# THE ACTION OF AMINES ON 2-SUBSTITUTED SEMICARBAZONES

## and other papers.

by

JAMES CHAPMAN.

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# ABBREVIATIONS.

| | |
|---|---|
| A. | Liebig's Annalen der Chemie. |
| Ber. | Berichte der Deutschen chemischen Gesellschaft. |
| Bull.Soc.Chim. | Bulletin de la société chimique de Paris. |
| C. | Chemisches Zentralblatt. |
| C.r. | Comptes rendus de l'académie des sciences. |
| G. | Gazzetta chimica italiana. |
| J.A.C.S. | Journal of the American Chemical Society. |
| J.C.S. | Journal of the Chemical Society. |
| J.pr. | Journal für praktische Chemie. |
| J.Roy.Tech.Coll. | Journal of the Royal Technical College of Glasgow. |
| J.Russ.Phys.-Chem.Soc. | Journal of the Russian Physical-Chemical Society. |
| Monatsh. | Monatschefte für Chemie. |

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d.= dextro-rotatory.

l.= laevo-rotatory.

r.= racemic.

n.= normal.

sym.= symmetrical.

M.Pt. = Melting-point.

B.Pt. = Boiling-point.

Mol. Wt. = Molecular Weight.

Ph.= $C_6H_5$.

## GENERAL INTRODUCTION AND SUMMARY.

This work is divided into three parts. The results obtained from the first two parts were almost entirely negative and they have been treated more briefly than the third part, which describes the action of amines on 2-substituted semicarbazones. The investigations are described, however, in the order in which they were carried out, as otherwise the connection between the different sections would not be obvious.

This introduction is intended merely to indicate the contents of each part and the circumstances which led to a change in the line of research at the ends of the first and second parts.

The first part describes some attempts which were made to resolve racemic benzoin into its optically active components. Various methods were used, advantage being taken of the fact that benzoin reacts quite readily with hydrazine to form a hydrazone. A basic group is thus introduced with which optically active acid substances might be expected to react. Such substances as d.camphor sulphonic acid and d.bromcamphor sulphonic chloride were used. It was also attempted to make benzoin react with l.menthyl hydrazine and with d.camphor hydrazone. The laevo-rotatory aldehydic glucoside, helicin, was also employed. For different reasons these methods were unsuccessful.

In the meantime, however, the resolution of benzoin had been successfully completed by Wilson and Hopper[1]. This was done by means of an optically active semicarbazide, δ-α-phenylethyl-semicarbazide which they had previously described[2].

It was then decided to investigate the action of δ(α-phenylethyl)semicarbazide on several other racemic substances closely related to benzoin. This constitutes the second part of the work.

The substances used were methyl-benzoin, furoin, piperonyloin and anisoin. Unfortunately none of these substances gave a crystalline product with δ(α-phenylethyl)semicarbazide such as was obtained with benzoin. Furoin and piperonyloin were too easily oxidised even by the atmosphere, while the other reactions yielded only oily and resinous products. Since no crystalline products were obtained this section of the

[1] J.C.S. 1928,2483.

[2] Wilson, Hopper & Crawford, J.C.S. 1922,121,866.

work was abandoned at this point.

It seemed possible that, if an optically active semicarbazide could be prepared, similar to $\delta(\alpha$-phenylethyl)semicarbazide but having a greater molecular weight, it might yield higher melting products with substances of the benzoin group. It was desired therefore, to substitute some additional group of atoms at a certain point in the $\delta(\alpha$-phenylethyl)semicarbazide molecule.

This substance, $\delta(\alpha$-phenylethyl)semicarbazide, was prepared by the interaction of $\alpha$-phenyl-ethylamine and acetone semicarbazone with subsequent loss of acetone by hydrolysis[1], thus,

$$(CH_3)_2C{:}N.NH.CO.NH_2 \quad + \quad NH_2CH(Ph)CH_3$$
$$= \quad (CH_3)_2C{:}N.NH.CO.NHCH(Ph)CH_3 \quad + \quad NH_3$$

$$(CH_3)_2C{:}N.NH.CO.NHCH(Ph)CH_3 \quad + \quad H_2O$$
$$= \quad (CH_3)_2C{:}O \quad + \quad NH_2NH.CO.NHCH(Ph)CH_3$$

The most obvious point at which to introduce the new group appeared to be the $\beta$- or 2-position

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[1] Wilson, Hopper and Crawford, J.C.S.1922,121,866.

of the semicarbazone[1]. It was unlikely that a group introduced in that position would prevent the reaction of the active semicarbazide with a ketonic group such as that of the benzoins. Indeed, a number of ketonic semicarbazones are known having groups substituted in the 2-position.

In order to prepare this new active semicarbazide it would have been necessary to start with a 2-substituted semicarbazone and to act on it with active $\alpha$-phenylethylamine.

Although several 2-substituted semicarbazones had been prepared, as is stated above, the reactions of these substances with amines had not been investigated. The reactions of unsubstituted semicarbazones with amines was first investigated by Borsche[2]. He used only aromatic amines and it was the extension of his work to include aliphatic amines and optically active amines which led to the preparation of optically active $\delta(\alpha$-phenylethyl)semicarbazide[3].

[1] The system used is, $NH_2NH.CO.NH_2$

$$\begin{array}{cccc} \alpha & \beta & & \delta \\ 1 & 2 & & 4 \end{array}$$

[2] Ber.1901,<u>34</u>,4297:1904,<u>37</u>,3177:1905,<u>38</u>,831.

[3] Page 3, and J.C.S.1925,<u>127</u>,103.

It was resolved, therefore, to investigate the reactions of 2-substituted semicarbazones with various amines and possibly to obtain another optically active semicarbazide.

These investigations constitute the third and most important part of the work.

The Appendix contains descriptions of some work which was carried out although not on the direct line of research. Some preparations are also included in cases where reference is made to these in the text. In many of these preparations, modifications have been introduced, usually with a view to increasing the yield.

# PART I.

## SOME ATTEMPTS TO BRING ABOUT THE RESOLUTION OF RACEMIC BENZOIN.

# PART I.

## INTRODUCTION.

### Summary of various methods of resolving racemic compounds.

Since the phenomenon of optical activity was first observed, the resolution of racemic substances into their optically active components has attracted many investigators with the result that a large amount of experimental work has been done on this subject. Most of the methods adopted depend ultimately on the process of fractionation by crystallisation for the separation of the enantiomorphs.

The most important contribution to the subject was the work of Pasteur on the resolution of acids and particularly of tartaric acid. He brought about this resolution by several different methods. The one of most general interest is that in which he combined the racemic acid with an optically active base.

In this reaction two salts are formed. If the base used is laevo-rotatory, these would be (a) d.acid-l.base, and (b) l.acid-l.base. These two salts are not enantiomorphous, that is, their molecules do not possess the relationship of an object to its mirror image, and as they probably show some difference of solubility, they may be separated by fractional crystallisation.

This method has been modified and extended in many different ways and its general principle can be applied to the resolution of almost any class of racemic compound. Pasteur and other workers resolved many acids in this way using as optically active bases the alkaloids, cinchonine, quinine, strychnine and brucine.

Racemic bases can be resolved in the same way by combination with an optically active acid. In this case, if a dextro-rotatory acid be used, the two salts formed would be (a) d.acid-l.base, and (b) d.acid-d.base, and these might then be separated by fractional crystallisation. In this way ethyl-piperidine and coniine were resolved using d.tartaric acid[1].

[1] Ladenburg, A.1888,247,85.

Dextro-tartaric acid was used successfully in a number of cases. Pope and Peachey[1], however, pointed out a disadvantage attached to the use of this acid. Tartaric acid has a small dissociation constant and, therefore, would form stable salts only with strong bases. In order to bring about the resolution of weak bases, it was necessary to find an optically active acid having a much greater dissociation constant. They found a suitable acid in d.camphor sulphonic acid, but showed that d.bromcamphor and d.chlorcamphor sulphonic acids were preferable in many cases. Camphor sulphonic acid was used with success in the resolution of tetra-hydroquinaldine[2] and camphoroxime[3]. Reychler[4] resolved tetrahydropapaverine by means of d.bromcamphor sulphonic acid but found that d.camphor sulphonic acid gave only a syrupy mixture.

Pope and Peachey[2] made some interesting observations on the resolution of externally compensated basic substances by optically active acids. Taking the case of an attempted resolution of a racemic base dlB

[1] Pope & Peachey, J.C.S.1898,73,893.

[2] Pope & Peachey, J.C.S.1899,75,1066.

[3] Pope, J.C.S.1899,75,1105.

[4] Bull.Soc.Chim.,1898,(iii),19,120.

by means of a dextro-rotatory acid dA, they pointed out that the disadvantage of the ordinary method of separating by fractional crystallisation is that the difference of solubilities of the two salts dB.dA and lB.dA is not sufficient to permit of the salts being isolated in a pure state. The solubilities of the salts dB.dA and lB.dA of a dextro-rotatory acid with a racemic base would hardly be expected to differ much since solubility is partly a function of the chemical composition of the salts. If, however, the salt lB.dA is the less soluble of the two, and if only sufficient of the acid dA, necessary for formation of this salt is added, the balance of acid required to dissolve the base being made up by adding the requisite amount of an inactive acid such as hydrochloric acid which forms comparatively soluble salts with the base, then it would be expected that the greater part of the lB would separate as the sparingly soluble salt lB.dA while the mother liquor would contain dB.HCl. Pope and Peachey obtained very good results by the adoption of this method. The principle could also be modified to suit particular cases. Thus in one case they mixed hot aqueous solutions of one molecular proportion of ammonium d.bromcamphor sulphonate and of two molecular proportions of racemic tetrahydroquinaldine hydrochloride. On cooling, they obtained l.tetrahydroquinaldine-d.brom-camphor sulphonate almost pure.

A further extension of this general method of resolving racemic compounds was made when Neuberg suggested the use of an optically active hydrazine as a means of resolving racemic aldehydes, ketones and acids. He experimented with the sugars and successfully resolved r.arabinose both by means of d.phenylamylhydrazine[1] and by l.menthylhydrazine[2].

Fundamentally this method is similar to the original method of Pasteur. Thus, if we start with a racemic ketone dlR:CO, and an optically active hydrazine dR'NH.$NH_2$ we should obtain two compounds dR:C:N.NHdR' and lR:C:N.NHdR'. It should now be possible to separate these substances by fractional crystallisation and to liberate the enantiomorphous ketones by hydrolysis.

Recently, an optically active semicarbazide was also used successfully for the resolution of a racemic ketone when Hopper and Wilson[3] brought about the resolution of benzoin by means of $\delta$($\alpha$-phenylethyl)semi-

[1] Neuberg & Federer, Ber.1905,38,868.

[2] Neuberg, Ber. 1903,36,1192.

[3] Hopper & Wilson, J.C.S.1928,2483.

-carbazide.

Another modification was introduced by Erlenmeyer. He suggested that racemic amines might be resolved by condensation with an optically active aldehyde. He used this method successfully in bringing about the resolution of r.isodiphenyl-oxy-ethylamine[1]. The aldehyde used was the glucoside, Helicin. The reaction can be represented by the equation,

$$\mathrm{Ph.CH(OH)CH(NH_2)Ph} + \mathrm{C_6H_{11}O_5.O.C_6H_4.CHO}$$
$$= \mathrm{Ph.CH(OH)CH(Ph)N{:}CH.C_6H_4.O.C_6H_{11}O_5.} + \mathrm{H_2O}$$

This product was then fractionated as before and the active forms of the amine liberated by hydrolysis with dilute hydrochloric acid.

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[1] Erlenmeyer, Ber.1903,36,976.

# THEORETICAL.

This work consisted of a series of attempts to resolve racemic benzoin,

Ph.CH(OH).CO.Ph.

Various methods were used, all of which depended primarily on the principles outlined in the introduction.

It will be seen that the investigations of these methods were not carried to completion in every case. When it became evident that any particular method was going to prove unsuitable, it was abandoned even if it were not quite clear what course the reaction had taken.

The first methods required that a basic group should be introduced to the benzoin molecule, which group might then be made to react with optically active acid substances. For this reason the racemic benzoin was converted to benzoin hydrazone,

$Ph.CH(OH).C(Ph):N.NH_2$

## Benzoin hydrazone + d.bromcamphor sulphonic chloride.

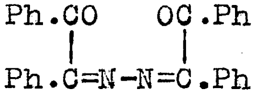
The first reaction attempted was that of benzoin hydrazone with the chloride of d.bromcamphor sulphonic acid. It was expected that this reaction would go according to the equation,

$$\begin{aligned} & \mathrm{Ph.CH(OH).C(Ph){:}N.NH_2} \quad + \quad \mathrm{C_{10}H_{14}OBr.SO_2Cl} \\ = \quad & \mathrm{Ph.CH(OH).C(Ph){:}N.NHSO_2.C_{10}H_{14}OBr} \quad + \quad \mathrm{HCl} \end{aligned}$$

This product would consist, of course, of equal numbers of molecules containing d.benzoin hydrazone united with d.bromcamphor sulphonic acid and l.benzoin hydrazone united with d.bromcamphor sulphonic acid. It was intended, if the reaction went as expected, that these should then be separated by fractional crystallisation.

The reaction was tried first using ether as solvent, pyridine being added to take up the hydrochloric acid which would be liberated. Equimolecular proportions of the substances were dissolved separately in ether without warming and the solutions were then mixed.

A red oil which separated after standing for a day, was the only product. The reaction was repeated using benzene as solvent. There was no evidence of reaction on standing in the cold and the solution was warmed. Pyridine hydrochloride separated, and on filtering this off, and concentrating the mother liquor, a yellowish brown substance was obtained. This appeared to be a substance which Curtius and Blümer obtained by heating benzoin hydrazone in alcoholic solution[1]. They describe it as "Bisbenzoylphenylazimethylene" and assign to it the formula,



$$\begin{array}{ccc} \text{Ph.CO} & & \text{OC.Ph} \\ | & & | \\ \text{Ph.C} & \text{=N-N=} & \text{C.Ph} \end{array}$$

No other products were isolated.

## <u>Sodium derivative of benzoin hydrazone + d.bromcamphor sulphonic chloride.</u>

The use of the sodium derivative of benzoin hydrazone avoided the necessity of having pyridine present as sodium chloride would be split off instead of hydrochloric acid. The reaction can be represented by this

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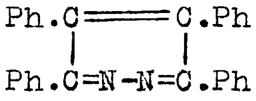
[1] Curtius & Blümer, J.pr.1895,(2),52,124.

equation,

$$\begin{aligned} & \mathrm{Ph.CH(OH).C(Ph){:}N.NHNa} \quad + \quad \mathrm{C_{10}H_{14}OBr.SO_2Cl} \\ = \quad & \mathrm{Ph.CH(OH).C(Ph){:}N.NHSO_2.C_{10}H_{14}OBr} \quad + \quad \mathrm{NaCl} \end{aligned}$$

Sodium chloride was obtained as expected but the only other solid product obtained consisted of a small quantity of clear crystals which appeared to melt with decomposition at about 250°. The residue was sticky and did not yield any other pure products. The substance which melted about 250° may have been the substance which Curtius and Blümer[1] obtained from benzoin hydrazone having the formula,



They stated its M.Pt. to be 246°. I obtained this substance, however, and found its M.Pt. to be 249°. A mixture of this substance with the product of the reaction showed no depression of M.Pt. but, on the other hand, the former substance, when heated alone to its M.Pt. showed no sign of decomposition.

The product from the reaction was not obtained in sufficient quantity for analysis and may

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[1] Curtius & Blümer, J.pr.1895,(2),52,124.

not have been quite pure.

## Benzoin hydrazone + d.camphor sulphonic acid.

The next optically active substance which was tried with benzoin hydrazone was d.camphor sulphonic acid. This, of course, was just a slight variation on the first reaction.

Equimolecular proportions of benzoin hydrazone and d.camphor sulphonic acid were dissolved in absolute alcohol and left to stand in the cold. Nothing having separated, the solution was taken to dryness when a mixture was obtained. This was found to consist of two substances, a yellow, crystalline solid M.Pt. 202°, and a white substance which decomposed between 265-270° and was difficult to purify.

The yellow substance M.Pt.202° was the same as that obtained from the reaction with d.bromcamphor sulphonic chloride, namely "Bisbenzoylphenylazimethylene".

The nitrogen content for the white solid was fairly near the theoretical figure for benzoin-hydrazone-d.camphor sulphonate. An attempt to hydrolyse this substance, however, gave no benzoin. The substance was boiled with different strengths of hydrochloric acid from normal up to concentrated acid. It seems unlikely that benzoin was present as it would certainly have separated from the solution had it been liberated. Benzoin hydrazone itself is easily hydrolysed with liberation of benzoin. It is possible, though unlikely, that the benzoin might be reduced during hydrolysis to hydrobenzoin which is more soluble. In any case, this method did not promise to be satisfactory as the product was difficult to crystallise and probably could not have been fractionated. Even had this been successful, it is necessary that the substance should be easily hydrolysed with liberation of the active ketone.

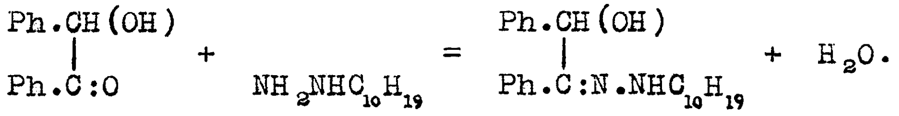
This reaction was repeated using two molecules of benzoin hydrazone to one molecule of d.camphor sulphonic acid. This was done in accordance with the methods of Pope and Peachey described on pages 8 and 9. It was hoped that either d.benzoin hydrazone or l.benzoin hydrazone might react more readily than the other giving a product which, if not pure would at least contain a large proportion of either d.benzoin-hydrazone-d.camphor sulphonate or l.benzoin-hydrazone-d.camphor sulphonate.

The only difference, however, in the

result was an increased yield of the substance M.Pt.202°.

## Benzoin + l.menthyl-hydrazine.

Neuberg and Federer[1] brought about the resolution of r.arabinose by means of optically active hydrazines. It was now attempted to adapt their method to the resolution of benzoin using l.menthyl-hydrazine. It was expected that this would react with benzoin according to the equation,



$$\begin{array}{l}\text{Ph.CH(OH)}\\ \;\;\;|\\ \text{Ph.C:O}\end{array} + NH_2NHC_{10}H_{19} = \begin{array}{l}\text{Ph.CH(OH)}\\ \;\;\;|\\ \text{Ph.C:N.NHC}_{10}\text{H}_{19}\end{array} + H_2O.$$

The product of this reaction would, of course, contain equal quantities of d.benzoin-l.menthyl-hydrazone and l.benzoin-l.menthyl-hydrazone. It was intended to separate these substances as before, by fractional crystallisation and then to recover the optically active forms of benzoin from the separate fractions by means of acid hydrolysis.

It was found, however, that these substances would not react, the benzoin being recovered unchanged. l.Menthyl-hydrazine was used in the form

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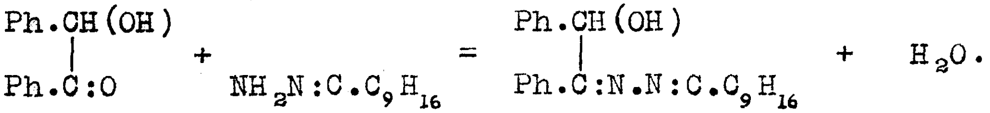
[1] Neuberg & Federer, Ber.1905,38,868.

of the hydrochloride and the reaction was carried out using pyridine as solvent.

Benzoin + d.camphor hydrazone.

It was next attempted to make benzoin react with d.camphor hydrazone. It was hoped that these substances would react in this way,



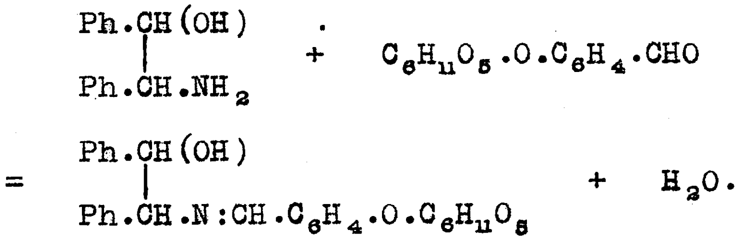
$$\begin{array}{l}\mathrm{Ph.CH(OH)}\\ \quad|\\ \mathrm{Ph.C{:}O}\end{array} + \mathrm{NH_2N{:}C.C_9H_{16}} = \begin{array}{l}\mathrm{Ph.CH(OH)}\\ \quad|\\ \mathrm{Ph.C{:}N.N{:}C.C_9H_{16}}\end{array} + \mathrm{H_2O}.$$

The subsequent treatment of this substance would then follow the course described under the previous reaction.

Benzoin and camphor hydrazone were first heated together in boiling alcohol for 9 hours. It was found, however, that under these conditions no reaction took place, the benzoin being recovered unchanged. It was decided, therefore, to increase the reaction temperature and n.butyl alcohol was selected as the new solvent. At the boiling-point (117°), decomposition apparently took place, ammonia being given off. On reducing the temperature to 100° ammonia was still being evolved and the method was then abandoned.

## Benzoin hydrazone + Helicin.

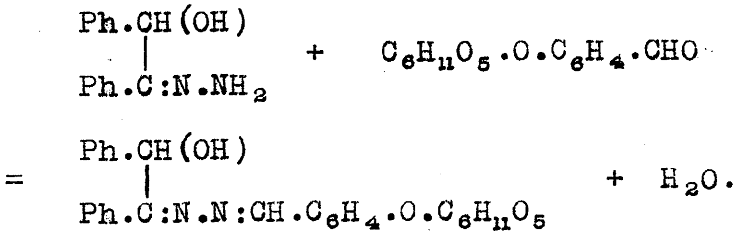
The next method adopted was that used by Erlenmeyer[1] for the resolution of racemic amines by condensation with an optically active aldehyde. He found that iso-diphenylhydroxyethylamine reacted in this way with helicin,



$$\begin{array}{l} Ph.CH(OH) \\ \quad | \\ Ph.CH.NH_2 \end{array} + C_6H_{11}O_5.O.C_6H_4.CHO$$

$$= \begin{array}{l} Ph.CH(OH) \\ \quad | \\ Ph.CH.N{:}CH.C_6H_4.O.C_6H_{11}O_5 \end{array} + H_2O.$$

It was hoped that benzoin hydrazone would react in a similar way with helicin, thus,



$$\begin{array}{l} Ph.CH(OH) \\ \quad | \\ Ph.C{:}N.NH_2 \end{array} + C_6H_{11}O_5.O.C_6H_4.CHO$$

$$= \begin{array}{l} Ph.CH(OH) \\ \quad | \\ Ph.C{:}N.N{:}CH.C_6H_4.O.C_6H_{11}O_5 \end{array} + H_2O.$$

However, the product of the reaction of benzoin hydrazone with helicin was obtained in a jelly-

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[1] See page 11.

-like form. Attempts were made to crystallise it from many different solvents and mixtures of solvents, but it resisted all such treatment. Indeed, after standing for more than a year it still retained its jelly-like form. A small quantity was ultimately obtained in a solid form after repeated purification using a benzene-alcohol mixture. It was very difficult to purify, however, and the same method applied to the bulk of the substance proved a failure. Under these conditions, fractionation by crystallisation was impossible and this method was therefore abandoned.

# EXPERIMENTAL.

## Preparation of benzoin hydrazone.

Benzoin hydrazone was prepared according to the method of Curtius and Blümer. It was found that a slight modification of this method gave improved results[1].

## Benzoin hydrazone + d.bromcamphor sulphonic chloride.

### (a) In ether, in the cold.

The reaction was tried first using ether as the solvent. Pyridine was used to take up the hydrochloric acid which is liberated. Equimolecular quantities of benzoin hydrazone, d.bromcamphor sulphonic chloride and pyridine were used.

Benzoin hydrazone was dissolved in dry ether and the requisite quantity of pyridine added. The bromcamphor sulphonic chloride was dissolved separately in ether and the two solutions were then mixed. No heat was used in making either of these solutions. After standing in the cold for a day, a red, oily substance

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[1] See Appendix page 114.

separated. This substance was insoluble in water, soluble in alcohol or boiling ether and insoluble in petroleum ether. It could not be crystallised from any mixtures of the common solvents.

(b) In benzene, in the cold.

The reaction was repeated in exactly the same way except that dry benzene was used as the solvent instead of ether. However, after standing for several days in the cold there was no evidence of a reaction having taken place.

(c) In benzene, at its B.Pt.

The solution used in (b) was then heated to its B.Pt. After boiling for about an hour a solid substance began to separate. This was shown to be pyridine hydrochloride. The solution was boiled for 5 hours and the pyridine hydrochloride was then filtered off. After concentrating the filtrate, and allowing it to stand overnight, it was found that a yellow-brown, crystalline substance had separated. This substance was soluble in alcohol, insoluble in ether or light petroleum. On recrystallising from alcohol, it was obtained as small, yellow crystals. The M.Pt. was 202°.

Curtius and Blümer[1] obtained a yellow

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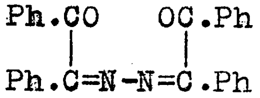
[1] See page 14.

substance M.Pt. 202°, on heating benzoin hydrazone. They give it the formula,



$$\begin{array}{c} Ph.CO \quad OC.Ph \\ | \qquad\quad | \\ Ph.C{=}N{-}N{=}C.Ph \end{array}$$

, $C_{28}H_{20}O_2N_2$ .

Found - - - - N = 7.08%

$C_{28}H_{20}O_2N_2$ requires N = 6.73%

## Sodium derivative of benzoin hydrazone + d.bromcamphor sulphonic chloride.

The preparation of a sodium derivative of benzoin hydrazone was described by Curtius and Blümer[1]. In this case, however, the sodium derivative was not isolated, the reaction being carried out in this way.

1.5 gms. of benzoin hydrazone was dissolved in absolute alcohol, and an equimolecular quantity of sodium also dissolved in absolute alcohol, was added. This solution was then mixed with a solution of 2 gms. of d.bromcamphor sulphonic chloride in absolute alcohol. In each case the minimum quantity of alcohol, necessary to bring about solution, was used.

After standing overnight, it was found that some sodium chloride had separated and this was then

[1] Curtius & Blümer, J.pr.1895,(2),52,128.

filtered off. The filtrate was left to stand for some days. Nothing separated and the alcohol was then removed in the vacuum desiccator. The residue, which was sticky, was pressed on a porous plate and again placed in an evacuated desiccator. After two days, the yellow-brown solid which remained on the plate was scraped off. This substance was then heated under reflux with carbon tetrachloride in which it was slightly soluble. On cooling the solution obtained, and adding ether , a solid substance came out of solution.

This substance, of which there was only a minute quantity, separated from the solution in the form of colourless needles. It was soluble in alcohol, slightly soluble in benzene, carbon tetrachloride and carbon disulphide, and insoluble in ether and light petroleum. On heating, it did not give a definite M.Pt. but decomposed gradually as the temperature approached 250°. One of the decomposition products of benzoin hydrazone is a substance M.Pt. 249°. A mixture of this substance with the product of this reaction showed no depression of M.Pt. The mixture melted gradually with signs of decomposition up to 249°.

However, the identity of this substance was not established. The quantity obtained was not sufficient to allow further purification or analysis. As this method was not at all promising, it was abandoned at this point.

## Benzoin hydrazone + d.camphor sulphonic acid.

This reaction was carried out in absolute alcohol which had been carefully dried by boiling for two days with metallic calcium. Equimolecular quantities of benzoin hydrazone and d.camphor sulphonic acid were dissolved in this alcohol in the cold. As before, the minimum quantity of solvent was used. These solutions were mixed and the mixture was left to stand overnight. Nothing having separated, it was then taken to dryness under reduced pressure. The residue consisted of a yellow solid. This was found to be a mixture which was separated into its components by means of benzene. On shaking with benzene, part of the mixture dissolved, leaving a pure white residue. The benzene solution was taken to dryness, and the residue, after recrystallising from alcohol, was found to consist of yellow crystals which had a M.Pt. 202°. This substance was shown to be identical with the "Bisbenzoylphenylazimethylene" obtained from the reaction with d.bromcamphor sulphonic chloride.

The white substance was dissolved in alcohol-benzene mixture and precipitated with petroleum ether. It melted with decomposition between 265-270°.

Found - - N = 5.86, 6.17%.

Benzoin hydrazone camphor sulphonate, $C_{24}H_{30}O_4SN_2$

requires N = 6.31%

An attempt was made to hydrolyse this substance. The substance was boiled first with normal hydrochloric acid. After several hours, however, nothing had separated and the concentration of the acid was therefore increased. There was no obvious result. Greater concentrations were used till at length, a portion of the substance was boiled with concentrated hydrochloric acid. Even this, however, did not produce benzoin and it was therefore concluded that the benzoin hydrazone molecule had undergone decomposition during the reaction.

The reaction was repeated using the substances in the proportion, two molecules of benzoin hydrazone to one molecule of d.camphor sulphonic acid. The same substances were obtained as before, the only difference being an increased yield of the substance M.Pt.202°.

## Benzoin + l.menthyl-hydrazine.

l.Menthyl-hydrazine was prepared according to the method of Kishner[1]. Menthyl-hydrazine is obtained by this method in the form of the hydrochloride.

1.6 gms. of menthyl-hydrazine hydrochloride and 1.25 gms. of benzoin were dissolved in dry pyridine and the mixture was then left to stand for 14 days. The pyridine which was used had previously been distilled over solid caustic potash. After standing for 14 days, nothing had separated and the solution was then taken to dryness under reduced pressure.

The residue was washed well with water and the resulting red mass was then dried in an evacuated desiccator. It was next treated with petroleum ether to which had been added a small quantity of ether. A large part of the substance did not dissolve readily and remained as a brown solid. This was recrystallised several times from alcohol. Its M.Pt. was then 134°. This substance was shown by comparison to be benzoin. As practically all the benzoin used, was recovered, it was evident that no reaction had taken place.

[1] Kishner, J.pr.1901,64,113.

## Benzoin + d.camphor hydrazone.

Camphor hydrazone was prepared by the method described by Kishner[1]. Equal parts by weight, of camphor and hydrazine hydrate (50%), are boiled for 170 hours in alcoholic solution. The alcohol is then distilled off on the water bath and the camphor hydrazone is distilled under reduced pressure.

Equimolecular quantities of benzoin and camphor hydrazone were dissolved in absolute alcohol and boiled under reflux for about 9 hours. It was found, on cooling at the end of that time, that benzoin separated from the solution, no reaction having taken place. It was then decided to try the reaction at a higher temperature and n.butyl alcohol was chosen as the solvent for this purpose. The alcohol was therefore distilled off and the residue dissolved in n.butyl alcohol. The reaction mixture was then heated to the boiling point of that solvent (117°). Some decomposition took place at that temperature, however, ammonia being given off. The temperature was then reduced to 100°, but on heating at this temperature for some time, ammonia was still being evolved and this method was then abandoned.

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[1] Kishner, J.Russ.Phys.-Chem.Soc.43,582-593.
C.1911,II,363.

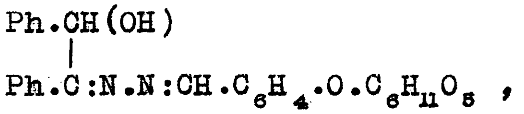
## Benzoin hydrazone + Helicin.

Equimolecular quantities of benzoin hydrazone and helicin were dissolved, the benzoin hydrazone in alcohol and the helicin in aqueous alcohol, and the solutions were mixed.

A yellowish-white substance separated almost immediately. Attempts to purify this substance by recrystallisation from alcohol gave a jelly-like substance. Precipitation with ether or petroleum from benzene gave the same result. Many other solvents and combinations of solvents were tried but these efforts met with little success. Aqueous alcohol (25% alcohol), gave slightly better results, and a benzene-alcohol mixture was also more successful than most of the others. A small quantity was ultimately obtained from the latter mixture as a white solid M.Pt.208°. An estimation of nitrogen was carried out on a portion which was first recrystallised from aqueous alcohol, then dried for a considerable time in an evacuated desiccator and finally recrystallised from benzene-alcohol mixture. It is doubtful, however, whether this substance was pure.

Found - - - - - - - N = 5.05%.

The substance which it was hoped to obtain has this formula,



$$\begin{array}{l}\mathrm{Ph.CH(OH)} \\ \quad | \\ \mathrm{Ph.C{:}N.N{:}CH.C_6H_4.O.C_6H_{11}O_5}\end{array}, \qquad \mathrm{C_{27}H_{28}O_7N_2}.$$

$C_{27}H_{28}O_7N_2$ requires $N = 5{\cdot}69\%$.

Little importance can be attached to the result of this estimation.

When these methods of purification were applied to the bulk of the substance they were found to be quite unsuccessful, the substance being obtained again as a jelly. After standing for almost two years in an open flask this substance still retained its jelly-like form. Attempts were made to obtain a rough fractionation by benzene-alcohol and aqueous alcohol but these were soon found to be quite hopeless.

# PART II

## THE ACTION OF $\delta(\alpha$-PHENYLETHYL)SEMICARBAZIDE ON SOME COMPOUNDS RELATED TO BENZOIN.

# PART II.

## INTRODUCTION.

The resolution of benzoin by Hopper and Wilson[1] appears to be the first recorded instance of an optically active semicarbazide being used for the resolution of a racemic aldehyde or ketone. Other optically active semicarbazides have been prepared, for example, camphoryl-$\psi$-semicarbazide[2], but there is no evidence of its being used for the resolution of racemic compounds.

The semicarbazide which was successfully employed by Hopper and Wilson for the resolution of benzoin was $\delta(\alpha$-phenylethyl)semicarbazide,

$NH_2NH.CO.NHCH(Ph)CH_3$.

This was prepared[3] by heating acetone semicarbazone with $\alpha$-phenylethylamine, forming acetone-$\delta(\alpha$-phenylethyl)semicarbazone from which acetone was subsequently removed by acid hydrolysis. The following equations represent these reactions.

[1] Hopper & Wilson, J.C.S.1928,2483.

[2] Forster & Fierz, J.C.S.1905,87,722.

[3] Wilson, Hopper & Crawford, J.C.S.1922,121,866.

$$(CH_3)_2C{:}N.NH.CO.NH_2 \quad + \quad NH_2CH(Ph)CH_3$$
$$= \quad (CH_3)_2C{:}N.NH.CO.NH.CH(Ph)CH_3 \quad + \quad NH_3$$

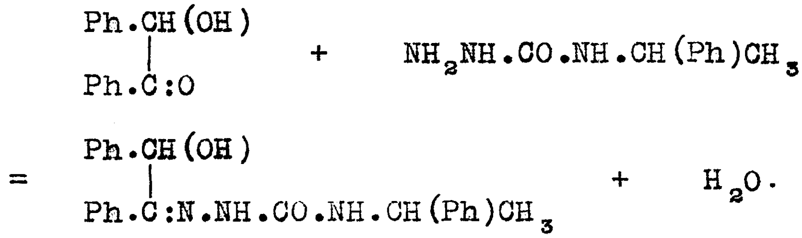
$$(CH_3)_2C{:}N.NH.CO.NH.CH(Ph)CH_3 \quad + \quad H_2O$$
$$= \quad NH_2NH.CO.NH.CH(Ph)CH_3 \quad + \quad (CH_3)_2C{:}O$$

It was found possible to obtain the hydrochloride of either the d. or the l.modification of $\delta$($\alpha$-phenylethyl)semicarbazide by using the appropriate active form of $\alpha$-phenylethylamine.

The object of this work was to find whether $\delta$($\alpha$-phenylethyl)semicarbazide would react in a similar manner with some other compounds related to benzoin. It was hoped that the resolution of the racemic forms of these substances might thus be effected.

# THEORETICAL.

Neuberg[1] took advantage of the reaction of ketones with hydrazine in bringing about the resolution of racemic sugars. Hopper and Wilson utilised the similar reaction of ketones with semicarbazide when they resolved benzoin by means of δ(α-phenylethyl)semicarbazide. These substances react in this way,



$$\begin{array}{l}\mathrm{Ph.CH(OH)}\\ \quad|\\ \mathrm{Ph.C{:}O}\end{array} \quad + \quad \mathrm{NH_2NH.CO.NH.CH(Ph)CH_3}$$

$$= \quad \begin{array}{l}\mathrm{Ph.CH(OH)}\\ \quad|\\ \mathrm{Ph.C{:}N.NH.CO.NH.CH(Ph)CH_3}\end{array} \quad + \quad \mathrm{H_2O}.$$

Before proceeding with the resolution of benzoin, Hopper and Wilson found, by experimenting with racemic δ(α-phenylethyl)semicarbazide and benzoin, that the reaction took place most smoothly in pyridine solution. Alcohol was also used but was not so satisfactory. There are four possible stereo-isomeric modifications of the product of this reaction. When pyridine was used as solvent three of the modifications were isolated.

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[1] See Part I, page 10.

This reaction was then repeated using dextro-rotatory $\delta(\alpha$-phenylethyl)semicarbazide. Pyridine was used as solvent as before, the hydrochloride of the base being used. This time, only one of the modifications was obtained in a crystalline form, the others being oily and very soluble. This substance was laevorotatory and, on hydrolysis with oxalic acid, liberated d.benzoin.

Similarly, by combining l.$\delta(\alpha$-phenylethyl) semicarbazide with r.benzoin, a dextro-rotatory semicarbazone was obtained, which yielded l.benzoin on hydrolysis.

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The reactions described here were carried out under the same conditions as were found to be satisfactory in the case of benzoin.

The substances used were methyl-benzoin, furoin, anisoin and piperonyloin. A series of experimental reactions was undertaken using racemic $\delta(\alpha$-phenyl-ethyl)semicarbazide hydrochloride. It was hoped that these reactions would follow the course represented by the general equation,

$$R.CH(OH).CO.R' \quad + \quad NH_2NH.CO.NH.CH(Ph)CH_3$$

$$= \quad R.CH(OH).C(R'):N.NH.CO.NH.CH(Ph)CH_3 \quad + \quad H_2O.$$

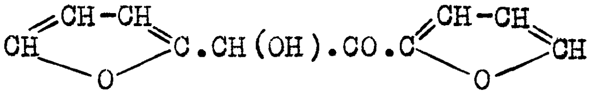
The results, however, were disappointing.

<u>Methyl-benzoin + $\delta(\alpha$-phenylethyl)semicarbazide.</u>

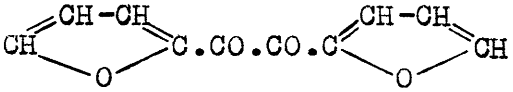
The first substance used was methyl-benzoin, $Ph.CH(OCH_3).CO.Ph$. From this reaction only an oily product was obtained.

<u>Furoin + $\delta(\alpha$-phenylethyl)semicarbazide.</u>

The next substance used was furoin,



This reaction gave a crystalline substance which, however, proved to be the diketone, furil,

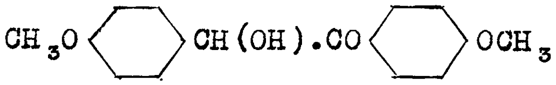


It was shown that the oxidation of the furoin to furil was not caused by the presence of $\delta(\alpha$-phenylethyl)semicarbazide since a solution of furoin in pyridine yielded furil after a short exposure to the atmosphere.

Fischer[1] showed that furoin in alcoholic solution containing a trace of sodium hydroxide, is very readily oxidised. It has not been observed before that pyridine has the same effect.

### Anisoin + δ(α-phenylethyl)semicarbazide.

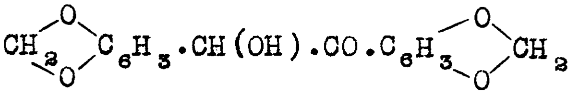
The third substance used was anisoin,



A solid was obtained which, however, was resinous in character. It melted at about 51° but could not be purified sufficiently for analysis.

### Piperonyloin + δ(α-phenylethyl)semicarbazide.

The next reaction tried was that of piperonyloin,



$$CH_2\left\langle {}^{O}_{O} \right\rangle C_6H_3.CH(OH).CO.C_6H_3\left\langle {}^{O}_{O} \right\rangle CH_2$$

The first time this reaction was carried out, a very small quantity of a yellow-brown powder was obtained. The M.Pt. was about 56°. It did not melt

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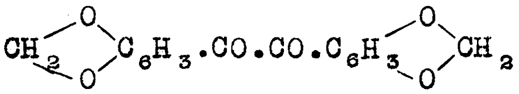
[1] Ber.1880,13,1337.

sharply and could not be purified further.

The reaction was repeated and this time the reaction mixture was left to stand for about twelve months. At the end of that time some crystals had separated. These were shown to be the diketone, piperil,



$$CH_2{<}^{O}_{O}{>}C_6H_3.CO.CO.C_6H_3{<}^{O}_{O}{>}CH_2$$

This substance can be obtained by oxidation of piperonyloin with Fehling's solution[1].

The remaining solution was worked up, but yielded only a sticky substance which could not be crystallised.

[1] Biltz & Wienands, A.1899,308,11.

# EXPERIMENTAL.

## Methyl-benzoin + $\delta$($\alpha$-phenylethyl)semicarbazide.

2.75 gms. of methyl-benzoin[1] was dissolved in 8 parts of pyridine and mixed with 2.5 gms. of $\delta$($\alpha$-phenylethyl)semicarbazide hydrochloride dissolved in about 5 parts of water.

There was no evidence of reaction on mixing, and the solution was left to stand for about 8 days. It was then darker in colour but nothing had separated.

On pouring into a large volume of water, a brown, heavy oil was precipitated. The vessel was then cooled in ice in order to solidify the oil as much as possible. The water was then decanted. The oily substance was shaken up repeatedly with cold water till most of the pyridine and pyridine hydrochloride were removed. This was then repeated several times with boiling water to remove the final traces. It was found necessary to cool the vessel in ice each time before decanting the washings as the oily substance became much more liquid in the hot water. When the substance had been well

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[1] Fischer, Ber.1893,26,2413.

washed, it was placed in a vacuum desiccator and dried as far as possible. It remained, however, in an oily state.

Many solvents and combinations of solvents were used in attempts to crystallise the substance but it resisted all such treatment.

On cooling in ice and salt, it stiffened considerably but did not actually become solid.

<u>Furoin + $\delta(\alpha$-phenylethyl)semicarbazide.</u>

2 gms. of furoin[1] was dissolved in 8 parts of pyridine and mixed with 2 gms. of $\delta(\alpha$-phenylethyl) semicarbazide hydrochloride,(1mol.:1mol.), dissolved in about 5 parts of cold water.

In this case a precipitate appeared almost immediately. It was a yellow, crystalline solid which, in the crude state, melted at 159°. It was soluble in alcohol and hot water. After recrystallising from hot water, it had M.Pt. 163°. It was shown to be the diketone furil, by comparison with a specimen of that substance.

Some furoin was dissolved in slightly warm pyridine. On cooling, it was found to have been oxidised

[1] Fischer, A.1882,<u>211</u>,218.

to furil, showing that oxidation during the reaction had not been brought about by the influence of $\delta(\alpha$-phenyl-ethyl)semicarbazide hydrochloride.

## Anisoin + $\delta(\alpha$-phenylethyl)semicarbazide.

The same method was followed as before, equimolecular quantities of anisoin[1] and $\delta(\alpha$-phenylethyl) semicarbazide hydrochloride being dissolved in 8 parts of pyridine and 5 parts of cold water respectively.

A precipitate appeared as the pyridine solution was poured into the aqueous solution. This disappeared, however, as more of the solution was added. After standing overnight, some of the anisoin had separated out. Sufficient pyridine was added to keep it in solution.

After standing for 15 days, the solution was poured into about 800 ccs. of ice-water. A yellow-brown oil was precipitated. It was treated in the same way as before, being washed first with cold, then with hot water, and dried in an evacuated desiccator. A few drops of dry ether were added to the substance and the vessel was again evacuated. The resulting froth solidified, after

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[1] Rossel, A.1869,151,33.

standing for some time, to a very pale yellow substance which melted gradually at about 55°.

This substance, however, although quite hard appeared to be resinous in character. In some solvents it dissolved and then came down as an oil, in others it seemed to become oily immediately it came in contact with the solvent. In order to bring it back to its original state, it was necessary to remove the solvent, dry the substance, dissolve in a few drops of ether and leave to stand as a froth in an evacuated desiccator as before.

### Piperonyloin + $\delta(\alpha$-phenylethyl)semicarbazide.

Piperonyloin was prepared according to the method of Perkin[1].

The reaction was carried out in exactly the same way as before. There was no change of appearance on mixing the solutions. After standing for six weeks, the solution was darker in colour, but no solid matter had separated.

On pouring into water mixed with ice, a light brown coloured oil was precipitated. This was

[1] Perkin, J.C.S.1891,59,164. See Appendix page 116.

allowed to settle as far as possible. It did not separate out completely, being apparently very light, and a quantity of it, which remained in suspension, had to be decanted with the water. It was washed with cold and hot water as usual. On drying, part of the oil had solidified to a brown solid.

This substance was easily soluble in alcohol, slightly soluble in hot ether, and insoluble in benzene and petroleum ether.

A portion was extracted with hot ether but was obtained again as a reddish-brown oil. This was dissolved in absolute alcohol. After taking off most of the alcohol in a vacuum desiccator, a light-yellow powder was obtained. Only a very small quantity was obtained. The M.Pt., which was not sharp, was about 56°.

An attempt was made to recrystallise this substance from various solvents. It was obtained again as a light powder. The M.Pt. showed no rise but was still indefinite. This substance differed in solubility from the product of similar M.Pt. obtained from the reaction with anisoin.

The reaction was repeated. This time the reaction mixture was left to stand for about twelve months. After about three months, a small deposit of crystals was observed. These increased in bulk very gradually and, at the end of the year, the crystals were filtered off and the rest of the mixture treated as before.

These crystals were found to be slightly soluble in hot alcohol. A small quantity, recrystallised from this solvent, melted at 170°. The substance could be recrystallised more easily from benzene. After further recrystallisation from the latter solvent it melted at 171.5°.

This substance was shown to be the diketone, piperil, by comparison with a specimen of that substance prepared by oxidising piperonyloin with Fehling's solution[1].

The solution remaining after the crystals had been removed was treated as before. On pouring into ice-water, a light-brown, sticky mass was precipitated.

It remained in the same condition after washing and drying and all attempts to improve its state were unsuccessful.

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[1] Biltz & Wienands, A.1899,308,11.

# PART III

## THE ACTION OF AMINES ON 2-SUBSTITUTED SEMICARBAZONES.

# PART III.

## INTRODUCTION.

The action of amines on semicarbazones was first investigated by Borsche and his collaborators[1]. He used only aromatic amines, and semicarbazones such as acetone semicarbazone. He found that these substances reacted generally according to the equation,

$$RR'C{:}N.NH.CO.NH_2 + R''NH_2 = RR'C{:}N.NH.CO.NHR'' + NH_3$$

This product, $RR'C{:}N.NH.CO.NHR''$, then yields on hydrolysis the semicarbazide, $NH_2NH.CO.NHR''$. The reactions with aniline, toluidines and naphthylamines were studied by Borsche.

This work has been extended by Wilson, Hopper and Crawford[2] to include aliphatic amines and aromatic amines containing the amino group in the side chain. They found that benzylamine, α-phenylethylamine, l.menthylamine and some esters of amino-acids reacted normally giving, for example, in the case of α-phenyl-

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[1] Ber.1901,34,4297:1904,37,3177:1905,38,831.

[2] J.C.S.1922,121,866:1925,127,103.

-ethylamine, acetone-$\delta(\alpha$-phenylethyl)semicarbazone which, on hydrolysis, gave $\delta(\alpha$-phenylethyl)semicarbazide. This is the semicarbazide used in the investigations described in part II of this work.

When this work is extended to include other amino-compounds such as hydrazine derivatives, some exceptions are found. Knöpfer[1] showed that phenylhydrazine, with the aromatic aldehydic semicarbazones reacted in quite a different way. In this case, there is a mutual replacement of phenylhydrazine and semicarbazide groups, thus,

$$R'CH:N.NH.CO.NH_2 + NH_2NHR'' = R'CH:N.NHR'' + NH_2NH.CO.NH_2$$

Wilson and Sutherland[2] found, however, that while acetone semicarbazone reacts with phenylhydrazine according to Knöpfer's scheme, benzophenone and acetophenone semicarbazones react with it according to the general scheme for amines propounded by Borsche.

Little is known of the reactions of semicarbazones having a group substituted in the 2-position and it is now proposed to investigate the action of amines on these substances.

[1] Monatsh.1910,31,87.

[2] J.C.S.1924,125,2145.

There are two systems used in naming substituted semicarbazones. The nitrogen atoms are designated in this way,

$$\begin{array}{llll} \mathrm{NH_2} & \mathrm{NH} & \mathrm{.CO.} & \mathrm{NH_2} \\ \alpha & \beta & & \delta \\ 1 & 2 & & 4 \end{array}$$

The first system is the one more generally used in dealing with monosubstituted semicarbazones. The second system, however, is a more convenient method of naming di-substituted semicarbazones.

The second system has been adopted throughout this work.

# THEORETICAL.

It was expected that the substitution of a group in the 2-position of a semicarbazone would in no way affect its reactions with amines, that is, that it would react according to the general equation,

$$RR'C{:}N.N(X).CO.NH_2 \quad + \quad R''NH_2$$
$$= \quad RR'C{:}N.N(X).CO.NHR'' \quad + \quad NH_3$$

It has been found, however, that while this equation represents the reactions of certain 2-substituted semicarbazones with amines, other semicarbazones behave in a different manner.

The first reaction which was investigated was that of acetone-2-phenyl-semicarbazone with benzylamine. Acetone semicarbazone reacts in this way with benzylamine,

$$(CH_3)_2C{:}N.NH.CO.NH_2 \quad + \quad NH_2CH_2Ph$$
$$= \quad (CH_3)_2C{:}N.NH.CO.NH.CH_2Ph \quad + \quad NH_3$$

Had the reaction with acetone-2-phenyl-semicarbazone taken the same course as that of acetone semicarbazone with benzylamine, the products would have been acetone-2-phenyl-4-benzyl-semicarbazone and ammonia, thus,

$$(CH_3)_2C:N.N(Ph).CO.NH_2 \quad + \quad NH_2CH_2Ph$$
$$= \quad (CH_3)_2C:N.N(Ph).CO.NH.CH_2Ph \quad + \quad NH_3$$

It was found, however, that this did not take place. Ammonia was split off as in the case of non-substituted semicarbazones but the other products were acetone phenylhydrazone and symmetrical dibenzylurea. The reaction can be represented by this equation,

$$(CH_3)_2C:N.N(Ph).CO.NH_2 \quad + \quad 2\ NH_2CH_2Ph$$
$$= \quad (CH_3)_2C:N.NHPh \quad + \quad CO(NH.CH_2Ph)_2 \quad + \quad NH_3$$

Acetone-2-phenyl-semicarbazone appears to react equally easily with aromatic and aliphatic amines. Aniline, p.toluidine, benzylamine, $\beta$-phenylethylamine and n.heptylamine all react in this way, giving acetone phenylhydrazone and a sym. di-substituted urea. The general equation is,

$$(CH_3)_2C:N.N(Ph).CO.NH_2 \quad + \quad 2\ NH_2R$$
$$= \quad (CH_3)_2C:N.NHPh \quad + \quad CO(NHR)_2 \quad + \quad NH_3$$

In the reaction with benzylamine, a small quantity of monobenzylurea was also produced. The production of monobenzylurea can be represented by the equation,

$$(CH_3)_2C{:}N.N(Ph).CO.NH_2 \quad + \quad NH_2CH_2Ph$$
$$= (CH_3)_2C{:}N.NHPh \quad + \quad NH_2.CO.NH.CH_2Ph$$

This reaction, however, requires further explanation. No semicarbazone has previously been shown to react in this way with an amine. In reactions described before, the primary stage has always been the elimination of ammonia with formation of a 4-substituted semicarbazone. According to this equation, a reaction takes place between a semicarbazone and a primary amine without liberation of ammonia. The intermediate stages of this change have been elucidated by subsequent investigations. These are described in some of the following pages.

No trace was found, in any of these reactions, of the normal product, that is, the 2.4-substituted semicarbazone.

This reaction of semicarbazones and amines to form substituted ureas has been observed before. Borsche[1] found that certain semicarbazones reacted primarily in the normal way, but that the product reacted with another molecule of the amine to give a di-substit-

[1] Ber.1901,<u>34</u>,4297:1904,<u>37</u>,3177.

-uted urea and the hydrazone of the aldehyde or ketone. For example, salicylaldehyde semicarbazone and aniline react according to the equation,

(I)

$$C_6H_4(OH)CH:N.NH.CO.NH_2 \quad + \quad NH_2Ph$$
$$= \quad C_6H_4(OH)CH:N.NH.CO.NHPh \quad + \quad NH_3$$

On further heating, the product of this reaction reacts with another molecule of amine,

(II)

$$C_6H_4(OH)CH:N.NH.CO.NHPh \quad + \quad NH_2Ph$$
$$= \quad C_6H_4(OH)CH:N.NH_2 \quad + \quad CO(NHPh)_2$$

The method adopted by Borsche in carrying out these reactions was to boil the semicarbazone in a large excess of the amine. In the reaction of salicylaldehyde semicarbazone, the amount of aniline used was five times by weight that of the semicarbazone which represents a molecular proportion of approximately ten molecules of aniline to one of salicylaldehyde semicarbazone.

In the case of acetone-2-phenyl-semicarbazone the reaction appears to be general for all types of amines and in no case was any of the intermediate product found, that is, the product from reaction I.

This was very unexpected, as in these

reactions with acetone-2-phenyl-semicarbazone the excess of amine was never more than 20% over the equimolecular quantity. Even in Borsche's reactions, where the amine was present in the proportion of ten molecules to one of the semicarbazone, a quantity of the 4-substituted semicarbazone was always found among the products. Indeed, in the majority of the reactions between semicarbazones and amines, the 4-substituted semicarbazone is the main product, or in other words, most of these reactions stop when the first stage has completed itself,

(I)
$$RR'C:N.NH.CO.NH_2 \quad + \quad NH_2R''$$
$$= \quad RR'C:N.NH.CO.NHR'' \quad + \quad NH_3$$

It is only on exceptional cases that the second reaction occurs to any marked degree.

If we accept Borsche's explanation as being applicable also to the case of acetone-2-phenyl-semicarbazone, the corresponding equations would be,

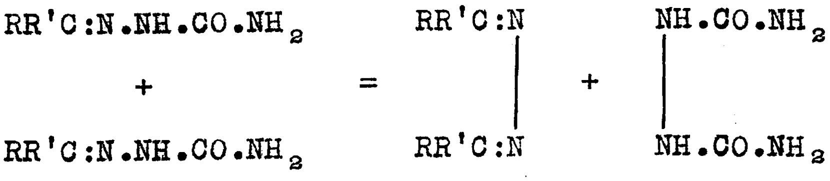
(I)
$$(CH_3)_2C:N.N(Ph).CO.NH_2 \quad + \quad NH_2R$$
$$= \quad (CH_3)_2C:N.N(Ph).CO.NHR \quad + \quad NH_3$$

(II)
$$(CH_3)_2C:N.N(Ph).CO.NHR \quad + \quad NH_2R$$
$$= \quad (CH_3)_2C:N.NHPh \quad + \quad CO(NHR)_2$$

We should, therefore, have expected that the reactions of acetone-2-phenyl-semicarbazone, when carried out under the conditions stated, would have yielded considerable quantities of 2.4.substituted semicarbazones.

The result of a thermal decomposition of acetone-2-phenyl-semicarbazone showed that the reactions of that substance with amines do not follow exactly, the scheme shown in equations I and II. The final result is the same but the intermediate stages are apparently different.

It has been shown by Scholtz[1], Borsche[2] and others that such semicarbazones as acetone semicarbazone decompose on heating into an azine and hydrazodicarbonamide. The general scheme for this decomposition can be represented thus,



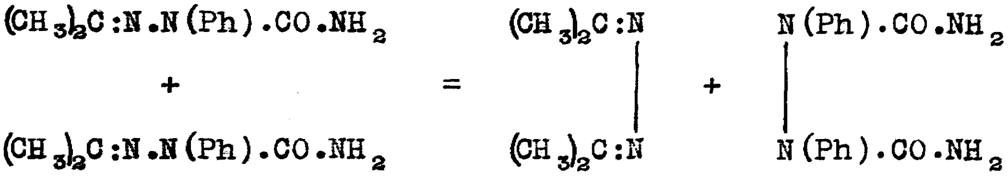
$$\begin{array}{c} RR'C{:}N.NH.CO.NH_2 \\ + \\ RR'C{:}N.NH.CO.NH_2 \end{array} = \begin{array}{c} RR'C{:}N \\ | \\ RR'C{:}N \end{array} + \begin{array}{c} NH.CO.NH_2 \\ | \\ NH.CO.NH_2 \end{array}$$

Assuming, then, that the phenyl group in the 2-position does not affect the course of the decomp-

[1] Ber.1896,29,611.

[2] Ber.1901,34,4297.

-osition, we should expect acetone-2-phenyl-semicarbazone, when heated, to give acetone ketazine and a substituted hydrazodicarbonamide.



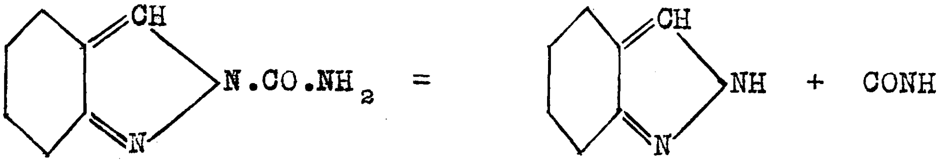
$$\begin{array}{c} (CH_3)_2C{:}N.N(Ph).CO.NH_2 \\ + \\ (CH_3)_2C{:}N.N(Ph).CO.NH_2 \end{array} = \begin{array}{c} (CH_3)_2C{:}N \\ | \\ (CH_3)_2C{:}N \end{array} + \begin{array}{c} N(Ph).CO.NH_2 \\ | \\ N(Ph).CO.NH_2 \end{array}$$

The result of this decomposition, however, was found to be quite different from that of ketonic semicarbazones with no group substituted in the 2-position.

On heating acetone-2-phenyl-semicarbazone to a maximum temperature of 180°, acetone phenylhydrazone and cyanuric acid were obtained. Acetone-2-phenyl-semicarbazone is prepared by the interaction of acetone phenylhydrazone and cyanic acid. It appears, therefore, that this reaction is reversed at high temperatures. The cyanic acid which is liberated, polymerises, of course, to form cyanuric acid.

$$\begin{array}{c} 3\,(CH_3)_2C{:}N.NHPh \;+\; 3\,HNCO \\ \downarrow \\ 3\,(CH_3)_2C{:}N.N(Ph).CO.NH_2 \\ \downarrow \\ 3\,(CH_3)_2C{:}N.NHPh \;+\; (HNCO)_3 \end{array}$$

Decomposition in this way has not been observed before in the case of a simple ketonic semicarbazone, whether substituted or unsubstituted. An analogy is found, however, in the case of tetrahydroindazol-2-carbonamide[1] which loses cyanic acid at about 220°, thus,



This substance, tetrahydroindazol-2-carbonamide can be considered as a cyclic semicarbazone.

The result of this decomposition revealed another possible explanation of the unexpected results obtained in the reactions of acetone-2-phenyl-semicarbazone with amines. If this decomposition took place at a lower temperature than that of the reactions, then these reactions were not characteristic of acetone-2-phenyl-semicarbazone as such, but were really the reactions of its decomposition products. As we have seen, these products are acetone phenylhydrazone and cyanic acid. Cyanic acid, however, reacts with amines to give substituted ureas. The products, therefore, should consist of acetone phenylhydrazone and substituted ureas

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[1] Auwers, Buschmann & Heidenreich, A.1923,435,281.

and this agrees with the results of these reactions.

It became necessary, then, to determine more exactly, the temperature of decomposition of acetone-2-phenyl-semicarbazone, or at least, to ascertain whether that temperature was higher or lower than the temperature at which its reactions with amines took place. These reactions usually required a temperature of about 160°. The lowest one was that of p.toluidine which commenced at 145°.

Acetone-2-phenyl-semicarbazone which melts at 140° was heated for an hour to 140-145°. Decomposition took place at this temperature, the products being the same as before.

It is obvious from this, that these reactions do not follow the same course as those investigated by Borsche. Instead, acetone-2-phenyl-semicarbazone first decomposes into acetone phenylhydrazone and cyanic acid which then unites with two molecules of the amine to give a di-substituted urea. Thus, taking the reaction with aniline as an example, the course of the reaction could be represented by these equations,

(I) $(CH_3)_2C:N.N(Ph).CO.NH_2 = (CH_3)_2C:N.NHPh + CONH$

(II) $CONH + 2\ NH_2Ph = CO(NHPh)_2 + NH_3$

The first reaction apparently takes place about 145° and the second at 155-160°.

The second reaction probably takes place in two stages. Even at ordinary temperatures, cyanic acid reacts with amines to give mono-substituted ureas. This is probably the first stage.

(IIa)

$$CONH \quad + \quad NH_2R \quad = \quad NH_2CO.NHR$$

The mono-substituted urea will then react with another molecule of the amine to give the di-substituted urea, thus,

(IIb)

$$NH_2CO.NHR \quad + \quad NH_2R \quad = \quad CO(NHR)_2 \quad + \quad NH_3$$

This explains the fact that no 2.4.substituted semicarbazones were obtained as these substances would not be formed at any stage of the reaction.

It also explains the fact that a quantity of monobenzyl urea was obtained in the reaction of acetone-2-phenyl-semicarbazone with benzylamine. Monobenzyl urea does not react as readily with the amine as some other mono-substituted ureas. In this case, therefore, the equation (IIb) would not go to completion. Thus, a mixture was obtained, containing monobenzyl-urea and also sym. dibenzyl-urea.

The action of heat on benzaldehyde-2-benzyl-semicarbazone was also investigated. It was expected that this substance would decompose in the same manner as acetone-2-phenyl-semicarbazone with liberation of benzaldehyde benzylhydrazone and cyanuric acid. As benzaldehyde benzylhydrazone is very unstable, the decomposition was carried out in an atmosphere of carbon dioxide.

However, after heating for 1½ hours at a temperature of 200°, a large proportion of the substance was recovered unchanged. The only other product obtained was a small quantity of a thick, yellow oil smelling of benzaldehyde.

In view of the fact that benzaldehyde-2-benzyl-semicarbazone was found to be more stable when heated than acetone-2-phenyl-semicarbazone it became interesting to investigate the reactions of this compound with amines. If it reacted at about the same temperature as acetone-2-phenyl-semicarbazone, about 160°, we should expect to obtain the normal product, that is, a 2.4.substituted semicarbazone, since, in this case, there would be no cyanic acid liberated at that temperature. If, however, no reaction took place till a temperature above 200° was reached, then it would appear that semicarbazones having groups substituted in the 2-position were much less reactive towards amines than unsubstituted semicarbazones. In this case, we would expect to obtain a substituted urea and benzaldehyde benzylhydrazone (or its decomposition products) since the reaction would apparently depend on the decomposition of the benzaldehyde-2-benzyl-semicarbazone.

The first reaction carried out was that with aniline. Ammonia was evolved as usual at about 160°. In this case, benzaldehyde-2-benzyl-4-phenyl-semicarbazone was obtained. It appears, therefore, that benzaldehyde-2-benzyl-semicarbazone reacts according to the general scheme propounded by Borsche for the reactions of amines and semicarbazones. This equation represents the reaction in this case.

$$\begin{aligned} & Ph.CH{:}N.N(Ph.CH_2).CO.NH_2 \quad + \quad NH_2Ph \\ = \; & Ph.CH{:}N.N(Ph.CH_2).CO.NHPh \quad + \quad NH_3 \end{aligned}$$

It was found that benzaldehyde-2-benzyl-semicarbazone reacted in the same way with p.toluidine. The normal product was also produced in the reaction with benzylamine but in this case, some sym. dibenzyl-urea was also produced. No benzaldehyde benzylhydrazone was obtained, but this was to be expected as this substance is unstable even at ordinary temperatures. Its main decomposition product is benzaldehyde and the presence of this substance was detected by its smell in the tarry residues from the mother liquor.

The 2.4.substituted semicarbazones obtained from these reactions have not been described before. Both substances are white, crystalline solids. Benzaldehyde-2-benzyl-4-p.tolyl-semicarbazone melts at 172°, and benzaldehyde-2.4-dibenzyl-semicarbazone at 123.5°.

The production of sym. dibenzyl-urea in the reaction with benzylamine was surprising as benzaldehyde-2-benzyl-semicarbazone was recovered unchanged after heating to a higher temperature than that of the reaction.

The fact that sym. dibenzyl-urea and benzaldehyde-2.4-dibenzyl-semicarbazone were produced in the same reaction would appear to favour the view that the former substance was obtained by the interaction of the latter substance with a further quantity of amine. That would mean that the reaction followed the same course as those investigated by Borsche, that is, according to these equations,

(I)

$$Ph.CH:N.N(Ph.CH_2).CO.NH_2 \quad + \quad NH_2CH_2Ph$$

$$= \quad Ph.CH:N.N(Ph.CH_2).CO.NH.CH_2Ph \quad + \quad NH_3$$

(II)

$$\begin{aligned} & Ph.CH{:}N.N(Ph.CH_2).CO.NH.CH_2Ph \quad + \quad NH_2CH_2Ph \\ = \quad & Ph.CH{:}N.NH.CH_2Ph \quad + \quad CO(NH.CH_2Ph)_2 \end{aligned}$$

The reactions of benzaldehyde-2-benzyl-semicarbazone with aniline and p.toluidine gave only the 2.4.substituted semicarbazones, no substituted ureas being produced. The reaction with benzylamine, however, required a higher temperature and, although it seems very unlikely that this could have happened, it might be argued that at this temperature the semicarbazone decomposed slightly with liberation of cyanic acid and subsequent formation of sym. dibenzyl-urea.

The next reaction tried was that of acetophenone-2-phenyl-semicarbazone with aniline. It was found that this semicarbazone behaved in exactly the same way as acetone-2-phenyl-semicarbazone, giving acetophenone phenylhydrazone and sym. diphenyl-urea.

No trace was found of acetophenone-2.4-diphenyl-semicarbazone. It seems probable, therefore, that this reaction took the same course as those of acetone-2-phenyl-semicarbazone, that is, that acetophenone-2-phenyl-semicarbazone first decomposed into acetophenone phenylhydrazone and cyanic acid which then combined with aniline to give sym. diphenyl-urea.

Additional evidence in favour of this is the fact that acetophenone-2-phenyl-semicarbazone has a lower M.Pt. than most members of its class. It melts at 126° (Rolla[1] states 122°) and it seems reasonable to suppose that its decomposition temperature might also be lower than those of the other 2-substituted semicarbazones used.

Benzaldehyde-2-methyl-semicarbazone, which was tried next, gave with aniline the normal product, benzaldehyde-2-methyl-4-phenyl-semicarbazone.

Nevertheless, with benzylamine it gave mainly sym. dibenzyl-urea and only a small quantity of benzaldehyde-2-methyl-4-benzyl-semicarbazone.

The reaction with aniline required a temperature of 180°, whereas with benzylamine, the temperature was only 170°. As the reaction with aniline gave benzaldehyde-2-methyl-4-phenyl-semicarbazone and no sym. diphenyl-urea, it follows that benzaldehyde-2-methyl-semicarbazone does not decompose with evolution of cyanic acid at a temperature of 180°. In the reaction with benzylamine, however, the temperature was only 170° yet sym. dibenzyl-urea was obtained as well as the normal product, benzaldehyde-2-methyl-4-benzyl-semicarbazone.

[1] Rolla, G.38,(i),327. See Appendix p. 118.

The latter substance, which has not been previously described, crystallises from alcohol in the form of plates melting at 106-107°. It is evident, then, that the sym. dibenzyl urea obtained in this reaction is not produced in the same way as that obtained in the reaction of acetone-2-phenyl-semicarbazone with benzylamine. The only obvious explanation is that it is produced in the same manner as the ureas and hydrazones found by Borsche in his reactions with salicylaldehyde semicarbazone. This would mean that the reaction had gone in two stages according to the equations,

(I)

$$\mathrm{Ph.CH{:}N.N(CH_3).CO.NH_2 \ + \ NH_2CH_2Ph}$$

$$= \ \mathrm{Ph.CH{:}N.N(CH_3).CO.NH.CH_2Ph \ + \ NH_3}$$

(II)

$$\mathrm{Ph.CH{:}N.N(CH_3).CO.NH.CH_2Ph \ + \ NH_2CH_2Ph}$$

$$= \ \mathrm{Ph.CH{:}N.NH(CH_3) \ + \ CO(NH.CH_2Ph)_2}$$

It will be seen from this, that benzaldehyde methylhydrazone should have been produced. This substance, however, was not obtained. The products consisted of benzaldehyde-2-methyl-4-benzyl-semicarbazone, sym. dibenzyl-urea, ammonia and a quantity of sticky, oily substances. From these substances, minute quantities of two solids were eventually isolated.

One of these melted at 63° and appears to have the empirical formula, $C_{17}H_{21}O_2N_2$. The other one melts at 207° and has the formula, $(C_{11}H_{12}O_3N_2)_n$. In each case, the quantity of substance obtained was too small to permit any further investigation.

Benzaldehyde methylhydrazone is described by Harries and Haga[1] as a crystalline solid, M.Pt. 179°. They state that when equimolecular quantities of methylhydrazine and benzaldehyde are mixed, this substance, normal benzaldehyde methylhydrazone is obtained along with another substance, tribenzalmethylhydrazone. The information about the normal benzaldehyde methylhydrazone is very meagre.

It was intended to prepare benzaldehyde methylhydrazone in order to find whether it would be stable under the conditions of the reaction, and if not, to find whether the substances having M.Pts. 63° and 207° would be among its decomposition products. It was found, however, on carrying out the reaction, that the substance M.Pt. 179° was not obtained. Even when a slight excess of methylhydrazine was used, the only solid product was the substance described as tribenzalmethylhydrazone.

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[1] Ber.1898,31,62.

After carrying out the reactions of benzaldehyde-2-methyl-semicarbazone with aniline and benzylamine, it was decided to investigate the action of amines on certain 2.4.substituted semicarbazones. In other words, it was decided to carry out separately, the second stage indicated in such reactions as that of benzaldehyde-2-methyl-semicarbazone with benzylamine.

Borsche's explanation[1] of the reactions of amines and semicarbazones required that certain semicarbazones substituted in the 4-position should react with amines to give a sym. di-substituted urea and the hydrazone of the aldehyde or ketone. He showed that this actually took place with some of these semicarbazones. The semicarbazones which he used, however, were substituted only in the 4-position. It has been shown that the presence of a group in the 2-position causes considerable differences in the character of the semicarbazone, for example, in its decomposition products. For this reason, it was thought advisable that some investigation should be made of the action of amines on semicarbazones substituted both in the 2- and the 4-positions. This was particularly the case since Borsche carried out his reactions in a much larger excess of amine than was present in the

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[1] See pages 50-51.

reactions described here. It was necessary, therefore, to find whether the same reactions would take place under conditions nearer those of the present work.

The reactions of benzaldehyde-2-methyl-4-phenyl-semicarbazone with aniline and of benzaldehyde-2-methyl-4-benzyl-semicarbazone with benzylamine were carried out. The results of these reactions give valuable support to the theory that the reaction of benzaldehyde-2-methyl-semicarbazone with benzylamine takes place in the two stages stated.

Benzaldehyde-2-methyl-4-phenyl-semicarbazone was heated with aniline to 180° for four hours. At the end of this time the substances were recovered unchanged. In the reaction of benzaldehyde-2-methyl-semicarbazone with aniline, which was also carried out at 180°, benzaldehyde-2-methyl-4-phenyl-semicarbazone was produced, but no sym. diphenyl-urea. These results agree well, since, as benzaldehyde-2-methyl-4-phenyl-semicarbazone does not react with aniline at 180°, the reaction of benzaldehyde-2-methyl-semicarbazone with aniline will stop at the first stage, that is, when this reaction has completed itself,

$$\begin{aligned} & Ph.CH{:}N.N(CH_3).CO.NH_2 \quad + \quad NH_2Ph \\ = \; & Ph.CH{:}N.N(CH_3).CO.NHPh \quad + \quad NH_3 \end{aligned}$$

Benzaldehyde-2-methyl-4-benzyl-semicarbazone with benzylamine gave sym. dibenzyl-urea, a small quantity of the semicarbazone being recovered unchanged. This also agrees with the results obtained before as benzaldehyde-2-methyl-semicarbazone with benzylamine gave a mixture of benzaldehyde-2-methyl-4-benzyl-semicarbazone and sym. dibenzyl-urea. This reaction takes place, therefore, in two stages, according to the equations,

(I)

$$Ph.CH{:}N.N(CH_3).CO.NH_2 \quad + \quad NH_2CH_2Ph$$

$$= \quad Ph.CH{:}N.N(CH_3).CO.NH.CH_2Ph \quad + \quad NH_3$$

(II)

$$Ph.CH{:}N.N(CH_3).CO.NH.CH_2Ph \quad + \quad NH_2CH_2Ph$$

$$= \quad Ph.CH{:}N.NH(CH_3) \quad + \quad CO(NH.CH_2Ph)_2$$

It will be remembered that one of the objects of this investigation of the action of amines on 2-substituted semicarbazones was the preparation of new optically active semicarbazides having a group substituted in the 2-position. Substances of that type could only be prepared from 2-substituted semicarbazones which react in the normal manner with amines giving 2.4.substituted semicarbazones. These 2.4.substituted semicarbazones must not react too readily with amines, otherwise substituted ureas and hydrazones will be obtained.

It has been shown that benzaldehyde-2-methyl-semicarbazone reacts in the normal manner with aniline, while with benzylamine the main product is sym. dibenzyl-urea although a small quantity of the normal product is obtained in this case also. It was decided to try the reaction of benzaldehyde-2-methyl-semicarbazone with α-phenylethylamine. For the experimental reaction the racemic form of the amine was used.

After heating to 175-180° for 2 hours, much of the benzaldehyde-2-methyl-semicarbazone remained unchanged. The only product which was isolated, apart from a sticky residue, was sym. di(α-phenylethyl)urea. Had this reaction been repeated on a larger scale, it is possible that a small quantity of benzaldehyde-2-methyl-4-(α-phenylethyl)semicarbazone might have been obtained. However, in view of the fact that sym. di(α-phenylethyl) urea was obtained while most of the benzaldehyde-2-methyl-semicarbazone remained unchanged, it is almost certain that the yield of the benzaldehyde-2-methyl-4-(α-phenylethyl)semicarbazone would be too small to make this method practicable as a means of preparing an optically active semicarbazide.

It was intended, also, to study the decomposition products of acetone-2.4-diphenyl-semicarbazone. This substance is described by Whyburn and Bailey[1] as a crystalline solid, M.Pt. 191°. On attempting to prepare it from the same starting materials, but under slightly different conditions, a substance was obtained, M.Pt. 138°. This preparation and the reactions of this substance are described in the Appendix.

[1] J.A.C.S.1928,50,912.

# CONCLUSION.

The substitution of a group in the 2-position of a semicarbazone affects its behaviour to a greater extent than was anticipated. The most striking difference is in the manner in which it decomposes on heating. It has been shown, for instance, that acetone-2-phenyl-semicarbazone decomposes on heating in an altogether different way from acetone semicarbazone. The decomposition products of acetone-2-phenyl-semicarbazone are acetone phenylhydrazone and cyanuric acid.

The reactions of a 2-substituted semicarbazone with amines appear to depend on its temperature of decomposition. Thus, acetone-2-phenyl-semicarbazone decomposes before the temperature is reached at which it will react with amines. In this case, therefore, no 2.4.substituted semicarbazones are formed at all, the products being acetone phenylhydrazone and sym. di-substituted ureas. The same thing occurs in the case of acetophenone-2-phenyl-semicarbazone.

The higher-melting semicarbazones, benzaldehyde-2-benzyl-semicarbazone and benzaldehyde-2-methyl-semicarbazone are much more stable when heated. These substances, with amines, give the normal products, that is, 2.4.substituted semicarbazones. These 2.4.substituted semicarbazones, however, may react with another molecule of the amine. This reaction has been observed before in the case of semicarbazones substituted in the 4-position. The reaction appears to take place much more readily in the case of 2.4.substituted semicarbazones than of those substituted only in the 4-position.

It was thought that this work might lead up to the preparation of a new optically active semicarbazide. That it has not done so is due partly to the low decomposition temperature of certain 2-substituted semicarbazones and also to the small yield of 2.4.substituted semicarbazone which was generally obtained when the reaction went in the normal manner. It is possible, however, that another 2-substituted semicarbazone may be found, which will prove more suitable as a starting material for the preparation of optically active semicarbazides.

# EXPERIMENTAL.

## Acetone-2-phenyl-semicarbazone + Benzylamine.

The reaction was first carried out in this way. Equimolecular quantities of acetone-2-phenyl-semicarbazone[1] and benzylamine were mixed and heated. Ammonia was evolved at 160° and the mixture was kept at that temperature for about an hour. It was then poured into a large bulk of ice-water in which it formed a brown, viscous mass. On purification, this yielded the solid products described below.

It was decided, however, to alter this method to some extent in order to isolate the more volatile products. The following method was adopted.

15 gms. of acetone-2-phenyl-semicarbazone and 8 gms. of benzylamine were mixed and heated. Ammonia was given off between 155-160°. The mixture was kept at 160° till evolution of ammonia had abated. The reaction lasted almost an hour. The reaction mixture was then cooled and heated again under 4 mm. pressure in order to distil any volatile products.

[1] Goodwin & Bailey, J.A.C.S.1924,<u>46</u>,2829.

See Appendix page 117.

The first distillate consisted of a few drops of an oil with a peculiar odour. This oil was insoluble in alkali, easily soluble in concentrated hydrochloric acid and darkened on standing exposed to the atmosphere.

At 110° and 4 mm. pressure a clear, slightly yellow liquid began to distil and solidified to some extent in the receiver. This substance was identified as acetone phenylhydrazone. On redistilling, its B.Pt. under 44 mm. pressure was found to be 160° which agrees with that given by Blanksma[1]. It was dissolved in glacial acetic acid to which was then added potassium cyanate. A substance M.Pt. 140° was obtained and was shown by comparison to be acetone-2-phenyl-semicarbazone[2]. The yield of acetone phenylhydrazone amounted to 6 gms.

Nothing else distilled on raising the temperature of the bath to 160°, the pressure being 4 mm.

The solid residue which remained in the flask was dissolved out with boiling alcohol. On cooling, fine, white needles separated. After recrystallising several times from alcohol and also from chloroform, these melted at 171°. This substance was identified as sym. dibenzyl-urea.

[1] C.1913,I,603.

[2] See Appendix page 117.

Found - - - N = 11.59, 11.69%.

$C_{15}H_{16}ON_2$ requires N = 11.67%

The M.Pt. of sym. dibenzyl-urea has been stated in various papers either as 167° or 169°. A specimen was prepared, however, from urea and benzylamine[1]. After several recrystallisations it melted at 171° and was shown to be identical with the substance obtained in the reaction. The yield of sym. dibenzyl-urea was 4 gms.

The mother liquor was taken to dryness and the residue was dissolved in ethyl acetate. A crystalline substance separated, which, after further recrystallisation from the same solvent, was obtained as colourless needles, M.Pt. 149°. This substance was shown to be monobenzyl-urea by analysis and comparison with a prepared specimen of that substance.

Found - - - - C = 63.77, H = 7.10, N = 18.45%.

$C_8H_{10}ON_2$ requires C = 63.99, H = 6.67, N = 18.66%.

Found - - - - Mol. Wt. = 156.

(By the ebullioscopic method using acetone as solvent.)

$C_8H_{10}ON_2$ requires Mol. Wt. = 150.

The mother liquor was taken to dryness

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[1] Davis & Blanchard, J.A.C.S.1923,45,1819.

again and left a tarry residue from which no other pure substance was obtained.

In toluene.

The reaction of acetone-2-phenyl-semicarbazone and benzylamine was repeated using toluene as a solvent. Some high-boiling paraffin was added to raise the B.Pt. The mixture was boiled for 3 hours. The temperature of the bath for the greater part of the time was between 155-160°. The highest temperature reached was 163°.

No reaction took place, the acetone-2-phenyl-semicarbazone being recovered unchanged.

Acetone-2-phenyl-semicarbazone + Aniline.

10 gms. of acetone-2-phenyl-semicarbazone and 6 gms. of aniline were mixed and heated.

About 105° a clear liquid distilled up the side of the flask but none of it came over into the receiver even after the temperature had been increased to 160°.

At 155° evolution of ammonia began and the mixture was kept between 155-160° till this had abated to some extent. The reaction lasted about 40 minutes.

The mixture was then distilled under reduced pressure. The pressure was reduced to 15 mm. and the mixture was again heated. Between 100-110°, a clear, slightly yellow liquid distilled and solidified in the receiver. This was shown to be acetone phenylhydrazone by acting on it with potassium cyanate in glacial acetic acid solution, when acetone-2-phenyl-semicarbazone was again obtained.

The temperature of the bath was gradually raised to 160° but no other products were obtained and the distillation was then stopped.

The solid residue which was left in the flask was recrystallised from alcohol. A white, crystalline substance was obtained having M.Pt. 237°. This was shown to be sym. diphenyl-urea by comparison with a stock sample.

On concentrating the solution, a further quantity of sym. diphenyl-urea was obtained. The alcohol was finally removed completely under reduced pressure. A considerable residue of a black, tarry substance remained. This was dissolved in benzene. On standing for some time, a small quantity of a solid was obtained which, after recrystallisation melted at 133°. This substance was not obtained in sufficient quantity for further purification. The tar which was obtained on concentration of the mother liquor yielded no other pure products.

## Acetone-2-phenyl-semicarbazone + p.Toluidine.

12 gms. of acetone-2-phenyl-semicarbazone was mixed with 8 gms. of p.toluidine and heated. The clear liquid noted in the last reaction was again observed at 110°.

Evolution of ammonia began at 144°. The mixture was kept at 145° for half an hour and the temperature was then raised to 150° for ten minutes to complete the reaction. During the reaction, a solid crust formed on the surface of the mixture.

When the reaction was finished, the mixture was distilled as before. Acetone phenylhydrazone was obtained and was identified in the same manner as before.

The solid residue was dissolved in boiling alcohol from which a crystalline solid was obtained immediately on cooling. After further recrystallisation from alcohol the M.Pt. was 260°. This was shown to be di-p.tolyl-urea by comparison with a prepared sample of that substance[1]. About 4 gms. of di-p.tolyl urea was obtained.

The mother liquor was then taken to dryness leaving a dark, tarry substance. This was easily soluble in benzene from which nothing separated even on cooling in ice. The benzene was then removed and an attempt was made to recrystallise the substance from chloroform. A sticky substance separated from this solution. After pressing out on a porous plate, it melted about 160°. It was then recrystallised from chloroform with the addition of a few drops of alcohol. It now melted about 162° but the M.Pt. was not yet sharp.

The quantity obtained was insufficient to allow further purification.

## Acetone-2-phenyl-semicarbazone + β-Phenylethylamine.

8 gms. of acetone-2-phenyl-semicarbazone and 6 gms. of β-phenylethylamine were heated together.

At 150° ammonia came off fairly steadily. The mixture was kept at 150-160° till the reaction was completed.

The mixture was then distilled under red-

[1] Manuelli, Ricca-Rosellini, G.29, II, 133.

uced pressure. Acetone phenylhydrazone was obtained and was identified as before.

The dark-coloured residue was dissolved in alcohol. A small quantity of a crystalline substance had separated on standing for 12 hours. A small quantity of petroleum ether was added and the solid which separated was filtered off. It was recrystallised first from benzene but it was found that it crystallised best from ethyl acetate as clusters of colourless needles, M.Pt. 136-137°.

It was shown to be identical with sym. di-($\beta$-phenylethyl)urea, by comparison with a prepared specimen of that substance.

The mother liquor yielded only a tarry substance from which no pure products were isolated.

## Acetone-2-phenyl-semicarbazone + n.Heptylamine.

5 gms. of acetone-2-phenyl-semicarbazone and 3.5 gms. of n.heptylamine were heated together in the usual way.

The mixture was heated till the amine was almost boiling. The temperature of the bath was 160-162°.

The reaction slowed down after about 45

minutes. The mixture was then distilled under reduced pressure and acetone phenylhydrazone was obtained and identified as before.

The residue was recrystallised from alcohol and gave a crystalline solid melting at 91°. This is the M.Pt. of sym. di-n.heptyl-urea[1].

Found - - - - - N = 11.05%.

$C_{15}H_{32}ON_2$ requires N = 10.94%.

On concentration, the mother liquor yielded a tarry substance.

## Action of Heat on Acetone-2-phenyl-semicarbazone.

### At 180°.

15 gms. of acetone-2-phenyl-semicarbazone was placed in a distilling flask and heated.

At 160° there was slight effervescence and a clear liquid was observed to distil inside the flask. The temperature was raised to 180°, however, in order to bring about complete decomposition. The mixture was kept at this temperature for 35 minutes. The total time of heating was about an hour and a quarter. There was

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[1] Manuelli, Ricca-Rosellini, G.29,II,135.

slight evolution of ammonia at 180°. When it was thought that decomposition was complete, the mixture was distilled under reduced pressure.

A clear, pale-yellow liquid distilled when the bath temperature was 135° and the pressure 15 mm. This liquid was shown to be acetone phenylhydrazone by reconversion to acetone-2-phenyl-semicarbazone. The yield of acetone phenylhydrazone was 7 gms.

It was attempted to dissolve out the residue in the flask with hot alcohol. It appeared to be soluble to a slight extent only. Methyl alcohol proved to be more suitable and a quantity of the substance was recrystallised several times from that solvent.

It was found that the substance could be heated to 350° without melting or darkening in colour. The substance was thought from its properties to be cyanuric acid and analysis confirmed this.

Found - - - - N = 32.50%.

$C_3H_3O_3N_3$ requires N = 32.55%.

No other products were isolated.

At 145°.

12 gms. of acetone-2-phenyl-semicarbazone

was heated to 140-145° for one hour. At the end of this time, the only change observed was a darkening of the colour of the liquid. No gas was evolved. It was then cooled and again heated to 145°, this time under 10 mm. pressure. A pale-yellow liquid distilled, B.Pt. $119^{\circ}_{10}$, and solidified to some extent in the receiver.

The distillate solidified in the form of plates, M.Pt. 40°. This substance was shown to be acetone phenylhydrazone. It was hydrolysed with dilute hydrochloric acid. This solution, after neutralisation with sodium hydroxide, gave the nitroprusside test for acetone and also reduced Fehling's solution. On treatment with potassium cyanate in glacial acetic acid, it gave acetone-2-phenyl-semicarbazone.

The residue in the flask, consisting of a mixture of solid and red, oily liquid, was treated with hot alcohol. A portion was almost insoluble. It was boiled up with benzene and again with alcohol to remove colouring matter. It was then recrystallised from water. The colourless crystals which were obtained did not melt at 330° and showed no signs of decomposition. This substance was identified as cyanuric acid. With ammonia and copper sulphate it gave the characteristic amethyst-coloured precipitate.

Found - - $N = 32.46, 32.49\%$.

$C_3H_3O_3N_3$ requires $N = 32.55\%$.

No other products were isolated.

## Action of Heat on Benzaldehyde-2-benzyl-semicarbazone[1].

About 5 gms. of benzaldehyde-2-benzyl-semicarbazone was heated in a distilling flask through which was passed a steady current of carbon dioxide.

The mixture was raised to 190° and kept at that temperature for $1\frac{1}{2}$ hours. It was then distilled under reduced pressure. This time the temperature was raised to 200°, the pressure being 6 mm. Nothing distilled, however.

The viscous mass in the flask was then dissolved in hot alcohol. A white, crystalline solid was deposited on cooling which, recrystallised from alcohol, melted at 159°.

This was shown, by comparison and analysis, to be unchanged benzaldehyde-2-benzyl-semicarbazone.

Found - - - - $N = 16.65\%$.

$C_{15}H_{15}ON_3$ requires $N = 16.60\%$.

When the remaining mother liquor was evap-

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[1] Bougault & Leboucq, C.r.1928,186,957.

orated, a thick yellow-brown oil was obtained which had the smell of benzaldehyde.

Benzaldehyde-2-benzyl-semicarbazone + Aniline.

5 gms. of benzaldehyde-2-benzyl-semicarbazone was mixed in a flask with 2 gms. of aniline and the mixture gradually heated in a glycerine bath. When the temperature reached 155° small bubbles of a gas were slowly evolved. However, this showed no signs of increasing and the heating was continued till the temperature was 165-170°. After the mixture had been at this temperature for about 20 minutes, ammonia was being steadily evolved. After a further 45 minutes, the reaction appeared to be nearing completion and the mixture was allowed to cool. When it had reached a temperature of about 50° an attempt was made to distil it under a pressure of 15 mm.

The temperature was gradually raised and a small quantity of a clear liquid distilled. It was identified as aniline by conversion to benzanilide and comparison with the latter substance. The quantity of aniline just amounted to a few drops. No other substance distilled on raising the temperature of the mixture to the reaction temperature, 170°.

The residue in the flask was dissolved in boiling alcohol. On cooling, a white, crystalline solid separated from the solution. After recrystallising several times from alcohol, the M.Pt. of this substance was 152°. This is the M.Pt. of benzaldehyde-2-benzyl-4-phenyl-semicarbazone which was prepared by Busch, Opfermann and Walther[1] by the action of benzaldehyde on 2-benzyl-4-phenyl-semicarbazide which was obtained from benzylhydrazine and phenyl isocyanate.

Analysis confirmed that the substance obtained in the reaction was benzaldehyde-2-benzyl-4-phenyl-semicarbazone.

Found - - - - N = 12.84%.
$C_{21}H_{19}ON_3$ requires N = 12.76%.

On taking the alcoholic solution to dryness, a tarry substance was obtained. A further quantity of benzaldehyde-2-benzyl-4-phenyl-semicarbazone was obtained but no other products were isolated.

## Benzaldehyde-2-benzyl-semicarbazone + p.Toluidine.

4.5 gms. of benzaldehyde-2-benzyl-semicarb-

[1] Ber.1904,37,2327.

azone and 2 gms. of p.toluidine were heated together.

At 165° there was brisk effervescence and ammonia was given off. A liquid was distilling inside the flask but the temperature was not raised high enough to cause it to come over.

The mixture was kept at 165-170° for 2 hours. It was then distilled under a pressure of 15 mm.

When the bath temperature was 140° a substance distilled and solidified in the condenser. This was found to be unchanged p.toluidine.

The residue in the flask was dissolved out with hot alcohol. After several recrystallisations from this solvent, it melted at 172°.

Found - - - N = 12.02, 12.13%.

$C_{22}H_{21}ON_3$ requires N = 12.23%.

This substance, benzaldehyde-2-benzyl-4-p.tolyl-semicarbazone, is insoluble in water and petroleum ether, soluble in hot alcohol and benzene and slightly soluble in hot ether.

## Benzaldehyde-2-benzyl-semicarbazone + Benzylamine.

Some benzaldehyde-2-benzyl-semicarbazone was heated in the same manner as before with an excess of benzylamine, about 15-20% over the equimolecular quantity.

This reaction required a higher temperature than the previous one. It was not until 185° was reached that a steady stream of ammonia was given off. The reaction appeared to go quite steadily for about an hour when the evolution of ammonia abated somewhat. The mixture was then cooled to some extent and an attempt was made, as before, to distil off the volatile products. In this case, however, nothing distilled on taking the temperature of the bath up to the reaction temperature, 185°, under a pressure of 14 mm.

The contents of the flask were then dissolved in boiling alcohol. On cooling, a crystalline solid separated which, after further recrystallisation from alcohol, melted at 171°. This was shown by comparison and analysis to be sym. dibenzyl-urea.

Found - - - - N = 11.61%.
$C_{15}H_{16}ON_2$ requires N = 11.68%

On concentrating the mother liquor a further quantity of solid separated. This was found to be a mixture of sym. dibenzyl-urea and another substance. A separation was brought about by the use, first of chloroform and then of benzene. In both of these solvents sym. dibenzyl-urea is less soluble than the second product of the reaction.

The latter substance was then recrystallised several times from alcohol. Its M.Pt. was then 123.5°. This substance appears to be the normal product, benzaldehyde-2.4-dibenzyl-semicarbazone. It is soluble in ether, acetone and chloroform in the cold, and in hot alcohol or benzene. It is insoluble in petroleum ether.

Found - - - - - N = 12.23%.

$C_{22}H_{21}ON_3$ requires N = 12.24%.

The mother liquor, when finally evaporated, yielded a tarry substance from which no other pure products were isolated. It had a strong smell of benzaldehyde.

On repeating this reaction it was found possible to make it take place at a lower temperature. This time the reaction mixture was heated to 175° for $1\frac{1}{4}$ hours. It was then worked up in the same manner as before and again yielded a mixture of sym. dibenzyl-urea and benzaldehyde-2.4-dibenzyl-semicarbazone.

## Acetophenone-2-phenyl-semicarbazone + Aniline.

7 gms. of acetophenone-2-phenyl-semicarbazone was heated slowly with 3 gms. of aniline.

Effervescence commenced very slowly at 135° and became slightly brisker at 145° when the smell of ammonia first became apparent. The mixture was kept at this temperature for 30 minutes. As the ammonia had been coming off very slowly the temperature was then increased again. At 155° there was a definite increase in the rate of evolution of the ammonia and the mixture was kept at that temperature till the reaction abated. This took place at the end of a further 45 minutes.

The mixture was then cooled and raised again to 160° under 15 mm. pressure. A very small quantity of a clear liquid distilled and solidified to some extent in the side-tube. This was not identified. No aniline was obtained.

The solid residue in the flask was dissolved in boiling alcohol. A white, crystalline substance separated on cooling. This was found to be a mixture melting over a wide range from 195-225°. It was treated with ether and partially dissolved. The ether extract was then taken to dryness leaving a solid residue. This was recrystallised several times from alcohol after which its M.Pt. was 104°. This substance was shown to be acetophenone phenylhydrazone by comparison with a prepared specimen of that substance.

The part which was insoluble or less soluble in ether was also recrystallised several times from alcohol. Its M.Pt. was then 238°. This substance was shown by comparison to be sym. diphenyl-urea.

No other products were isolated.

## Benzaldehyde-2-methyl-semicarbazone + Aniline.

### At 155-165° for 1 hour.

20 gms. of benzaldehyde-2-methyl-semicarbazone[1] and 13 gms. of aniline were heated together in the usual way. At 155° some ammonia was evolved. The temperature of the mixture was kept at 155-165° for one hour. It was then cooled and an attempt was made to distil it under reduced pressure. On raising the temperature some unchanged aniline distilled. 10 gms. of aniline was obtained. No other products distilled on raising the temperature to 165° under 4 mm. pressure.

The solid residue was then dissolved in

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[1] Young & Oates, J.C.S.1901,79,662.

boiling alcohol. On cooling, a white, crystalline substance separated. This was found to consist of unchanged benzaldehyde-2-methyl-semicarbazone. The only other product obtained, on evaporation of the mother liquor, was a small quantity of a thick, oily substance.

The reaction was therefore repeated at a higher temperature.

At 180° for 3 hours.

The last reaction was repeated in an attempt to bring it to completion.

9 gms. of benzaldehyde-2-methyl-semicarbazone and 6 gms. of aniline were heated together. The mixture was heated this time to 180° at which temperature ammonia was being evolved vigorously. It was kept at 180° for 3 hours when the reaction abated to some extent. It was then distilled as before. This time about 2 gms. of unchanged aniline was recovered.

The solid residue was dissolved in hot alcohol. On cooling, a white substance crystallised out. This was recrystallised several times from alcohol and then from a small quantity of benzene with the addition of petroleum ether. It was obtained from both solvents as clusters of small needles, M.Pt. 108°. This is the

M.Pt. of benzaldehyde-2-methyl-4-phenyl-semicarbazone which was prepared by Busch, Opfermann and Walther[1] by the action of benzaldehyde on 2-methyl-4-phenyl-semicarbazide. The latter substance was obtained from methylhydrazine and phenyl isocyanate.

Found - - - N = 16.71, 16.75%.

$C_{15}H_{15}ON_3$ requires N = 16.60%.

It is easily soluble in ether, benzene, chloroform and ethyl acetate, soluble in hot alcohol and insoluble in petroleum ether.

## Benzaldehyde-2-methyl-semicarbazone + Benzylamine.

### At 170° for 3 hours.

20 gms. of benzaldehyde-2-methyl-semicarbazone and 14 gms. of benzylamine were heated together in the usual manner. This semicarbazone appeared to be more soluble in the amine than any of the others previously used. It dissolved completely before its M.Pt. was reached. There was no evolution of ammonia up to the temperature at which it had all dissolved.

The first bubbles of gas were observed at

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[1] Ber.1904,37,2324.

153° but ammonia was not given off steadily till about 10° higher. The mixture was kept at 165-170° for 3 hrs. It was then cooled and heated to the same temperature under 14 mm. pressure. Nothing distilled. The residue in the flask was treated with boiling alcohol. On cooling, a substance crystallised in the form of long needles. After further recrystallisation from alcohol, the M.Pt. was 171°. This was shown by comparison to be sym. dibenzyl-urea.

The mother liquor was concentrated but nothing further separated and it was finally taken to dryness under reduced pressure. The residue was a red oil. This was then dissolved in hot benzene but it was eventually found necessary to remove this solvent also, nothing having separated. The addition of petroleum ether reprecipitated the oil. After the oil had been left to stand for two days, more solid separated and was removed from the oil by filtration. This was a further quantity of sym. dibenzyl-urea.

A portion of the oil was distilled under a pressure of 2 mm. The distillate was a pale yellow oil. The B.Pt. at this pressure was about 125°. The temperature of the bath was 170°. This portion of the oil was redistilled. After standing for several days it showed signs of solidifying. The remainder of the oil was then distilled under a pressure of less than 1 mm. up to a bath temperature of 185°. The distillate, which was redistilled, solidified in the receiver. After pressing out on a porous plate this substance was found to have a M.Pt. of 60°. It was recrystallised by dissolving in a small quantity of ether and precipitating with petroleum ether. After repeating this several times, the substance was obtained as long, colourless needles, M.Pt. 63°.

It is easily soluble in the cold, in alcohol, ether, benzene, chloroform, ethyl acetate and carbon disulphide and is insoluble in petroleum ether.

Analytical results indicate as its empirical formula, $C_{17}H_{21}O_2N_2$ , but its constitution has not been determined.

Found - - - - - C = 71.93, H = 7.13, N = 9.63%.
$C_{17}H_{21}O_2N_2$ requires C = 71.58, H = 7.37, N = 9.82%.

Found - - - - Mol.Wt. = 240 (By Rast's Method).
$C_{17}H_{21}O_2N_2$ requires Mol.Wt. = 285.

The quantity of substance available for this molecular weight determination was not sufficient to ensure an accurate result.

There was a residue in the flask after distilling up to 185° but when attempts were made to distil this at a higher temperature it decomposed.

At 170° for 1 hour.

The preceding reaction was repeated under slightly different conditions.

15 gms. of benzaldehyde-2-methyl-semicarbazone and 10.5 gms. of benzylamine were heated to 170°. The mixture was cooled at the end of one hour. It was then distilled up to 170° under 6 mm. pressure. From 140° (bath temp.), a clear liquid distilled and solidified in the condenser. Its B.Pt. was $90^{\circ}_{6}$. This solid appeared to be hygroscopic and its aqueous solution was alkaline to litmus although not strongly so. After pressing on a porous plate and leaving in an evacuated desiccator for two days, its M.Pt. was found to be 88-89°. After this treatment, an attempt was made to crystallise it from dry benzene. On standing, a substance M.Pt. 204° separated from this solution. After filtering this off, the filtrate was concentrated but the only product obtained was a thick oil smelling of benzaldehyde. The substance M.Pt. 204°, of which there was only a minute

quantity, was then recrystallised from benzene, when the M.Pt. rose to 207°.

Analysis indicates the empirical formula, n($C_{11}H_{12}O_3N_2$). The quantity obtained was insufficient for a molecular weight determination.

Found - - - - - C = 59.70, H = 5.41, N = 12.66%.

$C_{11}H_{12}O_3N_2$ requires C = 60.01, H = 5.45, N = 12.73%.

The residue after distillation was dissolved in hot alcohol. On cooling, a crystalline solid was obtained M.Pt. 171°. This was shown by comparison to be sym. dibenzyl-urea.

The mother liquor was then concentrated on the water bath. After standing for some time, a solid came out of solution. This was filtered off and boiled with ether. It was partially soluble. On cooling the ethereal extract, a crystalline substance separated out. After recrystallisation the M.Pt. was 106°. The portion of the substance which was insoluble in ether was dissolved in boiling alcohol. On cooling, a mixture was obtained consisting of needles and large rhomboidal plates. These plates were very large and were easily separated mechanically from the needles. The needles were shown to be sym. dibenzyl-urea. The plates were identical with the substance which had been extracted previously with ether. This substance, M.Pt. 106°, is the normal product of the reaction, benzaldehyde-2-methyl-4-benzyl-semicarbazone.

Found - - - - C = 71.85, H = 6.13, N = 15.96%.

$C_{16}H_{17}ON_3$ requires C = 71.91, H = 6.36, N = 15.72%.

The remainder of the alcohol was evaporated from the mother liquor on the water bath. The residue was a very thick, brown oil. This was treated with ether. The ethereal solution containing the more soluble part of the oil was decanted and dried over sodium sulphate. On addition of petroleum ether, the oily substance was obtained once more. The ether and petroleum were distilled off. After the oil had been left to stand in an evacuated desiccator for several days, an attempt was made to distil it. On heating it to 180° under 2 mm. pressure, a small quantity of a clear yellow oil distilled. It was finally heated to 200° under a pressure of 1 mm. but only a few more drops of the oil were obtained. Decomposition commenced at this temperature and the distillation was stopped.

This oil was similar in appearance and had the same odour as the oil from which was obtained the substance, M.Pt. 63°. Although this oil showed signs of going solid, the substance M.Pt. 63° has not been isolated from it.

Benzaldehyde-2-methyl-4-phenyl-semicarbazone + Aniline.

3.5 gms. of benzaldehyde-2-methyl-4-phenyl-semicarbazone and 1.3 gms. of aniline were heated together. The mixture was kept at 180° for 4 hours. It was then cooled and distilled under reduced pressure to 170°. Some unchanged aniline was the only distillate obtained.

The residue, a clear, resinous substance, was dissolved in hot alcohol. On cooling and allowing to stand for some time, a white crystalline substance separated, M.Pt. 107°. This substance was shown by comparison to be unchanged benzaldehyde-2-methyl-4-phenyl-semicarbazone.

After filtering off this substance, the mother liquor was concentrated on the water bath. Nothing having separated, the remaining alcohol was removed in an evacuated desiccator. The mixture of solid and oil which remained was pressed on a porous plate and left in an evacuated desiccator for two days. Attempts were made to crystallise this mixture from various solvents. A further quantity of benzaldehyde-2-methyl-

-4-phenyl-semicarbazone was obtained but apart from this the products were of an oily or resinous nature.

## Benzaldehyde-2-methyl-4-benzyl-semicarbazone + Benzylamine.

Equimolecular quantities of benzaldehyde-2-methyl-4-benzyl-semicarbazone and benzylamine were mixed and the mixture heated to 170° for $1\frac{1}{2}$ hours. At the end of this time, it was cooled and then heated under 16 mm. pressure. Nothing distilled on heating the mixture to 170° under this pressure. The contents of the flask were then dissolved in boiling alcohol. On cooling, a substance crystallised in the form of long needles, M.Pt. 171°. This was shown by comparison to be sym. dibenzyl-urea.

On concentrating the mother liquor, a small quantity of unchanged benzaldehyde-2-methyl-4-benzyl-semicarbazone was obtained. The unchanged substance amounted to little more than a trace. When the remaining alcohol was removed the residue was found to consist of an oil from which no other pure products were isolated.

## Benzaldehyde-2-methyl-semicarbazone + α-Phenylethylamine.

8.7 gms. of benzaldehyde-2-methyl-semicarbazone was heated with 7 gms. of racemic α-phenylethylamine. The mixture was heated to 175° for 45 minutes. Ammonia was evolved at this temperature. On cooling, a solid separated from the mixture. This was shown to be unchanged benzaldehyde-2-methyl-semicarbazone and the mixture was therefore heated again. It was kept at 175-180° for a further 1¼ hours. It was then distilled under reduced pressure. A few drops of α-phenylethylamine was obtained.

The residue was dissolved in hot alcohol. On cooling, unchanged benzaldehyde-2-methyl-semicarbazone came out of solution. On concentrating the mother liquor another white crystalline substance was obtained. After recrystallisation from alcohol, it melted at 179-180°. Ohlsson[1] gives the M.Pt. of sym. di(α-phenylethyl)urea (from the racemic amine) as 180°.

Found - - - - N = 10.74%.

$C_{17}H_{20}ON_2$ requires N = 10.44%.

Further concentration of the mother liquor yielded only an oil.

[1] Ber.1916,49,1341.

# APPENDIX.

## The Action of Carbonyl Chloride on Acetone Phenylhydrazone.

## Attempted Formation of Acetone-2-phenyl-4-benzyl-semicarbazone.

### Theoretical.

When it was found that the reaction of acetone-2-phenyl-semicarbazone with benzylamine did not go in the way anticipated, it was thought that some of the products of that reaction might be decomposition products of acetone-2-phenyl-4-benzyl-semicarbazone.

It was therefore proposed to attempt the preparation of this substance by some other method and then to study its decomposition products.

Busch and Walther[1] found that carbonyl chloride reacted with benzaldehyde phenylhydrazone according to this equation,

$$\mathrm{Ph.CH{:}N.NHPh + COCl_2 = Ph.CH{:}N.N(Ph).COCl + HCl.}$$

The reaction was carried out in benzene

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[1] Ber.1903,36,1358.

solution, pyridine being added to take up the hydrochloric acid.

They also showed that, if the product from this reaction were dissolved in alcohol and a quantity of aniline representing two molecules were added, and the mixture warmed, benzaldehyde-2.4-diphenyl-semicarbazone was obtained.

$$\begin{aligned} & Ph.CH{:}N.N(Ph).COCl \quad + \quad NH_2Ph \\ = \quad & Ph.CH{:}N.N(Ph).CO.NHPh \quad + \quad HCl \end{aligned}$$

It was hoped that acetone phenylhydrazone would react in the same way with carbonyl chloride and that the product of this reaction might react with benzylamine to give acetone-2-phenyl-4-benzyl-semicarbazone.

It was found that the first reaction took place in the same way as with benzaldehyde phenylhydrazone. The product from the second reaction, however, was not acetone-2-phenyl-4-benzyl-semicarbazone. The analytical results obtained agree fairly well with the theoretical figure for 2-phenyl-4-benzyl-semicarbazide. It is possible that hydrolysis took place during the second reaction. This investigation has not been continued.

## Experimental.

When this reaction was carried out first, the method used by Busch and Walther for a similar reaction was followed exactly.

10 gms. of acetone phenylhydrazone was dissolved in 150 ccs. of benzene and 7.5 gms. of pyridine was added. The mixture was then added gradually to 60 gms. of a 20% solution of phosgene in toluene which was cooled during the addition. On shaking up with water to remove pyridine hydrochloride a solid began to separate from the benzene solution. The water was run off and the solid filtered from the benzene. After recrystallising from benzene-alcohol mixture and from ethyl acetate it melted at 162°. The yield was poor.

It was found that a better yield was obtained by working up in this way. After adding the solution of acetone phenylhydrazone etc. to the cooled solution of phosgene, the mixture is left to stand for some time. The liquid is then poured off from the pyridine hydrochloride which has separated. The latter is dissolved in water and the aqueous solution is extracted with benzene, the benzene extract being afterwards added to the benzene-toluene mother liquor. This is then evaporated to dryness under reduced pressure. The residue is recrystallised as before.

Found - - - - - N = 13.56%.

$C_{10}H_{11}ON_2Cl$ requires N = 13.34%.

Attempted Formation of Acetone-2-phenyl-4-benzyl-semicarbazone.

About 0.5 gm. of the compound obtained from the last reaction was dissolved in alcohol. 0.5 gm. of benzylamine was added and the mixture warmed on the water bath for about 10 minutes. On standing overnight, a white substance had separated. After recrystallising from benzene the M.Pt. was 114°.

The substance is slightly soluble in cold water, easily in hot.

Found - - - - N = 17.20%.

2-Phenyl-4-benzyl-semicarbazide requires N = 17.42%.

## The Action of Potassium Cyanate in Glacial Acetic Acid on

### (i) Acetophenone Phenylhydrazone.

### (ii) Benzophenone Phenylhydrazone.

### Theoretical.

The number of 2-substituted semicarbazones which have been described is somewhat limited. In order to extend the scope of this work it was desirable to obtain more of these substances.

Acetone-2-phenyl-semicarbazone is prepared by the action of potassium cyanate on acetone phenylhydrazone in glacial acetic acid solution. Benzaldehyde benzylhydrazone also reacts in this way[1] but benzaldehyde phenylhydrazone will not react under those conditions[2].

Acetophenone-2-phenyl-semicarbazone is known[3] but was not prepared in this way. It was decided to investigate whether acetophenone phenylhydrazone would react with potassium cyanate in the same way as acetone phenylhydrazone.

The substance obtained had approximately the same nitrogen content as acetophenone-2-phenyl-semi-

[1] See page 117.

[2] Bailey & Read, J.A.C.S.1915,37,1888.

[3] Rolla, G.38,(i),327. See page 118.

carbazone. Its M.Pt. was 183°, however, whereas that of acetophenone-2-phenyl-semicarbazone is given by Rolla as 122°. (I have shown this to be 126°).

Acetophenone-4-phenyl-semicarbazone melts at 187° but a mixture of that substance with the product of the reaction showed a distinct depression of M.Pt.

Acetophenone was removed by hydrolysis from the product, M.Pt. 183°, and acetone was made to react with the residue. The product of this reaction melted at 156° which is the M.Pt. of acetone-4-phenyl-semicarbazone. However, it was shown by a depression of M.Pt. that the product of the reaction was not identical with that substance.

The action of potassium cyanate in glacial acetic acid on benzophenone phenylhydrazone was also tried. In this case, there was no reaction, the benzophenone phenylhydrazone being recovered unchanged.

## Experimental.

(i) 10.5 gms. of acetophenone phenylhydrazone was dissolved in about 30 ccs. of glacial acetic acid and 5 gms. of potassium cyanate was added to the solution which was well shaken during the addition. The mixture was then warmed to about 60° for 15 minutes and left to stand. On cooling, some unchanged acetophenone phenylhydrazone separated. Sufficient acetic acid was added to keep this in solution and a further 5 gms. of potassium cyanate was added. The mixture was heated to 60° for $1\frac{1}{2}$ hours. The temperature was raised to 80° and then allowed to cool. On the addition of water to a small portion, acetophenone phenylhydrazone was precipitated. However, on cooling the solution in ice, a solid separated which, after many recrystallisations from alcohol, melted at 183°.

Found - - - - $N = 16.72\%$.
$C_{15}H_{15}ON_3$ requires $N = 16.60\%$.

The substance was then hydrolysed with hydrochloric acid and the acetophenone was extracted with ether. On the addition of acetone and sodium acetate a substance was obtained, M.Pt. 156°. A mixture of this substance with acetone-4-phenyl-semicarbazone showed a depression of M.Pt.

(ii) 17 gms. of benzophenone phenylhydrazone was dissolved in about 175 ccs. of hot glacial acetic acid. 5 gms. of potassium cyanate was added gradually to the warm solution which was kept at a sufficiently high temperature to ensure that the benzophenone phenylhydrazone should remain in solution.

After the addition of the potassium cyanate the mixture was kept at 70-75° for about 2½ hours and was then cooled. Benzophenone phenylhydrazone was recovered unchanged.

More acetic acid was added as benzophenone phenylhydrazone is very sparingly soluble. A further 5 gms. of potassium cyanate was added gradually and the solution was warmed to 70° for 4 hours. Benzophenone phenylhydrazone was again recovered unchanged.

## The Action of Phenyl Isocyanate on Acetone Phenylhydrazone.

### Theoretical.

Whyburn and Bailey[1] heated phenyl isocyanate and acetone phenylhydrazone in a sealed tube to 100° and obtained a substance M.Pt. 191° which they state to be acetone-2.4-diphenyl-semicarbazone.

On heating these substances to 100° under reflux in a small quantity of benzene, this substance was not obtained. Two products were obtained, one melting at 208° and the other at 138°. The latter substance was analysed and gave figures approximating to the theoretical figures for acetone-2.4-diphenyl-semicarbazone.

On acting on 2.4.diphenyl-semicarbazide with acetone, a substance was obtained, M.Pt. 138°, which was shown to be identical with the substance obtained from the above reaction.

### Thermal Decomposition of the Substance, M.Pt.138°.

Acetone-2-phenyl-semicarbazone decomposes on heating to give acetone phenylhydrazone and cyanic acid, thus,

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[1] Whyburn & Bailey, J.A.C.S.1928,50,912.

$$(CH_3)_2C{:}N.N(Ph).CO.NH_2 \quad = \quad (CH_3)_2C{:}N.NHPh \quad + \quad CONH$$

It was expected, therefore, that acetone-2.4-diphenyl-semicarbazone would decompose in a similar manner, giving acetone phenylhydrazone and phenyl isocyanate. It was found that the substance M.Pt. 138° behaved in this way. A quantity of sym. diphenyl-urea, however, was also found. Phenyl isocyanate gives sym. diphenyl urea with aniline or water but it is difficult to explain how either of these substances could be present. No aqueous solvents were used in the purification of the substance.

## The Action of Aniline on the Substance M.Pt. 138°.

Acetone-2.4-diphenyl-semicarbazone with aniline would probably give acetone phenylhydrazone and sym. diphenyl-urea in the manner of other 2.4-substituted semicarbazones with amines.

It was found that these products were obtained when the substance M.Pt. 138° was acted on with aniline.

## Experimental.

When this reaction was carried out first, it was done in this way. Equimolecular quantities of acetone and phenylhydrazine were mixed. Benzene was then added and the solution was dried over anhydrous sodium sulphate. This was then filtered off and phenyl isocyanate was added to the solution. It was found, however, that this drying treatment was not severe enough. Carbanilide was formed through the action of phenyl isocyanate with water present. The acetone phenylhydrazone must be prepared separately, dried over potassium carbonate and distilled before use.

8 gms. of acetone phenylhydrazone and 5 gms. of phenyl isocyanate were mixed with the addition of 10 ccs. of benzene. After standing for two days, nothing had separated from the mixture which was then heated to 75-80° for $1\frac{1}{2}$ hours. Nothing separated on cooling and it was afterwards heated to its B.Pt. for a further 2 hrs. A small quantity of petroleum ether was added and the mixture was cooled in ice for a few hours. A crystalline solid separated. After recrystallisation from benzene, it melted at 138°.

Found - - - - C = 72.44, H = 6.48, N = 16.02, 15.68%.
$C_{16}H_{17}ON_3$ requires C = 71.91, H = 6.36, N = 15.73%.

A substance, M.Pt. 208° was also formed. It is less soluble in benzene than the substance M.Pt.138°. A better method of separating them, however, is by the use of chloroform in which the substance, M.Pt.138°, is much more soluble.

### Reaction of Acetone with 2.4-diphenyl-semicarbazide.

A small quantity of 2.4-diphenyl-semicarbazide was warmed with an excess of acetone. The mixture was allowed to boil gently for $1\frac{1}{2}$ hours. After standing overnight in an open flask, most of the acetone had evaporated and a solid crystallised in square plates. After recrystallising from benzene, it melted at 138°. This substance was identical with the one obtained from phenyl isocyanate and acetone phenylhydrazone.

### Thermal Decomposition of Substance, M.Pt. 138°.

6 gms. of the substance was heated to 160° for 1 hour. It was then cooled and distilled under 10 mm. pressure.

The first few drops of distillate had the strong smell of phenyl isocyanate. This portion was warmed with aniline. The product was recrystallised from alcohol. It melted at 238° and was shown, by comparison, to consist of sym. diphenyl-urea.

The remainder of the distillate was a liquid, B.Pt. 120° under 10 mm. pressure. This is about the B.Pt. of acetone phenylhydrazone at that pressure. It was hydrolysed and gave the nitroprusside test for acetone and reduced Fehling's solution.

The residue was extracted with boiling alcohol. On cooling, sym. diphenyl-urea was obtained.

### Reaction of Aniline with the Substance, M.Pt. 138°.

2.2 gms. of the substance M.Pt. 138° was heated with 0.9 gms. of aniline to 160° for 40 minutes.

On distilling under reduced pressure, a liquid was obtained having the B.Pt. of acetone phenylhydrazone. On hydrolysis, it gave the nitroprusside test for acetone and reduced Fehling's solution.

Sym. diphenyl-urea was obtained on treating the residue with boiling alcohol.

# PREPARATIONS.

## Part I.

### Benzoin hydrazone.

Curtius & Blümer, J.pr.52,(2),124.

40 gms. of benzoin is mixed with $11\frac{1}{2}$ gms. of hydrazine hydrate. Allow it to digest on the water-bath till it forms a homogeneous liquid. Heat for 4 hrs. and allow to stand for 8 days. The product forms a tough mass which is pounded in a mortar and rubbed up with ether. There remains a powder which is washed with ether and recrystallised from as little alcohol as possible. The M.Pt. is 75°.

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Using the method of Curtius and Blümer, it was found that a red jelly was formed on taking up with ether. This was recrystallised from alcohol and gave a solid M.Pt.249°. More satisfactory results were obtained by keeping the temperature just below the B.Pt. and restricting the time of heating to 3 hrs. The solution is then reduced to small bulk and left to stand overnight. It is purified in the same way as before.

Sodium derivative. 3 gms. of benzoin hydrazone are dissolved in as little absolute alcohol as possible and to this is added the exact calculated quantity of sodium also dissolved in absolute alcohol. The sodium derivative is precipitated with dry ether.

### 1.Menthyl-hydrazine.

Kishner, J.pr.1901,64,113.

20 gms. of 1.menthylamine hydrochloride is dissolved in water and 15 gms. of potassium hydrate is added. It is then cooled in ice and 20 gms. of bromine is added gradually with vigorous shaking. The bromamine settles to the bottom. After decanting the liquid and adding water at 0° it is mixed with $Ag_2O$ obtained from 20 gms. of silver nitrate. Menthone menthylhydrazone crystallises from alcohol as prisms, M.Pt.93°. Menthone menthylhydrazone is boiled for 1 hour with dilute hydrochloric acid and the menthone liberated is extracted with benzene. The aqueous solution is then evaporated to dryness, leaving 1.menthylhydrazine hydrochloride.

### d.Camphor hydrazone.

Kishner, J.Russ.Phys.-Chem.Soc.43,582-593.

200 gms. of camphor and 200 gms. of hydrazine hydrate (50%) are boiled for 170 hrs. in 750 gms. of alcohol. The alcohol is then removed on the water bath and the camphor hydrazone is distilled under reduced pressure. B.Pt. 143° at 33 mm. pressure.

## Part II.

### $\delta$($\alpha$-Phenylethyl)semicarbazide hydrochloride.

Wilson, Hopper & Crawford, J.C.S.1922,121,866 and Hopper, J.Roy.Tech.Coll.1927,4,52.

$\alpha$-Phenylethylamine is prepared by the reduction of acetophenone oxime. $\alpha$-Phenylethylamine (slightly more than one mol.) is heated with acetone semicarbazone (one mol.). The mixture is heated at 138° for 30 minutes under reflux and then at 142° for 20 minutes without the condenser. The reaction mixture is then poured into cold water. The acetone-$\delta$($\alpha$-phenylethyl)semicarbazone is collected and hydrolysed by heating with 10 times its weight of N.HCl in a boiling water bath. The solution when cold is extracted with ether and the aqueous portion is then taken to dryness. The residue is recrystallised from alcohol. M.Pt. 165° with decomposition.

### Piperonyloin.

Perkin, J.C.S.1891,59,164.

5 gms. of piperonal are dissolved in 20 gms. of alcohol, (50%), and 2 gms. of pure potassium cyanide is added. The whole is heated to gentle boiling under reflux for $3\frac{1}{2}$ hrs. After standing for 12 hrs. the yellow mass which separates is recrystallised first from ethyl alcohol then methyl alcohol and dried at 100°. The M.Pt. is 120°.

After drying at 100° it was found that the piperonyloin had been partially converted to a brown substance, M.Pt. about 170°. The drying temperature was reduced, the process being completed in an evacuated desiccator.

## Part III.

### Acetone-2-phenyl-semicarbazone.

Goodwin & Bailey, J.A.C.S.1924,46,2829.

To 50 gms. of acetone phenylhydrazone in 150 ccs. of glacial acetic acid and 50 ccs. of water, is added over a period of 20 minutes, 30 gms. of potassium cyanate. A temperature of 60° is maintained for 30 minutes to complete the reaction. Most of the acetone-2-phenyl-semicarbazone crystallises and additional yield is obtained by diluting and precipitating with ammonia. It is recrystallised from water or ethyl acetate. M.Pt. 140°.

It was found that ethyl acetate or fairly dilute alcohol gave better results than pure water.

### Benzaldehyde-2-benzyl-semicarbazone.

Bougault & Leboucq, C.r.1928,186,957.

Benzaldazine was reduced with sodium amalgam to benzalbenzylhydrazone. Benzylhydrazine was obtained from this and was converted to 2-benzyl-semicarbazide which was then treated with benzaldehyde to give the required product.

I have found, however, that it is unnecessary to decompose the benzaldehyde benzylhydrazone. Benzaldehyde-2-benzyl-semicarbazone can be prepared by the same method as acetone-2-phenyl-semicarbazone.

Benzaldehyde benzylhydrazone is dissolved in a mixture of 3 parts of glacial acetic acid and 1 part of water, and to this is added a 10% excess of potassium cyanate. It is left to stand for 12 hours. Benzaldehyde-2-benzyl-semicarbazone has then begun to separate. The yield is greatly increased by cooling the solution in ice. M.Pt. 159-160°.

### Acetophenone-2-phenyl-semicarbazone.

Rolla, G.38,(i),327.

This substance is prepared by acting on 2-phenyl-semicarbazide with acetophenone in aqueous alcohol as solvent.

The following quantities are used.

8 gms. 2-phenyl-semicarbazide hydrochloride.
8 gms. sodium acetate.
5 gms. acetophenone.
40 ccs. alcohol.
16 ccs. water.

Rolla gives the M.Pt. as 122°.

This method of preparation was used, the 2-phenyl-semicarbazide hydrochloride being obtained by hydrolysis of acetone-2-phenyl-semicarbazone. It was found, however, that the M.Pt. of the product was 126°

Found - - - - N = 16.74%.

$C_{15}H_{15}ON_3$ requires N = 16.60%.

<u>Benzaldehyde-2-methyl-semicarbazone</u>.

Von Brüning, A.1889,253, 6-11, and

Young & Oates, J.C.S.1901,79,662.

Nitroso-methyl-urea is prepared according to the method of von Brüning. 50 gms. of methyl-urea nitrate are dissolved in warm water to which finely divided ice is then added till crystallisation begins. To this is added the calculated quantity of solid sodium nitrite. Nitroso-methyl-urea comes out as small yellow plates, M.Pt. 123-124° with decomposition.

One part of nitroso-methyl-urea is suspended in 6 parts of water and to this is added 2½ parts of acetic acid in which the urea is not readily soluble. The temperature is kept between 5-15° and 4 parts of zinc powder are added during 2-3 hours with continuous shaking. More zinc and acid are added if necessary till the solution no longer reduces Fehling's solution. The solution is then filtered and the filtrate is shaken up with benzaldehyde. The product separates as a mass of white needles which are recrystallised from water and benzene. M.Pt. 159-160°.