REACTIONS of SEMIOXAMAZIDE

$NH_2 \cdot NH \cdot CO \cdot CO \cdot NH_2$

A THESIS

presented in fulfilment of the
requirements for the degree of
DOCTOR IN PHILOSOPHY

at the

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E.C. PICKERING.
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Note: Part of this work has been published in two communications to the Journal of the Chemical Society, viz :-

Derivatives of Semioxamazide. Part I. Wilson and Pickering, 1923. Vol.123. I. 394.

Derivatives of Semioxamazide. Part II. Wilson and Pickering, 1924. Vol.124. 1152.

Reprints of the above papers are enclosed in the pocket on the back cover of this thesis.

The Author wishes to acknowledge his appreciation of the keen interest shown and the invaluable advice given by Professor F.J. Wilson, D.Sc., etc., under whose direction the work was carried out.

- C O N T E N T S -

Theoretical.

Experimental.

INTRODUCTION.

The researches which are hereafter described form part of an extensive investigation which has been in progress in these laboratories for some years. The main part of this work has dealt with the reactions of semicarbazide ($NH_2 \cdot NH \cdot CO \cdot NH_2$.) and its derivatives. The Thiosemicarbazones ($\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!N \cdot NH \cdot C:S \cdot NH_2$) have however also been studied with interesting results and so it was thought that an examination of semioxamazide and its derivatives on parallel lines might be of value to the general scheme.

Semioxamazide ($NH_2 \cdot NH \cdot CO \cdot CO \cdot NH_2$.) was first prepared by Kerp and Unger (Ber., 1897, 30, 585) with the hope that it might have general application in the separation and characterisation of aldehydes and ketones. These expectations were not entirely realised for the authors state that whereas the reaction between semioxamazide and aldehydes is a general one resulting in the formation of the corresponding semioxamazone :-

$NH2 \cdot CO \cdot CO \cdot NH \cdot NH_2 + R \cdot C\begin{matrix} H \\ \leq O \end{matrix} = NH_2 \cdot CO \cdot CO \cdot NH \cdot N:C\begin{matrix} H \\ \leq R \end{matrix} + H_2O.$

with/

with ketones the reaction proceeds with difficulty and only under special conditions. They were not able, for instance, to prepare the semioxamazones of acetone, benzil and diphenylene ketone.

A further investigation was carried out by Radcliff and Loo (Perfumery and Essential Oil Record 1919, 10,39) who prepared a number of new semioxamazones and generally confirmed the conclusions of the previous workers in this field. Altogether the semioxamazones of some eleven aldehydes and eight ketones are described in the literature but of the reactions of these sub-:stances very little appears to be known.

The researches which are the subject of this thesis have been confined entirely to the derivatives obtained with ketones. The reactions of these compounds and of semioxamazide itself are being investigated along various lines and in the following pages are re-:corded the results which have been obtained up to the present date.

PART I.

PREPARATION OF KETONIC SEMIOXAMAZONES.

As has been indicated in the Introduction, the method adopted by previous investigators for preparing ketonic semioxamazones does not give satisfactory results. Many ketones do not give derivatives at all and others can only be prepared under special conditions. In the first part of this work therefore, the reaction between semioxamazide and ketones was studied with the object of finding conditions which would enable the reagent to have a more general application. In this respect encouraging results have been obtained and what appears to be a general method for the preparation of ketonic semioxamazones has been worked out. The method of preparation adopted by Kerp and Unger and other workers has always involved the solution of the semioxamazide in hot water and the addition of an alcoholic solution of the ketone. The mixture is then heated on the water bath for varying periods and if the reaction/

reaction has been successful the semioxamazone separates on cooling. It was early discovered in this investigation however, that the semioxamazones of many ketones, especially those of the lower aliphatic ketones, were very readily hydrolysed by water. Acetone semioxamazone, for example, is com-:pletely hydrolysed by warming with moist ether. It is this fact which largely accounts for the poor re-:sults obtained by the above method of preparation as any semioxamazone that is formed is immediately hydrolysed by the water present. If, however, the presence of water be avoided and the semioxamazide, suspended in absolute alcohol, is heated with the calculated quantity of ketone, acetone semioxamazone and most other semioxamazones can be obtained with ease. A further advance was made by the discovery that the addition of a little iodine to the reaction mixture had a remarkable effect in accelerating the rate of formation of the semioxamazones. The method that has now/

now been adopted is to heat on the water bath the calculated quantities of ketone and finely powdered semioxamazide in absolute alcohol; a little iodine is then added to the boiling liquid when the semioxamazide, which is insoluble in alcohol, rapidly dissolves and the semioxamazone separates on cooling. In the following table a few examples are given to illustrate the influence on the rate of formation of some semioxamazones of the addition of a little iodine. The end of the reaction is indicated by the complete solution of semioxamazide.

Ketone	Time of reaction	
	Without Iodine.	With Iodine.
Acetone	40 Minutes	2 Minutes.
Methylethyl ketone	45 "	3 "
Acetophenone	60 "	5 "
Benzyl acetone	180 "	4 "

In some cases it was not possible to prepare the semioxamazone without the aid of iodine, e.g., when benzil and semioxamazide were heated together in absolute alcohol for many hours no formation of semioxamazone was observed. With the addition of a little iodine on the other hand both the "mono" and the "di" derivatives were obtained.

In the case of unsaturated ketones the use of iodine is avoided, the ketone and semioxamazide in absolute alcohol are simply heated together until solution is complete.

The use of iodine in anil formation is referred to by Knoevenagel (J. pr. Chem., 1914, (ii) 89, 37).

By the above means the semioxamazones of the following ketones have been prepared :-

Acetone, methyl ethyl ketone, methyl isopropyl ketone, methyl iesbutyl ketone, methyl hexyl ketone, mesityl oxide, acetophenone, benzyl acetone, styryl methyl ketone/

ketone, phenyl P. tolyl ketone, benzil (mono and di derivatives), ethyl acetoacetate, dibenzyl ketone, acetyl acetone (mono and di derivatives).

With the exception of those of acetophenone and ethyl acetoacetate prepared by Kerp and Unger and benzylidene acetone prepared by Radcliff and Loo, these derivatives do not appear to have been described previously.

The following ketones did not react with semi-:oxamazide :- methyl tertiary butyl ketone (pinacoline), phenyl styryl ketone, camphor and fructose. In all the other cases tried the corresponding semioxamazone was obtained with ease. In addition to the ketonic semioxamazones already mentioned the following are described in the literature :- semioxamazones of methyl acetophenone, benzophenone, carvone, menthone and methyl hexanone.

The reaction between semioxamazide and ketones therefor appears to be a much more general one than was previously supposed/

supposed. The preparation by the above described method is a very simple one giving the semioxamazone in theoretical yield and in practically a pure condition. These derivatives also are all solids, easily purified by recrystallisation (provided it is borne in mind that dry solvents should be used) and the pure products all melt sharply. When it is considered also that semi-:oxamazide itself is quite easily obtained (See P. 80.) and is a stable substance easy to work with it is evident that it has great possibilities as a reagent.

The semioxamazone of styryl methyl ketone is markedly phototropic, rapidly changing from white to yellow on exposure to light, the melting point remain-:ing unchanged. If the yellow modification is re-crystallised from alcohol the white form is obtained.

Dibenzyl ketone semioxamazone was obtained in two dimorphic forms. It was deposited from concentrated alcoholic/

alcoholic solutions at temperatures above 40° in colourless prisms melting at 195°- 196°, while from more dilute solutions at temperatures below 40° colourless needles melting at 187°- 189° separated. A mixture of the two modifications softened at 187° and melted at 194°- 196°. It is interesting to observe that dibenzyl ketone semi-:carbazone is also described in the literature as occurr-:ing in two modifications. (Wedekind, Ber., 1901, 34. 2076; Senderens, Comp , rend., 1910, 150. 1337)

PART II.

METALLIC DERIVATIVES OF SEMIOXAMAZIDE and the SEMIOXAMAZONES.

In their original paper (Ber. 1897. 30. 585) Kerp and Unger describe the preparation of a copper salt of semioxamazide, the suggested formula for this compound being :-

$$NH_2 \cdot CO \cdot CO \cdot \underset{Cu}{N} \cdot NH_2$$

$$NH_2 \cdot CO \cdot CO \cdot \underset{Cu}{N} \cdot NH_2$$

This salt is obtained by treating an aqueous solution of semioxamazide HYDROCHLORIDE with concentrated cupric chloride solution. Associated with it was a substance having a composition agreeing with the formula :-

$NH_2 \cdot CO \cdot CO \cdot N\ (CuCl) \cdot NH_2 \cdot HCl$.

They also state that on treating semioxamazide with silver nitrate solution a silver salt is momentarily formed but this is not stable on account of the ease with which semioxamazide reduces silver nitrate.

In the course of this investigation both the sodium/

sodium and potassium derivatives of semioxamazide were isolated by treating a suspension of semioxamazide in absolute alcohol with sodium ethoxide and alcoholic potassium hydroxide solution respectively.
The semioxamazones were also found to yield sodium and potassium salts under similar conditions.

It is probable that in these salts the metal is united to the nitrogen atom of the imide group, the compounds having the general formula :-

$$\begin{matrix} R_1 \\ R_2 \end{matrix} > C : N \cdot \underset{\displaystyle X}{N} \cdot CO \cdot CO \cdot NH_2$$

The sodium derivative of semioxamazones of the following ketones were isolated :- Acetone, methyl ethyl ketone, mesityl oxide, styryl methyl ketone, and the corresponding potassium salt of acetophenone semioxamazone and styryl methyl ketone semioxamazone.

In another research carried out in these laboratories (Wilson and Burns, J.C.S. 1922. Vol.CXXI. P.867)/

P.867) the effect of warming halogen compounds with solutions of sodium derivatives of thiosemicarbazones has been studied and interesting results obtained. Benzyl chloride and the sodium salt of acetone thio-:semicarbazone for instance were found to react, sodium chloride and S-benzylthiosemicarbazone being formed :

$$CMe_2:N\cdot NH\cdot C(SNa)NH_2 + C_6H_5CH_2Cl = CMe_2:N\cdot NH\cdot C(S\cdot CH_2Ph):NH_2 + NaCl.$$

In the hope of establishing the constitution of the salts of semioxamazide and the semioxamazones by means of a similar reaction to the above, a number of these substances were treated with benzyl chloride in a like manner but no change could be observed. Even the addition of a catalyst such as acetonitrile and the use of the most favourable solvents for this type of reaction had no effect. When more drastic treatment was employed such as heating the sodium derivative with benzyl chloride at the boiling point of the latter, or/

or by using a solvent of a higher boiling point, e.g. toluene, the semioxamazide molecule appeared to be broken down, ammonia was evolved and a product obtained of m.p. 221°. This substance was not identified, but the reaction evidently had not proceeded in the manner desired and so this work was discontinued.

PART III.

ACTION OF AMINES ON SEMIOXAMAZIDE and SEMIOXAMAZONES.

The action of amines on semicarbazones was first investigated by Borsche and his collaborators (Ber., 1904, 34, 4299; 1904, 37, 3177; 1905. 38. 831) who found that semicarbazones react with aromatic amines mainly according to the scheme :-

$$\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!> C{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + NH_2R = \begin{matrix} R_1 \\ R_2 \end{matrix}\!\!> C{:}N{\cdot}NH{\cdot}CO{\cdot}NHR + NH_3$$

this product on hydrolysis yielding the semicarbazide $NH_2{\cdot}NH{\cdot}CO{\cdot}NHR$.

In some cases, however, an abnormal reaction resulted, the main products being a substituted carbamide and an azine. O. Hydroxy benzylidene acetone semicarbazone for instance on prolonged boiling with aniline yields S. phenyl carbamide and O. hydroxy benzylidene acetone azine :-

$$2.\ OH{\cdot}C_6H_4{\cdot}CH{:}CH{\cdot}C{\cdot}M_E{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + 4.C_6H_5NH_2 =$$

$$= 2\ CO\begin{matrix} NH{\cdot}C_6H_5 \\ NH{\cdot}C_6H_5 \end{matrix} + \begin{matrix} OH{\cdot}C_6H_4{\cdot}CH{:}CH{\cdot}C{\cdot}M_E{:}N \\ OH{\cdot}C_6H_4{\cdot}CH{:}CH{\cdot}C{\cdot}M_E{:}N \end{matrix} + 2\ NH_3 + N_2H_4$$

The action on semicarbazones of amines of a more aliphatic nature e.g. benzylamine and a.phenyl ethylamine has also been investigated by Wilson, Hopper and Crawford (J.C.S., 1922, Vol. CXXI., 1. P.867) who found that substitution took place in the normal manner described by Borsche.

A parallel investigation was carried out as part of this research on semioxamazide and its derivatives and it was found that the general tendency, when any action took place, was towards the formation of an azine and a substituted oxamide. The reaction being similar to what is described by Borsche as the abnormal reaction between aniline and o.hydroxy benzylideneacetone semi-:carbazone.

The amines used for this purpose included aniline, benzylamine, piperidine, diphenylamine, mono methyl-:aniline, carbazole and menthylamine and the results obtained may be summarised as follows :-

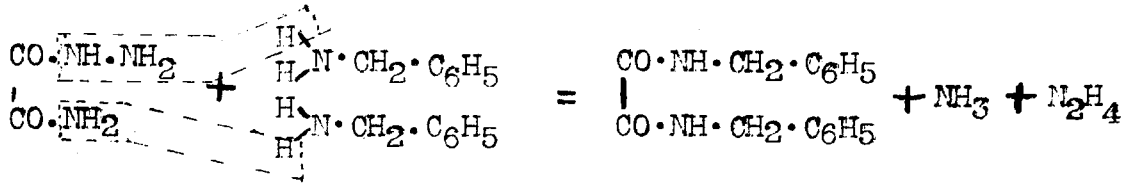
Aniline/

Aniline:

When aniline and dibenzyl ketone semioxamazone were heated together for half an hour at 190° no action took place nor was any change observed with semioxamazide itself.

Benzylamine:

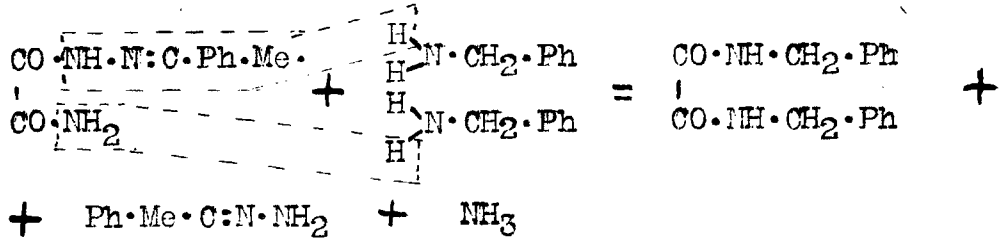
Benzylamine and semioxamazide reacted on heating together for two hours at 175 - 180°, ammonia was evolved and the other products were found to be s. dibenzyl oxamide and hydrazine. The reaction evidently having proceeded according to the scheme :-



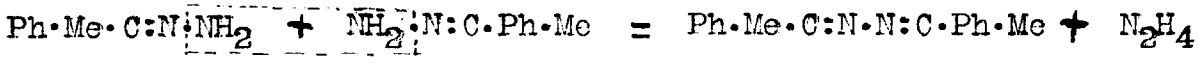
With semioxamazones benzylamine reacted in a similar manner, e.g. when acetophenone semioxamazone and benzyl-:amine were heated together at 150°, the products were ammonia, s.dibenzyl oxamide, methyl phenyl ketazine and hydrazine/

hydrazine. (See P 58.)

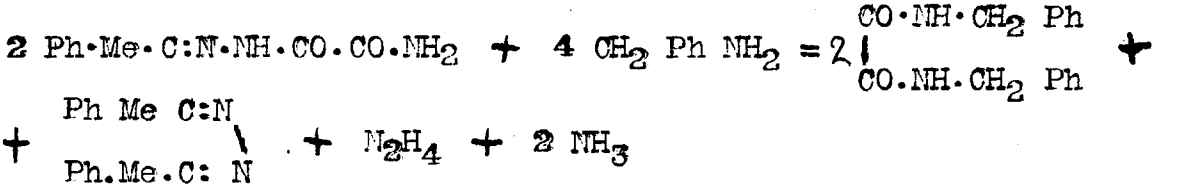
Presumably the first stage of the reaction involves the formation of ammonia, s dibenzyl oxamide and acetophenone hydrazone :-



Two molecules of the acetophenone hydrazone then react together giving acetophenone ketazine and hydrazine :-



The final result then is expressed by the following equation :-



With dibenzyl ketone semioxamazone the reaction took a similar course; the products obtained being dibenzyl ketone azine, s. dibenzyl oxamide, hydrazine -

and /

and ammonia :-

$$2\ (C_6H_5\cdot CH_2)_2{:}C{:}N\cdot NH\cdot CO\cdot CO\cdot NH_2 + 4\ CH_2Ph\ NH_2 =$$

$$= 2 \begin{matrix} CO\cdot NH\cdot CH_2\cdot Ph \\ CO\cdot NH\cdot CH_2\cdot Ph \end{matrix} + \begin{matrix} (C_6H_5\cdot CH_2)_2{:}\ C{:}N \\ (C_6H_5\cdot CH_2)_2{:}\ C{:}N \end{matrix} + N_2H_4 + 2\ NH_3$$

Dibenzyl ketone azine $(C_6H_5CH_2)_2{:}C{:}N\cdot N{:}C{:}(C_6H_5CH_2)_2$ which does not seem to have been described previously, was also obtained by treating dibenzyl ketone with hydrazine hydrate and the two specimens were found to be identical.

Piperidine:

The action of piperidine on acetophenone semi-:oxamazone was next investigated and the reaction was found to proceed in an entirely different manner from those previously described.

The products obtained by heating these two substances together were ammonia and acetophenonepiperidino - oxalylhydrazone :-

$$Ph\cdot Me\cdot C{:}N\cdot NH\cdot CO\cdot CO\cdot NH_2 + H\cdot N{:}C_5H_{10}$$
$$= Ph\cdot Me\cdot C{:}N\cdot NH\cdot CO\cdot CO\cdot NC_5H_{10} + NH_3.$$

The reaction was therefore quite similar to the one which usually occurs between semicarbazones and primary amines as described by Borsche and his collaborators (P. 14). From this hydrazone by hydrolysis with dilute hydrochloric acid piperidino - oxalylhydrazine ($NH_2 \cdot NH \cdot CO \cdot CO \cdot N : C_5H_{10}$) was obtained. The constitution of this hydrazine was shown by its synthesis from ethyl piperidino oxalate ($C_5H_{10} : N \cdot CO \cdot CO \cdot O \cdot Et$). This ester can be prepared quite easily by warming excess of ethyl oxalate with piperidine :-

$$\begin{matrix} CO \cdot O \cdot Et \\ CO \cdot O \cdot Et \end{matrix} + H : N : C_5H_{10} = C_5H_{10} : N \cdot CO \cdot CO \cdot O\ Et + Et\ OH$$

When the ethyl piperidino oxalate obtained in this way was heated with a molecular proportion of hydrazine hydrate in alcoholic solution piperidino-oxalylhydrazine was obtained :-

$$C_5H_{10}N \cdot CO \cdot CO \cdot O\ Et + NH_2 \cdot NH_2 = C_5H_{10} : N \cdot CO \cdot CO \cdot NH \cdot NH_2 + Et \cdot OH$$

The/

The two preparations were identical and gave the same benzylidene and m. nitro benzylidine derivatives.

Along with the piperidino-oxalylhydrazone in the above synthesis some oxalyldihydrazide $NH_2 \cdot NH \cdot CO \cdot CO \cdot NH \cdot NH_2$ was always formed as a by product, two molecules of the hydrazine evidently having acted on the ethyl piperidino-oxalate :-

$$\begin{array}{l} CO \cdot O \cdot ET \\ | \\ CO \cdot N : C_5H_{10} \end{array} + \begin{array}{l} H \cdot N \cdot H \cdot NH_2 \\ H \cdot N \cdot H \cdot NH_2 \end{array} = \begin{array}{l} CO \cdot NH \cdot NH_2 \\ | \\ CO \cdot NH \cdot NH_2 \end{array} + C_5H_{10}NH + Et\ OH$$

Piperidine and dibenzyl ketone semioxamazone also reacted when heated together ammonia being evolved. From the reaction mixture some dibenzyl ketone azine was isolated indicating that to a certain extent at any rate the reaction had proceeded according to the scheme :-

$$2(C_6H_5CH_2)_2 : C : N \cdot NH \cdot CO \cdot CO \cdot NH_2 + 4\ C_5H_{10} \cdot NH = \begin{array}{l} (C_6H_5CH_2)_2 : C : N \\ | \\ (C_6H_5CH_2)_2 : C : N \end{array} +$$

$$+ 2 \begin{array}{l} CO \cdot N : C_5H_{10} \\ | \\ CO \cdot N : C_5H_{10} \end{array} + N_2H_4 + 2\ NH_3$$

Semioxamazide itself did not react with piperidine on heating.

Diphenylamine, Mono methyl aniline, and Carbazole:

No reaction took place when the above amines were heated with acetophenone semioxamazone.

1. Menthylamine:

The action of this base on semioxamazide is described in Part IV.

The reaction between amines and semioxamazide and its derivatives therefore does not promise to be of any value for preparing substituted semioxamazides as can be done in the case of the corresponding semi-:carbazones. As has been shown, only in the case of the action of piperidine on a semi-oxamazone was a product obtained, viz : $\begin{matrix} CH_3 \\ C_6H_5 \end{matrix} \diagdown\!\diagup C{:}N{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}N{:}C_5H_{10}$ which on hydrolysis with hydrochloric acid gave a substituted semioxamazide $NH_2{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}N{:}C_5H_{10}$. As stated however, this substance was prepared by a synthetic process (P. 19.) and the latter method would appear to be a general one for preparing this type/

type of compound. The preparation of substituted semioxamazides by this means is a very easy one as it only involves two simple processes.

In the first stage an amine is warmed with excess of methyl or ethyl oxalate :-

$$\begin{matrix} CO\cdot OMe \\ | \\ CO\cdot OMe \end{matrix} + RNH_2 = \begin{matrix} CO\cdot NRH \\ | \\ CO\cdot OMe \end{matrix} + MeOH.$$

The ester thus obtained is then heated with a molecular proportion of hydrazine hydrate which yields the substituted semioxamazide :-

$$\begin{matrix} CO\cdot NRH \\ | \\ CO\cdot OMe \end{matrix} + NH_2\cdot NH_2 = \begin{matrix} CO\cdot NRH \\ | \\ CO\cdot NH\cdot NH_2 \end{matrix} + MeOH.$$

Menthyl semioxamazide $C_{10}H_{19}\cdot N^{H}CO\cdot CO\cdot NH\cdot NH_2$. (See P.25) and Phenyl semioxamazide $C_6H_5N^{H}CO\cdot CO\cdot NH\cdot NH_2$. have been synthesised in this way.

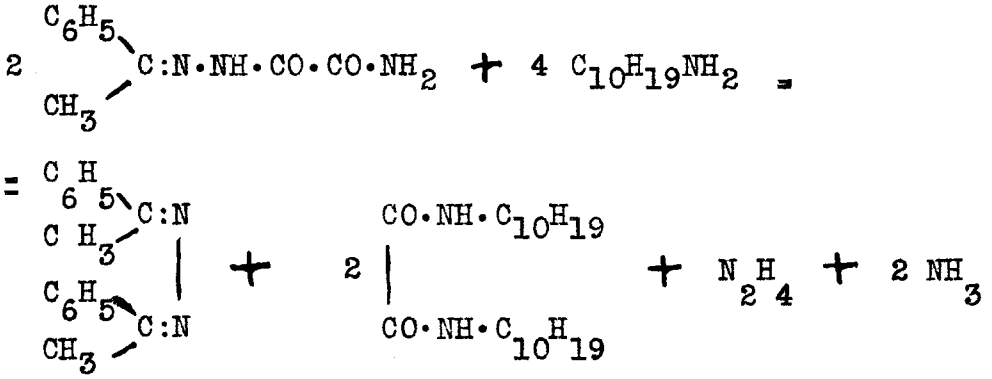
Phenyl semioxamazide which crystallises in white/

white plates from alcohol. m.p. 210°-211°. is obtained in good yield by this process and might therefore be used as a substitute for semioxamazide itself. Also, as has been indicated in Part I, the reaction between semioxamazide and ketones in absolute alcohol solution is a comparatively slow one unless iodine is used as a catalyst. This is probably due to the insolubility of semioxamazide in alcohol. The fact therefore that phenyl semioxamazide is moderately soluble in hot alcohol suggests the possibility that this substance might react more readily with ketones than semioxamazide itself under these conditions. This matter is being investigated at the present time.

PART IV.

PREPARATION OF AN OPTICALLY ACTIVE SEMIOXAMAZIDE.

An optically active semicarbazone was prepared by Wilson, Hopper and Crawford (J.C.S., 1922, Vol.121, P.867) by the action of a phenyl ethylamine on acetone semi-:carbazone and from this substance by hydrolysis with hydrochloric acid, the hydrochloride of an optically active semicarbazide was obtained. As a continuation of the study of the reaction between amines and semioxamazones, there-fore, and with the hope of preparing an optically active semioxamazide, the action of l.menthylamine on acetophenone semioxamazone was investigated. The desired result was not obtained however, as s.dimenthyl oxamide and aceto-:phenone ketazine were the only products isolated :-



The reaction is therefore similar to that which takes place/

place between benzylamine and semioxamazones (See P 16.)

This attempt at preparing an optically active semioxamazide having proved unsuccessful, the synthetic process which is described on P. 22. was resorted to. For this purpose some l. menthylamine $[\alpha]_D^{20} = -39.0^\circ$ was prepared, which on treatment with excess of methyl oxalate under suitable conditions yielded methyl l. menthylamino oxalate.

$$C_{10}H_{19}NH_2 + CH_3O{\cdot}CO{\cdot}CO{\cdot}OCH_3 = C_{10}H_{19}NH{\cdot}CO{\cdot}CO{\cdot}OCH_3 + CH_3OH.$$

This product is a thick viscous oil, B.p. 175°-177° at 10 m.m.
It is laevorotatory in chloroform solution.
5·69 . gr. in 100· C.C. chloroform gave $\alpha_D^{15} = -8{\cdot}43^\circ$
whence $[\alpha]_D^{15} = -74{\cdot}0^\circ$.

The methyl l. menthylamino oxalate was then treated with hydrazine hydrate and l. menthyl semi-oxamazide was obtained :-

$$C_{10}H_{19}{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}OCH_3 + NH_2\ NH_2 = C_{10}H_{19}{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}NH{\cdot}NH_2 + CH_3\ OH$$

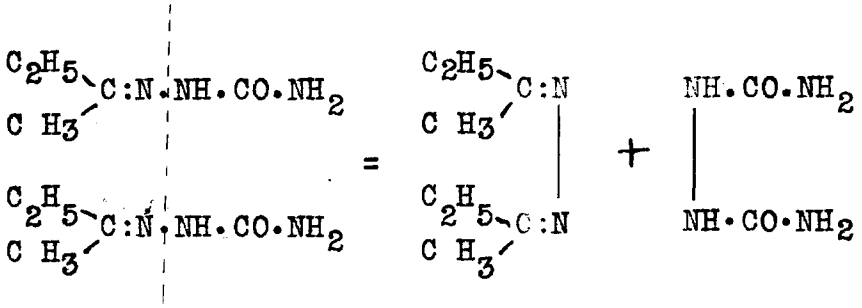
1. Menthyl semioxamazide crystallises from alcohol in white needles M.P. 195. 196°. It is readily soluble in pyridine and chloroform in the cold and is laevorotatory in chloroform solution.
$[\alpha]_D^{14} = -79.0°$ in chloroform. It yields derivatives with aldehydes in the ordinary way which are also optically active, e.g., the benzylidene derivative was prepared, and recrystallised from alcohol gave small prisms: M.P. 250.251.°
$[\alpha]_D^{17} = -51.3°$. in Chloroform.

It is hoped to continue this investigation and especially to find whether 1. menthyl semioxamazide has any value for resolving ~~optically active~~ racemic aldehydes and ketones.

PART V.

THE ACTION OF HEAT ON SEMIOXAMAZONES.

The action of heat on some semicarbazones has been investigated by Scholtz (Ber. 1896, 29. P. 611) who found for example that by the dry distillation of methyl ethyl ketone semicarbazone, the following decomposition took place :-

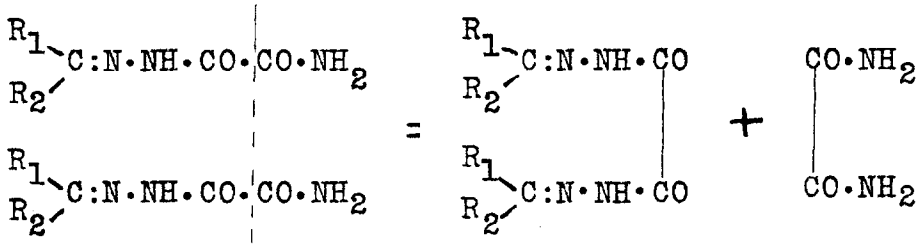


In their original paper dealing with semi-:oxamazide, Kerp and Unger (Ber. 1897. 30. 583) state that when this compound is heated, ammonia is liberated, and two substances are formed, one of which is a polymeride of cyanic acid probably having the composition $\begin{matrix} CO\cdot NH \\ | \\ CO\cdot NH \end{matrix}$ The other compound associated with it appears to be an ammonia derivative.

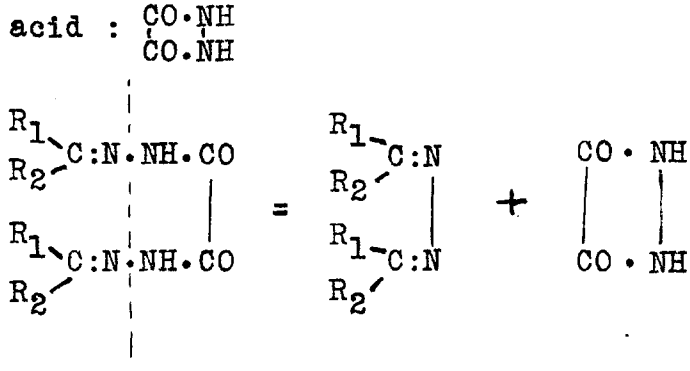
As/

As a part of this study of semioxamazones the action of heat on these compounds was investigated and the results obtained indicate that the reaction proceeds in the following manner :-

Two molecules of the semioxamazone react together oxamide is split off and the ketonic derivative of oxalyldihydrazide is formed :-



The oxalyldihydrazide derivative then breaks down giving a ketazine and cyclic hydrazide of oxalic acid :

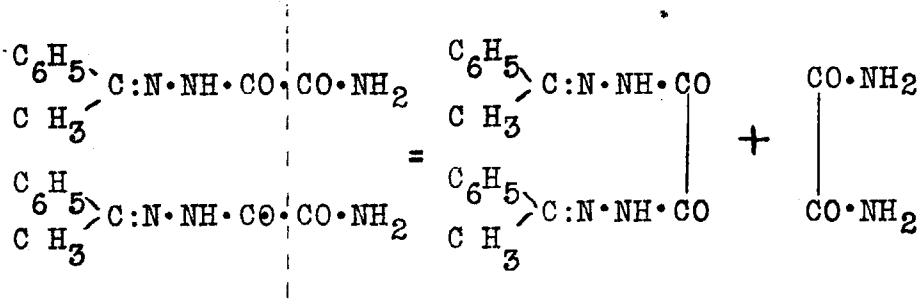


When acetophenone semioxamazone for example was/

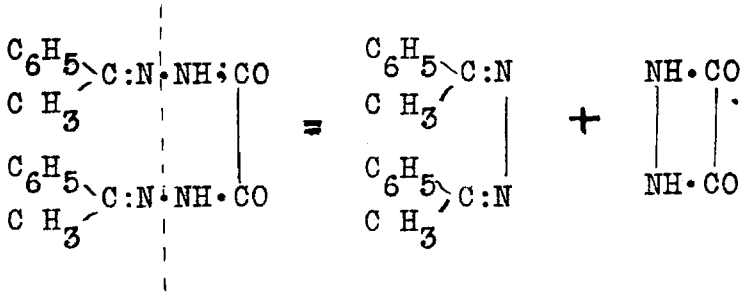
was heated for two hours at its melting point the products obtained were acetophenone ketazine, the acetophenone derivative of oxalyldihydrazide and a white powder insoluble in alcohol. This white powder on hydrolysis with sodium hydroxide gave off ammonia and the residue contained sodium oxalate. The residual solution also reduced silver nitrate solution in the cold, indicating the presence of hydrazine. These facts are consistent with the supposition that the powder is a mixture of oxamide and cyclic hydrazide of oxolic acid :- $\begin{matrix} CO\cdot NH \\ | \\ CO\cdot NH \end{matrix}$ The powder was analysed and was found to have a nitrogen content of 32.0% and 31.8% which is in agreement with the suggested view of its composition since a mixture of oxamide and the ring compound in molecular proportions would have a nitrogen content of 32.17%. The effect of heating acetophenone semioxamazone at its melting point may therefore be represented as follows :-

(I)/

1. Acetophenone oxalyldihydrazone and oxamide are formed from two molecules of the semioxamazone :-



2. The acetophenone oxalyldihydrazone then breaks down giving acetophenone ketazine and cyclic hydrazide of oxalic acid :-

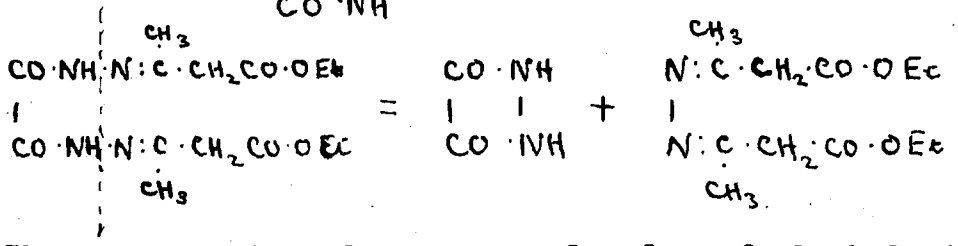


No satisfactory separation of the oxamide from the ring compound $\begin{matrix}CO\cdot NH\\ |\\ CO\cdot NH\end{matrix}$ was achieved but an examination of the action of heat on ethyl acetoacetate semioxamazone supplied additional evidence in support of the above view of the composition of the mixture.

The/

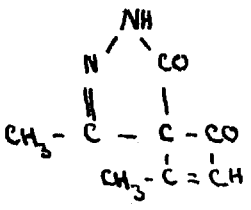
The products obtained by heating ethyl acetoacetate semioxamazone for two hours at its melting point were a substance of melting point 247°C and a white powder, insoluble in alcohol, and similar in every respect to that obtained in the acetophenone semioxamazone experiment. No evidence of the presence of the ketazine or the oxalyldihydrazone of ethyl acetoacetate was obtained. The action of heat on this dihydrazone has however already been investigated by ~~Rosengarten~~ Bulow & Loevenich (Ber. 40. 1. 1907) (see p. 87) (~~Ann. d. chem., 279 — 242. (1894)~~) who has shown that the course of the reaction is as follows :-

First of all the ethyl acetoacetate oxalyldihydrazone breaks down giving ethyl acetoacetate ketazine and the ring compound $\begin{matrix} CO\cdot NH \\ | \\ CO\cdot NH \end{matrix}$. :-

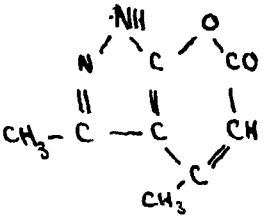


The ketazine then loses two molecules of alcohol giving a/

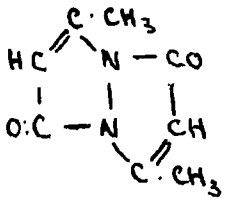
a compound of the empirical formula $C_8H_8O_2N_2$. Bulow & Schenck ~~Rosengarten~~ suggested three possible formulae for this compound, viz :



I



II.



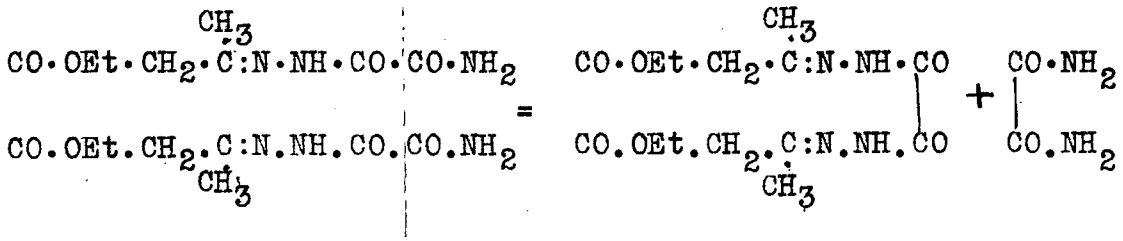
III.

In a later paper Wolff and Schreiner (Ber. 41. 553. (1907)) evidence is brought forward to show that the lactone structure No. II. is the correct one. Now this substance melts at 247° and is identical with the product obtained by heating ethyl acetoacetate semi-:oxamazone. It is evident therefore that the action of heat on the latter substance is to cause decomposition according to the following scheme :-

1st/

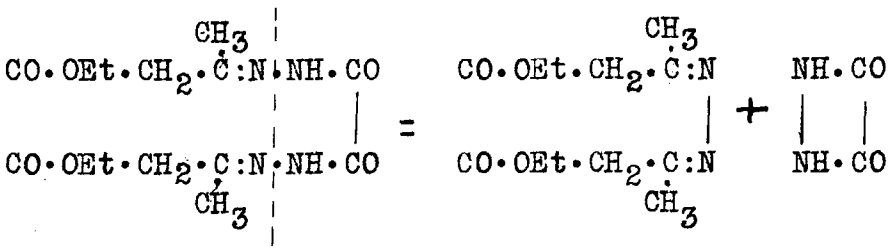
1st Stage:

Ethyl acetoacetate semioxamazone breaks down giving ethyl acetoacetate oxalyldihydrazone and oxamide :-



2nd Stage:

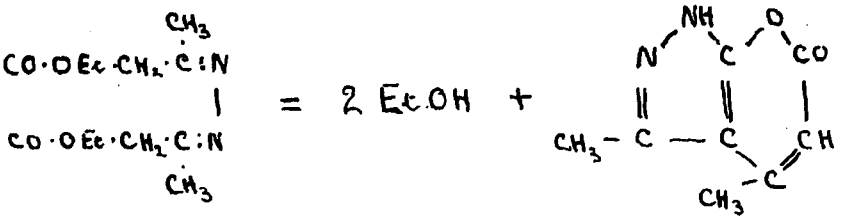
The oxalyldihydrazone then breaks down as shown by ~~Rosengarten~~ Bulow & Schenk giving ethyl acetoacetate azine and cyclic hydrazide of oxalic acid :-



3rd Stage:

The ketazine finally loses two molecules of alcohol and as the result of a rather complex molecular rearrangement/

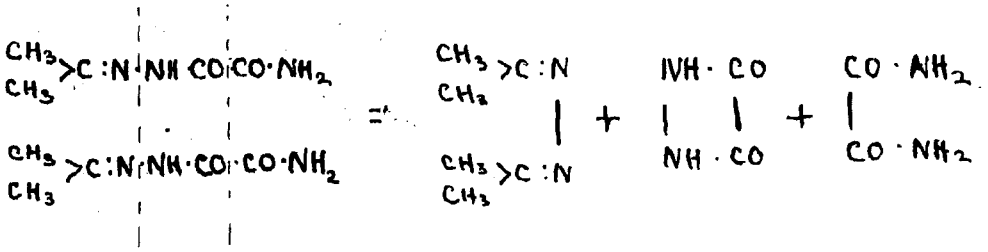
rearrangement the lactone is formed :-



The final products being the lactone M.P. 247° and the mixture of oxamide and cyclic hydrazide of oxalic acid.

The semioxamazones of acetone, methyl ethyl ketone and dibenzyl ketone were also heated at their melting points. The products in these cases were the corresponding ketazines and the mixture of oxamide and ring compound referred to above.

e.g. Acetone semioxamazone breaks down in the normal manner as follows :-

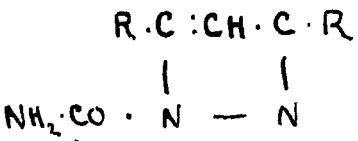


The intermediate products, i.e. the oxalyl dihydrazones of the ketones were not isolated in these particular cases.

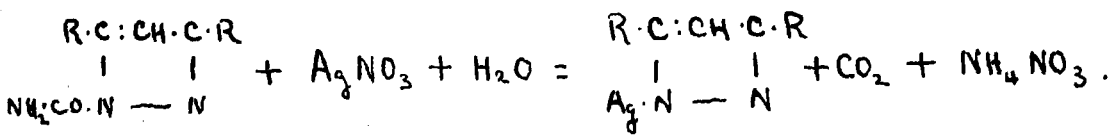
PART VI.

ACTION of SEMIOXAMAZIDE on b. DIKETONES.

In the course of an investigation on the reaction between semicarbazide and b. diketones Theodor Posner (Ber. 34. (1901) 3973) found that both carbonyl groups of the diketone reacted, with elimination of two molecules of water, and resulting in a compound of the type :-



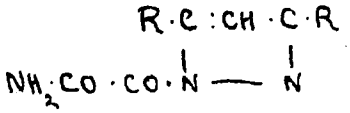
These compounds yield silver salts on treatment with silver nitrate solution :-



and these silver salts on hydrolysis with hydrochloric acid give pyrazole derivatives. By employing different diketones/

diketones a number of these derivatives have been prepared.

If the corresponding reaction took place with semioxamazide the product would be of the type -



In the course of this work a preliminary investigation on the action of diketones on semioxamazide was begun but no indication of the above reaction has been obtained so far. When acetyl acetone was heated with semioxamazide suspended in absolute alcohol, the products obtained were the "mono" and "di" semioxamazones of acetyl acetone.

This experiment was then repeated but with the addition of a little iodine to the reaction mixture.

In this case, the "mono" and "di" semioxamazones were obtained as before but in addition a third product was isolated crystallising in long prismatic needles, m.p. 115°.

These experiments were repeated several times with the same results; in every case the addition of a little iodine led to the formation of the third product m.p.115. This substance has not yet been identified. It does not contain iodine and it has a nitrogen content of 12.4%, but this figure does not agree with any of the possible compounds on the basis of Posner's reaction. The examination of this product is being continued and it is hoped to investigate the influence of iodine on this and other reactions of this type.

- EXPERIMENTAL -

PART I.

PREPARATION OF SEMIOXAMAZONES.

In the preparations described below where the use of iodine as a catalyst is referred to the following method is always adopted. The mixture consisting of dry, finely powdered semioxamazide, ketone (in a little more than molecular proportion) and absolute alcohol is heated until the alcohol is boiling vigorously and a few crystals of iodine are then added. In this way the best effects with iodine are obtained. In the preparation of acetone and methyl ethyl ketone semi-:oxamazones the alcohol was sometimes dispensed with and excess of dry ketone used as solvent. The addition of iodine in these cases was carried out in the same way as when alcohol was the solvent.

Acetonesemioxamazone, $CMe_2:N\cdot NH\cdot CO\cdot CO\cdot NH_2$--
Five grams of dry semioxamazide were heated with 30 c.c. of dry acetone on the water-bath for one hour, when the semioxamazide/

semioxamazide had completely dissolved; in presence of a little iodine, three minutes were sufficient. The product which separated on cooling crystallised from acetone in long, white needles melting at 147° (Found: N = 29.5. $C_5H_9O_2N_3$ requires N = 29.4 per cent.) The same substance was obtained by heating the calculated quantities of dry semioxamazide and dry acetone in absolute alcohol for forty minutes, or for two minutes in presence of a little iodine, and separated on cooling.

Methyl Ethyl Ketone Semioxamazone, $CMeEt:N\cdot NH\cdot CO\cdot CO\cdot NH_2$, was prepared by the same methods as the acetone derivative, in the first method forty-five minutes being required without iodine and one minute with iodine, and in the second method, ninety minutes without iodine and three minutes with iodine. The substance was recrystallised from absolute alcohol, from which it separated in small, colourless needles melting at/

at 127° (Found: N = 26.8. $C_6H_{11}O_2N_3$ requires N = 26.7 per cent). Like acetonesemioxamazone, it is hydrolysed on warming with moist ether or dilute alcohol.

Methyl iso Propyl Ketone Semioxamazone,

$CMePr^{\beta}:N\cdot NH\cdot CO\cdot CO\cdot NH_2$,

was prepared as in the previous cases; heating in absolute alcohol required seventy minutes without iodine and ten minutes with iodine. Recrystallisation from absolute alcohol gave colourless needles melting at 143° (Found: N = 24.7, $C_7H_{13}O_2N_3$ requires N = 24.5 per cent).

Methyl iso Butyl Ketone Semioxamazone,

$C_4H_9\cdot CMe:N\cdot NH\cdot CO\cdot CO\cdot NH_2$.

This semioxamazone is apparently not hydrolysed by water and was obtained by heating a concentrated aqueous solution of semioxamazide with the calculated quantity of the ketone in alcoholic solution for about half an hour/

hour, a method which was quite ineffective in the previous cases. The substance separated from the reaction mixture, on cooling, in colourless needles which, after recrystallisation from alcohol, melted at 133° (Found: N = 22.9. $C_8H_{15}O_2N_3$ requires N = 22.7 per cent).

Mesityl Oxide Semioxamazone, $CMe_2:CH\cdot CMe:N\cdot NH\cdot CO\cdot CO\cdot NH_2$, was prepared in the same way as methyl isobutyl ketone semioxamazone, one hour's heating being necessary, or by heating the ketone in absolute alcohol with semioxamazide. On cooling, the semi-:oxamazone slowly separated as a white powder, which was obtained in colourless plates, melting at 163 - 164° after recrystallisation from alcohol (Found : N = 23.0. $C_8H_{13}O_2N_3$ requires N = 22.9 per cent).

Acetophenonesemioxamazone, $CPhMe:N\cdot NH\cdot CO\cdot CO\cdot NH_2$, has already been described by Kerp and Unger and by Radcliffe and Loo (loc.cit.). We have prepared it by heating/

heating the ketone with semioxamazide in absolute alcohol without iodine (one hour) or with iodine (five minutes).

Benzylacetonesemioxamazone, $CH_2Ph \cdot CH_2 \cdot CMe:N \cdot NH \cdot CO \cdot CO \cdot NH_2$, was obtained by heating 2 grams of the ketone and 1 gram of semioxamazide in 20 c.c. of absolute alcohol without iodine (three hours) or with iodine (four minutes). The semioxamazone, which separated on cooling, was washed with ether and recrystallised from alcohol, from which it was deposited in small, colourless needles melting at 125° (Found: N = 18.3, 18.1, $C_{12}H_{15}O_2N_3$ requires N = 18.0 per cent).

Styryl Methyl Ketone Semioxamazone,

$CHPh:CH \cdot CMe:N \cdot NH \cdot CO \cdot CO \cdot NH_2$,

was prepared by the method described by Radcliffe and Loo. It rapidly becomes yellow on exposure to light, the melting point remaining unchanged.

Phenyl/

Phenyl p-Tolyl Ketone Semioxamazone,

$C_7H_7 \cdot CPh:N \cdot NH \cdot CO \cdot CO \cdot NH_2$,

obtained by heating molecular quantities of the ketone and semioxamazide in absolute alcohol with a little iodine, formed colourless prisms melting at 197° after recrystallisation from alcohol (Found : N = 15.0%. $C_{10}H_{15}O_2N_3$ requires N = 14.9%).

Methyl n-hexyl ketone semioxamazone,

$C_6H_{13} \cdot CMe:N \cdot NH \cdot CO \cdot CO \cdot NH_2$,

was prepared by boiling 2 grams of semioxamazide with 3 grams of the ketone in 25 grams of absolute alcohol, On addition of a few crystals of iodine, the semi-:oxamazide dissolved completely within 5 minutes and on cooling the semioxamazone was deposited in the pure condition as small, colourless needles, m.p. 115-116°. The substance was very readily hydrolysed, but could be recrystallised/

recrystallised from absolute alcohol (Found: N = 19.8. $C_{10}H_{19}O_2N_3$ requires N = 19.7 per cent).

Benzil monosemioxamazone, $PhCO\cdot CPh{:}N\cdot NH\cdot CO\cdot CO\cdot NH_2$, was obtained by boiling 0.5 gram of semioxamazide with 3 grams of benzil in 30 grams of absolute alcohol with addition of a little iodine, which effected complete solution in an hour; without addition of iodine there was no indication of any reaction. On cooling, the semioxamazone separated in long, colourless prisms which after recrystallisation from alcohol melted at 181 - 182° (Found: N = 14.2. $C_{16}H_{13}O_3N_3$ requires N = 14.2. per cent).

The disemioxamazone, $(CPh)_2{:}\ (N\cdot NH\cdot CO\cdot CO\cdot NH_2)_2$, which could not be obtained pure, was prepared in the usual way, using excess of semioxamazide and boiling for 4 hours. As it was insoluble in alcohol and in solvents generally, it was purified by extraction with hot acetone to remove excess of semioxamazide, and then with/

with hot alcohol; the disemioxamazone formed a white powder, m.p. 275 - 278° (decomp.) (Found: N = 21.2, 21.6. $C_{18}H_{16}O_4N_6$ requires N = 22.1 per cent.)

Dibenzyl ketone semioxamazone, $C(CH_2Ph)_2{:}N{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}NH_2$, which was prepared in the usual way, was found to be dimorphic. From a hot concentrated alcoholic solution colourless prisms melting at 195 - 196° were deposited at temperatures above 40°, whilst at temperatures below this and from more dilute solutions the semioxamazone crystallised in colourless needles, m.p. 187 - 189°. A mixture of the two forms softened at 187° and melted at 194 - 196° (Found : prisms - N = 14.3, needles N = 14.4. $C_{17}H_{17}O_2N_3$ requires N = 14.2 per cent).

PART II.

METALLIC DERIVATIVES of SEMIOXAMAZIDE and of SEMIOXAMAZONES.

Sodium Salt of Semioxamazide:

A suspension of 5 grams semioxamazide (1 mol.) in 200 ccs absolute alcohol was made and heated to boiling on the water bath. To the boiling mixture a solution of sodium ethoxide (1 atom) (1.5 grs. sodium in 100 ccs absolute alcohol) was slowly added and heating then continued for a further 30 minutes. The white granular precipitate which had formed was then filtered off, repeatedly washed with hot alcohol and finally dried.

The sodium salt of semioxamazide thus obtained is a white powder, insoluble in alcohol. It is soluble in water but readily undergoes hydrolysis.

Potassium/

Potassium Salt of Semioxamazide:

The potassium salt was prepared in a manner similar to that used in the case of the sodium salt but in place of the sodium ethoxide, a solution of potassium hydroxide in absolute alcohol was employed.

The Potassium salt also is a white powder, insoluble in alcohol.

Sodium Salt of Styryl Methyl Ketone Semioxamazone:

10 grs. of the semioxamazone were partly dissolved in boiling absolute alcohol and a solution of sodium ethoxide (1 gram sodium in 50 ccs absolute alcohol) added. The suspended semioxamazone dissolved and a bright yellow solution was obtained. On boiling this solution on the water bath for some time the sodium salt of the semioxamazone separated. This was filtered off, washed with hot alcohol and then dried in the steam oven.

The/

The sodium salt is a pale yellow powder, insoluble in alcohol. M.P. 230° (decomp.) turning red.

The sodium salts of acetone and methyl ethyl ketone semioxamazones were prepared in a similar manner.

Sodium Salt of Mesityl Oxide Semioxamazone:

1.2 grams of the semioxamazone were dissolved in absolute alcohol and the mixture heated on the water bath. A solution of sodium ethoxide containing approximately 0.2 gram of sodium was then added and boiling continued for half an hour. As no separation of sodium salt took place, the mixture was cooled and poured into excess of dry ether and the whole allowed to stand. After some time a small quantity of the sodium salt recrystallised in small cubes.

Potassium/

Potassium Salt of Styryl Methyl Ketone Semi-oxamazone:

The semioxamazone was suspended in absolute alcohol and a solution of potassium hydroxide in absolute alcohol added. The mixture was then allowed to stand for an hour in the cold. The insoluble product was separated and purified by refluxing with absolute alcohol and filtering hot.

The potassium salt is a yellow powder, slightly soluble in hot alcohol.

Analysis of the Metallic Derivatives:

The proportion of metal present in these metallic derivatives was determined either by igniting in a platinum crucible with a little concentrated sulphuric acid and weighing the sulphate produced or the salt was hydrolysed by warming with known excess of/

of standard acid. The amount of acid used was then determined by adding excess of standard alkali and titrating back, using methyl red as indicator; the equivalent of metal was then calculated.

The results given in the following list were obtained :-

(a) Sodium derivative of :

Acetonesemioxamazone. Found : Na = 13.5, 14.0.

$C_5H_8O_2N_3Na$ requires Na = 13.9 per cent.

Methyl ethyl ketone semioxamazone. Found : Na = 12.1.

$C_6H_{10}O_2N_3Na$

requires Na = 12.8 per cent.

Mesityl oxide semioxamazone. Found : Na = 10.8. $C_8H_{12}O_2N_3Na$ requires Na = 11.2 per cent.

Styryl methyl ketone semioxamazone. Found : Na = 8.8, 8.9.

$C_{12}H_{12}O_2N_3Na$ requires Na = 9.1 per cent.

Semioxamazide. (Found: Na = 18.0, 18.4.

$C_2H_4O_2N_3Na$ requires Na = 18.4 per cent.

(b) Potassium derivative of :

Acetophenonesemioxamazone. Found : K = 15.9.

$C_{10}H_{10}O_2N_3K$ requires K = 16.0 per cent.

Styryl methyl ketone semioxamazone.

Found : K = 14.4, 14.4. $C_{12}H_{12}O_2N_3K$ requires K = 14.5 per cent.

Action of Benzyl chloride on the metallic Derivatives of Semioxamazide:

Two grams of the dry potassium salt of semioxamazide suspended in absolute alcohol were treated with the molecular proportion of benzyl chloride and the mixture heated on the water bath for two hours. Under these conditions no action took place, the potassium salt being recovered unchanged. No change was observed also when ether, and ethyl acetate were used as diluents in place of the alcohol nor when acetonitrile was added in the hope of catalysing the reaction.

When toluene was employed instead of the absolute alcohol and the mixture of potassium salt of semioxamazide, benzyl chloride and toluene was heated over a wire gauze for several hours, ammonia was evolved and on cooling a small quantity of a white crystalline substance separated from the toluene. This substance was/

was separated from the insoluble potassium salt by filtering the toluene solution whilst hot. Finally by recrystallising from alcohol long silky needles were obtained. m.p. 220 - 221°.

The same compound was obtained in larger yield when the potassium salt of semioxamazide was heated with excess of benzyl chloride for two hours, the product being extracted with toluene and recrystallised from alcohol as described above.

The analysis of this substance showed it to have a nitrogen content of 14.6 - 14.8 per cent, but it has not yet been definitely identified.

PART III.

ACTION OF AMINES on SEMIOXAMAZIDE AND SOME SEMIOXAMAZONES.

Benzylamine and Semioxamazide: These two reactants, using excess of the amine, were heated together under reflux in a glycerol bath to 175-180° until complete solution had been effected (about 2 hours); a copious evolution of ammonia took place. The reaction mixture was cooled and treated with a little alcohol which caused an immediate separation of a white powder which after recrystallisation from alcohol was obtained in long silky needles melting at 217-218° and was identified as s. dibenzyloxamide by comparison with a specimen made from benzylamine and methyl oxalate and by analysis. (Found : N = 10.6, 10.6, Calc., N = 10.5 per cent). The liquid remaining after removal of the dibenzyloxamide was distilled, the distillate reduced silver nitrate in the cold indicating the presence of hydrazine.

Benzylamine/

Benzylamine and Dibenzyl Ketone Semioxamazone:

These two substances were heated together to 150° for three hours, the amine being in excess: the semioxamazone gradually dissolved with evolution of ammonia. On cooling some solid separated, ether was added and the solid after filtration was identified as s. dibenzyloxamide. The filtrate was freed from ether by distillation and a portion was distilled, hydrazine was identified in the distillate by its reducing action on silver nitrate and on Fehling's solution. The remainder was poured into ice-cold dilute acetic acid, a solid separated part of which dissolved in ether, the insoluble portion being di-:benzyloxamide. The ethereal solution was evaporated and the residue recrystallised from alcohol which deposited small colourless prisms of dibenzylketazine melting at 95-96°: the melting-point was not altered by addition of some of the ketazine prepared by the method/

method described below. This ketazine, which does not seem to have been previously prepared, was also obtained by heating 7 grams of dibenzyl ketone with 1.5 grams of hydrazine hydrate in a sealed tube to 100° for 12 hours. Alcohol was then added, after cooling and stirring a solid separated which after recrystallisation from alcohol formed small colourless prisms melting at 95-96°.

(Found: N = 6.7. $C_{30}H_{28}N_4$ requires N = 6.7 per cent).

Benzylamine and Acetophenone Semioxamazone:

The semioxamazone was heated to 155° - 160° with excess of benzylamine under reflux. Ammonia was evolved and at the end of one and a half hours complete solution had been effected. On cooling a little alcohol was added, this caused the separation of dibenzyloxamide which was filtered off, the filtrate on pouring into ice-cold dilute acetic acid deposited a yellow solid which/

which was freed from dibenzyloxamide by extraction with ether and filtering. The ether was evaporated and the residue recrystallised from alcohol from which yellow needles of methyl phenyl ketazine melting at 129° - 130° were deposited. (Found: N = 11.9 Calc., N = 11.9 per cent). The melting-point of this ketazine is variously given in the literature as 121° or 127° - 128°, a specimen prepared by the method of Curtius and Thun (J.Pr.Chem., 1891, (2) 44, 167) was found to melt at 129-130°; a mixed melting-point of the two specimens showed no depression.

Piperidine and Acetophenone Semioxamazone:

3 grams of the semioxamazone and 5 grams of piperidine were boiled under reflux for four and a half hours when solution, accompanied by evolution of ammonia, was complete. On cooling 10 cc. of alcohol were added, 2 grams of a solid separated which after several recrystallisation from alcohol was finally obtained as a/

a white microcrystalline powder melting at 174°-175°. The mother-liquers on evaporation to dryness under reduced pressure gave an oil which solidified on the addition of a little alcohol, this solid the amount of which was small melted at 145°-155° and was not obtained pure. The substance melting at 174-175° was acetophenone piperidyloxalylhydrazone. (Found: N = 14.7, 14.8. $C_{15}H_{19}O_2N_3$ requires N = 15.0 per cent). 4 grams of this substance were mixed with 10 cc of water and 5 c.c. N/10 hydrochloric acid, and distilled in steam as long as acetophenone passed over. The contents of the flask after being made just alkaline with sodium carbonate were evaporated to dryness under reduced pressure, and the viscous oil remaining was freed from sodium salts by extracting with absolute alcohol and filtering. The residue obtained by evaporation of this alcoholic solution solidified on keeping in a vacuum over sulphuric acid. Recrystallisation from/

from a mixture of benzene and light petroleum gave colourless transparent plates of piperidyloxalylhydrazine melting at 77-79°. (Found: N = 24.4. $C_7H_{13}O_2N_3$ requires N = 24.5 per cent). The hydrochloride was obtained as a white powder by addition of a benzene solution of hydrogen chloride to a benzene solution of the base, it melted with decomposition at 180°. (Found: A = 17.5, $C_7H_{14}O_2N_3Cl$ requires A = 17.1 per cent). The benzylidene derivative was prepared by mixing alcoholic solutions of 2 grams of the hydrazine and 1 gram of benzaldehyde and warming for two minutes. On cooling colourless needles separated which after recrystallisation from alcohol melted at 201° - 202°. (Found: N = 16.3. $C_{14}H_{17}O_2N_3$ requires N = 16.2 per cent-).

The synthesis of piperidyloxalylhydrazine was effected by gently boiling molecular quantities of ethyl piperidyloxalate and hydrazine hydrate in alcoholic solution for about an hour.

Oxalyldihydrazide/

Oxalyldihydrazide was a by-product of this reaction and separated out since it is almost insoluble in alcohol, the filtrate was evaporated and the residue solidified on keeping in a vacuum over sulphuric acid. Recrystallisation from a mixture of benzene and light petroleum gave a specimen of the hydrazine identical with the one just described, the benzylidene derivatives were also identical.

Piperidine and Dibenzyl Ketone Semioxamazone:

3 grams piperidine and 3 grams dibenzyl ketone semioxamazone were made into a paste and heated together for 3 hours at 125° c. (when evolution of ammonia had ceased). The solution was then cooled, absolute alcohol added, and the whole allowed to stand overnight. The white product which separated was removed by filtration and extracted with ether. The ethereal solution was then evaporated and the residue recrystallised from/

from alcohol, which deposited small prisms of dibenzyl ketazine, m.p. 95-96°. The portion insoluble in ether proved to be unchanged semioxamazone. The original alcohol mother liquor was evaporated under reduced pressure on the water bath until no more distillate came over and the residue was then extracted with ether. When the ether was removed a syrup was obtained, but this was not further examined.

PREPARATION of PHENYL SEMIOXAMAZIDE

$C_6H_5NH.CO.CO.NH.NH_2$.

(1) Preparation of methyl ester of oxanilic acid -

15 grs. of methyl oxalate were heated on the water bath and 6 grams aniline slowly added to the molten mass, thus keeping the oxalate always in excess. After all the aniline had been added heating was continued for 30 minutes. The excess methyl oxalate was then distilled off under reduced pressure. The residue in the flask was then boiled with 50 ccs absolute alcohol and filtered warm. The sparingly soluble product which separated in this way melted at 245° and was identified as oxanilide. From the filtrate a crop of well formed prismatic crystals was obtained M.P. 114° recrystallised from alcohol M.p.114.° This product being the desired methyl ester of oxanilic acid. M.P. 114° (B. II. P. 407). The yield of ester is/

is a good one, only a small quantity of oxanilide being formed as a by-product.

(2) Phenyl Semioxamazide -

$C_6H_5 NH \cdot CO \cdot CO \cdot NH \cdot NH_2$.

3 grs, of the methyl ester prepared as described in the previous experiment, were dissolved in 30 c.c. absolute alcohol and 1.5 gram. hydrazine hydrate added. The mixture was then heated on the water bath for one hour. A white solid was thrown down and, after cooling the mixture, was filtered off. This product after recrystallisation from hot alcohol melted at 209-210, recrystallised from water M.P. 210° - 211°.

Analysis: Found N = 23.5%. Phenyl Semioxamazide $C_8H_9O_2N_3$ requires N = 23.3%.

Phenyl semioxamazide obtained in this way crystallises from hot alcohol in small plates m.p. 210-211°.
It is moderately soluble in hot alcohol and in hot water.

PART IV.

PREPARATION of an OPTICALLY ACTIVE SEMIOXAMAZIDE.

The l menthylamine used in the following experiments was prepared as described in the appendix : P. 82. and had $[\alpha]_D^{20} = -39.0^\circ$.

Action of Acetophenone Semioxamazone on l. menthylamine:

1 gram of acetophenone semioxamazone was made into a paste with 2.5 grams of l.menthylamine and the mixture heated at 170-175° until no more ammonia was evolved. The molten mass was then cooled to about 70° and a little absolute alcohol added which caused an immediate separation of a white powder m.p.225-227°, after recrystallisation from alcohol m.p.228-229.° This product was identified as S. l.dimenthyl oxamide, by analysis and by comparison with an authentic specimen prepared/

prepared as described later. (Found: N = 7.87. 7.71. $C_{22}H_{40}O_2N_2$ requires 7.69%). The mother liquor on standing deposited a crop of yellow needles m.p. 129°, which were identified as acetophenone ketazine.

Preparation of S. l.dimenthyl oxamide:

0.5 grams methyl oxalate was heated with 1.5 grams l.menthylamine. After heating for one hour a white product separated. Heating was continued for half an hour and absolute alcohol then added and the white product crystallised out. The dimenthyl oxamide thus obtained was found to melt sharply at 229° and gave no depression when mixed with the product obtained in the experiment on the action of l.menthylamine on acetophenone semioxamazone.

Preparation/

Preparation of Methyl l. menthylamine oxalate:

$$CO \cdot NH \cdot C_{10}H_{17}$$
$$CO \cdot O \cdot CH_3$$

60 grs. methyl oxalate (large excess) were melted and 31 grams l. menthylamine $\left([\alpha]_D^{20} : -39.0\right)$ added and the mixture heated on the water bath for 4 hours. 50 c.c. absolute alcohol were then added and the mixture allowed to cool. The white precipitate of l. dimenthyl oxamide, M.P. 229° which separated was filtered off and the filtrate, after removal of the alcohol, was distilled under reduced pressure. Two fractions were obtained, the first boiling at 80° at a pressure of 18 m.m. was unchanged methyl oxalate, the second, b.p. 185-187° at 15 m.m. was the required l.menthyl oxalate. The l.menthylamino oxalate thus obtained was a pale yellow, thick viscous liquid.

(Analysis - $C_{13}H_{23}O_3N$ requires N = 5.8%. Found 6.0 - 6.08%.

Preparation of l. Menthyl Semioxamazide:

($C_{10}H_{19}NH \cdot CO \cdot CO \cdot NH \cdot NH_2$)

In this preparation 20 gram. of the methyl.l. menthylamino oxalate were mixed with 8 gram. of 100% hydrazine hydrate and the mixture heated on the water bath for 15 minutes. A solid mass was obtained. To this was added 180 ccs. of absolute alcohol and heating continued until a clear solution was obtained. On cooling this solution needle shaped crystals of l. menthyl semioxamazide were obtained m.p. 195-196°, recrystallised from alcohol. m.p. 195° - 196°.

(Analysis: $C_{12}H_{23}N_3O_2$ requires N = 17.4%

Found - N = 17.6. 17.7%.

l. menthyl semioxamazide is soluble in hot alcohol, readily soluble in pyridine and chloroform in the cold.

It was laevorotatory in chloroform solution: 2.5 grs. in 100 cc. of chloroform gave $\alpha_D^{14} = -3.95^\circ$ (l=2) whence $[\alpha]_D^{14} = -79.0^\circ$.

Preparation of the Benzylidine Derivative of l.menthyl-Semioxamazide. $C_6H_5CH{\cdot}N{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}NH{\cdot}C_{10}H_{19}$

To prepare this derivative 2 gram of the l. menthyl semioxamazide were dissolved in 50 cc. absolute alcohol and a solution of 1.5 gram benzaldehyde in 25 cc absolute alcohol added and the mixture heated on the water bath. The benzylidene derivative which is only sparingly soluble in hot alcohol soon began to separate in small prisms. After 15 minutes, heating was discontinued and the mixture cooled when most of the product crystallised out.

This benzylidine derivative of l.menthyl semi-:oxamazide after recrystallisation from hot alcohol melted at 250-251°. It was sparingly soluble in hot alcohol, readily soluble in chloroform in the cold and to a less extent in pyridine.

(Analysis: $C_{19}H_{27}O_2N_3$ requires N = 12.76%

Found:- N = 12.8 - 12.9%

It was laevorotatory in chloroform solution.

2.002 gram in 50 ccs chloroform gave $\alpha_D^{17} = -4.11°$ (l = 2)

whence $[\alpha]_D^{17} = -51.3$.

PART V.

ACTION OF HEAT ON SEMIOXAMAZONES.

Action of heat on Acetophenone Semioxamazone:

7 grams of acetophenone semioxamazone were maintained at a temperature of 206°c for six hours. After about half an hour a solid began to separate from the molten mass and at the end of six hours a semi-solid mass was obtained. This was then cooled, finely powdered and extracted with absolute alcohol. The white powder, insoluble in alcohol, separated in this way, was identified by hydrolysis and analysis as a mixture of oxamide and cyclic hydrazide of oxalic acid. (See Page 29.)

The alcoholic solution, obtained after removal of the powder, was concentrated and the yellowish mass which separated on standing filtered off; it was then dried and extracted with ether. The residue obtained after removal of the ether, was recrystallised from alcohol and/

and identified as acetophenone ketazine M.P. 129-130°. The portion insoluble in ether was redissolved in excess of alcohol, and the dilute solution thus obtained on long standing deposited a small quantity of a pure substance, M.P. 248° which was identified as acetophenone oxalyldihydrazide by comparison with an authentic specimen prepared as described below. From the mother liquor after removal of this small quantity of oxalyldihydrazone only unchanged aceto-:phenone semioxamazone was recovered.

Preparation of Acetophenoneoxalyldihydrazone:

A mixture containing molecular proportions of acetophenone and oxalyl dihydrazide(obtained as a by-product in the synthesis of piperidineoxalylhydrazine) dissolved in excess of absolute alcohol was heated on the water bath for three hours. At the end of this time no perceptible reaction had taken place but on the/

the addition of a crystal of iodine within two or three minutes a flock of fine needles was thrown out of solution. The melting point of the product after recrystallisation from alcohol was 250°.

Analysis: Found N = 17.02. 17.03 per cent.

$C_{18}H_{18}N_4O_2$ requires 17.39. % N.

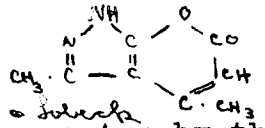
Preparation of Ethyl Acetoacetate Semioxamazone:

2 gram of semioxamazide were heated with 3 gram. ethyl acetoacetate in 35 gram. absolute alcohol. After 30 minutes the semioxamazide had completely dissolved and on cooling the solution the semioxamazone of ethyl acetoacetate separated in small needles - m.p. 127-128.° recrystallised from alcohol M.P. 128-129.°

Note: The above experiment was repeated but with the addition of a little iodine. In this case however, the iodine did not accelerate the reaction, in fact if anything it appeared to retard it.

Action of Heat on Ethyl Acetoacetate semioxamazone:

2 gram. of ethyl acetoacetate semioxamazone were heated for two hours at 130-135°c. After about one hour a solid began to separate from the molten liquor and by the time heating was discontinued a semi-solid mass had been produced. Absolute alcohol was then added, the mixture refluxed for a few minutes and filtered from the insoluble white powder which was identified as a mixture of oxamide and cyclic hydrazide of oxalic acid (See Pages 29 & 31). The alcoholic solution was next submitted to fractional crystallisation, the first product deposited being a sparingly soluble substance, melting at 247°c, after recrystallising from alcohol from which it separated in well defined prismatic needles. This substance was identified as the lactone



Bulow & Schenck

obtained by ~~Rosengarten~~ by the action of heat on the oxalyldihydrazone of ethylacetoacetate. (Analysis - Found N = 17.3, 17.14 per cent. $C_8H_8O_2N_2$ requires 17.07 per cent).

A specimen of the lactone was prepared by Bulow & Sobecki's ~~Rosengarten's~~ method and was found to be identical with the product obtained as described above. Subsequent crops obtained by continuing the fractionation of the alcoholic solution proved to be unchanged ethyl acetoacetate semioxamazone.

Action of Heat on Acetone Semioxamazone:

In carrying out this experiment the dry acetone semioxamazone was placed in a 100 ccs distillation flask and heated at 180° c. The mouth of the flask was sealed with a tightly fitting cork whilst the delivery tube passed through a piece of pressure tubing into the neck of another small distillation flask, the delivery tube of the receiving flask being connected to a water suction pump.

The heating of the semioxamazone was continued for/

for four hours during which time a small quantity of a liquid collected in the receiving flask. At the end of four hours the pressure in the apparatus was slightly reduced when a further quantity of liquid was collected. When no more liquid distilled over, heating was discontinued. The liquid product was identified as acetone ketazine c.p. 131. 133° c. The residue in the flask was insoluble in alcohol and was found to be the usual mixture of oxamide and cyclic hydrazide of oxalic acid.

Action of Heat on Methyl Ethyl Ketone Semioxamazone:

The action of heat on this semioxamazone was investigated in precisely the same manner as with acetone semioxamazone. In this case also a liquid was obtained, which was identified as methyl ethyl ketazine, c.p. 167°. The residue in the flask was found to be the usual mixture of oxamide and cyclic hydrazide of oxalic acid.

Action of Heat on Dibenzyl Ketone Semioxamazone:

5 grs. of the semioxamazone were heated for $1\frac{3}{4}$ hours at 200°. A little ammonia was evolved and a small white sublimate was observed on the sides of the tube. On cooling the molten mass solidified and it was then powdered and extracted with ether. On evaporating the ether extract a residue was obtained which, recrystallised from alcohol gave colourless prisms M.P. 95 - 96°, identified as Dibenzyl ketazine. The portion insoluble in ether was next extracted with absolute alcohol and the alcohol extract submitted to fractional crystallisation. The sole product isolated was unchanged dibenzyl ketone semioxamazone. The residue left after the alcohol extraction was identified as a mixture of oxamide and cyclic hydrazide of oxalic acid in the usual way.

PART VI.

ACTION OF β.DIKETONES ON SEMIOXAMAZIDE.

Acetyl Acetone:

Two gram. of semioxamazide were heated with $2\frac{1}{2}$ gram. of acetyl acetone in absolute alcohol for one hour. The mixture was then filtered and the insoluble portion purified by boiling for some time with acetone, to remove unchanged semioxamazide, washed with absolute alcohol and finally recrystallised from water. Analysis indicated that this product was the disemioxamazone of acetyl acetone. (Found: N = 31.0, 30.9 per cent, C $H_{14}O_4N_6$ requires N = 31.1 per cent).

The filtrate obtained after separating the insoluble product was evaporated under reduced pressure at ordinary temperatures. When nearly all the alcohol had been removed another product began to crystallise in square prisms, M.P. 133-135°, recrystallised from alcohol/

alcohol - M.P. 133-135°. This was identified by analysis as the mono semioxamazone of acetyl acetone (Found - N = 23.0 per cent. $C_7H_{11}O_3N_3$ requires N - 22.7 per cent).

The above experiment was repeated but with the addition of a little iodine to the reaction mixture and heating was continued for half an hour. As before the disemioxamazone was obtained as an insoluble product and was filtered off. The filtrate on cooling deposited a crop of long prismatic needles, m.p. 113-115°, recrystallised from alcohol. m.p. 115°. This substance was analysed and found to have a nitrogen content of 12.40. 12.36 per cent but it has not yet been identified. From the mother liquor on evaporation under reduced pressure at ordinary temperatures the mono semioxamazone of acetyl acetone was obtained as before.

APPENDIX.

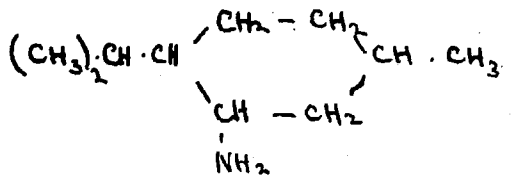
PREPARATION OF SEMIOXAMAZIDE.

The semioxamazide used in this research was prepared by the original method of Kerp and Unger (Ber. 30. P. 587). To a solution of 9 gram. caustic potash in 100 ccs of water was added 10 gram. of finely powdered hydrazine sulphate, followed by 100 ccs of 95 per cent alcohol, which achieved the purpose of throwing out of solution the potassium sulphate formed, and this, after well stirring was filtered off. The filtrate containing the hydrazine was mixed with 9 grams of powdered oxamethane, and the whole heated on a water bath until a clear solution resulted; on allowing this mixture to cool slowly, crystals of semi-oxamazide separated; these are filtered off, dried on a tile, and recrystallised from boiling water, from which they separate in small shining plates, melting at 221-222°.

Semioxamazide/

Semioxamazide is readily soluble in hot water and in acids and alkalies, but is insoluble in alcohol or ether.

PREPARATION of l. MENTHYLAMINE.



I. Preparation of l. Menthone from l. menthol:

Beckmann. ann. 289.250. 325 (1889).

The l. menthol was oxidised to l.menthone by means of potassium dichromate in sulphuric acid. The oxidising mixture was made by dissolving 60 grams. (1 Mol.) of potassium dichromate and 50 gram. ($2\frac{1}{2}$ mols.) of concentrated sulphuric acid in 300 gram. of water at a temperature of 30°. The l.menthol (45 grams.) was then added whereupon the colour of the mixture became a deep black owing to the formation of a chromium compound. When this mixture was shaken the temperature began to rise and at 53° a softening of the menthol indicated that oxidation had begun. At this stage of/

of the preparation it is necessary to keep the temperature below 55° otherwise some of the "d" isomer may be formed. After about 45 minutes the oxidation was complete and the l.menthone had formed a brown oily layer on the surface of the mixture. This was then extracted with ether and the ethereal extract washed with water and dilute caustic soda until a clear solution was obtained.

For the final purification steam distillation was resorted to, the l.menthone being introduced to the distilling flask at the same rate as it distilled, thus avoiding large excess in contact with the boiling water. The oily layer in the distillate was then extracted and dried over anhydrous sodium sulphate.

Preparation of l. Menthoneoxime:

In this preparation 20 parts of l.menthone (1 mol) were/

were dissolved in $2\frac{1}{2}$ times this quantity of 90% alcohol and 12 parts (1.3 mol.) of hydroxylamine hydrochloride added. A little more than the calculated quantity of sodium bicarbonate was then added in small quantities at a time and the mixture then allowed to stand in ice overnight. The oxime separated as a solid mass and was filtered off and pressed on a porous plate to free it from adhering liquid. On recrystallis-:ing from dilute alcohol a product was obtained M.P.58°.

Reduction of the l. menthone oxime:

Wallach Ann. 276. 1893 P. 276.

60 gram. of the oxime were dissolved in 450 ccs absolute alcohol and then heated to boiling on the water bath. To the boiling liquid 90 gram. of sodium were then added in small pieces at a time. The sodium was introduced through the upright limb of a Y tube, to the sloping arm of which a condenser was attached/

attached. Towards the end of the operation as sodium ethoxide began to separate a little more alcohol was added as required. From time to time the mixture was tested for oxime by withdrawing a few ccs, heating this with dilute hydrochloric acid and then adding Fehling's solution. The presence of unchanged oxime was shown by immediate reduction.

When the reduction was completed the mixture was distilled in steam. Alcohol and l. menthylamine passed over at first and a clear solution was obtained but after a time the distillate became turbid and so the receiver was changed. In the second fraction the l.menthylamine separated completely from the water on standing and was removed and dried over anhydrous sodium sulphate. It was then distilled in an atmosphere of purified hydrogen directly into a polarimeter tube and the rotation taken.

The/

The first fraction of the distillate was a dilute alcoholic solution of l.menthylamine. This solution was therefor just acidified with hydrochloric acid and the solvent evaporated off when l.menthylamine hydrochloride separated in fine needles. These yield the base on treatment with caustic soda.

The l.menthylamine obtained in this way was a colourless liquid B.P. 206.7. $[\alpha]_D^{11} = -39.0^\circ$.

Note: The value of $[\alpha]_D^{11}$ given by Wallach (loc.cit.) $= -38.47^\circ$ By Kenyon and Pickard (J.C.S. 107. 36. 50.55) $= -39.97^\circ$.

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