10}O_2N_2S$ requires N, 12·61; S, 14·38%

As in the case of the ethyl ester, concentration of the aqueous-alcoholic mother-liquors did not give a further yield of the compound.

In both cases, the solid obtained by concentration of these mother-liquors was of high m.p. (210 to 220°). It appeared that the esters had been hydrolysed to the free acid $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH_2\cdot CO_2H$, and a subsequent experiment, in which this acid was obtained pure, confirmed this view. (compare page 69).

Hydrolysis of the esters with sodium hydroxide solution or concentrated hydrochloric acid did not lead to very definite

results. Heating with sodium hydroxide solution for several hours did not decompose the compounds to mercaptoacetic acid, as was expected by analogy with the corresponding derivatives from ethylenethiocarbamide. Acidification of the alkaline solution caused the precipitation of the same high-melting solid mentioned before; it was, however, very impure.

Further experimental evidence confirmed the presence of the group C·S·C in the esters. Neither ester developed any noticeable blackening on heating with very concentrated sodium hydroxide solution and the subsequent addition of a lead salt, whilst *o*-phenylenethiocarbamide under these conditions produced strong blackening.

Whilst potassium permanganate solution was rapidly reduced by *o*-phenylenethiocarbamide, there was scarcely any action with the esters.

There was no indication that the esters formed a disulphide on treatment with iodine.

Thus, the group C:S present in *o*-phenylenethiocarbamide appeared to be absent in the esters, proving the alternative structure with the group C·S·C to be correct.

Hydrolysis with concentrated hydrochloric acid was carried out under various conditions of time, temperature and pressure, but in each case the solid product was of indefinite m.p., and repeated crystallisation did not give the substance pure.

The results of the analysis of the purest sample obtained

indicated it to be *benziminazole-2-mercaptoacetic acid*, $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH_2\cdot CO_2H$, but both nitrogen and sulphur values were low. The properties of the substance indicated it to be an acid. It was soluble in sodium hydroxide solution and was reprecipitated on acidification (this did not serve as a method of purification); it was also very soluble in pyridine. It formed a silver salt which was purified and analysed, but again the analysis differed somewhat from the theoretical value. The acid was subsequently obtained pure by the interaction of *o*-phenylenethiocarbamide and chloroacetic acid in aqueous solution (compare page 69), and no further attempts were made to obtain it by the hydrolysis of its esters.

Action of Sodium powder on the Esters in Benzene solution.

An attempt was made to obtain the dicyclic compound by heating *o*-phenylenethiocarbamide and ethyl chloroacetate together in pyridine solution; no reaction took place, however, the *o*-phenylenethiocarbamide being recovered unchanged. Attention was therefore directed to the possibility of removing 1 molecule of alcohol from the open-chain esters by means of sodium.

Benziminazole-2-mercaptoaceto-1-lactam, $C_6H_4\langle^{N}_{N}\rangle\!\!\begin{matrix}CO\text{—}CH_2\\ |\\ C\text{—}S\end{matrix}$

Sodium powder in excess was added to a hot benzene solution of ethyl benziminazole-2-mercaptoacetate, and boiling under

reflux on the water-bath continued for half-an-hour.
A slow effervescence took place and a deep-yellow solid was deposited. The benzene solution was decanted, filtered and evaporated to dryness, giving a solid which crystallised from alcohol in prismatic needles, m.p.181°. It was soluble in alcohol, benzene and chloroform, but insoluble in water, ether and light petroleum. Yield 25%.
In addition to the ordinary analysis, a determination of molecular weight was made, by the ebullioscopic method in benzene.

Found:	N, 14·68; S, 16·98%; *M*, 187
$C_9H_6ON_2S$ requires	N, 14·73; S, 16·84%; *M*, 190

It was not found possible to increase the yield of the dicyclic compound above 25%. The yellow solid containing the excess of sodium was extracted several times with hot benzene, but on evaporation the benzene gave no residue.
Variations of the method with respect to time were less successful; it was found, however, that by carrying out the reaction with very gentle boiling the formation of the yellow solid was minimised. The benzene solution then gave a residue consisting of the dicyclic compound along with a considerable amount of unaltered ester. Crystallisation from alcohol easily brought about a separation; the lactam was deposited pure, while the ester, owing to its great solubility in alcohol, remained in solution. It was subsequently recovered by the addition of

water to the mother-liquors, and could then be treated with sodium to give a 25% yield of the lactam.

The yellow substance formed in the course of the reaction could not be readily separated from the sodium ethoxide and excess of sodium powder, and as it was obviously not the dicyclic compound, it was not further investigated.

Similar treatment of methyl benziminazole-2-mercaptoacetate with sodium powder gave a 25% yield of the same dicyclic compound; this definitely proved that ring-closure had taken place by elimination of ethyl or methyl alcohol.

Hydrolysis of the lactam with alkali or acid did not form mercaptoacetic acid, but the same impure acid as was obtained by the hydrolysis of the open-chain esters.

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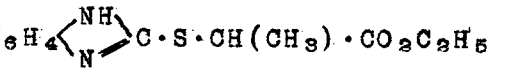
3. Ethyl α-Bromopropionate, $CH_3 \cdot CHBr \cdot CO_2C_2H_5$.

Ethyl Benziminazole-2-α-mercaptopropionate,



o-Phenylenethiocarbamide was treated with sodium ethoxide (1 mol.) and ethyl α-bromopropionate (1 mol.) in the same manner as in the previous experiments using the esters of chloroacetic acid. The product of the reaction crystallised from the diluted alcoholic solution; after drying, recrystallisation from ether-light petroleum gave prismatic plates,

As was the case with the previous members of this series, the

present compound appeared to exhibit dimorphism, and for a few minutes after crystallisation, the m.p. was indefinite; the m.p. of the stable form was 100°. It was soluble in alcohol, ether, benzene and chloroform, but insoluble in water and light petroleum. Yield 90%.

Found: N, 11·27; S, 12·78%

$C_{12}H_{14}O_2N_2S$ requires N, 11·20; S, 12·80%

Hydrolysis of the ester with sodium hydroxide solution did not cause the formation of α-mercaptopropionic acid. The addition of a lead salt to the alkaline solution caused no blackening, indicating the absence of the group C:S.

Boiling with concentrated hydrochloric acid appeared to hydrolyse the ester to *benziminazole-2-α-mercaptopropionic acid*, $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH(CH_3)\cdot CO_2H$. It was, however, very impure, and was obtained pure in the course of a subsequent reaction (compare page 65).

Action of Sodium on Ethyl Benziminazole-2-α-mercapto-propionate in Benzene solution.

In the expectation of obtaining ring-closure with this ester in the same manner as with the previous compounds of the series, it was heated in benzene solution with excess of sodium powder. A similar yellow solid was formed, but the quantity appeared greater than in the previous reactions. After heating for half-an-hour under reflux, the benzene solution was filtered and

evaporated; the residue, which was almost negligible in quantity, was found to be unaltered ester. Evidently the entire product of the reaction was mixed with the excess of sodium powder; it was quite insoluble in benzene, and attempts to extract it with other solvents (which would have no action on sodium) led to extensive charring.

In order that the solid might be more easily removed from the excess of sodium, the reaction was repeated using sodium in the form of wire instead of powder. The reaction proceeded more slowly and the yellow solid which appeared was occasionally detached from the sodium by means of a glass rod, in order to expose fresh surface of sodium. After one and a half hours, the benzene was decanted. filtered and evaporated, giving, as before, only a trace of unaltered ester. The entire residue was dried in an evacuated desiccator, and the most of the sodium mechanically removed. The remainder of the solid was then dissolved in warm absolute alcohol and a few drops of concentrated hydrochloric acid added to neutralise the sodium ethoxide. The small amount of sodium chloride formed was filtered, and the filtrate, on cooling and concentrating in a desiccator, deposited a solid which crystallised from absolute alcohol–light petroleum; it melted at 179° (decomp.) and was soluble in water and alcohol, but insoluble in other solvents.

Found: N, 12·49; S, 14·46%

$C_{10}H_{10}O_2N_2S$ requires N, 12·61; S, 14·41%

The acidic properties of the compound and the analysis indicated it to be *benziminazole-2-α-mercaptopropionic acid*, $C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH(CH_3)\cdot CO_2H$ which was previously obtained impure by the hydrolysis of its ethyl ester (compare page 64).

It would appear that this acid could only be formed in the course of the foregoing reaction by the hydration of the dicyclic compound, as without doubt, the sodium had reacted with the open-chain ester. It was thought that the aqueous hydrochloric acid used for neutralisation had probably brought this about, and it was decided to modify the method, using dry gaseous hydrochloric acid to neutralise the sodium ethoxide.

The reaction was carried out as before, and after removing as much as possible of the excess sodium, the residue was dissolved in absolute alcohol. Into this solution was passed dry hydrochloric acid gas until the solution was neutral. Neutralisation was attended by the formation of an extremely disagreeable odour resembling mercaptan, even when the reaction-vessel was cooled in a freezing-mixture. After filtering off the precipitated sodium chloride, the solution was concentrated in an evacuated desiccator, and the ultimate residue was a yellowish gum which did not become solid. Acetone was found to be the only suitable solvent for crystallisation, and two recrystallisations gave the compound as a white, almost amorphous powder, m.p. 118-119°; it was very soluble in water, forming an acid solution, very soluble in alcohol and chloroform, and

insoluble in ether, benzene and light petroleum.
The molecular weight was determined by the ebullioscopic method in chloroform.

Found: N, 10·33% ; *M*, 112.

The analysis does not agree with that of the dicyclic compound, which requires N, 13·73% and *M*, 204.
The low nitrogen-content and the low molecular weight indicated it to be a decomposition product. It was not identified.

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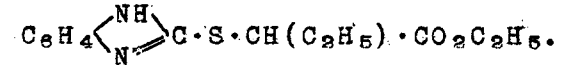
4. Ethyl α-Bromo-*n*-butyrate.

Ethyl Benziminazole-2-α-mercapto-n-butyrate,



$$C_6H_4\langle^{NH}_{N}\rangle C\cdot S\cdot CH(C_2H_5)\cdot CO_2C_2H_5.$$

Carried out in the usual manner, using ethyl α-bromo-*n*-butyate, the reaction gave a compound of similar properties and solubility. The phenomenon which may be dimorphism was again shown. The substance crystallised from ether-light petroleum in long prismatic needles, m.p. (in stable form) 108–109°
Yield 90%.

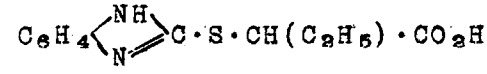
Found: N, 10·63; S, 12·30%

$C_{13}H_{18}O_2N_2S$ requires N, 10·60; S, 12·12%

As with the previous members of this series, the present compound was not decomposed to the mercapto-acid by boiling with sodium hydroxide solution; the subsequent addition of a lead salt produced no blackening.

Hydrolysis with hydrochloric acid led to a more definite result with this ester.

Benziminazole-2-α-mercapto-n-butyric acid,



The foregoing ester was boiled for half-an-hour under reflux with concentrated hydrochloric acid, and the solution evaporated to dryness on the water-bath and finally in an evacuated desiccator with soda-lime over sulphuric acid. The solid residue crystallised from hot water in glistening plates, m.p. 176° (with decomp.). The compound was soluble in water and alcohol, but insoluble in ether, benzene, chloroform and light petroleum. It had all the usual properties of an acid.

Found: N, 11·92; S, 13·74%

$C_{11}H_{12}O_2N_2S$ requires N, 11·87; S, 13·56%

Attempts were made to effect ring-closure by heating this acid with acetic anhydride or anhydrous oxalic acid, but these were unsuccessful.

Action of Sodium on Ethyl Benziminazole-2-α-mercapto-*n*-butyrate in Benzene solution.

Unsuccessful attempts having been made to bring about ring-closure of this ester by heating in benzene solution with phosphoric anhydride, the benzene solution was heated with excess of sodium wire, in the same manner as in the case of

ethyl benziminazole-2-α-mercaptopropionate.

A similar yellow solid was formed, and the benzene solution on evaporation gave a trace of unaltered ester only. The separation of the excess of sodium was effected as before, and the residue dissolved in absolute alcohol. Neutralisation with gaseous hydrochloric acid again caused the formation of a very disagreeable odour. The product of the reaction was also similar to the previous one, and was obtained from hot acetone as a white amorphous powder, m.p. 120°. Mixed m.p. determination showed it to be different from the compound of m.p. 119° which was obtained from the other ester.

Found: N, 9·66; S, 10·22%

The substance was not identified.

Action of Chloroacetic Acid on *o*-Phenylenethiocarbamide in Aqueous solution.

Benziminazole-2-mercaptoacetic acid, $C_6H_4\langle^{NH}_{N}\rangle C \cdot S \cdot CH_2 \cdot CO_2H$.

o-Phenylenethiocarbamide was dissolved in hot water along with chloroacetic acid (1 mol.), and the solution boiled under reflux for three hours. The crystals which separated on cooling were collected; the m.p. was indefinite, being over the range 190-210°. The substance was soluble in water and alcohol, but insoluble in other solvents. Recrystallisation from water or alcohol did not at first greatly improve the m.p. which

continued over a range of several degrees. It was found, however, that the first crop of crystals which separated from a hot aqueous solution were needles, m.p. 215°(decomp.) although the remainder of the crop still appeared to be a mixture, melting unsharply.

Analysis of the compound of m.p. 215° showed it to be the acid which was previously obtained impure by the hydrolysis of its esters.(compare pages 60 and 61).

Found: N, 18·46%

$C_9H_8O_2N_2S$ requires N, 18·46%

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7. Experiments with *ortho*-BENZOYLENETHIOCARBAMIDE, $C_6H_4\langle^{CO—NH}_{NH—C:S}$

ortho-Benzoylenethiocarbamide was prepared by the method of Rupe (*Ber.*, 1897, 30, 1089).

Reaction with Ethyl Chloroacetate:

(a) in presence of sodium ethoxide.

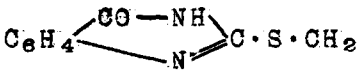
o-Benzoylenethiocarbamide dissolved in absolute alcohol was treated in the usual manner with sodium ethoxide (1 mol.), and after ten minutes' heating, ethyl chloroacetate (slightly more than 1 mol.) added. Sodium chloride was at once precipitated, and after heating for half-an-hour, the hot solution was filtered. No solid deposited from the filtrate even after concentration, and when all the solvent had been removed by allowing to stand in an evacuated desiccator, a pale-yellow, mobile oil remained. This was distilled under the high vacuum of the mercury pump (less than 1mm.); two main fractions were obtained, and these were separately analysed.

(1) b.p. 104–105°; Found: N, 8·93; S, 12·55, 12·56%

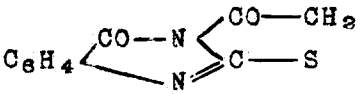
(2) b.p. 106–107°; Found: N, 8·91; S, 10·14, 10·38%

Whilst the nitrogen value was the same for both fractions, the sulphur values were widely different, indicating that the oil was a mixture which could not be separated into its components by distillation. None of the analytical results agreed with those required by either of the probable products of the

reaction,



requires N, 10·60; S, 12·12%



requires N, 12·84; S, 14·68%

Hydrolysis of a small quantity of the oil by boiling with sodium hydroxide solution gave mercaptoacetic acid (by Andreasch's test), indicating the presence of a substance containing the C·S·C group.

The original experiment was repeated, on this occasion with not more than 1 mol. of ethyl chloroacetate, and the oil distilled under vacuum as before. The side tube of the distilling-flask was filled with small pieces of glass tubing to act as a fractionating column. The fractions obtained were:-

(1) b.p. 104-105°

(2) b.p. 106-107°

(3) b.p. 110-111°; Found: S, 11·35%.

(4) b.p. above 115°

The fraction of b.p. above 115° was prepared for a further fractional distillation, and when air had been bubbling through the oil for a few minutes, a small quantity of a crystalline solid separated. The quantity did not increase on longer standing nor on cooling in a freezing-mixture. The solid was collected, and recrystallisation from absolute alcohol gave fine needles, m.p.149°; it was soluble in alcohol and benzene,

and sparingly soluble in light petroleum.

Found: S, 12·09%

$C_{12}H_{12}O_3N_2S$ requires S, 12·12%

Analysis showed the compound to be *ethyl 4-keto-3:4-dihydro-quinazoline-2-mercaptoacetate*, $C_6H_4\langle^{CO-NH}_{N=}\rangle C\cdot S\cdot CH_2\cdot CO_2C_2H_5$.

No further quantities of the substance were obtained.

Action of Sodium on the Oil in Benzene solution.

In the hope of obtaining the dicyclic compound, some of the oil obtained in the reaction with ethyl chloroacetate was heated in benzene solution with sodium wire. Evolution of gas indicated that a reaction was taking place, but the mixture very soon became dark and tarry, and on examination gave no results.

(b) in pyridine solution.

Molecular quantities of *o*-benzoylenethiocarbamide and ethyl chloroacetate were boiled in pyridine solution. The solution soon became almost black in colour, and removal of the pyridine under reduced pressure left a black, tarry residue which did not crystallise.

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8. Experiments with THIOCARBOHYDRAZIDE, $NH_2 \cdot NH \cdot CS \cdot NH \cdot NH_2$.

Attempts were made to prepare this substance by the method of Guha and Dé (*J. Chem. Soc.*, 1924, 125, 1215), but although the directions were followed in closest detail only traces at most of thiocarbohydrazide were obtained; the most of the product was, evidently, dithio-*b*-urazine. Variations of the method were likewise unsuccessful.

Thiocarbohydrazide was prepared by the method of Stollé and Bowles (*Ber.*, 1908, 41, 1099). Owing to lack of detail in the paper, considerable difficulty was experienced in obtaining the substance in quantity, but after repeated experiments, a process was adopted whereby a satisfactory yield of thiocarbohydrazide was obtained. The method is described in the Appendix (page 105).

Diacetonethiocarbohydrazone, $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:N \cdot NH \cdot CS \cdot NH \cdot N:C\!<\!\!\begin{matrix} CH_3 \\ CH_3 \end{matrix}$

Thiocarbohydrazide was heated under reflux with a large excess of dry acetone. After several hours all the solid had dissolved. The solution was then concentrated, and on cooling, crystals separated. Recrystallisation from absolute alcohol-light petroleum gave the compound as prismatic plates, m.p. 192° (decomp.). It was very soluble in alcohol and acetone and insoluble in light petroleum. Yield 90%.

Found: N, 30·28%

Calculated for $C_7H_{14}N_4S$: N, 30·11%

Prolonged boiling in the preparation appeared to be necessary to give the substance pure; otherwise the product was a mixture of mono- and di-acetonethiocarbohydrazones, giving analytical results for nitrogen which were high.

Diacetophenonethiocarbohydrazone, $\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}N{:}C\!<\!\!\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}$

Thiocarbohydrazide was heated in alcoholic suspension with acetophenone (slightly more than 2 mols.). After a few minutes a yellow colour developed and a clear solution soon resulted. Almost immediately, however, crystals commenced to separate, and soon the solution became almost solid. At the end of an hour the mass was cooled and the solid collected by filtration. It crystallised from alcohol-chloroform in very pale yellow, fine, prismatic needles, m.p. 199° with darkening in colour from 175° upwards. It was very soluble in chloroform, soluble in benzene, sparingly soluble in alcohol, ether and light petroleum and insoluble in water. Yield 90-95%.

Found: N, 18·11; S, 10·30%

Calculated for $C_{17}H_{18}N_4S$: N, 18·06; S, 10·32%

These two thiocarbohydrazones have been prepared by Guha and Dé (*J. Indian Chem. Soc.*, 1925, 2, 225) by methods differing in detail. They give the m.ps. of the diacetone and diacetophenone derivatives as 195° and 185° respectively.

Bis-dibenzyl ketone thiocarbohydrazone,

$$\begin{matrix} C_6H_5\cdot CH_2 \\ C_6H_5\cdot CH_2 \end{matrix}\!\!>\!C:N\cdot NH\cdot CS\cdot NH\cdot N:C\!<\!\!\begin{matrix} CH_2\cdot C_6H_5 \\ CH_2\cdot C_6H_5 \end{matrix}$$

Thiocarbohydrazide was heated with dibenzyl ketone (slightly more than 2 mols.) in alcohol until a clear yellow solution resulted. The solid which deposited on cooling crystallised from alcohol in fine needles, m.p. 143°. It was soluble in the usual solvents except water and light petroleum. Yield 90%.

Found: N, 11·39; S, 8·36%

$C_{31}H_{30}N_4S$ requires N, 11·48; S, 8·53%

Mono(ethyl acetoacetate) thiocarbohydrazone,

$$\begin{matrix} C_2H_5O_2C\cdot CH_2 \\ CH_3 \end{matrix}\!\!>\!C:N\cdot NH\cdot CS\cdot NH\cdot NH_2.$$

Thiocarbohydrazide in absolute alcoholic suspension was treated with ethyl acetoacetate (1 mol.) and the mixture boiled under reflux. After a few minutes the thiocarbohydrazide dissolved, and at the end of fifteen minutes' heating the solution was cooled. A white flocculent solid was deposited, and a further small quantity was obtained by concentration of the mother-liquors. The compound crystallised from alcohol in fine, prismatic needles, m.p. 160°; it was soluble in water, alcohol, benzene and chloroform, and very sparingly soluble in light petroleum. Yield 95%.

Found: N, 25·71; S, 14·67%

$C_7H_{14}O_2N_4S$ requires N, 25·88; S, 14·68%

On shaking an aqueous solution of the compound with benzaldehyde a yellowish solid separated; this crystallised from alcohol in small, almost colourless needles, m.p. 196°. From its properties, analysis and by comparisom with an authentic specimen, it was evidently identical with dibenzaldehydethiocarbohydrazone, $C_6H_5 \cdot CH:N \cdot NH \cdot CS \cdot NH \cdot N:CH \cdot C_6H_5$ previously described by Stollé and Bowles (*loc. cit.*).

Found: N, 19·61%

Calculated for $C_{15}H_{14}N_4S$: N, 19·85%

The formation of this compound showed that the benzaldehyde had preferentially displaced the ethyl acetoacetate residue.

Di(ethyl acetoacetate)thiocarbohydrazone,

$$C_2H_5O_2C \cdot CH_2 \atop CH_3 > C:N \cdot NH \cdot CS \cdot NH \cdot N:C < CH_2 \cdot CO_2C_2H_5 \atop CH_3$$

Thiocarbohydrazide and ethyl acetoacetate (2 mols.) were heated together in alcoholic solution under reflux. Solution of the thiocarbohydrazide readily took place, and after one hour's heating, the solution was cooled. No solid was deposited even after concentration, and removal of the solvent in an evacuated desiccator, gave an opaque syrupy liquid. This syrup would not solidify by cooling in a freezing-mixture. It was dissolved in a benzene-light petroleum mixture and on cooling there separated a very small amount of a crystalline solid, m.p. 150° (unsharp). This solid, which was probably an impure form of the mono-derivative, was filtered off, and the filtrate concentrated as before.

The pale-yellow oil which remained was now quite clear; it did not solidify on cooling, and was well washed with light petroleum (to remove any ethyl acetoacetate), dried and analysed. It was soluble in the usual solvents except light petroleum. Yield 80%.

Found: N, 16·96; S, 9·48%

$C_{18}H_{22}O_4N_4S$ requires N, 16·97; S, 9·70%

As in the case of the mono-derivative, treatment of this compound with benzaldehyde gave dibenzaldehydethiocarbohydrazone, both ethyl acetoacetate residues being displaced.

In order to find a suitable thiocarbohydrazone to react in presence of sodium ethoxide with esters of α-halogeno-acids, trial experiments were made with the two most conveniently formed — dibenzaldehydethiocarbohydrazone (Stollé and Bowles, *loc. cit.*) and diacetophenonethiocarbohydrazone. Of these, the latter gave the most favourable result with ethyl chloroacetate, and it was employed throughout the series of reactions. The sodium derivative was obtained pure.

Sodium Derivative of Diacetophenonethiocarbohydrazone,

$$\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C{:}N{\cdot}N{:}C(SNa){\cdot}NH{\cdot}N{:}C\!<\!\!\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}$$

Sodium ethoxide (1 mol.) in alcohol was added to an absolute alcoholic suspension of diacetophenonethiocarbohydrazone; A clear yellow solution was formed and after heating for ten

minutes the solution was cooled. The addition of dry ether caused the precipitation of a pale-yellow solid; this was collected, washed with ether, and dried in an evacuated desiccator over sulphuric acid. It dissolved in water forming an alkaline solution.

Found: Na, 6·90%

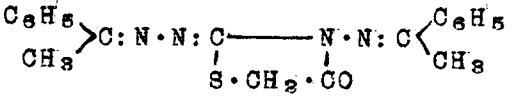
$C_{17}H_{17}N_4SNa$ requires Na, 6·93%

As in previous cases, it was unnecessary to isolate this derivative for the purpose of the reactions.

Action of Esters of α-Halogeno-acids on the Sodium derivative of Diacetophenonethiocarbohydrazone.

1. Ethyl Chloroacetate.

9-Phenylmethylmethyleneamino-2:4-diketotetrahydrothiazole-2-phenylmethylmethylenehydrazone,



Diacetophenonethiocarbohydrazone was boiled for ten minutes with sodium ethoxide (1 mol.) in alcohol, and to the warm solution ethyl chloroacetate (very slightly more than 1 mol.) added. Sodium chloride was immediately precipitated, and after heating for half-an-hour was filtered off and washed with a little hot absolute alcohol. The filtrate and washings on cooling deposited a yellowish solid which crystallised from alcohol-benzene in colourless needles, m.p. 175°. It was soluble

in alcohol, ether, benzene and chloroform, but insoluble in water and light petroleum. Yield 80%.

Found: N, 15·95; S, 9·27%

$C_{19}H_{18}ON_4S$ requires N, 16·00; S, 9·14%

3-Amino-2:4-diketotetrahydrothiazole-2-hydrazone Dihydrochloride,

$$NH_2\cdot N{:}\,C(S\cdot CH_2\cdot CO)\text{———}N\cdot NH_2, 2HCl$$

The foregoing compound was boiled under reflux for about ten minutes with a slight excess of N-hydrochloric acid. Acetophenone was liberated and remained as an oil from which the aqueous portion was decanted; final traces of acetophenone were removed by ether-extraction when cold. The aqueous portion was evaporated to small bulk under reduced pressure, and finally to dryness in an evacuated desiccator with soda-lime over sulphuric acid. The residue was a crystalline, extremely deliquescent solid which had to be manipulated in a dry atmosphere. The m.p. was indefinite.

Found: S, 14·49%

$C_4H_8ON_4S, 2HCl$ requires S, 14·61%

The *dibenzylidene* derivative, $C_6H_5\cdot CH{:}N\cdot N{:}\,C(S\cdot CH_2\cdot CO)\text{———}N\cdot N{:}CH\cdot C_6H_5$, was prepared by shaking an aqueous solution of the dihydrochloride with benzaldehyde. The product crystallised from alcohol in glistening plates, m.p. 188°; it was soluble in alcohol, ether and benzene, and insoluble in water and light petroleum.

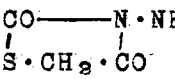
Found: N, 17·55%

$C_{17}H_{14}ON_4S$ requires N, 17·39%

Attempts to liberate the free hydrazone by treatment of the dihydrochloride in aqueous solution with sodium carbonate resulted in decomposition.

The hydrazone was subsequently obtained in a fairly pure by a different reaction (compare page 86).

3-Amino-2:4-diketotetrahydrothiazole Hydrochloride,



The hydrolysis of the compound of m.p. 175° was carried a stage further by boiling in an open vessel for about half-an-hour with concentrated hydrochloric acid. Most of the liberated acetophenone volatilised, and final traces were removed by ether-extraction when cold. The acid solution was evaporated to dryness on the water-bath and finally in an evacuated desiccator with soda-lime over sulphuric acid. The residue, after being washed with dry ether, was extracted with a little hot absolute alcohol; hydrazine hydrochloride (proved by conversion into benzalazine) remained undissolved. The alcoholic 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. The m.p. was indefinite.

Found: S, 19·09, 18·99%

$C_3H_4O_2N_2S,HCl$ requires S, 18·99%

The hydrochloride was obtained in good yield, but attempts to liberate the free base were unsuccessful.

The *benzylidene* derivative, $\begin{matrix}CO\text{——}N\cdot N:CH\cdot C_6H_5\\ |\qquad\quad |\\ S\cdot CH_2\cdot CO\end{matrix}$, was prepared from the hydrochloride by shaking with benzaldehyde in aqueous solution; it crystallised from alcohol in fine needles, m.p. 158°, and was insoluble in water, ether and light petroleum.

Found: S, 14·60%

$C_{10}H_8O_2N_2S$ requires S, 14·54%

2. Ethyl α-Bromopropionate.

3-Phenylmethylmethyleneamino-2:4-diketo-5-methyltetrahydrothiazole-2-phenylmethylmethylenehydrazone,

$$\begin{matrix}C_6H_5\\ CH_3\end{matrix}\!\!>C:N\cdot N:\underset{\displaystyle S\cdot CH(CH_3)\cdot CO}{C\text{——}N}\cdot N:C<\!\!\begin{matrix}C_6H_5\\ CH_3\end{matrix}$$

This reaction was carried out in exactly the same manner as in the case of ethyl chloroacetate, using ethyl α-bromopropionate(just more than 1 mol.). After removal of the sodium bromide the solution deposited a solid on cooling. It showed a similar solubility to the previous compound, and crystallised from alcohol in prismatic needles, m.p. 150°. Yield 90%.

Found: N, 15·45; S, 8·67%

$C_{20}H_{20}ON_4S$ requires N, 15·38; S, 8·79%

Hydrolysis of this compound did not lead to very definite results; there was apparently no sharp distinction between the

action of dilute and concentrated hydrochloric acid as in the case of the first member of the series.

Hydrolysis with N-hydrochloric acid removed acetophenone as before, but concentration of the aqueous liquor gave a mixture containing hydrazine hydrochloride, showing that the hydrolysis had been carried beyond the first stage. Owing to the deliquescent nature of the hydrochlorides, it was not possible to effect a separation. Repeated experiments showed that even extremely dilute hydrochloric acid removed some hydrazine in addition to acetophenone, and the analytical results of the hydrochlorides obtained varied in each experiment.

Hydrolysis with concentrated hydrochloric acid did not give the 3-amino-2:4-diketo-5-methyltetrahydrothiazole hydrochloride as expected. The thiazole-ring appeared to be completely broken, and the products were hydrazine hydrochloride, acetophenone, and an oil which was identified as α-mercaptopropionic acid, $CH_3 \cdot CH(SH) \cdot CO_2H$ by its colour reaction with ferric chloride solution.

Repeated experiments with varying strengths of acid failed to give the necessary conditions for the formation of any one of the hydrochlorides alone.

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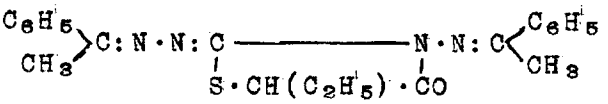
3. Ethyl α-Bromo-*n*-butyrate.

3-Phenylmethylmethyleneamino-2:4-diketo-5-ethyltetrahydrothiazole-2-phenylmethylmethylenehydrazone,



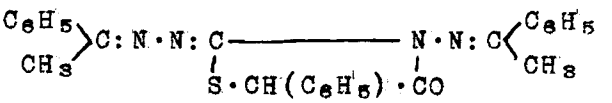
The reaction was carried out in the usual manner with ethyl α-bromo-*n*-butyrate, and the product was deposited from the alcoholic filtrate on cooling. It showed a similar solubility to the previous compounds of the series, and crystallised from alcohol in needles, m.p. 110°. Yield 90%.

Found: N, 15·04; S, 8·42%

$C_{21}H_{22}ON_4S$ requires N, 14·81; S, 8·47%

4. Ethyl Phenylbromoacetate.

3-Phenylmethylmethyleneamino-2:4-diketo-5-phenyltetrahydrothiazole-2-phenylmethylmethylenehydrazone,



The reaction was carried out as before, using ethyl phenylbromoacetate; in this case, the product of the reaction was more soluble in alcohol than the previous compounds, and further crops were obtained by concentration of the mother-liquors. Recrystallisation from alcohol-benzene gave the compound in prismatic needles, m.p. 165°; it was soluble in alcohol, ether, benzene and chloroform, very sparingly soluble in light petroleum, and

insoluble in water. Yield 80%.

Found: N, 13·18; S, 7·42%

$C_{25}H_{22}ON_4S$ requires N, 13·14; S, 7·51%

On hydrolysis, the two foregoing compounds behaved in a similar manner to the compound derived from ethyl α-bromopropionate.

Dilute hydrochloric acid hydrolysed the compounds to acetophenone and mixtures containing hydrazine hydrochloride, the dihydochloride of the intermediate hydrazone, and the hydrochloride of the thiazole.

Concentrated hydrochloric acid gave acetophenone, hydrazine hydrochloride, and the corresponding mercapto-acid.

It was not found possible to arrest the hydrolysis at the first stage in order to obtain only the dihydrochloride of the hydrazone, nor was it possible to find an acid of the required strength to remove acetophenone and hydrazine without causing rupture of the thiazole-ring.

Action of Esters of α-Halogeno-acids on the Sodium derivative of Thiocarbohydrazide.

As discussed in the theoretical section, it was decided to investigate the possibility of a reaction between thiocarbohydrazide (in presence of sodium ethoxide) and the esters of α-halogeno-acids.

Thiocarbohydrazide in absolute alcoholic suspension was treated with sodium ethoxide (1 mol.) in alcohol; the solution which was formed was heated for ten minutes. No attempts were made to isolate the sodium derivative, and the alcoholic solution was employed directly to react with the esters.

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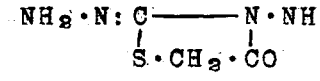
1. Ethyl Chloroacetate.

3-Amino-2: 4-diketotetrahydrothiazole-2-hydrazone,



To the alcoholic solution of the sodium derivative of thiocarbohydrazide (obtained as described above) was added ethyl chloroacetate (1 mol.). After heating for half-an-hour the precipitated sodium chloride was filtered off, and the filtrate on cooling deposited a crystalline solid, m.p. 110-114°. Recrystallisation from alcohol gave the compound in prismatic needles, m.p. 119-120°; it was soluble in water, alcohol and pyridine, but insoluble in other organic solvents.
The analytical results differed somewhat from the theoretical values, but they were not altered by repeated crystallisation

of the compound either from alcohol or pyridine-light petroleum.

Found: N, 39·54, 39·51; S, 28·14%

$C_3H_6ON_4S$ requires N, 38·35; S, 21·92%

The compound was quite different from that obtained by Guha and Dé (*J. Indian Chem. Soc.*, 1925, 1, 141) by the interaction of thiocarbohydrazide and ethyl chloroacetate (1 mol.) in presence of potassium hydroxide (1 mol.).

Whatever the impurity was, it evidently could not be removed by repeated crystallisation of the compound; essentially the product was 3-amino-2:4-diketotetrahydrothiazole-2-hydrazone, for on warming with benzaldehyde in aqueous alcoholic solution, it readily gave a dibenzylidene derivative which crystallised from alcohol in glistening plates, m.p. 139°, and was identical with the dibenzylidene derivative previously prepared from the dihydrochloride of this hydrazone. (compare page 80).

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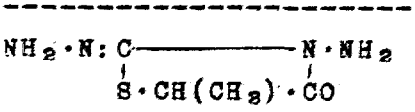
2. Ethyl α-Bromopropionate.

3-Amino-2:4-diketo-5-methyltetrahydrothiazole-2-hydrazone,



The alcoholic solution of the sodium derivative of thiocarbohydrazide (prepared as before) was treated with ethyl α-bromopropionate (1 mol.); heating was continued for half-an-hour, a little dry benzene being added to assist the precipitation of sodium bromide. The solution was filtered hot and on cooling,

the filtrate deposited a very small quantity of solid. This was identified as unaltered thiocarbohydrazide, by conversion into the dibenzylidene derivative, m.p. 196°, and comparing with an authentic specimen.

Concentration of the mother-liquors gave a further yield of solid which crystallised from absolute alcohol-light petroleum in rhombic plates, m.p. 100-101°. It was soluble in water and alcohol, and insoluble in light petroleum.

Found: S, 19·95%

$C_4H_8ON_4S$ requires S, 20·00%.

The *dibenzylidene* derivative, $C_6H_5\cdot CH:N\cdot N:C(S\cdot CH(CH_3)\cdot CO)\cdot N\cdot N:CH\cdot C_6H_5$ prepared by heating the base in alcoholic solution with benzaldehyde, crystallised from aqueous alcohol in small, prismatic needles, m.p. 114°. It was soluble in alcohol, ether and benzene, but insoluble in water and light petroleum.

Found: N, 16·69%

$C_{18}H_{18}ON_4S$ requires N, 16·66%

3. Ethyl ∝-Bromo-*n*-butyrate.

3-Amino-2:4-diketo-5-ethyltetrahydrothiazole-2-hydrazone,

$NH_2\cdot N:C(S\cdot CH(C_2H_5)\cdot CO)\cdot N\cdot NH_2$

The reaction was carried out in the same manner as before, using ethyl ∝-bromo-*n*-butyrate (1 mol.) The filtrate after half-an-hour's heating deposited a small amount of unaltered

thiocarbohydrazide, and on concentration, a solid of m.p. 92–93°. Recrystallisation from absolute alcohol gave fine, glistening plates, m.p. 92–93°; the compound was very soluble in water and alcohol.

Found: S, 16·08%

$C_5H_{10}ON_4S$ requires S, 18·40%

Repeated crystallisation of the substance did not alter the m.p., nor bring the analytical result nearer the theoretical value; the results for different samples were not consistent, indicating mixtures to be present.

As in the case of the product obtained from ethyl chloroacetate this substance was essentially the hydrazone, for it readily gave the *dibenzylidene* derivative, $C_6H_5 \cdot CH:N \cdot N:C(S \cdot CH(C_2H_5) \cdot CO) \cdot N \cdot N:CH \cdot C_6H_5$ on treatment with benzaldehyde. This derivative crystallised from alcohol in almost colourless, prismatic needles, m.p. 106°; it was soluble in alcohol, ether and benzene, and insoluble in water and light petroleum.

Found: N, 16·01%

$C_{19}H_{18}ON_4S$ requires N, 16·00%

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9. Experiments with HYDRAZODICARBONTHIOAMIDE, $NH_2 \cdot CS \cdot NH \cdot NH \cdot CS \cdot NH_2$.

Hydrazodicarbonthioamide was prepared by the method of Freund and Wischewiansky (*Ber.*, 1893, 26, 2877).

Reaction with Ethyl Chloroacetate in presence of Sodium Ethoxide.

2:4-Diketotetrahydrothiazole-2-ketazine, $\begin{matrix} NH & & C & N \cdot N & C & & NH \\ | & & \| & & | & & | \\ CO \cdot CH_2 \cdot S & & & & S \cdot CH_2 \cdot CO & & \end{matrix}$

Hydrazodicarbonthioamide in hot absolute alcohol, was treated with sodium ethoxide (2 mols.) in alcohol. The yellow solution at first formed soon became colourless, and after heating for ten minutes, ethyl chloroacetate (very slightly more than 2 mols.) was added. The bulky precipitate which was immediately formed was collected after half-an-hour's heating, washed with warm water until free from sodium chloride, and then with alcohol and ether. The substance was quite insoluble in water and all organic solvents including glacial acetic acid and "dioxan". It decomposed at a high temperature without melting. A sample was carefully washed, dried and analysed. Yield 100%.

Found: N, 24·13; S, 27·63%

$C_6H_6O_2N_4S$ requires N, 24·35; S, 27·83%

The compound was evidently identical with that previously prepared by Frerichs and Förster (*Ann.*, 1909, 371, 257) and by

Frerichs and Höller (*Ann.*, 1913, 398, 256) by the interaction of hydrazodicarbonthioamide and chloroacetic acid in aqueous solution, and to which they gave the structure

bis-thiohydantoin, $NH{:}C(S{\cdot}CH_2{\cdot}CO)N{-}N(OC{\cdot}CH_2{\cdot}S)C{:}NH$.

Hydrolysis of the compound (irrespective of the method of preparation) gave results which favoured the ketazine-structure in preference to the thiohydantoin-structure given by Frerichs.

As noted by these Authors, the compound dissolved in cold sodium hydroxide solution, and was reprecipitated on acidifying; but, boiling of the sodium hydroxide solution for five minutes caused hydrolysis, the addition of hydrochloric acid no longer caused precipitation, and the presence of mercaptoacetic acid was proved by Andreasch's test. This showed rupture of the ring, but proved the arrangement C·S·C.

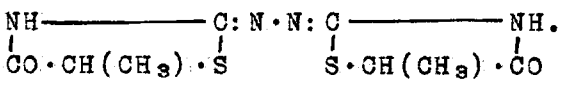
The compound was boiled under reflux with concentrated hydrochloric acid until it had completely dissolved. The solution was evaporated to dryness on the water-bath, and finally in an evacuated desiccator with soda-lime over sulphuric acid. The solid residue was extracted with hot benzene, and on cooling, the benzene solution deposited a crystalline solid, m.p. 126°. Comparison with an authentic specimen showed this to be identical with 2:4-diketotetrahydrothiazole $NH(CO{\cdot}CH_2{\cdot}S)CO$, previously prepared by different methods by Wheeler and Barnes (*Amer. Chem. J.*, 1900, 24, 60) and by Wilson and Burns (*J. Chem. Soc.*, 1922, 121, 870).

That portion of the hydrolysis-residue insoluble in benzene was found to be hydrazine hydrochloride (proved by conversion into benzalazine).

The formation of these two substances cannot be easily explained from the structure given by Frerichs; on the other hand these are the products which would be expected by the hydrolysis of a compound of the ketazine type.

Reaction with α-Bromopropionic Acid in Aqueous solution.

2:4-Diketo-5-methyltetrahydrothiazole-2-ketazine,



Hydrazodicarbonthioamide was boiled in aqueous solution with α-bromopropionic acid (2 mols.); the solid which was deposited in a very few minutes was collected, washed with water, dried and recrystallised from hot glacial acetic acid. Frerichs and Höller (*loc. cit.*) who prepared the compound by the above method, and assigned to it the thiohydantoin-structure, stated the m.p. to be "over 280°"; the m.p. was now found to be sharp at 289°.

The substance was boiled for half-an-hour with concentrated hydrochloric acid, and the solution evaporated to dryness in the usual manner. The semi-solid residue was extracted with hot benzene and the undissolved portion identified as hydrazine hydrochloride, by conversion into benzalazine.

On evaporating the benzene solution a viscous oil remained which distilled at 166-168° at 20mm. pressure. On standing, it solidified to a crystalline solid, which crystallised from benzene-light petroleum. The m.p. was 46-47°.

From its properties, it was evidently identical with 2:4-diketo-5-methyltetrahydrothiazole, $\begin{matrix}NH\text{———}CO\\ |\quad\quad\quad |\\ CO\cdot CH(CH_3)\cdot S\end{matrix}$, previously described by Wheeler and Barnes (*loc. cit.*) and Wilson and Burns (*J. Chem. Soc.*, 1923, 123, 799), who prepared it by different methods.

Reaction with α-Bromo-*n*-butyric acid in Aqueous solution.

2:4-Diketo-5-ethyltetrahydrothiazole-2-ketazine,

$$\begin{matrix}NH\text{———}C:N\cdot N:C\text{———}NH\\ |\quad\quad\quad |\quad\quad\quad |\quad\quad\quad |\\ CO\cdot CH(C_2H_5)\cdot S\quad\quad S\cdot CH(C_2H_5)\cdot CO\end{matrix}$$

Hydrazodicarbonthioamide was boiled in aqueous solution with α-bromo-*n*-butyric acid (2 mols.); the solid which deposited was collected, washed with water, dried and crystallised from hot glacial acetic acid in weakly rose-coloured plates. The m.p. was found to be 233° (Frerichs gives 225-226°). The acetic acid of crystallisation was removed by washing the compound with ether and allowing it to stand exposed to the air.

Found: N, 19·55%

Calculated for $C_{10}H_{14}O_2N_4S_2$: N, 19·58%

The substance was hydrolysed by boiling with concentrated hydrochloric acid and the solution evaporated to dryness in the

usual manner. The residue was extracted with hot benzene, and the undissolved portion found to consist of hydrazine hydrochloride only.

On evaporation, the benzene solution gave a colourless oil which solidified on cooling in a freezing-mixture; it crystallised from benzene-light petroleum in prisms, m.p. 64-65°.

From its properties it was evidenly identical with 2:4-diketo-5-ethyltetrahydrothiazole, $\begin{matrix}NH\text{——————}CO\\ |\qquad\qquad\quad |\\ CO\cdot CH(C_2H_5)\cdot S\end{matrix}$, previously described by Wheeler and Barnes (*loc. cit.*) and by Wilson and Burns (*loc. cit.*).

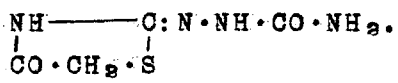
10. Experiments with HYDRAZOTHIODICARBONAMIDE, $NH_2 \cdot CS \cdot NH \cdot NH \cdot CO \cdot NH_2$.

Hydrazothiodicarbonamide was prepared by the method of Freund and Schander (*Ber.*, 1896, 22, 2508).

This thiocarbamide was found to be quite insoluble in alcoholic sodium ethoxide and also in pyridine. Hence, the only possibility of thiazole-formation lay in a reaction with chloroacetic acid in aqueous solution.

Reaction with Chloroacetic Acid in Aqueous solution.

2:4-Diketotetrahydrothiazole-2-semicarbazone,



Hydrazothiodicarbonamide was boiled in aqueous solution along with chloroacetic acid (1 mol.). At the end of two minutes a crystalline solid commenced to separate, and the quantity increased so rapidly that after five minutes boiling could no longer be continued. The solid was filtered off while hot, and the filtrate deposited only a very small amount of solid on cooling. The substance was insoluble in all organic solvents, and only very sparingly soluble in hot water. Recrystallised from hot water, it was obtained as small, glistening plates; it commenced to decompose, turning brown, at 210° and melted with complete decomposition at 221–222°. Yield 35%.

Found: N, 32·00; S, 18·46%

$C_4H_6O_2N_4S$ requires N, 32·19; S, 18·40%

Since the yield of the semicarbazone was only 35%, the mother-liquors of the reaction were boiled under reflux for a further period of fifteen minutes; no more solid was deposited, even on cooling.

The solution was then concentrated under reduced pressure, and finally taken to dryness in an evacuated desiccator containing soda-lime; the residue was a crystalline solid. The total weight of solid thus obtained from the reaction was somewhat greater than the theoretical weight, calculated as 2:4-diketo-tetrahydrothiazole-2-semicarbazone.

The solid residue was extracted several times with hot benzene, and on cooling, there crystallised from the solution a solid, m.p. 128° which was identified as 2:4-diketotetrahydrothiazole, NH———CO, by comparison with an authentic specimen.
CO·CH_2·S

That portion of the residue insoluble in benzene contained no sulphur, and was identified as semicarbazide hydrochloride, $NH_2·NH·CO·NH_3$,HCl. It was very soluble in water, and on shaking with benzaldehyde, the solution gave a solid which crystallised from alcohol in needles. This derivative softened at 220° and melted at 228°; it was soluble in alcohol, and very sparingly soluble in ether.

Found: N, 25·68%

Calculated for $C_8H_9ON_3$: N, 25·77%

The properties and analysis of the substance indicated it to be benzaldehyde semicarbazone, $C_6H_5 \cdot CH:N \cdot NH \cdot CO \cdot NH_2$ and confirmation was afforded by a mixed m.p. test with an authentic specimen, when no depression was shown.

Thus it appeared that the hydrochloric acid eliminated in the course of the reaction between the hydrazothiodicarbonamide and the chloroacetic acid had brought about a partial hydrolysis of the 2:4-diketotetrahydrothiazole-2-semicarbazone. This fact accounted for the small yield of the semicarbazone and also the apparent high yield of solid products from the reaction.

As was the case with the corresponding ketazine (compare page 91) this semicarbazone was soluble in cold sodium hydroxide solution and was reprecipitated on acidification; but, when the sodium hydroxide solution was boiled for a few minutes, the addition of acid no longer caused precipitation, and the presence of mercaptoacetic acid was proved by Andreasch's test. This showed the arrangement C·S·C in the ring.

The semicarbazone was boiled for two hours under reflux with N-hydrochloric acid; a very small amount of solid which remained was removed by filtration, and the solution concentrated and finally taken to dryness in the usual manner. Extraction of the solid residue with hot benzene removed 2:4-diketotetrahydrothiazole, semicarbazide hydrochloride remaining undissolved; both substances were identified as before.

Hydrolysis of the compound with concentrated hydrochloric acid

gave a residue which consisted of 2:4-diketotetrahydrothiazole, hydrazine hydrochloride and ammonium chloride, the two latter substances being formed by the hydrolysis of the semicarbazide hydrochloride.

The results of the hydrolysis prove the correctness of the structure assigned to the compound.

APPENDIX

The following pages contain a description of some of the preparations carried out in the course of the research, including those of the various thiocarbamides employed.

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1. δ-Phenylthiosemicarbazide, $NH_2 \cdot NH \cdot CS \cdot NHC_6H_5$.

(Pulvermacher, *Ber.*, 1894, 27, 615.)

$$C_6H_5 \cdot N:C:S + NH_2 \cdot NH_2 = NH_2 \cdot NH \cdot CS \cdot NHC_6H_5$$

To an alcoholic solution of pure hydrazine hydrate cooled in ice was gradually added phenyl mustard oil (slightly less than 1 mol.), with constant shaking of the reaction-vessel. A solid separated at once, and after the solution had almost solidified the crystals were filtered off and washed with cold alcohol. Recrystallisation from hot alcohol gave the compound as prisms, m.p. 140°. Yield almost theoretical.

The compound was soluble in hot water, alcohol and chloroform, only very sparingly soluble in benzene, and insoluble in ether and light petroleum.

---

2. α-Phenylthiosemicarbazide, $NHC_6H_5 \cdot NH \cdot CS \cdot NH_2$.

(Fischer and Besthorn, *Ann.*, 1882, 212, 324.)

A mixture of molecular quantities of phenylhydrazine hydrochloride and ammonium thiocyanate was boiled under reflux for

twelve hours with two and a half times the weight of absolute alcohol. The crystalline solid which had separated after standing for twelve hours was collected and washed with a little cold water. It recrystallised from alcohol in prisms, m.p. 200-201°; it was readily soluble in alcohol, ether, benzene and chloroform.

---

8. Ethyl Phenylbromoacetate, $CH(C_6H_5)Br \cdot CO_2C_2H_5$.

(Hell and Wenizweig, *Ber.*, 1895, 28, 2447.)

This ester was prepared from mandelic acid, $C_6H_5 \cdot CH(OH) \cdot COOH$ by substituting both hydroxyl groups with bromine, using amorphous phosphorus, and decomposing the resulting bromacid-bromide with absolute alcohol.

15·2gm. mandelic acid were intimately mixed with 6·0gm. red phosphorus by grinding the two together in a mortar and the mixture placed in the reaction-flask which was connected to a reflux condenser carrying an arrangement for admitting bromine and for absorbing hydrogen bromide. Bromine was added very slowly, the reaction at first being exceedingly vigorous, and necessitating the cooling of the reaction-vessel in a freezing-mixture. The reaction gradually became less violent, and after 80gm. bromine had been added, the whole was warmed on the water-bath until hydrogen bromide ceased to be evolved.

The bromacid-bromide so obtained was cooled in a freezing-mixture and decomposed by adding, drop by drop, a slight excess (about

ten c.cs.) of absolute alcohol. This reaction was also very vigorous and effective cooling was necessary.

The ester so formed was poured off and washed with water until free from acid; it was then dried over anhydrous sodium sulphate and distilled under reduced pressure.

Several different boiling-points are recorded in the literature; several observers, however, give 145° at 15mm., and this corresponded with the main fraction obtained in the distillation.

---

4. Ethylenethiocarbamide, $\begin{matrix}CH_2—NH\\ |\\ CH_2—NH\end{matrix}\rangle C:S.$

(Hofmann, *Ber.*, 1872, 5, 242.)

$$(C_2H_4)H_4N_2 + CS_2 = (C_2H_4)H_4N_2 \cdot CS_2$$

$$(C_2H_4)H_4N_2 \cdot CS_2 = C_3H_6N_2S + H_2S$$

To an alcoholic solution of ethylenediamine was gradually added an alcoholic solution of carbon disulphide (just more than 1 mol.). A yellowish, opaque, gummy mass was immediately formed; on standing for a short time this mass changed into an almost white amorphous powder, almost insoluble in alcohol.

This solid was collected, dissolved in water, and the solution boiled until hydrogen sulphide was no longer evolved.

Ethylenethiocarbamide was deposited on cooling, and recrystallised from hot water in prisms, m.p. 196°; it was soluble in alcohol, but only sparingly soluble in ether. As stated in the experimental section, the m.p. was 2° higher than that given by Hofmann (compare page 47). Yield 80%.

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5. *l*-Menthyl Chloroacetate, $CH_2Cl \cdot CO_2C_{10}H_{19}$.

(Frankland and Barrow, *J. Chem. Soc.*, 1914, 105, 992.)

20gm. menthol and 8·3gm. chloroacetic acid were melted together and saturated with dry hydrogen chloride gas. After heating for two and a half hours on the water-bath, a small quantity of water which had formed during the reaction was removed by means of a separating-funnel. The mixture was again saturated with hydrogen chloride and a further small quantity of water removed. The resulting liquid was distilled under reduced pressure, and the fraction boiling at 137-140° at 14mm. collected separately.

---

6. *n*-Butyl Chloroacetate, $CH_2Cl \cdot CO_2C_4H_9$.

(Gehring, *Bull. Soc. chim.*, [2], 1886, 46, 147.)

18·9gm. chloroacetic acid were dissolved in 14·8gm. *normal* butyl alcohol, contained in a flask fitted with a reflux condenser. The solution was then thoroughly saturated with dry hydrogen chloride gas; during the passage of the gas the solution warmed considerably. After having been saturated, the mixture was allowed to stand for several hours, and the reaction then completed by heating on the water-bath for two hours and finally for a short time in an oil-bath up to 135°, hydrogen chloride being passed continuously.

After cooling, the liquid was poured into water, and the oil which fell to the bottom separated. This was washed with water,

dried over anhydrous calcium chloride and distilled. The main fraction boiling at 179–180° was collected separately.

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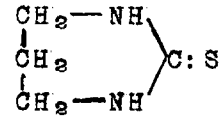
7. Trimethylenethiocarbamide, 

(Schacht, *Arch. Pharm.*, 1897, 235, 461.)

This thiocarbamide was prepared in a similar manner to ethylenethiocarbamide.

To a well-cooled solution of trimethylenediamine in alcohol was added carbon disulphide (just over 1 mol.) in alcohol. A sticky mass was formed which did not become solid even after standing for a considerable time. The alcoholic liquor was decanted, the mass dissolved in water, and the solution boiled until hydrogen sulphide ceased to be evolved. On cooling, trimethylenethiocarbamide was deposited; it recrystallised from alcohol in rhombic prisms, m.p. 207°.

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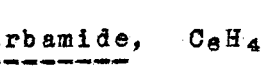
8. *ortho*-Phenylenethiocarbamide, 

(Lellmann, *Ann.*, 1883, 221, 9.)

To *ortho*-phenylenediamine was added the necessary quantity of hydrochloric acid to form the dihydrochloride, and then somewhat more than 2 mols. of ammonium thiocyanate. The solution, which became brown in colour, was evaporated to a syrupy consistency on the water-bath. The *o*-phenylenediamine dithiocyanate so formed is easily soluble in water; to change this salt to

o-phenylenethiocarbamide, the mass was heated for one hour in an air-bath at 120-130°, and the hard, dry product thus obtained digested with cold water. By this process the salts present dissolved, and the thiocarbamide, which remained undissolved, was filtered off. It was in the form of greyish leaflets, and was purified by dissolving in boiling alcohol and diluting the solution with water until turbid. On cooling, the thiocarbamide crystallised in almost colourless plates. The m.p. was found to be 296°, which agrees with one reference in the literature; Lellmann gives 290°. It was readily soluble in alcohol, only sparingly soluble in water, and insoluble in benzene, chloroform and light petroleum. Yield 75-80%.

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9. Ethyl α-Bromopropionate, $CH_3 \cdot CHBr \cdot CO_2C_2H_5$.

(Zelinsky, *Ber.*, 1887, 20, 2026.)

To 30gm. propionic acid were added 3·1gm. amorphous phosphorus, and drop by drop, 40gm. bromine. When hydrogen bromide ceased to be evolved, the mixture was warmed under an efficient reflux condenser and a further quantity of 64gm. bromine added. The bromination proceeded rapidly at a temperature of 40-50°C, and the reaction was finished when no bromine vapour was seen in the condenser.

The resulting bromacid-bromide was cooled and decomposed by the cautious addition of a slight excess of absolute alcohol. The ester so formed was poured into water, washed free from acid

with a dilute solution of sodium carbonate, dried over anhydrous sodium sulphate and distilled. The ester distilled at 156–160° without decomposition.

---

10. *ortho*-Benzoylenethiocarbamide, $C_6H_4\begin{cases}CO—NH\\ NH—C:S\end{cases}$

(Rupe, *Ber.*, 1897, 30, 1089.)

Ethyl anthranilate was dissolved in dry ether and the solution saturated with dry hydrogen chloride gas; the hydrochloride was precipitated and was collected, washed with ether and dried.

To a concentrated cold aqueous solution of ethyl anthranilate hydrochloride was added an aqueous solution of potassium thiocyanate (slightly more than 1 mol.); *o*-benzoylenethiocarbamide was immediately formed as a mass of needles.

It recrystallised from benzene and melted at 121°.

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11. Thiocarbohydrazide, $NH_2\cdot NH\cdot CS\cdot NH\cdot NH_2$.

(Stollé and Bowles, *Ber.*, 1908, 41, 1099.)

$$2(NH_2\cdot NH_2) + CS_2 = NH_2\cdot NH\cdot CS\cdot S\cdot N_2H_5$$

$$NH_2\cdot NH\cdot CS\cdot S\cdot N_2H_5 + PbO = NH_2\cdot NH\cdot CS\cdot NH\cdot NH_2 + H_2O + PbS.$$

Hydrazine and carbon disulphide form the addition product hydrazine dithiocarbazinate; by treatment with lead oxide, this substance loses one atom of sulphur and two atoms of hydrogen, and is transformed into thiocarbohydrazide. The following method gave the best yield of thiocarbohydrazide.

To an alcoholic solution of hydrazine hydrate (or the aqueous solution obtained by distilling hydrazine sulphate with sodium hydroxide) well cooled in ice was added carbon disulphide (somewhat more than 1 mol.); during this process the solution was vigorously stirred. In a short time, hydrazine dithiocarbazinate was deposited as a white crystalline solid.

This solid was collected, washed with a little cold water and dissolved in warm water. The solution was heated on the water-bath and finely powdered lead oxide (litharge) added in small quantities at a time. Continuous and very vigorous stirring was essential throughout the reaction. The lead oxide was rapidly turned black due to the formation of sulphide.

Heating and the addition of lead oxide was continued until hydrogen sulphide was no longer detected and ammonia commenced to be evolved; this required from three to five hours, depending on the rate of heating. Small quantities of warm water were added from time to time to prevent the solution from becoming too concentrated; unless this was done, there was considerable loss of thiocarbohydrazide due to decomposition.

At the end of the necessary time the hot mixture was filtered, and the residue extracted several times with hot water. On cooling, the filtrate and washings deposited thiocarbohydrazide; it was pure after one recrystallisation from hot water, m.p. 169°. As reported by Stollé and Bowles, the yield is very variable; the best was about 40% as claimed by these observers.

12. Hydrazodicarbonthioamide, $NH_2 \cdot CS \cdot NH \cdot NH \cdot CS \cdot NH_2$.

(Freund and Wischnewiansky, *Ber.*, 1893, 26, 2877.)

Hydrazine sulphate and ammonium thiocyanate (2 mols.) were boiled together in aqueous solution for several hours. Hydrazodicarbonthioamide was deposited on cooling; it recrystallised from hot water in long prisms, m.p. 214-215°.

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13. Thiosemicarbazide, $NH_2 \cdot NH \cdot CS \cdot NH_2$.

(Freund and Schander, *Ber.*, 1896, 29, 2500.)

100gm. hydrazine sulphate were warmed in a beaker with 400 c.c. of distilled water. 54gm. anhydrous potassium carbonate were then added in small quantities at a time with constant stirring; a brisk wvolution of carbon dioxide took place, and the readily-soluble normal sulphate was formed.

80gm. potassium thiocyanate were added, the mixture stirred and heated to boiling-point; a double decomposition took place, with the formation of hydrazine thiocyanate and potassium sulphate. After five minutes' boiling, the potassium sulphate was precipitated by the addition of 500c.cs. hot alcohol, and removed by filtering the hot solution at the pump. The filtrate containing the hydrazine thiocyanate was distilled to remove as much alcohol as possible and then evaporated in a porcelain basin over a free flame; during this evaporation the liquid was continuously stirred. After a time, the evolution of steam ceased and the mass commenced to effervesce, ammonia being evolved. When the

reaction became too violent, it was checked by the addition of a little cold water. On cooling, the reaction-mixture solidified to a crystalline mass of thiosemicarbazide. A small quantity of cold water was added, the paste filtered and the filtrate evaporated to a syrup as before; this was repeated four or five times. The various crops of crystals were combined and recrystallised from water, the mother-liquors yielding more thiosemicarbazide on concentration. The m.p. of the product was 182·5°.

Yield 43gm.

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14. Hydrazothiodicarbonamide, $NH_2 \cdot CS \cdot NH \cdot NH \cdot CO \cdot NH_2$.

(Freund and Schander, *Ber.*, 1898, 22, 2508.)

This thiocarbamide was prepared from thiosemicarbazide hydrochloride and potassium cyanate.

Finely powdered thiosemicarbazide was ground in a mortar with concentrated hydrochloric acid; it was rapidly converted to the hydrochloride, which was filtered off as a crystalline mass; the salt dissolves in four parts of water at the ordinary temperature.

To an aqueous solution of thiosemicarbazide hydrochloride (at ordinary temperature) was added an aqueous solution of potassium cyanate (1 mol.). A crystalline mass separated at once; this was collected and recrystallisation from hot water gave hydrazothiodicarbonamide in needles. It sintered about 210° and melted with complete decomposition between 218 and 220°.

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15. Acetonethiosemicarbazone, $(CH_3)_2C{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2$.

(Freund and Schander, *Ber.*, 1902, **35**, 2602.)

Thiosemicarbazide was gently boiled under reflux with an equal weight of acetone. Solution of the thiosemicarbazide soon took place, and on cooling the thiosemicarbazone was deposited. It sintered at 174° and melted at 182°.

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16. Acetophenonethiosemicarbazone, $(C_6H_5)(CH_3)C{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2$.

(Neuberg and Neimann, *Ber.*, 1902, **35**, 2409.)

Thiosemicarbazide and acetophenone (in molecular proportions) were boiled together for two hours in aqueous alcoholic solution. On cooling, the thiosemicarbazone separated as an oil which soon solidified. Recrystallisation from benzene gave the compound pure, m.p. 108°.

BIBLIOGRAPHY

The following is a list, in alphabetical order, of the principal papers consulted in the course of the investigation. It includes those describing the preparations of the substances as given in the Appendix.

Brown, Pickering and Wilson, *J. Chem. Soc.*, 1927, **131**, 107.

Evers, *Ber.*, 1888, **21**, 975.

Fischer and Besthorn, *Ber.*, 1882, **212**, 324.

Frankland and Barrow, *J. Chem. Soc.*, 1914, **105**, 992.

Frerichs and Förster, *Ann.*, 1909, **371**, 257.

Frerichs and Höller, *Ann.*, 1913, **398**, 256.

Freund and Schander, *Ber.*, 1896, **29**, 2508.

do. *Ber.*, 1902, **35**, 2602.

Freund and Wischewiansky, *Ber.*, 1893, **26**, 2877.

Gehring, *Bull. Soc. chim.*, [2], 1886, **46**, 147.

Guha and Dé, *J. Chem. Soc.*, 1924, **125**, 1215.

do. *J. Indian Chem. Soc.*, 1925, **1**, 141.

do. *J. Indian Chem. Soc.*, 1925, **2**, 225.

Hell and Wenizweig, *Ber.*, 1895, **28**, 2447.

Hemmelmayr, *Monatsh.*, 1891, **12**, 90.

Hofmann, *Ber.*, 1872, **5**, 242.

Lange, *Ber.*, 1879, **12**, 597.

Lellmann, *Ann.*, 1883, **221**, 9.

Neuberg and Neimann, *Ber.*, 1902, **35**, 2409.

Pulvermacher,	*Ber.*, 1894, **27**, 615.
Rupe,	*Ber.*, 1897, **30**, 1089.
Schacht,	*Arch. Pharm.*, 1897, **235**, 461.
Stolle and Bowles,	*Ber.*, 1908, **41**, 1099.
Wheeler and Barnes,	*Amer. Chem. J.*, 1900, **24**, 60.
Wheeler and Johnson,	*J. Amer. Chem. Soc.*, 1902, **24**, 690.
Wilson and Burns,	*J. Chem. Soc.*, 1922, **121**, 870.
do.	*J. Chem. Soc.*, 1923, **123**, 799.
Zelinsky,	*Ber.*, 1887, **20**, 2026.
