REACTIONS

OF THE

THIOSEMICARBAZONES

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This work was carried out in The Royal Technical College, to the Governors of which the Author tenders his grateful thanks for assistance given and for opportunity afforded him.

He also wishes to put on record his sincerest thanks for the unstinted advice and help which he has received from Professor Forsyth J. Wilson, the Director and Supervisor of the Research, during the course of the work and during the compilation of this report.

C O N T E N T S.

S U M M A R Y

The investigation described in the following pages forms one portion of an extensive research programme being carried out in the Department of Organic Chemistry of The Royal Technical College. The work is under the general supervision of Professor Forsyth J. Wilson and includes the reactions of the semicarbazones and semioxamazones as well as those of the thiosemicarbazones.

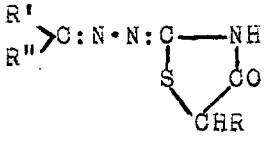
Neuberg and Neimann (Ber. 1902, 35, 2049) have shown that the thiosemicarbazones $\begin{matrix} R' \\ R'' \end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2$, possess the property of forming metallic derivatives, one of the hydrogen atoms being replaced by an equivalent of silver, copper, or mercury. The present investigation was under--taken to determine if, by the action of halogenated compounds, the hydrogen atom replaceable by metal could be replaced by alkyl or other substituents.

The known metallic derivatives were found to be unsuitable for this work and the sodium derivative of acetone thiosemicarbazone was the starting material chiefly employed.

The reactions of the sodium derivative with ethyl bromide, propyl bromide, n-butyl bromide, benzyl chloride and allyl iodide were investigated, with the result that a new series of S - alkylated thiosemicarbazones has been obtained. The products of hydrolysis of these S-alkylated compounds have also been examined.

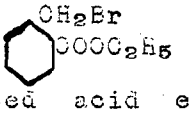
An attempt was made to prepare an optically active thiosemicarbazone by the action of l-menthyl chloroacetate on the sodium derivative but the product obtained proved to be a ψ - thiohydantoin derivative of a new type; a ring closure having been effected.

This rather interesting result led to the investigation of the action of the sodium derivative on the esters of halogenated acids. In the case of the esters of chloroacetic acid, ethyl α-bromopropionate, ethyl α-bromo-n-butyr--ate, and ethyl bromophenylacetate the products of the reaction were found to be derivatives of 2·4 diketotetrahydrothiazoles of the type



The products of hydrolysis of these cyclic compounds were also examined.

The esters of β-halogenated acids do not yield a six membered ring but were found to lose hydrogen halide with formation of the esters of the corresponding unsaturated acid. The cases investigated were those of ethyl β-bromo-n-butyrate and ethyl β-bromo-β-phenylpropionate with acetone sodio thiosemicarbazone.

The action of the esters of γ-halogenated acids was found to proceed as in the case of those of the β-halogenated acids; ethyl γ-chloro-n-butyrate, ethyl γ-chlor valerate, and ethyl γ-chloroisocaproate yielding esters of unsaturated acids by loss of hydrogen halide. The reaction between ethyl ω-bromo-o-toluate,  which may be regarded as a γ-halogenated acid ester, and acetone sodio thiosemicarbazone was found to proceed exactly as in the case of the alkyl halides; the structure of the product, as deduced from a study of the products of hydrolysis, being analogous.

Another attempt to obtain an optically active thiosemicarbazone by the action of 1-dimethyl chloro-

-succinate on the sodium derivative gave a solid of low melting point which did not contain sulphur or nitrogen and was not, therefore, further investigated.

Ethyl chlorocarbonate and phenyl chlorocarbonate have been found to react with the sodium derivative of acetone thiosemicarbazone in benzene suspension, with formation chiefly of the 1-carbethoxy or 1-carbophenoxy thiosemicarb--azide R·OOC·NH·NH·CS·NH_2. Carbon dioxide is also formed, together with varying amounts of diethyl carbonate or diphenyl carbonate and the carboethoxy or carbophenoxy derivative of the thiosemicarbazone.

The action of iodine on the sodium derivative of acetone thiosemicarbazone was tried but was found to give negative results; ethylene dibromide also failed to react.

Preliminary work on the action of the amines on the thiosemicarbazones showed that aniline reacts with acetone thiosemicarbazone at 160°C. with vigorous evolution of ammonia and formation of a resinous product which could not be purified. Benzylamine reacts with acetone thiosemicarbazone at 140-145°C., ammonia is evolved and a mixture of products formed, while with acetophenone thiosemicarbazone benzylamine reacts at a temperature of 130-135°C. with formation chiefly of the corresponding 4-benzyl thiosemicarbazone $\begin{matrix}CH_3\\C_6H_5\end{matrix}\!\!>\!C{:}N\cdot NH\cdot CS\cdot NHCH_2\cdot C_6H_5$; a yield of 60% of the theoretical being obtained.

T H E O R E T I C A L.

On heating hydrazine thiocyanate a violent reaction takes place, with formation of thiosemicarbazide, $NH_2 \cdot NH \cdot CS \cdot NH_2$, (Freund and Schander Ber. 1896, 29, 2500), a basic substance which melts at 178-179°C., and which reacts with aldehydes and ketones in an analogous manner to hydroxylamine, semicarbazide, and phenylhydrazine:

$$\begin{matrix} R' \\ R'' \end{matrix}\!\!>\!C\!:\!O \; + \; H_2N \cdot NH \cdot CS \cdot NH_2 \; = \; \begin{matrix} R' \\ R'' \end{matrix}\!\!>\!C\!:\!N \cdot NH \cdot CS \cdot NH_2$$

The compounds thus formed are termed thiosemicarbazones and are sometimes employed in the identification and separation of aldehydes and ketones.

The thiosemicarbazones of numerous aldehydes and ketones have been prepared, chiefly by Neuberg and Neimann (Ber. 1902, 35, 2049). The first named investigators showed that these thiosemicarbazones could form metallic derivatives, one of the hydrogen atoms being replaceable by an equivalent of the metal which is apparently linked to sulphur

$$\begin{matrix} R' \\ R'' \end{matrix}\!\!>\!C\!:\!N \cdot NH \cdot C\!<\!\begin{matrix} NH \\ S \cdot M \end{matrix} \qquad \text{or} \qquad \begin{matrix} R' \\ R'' \end{matrix}\!\!>\!C\!:\!N \cdot N\!:\!C\!<\!\begin{matrix} NH_2 \\ S \cdot M \end{matrix}$$

A number of the silver, copper, and mercury compounds were described and the method of preparation briefly indicated.

By the action of methyl iodide on thiosemicarbazide, Freund and Paradies (BER. 1901, 34, 3114) obtained the hydriodide of a methyl/thiol derivative which might be represented as either

$$NH_2 \cdot NH \cdot C\!<\!\begin{matrix} NH \\ S \cdot CH_3 \end{matrix} HI \qquad \text{or} \qquad NH_2 \cdot N\!:\!C\!<\!\begin{matrix} NH_2 \\ S \cdot CH_3 \end{matrix} HI$$

The alkyl and aryl derivatives of thiosemicarbazide as well as the base itself have been studied by

several investigators, more particularly by Busch and his collaborators, (Ber. 1901, 34, 320; 1903, 36, 1362; 1904, 37, 2318; 1909, 42, 4596, 4602) and earlier by Markwald (Ber. 1892, 25,(2), 3098) and Dixon (J.C.S. 1892, 61, 1012).

The products of the interaction of thiosemicarbazide and acid chlorides have been examined by Fromm and others (Ann. 1923, 433, 1; 434, 285)

With the thiosemicarbazones themselves, however, and also with their metallic derivatives, where the reactive $NH_2 \cdot N<$ group of the thiosemicarbazide is absent, comparatively little work has been done; in this paper the behaviour of metallic derivatives towards various types of halogenated compounds has been investigated. A preliminary study has also been made of the action of amines on the thiosemicarbazones.

As already indicated in the summary the primary object of this work was to determine whether, by the action of halogenated compounds, the hydrogen atom replaceable by metal could be replaced by alkyl or other substituents, and to investigate the properties of these substituted thiosemicarbazones. The formation of a cyclic compound by the interaction of acetone sodio thiosemicarbazone and the esters of chloro-acetic acid led to a study of the action of α-, β-, and γ-halogenated acids on this metallic derivative. The action of chloroformic esters and certain other halogenated compounds was also investigated.

The thiosemicarbazone of acetone was chosen as the starting material because of the ready and cheap production in quantity, while of the known metallic derivatives, that of silver appeared to offer the greatest possibilities.

A suspension of the finely ground silver derivative in ether was treated with alkyl halides but an examination of the mixture, even after 12 hours boiling, showed that no reaction had taken place. The ether was replaced by petroleum ether of boiling point 60°C., and in subsequent experiments with petroleum ethers of boiling point 80°C., boiling point 100°C., and finally with ligroin of boiling point 120°C., but in each case, even after 12 hours boiling at the much higher temperature, there was no evidence of chemical action. When heated in the presence of alcohol or benzene the silver derivative was found to be very rapidly and completely decomposed; free sulphur was found in some of the reaction mixtures.

Negative results having been obtained with the silver compound, sodium ethoxide was tried as a means of intro-ducing the alkyl group. This led to the isolation of acetone sodio-thiosemicarbazone

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{:}N{\cdot}N{:}C\!<\!\begin{matrix}NH_2\\S{\cdot}Na\end{matrix}$$

which has not previously been described; it is readily prepared by the action of sodium ethoxide on an alcoholic solution of acetone thiosemicarbazone, and was found to be the most suitable metallic derivative for the work on hand.

In alcoholic solution the sodium derivative reacts with alkyl halides in accordance with the scheme

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{:}N{\cdot}N{:}C\!<\!\begin{matrix}NH_2\\S{\cdot}Na\end{matrix} + BrR = \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{:}N{\cdot}N{:}C\!<\!\begin{matrix}NH_2\\S{\cdot}R\end{matrix}$$

sodium halide separates and an alkyl substituted thiosemicarbazone is obtained in which the alkyl group is attached to sulphur. In actual practice, where the reaction is being carried out in alcoholic solution, it

has been found unnecessary to isolate the sodium derivative.

The S-alkylated thiosemicarbazones are relatively stable substances the melting points of which are, in general, much lower than those of the isomeric N-substit--uted compounds. They are exceedingly soluble in all the usual organic solvents, such as alcohol, benzene, and ether, and are best crystallised from petroleum ether from which they separate as fine transparent needles or prisms. They are practically insoluble water. The propyl and butyl compounds have been purified by distillation under reduced pressure. The following members of the series have been prepared;-

Acetone S-ethyl thiosemicarbazone

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C:N\cdot N:C\!<\!\begin{matrix}NH_2\\S\cdot C_2H_5\end{matrix}$$

Acetone S-propyl thiosemicarbazone

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C:N\cdot N:C\!<\!\begin{matrix}NH_2\\S\cdot C_3H_7\end{matrix}$$

Acetone S-butyl thiosemicarbazone

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C:N\cdot N:C\!<\!\begin{matrix}NH_2\\S\cdot C_4H_9\end{matrix}$$

Acetone S-allyl thiosemicarbazone

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C:N\cdot N:C\!<\!\begin{matrix}NH_2\\S\cdot C_3H_5\end{matrix}$$

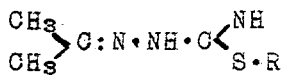
Acetone S-benzyl thiosemicarbazone

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C:N\cdot N:C\!<\!\begin{matrix}NH_2\\S\cdot CH_2\cdot C_6H_5\end{matrix}$$

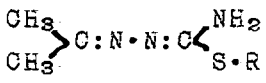
The structure ascribed to the compounds obtained by the action of alkyl halides on acetone sodio-thiosemicarb--azone has been arrived at by a consideration of the products of hydrolysis.

When heated under a reflux condenser with caustic

soda solution of twice normal strength until solution is complete these substances decompose yielding acetone, hydrazine, ammonia, and the mercaptan corresponding to the alkyl group present. [The methods adopted for the isolation and identification of the various hydrolysis products are detailed in the 'Experimental' portion of this report]. The formation of the mercaptan proves the linking of the alkyl group to sulphur; and the structure, therefore, might be represented by one or other of the formulae;-

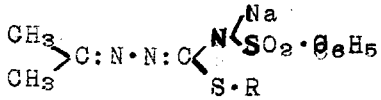


(1)

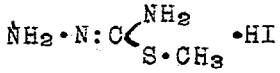


(2)

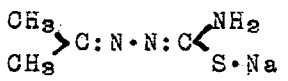
Formula (1), however, is inadmissible, since by the method of Busch, Opfermann and Walther (Ber. 1904, 37, 2322) the presence of an $-NH_2$ group in the molecule can be shown; the S-alkylated compounds on treatment with benzene sulphonyl chloride and sodium ethoxide yield the sodium salt of a sulphonamide



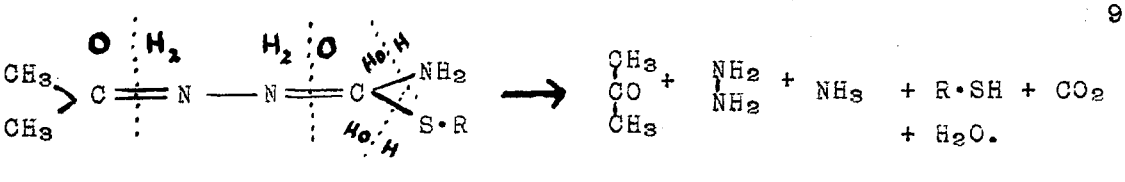
BY analogy the hydroiodide of the methyl thiol derivative obtained by Freund and Paradies would have the structure



and the sodium derivative of acetone thiosemicarbazone would best be represented by

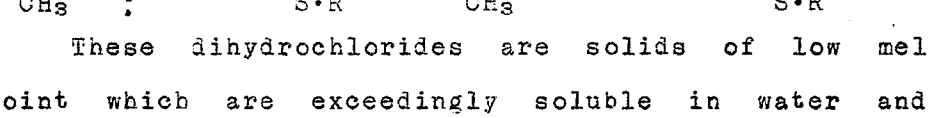


The complete hydrolysis by means of caustic soda would take place according to the scheme,



These structural formulae receive confirmation from the products of the reaction between the esters of α-halogenated acids and acetone sodio-thiosemicarbazone.

A less drastic hydrolysis resulting in the splitting off of acetone only from the molecule, is effected by heating the S-alkylated thiosemicarbazones under a reflux condenser with dilute hydrochloric acid of not more than normal strength. The dihydrochlorides of the corresponding S-alkylated thiosemicarbazides are obtained as indicated in the scheme



These dihydrochlorides are solids of low melting point which are exceedingly soluble in water and very hygroscopic.

The following dihydrochlorides were examined;-

S-ethyl thiosemicarbazide dihydrochloride

$$H_2N\cdot N = C\begin{matrix}NH_2\\ S\cdot C_2H_5\end{matrix} \quad 2HCl$$

S-propyl thiosemicarbazide dihydrochloride

$$H_2N\cdot N = C\begin{matrix}NH_2\\ S\cdot C_3H_7\end{matrix} \quad 2HCl$$

S-butyl thiosemicarbazide dihydrochloride

$$H_2N\cdot N = C\begin{matrix}NH_2\\ S\cdot C_4H_9\end{matrix} \quad 2HCl$$

S-allyl thiosemicarbazide dihydrochloride

$$H_2N\cdot N = C\begin{matrix}NH_2\\ S\cdot C_3H_5\end{matrix} \quad 2HCl$$

The dihydrochloride of S-benzyl thiosemicarbazide, $H_2N\cdot N=C\begin{matrix}NH_2\\ S\cdot CH_2\cdot C_6H_5\end{matrix}\ 2HCl$, could not be obtained in the pure state but a monohydrochloride, corresponding to the

hydriodide of Freund and Paradies was obtained. The sulphate corresponding was obtained by a somewhat similar method.

When shaken with benzaldehyde in aqueous solution the dihydrochlorides readily react with the aldehyde to form the hydrochloride of the corresponding benzilidene S-alkylated thiosemicarbazone by the loss of the elements of water and one molecule of hydrochloric acid.

$$C_6H_5\cdot CHO + H_2N\cdot N=C\begin{matrix}NH_2\\S\cdot R\end{matrix} 2HCl \longrightarrow C_6H_5\cdot CH=N-N=C\begin{matrix}NH_2\\S\cdot R\end{matrix} HCl$$

The hydrochlorides of the benzaldehyde S-alkylated thiosemicarbazones are comparatively insoluble in water and ether but are readily soluble in alcohol. They were purified by dissolving in the latter solvent and precipitating with ether, when they separated usually in the form of lustrous white plates or needles of high melting point.

The addition of the calculated quantity of sodium carbonate to the above hydrochlorides in aqueous alcoholic solution effected the removal of the hydrochloric acid from the molecule, yielding the corresponding benzaldehyde S-alkylated thiosemicarbazones $C_6H_5\cdot CH=N-N=C\begin{matrix}NH_2\\S\cdot R\end{matrix}$. These compounds closely resemble the original acetone derivatives in their solubilities and general properties

$$2\ C_6H_5\cdot CH=N\cdot N=C\begin{matrix}NH_2\\S\cdot R\end{matrix} HCl + Na_2CO_3 \longrightarrow C_6H_5\cdot CH=N\cdot N=C\begin{matrix}NH_2\\S\cdot R\end{matrix} + 2NaCl + H_2O + CO_2$$

Several attempts were made to prepare the free S-alkylated thiosemicarbazides, $H_2N\cdot N=C\begin{matrix}NH_2\\S\cdot R\end{matrix}$, from the dihydrochlorides both by the addition of the calculated quantity of anhydrous sodium carbonate and by the action of sodium ethoxide, but without success. The free bases appear to be solids of low melting point which are very

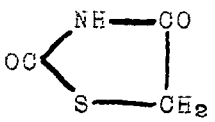
unstable and rapidly become discoloured on exposure to light and air. They were soluble in the usual solvents but could not be re/crystallised and were not obtained in the pure state.

ESTERS OF HALOGENATED ACIDS.

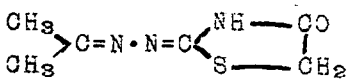
In the hope of obtaining an optically active S-substituted thiosemicarbazone the action of l-menthyl-chloroacetate on an alcoholic solution of acetone sodio-thiosemicarbazone was tried. Examination of the resulting product, however, showed that the reaction did not proceed in accordance with the following equation,

$$(CH_3)_2C = N - N = C\langle^{NH_2}_{S\cdot Na} + Cl\cdot CH_2\cdot COOC_{10}H_{19} \longrightarrow (CH_3)_2C = N - N = C\langle^{NH_2}_{S\cdot CH_2\cdot COOC_{10}H_{19}}.$$

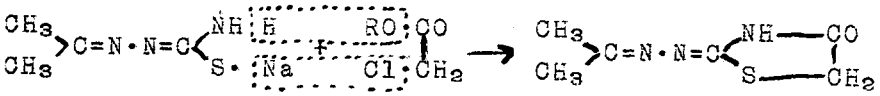
Menthol was liberated during the reaction and a substance formed which, when pure, had a melting point of 175-176°C. By the action of the ethyl ester of chloroacetic acid the same substance was obtained. The compound resisted the action of twice normal hydrochloric acid but boiling with the concentrated acid effected a smooth hydrolysis into acetone, hydrazine hydrochloride, and 2:4-diketo-tetrahydrothiazole



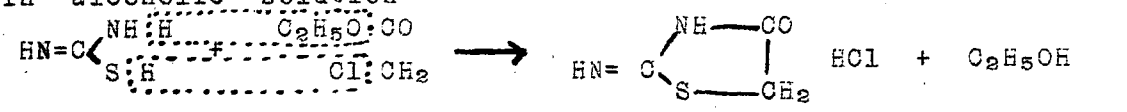
The structure of the product, therefore, would be



, a ψ-thiohydantoin derivative of a new type; while the reaction between the esters of chloracetic acid and acetone sodio-thiosemicarbazone would proceed as indicated by the equation



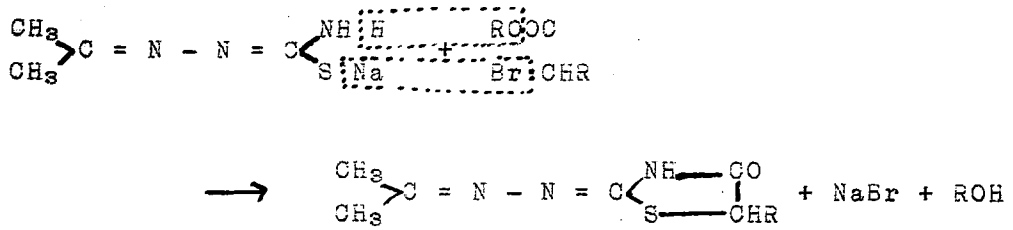
This reaction is similar to that which takes place on heating together ethyl chloro-acetate and thiocarbamide in alcoholic solution



ψ-thiohydantoin hydrochloride being formed with liberation of alcohol (Mulder, Ber., 1875, 8, 1264; Claesson, Ber., 1877, 10, 1852).

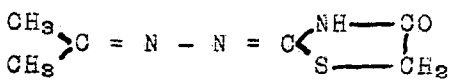
Action of Esters of α-halogenated Acids.

The reactions between the sodium derivative of acetone thiosemicarbazone and ethyl α-bromo-n-butyrate, ethyl α-bromopropionate, and ethyl phenyl bromoacetate were then investigated. With each of these esters the resulting product was found to be the 2-isopropylidene hydrazone derivative of a 2:4-diketotetrahydrothiazole, corresponding to the product formed by the interaction of acetone sodio-thiosemicarbazone and the esters of chloro-acetic acid. The reaction, therefore, would appear to be a general one, and to proceed in accordance with the scheme

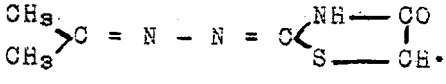


Of the series of ψ-thiohydantoin derivatives the following members have been prepared and examined;-

2:4-diketotetrahydrothiazole-2-isopropylidene hydrazone,

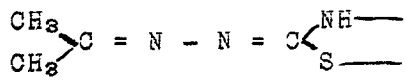
 , from the esters of chloroacetic acid.

2:4-diketo-5-methyltetrahydrothiazole-2-isopropylidene hydrazone

 , from the esters of

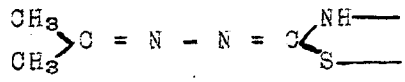
α-bromopropionic acid.

2:4 – diketo-5-ethyltetrahydrothiazole-2-isopropylidene hydrazone



, from the esters of α-bromo-n-butyric acid.

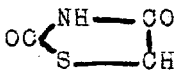
2:4 – diketo-5-phenyltetrahydrothiazole-2-isopropylidene hydrazone



, from the esters of phenylbromoacetic acid.

In the above preparations the yields are of the order of 70–75 per cent of the theoretical, the products being solids, the melting points of which range from 116°C. upwards. They are slightly soluble in benzene, sparingly soluble in ether or water, and may be recrystallised from alcohol, from which they separate in fine white glistening needles.

As in the case of the first mentioned, they are completely hydrolysed by boiling under a reflux condenser with concentrated hydrochloric acid for several hours. Acetone and hydrazine are removed and a satisfactory yield obtained of a 2:4 – diketo-5-alkylated-tetrahydrothiazole



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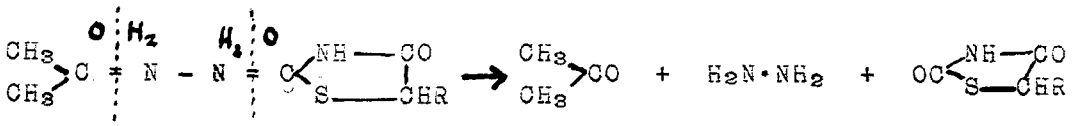
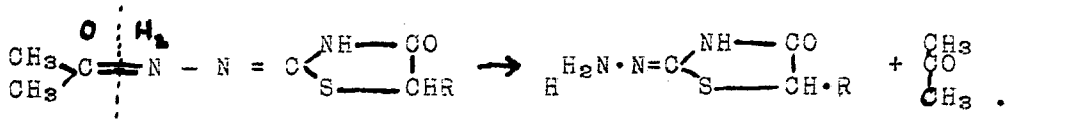


The 2:4 – diketotetrahydrothiazoles so obtained are identical with those described in the literature by other investigators and prepared by other methods.

It was not found possible, as has already been mentioned, to remove acetone only from the molecule in the case of the first mentioned and so obtain the intermediate hydrazone. From the products in which an alkyl or aryl substituent had replaced one of the

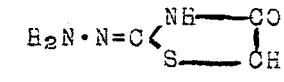
hydrogen atoms attached to the -5- carbon atom of the ring, however, by boiling for about fifteen minutes with dilute hydrochloric acid, of not more than twice normal strength, the corresponding hydrazone could be isolated as the hydrochloride.



In the cases investigated the two types of hydrolysis were quite sharply distinguished, that is to say, where acetone only was removed by the use of dilute hydrochloric acid, the product was the pure hydrochloride of the hydrazone, quite free from admixture with hydrazine hydrochloride or 2:4-diketotetrahydrothiazole.

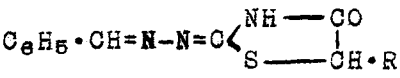
The hydrochlorides of these hydrazones, which, it is believed represent a new series of ψ-thiohydantoin derivatives can be readily obtained in good yield, and are well defined crystalline salts which appear to be quite stable. They are readily soluble in water, sparingly soluble in organic solvents and melt, with decomposition at temperatures well above 200°C.

A number of attempts were made, by various methods, to obtain the free hydrazones from these hydrochlorides, but the results, on the whole, were unsatisfactory owing to the unstable nature of the hydrazones. Only one of these bases, 2:4-diketo-5-ethyltetrahydrothiazole

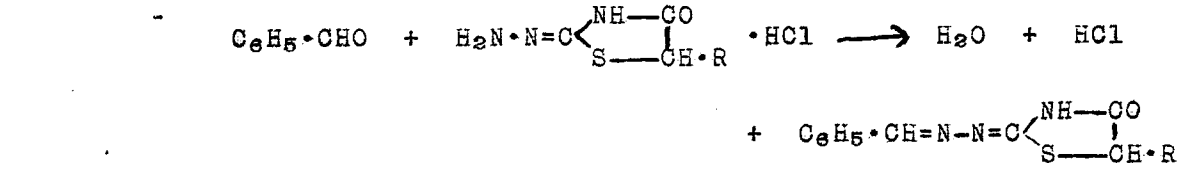


was obtained as a granular powder by the action of the necessary amount of sodium carbonate on the corresponding hydrochloride. The substance was only moderately stable and the reference sample was found to have become much discoloured after about two months storage even in the dark.

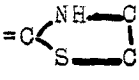
In aqueous solution the hydrochlorides react readily with benzaldehyde to give the benzylidene derivatives

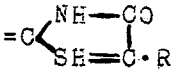


, by loss of hydrochloric acid and elimination of the elements of water. The products so obtained closely resemble the original acetone compounds in their solubility relations and other properties.

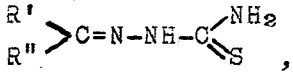


All the cyclic compounds examined were soluble in aqueous sodium hydroxide and appeared to form silver derivatives, probably this is due to the tetrahydrothiazole complex which contains a potential acidic group as it might exist in the tautomeric forms

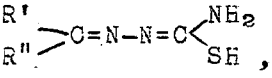
(1)  ,

(2) 

The form having structure (2) and containing the >SH group would yield metallic derivatives, the metal being attached to sulphur, as in the case of the thiosemicarbazones of which the tautomeric forms would be



(1)



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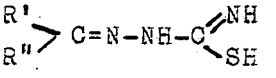


(3)

The question of the tautomerism of the ψ-thiohydantoin derivatives was not investigated nor was that of the preparation and properties of their metallic derivatives.

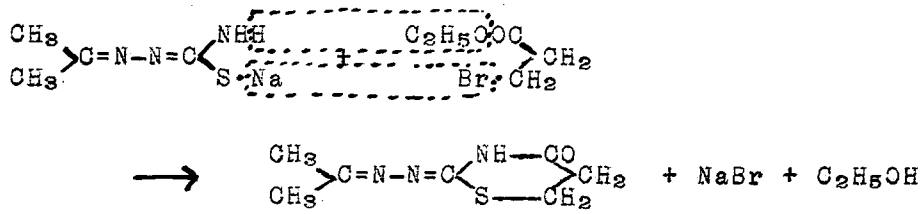
In the -5-alkylated hydrazones and also in the corresponding 2:4 - diketotetrahydrothiazoles the -5- carbon atom of the ring is an asymmetric carbon atom so that it should be possible to bring about the synthesis of

an optically active product. Two methods suggest themselves; firstly resolution of the α-halogenated ester before carrying out the ring closure, and secondly resolution of the racemic hydrazone hydrochloride by condensing with an optically active aldehyde or ketone. This work, however has been held over for the present.

Action of Esters of β-halogenated Acids

Following the action of the esters of α-halogenated acids, the action of the esters of β-halogenated acids on acetone sodio-thiosemicarbazone was studied.

In the cases investigated the reaction did not proceed according to the equation

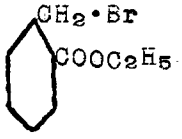


The β-halogenated acids were found to lose hydrogen halide, and the products of reaction were invariably acetone thiosemisarbazone, sodium halide, and the ester of the unsaturated acid corresponding to the β-halogenated acid employed. The unsaturated esters were characterised by their possessing the general properties of unsaturated compounds and by their boiling points.

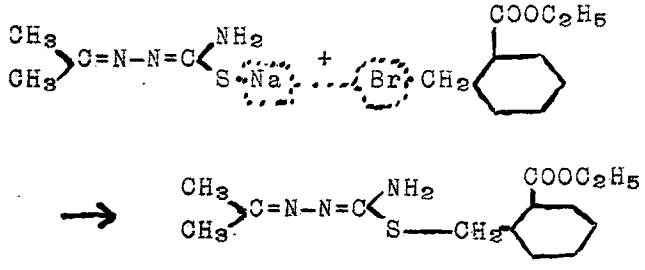
Action of the Esters of γ-halogenated Acids.

The action of the esters of γ-halogenated acids was found to proceed chiefly as in the case of the esters of the β-halogenated acids. The principal products obtained were acetone thiosemicarbazone, sodium halide, and the ester of an unsaturated acid formed by loss of hydrogen halide from the ester of the γ-halogenated acid. In

each case, however, there was also formed a small proportion of an unstable substance containing Nitrogen and Sulphur in the molecule. These substances were decomposed on distillation, even at pressures below one millimetre; they did not solidify on cooling in solid carbon dioxide and ether, and could not be crystallised.

With ethyl ω-bromo-o-toluate 

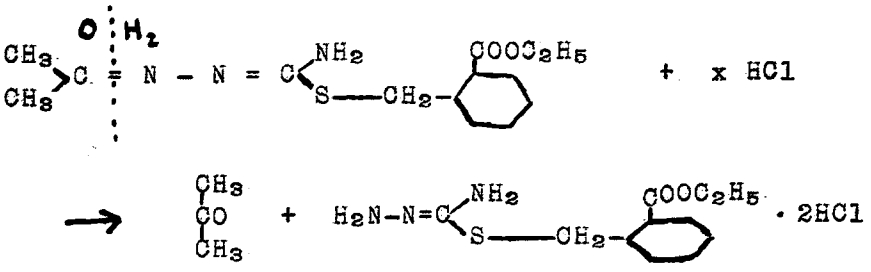
which may be regarded as the ester of a γ-halogenated acid, the sodium derivative of acetone thiosemicarbazone readily reacts. The reaction follows the course of the general reaction of alkyl halides on acetone sodio-thiosemicarbazone and may be represented as taking place according to the scheme:



The resulting product in all its reactions and general properties closely resembles the S-alkylated thiosemicarbazones. Thus it is exceedingly soluble in the usual organic solvents, is practically insoluble in water, and is best crystallised from petroleum ether from which it separates as pale yellow prisms.

Boiling under a reflux condenser for about a quarter of an hour with excess of normal hydrochloric acid effects the removal of acetone only from the molecule yielding the dihydrochloride of the corresponding hydrazone. The hydrolysis is exactly analogous to that undergone by the S-alkylated thiosemicarbazones under similar conditions

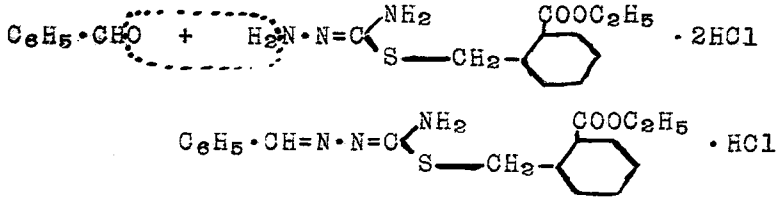
and would be represented by the scheme



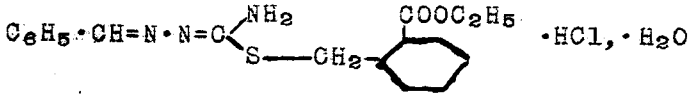
The dihydrochloride so obtained is a white micro-crystalline solid, which is hygroscopic and exceedingly soluble in water.

It is of interest to note that, in this hydrolysis and formation of the dihydrochloride, the carbethoxy group remains intact. Employing, therefore, an optically active ester of ω-bromo-o-toluic acid, it seems reasonable to expect that an optically active product could be obtained fairly readily.

In aqueous solution the dihydrochloride condenses readily with benzaldehyde with loss of the elements of water and one molecule of hydrochloric acid, to form the hydrochloride of the corresponding benzylidene derivative:



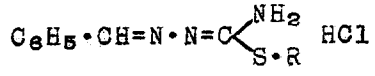
The hydrochloride so obtained, like those of the corresponding S-alkyl compounds is only slightly soluble in water. Recrystallised from aqueous alcohol by precipitating with ether the product separates with one molecule of water of crystallisation.



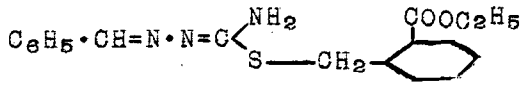
The analogous S-alkylated compounds do not contain

water of crystallisation.

As in the case of the corresponding hydrochlorides of the benzaldehyde S-alkyl thiosemicarbazones



, the addition of the calculated quantity of sodium carbonate effects the removal of the hydrochloric acid from the molecule. The product so obtained,

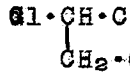


, closely resembles the original acetone compound in every particular, having the same crystalline form, similar solubility relations, and a melting point of 74°C., while that of the acetone compound is 66°C.

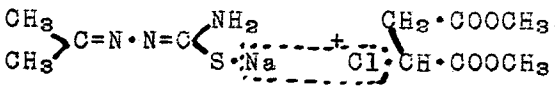
Action of the Esters of halogenated dibasic Acids.

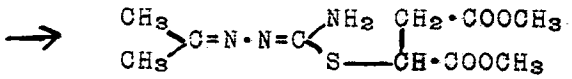
Action of dimethyl 1-chloro- succinate.

On the addition of dimethyl chloro-succinate



to an alcoholic solution of the sodium derivative of acetone thiosemicarbazone, sodium chloride separates almost immediately. An examination of the resulting mixture, however, shows that the reaction does not proceed according to the scheme,





The acetone thiosemicarbazone is practically all recovered, and a substance of low melting point obtained which does not contain nitrogen or sulphur. This low melting product has a rather pleasant odour, and is

presumably the ester of an unsaturated acid, the reaction proceeding as in the case of the esters of β halogenated acids. The compound has not been obtained in the pure state in sufficient quantity to characterise it, but might possibly be methyl fumarate, which, when pure, melts at 102°C.

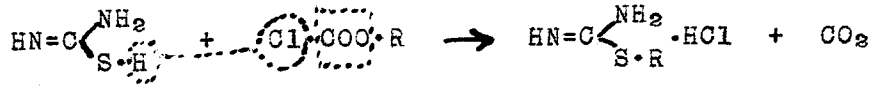
Dimethyl 1-chloro-succinate does not react with a suspension of finely divided acetone sodio-thiosemicarbazone in benzene.

The work on this section of the programme, however, has only been of a preliminary nature so far, but it is intended to extend the investigation to the action of the esters of other halogenated dibasic acids.

ACTION OF CHLOROFORMIC ESTERS.

The chloroformic esters were found to react readily and vigorously with a suspension of the sodium derivative of acetone thiosemicarbazone in a fine state of division in benzene. The mixture became hot, sodium chloride separated and a certain amount of carbon dioxide was evolved. The products obtained were crystallised from alcohol from which they separated as fine white needles of high melting point.

It has been shown by Dixon (J.C.S. 1903, 83, 550) that thiocarbamide and mono-substituted thiocarbamides react with chloroformic esters in the heat, with evolution of carbon dioxide and formation of the hydrochloride of a ψ-thiocarbamide in which the hydrocarbon residue of the chloroformic ester is linked to sulphur, since heating with sodium hydroxide yields a mercaptan. The reaction may be represented by the scheme:



At first it was thought that the reaction of the chloroformic esters on acetone sodio-thiosemicarbazone was analogous to the above but a complete analysis of the products and examination of their properties showed that this was not the case.

Thus, they are of high melting point while in the cases where the substituent is linked to sulphur, for example the S-alkylated thiosemicarbazones $\begin{matrix} R' \\ R'' \end{matrix}\!>\!C{=}N{-}N{=}C\!<\!\begin{matrix} NH_2 \\ S\cdot R \end{matrix}$ the melting points are well below 100°C.
While examining the action of mercuric oxide, alkaline lead acetate, and alkaline silver nitrate on these substances it was noted that they formed metallic derivatives, indicating the possible presence of an -SH group in the molecule; the ready solubility in sodium hydroxide tends to support this view.

Although easily soluble in alkali they are stable and strongly resist hydrolysis; complete hydrolysis of the phenyl chloroformic ester product was effected by heating under pressure in a Carius tube with concentrated hydrochloric acid. The products of hydrolysis were phenol, hydrazine hydrochloride, ammonium chloride and a gas smell smelling strongly of sulphuretted hydrogen; the gas could not be collected on opening the tube but was presumably a mixture of carbon dioxide and sulphuretted hydrogen containing, perhaps, carbon oxysulphide.

Complete analysis of the principel products obtained by the action of ethyl chloroformate and phenyl chloroformate showed them to have the empirical formulae $C_4H_9O_2N_3S$ and $C_8H_9O_2N_3S$ respectively.

Finally the ethyl chloroformate product was shown to

be identical with 1-carbethoxy thiosemicarbazide $C_2H_5OOC\cdot NH\cdot NH\cdot CS\cdot NH_2$ obtained by Fromm and Nehring(Ber. 1923 56, 1374) by the direct action of ethyl chloroformic ester on thiosemicarbazide in alcoholic solution.

The principal products, therefore, of the action of chloroformic esters on a suspension of acetone sodio-thiosemicarbazone are compounds of the type $ROOC\cdot NH\cdot NH\cdot CS\cdot NH_2$. The cases investigated were those of methyl, ethyl and phenyl chloroformates, and the yields obtained were of the order of 60% of the theoretical.

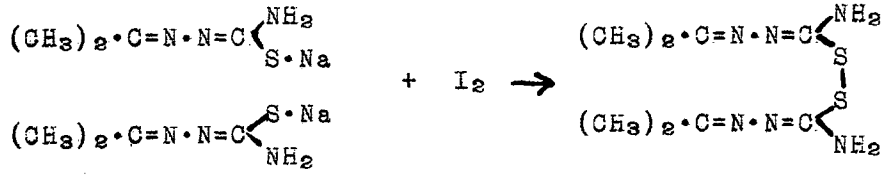
In addition to the above mentioned substances there is also formed in each case a small proportion of another product which is very much more soluble, has a melting point about 50°C. lower, and is obtained in the form of large transparent prisms from a mixture of carbon disulphide and petroleum ether. With some difficulty, owing to the extreme solubility and the small proportion in which the substance is formed, a quantity of the phenyl chloro carbonate compound sufficient for analysis was obtained. The nitrogen content indicates that this product is most probably $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C=N-N=C\!<\!\begin{matrix} NH_2 \\ S\cdot COOC_6H_5 \end{matrix}$, and the general properties tend to support the view that the carbophenoxy group is linked to sulphur. The low melting products from the reactions with methyl and ethyl chloroformates were not obtained pure in sufficient quantity for analysis.

The course of the reaction in the case of the ~~chlo~~ chloroformates could not be followed owing to the unsatisfactory nature of the viscous products.

The thiosemicarbazones of ketones of higher molecular weight were also tried but the results were again unsatisfactory.

ACTION OF IODINE ON ACETONE SODIO- THIOSEMICARBAZONE

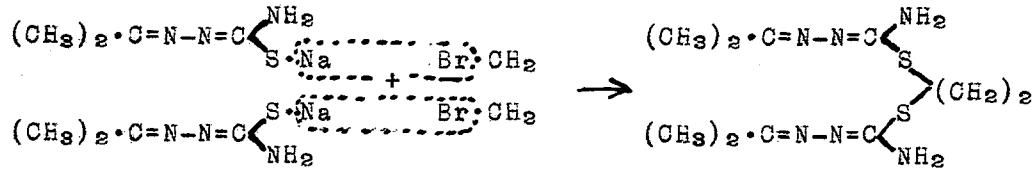
The action of iodine on an alcoholic solution of acetone sodio-thiosemicarbazone was investigated to determine whether two thiosemicarbazone residues might unite on removal of the sodium:



Examination of the products. however, showed that the reaction did not proceed in accordance with the above equation; the colour of the iodine disappeared and sodium iodide was formed but the whole of the acetone thiosemicarbazone was recovered unchanged.

ACTION OF ETHYLENE DIBROMIDE.

A further attempt was made to link up two thiosemicarbazone residues by the action of ethylene dibromide on acetone sodio-thiosemicarbazone in alcoholic solution, when it was thought that the following reaction might take place:-



It was found, however, that ethylene dibromide did not react with acetone sodio-thiosemicarbazone even after eight hours boiling on the waterbath under a reflux condenser.

ACTION OF AMINES ON THIOSEMICARBAZONES.

The action of aniline, the toluidines, the naphthylamines and other similar aromatic amino compounds on the semicarbazones has been studied by Borsche and others (Ber. 1901, 34, 4299; 1904, 37, 3177; 1905, 38, 831). These investigators have shown that on heating the reacting substances together, ammonia is evolved and that the principal product is the 4- or δ- substituted semicarbazone, the reaction proceeding according to the equation:

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C{=}N{-}NH{\cdot}CO{\cdot}NH\boxed{H + H_2N}R \longrightarrow \begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C{=}N{\cdot}NH{\cdot}CO{\cdot}NHR + NH_3$$

On hydrolysis the semicarbazone was found to yield the corresponding semicarbazide $H_2N{\cdot}NH{\cdot}CO{\cdot}NHR$.

More recently Wilson, Hopper, and Crawford (J.C.S., 1922, 121, 866) have investigated the action of the aliphatic amines and of aromatic amines containing the amino group in the side chain, and have shown that the reaction in many cases follows a similar course.

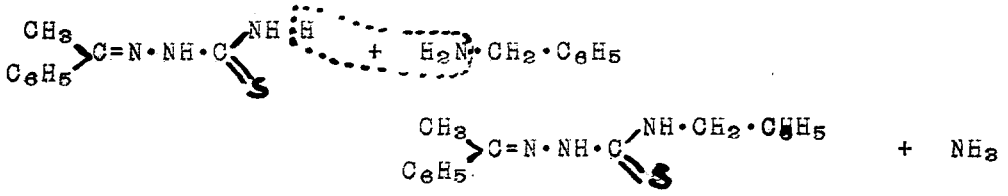
Wilson and Pickering (J.C.S., 1924, 125, 1152) have examined the action of amino compounds on the semioxamazones.

The following report gives a short account of the preliminary work on the action of amino compounds on the thiosemicarbazones, which, so far, does not appear to have been investigated.

Aniline has been found to react with acetone thiosemicarbazone at 160°C. with brisk evolution of ammonia and the formation of a certain amount of sulphuretted hydrogen. There appeared to be considerable decomposition and the resulting product was resinous and viscous in character and could not be purified.

At a temperature of 140–145°C. benzylamine was found to react with acetone thiosemicarbazone with evolution of ammonia; there did not appear to be any appreciable quantity of sulphuretted hydrogen formed. A solid product was obtained which is evidently a mixture and has not, so far, been satisfactorily separated into its constituents.

Acetophenone thiosemicarbazone reacts with benzylamine at a temperature of 130–135°C. ammonia being evolved and a 60% yield of acetophenone 4-benzyl thiosemicarbazone being obtained. The reaction in this case, therefore, would appear to proceed normally, that is in accordance with the equation:



The product does not hydrolyse readily, however, and the corresponding thiosemicarbazide has not, so far, been obtained. A complete hydrolysis, effected by heating under pressure in a Carius tube with concentrated acid showed that benzylamine and hydrazine could be obtained from the product.

The work is being proceeded with and the action of the hydrazines on the thiosemicarbazones in the heat may be examined at the same time.

E X P E R I M E N T A L .

Acetone sodio-thiosemicarbazone $(CH_3)_2C{=}N{-}N{=}C(NH_2)(S{\cdot}Na)$

The sodium derivative of acetone thiosemicarbazone was obtained by adding the calculated quantity of sodium ethoxide in alcohol to the thiosemicarbazone dissolved in the minimum quantity of hot alcohol, boiling for five minutes under a reflux condenser, and then adding to the cold solution three or four times its volume of ether. The product, which separates in a very finely divided condition, was filtered off on a Buchner funnel, washed well with ether and dried in a vacuum over sulphuric acid. Yield 90–95% of the theoretical. The derivative was a white powder, readily soluble in alcohol or water, and practically insoluble in ether or benzene; the aqueous solution reacts strongly alkaline.

The sodium content was determined by dissolving about 0·3 gms. in distilled water, heating just to boiling to ensure complete hydrolysis and titrating with N/10 hydrochloric acid.

Weight taken	0·330 gms.	0·308 gms.	0·352 gms.
Vol. N/10 HCl (factor 1·007)	21·51 ccs.	20·40 ccs.	22·95 ccs.
Sodium%	15·10%	15·30%	15·10%

$C_4H_8N_3SNa$ requires 15·03% Na.

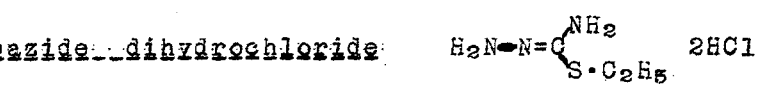
Acetone S-ethyl thiosemicarbazone $(CH_3)_2C{=}N{-}N{=}C(NH_2)(S{\cdot}C_2H_5)$

The calculated quantity of ethyl bromide was added to the sodium derivative of acetone thiosemicarbazone

dissolved in the minimum quantity of alcohol and the whole allowed to stand overnight. The mixture was then heated to boiling point for about five minutes under a reflux condenser to complete the reaction, the sodium bromide which separated was filtered off, and the filtrate evaporated to dryness under reduced pressure at as low a temperature as possible. The resulting pasty mass was pressed on a porous porcelain plate to remove oily impurities and recrystallised from petroleum ether. The substance separated as flat transparent prisms of melting point 55°C. possessing a slight unpleasant odour. The product was readily soluble in all the usual organic solvents, e.g. alcohol, benzene, ether, but was not appreciably soluble in water.

0·1367 gms substance gave 31·1 ccs. N_2 at 19°C. and 762 mm.
0·1346 " " " 31·0 ccs. N_2 at 21°C. and 764 mm.

Nitrogen content found 26·23% and 26·37%
Theory $C_6H_{13}N_3S$ requires 26·42%

S-ethyl thiosemicarbazide dihydrochloride 

Acetone S-ethyl thiosemicarbazide was heated in a waterbath with excess of dilute hydrochloric acid of half normal strength for about a quarter of an hour. The resulting acid solution was extracted several times with ether, to remove any unaltered substance and mercaptan, then evaporated to small bulk under reduced pressure at as low a temperature as possible. A syrupy product was so obtained which, after drying for about three weeks in vacuum over sulphuric acid and finally for several days over phosphorus pentoxide, formed a white amorphous

solid of melting point 60°C. The dihydrochloride was exceedingly hygroscopic and special precautions had to be observed in weighing out the quantities for analysis. It was readily soluble in water but practically insoluble in perfectly dry ether or benzene.

The hydrochloric acid content was determined by the Carius method.

0·2140 gm. substance yield 0·3168 gm. AgCl. = 37·61%HCl

0·3622 " " " 0·5370 " " = 37·72% HCl

Theoretical $C_3H_9N_3S,2HCl$ requires 38·02% HCl.

Benzaldehyde S-ethyl thiosemicarbazone mono hydrochloride

$$C_6H_5\cdot CH=N-N=C\begin{matrix}NH_2\\S\cdot C_2H_5\end{matrix}\cdot HCl$$

This substance was obtained by shaking an aqueous solution of S-ethyl thiosemicarbazide dihydrochloride with benzaldehyde when condensation readily occurred with separation of the benzylidene derivative. The product was practically insoluble in water but readily soluble in alcohol. It was purified by dissolving in alcohol and precipitating with ether when it was collected in the form of fine white needles of melting point 195°C.

0·1430 gms. substance gave 22·1ccs. N_2 at 22°C. and 746 mms.

0·1425 " " " 21·5ccs. " at 17°C. and 747 mms.

Found nitrogen content 17·17%, 17·24%.

Theoretically $C_{10}H_{13}N_3S,HCl$ requires 17·25%.

Benzaldehyde S-ethyl thiosemicarbazone $C_6H_5\cdot CH=N-N=C\begin{matrix}NH_2\\S\cdot C_2H_5\end{matrix}$

The hydrochloric acid in the above monohydrochloride was removed by means of the calculated quantity of sodium

carbonate. The sodium carbonate was dissolved in a few ccs. of water, the hydrochloride was added and then several volumes of alcohol. There was brisk effervescence and when solution was complete and the reaction ceased, the liquid was filtered. The filtrate was evaporated to dryness under reduced pressure at as low a temperature as possible, and the product removed from the admixed sodium chloride by extraction with petroleum ether. Benzaldehyde S-ethyl thiosemicarbazone crystallises in transparent prisms of melting point 66°C. and closely resembles in every particular the original acetone derivative.

0·1535 gms. substance gave 27·0 cc. N_2 at 19°C. and 761 mms.

Nitrogen content found 20·25% N_2

Theoretically $C_{10}H_{13}N_3S$ requires 20·29% N_2

Acetone S-propyl thiosemicarbazone $(CH_3)_2C{=}N{-}N{=}C(NH_2)(S{\cdot}C_3H_7)$

The details of this preparation are essentially the same as in the case of S-ethyl compound. To the acetone sodio-thiosemicarbazone dissolved in the minimum quantity of alcohol the calculated quantity of propyl bromide was added. After boiling for a few minutes under a reflux condenser to complete the reaction, and filtering off any sodium bromide, the alcohol was removed under reduced pressure at as low a temprature as possible. The product was separated from the associated sodium bromide and acetone thiosemicarbazone by extracting the pasty mass with dry ether in which the S-alkylated thiosemicarbazones are readily soluble. After drying the ethereal solution over anhydrous sodium sulphate the ether was removed in a

current of dry air and the S-propyl derivative purified by distillation under reduced pressure. The product was obtained as a colourless oil B.P. 121°C. at 7 mms., intense cooling, by means of solid carbon dioxide and ether gave a solid product of melting point 26-27°C. Acetone S-propyl thiosemicarbazone like the S-ethyl homologue is readily soluble in alcohol, benzene, and ether and practically insoluble in water.

0·1420 gms. substance gave 30·4 ccs. N_2 at 24°C. and 763 mms.

0·1416 " " " 30·1 " " at 17°C. and 744 mms.

Nitrogen content found 24·13% and 24·15% N_2

Theoretically $C_7H_{15}N_3S$ requires 24·28% N_2

S-propyl thiosemicarbazide dihydrochloride

$$H_2N\cdot N=C\begin{matrix}NH_2\\ S\cdot C_3H_7\end{matrix}\cdot 2HCl$$

The dihydrochloride was obtained, like the corresponding S-ethyl compound, by hydrolysis of the above acetone derivative with dilute hydrochloric acid of not more than half normal strength. After removal of the water and acid under reduced pressure the product was a pasty semi-solid mass which only solidified after drying for about six weeks over concentrated sulphuric acid in vacuo. It is exceedingly hygroscopic and readily soluble in water. The hydrochloric acid content was determined by the Carius method.

0·3210 gms. substance gave 0·4450 gms, AgCl.

0·2730 gms. substance gave 0·3760 gms. AgCl.

Hydrochloric Acid content found 35·27% and 35·04%.

Theoretically $C_4H_{11}N_3S,2HCl$ requires 35·43%.

Benzaldehyde S-propyl thiosemicarbazone monohydrochloride

$C_6H_5 \cdot CH=N-N=C\begin{matrix}NH_2 \\ S \cdot C_3H_7\end{matrix} \cdot HCl$, was obtained by shaking benzaldehyde with an aqueous solution of the above dihydrochloride. An appreciable amount of heat was evolved and the product separated in the form of a paste with any excess benzaldehyde. The product was purified by dissolving in the minimum quantity of alcohol and precipitating, by the addition of ether, as fine white lustrous needles of melting point 209°C.

0·1467 gms substance gave 20·7 ccs. N_2 at 20°C and 765 mms.

0·1543 " " " 22·0 ccs. N_2 at 20°C and 761 mms.

Nitrogen content found 16·24% and 16·32%

Theoretically $C_{10}H_{16}N_3S,HCl$ requires 16·34%.

Benzaldehyde S-propyl thiosemicarbazone $C_6H_5 \cdot CH=N-N=C\begin{matrix}NH_2 \\ S \cdot C_3H_7\end{matrix}$

Was obtained by the removal of the hydrochloric acid from the above hydrochloride by means of sodium carbonate. After taking off the water and alcohol under reduced pressure the resulting pasty mass of sodium chloride and the product was extracted with dry ether. The ethereal solution was dried over anhydrous sodium sulphate, the ether removed in a current of dry air, and the product solidified by cooling with solid carbon dioxide and ether. Oily impurities were removed by pressing out on a porous plate and the thiosemicarbazone was recrystallised from petroleum ether. It was found necessary to inoculate with small pieces of the solid from the first crystallisation. The product formed transparent rhombic prisms of melting point 54°C.

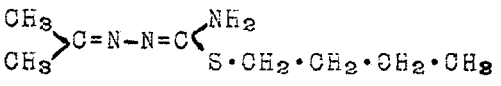
0·1535 gms. substance gave 25·6 ccs. N_2 at 16°C and 746 mms.

0·1510 gms. substance gave 25·2 ccs. N_2 at 18°C. and 746 mms.

Nitrogen content found 19·08% and 18·91%.

Theoretically $C_{10}H_{18}N_3S$ requires 19·00%.

Acetone S-n-butyl thiosemicarbazone.



In the preparation of the S-alkylated thiosemicarbazones already described the sodium derivative of acetone thiosemicarbazone was treated with the calculated quantity of the corresponding alkyl halide; the alternative method of preparation which does not involve the actual isolation of acetone sodio-thiosemicarbazone, was carried out as follows.

A weighed quantity of acetone thiosemicarbazone was dissolved in the minimum amount of boiling alcohol, the calculated quantity of sodium ethoxide in alcoholic solution was added and the mixture heated under a reflux condenser for about a quarter of an hour. The resulting solution of the sodium derivative was cooled, the necessary quantity of n-butyl bromide added and the whole allowed to stand overnight. The mixture was heated under a reflux condenser for about half an hour to complete the reaction and, after cooling, the sodium bromide which separated was filtered off.

The alcohol was removed at as low a temperature as possible under reduced pressure and the pasty residue of of the product together with acetone thiosemicarbazone was extracted with ether. After drying the ethereal solution over anhydrous sodium sulphate the ether was removed in a current of dry air and the product

distilled under reduced pressure. The fraction up to about 100°C. possessed a strong smell of mercaptan, but the main portion boiling at 146°C. under a pressure of 16mm. was a water clear oil having a faint garlic odour. The derivative was soluble in the usual organic solvents, ether, alcohol, acetone, and benzene but practically insoluble in water. Cooling with solid carbon dioxide and ether gave a white solid product of melting point 16°C.

0·1190 gms gave 23·0 ccs. N_2 at 18°C. and 763 mms.

0·1146 gms. gave 22·2 ccs. N_2 at 19°C. and 766 mms.

Nitrogen content found 22·42% and 22·39%.

Theoretically $C_8H_{17}N_3S$ requires 22·46%.

S-n-butyl thiosemicarbazide dihydrochloride

$$H_2N\cdot N=C\begin{matrix}NH_2\\ \diagdown\\ S\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_3\end{matrix}\cdot 2HCl$$

The dihydrochloride was obtained by the hydrolysis of the butyl derivative with half normal hydrochloric acid in the usual manner. The acid solution was extracted with ether to remove any mercaptan and unaltered substance then evaporated to small bulk under reduced pressure. Prolonged drying over sulphuric acid in a vacuum desiccator gave a white product M.P. 100-101°C. with apparently slight decomposition. The product, in common with the ethyl and propyl compounds was only slightly soluble in organic solvents, was exceedingly hygroscopic, and was readily soluble in water.

0·1840 gms. gave 21·7 ccs. N_2 at 14°C. and 763 mms. = 19·13%N_2

0·3064 gms. gave 0·3985 gms. AgCl = 33·07% HCl.

$C_5H_{13}N_3S\cdot 2HCl$ requires 19·09% N_2 and 33·18% HCl.

Benzaldehyde S-n-butyl thiosemicarbazone monohydrochloride

$$C_6H_5 \cdot CH=N-N=C\begin{matrix}NH_2\\S \cdot C_4H_9\end{matrix} \cdot HCl$$

Was prepared by vigorously shaking an aqueous solution of the dihydrochloride with benzaldehyde. The product was purified by dissolving in the minimum quantity of alcohol and precipitating by adding several times the volume of ether, when it separated as fine white lustrous needles M.P. 185°C. The monohydrochloride was readily soluble in alcohol but practically insoluble in benzene and ether and water.

0·1643 gms. gave 21·6 ccs. N_2 at 11°C. and 741°C. = 15·28%N_2

0·1712 gms. gave 22·8 ccs. N_2 at 12·6°C. and 746°. = 15·38% N_2

0·2518 gms. gave 0·1320 gms. AgCl = 13·38% HCl.

$C_{12}H_{17}N_3S \cdot HCl$ requires 15·47% N_2 and 13·44% HCl.

Benzaldehyde S-n-butyl thiosemicarbazone

$$C_6H_5 \cdot CH=N-N=C\begin{matrix}NH_2\\S \cdot C_4H_9\end{matrix}$$

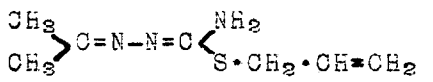
The hydrochloric acid in the above monohydrochloride was removed by the action of the calculated quantity of sodium carbonate as has already been described. The product thus obtained was a thick viscous oil which could not be distilled since it decomposed at a temperature of 210°C. under a pressure of 1 mm. Purification was effected by cooling with solid carbon dioxide and ether, pressing out the mass on a porous plate to remove oily impurities and recrystallising from petroleum ether when short transparent prisms were obtained M.P. 50°C. The properties of the compound closely resembled those of the corresponding ethyl and propyl derivatives.

0·1608 gms. gave 24·6 ccs. N_2 at 20°C. and 765·5 mms. = 17·61%

0·1510 gms. gave 23·3 ccs. N_2 at 19°C. and 762 mms. =17·79%N_2

$C_{12}H_{17}N_3S$ requires 17·87% N_2.

Acetone S-allyl thiosemicarbazone



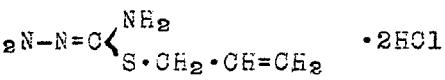
Was obtained by the action of allyl iodide using either of the methods already described for the preparation of S-alkyl thiosemicarbazones. Since sodium iodide is soluble in alcohol, the reaction mixture was evaporated to dryness under reduced pressure and the product extracted by means of dry ether. After drying the ethereal solution over anhydrous sodium sulphate the ether was removed in a current of dry air and the product recrystallised from petroleum ether; flat transparent prisms were thus obtained M.P. 51°C. Like the other S-alkylated thiosemicarbazones the allyl compound was readily soluble in alcohol, ether, and benzene and practically insoluble in water.

0·1574 gms. gave 33·1 ccs. N_2 at 18°C. and 767 mms. = 24·50%

0·1520 gms. gave 32·4 ccs. N_2 at 20°C. and 764 mms. = 24·51%

$C_7H_{13}N_3S$ requires 24·56% N_2.

S-allyl thiosemicarbazide dihydrochloride



Like the other dihydrochlorides the allyl compound was obtained by the hydrolysis of the isopropylidene derivative by means of dilute hydrochloric acid.

Evaporation of the acid liquor under reduced pressure gave a thick syrupy product which on prolonged drying over sulphuric acid in a vacuum desiccator was converted into a white solid M.P. 75°C., very soluble in water and exceedingly hygroscopic.

0·2064 gms. gave 0·2839 gms. AgCl = 35·00% HCl

0·2588 gms. gave 0·3600 gms. AgCl = 35·4% HCl.

$C_4H_9N_3S \cdot 2HCl$ requires 35·86% HCl.

Benzaldehyde S-allyl thiosemicarbazone monohydrochloride.

$$C_6H_5 \cdot CH=N-N=C\begin{matrix}NH_2 \\ S \cdot CH_2 \cdot CH=CH_2\end{matrix} \quad HCl$$

Was prepared by the general method for preparing compounds of this type, by vigorously shaking an aqueous solution of the dihydrochloride with a slight excess of benzaldehyde. The excess of benzaldehyde was removed by extraction with ether after which the substance was recrystallised in the usual manner by dissolving in a small quantity of alcohol and precipitating with ether. The derivative was obtained as lustrous white plates M.P. 190°C., readily soluble in alcohol and only slightly soluble in ether, benzene or water.

0·1584 gms. gave 22 ccs. N_2 at 17°C. and 764 mms. = 16·21%N_2

0·1620 gms. gave 22·5 ccs. N_2 at 17°C. and 764 mms. =16·17%N_2

0·2995 gms. gave 0·1668 gms. AgCl (in Carius) =14·17% HCl.

$C_{11}H_{13}N_3S \cdot HCl$ requires 16·44% N_2 and 14·29% HCl.

Benzaldehyde S-allyl thiosemicarbazone.

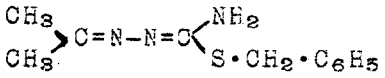
$$C_6H_5 \cdot CH=N-N=C\begin{matrix}NH_2 \\ S \cdot CH_2 \cdot CH=CH_2\end{matrix}$$

Was obtained by the removal of the hydrochloric acid from the above hydrochloride by means of sodium carbonate in the usual manner. The product, recrystallised from petroleum ether, was collected as transparent rhombic prisms M.P. 42°C. closely resembling the other compounds of this type in solubility relations.

0·1576 gms. gave 26·0 ccs. N_2 at 19°C. and 762 mms. =19·08%N_2

$C_{11}H_{13}N_3S$ requires 19·18% N_2

Acetone S-benzyl thiosemicarbazone



The benzyl derivative was obtained by either of the usual methods, using the calculated quantity of benzyl chloride. The pasty mass obtained by evaporating down the alcoholic solution was pressed out on porous porcelain to remove oily impurities then recrystallised from petroleum ether when the pure derivative was obtained as long colourless needles of melting point 51–53°C.
The product was exceedingly soluble in alcohol, benzene and ether.

0·1552 gms. gave 26·0 ccs. N_2 at 18°C. and 752 mms. =19·14%N_2

0·1590 gms. gave 26·4 ccs. N_2 at 18°C. and 754 mms. =19·03%N_2

$C_{11}H_{15}N_3S$ requires 19·00% N_2

The molecular weight was determined by the cryoscopic method in benzene K=50.

0·2155 gms. depressed freezing point 0·284°C. M.W.=217.

0·2100 gms. " " " 0·266°C. M.W.=225.

$C_{11}H_{15}N_3S$ requires 221.

S-benzyl thiosemicarbazide monohydrochloride

$$H_2N\cdot N=C\begin{matrix}NH_2\\ S\cdot CH_2\cdot C_6H_5\end{matrix}\cdot HCl$$

Hydrolysis of acetone S-benzyl thiosemicarbazone by means of dilute hydrochloric acid gave a crystalline product the melting point of which was indefinite. The analysis showed that the substance was probably a mixture of the mono- and dihydrochlorides. What proved to be the monohydrochloride was obtained by adding a slight excess of sodium carbonate solution to the aqueous solution of the hydrolysis and extracting the free base with ether. After drying over anhydrous sodium sulphate a current of dry hydrochloric acid gas was passed through the ethereal solution and the white precipitate which formed was immediately filtered off and washed with dry ether. The product was a white granular substance M.P. 124-126°C. with decomposition., soluble in water and alcohol, slightly hygroscopic.

0·1550 gms. gave 25·75 cc. N_2 at 20°C. and 752 mm. =18·81% N_2

0·1588 gms. gave 26·35 cc. N_2 at 18°C. and 754 mm. =19·00% N_2

$C_8H_{11}N_3S\cdot HCl$ requires 19·31% N_2.

S-benzyl thiosemicarbazide sulphate

$$\left[H_2N\cdot N=C\begin{matrix}NH_2\\ S\cdot CH_2\cdot C_6H_5\end{matrix}\right]_2 H_2SO_4$$

The sulphate was prepared by adding a drop or two of concentrated sulphuric acid to an excess of the impure base in ethereal solution. The precipitate which separated was crystallised from alcohol when the product was obtained in small colourless needles of melting point 148°C. with some decomposition. The substance was soluble

in water and alcohol and insoluble in ether.

Found H_2SO_4 = 21·10% as $BaSO_4$

$(C_8H_{11}N_3S)_2 \cdot H_2SO_4$ requires 21·30% H_2SO_4

Benzaldehyde S-benzyl thiosemicarbazone

$$C_6H_5 \cdot CH=N-N=C\begin{matrix}NH_2\\ S \cdot CH_2 \cdot C_6H_5\end{matrix}$$

Was prepared by vigorously shaking up an aqueous solution of the hydrochloride with excess of benzaldehyde. After standing overnight the substance was collected and recrystallised from alcohol from which it separated as colourless crystals melting at 190°C.

Found N = 15·5%

$C_{15}H_{15}N_3S$ requires 15·61%.

Drastic hydrolysis of the acetone S-alkylated thiosemicarbazones

With a view to arriving at some idea of the constitution of the S-alkyl thiosemicarbazones a drastic hydrolysis was effected by means of caustic alkali.

The S-benzyl derivative was chosen for the purpose as the corresponding mercaptan was much less volatile and therefore more likely to be readily identified than would be the case with a lighter substituent.

Acetone S-benzyl thiosemicarbazone was heated under an efficient reflux condenser with an excess of 20% aqueous sodium hydroxide until solution was complete, that is, for about 2 to 3 hours. During the heating a considerable quantity of ammonia was evolved and was identified by its characteristic odour and colouring of litmus paper.

The reaction mixture was allowed to cool, the condenser was washed down with a little water, and then the alkaline solution was carefully distilled up to a temp. of 85°C. using a short fractionating still head. Acetone was identified in the distillate by the odour, the iodoform reaction, the sodium nitroprusside test and by the preparation of the oxime.

Hydrazine was shown to be present by continuing the distillation up to a temperature of 120°C. without the still head, when the hydrazine hydrate distilled. The confirmatory tests applied in the case of hydrazine were the reduction of Fehling's solution and the formation of benzal azine, $C_6H_5 \cdot CH=N-N=CH \cdot C_6H_5$, M.P. 93°C., on shaking in aqueous solution with benzaldehyde.

The alkaline residue remaining after distilling off the hydrazine effervesced vigorously on the addition of

dilute acid and carbon dioxide was evolved in quantity. The mercaptan, which had so far been retained in the form of the sodium salt was also liberated and was removed by extracting the now acid liquor with ether. The ethereal solution was dried over anhydrous sodium sulphate and the mercaptan confirmed by the boiling point

All the products of the complete hydrolysis, namely, acetone, hydrazine, carbon dioxide, ammonia and benzyl mercaptan were thus identified.

Action of benzene sulphonyl chloride $C_6H_5{\cdot}SO_2{\cdot}Cl$, on acetone S-benzyl thiosemicarbazone.

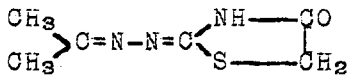
Acetone S-benzyl thiosemicarbazone reacted only very slowly with benzene sulphonyl chloride on shaking with aqueous alkali; the reaction readily occurred, however, in alcoholic solution. The substance was dissolved in absolute alcohol, sodium ethoxide (2 mols) was added then benzene sulphonyl chloride (1 mol). The mixture was boiled for a few minutes, filtered hot from the sodium chloride and then two or three volumes of ether were added to the cold solution. The sodium derivative of the sulphonamide separated as a white powder, extremely soluble in water less soluble in alcohol, and insoluble in ether.

Analysis. Sulphur (by Carius) 16·73% and 16·90%.

Theoretically $C_{17}H_{18}O_2N_3S_2Na$ requires 16·71%.

Action of esters of α-halogenated acids.

2·4-diketotetrahydrothiazole-2-isopropylidene hydrazone



1-menthyl chloroacetate and the sodium derivative of acetone thiosemicarbazone were heated together in alcoholic solution. Sodium chloride separated and the solution on concentration yielded menthol and a substance melting at 175-176°C. It was found that the employment of ethyl chloroacetate resulted in the formation of the same substance.

Ethyl chloroacetate (1 mol) was added to a warm a alcoholic solution of acetone sodio-thiosemicarbazone (1 mol), sodium chloride separated at once, and the reaction was completed by boiling on the water bath under a reflux condenser for half an hour. The solid which separated on cooling was collected, washed with water and recrystallised from alcohol from which it was deposited in colourless plates melting at 175-176°C. The product was readily soluble in warm aqueous sodium hydroxide from which it was reprecipitated unchanged on acidification and readily soluble in hot alcohol or chloroform, and somewhat soluble in hot water. The yield was 80% of the theoretical.

0·1476 gms. gave 30·4 ccs. N_2 at 14°C. and 762 mms. =24·85% N_2

0·1509 gms. gave 30·9 ccs. N_2 at 12°C. and 763 mms. =24·86% N_2

$C_6H_9ON_3S$ requires 24·54% N_2.

The molecular weight was determined by the ebullioscopic method using alcohol (K=11·5) as solvent.

0·2030 gms. gave 0·116°C. elevation of boiling point.

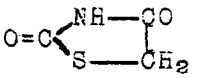
∴ M. W. = 153.

0·1946 gms. gave 0·108°C. elevation of boiling point

∴ M.W. = 162

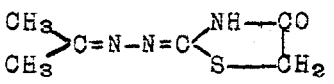
$C_8H_9ON_3S$ requires M.W. = 171.

To determine the constitution of this compound it was hydrolysed by warming with very dilute hydrochloric acid. Acetone, recognised by its smell and by the iodoform reaction, distilled over, and there was obtained what appeared to be the hydrochloride of a base, which, however, rapidly decomposed giving a substance insoluble in all organic solvents. A very smooth hydrolysis was effected by boiling the substance of M.P. 175-176°C. with concentrated hydrochloric acid; the solution was evaporated to dryness on the water bath and the residue allowed to remain for some time in a vacuum desiccator over conc. sulphuric acid and soda lime. The crystalline mass so obtained was repeatedly extracted with hot chloroform which, on cooling, deposited 2·4-diketotetrahydrothiazole

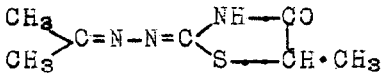


, identified by its melting point and by comparison with a known specimen. The residue insoluble in chloroform was very soluble in water and was identified as hydrazine hydrochloride by the reduction of Fehling's solution, by conversion into hydrazine sulphate and by formation of benzalazine on shaking the aqueous solution with benzaldehyde.

The substance melting at 175-176°C. was therefore a ψ-thiohydantoin derivative of the structure,



2:4-diketo-5-methyl-tetrahydrothiazole-2-isopropylidene hydrazone.



Acetone thiosemicarbazone dissolved in boiling alcohol was treated with sodium ethoxide (1 mol) dissolved in alcohol and the mixture heated under a reflux condenser for about ten minutes. The alcoholic solution of acetone sodio-thiosemicarbazone so obtained was cooled, slightly more than the calculated quantity of ethyl α-bromo-propionate added, the whole allowed to stand at room temperature for an hour and then boiled for half an hour under a reflux condenser to complete the reaction. The sodium bromide which separated was removed by filtering the boiling solution, which, on cooling, deposited the tetrahydrothiazole derivative. The product was recrystallise from alcohol from which it separated in the form of fine white needles of melting point 150°C. The compound was slightly soluble in benzene but only sparingly so in ether or water; it was readily soluble on warming with aqueous alkali from which solution it was reprecipitated by acidifying.

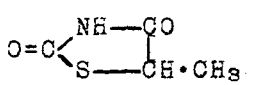
The above method may be varied by dissolving the previously prepared acetone sodio-thiosemicarbazone in alcohol, adding the ester and proceeding as described.

0·1508 gms. gave 29·7 ccs. N_2 at 14°C. and 746 mms. =22·73% N_2

0·1498 gms. gave 29·3 ccs. N_2 at 12°C. and 742 mms. =22·66% N_2

$C_7H_{11}ON_3S$ requires 22·70% N_2.

2:4-diketo-5-methyltetrahydrothiazole



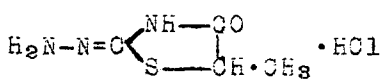
Complete hydrolysis of the above isopropylidene derivative was effected by boiling under a reflux condenser with concentrated hydrochloric acid for three hours. The solution was then evaporated to dryness on the water bath and the residue extracted with hot benzene; the undissolved crystalline solid was identified as hydrazine hydrochloride by the reduction of Fehling's solution and formation of benzalazine on shaking with benzaldehyde. The benzene solution was dried over anhydrous sodium sulphate and on evaporation gave an oil which distilled at 165-168°C. under a pressure of 20 mms; the distillate on cooling by means of solid carbon dioxide and ether solidified to a crystalline mass which melted at 46-47°C. From its properties the substance is evidently that already described by Wheeler and Barnes (Amer. Chem. J. 1900, 24, 78), who prepared it by a different method.

0·1514 gms. gave 14·0 ccs. N_2 at 14°C. and 744·5 mms.

= 10·64% N_2.

$C_4H_5O_2NS$ requires 10·69% N_2

2:4-diketo-5-methyltetrahydrothiazole-2-hydrazone hydrochloride



The isopropylidene derivative was hydrolysed by boiling with hydrochloric acid of twice normal strength under a reflux condenser for about fifteen minutes. The acid solution, after filtration from a small quantity of insoluble matter, was evaporated to dryness under reduced pressure at a temperature of 40-50°C. Acetone was recognised in the distillate by its odour and by the iodoform reaction. The residue consisting of the

hydrochloride, was a white granular crystalline substance which was slightly hygroscopic, very soluble in water, but only slightly soluble in alcohol and practically insoluble in ether. The substance decomposed on heating to temperatures above 220°C.

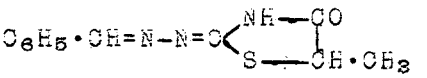
The aqueous solution gave a precipitate of silver chloride with silver nitrate and nitric acid and it appeared to give a silver salt, probably due to the tetrahydrothiazole complex, but this was not investigated. The substance reduced Fehling's solution on boiling.

0·1450 gms. gave 22·4 ccs. N_2 at 16°C. and 770 mms. =22·99% N

0·1560 gms. gave 30·8 ccs. N_2 at 14°C. and 770·5 mms.=23·15%N_2

$C_4H_7ON_3S \cdot HCl$ requires 23·14% N_2

2:4-diketo-5-methyltetrahydrothiazole-2-benzylidenehydrazone

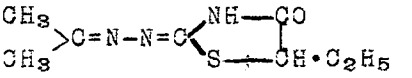


Was obtained by vigorously shaking an aqueous solution of the hydrochloride with benzaldehyde and recrystallising the product from alcohol from which it was deposited in the form of fine white needles melting at 236°C. The substance was only slightly soluble in cold alcohol or in water.

0·0692 gms. gave 10·8 ccs. N_2 at 20°C. and 767 mms.

Found 18·03% N_2. $C_{11}H_{11}ON_3S$ requires 18·03%.

2:4-diketo-5-ethyltetrahydrothiazole-2-isopropylidenehydrazone



Was obtained by the action of ethyl α-bromo-n-

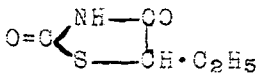
butyrate on the sodium derivative of acetone thiosemicarbazone in alcoholic solution. The reaction was carried out in exactly the same way as with the ethyl α bromo propionate. Recrystallised from alcoholic solution the product was obtained in the form of fine white glistening needles melting at 116°C. The substance was only slightly soluble in ether, benzene or water.

0·1814 gms. gave 23·8 ccs. N_2 at 15·5°C. and 754 mms. =20·99%N

0·1860 gms. gave 24·8 N_2 at 17°C. and 754 mms. = 20·90% N_2.

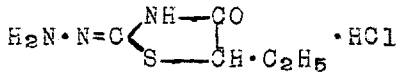
$C_8H_{13}ON_3S$ requires 21·11% N_2.

2:4-diketo-5-ethyltetrahydrothiazole



Was prepared from the preceeding isopropylidene derivative by boiling with concentrated hydrochloric acid as in the previous case. After recrystallisation from a mixture of benzene and petroleum etuer it melted at 63-64°C., was readily soluble in alcohol, ether or benzene and less soluble in light petroleum. It agreed in melting point with the substance previously described by Wheeler and Barnes (loc. cit. 76) and prepared by a different method.

2:4-diketo-5-ethyltetrahydrothiazole-2-hydrazone hydrochloride.



The hydrochloride was obtained from the isopropylidene derivative by hydrolysis which was effected by boiling under a reflux condenser with 2N hydrochloric acid as in the case of the corresponding -5-methyl compound.

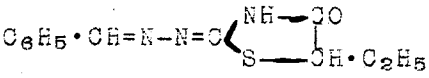
The product was a white granular crystalline solid, sli slightly deliquescent, soluble in water, slightly soluble in alcohol, and practically insoluble in ether. The hydrochloride decomposed on heating at a temperature of 215-220°C.

0·1264 gms. gave 24·0 ccs. N_2 at 14°C. and 730 mms. = 21·44%

0·1330 gms. gave 24·6 ccs. N_2 at 14°C. and 749 mms. = 21·39%N_2

$C_5H_9ON_3S \cdot HCl$ requires 21·49% N_2

2:4-diketo-5-ethyltetrahydrothiazole-2-benzylidenehydrazone

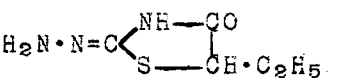


The benzylidene derivative was prepared by vigorously shaking an aqueous solution of the above hydrochloride with benzaldehyde in the usual way. The pasty mass so obtained was washed with ether to remove excess benzaldehyde and after recrystallisation from alcohol the product was obtained in the form of white microscopic needles having a melting point of 206°C. The substance was practically insoluble in ether, water, or cold alcohol.

0·1528 gms. gave 22·1 ccs. N_2 at 15°C. and 758 mms. =16·9% N_2

$C_{12}H_{13}ON_3S$ requires 17·0% N_2

2:4-Diketo-5-ethyltetrahydrothiazole-2-hydrazone



The free base was prepared by the removal of the hydrochloric acid from the hydrochloride by means of the calculated quantity of sodium carbonate in aqueous soln. After the effervescence had ceased the solution was evap-

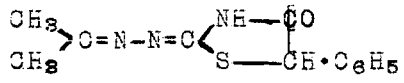
orated to dryness at room temperature in a vacuum over sulphuric acid, the residue was washed with a small quantity of water to remove sodium chloride, and analysed after drying in a vacuum desiccator over sulphuric acid.

The product was a white crystalline powder soluble in hot alcohol, slightly soluble in benzene, ether, or water. It melted at 139°C. and was only moderately stable becoming discoloured on keeping.

0·0920 gms. gave 20·7 ccs. N_2 at 13°C. and 750 mms. =26·23%N_2

$C_5H_9ON_3S$ requires 26·41% N_2.

2:4-Diketo-5-phenyltetrahydrothiazole-2-isopropylidene hydrazone



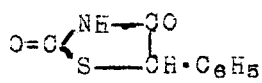
Was prepared by the usual method from ethyl phenylbromoacetate and the sodium derivative of acetone thiosemicarbazone. The substance closely resembled in every particular the other products of this type already described. Recrystallised from alcohol the compound was obtained in the form of fine white needles melting at 198-199°C., which were not appreciably soluble in benzene ether or water.

0·1562 gms. gave 22·45 ccs. at 13·5°C. and 757 mms. =16·89%N_2

0·1587 gms. gave 23·15 ccs. N_2 at 15°C. and 755 mms.=16·96%N_2

$C_{12}H_{13}ON_3S$ requires 17·00%N_2

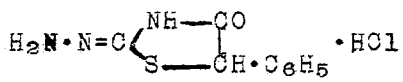
2:4-Diketo-5-phenyltetrahydrothiazole



Was obtained by the hydrolysis of the preceeding

isopropylidene derivative, effected by means of prolonged boiling with concentrated hydrochloric acid in the usual way. After recrystallisation from a mixture of petroleum ether and absolute alcohol it melted at 125-126°C. and corresponded in all its properties with the compound described by Wheeler (Amer. Chem. J. 1901, 26,352) and obtained by him according to another method.

2:4-Diketo-5-phenyltetrahydrothiazole-2-hydrazone hydrochloride



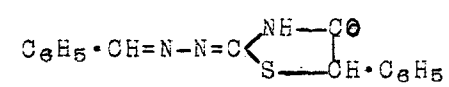
The hydrochloride was prepared from the isopropylidene derivative by hydrolysis with dilute hydrochloric acid in the usual way. The product was a white micro-crystalline solid which decomposed on heating at 240°C. It was rather sparingly soluble in cold water, soluble only with difficulty in alcohol and practically insoluble in ether.

0·1538 gms. gave 21·6 ccs. N_2 at 12°C. and 768 mms. =17·15% N_2

0·1539 gms. gave 22·0 ccs. N_2 at 15·5°C. and 768 mms.=17·27%N_2

$C_9H_9ON_3S \cdot HCl$ requires 17·25% N_2

2:4-Diketo-5-phenyltetrahydrothiazole-2-benzylidene hydrazone



Was prepared in the usual way by the action of benzaldehyde on an aqueous solution of the hydrochloride. Recrystallised from alcohol the product was obtained as microscopic white hair-like crystals melting at 257°C., and, like the other compounds of this type, was only slightly soluble in cold alcohol, benzene, ether, or water.

0·1199 gms. gave 14·3 ccs. N_2 at 13·5°C. and 764 mms. =14·15% N_2

$C_{18}H_{13}ON_3S$ requires 14·23% N_2

Action of Esters of β-halogenated Acids.

The esters employed were ethyl β-chloro-n-butyrate and ethyl β-bromo-β-phenylpropionate.

Action of β-chloro-n-butyric ester:-

(a) A weighed quantity of acetone thiosemicarbazone was just dissolved in boiling alcohol, the calculated amount of sodium ethoxide was then added and the mixture boiled for ten minutes under a reflux condenser. The resulting alcoholic solution of the sodium derivative was cooled to room temperature and the necessary quantity of the ester added. There appeared to be an immediate reaction accompanied by a decided rise in temperature and separation of sodium halide.

The sodium chloride was filtered off, the filtrate was evaporated to small bulk under reduced pressure at as low a temperature as possible, and the pasty mass so obtained was extracted with ether. The residue after extraction with ether was shown to be acetone thiosemicarbazone by the melting point and by comparison with a known specimen. The ethereal solution was dried over anhydrous sodium sulphate and the ether carefully removed in a current of dry air. The resulting product was a water clear liquid boiling at 138-140°C. at atmospheric pressure; it did not contain nitrogen or sulphur and was apparently unsaturated in character.

These properties indicate ethyl crotonate and that the reaction did not proceed as was expected but

resulted in a simple removal of hydrogen halide from the β halogenated acid with formation of the corresponding unsaturated compound.

(b) In this experiment the sodium derivative of acetone thiosemicarbazone was isolated, a quantity (weighed) was dissolved in absolute alcohol and the alcoholic solution cooled in a good freezing mixture of ice and salt. The calculated amount of the β-halogenated ester, also well cooled, was slowly added but the reaction appeared to proceed almost instantaneously. After allowing the mixture to stand overnight it was examined but in this experiment also it was found that the products were ~~sodi~~ sodium halide and ethyl crotonate only.

(c) Acetone sodio-thiosemicarbazone was prepared, dried, finely ground, and a weighed quantity suspended in dry benzene. The necessary amount of chloro ester was added but no reaction occurred even after boiling for several hours under a reflux condenser, the sodium derivative being removed unchanged.

In the case of ethyl β-bromo-β-phenylpropionate the results obtained were found to correspond exactly with those just described for ethyl β-chloro-n-butyrate. The unsaturated ester in this case was ethyl cinnamate.

Action of Esters of γ-halogenated Acids.

Action of ethyl γ-chloro-n-butyrate, $CH_2Cl \cdot CH_2 \cdot CH_2 \cdot COO \cdot C_2H_5$

(a) To an alcoholic solution of the sodium derivative of acetone thiosemicarbazone cooled in ice-water, the calculated quantity of the chloro ester, also cooled,

was added. There appeared to be an almost instantaneous reaction, but the whole was allowed to stand overnight before the mixture was examined. The solid crystalline mass which settled out was filtered off and extracted with absolute alcohol. It was found to be a mixture of sodium halide and acetone thiosemicarbazone, the amounts being;- sodium halide 98% theory, and thiosemicarbazone 50% theory.

The alcoholic filtrate was evaporated to small bulk at room temperature, under reduced pressure and the resulting pasty product extracted with dry ether. After drying over anhydrous sodium sulphate the ether was removed in a current of dry air yielding a liquid part of which distilled at 76°C. under a pressure of 15 mms. was unsaturated in character, and did not contain nitrogen or sulphur. This more volatile portion was apparently ethyl vinylacetate. The pressure was reduced still further until the product was free from unsaturated ester, then attempts were made by cooling in various freezing mixtures finally in solid carbon dioxide and ether, to obtain a crystalline product, but the liquid residue could not be solidified.

When distillation was attempted there was apparent decomposition, a fraction was obtained boiling at 166-168° under a pressure of 0·5 mms. This product contained sulphur and nitrogen and analysis gave the following figures :- Nitrogen 9·84%. Sulphur (by Carius) 13·83% , 13·69% A resinous residue which could not be purified was left in the distillation flask.

(b) The sodium derivative of acetone thiosemicarbazone was prepared and suspended in a finely divided condition

in dry benzene. No action took place on adding the calculated quantity of ethyl γ-chloro-n-butyrate, even after several hours boiling.

(c) This experiment was carried out as described in (a) except that after standing overnight the reaction mixture was boiled under a reflux condenser to complete the reaction. The results were unsatisfactory.

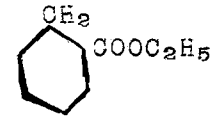
Action of ethyl γ-chlorovalerate, $CH_3 \cdot CH \cdot CH_2 \cdot CH_2 \cdot COOC_2H_5$

The experiments were carried out as has just been described for γ-chloro-n-butyric ester but the results obtained were also unsatisfactory. The unsaturated compound obtained boiled at 78°C. under a pressure of 15 mms.. Using benzene there was no reaction, the sodium derivative being recovered unchanged.

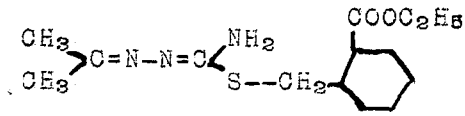
Action of ethyl γ-chloro-isocaproate, $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C(Cl)CH_2 \cdot CH_2 \cdot COOC_2H_5$

The results obtained were of a negative character as in the case of the two γ-chloro esters already described. The unsaturated compound obtained in this case boiled at 86°C. under a pressure of 9? mms. and at 99°C under a pressure of 22 mms.

Using the sodium derivative in suspension in benzene no evidence of chemical action could be detected. The results indicate that benzene exerts an inhibiting action except in the case of exceedingly reactive halogenated compounds such as the chloroformic esters. Even when reaction takes place, using benzene as a solvent, it does so abnormally; that is to say the substituent is not linked to sulphur as in cases where alcohol is used.

Action of ethyl ω-bromo-o-toluate, 

Acetone S-o-carbethoxy benzylthiosemicarbazone



An alcoholic solution of the sodium derivative of acetone thiosemicarbazone was prepared in the usual manner, well cooled in ice-water, and the calculated amount of ethyl ω-bromo-o-toluate, also cooled, was slowly added. Sodium bromide separated at once but the whole was allowed to stand overnight, then was boiled for half an hour under a reflux condenser to complete the reaction.

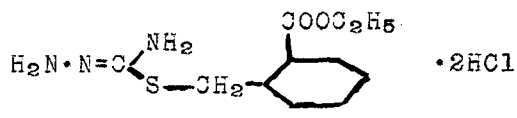
The sodium halide was filtered off and the filtrate evaporated to small bulk under reduced pressure. The low melting product thus obtained was purified by recrystallising several times from petroleum ether to which had been added a little benzene. From this mixed solvent the compound separated as pale yellow transparent prisms containing both nitrogen and sulphur and melting at 66°C. The substance was exceedingly soluble in ether, alcohol, and benzene and practically insoluble in water. The yield was 70% of the theoretical.

0·1586 gm. gave 18·8 cc. N_2 at 11·5°C. and 770 mm. =14·29% N_2.

0·1572 gm. gave 19·6 cc. N_2 at 16·5°C. and 751 mm. =14·35% N_2.

$C_{14}H_{19}N_3SO_2$ requires 14·33% N_2.

S-o-carbethoxy-benzyl thiosemicarbazide dihydrochloride



The dihydrochloride was prepared from the acetone derivative just described, by hydrolysis; this was effected by boiling the substance for a quarter of an hour under a reflux condenser with an excess of hydrochloric acid of normal strength, exactly as in the case of the S-alkylated thiosemicarbazones.

The acid solution so obtained was evaporated to dryness under reduced pressure at a temperature of about 50°C., yielding a white deliquescent solid melting at 125-130°C., with decomposition. The product, like the S-alkylated dihydrochlorides, was exceedingly soluble in water, slightly soluble in cold alcohol, and practically insoluble in ether.

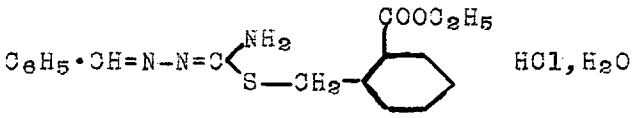
0·1750 gm. gave 19·1 cc. N_2 at 11°C. and 741 mm. = 12·69% N_2.

0·1624 gm. gave 0·1417 gm. AgCl = 22·2% HCl.

0·1800 gm. gave 0·1574 gm. AgCl = 22·25% HCl.

$C_{11}H_{15}N_3SO_2 \cdot 2HCl$ requires 12·88% N_2; 22·89% HCl.

Benzaldehyde S-o-carbethoxybenzyl thiosemicarbazone monohydrochloride.



The benzylidene derivative was obtained in the usual manner by vigorously shaking an aqueous solution of the dihydrochloride with an excess of benzaldehyde. The excess benzaldehyde was removed by extracting the pasty reaction product with ether and the benzilidene derivative was purified, as in the case of the corresponding benzilidene S-alkylated compounds, by dissolving in aqueous alcohol and precipitating by the addition of several volumes of ether.

The substance separated as lustrous white plates

melting at 115°C., soluble in alcohol, less so in benzene and practically insoluble in ether or water. ~~The analytic~~

The analytical results indicate that by this method of purification the hydrochloride crystallised with one molecule of water of crystallisation; the corresponding S-alkylated compounds do not appear to contain water of crystallisation.

0·1960 gm. gave 17·5 cc. N_2 at 12°C. and 749 mm. = 10·45% N_2

0·2084 gm. gave 18·35 cc. N_2 at 10·5°C. and 758 mm. =10·50%N_2

0·2396 gm. gave 0·0822 gm. AgCl = 8·73% HCl

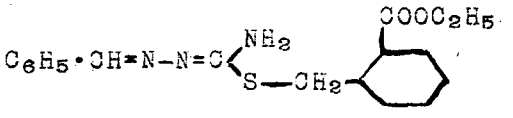
0·1980 gm. gave 0·0YUR gm. AgCl = 8·66% HCl

$C_{18}H_{19}O_2N_3S \cdot HCl \cdot H_2O$ requires 10·6% N_2 and 9·22% HCl

Compare

$C_{18}H_{19}O_2N_3S \cdot HCl$ requires 11·18% N_2 and 9·62% HCl.

Benzaldehyde S-o-carbethoxybenzyl thiosemicarbazone



A weighed quantity of the above hydrochloride was added to an equivalent of anhydrous sodium carbonate dissolved in the minimum amount of water, Sufficient alcohol was added to effect complete solution, on which there was brisk effervescence and evolution of carbon dioxide. When the reaction ceased the mixture was evaporated to dryness under reduced pressure at as low a temperature as possible. The product was removed from the admixed sodium shloride by extraction with ether, the ethereal solution was dried over anhydrous sodium sulphate and the ether removed in a current of dry air.

The thiosemicarbazone was purified by recrystallisation

from petroleum ether to which a little benzene had been added, and was obtained as short transparent prisms melting at 74°C. readily soluble in alcohol, benzene, and ether.

0·2008 gm. gave 20·75 cc. N_2 at 14°C. and 760 mm. =12·15% N_2.

0·2036 gm. gave 20·8 cc. N_2 at 13°C. and 768 mm. = 12·20% N_2.

$C_{18}H_{19}O_2N_3S$ requires 12·32% N_2.

Action of 1-dimethyl-chlorosuccinate, $\begin{matrix} CHCl\cdot COOCH_3 \\ CH_2\cdot COOCH_3 \end{matrix}$

An alcoholic solution of the sodium derivative of acetone thiosemicarbazone was prepared by the addition of the necessary amount of sodium ethoxide in alcoholic solution to an alcoholic solution of the thiosemicarbazone in the usual manner. The solution was well cooled in ice-water and the calculated quantity of the dimethyl chlorosuccinate, also cooled, was added. Sodium chloride separated and the reaction seemed to go smoothly but on working up the reaction mixture after allowing to stand it was found that the product was a low melting solid which did not contain sulphur or nitrogen. The acetone thiosemicarbazone was practically all recovered. The product was not examined further.

Action of Chloroformic Esters.

Action of ethyl chloroformate, $Cl \cdot COOC_2H_5$

1-carbethoxy thiosemicarbazide $C_2H_5 \cdot OOC \cdot NH \cdot NH \cdot CS \cdot NH_2$

Ethyl chloroformate (1 mol) was gradually added, with shaking, to the sodium derivative (1 mol) suspended in a small quantity of dry benzene. The mixture became sufficiently hot to cause the benzene to boil, and carbon dioxide was evolved. The reaction was completed by boiling under a reflux condenser for an hour on the water bath.

The resulting crude product was filtered, washed with water to remove sodium chloride, and purified by re recrystallising from alcohol. The substance separated in colourless lustrous plates melting at 188-189°C., was readily soluble in hot acetone, moderately soluble in boiling alcohol and almost insoluble in benzene and chloroform. It dissolved in hot water, or cold aqueous sodium hydroxide and slowly dissolved in concentrated hydrochloric acid.

The yields were very variable but a maximum of 60% of the 1-carbethoxy thiosemicarbazide was obtained by using 1·5 mols chloroformic ester to 1 mol of acetone sodio-thiosemicarbazone and 3 ccs. of benzene to each gram of the sodium derivative. Using either ester or benzene in excess of the quantities mentioned was found to give a gelatinous product which could not be purified.

Analysis C= 29·62%; H_2 =5·40%; N_2 = 25·60%; S = 19·90%.

Molecular Weight (Ebullioscopic method in acetone). 145; 149

Theoretically $C_4H_9O_2N_3S$ requires Mol. Wt. = 163.

C = 29·45%; H_2 = 5·52%; N_2 = 25·76%; S = 19·62%.

The identity of the 1-carbethoxy thiosemicarbazide was confirmed by comparison with a specimen of the substance prepared by the method of Fromm and Nehring, (Ber. 1923, 1374).

In addition to the main product just described there was obtained from the benzene filtrate a small quantity [about 10% of the total yield was the maximum] of a substance which was much more soluble in alcohol and benzene. After repeated recrystallisation from a mixture of carbon disulphide and petroleum ether the substance melted at 134-135°C. with slight decomposition.

It was found that if alcohol were used instead of benzene the reaction took a different course. Sodium chloride separated but acetone thiosemicarbazone was formed the alcohol apparently reacting with the ethyl chloroformate.

Action of phenyl chloroformic ester. $C_6H_5 \cdot OOC \cdot Cl$

1-carbophenoxy thiosemicarbazide $C_6H_5 \cdot COO \cdot NH \cdot NH \cdot CS \cdot NH_2$

The action of phenyl chlorocarbonate, $Cl \cdot COO \cdot C_6H_5$, on the sodium derivative of acetone thiosemicarbazone was found to proceed exactly as in the case of the ethyl chloroformic ester. The reaction was carried out in a similar manner the sodium derivative being placed in a flask, the benzene added and the phenyl chloroformic ester added drop by drop until the reaction started, then as required to keep it going. After all the phenyl chloroformate had been added the mixture was heated on the water bath for an hour. A maximum yield of 60-65% of the 1-carbophenoxy thiosemicarbazide was obtained using the same relative quantities of the various reagents as

has already been described for the action of ethyl chloro carbonate.

The reaction mixture was filtered, the residue washed with a little absolute alcohol to remove adhering benzene and then with cold water till free from sodium chloride. The product recrystallised from alcohol was obtained as lustrous white plates melting at 194-199°C. with decomposition; crystallised by dissolving in dry acetone and precipitating with petroleum ether the compound had the same melting point 194-199°C. with decomposition.

1-carbophenoxy thiosemicarbazide is soluble in acetone, less so in alcohol, benzene, and chloroform, and ~~insoluble~~ practically insoluble in cold water; soluble in hot water on prolonged heating but partially hydrolysed as small quantities of phenol could be detected in the steam.

Analysis. C = 45·34%. H_2 = 4·36%. N_2 = 19·32%. S = 15·38%.

Mol.Wt. (Ebullioscopic method in acetone) 198; 208.

Theoretically $C_8H_9O_2N_3S$ requires Mol. Wt. 211.

C = 45·50%. H_2 = 4·26%. N_2 = 19·90%. S = 15·16%.

From the benzene filtrate a small quantity of another product was obtained, which, when recrystallised from a mixture of carbon disulphide and petroleum ether, separated as small transparent plates melting at 149°C. It was ~~much~~ more readily soluble in alcohol and benzene than 1-carbophenoxy thiosemicarbazide.

Nitrogen content found 16·70%.

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C=N-N=C\!<\!\begin{matrix} NH_2 \\ S\cdot COO\cdot C_6H_5 \end{matrix}$$ = $C_{11}H_{13}O_2N_3S$ requires 16·74% N_2

Action of methyl chloroformate, $Cl \cdot COO \cdot CH_3$

The reaction was carried out exactly according to the methods already described and again the principal product was found to be of the type $R \cdot OOC \cdot NH \cdot NH \cdot CS \cdot NH_2$. M.P. 191-198°C.

Nitrogen content found = 28·05%.

$CH_3 \cdot OOC \cdot NH \cdot NH \cdot CS \cdot NH_2$ requires 28·18% N_2.

Hydrolysis of 1-carbophenoxy thiosemicarbazide.

A quantity of the compound $C_6H_5 \cdot OOC \cdot NH \cdot NH \cdot CS \cdot NH_2$ was completely hydrolysed by heating in a Carius tube with an excess of concentrated hydrochloric acid for six hours at a temperature of 120°C. On releasing the pressure, which was apparently considerable, a quantity of gas, smelling strongly of sulphuretted hydrogen escaped, while remaining in the tube was a crystalline white solid and a brown liquid which was evidently lighter than, and immiscible with, the excess acid.

The liquid contents of the tube were decanted off, the crystalline residue washed several times by decantation with concentrated hydrochloric acid, then several times with ether and dried by connecting the Carius tube to a desiccating arrangement and exhausting the whole system. The crystalline product obtained in this way was shown to be hydrazine hydrochloride by the ready reduction of Fehling's solution, and formation of benzalazine, $C_6H_5 \cdot CH=N-N=CH \cdot C_6H_5$, on shaking the aqueous solution with benzaldehyde.

The acid solution was diluted somewhat, extracted with ether, the ethereal solution dried and the brown liquid shown to be phenol by the smell, the violet

colouration with ferric chloride and formation of tribromophenol, M.P. 92°C., with bromine water.

The aqueous acid remaining was examined for other possible products of hydrolysis but only ammonium chloride was obtained which was identified by formation of ammonia and by the Nessler reaction.

Action of Iodine on Acetone sodio-thiosemicarbazone.

An alcoholic solution of the sodium derivative of acetone thiosemicarbazone was prepared in the usual manner by the addition of the necessary quantity of sodium ethoxide to acetone thiosemicarbazone just dissolved in alcohol. The solution was cooled to room temperature then the calculated quantity of iodine was added, and the whole allowed to stand for several days.

The colour of the iodine was gradually discharged but an examination of the reaction mixture showed that the resulting product was acetone thiosemicarbazone which was recovered to the extent of 80-85%.

The identity of the substance was established by comparison with a known specimen.

Sodium iodide was also formed but no evidence of the linking up of two thiosemicarbazone residues through sulphur could be detected.

Action of Ethylene dibromide.

To an alcoholic solution of acetone sodio-thiosemicarbazone the calculated quantity of ethylene dibromide was added, the mixture allowed to stand overnight and then boiled for an hour on the waterbath under a reflux condenser.

There was no separation of sodium bromide and examination showed that no chemical action had taken place.

The experiment was repeated under varying conditions as to time of contact and relative proportions of reagents but in every case the sodium derivative could be recovered unchanged.

Action of Aniline on Acetone thiosemicarbazone.

Finely powdered acetone thiosemicarbazone (one mol) and aniline (one mol) were placed in a boiling tube closed with a cork carrying an air condenser.

The mixture was heated in a glycerine bath at a temperature of 160°C. Ammonia was evolved but as there did not appear to be any change in the rate of evolution of the ammonia the heating was stopped at the end of two hours.

During the heating sulphuretted hydrogen was noticed in fair quantity mixed with the ammonia.

The reaction mixture was poured into an excess of dilute acetic acid but the resulting product was a gummy mass which could not be crystallised from solvents.

Needle shaped crystals were observed in the air condenser; these crystals were water soluble, when acidified they evolved sulphuretted hydrogen, and they instantly reduced Fehling's solution in the cold.

In another experiment the reaction mixture was allowed to cool somewhat and a little benzene was added but again the product was resinous in character.

Action of Benzylamine on Acetone thiosemicarbazone.

The reaction was carried out as in the preceeding case, equivalent quantities of benzylamine and acetone thiosemicarbazone being heated together in a glycerine bath.

The ammonia was evolved at a lower temperature, however, and after heating for one and a half hours at 140-145°C. the reaction mixture was allowed to cool and a small quantity of alcohol added to the still molten

product to prevent the whole solidifying. A solid crystalline substance separated which was filtered off and was found to melt at about 146°C. The melting was indefinite and analysis showed that a mixture of substance had been obtained. The products have not yet been fully worked up.

Action of Benzylamine on Acetophenone thiosemicarbazone.

Equivalent quantities of acetophenone thiosemicarbazone and benzylamine were heated together. The reaction started at 130°C. and this temperature was maintained for an hour and a half. The reaction mixture was cooled to about 80°C., and a small quantity of benzene added. After cooling further, twice the volume of ether was added and the crude solid product filtered off.

Recrystallised three times from benzene the substance was obtained as very small white prisms melting at 157 -158°C., soluble in benzene and alcohol, but difficultly soluble in ether.

0·1596 gms. gave 20·4 ccs. N_2 at 20°C. and 764 mms. = 14·7% N_2

0·1545 gms. gave 19·7 ccs. N_2 at 17·5°C. and 759 mms.=14·76% N_2

$$\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C{=}N\cdot NH\cdot CS\cdot NH\cdot CH_2\cdot C_6H_5 \quad = \quad C_{16}H_{17}N_3S \text{ requires } 14{\cdot}84\%\ N_2.$$

Hydrolysis of Acetophenone 4-benzyl-thiosemicarbazone

The product formed by the interaction of benzylamine and acetophenone thiosemicarbazone is not appreciably hydrolysed on boiling for two hours with 2N hydrochloric acid.

A complete hydrolysis was effected by heating in a

Carius tube with excess of concentrated acid at a temperature of 18P°C. for six hours.

On releasing the pressure sulphuretted hydrogen was recognised and remaining in the tube was a white crystalline solid together with a dark coloured viscous syruo. The solid after washing with concentrated hydrochloric acid by decantation and then with absolute alcohol, was shown to be hydrazine hydrochloride by the formation of benzalazine, $C_6H_5 \cdot CH=N-N=CH \cdot C_6H_5$, on shaking an aqueous solution with benzaldehyde, and by the ready reduction of Fehling's solution.

The hydrochloric acid was extracted with ether and the ethereal extracts dried over anhydrous sodium sulphate.

The alcohol washings and the acid after extraction with ether were evaporated to dryness and the solid obtained recrystallised by dissolving in alcohol and reprecipitating with ether, when its melting point was found to be 243°C. Benzylamine hydrochloride is reported in the literature by various observers to melt at temperatures ranging from 240°C. to 255·5°C.

The hydrolysis product was shown to be benzylamine hydrochloride by preparing the benzoyl derivative by the Schotten-Baumann reaction and comparing with an authentic specimen.

A P P E N D I X .

[Experimental]

Thiosemicarbazide $H_2N \cdot NH \cdot CS \cdot NH_2$ (Freund and Schander, Ber. 1896, 29, 2500).

100 gms. (2mols) of commercial hydrazine sulphate were placed in a beaker, 400 ccs. of cold distilled water added and the mixture warmed. 54 gms. (1 mol) anhydrous potassium carbonate were then added, in small quantities at a time, with constant stirring; there was a brisk evolution of carbon dioxide and the readily soluble normal hydrazine sulphate was formed.

80 gms. (2 mols) of potassium sulphocyanide were added, the mixture stirred and then heated to boiling; a double decomposition takes place with formation of hydrazine sulphocyanide and potassium sulphate. After boiling for five minutes the potassium sulphate was completely precipitated by the addition of 500 ccs. of commercial alcohol, and removed by filtering the hot solution at the pump.

The filtrate containing the hydrazine sulphocyanide was distilled to remove as much alcohol as possible and was then evaporated down over a free flame in a porcelain basin. The liquid was stirred continuously during this evaporation and after a time the evolution of steam ceased and the substance, which appeared to be a molten slightly yellow solid, began to effervesce and ammonia was evolved. The reaction was very vigorous and when it became too violent it was checked by the addition of a little cold water. During this vigorous reaction the mass was stirred thoroughly and continuously.

On cooling, the reaction mixture solidified to a

crystalline mass of thiosemicarbazide.

A little water was added, the paste filtered, and the filtrate evaporated down to a syrup as before. This was repeated four or five times.

The various crops of crystals were then combined and recrystallised from water, the mother liquor being evaporated down to yield a further crop of thiosemicarbazide. M.P. 182·5°C. Yield 42 gms.

Acetone thiosemicarbazone.

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

The method of Freund and Schander, (Ber. 1902, 35, 2602) was found to give a poor product which required repeated crystallisation, but the following modification gave a good product in one operation.

30 gms of thiosemicarbazide were heated under a reflux condenser with a mixture of 200 ccs. of alcohol and 70 ccs. of acetone until solution was complete. The reaction mixture was filtered hot and on cooling the acetone thiosemicarbazone separated as fine white needle shaped crystals melting sharply at 178-179°C. Yield 80% theoretical

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Silver derivative of acetone thiosemicarbazone.

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{=}N{-}N{=}C\!<\!\begin{matrix}NH_2\\S\cdot Ag\end{matrix}$$

Neuberg and Neimann, (Ber. 1902, 35, 2049)

By the gradual addition, with constant stirring, of an alcoholic solution of silver nitrate to a cold alcoholic solution of acetone thiosemicarbazone until a permanent

precipitate was formed, the silver derivative was not obtained, but a light bulky white powder was formed, which was relatively stable to light and had only about half of the silver content of the true metallic compound.

Found:- 22·79%, 23·03%, and 22·90% silver.

$C_4H_8N_3SAg$ requires 45·35% silver.

The derivative was obtained by the addition of a cold alcoholic solution of acetone thiosemicarbazone, in small quantities at a time, to an excess of alcoholic silver nitrate. That is, the presence of a decided excess of silver nitrate during the whole of the reaction is an essential condition for the formation of the metallic compound.

The product was filtered off, well washed with alcohol, then with dry ether and finally dried in a vacuum desiccator over sulphuric acid. The preparation was carried out in a dark room as the compound was sensitive to light as described by Neuberg and Neimann.

It was found to be even more sensitive to certain organic solvents being completely decomposed on warming with either benzene or alcohol.

The silver was estimated by warming on a water bath with an excess of 30% nitric acid, diluting with water and titrating with standard thiocyanate using iron alum as indicator. The product obtained was not very pure.

Analysis.- found 43·65%, 43·90%, 44·00% Ag.

$C_4H_8N_3SAg$ requires 45·35%.

Benzaldehyde thiosemicarbazone $C_6H_5 \cdot CH=N-N \cdot CS \cdot NH_2$

Young and Eyre (J.C.S. 1901, 79, 57).

A weighed quantity of thiosemicarbazide was dissolved in hot alcohol and a slight excess of benzaldehyde added On cooling some of the thiosemicarbazone separated as fine hair-like crystals, the remainder was precipitated by the addition of water to the alcoholic solution.

The product, readily soluble in hot alcohol and slightly so in boiling water, was recrystallised from alcohol. M.P. 159-160°C. Yield 75-80% theoretical.

Acetophenone thiosemicarbazone $\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C=N \cdot NH \cdot CS \cdot NH_2$

Neuberg and Neimann (BER. 1902, 35, 2052).

Obtained by heating equivalent quantities of the components for two hours under a reflux condenser in aqueous alcoholic solution. Removal of the alcohol under reduced pressure gave an oil which solidified and was recrystallised from benzene giving a product melting at 108°C.

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l-menthyl chloroacetate $Cl \cdot CH_2 \cdot COO \cdot C_{10}H_{19}$

Frankland and Barrow (J.C.S. 1914, 105, 992).

102 gms. of menthol and 50 gms. chloroacetic acid were melted together and saturated with dry hydrochloric acid gas. After heating for 2 1/2 hours on a water bath a small quantity of water formed during the reaction separated out. This was removed and the mixture again saturated with hydrochloric acid gas. After the separation of a further small quantity of water, the liquid was

distilled under reduced pressure and the fraction boiling at 135-138°C. at 12 mms. pressure, collected separately.

On redistilling, 75 gms. of the l-menthyl chloroacetate were obtained as a colourless oil having a menthol like odour, and boiling at 137°C. at 12 mms. The product quickly solidified to a white crystalline mass; the purity was estimated by determining the specific rotation.

$\alpha = -77{\cdot}07°$, $l = 1$, $d\ 44/4 = 1{\cdot}017$.

$$[\alpha]_D^{44} = -75{\cdot}75.$$

Ethyl α-bromopropionate $CH_3 \cdot CHBr \cdot COO \cdot C_2H_5$

Zelinsky (Ber. 1887, 20, 2026)

To 30 gms. propionic acid were added 3·1 gms. amorphous phosphorus, and, drop by drop, 40 gms. bromine until no more hydrogen bromide was evolved. The mixture was then warmed under an afficient reflux condenser on a water bath and a further quantity of 64 gms. bromine slowly added.

[The bromination proceeds very rapidly at a temperature between 40°C. and 50°C. and is finished when no more bromine vapour is observed in the condenser].

The resulting brom-acid bromide was cooled, decomposed by the cautious addition of a slight excess of absolute alcohol, the ester separated by the addition of water, washed free from acid with dilute sodium carbonate solution, dried over anhydrous sodium sulphate, and distilled.

30 gms. propionic acid gave 64 gms. ethyl α-bromopropionate distilling without decomposition at 156-160°C.

Ethyl phenylbromacetate $C_6H_5 \cdot CHBr \cdot COO \cdot C_2H_5$

Hell and Weinzweig (Ber. 1895, 28, 2447)

The ester was prepared from mandelic acid by substituting both hydroxyl groups by bromine, using amorphous phosphorus, and decomposing the resulting bromacid bromide with absolute alcohol.

The mandelic acid was intimately mixed with the red phosphorus by grinding the two together in a mortar and the mixture was placed in a reaction flask which was connected to a reflux condenser carrying an arrangement for admitting bromine and absorbing hydrogen bromide.

Bromine was added very slowly and carefully, the reaction at first being exceedingly vigorous and necessitating cooling of the reaction vessels in a freezing mixture. The reaction gradually became less violent and after all the bromine had been added the whole was warmed on a water bath until no more hydrogen bromide was evolved.

The acid bromide so obtained was again cooled in a freezing mixture and decomposed by adding absolute alcohol drop by drop. This reaction was also very vigorous and effective cooling was necessary.

The ethyl phenylbromo acetate was washed with water till free from acid, dried over anhydrous sodium sulphate and distilled under reduced pressure. B.P. 175°C. at 25 mm.

Hell and Weinzweig state that the best yield is obtained using mandelic acid 15·2 gms. red phosphorus 6·0 gms., and bromine 80·0 gms.

Ethyl β-chloro-n-butyrate $CH_3 \cdot CHCl \cdot CH_2 \cdot COO \cdot C_2H_5$

Loven and Johansson (Ber. 1915, 48, 1256)

β-chloro-n-butyric acid was dissolved in absolute alcohol, saturated with dry hydrochloric acid gas at a temperature of 0°C. and allowed to stand for 24 hours. The mixture was then poured into water, washed free from acid, dried over anhydrous sodium sulphate and distilled under reduced pressure. B.P. 65-65·4°C. at 15 mms., 54·4 -54·7°C. at 10 mms.

The β-chloro-n-butyric acid was prepared by the method of Schiebler, (Ber. 1915, 48, 1443). A solution of crotonic acid in dry ether was saturated with dry hydrochloric acid gas, placed in a pressure flask which was firmly stoppered and allowed to stand for three days at room temperature. The flask was then cautiously opened, the ether evaporated off and the β-chloro-n-butyric acid distilled under reduced pressure. The yield was almost quantitative and the product immediately pure.
B.P. 108°C. at 16 mms.

Ethyl β-bromo-β-phenylpropionate $\begin{matrix} Br \\ C_6H_5 \end{matrix}\!\!>\!CH \cdot CH_2 \cdot COO \cdot C_2H_5$

Zalkind (J. Russ. Phys. Chem. Soc. 1914, 490).

The ester was prepared by the addition of hydrogen bromide to ethyl cinnamate. The latter was dissolved in an equal weight of absolute alcohol, the solution cooled in ice water and saturated with dry gaseous hydrobromic acid.

After standing for twenty four hours at room tempera ture the reaction mixture was poured into cold water, the lower oily layer washed with with water, then with

a very dilute solution of sodium carbonate and dried over calcium chloride. To remove the ethyl bromide accompanying the bromo ester, the product was cautiously heated to a temperature of not more than 40°C. under reduced pressure. At this temperature the pressure was maintained at below 20 mms. resulting in the complete removal of all the ethyl bromide.

A thick oily liquid remains having a slight pleasant odour; this is the pure β-halogenated ester, which easily loses hydrogen bromide on heating and can not be purified by distillation even under reduced pressure

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Dimethyl-chlorosuccinate $\begin{matrix} CH_2 \cdot COO \cdot CH_3 \\ | \\ Cl \cdot CH \cdot COO \cdot CH_3 \end{matrix}$

Walden (BER. 1895, 28, 1290)

The hydroxyl group of dimethyl malate was replaced by halogen by means of phosphorus pentachloride.

52 gms. of dimethyl malate were dissolved in 280 ccs of chloroform and 75 gms. of phosphorus pentachloride were added in small quantities at a time without external heating.

When the evolution of hydrochloric acid ceased the reaction was completed by heating for half an hour on the water bath whereby the temperature was raised to about 65°C. After washing with cold water and dilute sodium carbonate solution, the product was dried over anhydrous calcium chloride and distilled under reduced pressure.

The dimethyl chlorosuccinate distilled at 123-128°C. at 24-26 mms. and 107°C. at 15 mms. Yield 42 gms.

The dimethyl mallate for the preceeding preparation was obtained by the method of Frankland and Wharton (J.C.S. 1899, 75, 338).

50 gms. of finely powdered malic acid were dried in a vacuum desiccator for three days, and mixed with 100 gms. of absolute methyl alcohol in which solution was nearly complete. A slow stream of carefully dried hydrochloric acid gas was then passed through the liquid which was kept at a temperature of -18°C. in a freezing mixture.

When completely saturated the liquid was allowed to stand for 24 hours and a current of dry air drawn through for 48 hours. After this it was placed in a vacuum desiccator over slaked lime until the smell of hydrochloric acid had almost disappeared. The excess of alcohol was then distilled off under reduced pressure at as low a temperature as possible.

The dimethyl mallate was subsequently purified by distillation. B.P. 129°C. at 11 mms.

Phenyl chloroformate $Cl \cdot COO \cdot C_6H_5$

Barral and Movel (C.R. 1899, 128, 1579),

An equivalent of a 3% to 5% aqueous solution of sodium phenoxide was added in small quantities at a time to a 20% solution of carbonyl chloride in toluene, the whole being well shaken after each addition.

The mixture at first became milky but cleared on shaking owing to the solubility of the chlorocarbonate in toluene. The reaction was complete when the lower aqueous layer became quite clear.

The toluene layer was separated, dried over

anhydrous calcium chloride, then the toluene and excess phosgene were removed under reduced pressure. The liquid residue was distilled, again under reduced pressure, at a temperature of 100-120°C. when the product was obtained boiling without decomposition.

The substance remaining in the flask was found to be diphenyl carbonate. The chloroformic ester was purified by redistillation.

Barral and Morel give the following precautions which should be observed in order to obtain satisfactory yields

The sodium phenoxide solution used must be dilute, the best results are obtained using a concentration of from 3% to 5%.

The evolution of heat should be avoided, the rate of addition and shaking being regulated so that the temperature does not rise above 30-40°C.

They also mention that the yield appears to depend on the particular phenol employed. It might be added that the present writer has found that, to obtain any of the chloroformate at all it is absolutely essential that the reaction mixture should be alkaline at the end of the reaction, as the chloroformate, which is comparatively stable towards alkalies at the dilutions and temperatures employed, is very readily decomposed by acids.

A quantity of phosgene for the preceeding preparation was obtained by the method of Grignard and Urbain (C.R. 1919, 169, 17-20. J.S.C.I. abs. 1919, 575)

Carbon tetrachloride was oxidised by anhydrous sulphuric acid, in the presence of infusorial earth

(Kieselguhr) as a catalyst, at a temperature of 80-90°C.

4-Ethyl thiosemicarbazide $H_2N \cdot NH \cdot CS \cdot NH \cdot C_2H_5$

Freund and Schwartz (Ber. 1896, 29, 2486)

To a well cooled alcoholic solution of hydrazine hydrate a little less than the calculated quantity of ethyl mustard oil, also well cooled in ice-water, was added.

The 4-ethyl thiosemicarbazide crystallised out in star shaped clusters, and after being recrystallised from alcohol melted at 84°C.

The ethyl mustard oil was prepared from carbon bisulphide and ethylamine by the method of Anschutz (Ann., 1908, 359, 203) as follows

An ethereal solution of carbon bisulphide was added to two equivalents of ethylamine, also dissolved in ether The ethyl ammonium compound

$$S=C\begin{matrix}S \cdot NH_3 \cdot C_2H_5 \\ NH \cdot C_2H_5\end{matrix}$$

was precipitated immediately, an almost theoretical yield being obtained M.P. 102°C.

28 gms. of the above ethyl ammonium compound dissolved in 400 ccs. of water and well cooled were dropped, with gentle shaking, into a solution of 38 gms. of mercuric chloride in 400 ccs. of acetone well cooled in an ice and salt freezing mixture. The mercuric chloride compound separated as small pure white plates which became discoloured during filtration and washing. The product was dried in a vacuum desiccator.

60 gms. of the metallic derivative were covered with 300 ccs. of water and steam distilled, the condenser

being connected to an empty receiver which was cooled in an ice, and salt freezing mixture.

After two and a half distillation the contents of the receiver were extracted several times with ether. The ethereal extracts were dried over anhydrous calcium chloride and the ether distilled off, using a short fractionating column, on a water bath at 45°C.

The ethyl mustard oil C_2H_5NCS was then distilled and came over at 133°C., a yield of 9 gms. being obtained. A further quantity was recovered by redistilling carefully the first runnings and the residual oil.

Ethyl γ-chlorovalerate $CH_3 \cdot CHCl \cdot CH_2 \cdot COO \cdot C_2H_5$

Noyes and Cox (J. Amer. Chem. Soc. 1903, 25, 1094)

γ-valerolactone was dissolved in a slight excess of absolute alcohol and dry hydrochloric acid gas passed through the solution until saturated, the mixture being well cooled the while. After standing overnight the ester was separated by pouring into water, washed with dilute sodium carbonate, dried over anhydrous sodium sulphate, and finally distilled.

The γ-valerolactone for the above was prepared from levulinic acid by several methods but the yields in every case were poor.

[a] Fittig and Wolff, (Ann. 1881, 208, 106)

5 gms. pure levulinic acid were dissolved in 250 ccs. of water, and to the solution, cooled at first in ice, a large excess of sodium amalgam was added in small quantities at a time over a period of several days. (For 1 gm. acid about 60 gms. of 4% amalgam were used).

After the evolution of hydrogen had ceased, the

mercury was removed, the solution acidified with sulphuric acid and the whole boiled for a few minutes under a reflux condenser. The cooled solution was again made alkaline with alkali carbonate and repeatedly ~~or~~ extracted with ether. On distilling off the ether a colourless liquid remained which after drying with anhydrous potassium carbonate boiled at 206°C.

[b] Neugebauer (Ann. 1885, 227, 100)

The levulinic acid was redistilled in vacuo, and worked up for the lactone in 10 gm. lots.

Each lot was mixed with an equal volume of water and in the course of 14 days, with frequent shaking, 800 gms. of 4% sodium amalgam were added. (With each addition of amalgam a little water was added, so that there was a slow evolution of hydrogen)

The aqueous solution after separation of the mercury was acidified with sulphuric acid, boiled under a reflux condenser for 5 minutes, neutralised with sodium carbonate and, after cooling, extracted with ether. The ethereal solution was dried over ignited potassium carbonate, distilled, and the lactone rectified.

This paper also gives the preparation of levulinic acid from sugar.

[c] Taylor and Close (J. Amer. Chem. Soc. 1917, 39, 422)

The preparation of levulinic acid is described in ~~the~~ this paper.

80 gms. levulinic acid were reduced in alkaline solution by the use of 5% sodium amalgam. The reduction was carried out in a vessel surrounded by ice and the mixture constantly stirred. 400 gms of the amalgam were added in 20 gm. lots every few hours, small quantities

of 2:1 hydrochloric acid also being added from time to time as required to prevent the mixture becoming thick and viscous.

The mercury was removed when the reduction was ~~compl~~ complete and 75 ccs. of concentrated hydrochloric acid were added. After boiling under a reflux condenser for 10 minutes the mixture was cooled, extracted with ether, and the ethereal extract dried over freshly ignited potassium carbonate. The ether was distilled off and the residual lactone fractionated, when it was obtained as a sweet smelling colourless liquid, B.P. 207°C.

Ethyl γ-chloro-iso-caproate. CH_3 CH_3 >C·Cl·CH_2·CH_2·COO·C_2H_5

Jones and Tattersal (J.C.S. 1904, 85, 1693)

50 gms. isocaprolactone dissolved in 150 ccs. absolute alcohol, and the solution, cooled in ice water, were saturated with dry hydrochloric acid gas, 90-100 gms. being required. After standing overnight the reaction mixture was poured on crushed ice, the ester which separated was washed two or three times with small quantities of salt water, and dried over anhydrous sodium sulphate. The ester in the aqueous solutions was recovered by extracting several times with petroleum ether.

The lactone was prepared by the action of methyl magnesium iodide on ethyl levulate as follows.

36 gms. of ethyl levulate dissolved in about four times its volume of dry ether were slowly added to a well cooled ethereal solution of the Grignard reagent prepared from 7 gms. magnesium and 40 gms. of methyl iodide.

After about an hour the resulting magnesium compound was decomposed by the cautious addition of water and dilute sulphuric acid. The ethereal layer was separated and the acid solution extracted twice with small quantity of ether. The ethereal solutions were washed free from iodine with dilute sodium hydrogen sulphite, dried over calcium chloride and distilled.

The fraction distilling at 140-150°C under a pressure of 100 mms. was a mixture of isocaprolactone with much unchanged ethyl levulate.

A separation was effected by hydrolysing with alcoholic potash, diluting with water and evaporating till free from alcohol. The concentrated liquid was acidified with hydrochloric acid, and heated for 15 minutes on the water bath to convert the γ-hydroxy-iso-caproic acid into the lactone. The whole was then cooled, extracted several times with ether, the ethereal extract washed with dilute sodium carbonate to remove the levulinic acid, dried over calcium chloride and distilled.

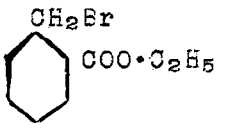
Isocaprolactone B.P. 205-207°C.

The ethyl levulate was prepared by the usual method, Conrad (Ann. 1877, 188, 225) also Grote, Kehrer and Tollens, (Ann. 1881, 206, 221).

Pure levulinic acid was dissolved in excess absolute alcohol and saturated with hydrochloric acid gas, it was gently warmed. The reaction mixture does not separate into two layers so ether was added. The ethereal solution was washed with dilute sodium carbonate and fractionated several times. B.P. 200-201°C. at 756 mms.

Isocaprolactone was also prepared by the oxidation of isocaproic acid by means of potassium permanganate in alkaline solution according to the method of Noyes

(J. Amer. Chem. Soc. 1901, 23, 392)

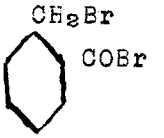
Ethyl ω-bromo-o-toluate 

Davies and Perkin (J.C.S. 1922, 121, 2203)

This ester was prepared by slowly adding melted ω-bromo-o-toluyl bromide (91 gms.) to absolute alcohol (150 ccs.) the whole being well shaken and cooled in ice.

After standing overnight the product was poured into water, the bromo ester extracted with ether, and the ethereal solution well washed with water and dilute sodium carbonate. The ethereal solution was well dried over anhydrous sodium sulphate and the ether removed under reduced pressure.

Ethyl ω-bromo-o-toluate can not be purified by distillation as it readily forms phthalide with elimination of ethyl bromide.

ω-bromo-o-toluyl bromide 

for the above preparation was obtained as follows;

o-toluyl chloride was treated with bromine at a temperature of 185°C. when the hydrobromic formed during the bromination of the methyl group reacts with the -COCl group giving the acid bromide; the o-toluyl chloride was prepared by boiling o-toluic acid with thionyl chloride (10% excess of the thionyl chloride being employed). The acid chloride distilled without decomposition at 213°C. at 760 mms.

To carry out the bromination 15·5 ccs. of bromine

(2 atoms) were slowly added to 46·35 gms. of the acid chloride (1 mol) which was maintained, by means of a metal bath at a temperature of 185-190°C.

The orifice of the dropping funnel was placed well below the surface of the acid chloride to prevent, as far as possible, loss of bromine and hydrogen bromide.

The reaction proceeded smothely and was completed in an hour.

Repeated distillation under reduced pressure gave the pure bromo-acid bromide boiling at 170-171°C. at 38 mms. M.P. 33-34°C.

1-carbethoxy thiosemicarbazide $C_2H_5 \cdot OOC \cdot NH \cdot NH \cdot CS \cdot NH_2$

Fromm and Nehring (Ber. 1923, 56, 1874)

To a solution of thiosemicarbazide in about 10 times its weight of absolute alcohol an equivalent amount of ethyl chloroformate was added and the whole heated for half an hour.

The product separated as white crystals melting at 184°C. Stable to acids and does not react with benzaldehyde.

B I B L I O G R A P H Y.

The following is a list of the principal papers on this subject, together with those describing the preparation of any of the special substances mentioned in the course of the report.

The contractions have their usual significance.

1. Neuberg and Neimann (Ber. 1902, 35, 2049).
2. Freund and Schander (Ber. 1896, 29, 2500).
3. Freund and Paradies (Ber. 1901, 34, 3114).
4. Busch and collaborators (Ber. 1901, 34, 320).
5. " " " (Ber. 1903, 36, 1382).
6. " " " (Ber. 1904, 37, 2318).
7. " " " (Ber. 1909, 42, 4602).
8. Markwald (Ber. 1892, 25, (2), 3098).
9. Dixon (J.C.S. 1892, 61, 1012).
10. Fromm and collaborators (Ann. 1923, 433, 1).
11. " " " (Ann. 1923, 434, 285).
12. Dixon (J.C.S. 1903, 83, 550).
13. Borsche (Ber. 1901, 34, 4299).
14. Borsche and collaborators (Ber. 1904, 37, 3177).
15. " " " (Ber. 1905, 38, 831).
16. Wilson, Hopper, and Crawford (J.C.S. 1922, 121, 866).
17. Wilson and Pickering (J.C.S. 1924, 125, 1152).
18. Wheeler and Barnes (Amer. Chem. J. 1900, 24, 78).
19. Wheeler (Amer. Chem. J. 1901, 26, 352).
20. Fromm and Nehring (Ber. 1923, **56**, 1374)
21. Freund and Schander (BER. 1902, 35, 2602).
22. Young and Eyre (J.C.S. 1901, 79, 57).
23. Frankland and Barrow (J.C.S. 1914, 105, 992).

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

25. Hell and Weinzweig (Ber. 1895, 28, 2447).

26. Loven and Johansson (Ber. 1915, 48, 1256).

27. Schiebler (Ber. 1915, 48, 1443).

28. Zalkind (J. Russ. Phys. Chem. Soc. 1914, 490).

29. Walden (Ber. 1895, 28, 1290).

30. Frankland and Wharton (J.C.S. 1899, 75, 338).

31. Barral and Morel (C.R. 1899, 128,1579)

32. Grignard and Urbain (C.R. 1919, 169, 17).

33. Freund and Schwartz (Ber. 1896, 29, 2486).

34. Noyes and Cox (J. Amer. Chem. Soc. 1903, 25, 1094).

35. Fittig and Wolff (Ann. 1881, 208, 106).

36. Neugebauer (Ann. 1885, 227, 100).

37. Taylor and Close (J. Amer. Chem. Soc. 1917, 39, 422).

38. Jones and Tattersal (J.C.S. 1904, 85, 1693).

39. Davies and Perkin (J.C.S. 1922, 121, 2203).