# THE ACTION OF AMINES, PARTICULARLY SECONDARY AMINES, ON SEMICARBAZONES.

A THESIS PRESENTED BY
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This research was carried out in the Royal Technical College, Glasgow, to the Governors of which the Author tenders her grateful thanks for her appointment as Research Assistant, and for the opportunities afforded her in the work.

The Author wishes to acknowledge her appreciation of the very keen interest shown in the work, and of much valuable advice given by Professor F.J.Wilson who has supervised this research.

Note:-

The section of the work relating to the action of Piperidine on Acetonesemicarbazone has already been published in the Journal of the Chemical Society, a copy of the paper is included with this thesis.

Where reference is made in the text to another section of the work, the letters "a" and "b" following the number of the page indicate top and bottom halves respectively.

# CONTENTS.

# ABBREVIATIONS.

| | |
|---|---|
| Ann. | Justus Liebig's Annalen der Chemie. |
| Ann. Chim. Phys. | Annales de Chimie et de Physique. |
| Atti R. accad. L. | Atti della Reale Accademia Lincei. |
| Ber. | Berichte der Deutschen chemischen Gesellschaft. |
| Compt. rend. | Comptes rendus , Paris. |
| Gazz. | Gazzetta chimica italiana. |
| J. | Journal of the Chemical Society. |
| J. Am. C. S. | Journal of the American Chemical Society. |
| J. für Prakt. Chem. | Journal für Praktische Chemie. |
| J.S.C.I. | Journal of the Society of Chemical Industry. |
| P. | Proceedings of the Chemical Society. |

## PIPERIDINE AND ACETONESEMICARBAZONE.

Plan showing connection between derivatives.

Acetonesemicarbazone and piperidine reaction.
( anhydrous conditions )
↓
(1) Acetonepiperidinoformylhydrazone.
$CMe_2:N\cdot NH\cdot CO\cdot NC_5H_{10}$
Hydrolysis by water with loss of acetone, loss of piperidine from two mols., and recombination with acetone.
↓
(11) Acetone-ε-piperidinoformylcarbohydrazone-hydrate.
$CMe_2(OH)\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$ .
Hydrolysis by water with loss of acetone and replacement of latter by benzaldehyde.
↓
(111) Benzaldehyde-ε-piperidinoformylcarbohydrazone.
$CHPh:N\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$ .
Hydrolysis by water with loss of acetone and combination of base with acetophenone.
↓
(1V) Acetophenone-ε-piperidinoformylcarbohydrazone.
$CPhMe:N\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$ .
Hydrolysis of (11), (111) and (1V) with dilute hydrochloric acid.
↓
(V) ε-Piperidinoformylcarbohydrazide hydrochloride.
$NH_2\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10},HCl,H_2O$ .
[ Hydrolysis of (11) with picric acid.
ε-Piperidinoformylcarbohydrazide picrate.
$NH_2\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10},C_6H_3O_7N_3$ .]

## PIPERIDINE AND ACETOPHENONESEMICARBAZONE.

Continuation of plan.

Acetophenonesemicarbazone and piperidine reaction.
↓
(V1) Acetophenonepiperidinoformylhydrazone.
$CPhMe:N\cdot NH\cdot CO\cdot NC_5H_{10}$ .
Hydrolysis with dilute hydrochloric acid, loss of acetophenone.
↓
(V11) Piperidinoformylhydrazide hydrochloride.
$NH_2\cdot NH\cdot CO\cdot NC_5H_{10},HCl$ .
Combination with benzaldehyde.
↓
(V111) Benzaldehydepiperidinoformylhydrazone.
$CHPh:N\cdot NH\cdot CO\cdot NC_5H_{10}$ .
Formation of normal base, loss of piperidine from two mols., and combination with acetone.
↓
(11) Acetone-ε-piperidinoformylcarbohydrazone-hydrate.
$CMe_2(OH)\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$ .
Hydrolysis with water, loss of acetone.
↓
(1X) ε-Piperidinoformylcarbohydrazide.
$NH_2\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$ .

[ Hydrolysis by water of (1), with loss of acetone and loss of piperidine from two molecules of the base.
↓
(1X) ε-Piperidinoformylcarbohydrazide.]

# INTRODUCTION.

This investigation on the action of certain secondary amines and one primary amine on semicarbazones, forms part of a scheme of work which has been followed out for a considerable number of years, under the direction of Professor F.J.Wilson, D.Sc.,F.I.C., in the Organic Chemistry Department of this College.

The scheme is concerned with the reactions of semicarbazones and 2-substituted semicarbazones, $RR^1C{:}N\cdot NH\cdot CO\cdot NH_2$,[a] $RR^1C{:}N\cdot NR^2\cdot CO\cdot NH_2$,[b] thiosemicarbazones, $RR^1C{:}N\cdot NH\cdot CS\cdot NH_2$,[c] and semioxamazones, $RR^1C{:}N\cdot NH\cdot CO\cdot CO\cdot NH_2$.[d]

The action of amines on these substances has been extensively investigated.

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[a] Wilson, Hopper and Crawford, J., 1922, 121, 866.
[a] Wilson and Crawford, J., 1925, 127, 103.
[b] Wilson and Chapman, J., 1931, 507.
[c] Wilson, Baird and Burns, J., 1927, 2527.
[d] Wilson and Pickering, J., 1924, 125, 1152.

$(CH_3)_2{:}C{:}N\cdot NH\cdot CO\cdot NH_2$ .

$(CH_3)_2{:}\overline{C{:}\overset{\alpha}{N}\cdot\overset{\beta}{NH}\cdot\overset{\gamma}{CO}\cdot\overset{\delta}{NH}\cdot\underset{\varepsilon}{NH_2}}$ .

The first work on the action of amines on semicarbazones was carried out by Borsche and his collaborators, ( Ber. 1901, 34, 4297; 1904, 37, 3177; 1905, 38, 831; ) who found that the two substances reacted on heating to form δ-arylsemicarbazones with liberation of ammonia, as in the following general equation :

$$CRR^1:N\cdot NH\cdot CO\cdot NH_2 + R^2NH_2 = CRR^1:N\cdot NH\cdot CO\cdot NHR^2 + NH_3$$

The latter product could be hydrolysed with dilute hydrochloric acid to give δ-arylsemicarbazide hydrochloride with liberation of the ketone or aldehyde.

$$CRR^1:N\cdot NH\cdot CO\cdot NHR^2 + HCl + H_2O$$

$$= CRR^1:O + NH_2\cdot NH\cdot CO\cdot NHR^2,HCl .$$

On treatment of the hydrochloride with alkali the base corresponding to the above salt, viz. δ-arylsemicarbazide could generally be isolated.

The amines studied by Borsche included aniline, the toluidines, the naphthylamines, and similar amino compounds, all of which conformed to the above general reactions.

The investigation has been extended ( Wilson, Hopper and Crawford, loc. cit. ) and the same reaction has been found to take place with other primary amines in which the amino group occurs in a side chain, and also with certain aliphatic amines. Benzylamine, α-phenylethylamine and l-menthylamine/

-amine were among those investigated.

These authors suggested that optically active semicarbazides might be useful in the resolution of certain racemic aldehydes and ketones, since the $\delta$-substituted semicarbazide obtained by hydrolysis could recombine with those to form different $\delta$-substituted semicarbazones. In a later paper Wilson and Hopper (J., 1928, 2483.) accomplished a resolution of benzoin using d-$\delta$-($\alpha$-phenylethyl)semicarbazide hydrochloride and also the l-isomer. It was thought that possibly other optically active substituted semicarbazides might be used with advantage, and that those of higher molecular weight might give good yields of solid products free from oils, when combined with the substances to be resolved.

It was with this in view that the preparation of $\alpha$-naphthylbenzylamine (Busch and Leefhelm, J. für Prakt. Chem. (2) 77, 14 (1908). ) was undertaken, as it seemed a very suitable one for the purpose, and capable of easy resolution into its enantiomorphs by means of tartaric acid. (Berlingozzi, Gazz. Chim. Ital. 50, (1920) 215 and 321.)
The primary base was, however, not isolated in a pure state from the hydrochloride as it decomposed too rapidly with loss of ammonia to form the secondary di(naphthylbenzyl)amine.

$$2C_{10}H_7CH(C_6H_5)\cdot NH_2 \quad = \quad NH_3 \quad + \quad \begin{matrix} C_{10}H_7(C_6H_5)CH. \\ C_{10}H_7(C_6H_5)CH \end{matrix}\!\cdot NH$$

The secondary amine also contained asymmetric carbon, and, if secondary amines could react with semicarbazones in accordance with the general equation, to produce , on subsequent hydrolysis, δ-substituted semicarbazides, this amine might prove suitable.

No work had apparently been carried out on the action of secondary amines on semicarbazones, so it was decided to investigate the reactions with a number of amines, and find out whether their behaviour was similar to that of the primary amines.

Acetonesemicarbazone, acetophenonesemicarbazone and benzaldehydesemicarbazone were employed for the experiments.

The general method was to heat the amine and the semicarbazone in equimolecular quantities in toluene.

The use of the amine itself as a solvent was avoided , since δ-substitutedsemicarbazones may themselves react with amine to give a carbamide and a hydrazone when the substances are kept at a high temperature for a considerable time.

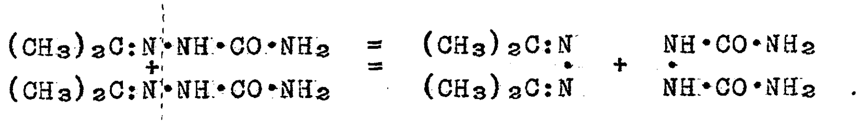
$$RR^1C{:}N{\cdot}NH{\cdot}CO{\cdot}NHR^2 \quad + \quad NH_2R^2 \quad = \quad CO(NHR^2)_2 \quad + \quad RR^1C{:}N{\cdot}NH_2.$$

In every case examined the duration of heating was considerably longer than had been necessary with primary amines.

The possibility of formation of decomposition products of the semicarbazones had also to be taken into consideration.

Semicarbazones/

Semicarbazones may decompose on heating to give an azine and hydrazodicarbonamide.

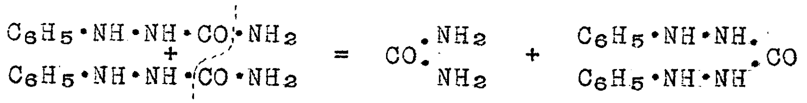


$$\begin{array}{l}(CH_3)_2C{:}N\cdot NH\cdot CO\cdot NH_2\\ \quad +\\ (CH_3)_2C{:}N\cdot NH\cdot CO\cdot NH_2\end{array} = \begin{array}{l}(CH_3)_2C{:}N\\ \qquad\quad\cdot\\ (CH_3)_2C{:}N\end{array} + \begin{array}{l}NH\cdot CO\cdot NH_2\\ \cdot\\ NH\cdot CO\cdot NH_2\end{array}.$$

( Curtius, Ber. 26,405; 27,57;)

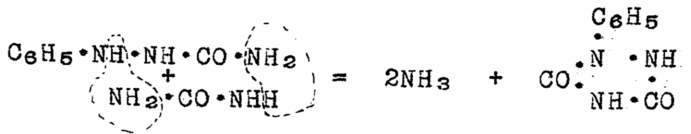
Ammonia may be evolved from decomposition of hydrazine, $3NH_2\cdot NH_2 = 4NH_3 + N_2$, or from decomposition of the semicarbazone. ( Acetonesemicarbazone heated in toluene at 110°-115° gives ammonia.)

Various other types of decomposition may also take place. According to Poth and Bailey, ( J. Am. C. S. 45,3008) α-phenylsemicarbazide may decompose to give urea and diphenylcarbazide.

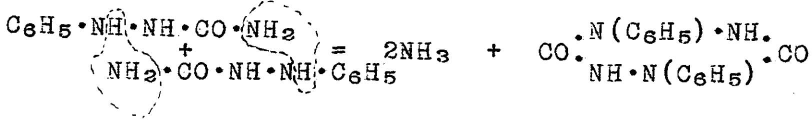


$$\begin{array}{l}C_6H_5\cdot NH\cdot NH\cdot CO\cdot NH_2\\ \qquad\qquad +\\ C_6H_5\cdot NH\cdot NH\cdot CO\cdot NH_2\end{array} = CO\begin{array}{l}\cdot NH_2\\ \cdot NH_2\end{array} + \begin{array}{l}C_6H_5\cdot NH\cdot NH.\\ C_6H_5\cdot NH\cdot NH\end{array}\cdot CO \qquad 1.$$

A similar decomposition seems possible with acetonesemicarbazone. A second reaction may occur with the urea formed giving ammonia and phenylurazole, diphenylurazole may also be produced in accordance with the third equation.



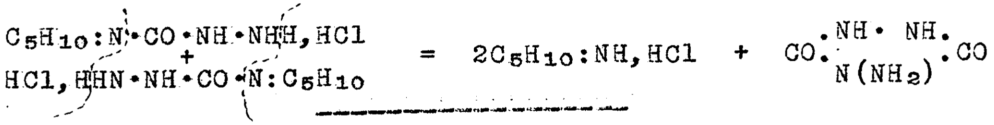
$$\begin{array}{l}C_6H_5\cdot NH\cdot NH\cdot CO\cdot NH_2\\ \qquad\qquad +\\ \qquad NH_2\cdot CO\cdot NHH\end{array} = 2NH_3 + CO\begin{array}{l}\overset{C_6H_5}{\cdot N}\ \cdot NH\\ \qquad\ \ \cdot\\ NH\cdot CO\end{array} \qquad 2.$$



$$\begin{array}{l}C_6H_5\cdot NH\cdot NH\cdot CO\cdot NH_2\\ \qquad\qquad +\\ \qquad NH_2\cdot CO\cdot NH\cdot NH\cdot C_6H_5\end{array} = 2NH_3 + CO\begin{array}{l}\cdot N(C_6H_5)\cdot NH.\\ \cdot NH\cdot N(C_6H_5)\end{array}\cdot CO \qquad 3.$$

The formation of 4-aminourazole and piperidine hydrochloride from/

from thermal decomposition of the piperidinosemicarbazide hydrochloride ( Substance (V11) . Page 38b .) is similar to these last two reactions.



$$\begin{matrix} C_5H_{10}{:}N\cdot CO\cdot NH\cdot NHH,HCl \\ + \\ HCl,HHN\cdot NH\cdot CO\cdot N{:}C_5H_{10} \end{matrix} = 2C_5H_{10}{:}NH,HCl + CO\begin{matrix}\cdot NH\cdot NH\cdot \\ N(NH_2)\end{matrix}CO$$

Amino compounds of the aniline type e.g. methylaniline and benzylaniline seem to react only to a very slight extent with semicarbazones, with more basic amines such as dibenzylamine and piperidine the reaction is much more vigorous.
This is in agreement with the observations on primary amines. ( Crawford, Private communication.)

Piperidine was expected to react normally with semicarbazones, particularly since it reacts with acetophenonesemioxamazone to form acetophenonepiperidinooxalylhydrazone and ammonia. In this the semioxamazone has behaved in exactly similar fashion to a semicarbazone, which is exceptional. ( W Wilson and Pickering, loc. cit.).

Two series of derivatives were, however, obtained from the piperidine reactions. ( See plan on page 3 ,extending.) The normal acetonesemicarbazone derivative, viz. acetone-piperidinoformylhydrazone (1) was hygroscopic and was hydrolysed by water with loss of acetone. Two molecules of the base/

base, produced in solution, lost one molecule of piperidine giving rise to an abnormal base (1X) which united with acetone to give acetone-$\varepsilon$-piperidinoformylcarbohydrazone-hydrate (11). This base (1X) or acetone derivative (11) gave a series of abnormal derivatives (111), (1V), and (V).

( See page 3 .)

$$C_5H_{10}N\cdot CO\cdot NH\cdot NHH \; + \; C_5H_{10}N\cdot CO\cdot NH\cdot NH_2$$

$$= \; C_5H_{10}NH \; + \; C_5H_{10}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH_2 \, .$$

This reaction also is comparable to that cited above by Poth and Bailey. ( Page 10b , Eqn. 3.)

The normal $\delta$-substituted semicarbazide of this series, viz. piperidinoformylhydrazide was too unstable to permit of its isolation from the hydrochloride (V11) which was obtained.

The next amine investigated was methyl aniline. The reaction was very slow and the structure of the derivative isolated was not determined.

Benzylaniline reacted slowly but gave a small yield of the $\delta$-substituted semicarbazone, this, however, did not give a stable semicarbazide hydrochloride on hydrolysis.

Dibenzylamine also gave normal $\delta$-substituted semicarbazones ( acetone, acetophenone and benzaldehyde ), no $\delta$-substituted semi/

semicarbazide hydrochloride could, however, be obtained by boiling these with dilute hydrochloric acid, since the semicarbazide was itself completely hydrolysed producing hydrazine hydrochloride and dibenzylamine hydrochloride.

In the experiment with acetonesemicarbazone a secondary reaction set in by which two molecules of the acetonedibenzylaminoformylhydrazone ($\delta$-substituted semicarbazone) combined with loss of acetoneketazine to form a hydrazodicarbonamide derivative, viz. s-di(dibenzylaminoformyl)hydrazide.

$$\begin{array}{l} (CH_3)_2C{:}N\vdots\cdot NH\cdot CO\cdot N{:}(CH_2C_6H_5)_2 \\ \qquad\qquad + \\ (CH_3)_2C{:}N\vdots\cdot NH\cdot CO\cdot N{:}(CH_2C_6H_5)_2 \end{array} = \begin{array}{l} (CH_3)_2{:}N \\ \quad\;\; \cdot \\ (CH_3)_2{:}N \end{array} + \begin{array}{l} NH\cdot CO\cdot N(CH_2C_6H_5)_2 \\ \cdot \\ NH\cdot CO\cdot N(CH_2C_6H_5)_2 \end{array}$$

A somewhat similar reaction is reported with $\delta$-$\beta$-naphthylthiosemicarbazide hydrochloride ( Wilson, Baird and Burns, loc. cit. p.2533.) in which two molecules combine with loss of hydrazine hydrochloride to give hydrazinedithiocarbo-$\beta$-naphthylamide.

$$\begin{array}{l} NH_2\vdots\cdot NH\cdot CS\cdot NH\cdot C_{10}H_7,HCl \\ \qquad + \\ NH_2\vdots\cdot NH\cdot CS\cdot NH\cdot C_{10}H_7,HCl \end{array} = \begin{array}{l} NH_2,HCl \\ \cdot \\ NH_2,HCl \end{array} + \begin{array}{l} NH\cdot CS\cdot NH\cdot C_{10}H_7 \\ \cdot \\ NH\cdot CS\cdot NH\cdot C_{10}H_7 \end{array}$$

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The next amine investigated was a primary amine which occurs in nature as the d-isomer in the extraction products of the Chinese drug Ma Huang. The normal benzaldehyde-

nor/

-norψ ephedrinoformylhydrazone was obtained, and a hydrochloride of the δ-substituted semicarbazide. The latter, however, decomposed , giving an oxazol derivative and hydrazine hydrochloride, (p.125). The δ-substituted semicarbazide hydrochloride could be made to recombine with benzaldehyde, but only extremely slowly and to give a poor yield. Attempts were also made to combine this substance with racemic benzoin and with p-methoxyhydratropaldehyde but only oils resulted. The reaction with benzoin was attempted both in alcoholic solution by the method of Baeyer(Ber.,1894,27,1918), and in pyridine solution according to the method used by Wilson and Hopper, (J.,1928,2485) but the active base was apparently unsuitable.

Three other secondary amines were then examined. Tetrahydroquinaldine reacted extremely slowly with acetophenonesemicarbazone giving merely a trace of an abnormal product. Dipropylamine gave a very small yield of a compound insufficient to permit of further examination. From ethylbenzylamine, however, a good yield of acetophenoneethylbenzylaminoformylhydrazone was obtained. This substance could be hydrolysed without separation of hydrazine hydrochloride, as had occurred with the dibenzylamine compounds.

A comparison of the results obtained with the various amines shows/

shows, that those containing the benzyl group seem to react readily, and in accordance with the general equation.

In view of the abnormal behaviour of nor d ψ ephedrino-formylhydrazide hydrochloride which seemed to render it unsuitable for the type of resolution aimed at, the investigation of the action of ephedrine and ψephedrine, a secondary amine, $C_6H_5CH(OH)\cdot CH(CH_3)\cdot NHCH_3$ , might be of value.

# α-NAPHTHYLBENZYLAMINE.

# α-NAPHTHYLPHENYLAMINOMETHANE.

## (α-Naphthylbenzylamine).

The hydrochloride of this amine was described as having been obtained by the action of tin and hydrochloric acid on the oximes of phenyl-α-naphthylketone, ( Atti. R. accad. L. 1914, [V] 23, i, 340-346). This ketone can be prepared from α-naphthyl magnesium bromide and benzoyl chloride( Ber., 1904, 37, 2753-2764).

Betti and Poccianti ( Gazz., 45, 1, 372 [1915]) prepared α-napthyl benzylamine hydrochloride and found it to be identical with that prepared by Busch and Leefhelm from α-naphthyl magnesium bromide and hydrobenzamide, ( J. für Prakt. Chem. , 1908, [2], 77, 14).

$$2MgC_{10}H_7Br + CHPh(N:CHPh)_2 = CHPh[N(MgBr)CH(C_{10}H_7)Ph]_2$$

$$\xrightarrow[+3H_2O]{} CHPhO + 2NH_2\cdot CH(C_{10}H_7)Ph + 2Mg(OH)Br$$

The above is the type of reaction involved, but the behaviour of α-naphthyl magnesium bromide with hydrobenzamide is abnormal in that considerable quantities of isoamarine are formed. This intra-molecular change which takes place normally with hydrobenzamide at 240°, occurs here below 100°.

$$CHPh(N:CHPh)_2 = CHPhNH\cdot CPh:NCHPh .$$

Busch and Leefhelm described the free base, α-naphthylbenzylamine, as an oily substance which solidified on standing to give tufts of crystals M.Pt. 121°.

Berlingozzi/

Berlingozzi (Gazz., 1920, 50, 215.) prepared α-naphthylbenzylamine by the reduction of the oximes of phenyl-α-naphthylketone, and described it as a transparent crystalline solid melting at 56°-59°. In a later paper (Gazz., 50, 1, 323) Berlingozzi repeated the preparation given by Busch and Leefhelm, and, starting from α-bromnaphthalene, magnesium and hydrobenzamide, he again obtained the base in crystalline form melting at 56°-59°. A resolution of the racemic base by means of tartaric acid was accomplished later, (Gazz., 1920, 50, [2], 56).

α-Naphthylbenzylamine hydrochloride was prepared by Busch and Leefhelm's method, being obtained as pale buff-coloured small crystals melting with decomposition at 278°. The mother-liquors (alcoholic) rapidly darkened in colour, and subsequent fractions of crystals were brown. Several attempts were made to obtain the pure base, but in every case some decomposition had taken place, and mixtures of the primary and secondary amines formed in accordance with the equation:-

$$2C_{10}H_7\cdot CHPh\cdot NH_2 \;=\; NH_3 \;+\; (C_{10}H_7\cdot CHPh)_2{:}NH\ .$$

When the primary amine appeared to decompose so readily, the substance was considered unsuitable for the preparation of δ-substituted semicarbazones, as this necessitated comparatively high temperatures. Before the secondary amine could be used, it was desirable to ascertain whether secondary amines conformed to the general reaction given on page 7a.

## EXPERIMENTAL.

### PREPARATION OF α-NAPHTHYLBENZYLAMINE HYDROCHLORIDE.

3·2 gm. of thoroughly cleaned magnesium ribbon cut into small pieces was placed in a flask with 27·6 gm. α-monobromnaphthalene dissolved in about 100ccs. pure dry ether. The liquid was then warmed under reflux until solution was complete; the addition of a few drops of methyl iodide proved very beneficial in hastening the start of the reaction. The olive-green coloured solution was cooled and the hydrobenzamide ( 20 gm.) added in small quantities. During the addition the liquid was thoroughly cooled to minimise the conversion of the hydrobenzamide to isoamarine. The mass became cherry-red in colour. After the ether had been distilled off, the residue was slightly warmed and treated with aqueous HCl. Benzaldehyde was liberated in accordance with the equation given, (p.17) and this was removed by steam distillation along with a considerable quantity of naphthalene . Ammonium chloride followed by excess of ammonia was added to the acid solution, and the base which separated was extracted with ether. This ethereal solution was at first a golden yellow colour but it gradually turned greenish-brown, exhibiting slight fluorescence, and a quantity of white crystals separated. These were identified as isoamarine produced from the/

the hydrobenzamide by intra-molecular change. When no more of these crystals appeared to be separating, the ether was evaporated, and the base obtained as a thick dark yellow oil.

The hydrochloride was formed as a pasty solid when the oil was mixed with the dilute acid, this substance was then removed and purified by recrystallization from alcohol.

The salt formed in slightly coloured crystals, M.Pt. 278°, but the alcoholic solutions darkened on evaporation depositing later fractions much darker in colour.

The base was liberated from the hydrochloride by gently grinding the latter with a very dilute solution of caustic soda, and then rapidly extracting the alkaline mixture with ether. Petroleum ether was added to the extract until the liquid was slightly turbid. On standing, a precipitate separated out, this was, however, a mixture of the primary and secondary amines formed by spontaneous decomposition of the primary amine, with loss of ammonia. Various fractions of the base were obtained, the melting points being : 80°-85°, 120°-125° and 90°-93°, in every instance the ethereal solution had smelt strongly of ammonia. The melting point of the primary base was stated by Berlingozzi to be 56°-59°, whereas Busch and Leefhelm had originally given 121° as the figure. The secondary amine , di($\alpha$-naphthylbenzyl)amine, was described as melting at 181°.

# PIPERIDINE.

# THE ACTION OF PIPERIDINE ON ACETONESEMICARBAZONE.

## THEORETICAL.

The interaction of acetonesemicarbazone and the amine was first investigated; it was expected that this would follow the normal course and yield acetonepiperidinoformylhydrazone, substance (1), with evolution of ammonia as indicated in the following equation:-

$$CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 \quad + \quad NHC_5H_{10} \quad = \quad \underset{(1)}{CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10}} \quad + \quad NH_3.$$

The substances, in equimolecular quantities, were heated under reflux in toluene. Ammonia was evolved strongly, and at the end of the reaction no unchanged acetonesemicarbazone separated from the toluene on cooling. No hydrazodicarbonamide appeared to have been formed, and this also indicated that combination between the semicarbazone and the amine had taken place.

The main product, which was isolated in a practically pure state, was a crystalline solid, M.Pt. 145°. This compound was analysed and a molecular formula, $C_{10}H_{21}O_3N_5$ obtained; this showed clearly that it was not the expected derivative $CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10}$ (1), the molecular formula of which is $C_9H_{17}ON_3$. The compound obtained, substance (11), was/

was then examined.

Hydrolysis was accomplished readily with dilute mineral acid and with picric acid, acetone being liberated.

An aqueous solution of the substance was prepared, and to this was added a small quantity of benzaldehyde dissolved in sufficient alcohol to give a homogeneous solution with the water. A white crystalline precipitate separated out, which, when purified, melted at 211°. This was substance (111). When distilled with dilute sulphuric acid, this compound was hydrolysed, and benzaldehyde was detected in the distillate: acetone was, however, absent, indicating that replacement had occurred. The molecular formula determined by analysis was $C_{14}H_{19}O_2N_5$.

The acetone derivative (11) was treated in a similar manner with acetophenone. As with benzaldehyde, the acetone residue was replaced by an acetophenone residue to give substance (1V). This product, when purified, melted at 204°, and the molecular formula found was $C_{15}H_{21}O_2N_5$. Hydrolysis with dilute mineral acid liberated acetophenone.

Substance (11) was hydrolysed with dilute hydrochloric acid to remove acetone. The residue on concentration in vacuo deposited a small quantity of crystals which were identified as hydrazine dihydrochloride by 1) melting point 198°. 2) the reduction/

reduction of Fehling's solution without heating, and 3) by the formation of benzalazine, M.Pt. 93°.
A hydrochloride was also obtained which, on treatment with benzaldehyde in aqueous alcohol yielded substance (111), and from which by treatment with acetone and acetophenone respectively substances (11) and (1V) were also obtained. This same hydrochloride, substance (V), was produced when substances (111) and (1V) were hydrolysed with dilute acid.

The hydrochloride (V) exhibited dimorphism.
When crystallized from water or alcohol—ether slightly acidified with hydrochloric acid, white crystalline plates M.Pt. 144° were obtained; slow crystallization from absolute alcohol by the addition of ether and light petroleum yielded long prisms melting at 185°. When the two forms were mixed the melting point was that of the second, viz. 185°. Both forms of the salt gave on analysis the molecular formula $C_7H_{17}O_3N_5,HCl$.

Substance (11) had already been hydrolysed by picric acid, and a picrate was now isolated from the residue. The same picrate was obtained by adding picric acid to an aqueous solution of the hydrochloride (V). The picrate was a bright yellow substance melting with decomposition at 204°, and having a molecular formula $C_{13}H_{18}O_9N_8$, or possibly $C_7H_{15}O_2N_5$, $C_6H_3O_7N_3$, if one molecule of picric acid is present.

Substances/

Substances (11), (111), (1V), (V) and the picrate formed a closely related series of derivatives which were shown by the analytical results to be abnormal.

A later reaction between acetophenonesemicarbazone and piperidine produced a derivative of a normal series. The constitution of the abnormal derivatives was not determined until substance (11) had been prepared from the normal series.

## THE ACTION OF PIPERIDINE ON BENZALDEHYDESEMICARBAZONE.

Benzaldehydesemicarbazone and piperidine were heated together under reflux in toluene suspension at 130°-135° for eight hours but no reaction had apparently occurred, since only unchanged starting materials were recovered. The substances were then heated together in a sealed tube at 165° for six hours, but, on working up the contents, only some unchanged benzaldehydesemicarbazone and benzalazine from decomposition of the latter were obtained.

## THE ACTION OF PIPERIDINE ON ACETOPHENONESEMICARBAZONE.

Acetophenonesemicarbazone was next tried and this was heated with piperidine in solvent naphtha. Ammonia was evolved during the reaction which was allowed to proceed until the semicarbazone had been completely dissolved. A white crystalline product, M.Pt. 168°, was obtained from the solution. This substance (V1) was shown by hydrolysis to contain an acetophenone residue, and the presence of a hydrazine linkage also, was proved by the reduction of Fehling's solution. The product was identified as acetophenonepiperidinoformylhydrazone and this was confirmed by the analysis. The reaction between the amine and the semicarbazone has therefore proceeded normally.

$$\mathrm{CPhMe{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + NC_5H_{10} = \underline{CPhMe{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10}}\ (V1) + NH_3}$$

When hydrolysed with 1% hydrochloric acid, acetophenonepiperidinoformylhydrazone yielded the corresponding hydrochloride as white needles melting at 189°. Substance (V11) was accordingly piperidinoformylhydrazide hydrochloride.

$$\mathrm{CPhMe{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10} + H_2O + HCl = CPhMe{:}O +}$$

$$\mathrm{\underline{NH_2{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10},HCl}\ (V11)\ .}$$

The/

The benzaldehyde compound of this second series was prepared by combining the hydrochloride (V11) with benzaldehyde. The reaction was carried out in aqueous alcohol, and a white precipitate of the expected derivative (V111) separated. This product was purified by repeated crystallization, being finally obtained as long thread-like prisms, M.Pt. 179°. The substance was proved by analysis to be benzaldehyde-piperidinoformylhydrazone.

$$NH_2{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10},HCl \quad + \quad CHPhO \quad = \quad CHPh{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10} + H_2O + HCl.$$

Attempts were made to prepare the acetone derivative of this series, viz. acetonepiperidinoformylhydrazone (1) which had not yet been obtained. It was thought that the action of acetone on the hydrochloride (V11), or the corresponding acetate should give this derivative. The hydrochloride was mixed with potassium acetate in alcoholic solution so that the potassium chloride would be precipitated. The residue was then treated with acetone and concentrated. Subsequent precipitation with ether produced the acetone derivative of the abnormal series (11).

Another method for the synthesis of substituted formylhydrazones was then investigated, and this confirmed the structure/

structure of benzaldehydepiperidinoformylhydrazone (V111), and therefore also that of substances (V1) and (V11). Piperidinoformyl chloride ( Wallach and Lehmann, Ann., 1887, 237, 249 ) was added to hydrazine hydrate ( 2mols.) in alcoholic solution. Hydrochloric acid was eliminated and neutralised by the second molecule of hydrazine to give a precipitate of the monohydrochloride. Benzaldehyde was added to the alcoholic solution which now contained piperidinoformylhydrazide. Addition of water caused precipitation of benzaldehydepiperidinoformylhydrazone. (Eqn. on p. 33 b.)

## THE DEDUCTION OF FORMULAE FOR THE ABNORMAL SERIES OF DERIVATIVES. (11) (111) (1V) (V) .

The members of the abnormal series and the data known concerning them are given in the following table.

(11) ... Molecular formula $C_{10}H_{21}O_3N_5$. Acetone derivative.

(111) ... Molecular formula $C_{14}H_{19}O_2N_5$ . Benzaldehyde derivative, acetone replaced.

(1V) ... Molecular formula $C_{15}H_{21}O_2N_5$ . Acetophenone derivative, acetone replaced.

(V) ... Molecular formula $C_7H_{17}O_3N_5$,HCl. Hydrochloride of base corresponding to substances (11), (111), (1V)

The picrate of this series was also known, its molecular formula being $C_{13}H_{18}O_9N_8$ or probably $C_7H_{15}O_2N_5,C_6H_3O_7N_3$. These substances were all derivatives of a common base which was shown by the reduction of Fehling's solution, to contain a hydrazine linkage.

A complete hydrolysis of (11) had been carried out by boiling it with concentrated hydrochloric acid for three hours. The residue after evaporation had been extracted with alcohol. A deposit of white crystals remaining undissolved were identified as hydrazine dihydrochloride. Ether added in excess to the alcoholic extract precipitated piperidine hydrochloride M.Pt. 237°, which was identified by a mixed melting point determination with an authentic specimen, and confirmed by the production of benzenesulphonpiperidide, M.Pt. 92°.

When the base was known to contain both a hydrazine residue and a piperidine residue, it was decided to carry out a complete hydrolysis and to determine quantitatively the acetone, hydrazine and piperidine produced.

An estimation was carried out with substance (11). Acetone was separated by distillation and estimated, 1% $H_2SO_4$ was used for this first hydrolysis. The residue was then completely hydrolysed with conc. HCl, and divided into two portions. Hydrazine was estimated in the first by measuring the nitrogen evolved/

evolved on destroying the base with Fehling's solution: and piperidine in the second by collecting in standard acid the piperidine which distilled from the strongly alkaline Fehling's solution, hydrazino nitrogen escaping as free nitrogen. Ammonia was tested for several times in various hydrolysis residues , but in no instance was it found. The percentage of nitrogen derived from the piperidine residue in the compound, and the percentage of nitrogen present in hydrazino form, accounted for the total nitrogen content in the substance. The values obtained indicated that the substance gave on hydrolysis, acetone, hydrazine hydrochloride and piperidine hydrochloride in the molecular ratios 1:2:1 .

Two hydrazine residues account for 4 nitrogen atoms, and one piperidine residue for 1 nitrogen atom; this is therefore in agreement with the molecular formulae obtained from analysis, since each substance contained in the molecule 5N.

The presence of only one acetone residue is in agreement with the fact that the difference between the molecular formulae of (111) and (1V) is $CH_2$ which is also the difference between the molecular formulae of benzaldehyde and acetophenone.

Removal of benzaldehyde from (111), or acetophenone from (1V) by hydrolysis would give as molecular formula for the base $C_7H_{15}O_2N_5$.

$C_{14}H_{19}O_2N_5 \; + \; H_2O \; - \; C_6H_5CHO \; = \; C_7H_{15}O_2N_5$ .

This differs from the formula of the hydrochloride (V) by $H_2O$ and HCl, (V) is therefore base,$H_2O$,HCl. $C_7H_{15}O_2N_5$ is, however, identical with the formula of the picrate after subtraction of picric acid.

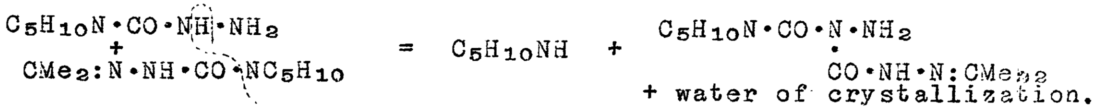
Substance (11) is $C_7H_{15}O_2N_5$ + one molecule of acetone without elimination of water, or + an acetone residue and one molecule of water of crystallization.

The base $C_7H_{15}O_2N_5$ which was proved to contain one piperidine residue, $C_5H_{10}N-$ and two hydrazine residues, 2( $-NH{\cdot}NH-$ ) must therefore be :- $C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH_2$ or $C_5H_{10}N{\cdot}CO{\cdot}N(NH_2){\cdot}CO{\cdot}NH{\cdot}NH_2$ .

The formation of substance (11) from acetonesemicarbazone and piperidine in accordance with the following equations was at one time considered possible. This would give the second structure suggested for the base. This structure was, however, disproved when only mono-derivatives were formed with even excess of the aldehyde and ketones.

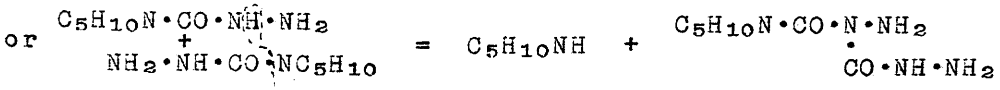
$$C_5H_{10}NH \; + \; NH_2{\cdot}CO{\cdot}NH{\cdot}N{:}CMe_2 \; = \; C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}N{:}CMe_2 \; + \; NH_3$$

$$C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}N{:}CMe_2 \; + \underset{\text{(from air.)}}{H_2O} = \; C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2 \; + \; CMe_2O$$

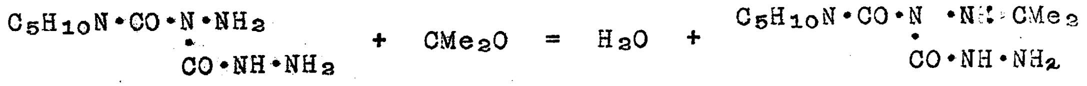


$$\begin{array}{c} C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2 \\ + \\ CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10} \end{array} = \; C_5H_{10}NH \; + \begin{array}{l} C_5H_{10}N{\cdot}CO{\cdot}N{\cdot}NH_2 \\ \qquad\qquad\quad CO{\cdot}NH{\cdot}N{:}CMe_2 \end{array}$$

+ water of crystallization.



$$\text{or} \begin{array}{c} C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2 \\ + \\ NH_2{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10} \end{array} = \; C_5H_{10}NH \; + \begin{array}{l} C_5H_{10}N{\cdot}CO{\cdot}N{\cdot}NH_2 \\ \qquad\qquad\quad CO{\cdot}NH{\cdot}NH_2 \end{array}$$



$$C_5H_{10}N\cdot CO\cdot \underset{CO\cdot NH\cdot NH_2}{N}\cdot NH_2 + CMe_2O = H_2O + C_5H_{10}N\cdot CO\cdot \underset{CO\cdot NH\cdot NH_2}{N}\cdot N:CMe_2$$

(water of crystallization)

The structure of the base is therefore formulated:-

$C_5H_{10}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH_2$ .

Substance (11) is then : $CMe_2:N\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10},H_2O$.

" (111) $CHPh:N\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$ .

" (1V) $CPhMe:N\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$ .

" (V) $NH_2\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10},HCl,H_2O$ .

Picrate $NH_2\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10},C_6H_3O_7N_3$ .

Several attempts were made to remove water from (11). In one experiment it was heated to within three degrees of the melting point ( 145° ) at a reduced pressure of 2mm. mercury, but its composition remained unchanged. When treated with phosphorus pentoxide in chloroform solution an unstable phosphate was formed. It was not until the substance was heated four degrees above the melting point that water was liberated, but decomposition also ensued. From this it appears that the compound should be formulated, not as containing water of crystallization, but rather as being a hydrate; in support of this conclusion there is an analogy in a case reported by Read and Smith, ( J., 1922, 121, 1869 ).

Substance (11) is accordingly reformulated as

$CMe_2(OH)\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$ . i.e./

i.e. acetone-ε-piperidinoformylcarbohydrazone hydrate. (111) and (1V) are respectively benzaldehyde-ε-piperidinoformylcarbohydrazone and acetophenone-ε-piperidinoformylcarbohydrazone.

The reactions by which the base, ε-piperidinoformylcarbohydrazide, could be formed were now considered. Substance (11) had been obtained in an attempt to combine acetone with the hydrochloride (V11) of the normal series, so that the formation of the abnormal base , in this instance, must be due to decomposition of the normal base.

The benzaldehyde derivative of the normal series had been obtained from piperidinoformyl chloride and hydrazine by the following reactions:- ( see page 28a ).

$$C_5H_{10}N{\cdot}COCl \quad + \quad 2NH_2{\cdot}NH_2 \quad = \quad C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2 \quad + \quad NH_2{\cdot}NH_2,HCl$$

$$C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2 \quad + \quad C_6H_5CHO \quad = \quad C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}N{:}CHC_6H_5 \quad + \quad H_2O \ .$$

The alcoholic solution which was therefore known to contain the normal base, piperidinoformylhydrazide, was now treated with acetone, but instead of giving acetonepiperidinoformylhydrazone, the reaction produced a mixture of piperidine hydrochloride and substance (11).

The mode of decomposition is accordingly a loss of piperidine from two molecules of the normal base giving ε-piperidinoformylcarbohydrazide which subsequently unites with acetone to yield /

yield substance (11).

$$C_5H_{10}{:}N\cdot CO\cdot NH\cdot NHH \quad + \quad C_5H_{10}{:}N\cdot CO\cdot NH\cdot NH_2 \quad = \quad C_5H_{10}NH$$

$$+ \quad C_5H_{10}{:}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH_2$$

$$C_5H_{10}{:}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH_2 \quad + \quad CMe_2O \quad =$$

$$C_5H_{10}{:}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH\cdot CMe_2\cdot OH \quad (11).$$

( cf. page <u>10b, eqn. 3.)</u>

The foregoing reactions explained the production of acetone-ε-piperidinoformylcarbohydrazone hydrate from the normal base with the abnormal base as intermediate stage. These reactions did not at first appear to explain the original preparation of (11) from acetonesemicarbazone and piperidine. The following reactions indicate another theory that was considered.

$$C_5H_{10}NH \quad + \quad NH_2\cdot CO\cdot NH\cdot N{:}CMe_2 \quad = \quad C_5H_{10}N\cdot CO\cdot NH\cdot N{:}CMe_2 \quad + \quad NH_3$$

$$\begin{array}{c} C_5H_{10}N\cdot CO\cdot NH\cdot N{:}CMe_2 \\ + \\ C_5H_{10}N\cdot CO\cdot NH\cdot N{:}CMe_2 \end{array} \quad = \quad \begin{array}{c} N{:}CMe_2 \\ \cdot \\ N{:}CMe_2 \end{array} \quad + \quad C_5H_{10}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}$$

Product [A] Product [B]

$$\begin{array}{c} C_5H_{10}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10} \\ + \\ CMe_2{:}N\cdot NH\cdot CO\cdot NC_5H_{10} \end{array} \quad = \quad CO\begin{array}{l} \cdot NC_5H_{10} \\ \cdot NC_5H_{10} \end{array} \quad \text{Product [C]}$$

$$+ \quad C_5H_{10}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot N{:}CMe_2, \text{water of cryst}^{n}.$$

If such had been the case, some indication of the course of the reaction would have been given by an examination of all the products. A large quantity of Product [A] , acetone-ketazine/

ketazine, would have been expected, a somewhat smaller yield of Product [C], dipiperidyl carbamide, and, in all probability, a small quantity of Product [B] which is hydrazidicarbonpiperidide. A trace of acetoneketazine was found, but decomposition of acetonesemicarbazone itself would yield this.

Hydrazidicarbonpiperidide is known, ( Kesting, Ber., 1924, 57, 1324 ). This substance, being sparingly soluble in ether, would, if formed, have been precipitated with substance (11). In view of the non-occurrence of these by-products, this theory was considered improbable.

The essential difference between this theory and the previous one, when applied to the formation of the abnormal molecule from the acetonesemicarbazone and piperidine reaction, is that water is necessary in the former to produce the free piperidinoformylhydrazide, ( two molecules of which react ), and in the latter theory water is not required.

Since a ketonic or aldehydic substituent in the $\alpha$-position rendered it impossible for the abnormal molecule to be produced from the normal molecule by loss of piperidine, it now became necessary to determine whether hydrolysis had taken place at some stage of the reaction. The original preparation was accordingly repeated under anhydrous conditions.

## THE ACTION OF PIPERIDINE ON ACETONESEMICARBAZONE.

### (anhydrous conditions)

The reaction between the amine and the semicarbazone under anhydrous conditions gave a compound, M.Pt. 101°, which was deposited in compact rosettes of prisms from petroleum ether.

When an aqueous solution of this substance was shaken with a few drops of benzaldehyde dissolved in a little alcohol, a precipitate of benzaldehydepiperidinoformylhydrazone formed rapidly; in a similar manner the acetophenone derivative (V1) of the normal series could be produced. This indicated that the product was acetonepiperidinoformylhydrazone (1). The derivative was shown by hydrolysis to contain an acetone residue and also a hydrazine linkage; and analysis confirmed the formula as being $CMe_2:N\cdot NH\cdot CO\cdot NC_5H_{10}$ , (1).

The substance was hygroscopic, and when left exposed to the air, it gradually decomposed forming an alkaline solution. Ethereal solutions also absorbed moisture readily, and slowly deposited a precipitate of substance (11).

When (1) was boiled with water , acetone was liberated at once and then the solution became strongly alkaline: on longer boiling, piperidine also was detected in the distillate. A quantity was boiled with water until this decomposition seemed complete. /

complete. Some benzaldehyde dissolved in alcohol was then added to the solution, and in a short time a precipitate of benzaldehyde-ε-piperidinoformylcarbohydrazone separated. A second quantity was boiled with water as before, and the solution evaporated to dryness. The solid obtained, M.Pt. 106°-108°, was found to be the base, ε-piperidinoformylcarbohydrazide (1X), since combination with acetone, benzaldehyde and acetophenone produced substances (11), (111) and (1V) respectively.

Substance (11) was boiled with water and it also was found to undergo hydrolysis producing the base (1X) and acetone.

When air-dried the base contained one molecule of water of crystallization, but this could be removed by keeping the substance in a high vacuum over concentrated sulphuric acid. The anhydrous substance which also crystallized in plates, M.Pt. 106°-107°, appeared to be less stable than the hydrated product.

The foregoing results proved that, in the reaction between piperidine and acetonesemicarbazone, the normal product (1) was first produced. If no moisture were present the substance did not decompose, but, if hydrolysis occurred, the abnormal compound was then produced.

In view of these results, the theory discussed on page 34b was discarded in favour of the one immediately preceding it, and the formation of acetone-ε-piperidinoformylcarbohydrazone hydrate/

hydrate from acetonesemicarbazone and piperidine explained by the following reactions :

$$2CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 \;+\; 2C_5H_{10}NH \xrightarrow{-2NH_3} 2CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10} \quad (1)$$

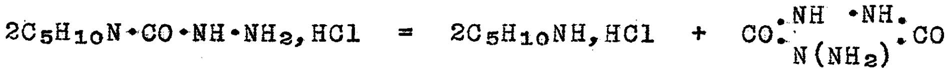
$$\xrightarrow[-2CMe_2O]{+2H_2O} 2C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2 \xrightarrow{-C_5H_{10}NH}$$

$$C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH_2 \quad (1X) \xrightarrow{+CMe_2O}$$

$$C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CMe_2{\cdot}OH \quad (11).$$

Attempts to isolate the base $C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2$ from the piperidinoformylhydrazide hydrochloride were unsuccessful, as this base appeared to decompose readily.

Thermal decomposition of piperidinoformylhydrazide hydrochloride proceeded a stage farther than the reaction shown above, but apparently on exactly similar lines to the decomposition of the base; two molecules of piperidine hydrochloride were liberated leaving 4-aminourazole.



$$2C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2,HCl \;=\; 2C_5H_{10}NH,HCl \;+\; CO{<}\begin{matrix}NH\cdot NH\\ N(NH_2)\end{matrix}{>}CO$$

## EXPERIMENTAL.

### PIPERIDINE AND ACETONESEMICARBAZONE (non-anhydrous conditions)

The piperidine used had been dried and distilled but no precautions were taken to prevent moisture from the air entering the condenser during the reaction.

The acetonesemicarbazone was prepared from semicarbazide hydrochloride and acetone.

Equimolecular quantities of the two substances were heated under reflux in toluene for nine hours at 130°.

The vapour attacked corks and rubber stoppers very readily causing a good deal of discoloration to the liquid; this effect was partly overcome by wrapping the corks in tinfoil, but Patterson flasks with ground-in condensers were subsequently used. Ammonia was evolved during the heating, the evolution being quite rapid after a short time and diminishing towards the end of the period.

After nine hours refluxing the solution was allowed to cool and a small quantity of unchanged acetonesemicarbazone separated out, no hydrazodicarbonamide appeared to have been formed.

The filtrate was evaporated under reduced pressure giving a very viscous brown oil. This was dissolved in a few ccs. of alcohol, and then a large excess of ether added. The addition of a/

of a small quantity of water facilitated crystallization, as it was necessary for the hydrolysis outlined in the theoretical section, any moisture already present having been obtained almost entirely from the atmosphere. The liquid was warmed until the oil dissolved in the ether, then it was set aside to crystallize. After standing overnight a crop of white crystals had separated, and these when washed with ether melted at 141°-143°. To purify the substance it was dissolved in a small quantity of absolute alcohol, discolored fractions were cleaned with decolorising carbon, solution was filtered and the crystals reprecipitated by the addition of much ether. The substance was also crystallized from chloroform by the addition of petroleum, from hot acetone, water and benzene. The crystals were very long prisms M.Pt. 145°C

On analysis the following results were obtained:-

C, 46·6; H, 7·9, 8·1; N, 27·2, 26·9%. (macro Dumas).

The results of the nitrogen estimations were irregular at first, possibly due to formation of methane from the two methyl groups attached to the same carbon atom, ( Haas, J., 1906, 59, 570; Dunstan and Carr , P., 1896, 12, 48 ). This difficulty was, however, overcome by using a tube filling of copper oxide impregnated with 5% cobalt oxide. ( Campbell and Gray, J.S.C.I., 1930, 49, 450 ). Micro Dumas determinations were/

were carried out at a later stage, values of 27·3 and 27·1% being arrived at without any additional precautions being necessary. The substance proved totally unsuitable for estimation by the Kjeldahl method. The molecular weight by the cryoscopic method in nitrobenzene was 311.
A molecular formula $C_{10}H_{21}O_3N_5$ requires C, 46·3, H, 8·1, N 27·0% and M.W. 259. This was Substance (11).

### Preparation of Benzaldehyde-ε-piperidinoformylcarbohydrazone.

A saturated solution of substance (11) in hot water was prepared and a few drops of benzaldehyde added with sufficient alcohol to prevent turbidity. A white crystalline precipitate separated M.Pt. 197-198°. After repeated crystallization by addition of water to an alcoholic solution, the pure substance was obtained in the form of long felted thread-like prisms M.Pt. 211°, soluble in alcohol and ether, insoluble in water. (Found :- C, 57·8, H, 6·6, N, 24·4, 24·5%. $C_{14}H_{19}O_2N_5$ requires C, 58·1, H, 6·6, N, 24·2%).

Preparation of Acetophenone-ε-piperidinoformylcarbohydrazone.

A quantity of substance (11) dissolved in water was treated in a similar manner with acetophenone dissolved in a little alcohol. Needle-like prisms formed in branching tufts, and these, when recrystallized from alcohol-water, melted at 204°, were easily soluble in alcohol and chloroform, slightly soluble in ether, and insoluble in petroleum ether and water.

( Found :- C,59·3, H,6·7, N,23·1%. $C_{15}H_{21}O_2N_5$ i.e. $C_5H_{10}$:N·CO·NH·NH·CO·NH·N:CMePh requires C,59·4, H,6·9, N,23·1%.

Hydrolysis of Acetone-ε-piperidinoformylcarbohydrazone hydrate.

Qualitative: Substance (11) was hydrolysed by boiling it with dilute hydrochloric acid. Acetone was identified in the distillate, and the residue on concentration in vacuo deposited crystals of hydrazine dihydrochloride recognised by conversion to benzalazine. The remaining liquid was evaporated to dryness and extracted with absolute alcohol which left the hydrazine hydrochloride undissolved; ether added in excess slowly precipitated a substance which was a mixture of ε-piperidinoformylcarbohydrazide hydrochloride (V) and piperidine hydrochloride. The latter was identified by the formation of benzenesulphonpiperidide, M.Pt. 32°. The hydrazine hydrochloride and the piperidine hydrochloride were produced by substance (V) itself undergoing a further hydrolysis.

## Quantitative Estimation of Hydrolysis Products.

A known weight of the substance (11) was distilled with 1% sulphuric acid. Acetone distilled over and was collected in a stout glass bottle containing mercuric oxide dissolved in sulphuric acid. After the distillation of the acetone was complete, the stopper of the bottle was wired in and the latter heated for ten minutes in a boiling waterbath.

The white precipitate was filtered off on to a previously dried and weighed filter paper, dried in a desiccator over sulphuric acid, and its weight found. ( Method of Denigès, Compt. rend. 1898,127,963). The ppt. was $(HgSO_4)_2,3HgOC_3H_6O$ .

The solution remaining in the distilling flask was then boiled for three hours with 20% hydrochloric acid, made up to 100ccs. and divided into two parts.

Hydrazine was estimated in one portion by measuring the nitrogen evolved on heating with Fehling's solution. ( $Na_2CO_3$ was substituted for NaOH in the solution used).

The nitrogen was collected in a nitrometer over 50% KOH, air being removed from the apparatus before introducing the Fehling's solution to the liquid to be estimated, partially by water vapour and partially by a current of $CO_2$ generated from $NaHCO_3$.

The piperidine was estimated in the second portion by distilling with/

with Fehling's solution (NaOH) and allowing the piperidine to pass over into a flask containing a known quantity of standard acid. The piperidine distilled over was estimated by titration. The molecular ratios were acetone : 1·0, hydrazine : 1·9, piperidine : 1·025.

The above method tends to give a high result for piperidine and a low result for hydrazine owing to the fact that some ammonia is produced, and the conversion of hydrazine to nitrogen is therefore not quite quantitative.

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Hydrolysis of (11) to obtain ε-piperidinoformylcarbohydrazide hydrochloride.

Substance (11) was refluxed for ½ hour with 1% hydrochloric acid and the solution evaporated to dryness under reduced pressure. ( acetone in distillate). The residue crystallized from water or alcohol-ether ( slightly acidified with HCl) in plates M.Pt. 144°. When allowed to crystallize slowly from absolute alcohol - petroleum ether the ε-piperidinoformylcarbohydrazide hydrochloride (V) was obtained in the form of long prisms M.Pt. 185°-186° with decomposition.

A mixture of the two hydrochlorides melted at the higher temperature.

Hydrolysis of benzaldehyde-ε-piperidinoformylcarbohydrazone with 3%/

with 3% hydrochloric acid yielded benzaldehyde and the same hydrochloride in either form depending on the mode of crystallization.

( Found in substance of M.Pt. 144°:-

C, 32·6; H, 7·0; N, 27·5; Cl, 13·8%.

Found in substance of M.Pt. 185-186° :-

C, 33·1; H, 6·9; N, 27·5; Cl, 14·0%.

$C_7H_{15}O_2N_5,HCl,H_2O$ requires :-

C, 32·9; H, 7·1; N, 27·4; Cl, 13·9%).

### ε-Piperidinoformylcarbohydrazide picrate.

Acetone-ε-piperidinoformylcarbohydrazone hydrate was boiled with an aqueous solution of picric acid. Acetone was identified in the distillate, and the residue on cooling deposited rosettes of long bright yellow prisms of ε-piperidinoformylcarbohydrazide picrate. The substance was recrystallized from alcohol and melted with decomposition at 204°.
The picrate was carefully diluted with pure dry silica in the estimations of carbon, hydrogen and nitrogen.

(Found :- C, 35·8; H, 4·2; N, 25·9;

$C_7H_{15}O_2N_5,C_6H_3O_7N_3$ requires C, 36·3; H, 4·2; N, 26·0% ).

Both forms of the hydrochloride (V) gave the same picrate on mixing with picric acid in water.

Benzaldehyde-ε-piperidinoformylcarbohydrazone and acetophenone-ε-piperidinoformylcarbohydrazone were readily prepared from ε-piperidinoformylcarbohydrazide hydrochloride. The hydrochloride was shaken with the benzaldehyde and acetophenone respectively in water containing sufficient alcohol to render the solution homogeneous. Owing to the relative insolubilities of (111) and (1V) in water they separated out easily. This method had to be slightly modified for the preparation of the acetone derivative (11). The hydrochloride was dissolved in absolute alcohol and mixed with the calculated quantity of potassium acetate also dissolved in alcohol. Acetone was added and the liquid filtered to remove the precipitated potassium chloride, then evaporated to small bulk in a desiccator. Ether in excess was next added, but not until a drop of water was also introduced did the derivative (11) begin to crystallize.

## PREPARATION OF ACETOPHENONEPIPERIDINOFORMYLHYDRAZONE.

Equimolecular quantities of piperidine and acetophenonesemicarbazone were placed in a flask fitted with a ground-in condenser; 100ccs. solvent naphtha (B.Pt.170°-190°) and a few ccs. of toluene were then added. The mixture was heated at 125°-135° under reflux for thirty hours; ammonia was evolved fairly strongly and the semicarbazone gradually dissolved.

The reaction was complete when no undissolved substance remained in the hot liquid. Some decolorising carbon was added, and the solution then separated through a heated filter; on cooling the liquid, crystals formed rapidly until the mass was almost solid. The oil was pressed out on a Büchner filter and the yield washed with a small quantity of ether. The acetophenonepiperidinoformylhydrazone was recrystallized from alcohol-water, chloroform-petroleum ether and ether, the crystals being long colourless prisms in each case, M.Pt.168°. The yield (twice crystallized) amounted to rather more than 60% of theoretical. Found :- N, 17·1%;

$C_5H_{10}:N\cdot CO\cdot NH\cdot N:C(CH_3)C_6H_5$ , $C_{14}H_{19}ON_3$ requires :- N, 17·1%.

An attempt to carry out the reaction more quickly by heating the reactants without solvent in a sealed tube at 150° for six hours gave acetophenoneazine and decomposition products.

## PREPARATION OF PIPERIDINOFORMYLHYDRAZIDE HYDROCHLORIDE. (V11).

This substance was obtained by hydrolysis of acetophenone-piperidinoformylhydrazone (V1). The latter was boiled vigorously with 1% hydrochloric acid, acetophenone was collected and identified in the distillate and the residue was evaporated to dryness under reduced pressure. The creamy white solid remaining was dissolved in a small volume of alcohol, then ether added in large excess precipitated the piperidinoformylhydrazide hydrochloride as colourless needle-like prisms M.Pt. 189°. ( Found :- N, 23·6% ; $C_6H_{14}ON_4.HCl$ i.e. $C_5H_{10}N\cdot CO\cdot NH\cdot NH_2,HCl$ requires N, 23·5%.

## PREPARATION OF BENZALDEHYDEPIPERIDINOFORMYLHYDRAZONE. (V111).

To a slightly alcoholic aqueous solution of the hydrochloride prepared above, the equivalent quantity of potassium acetate dissolved in water was added. The liquid was filtered free from a small precipitate of potassium chloride and mixed with a few drops of benzaldehyde. A thick white precipitate formed rapidly and this was filtered , washed with water containing some alcohol, dried, and recrystallized several times from 1) ethylene dichloride-petroleum ether, 2) chloroform-petroleum ether, 3) alcohol-water and

4) acetone. When purified it consisted of very fine long prisms, M.Pt. 179° and containing 18·2% nitrogen. $C_5H_{10}:N\cdot CO\cdot NH\cdot N:CHC_6H_5$, ($C_{14}H_{17}ON_4$) requires N, 18·2%. This substance (V111) was insoluble in water and petroleum ether, but dissolved readily in chloroform, ethylene dichloride, alcohol, ether, acetone and benzene.

THE INTERACTION OF HYDROCHLORIDE (V11) AND ACETONE.

1. 6 gm. piperidinoformylhydrazide hydrochloride and 3·33 gm. potassium acetate were dissolved separately in aqueous alcohol and the solutions mixed. Potassium chloride was filtered off, acetone added and the solution evaporated to dryness under reduced pressure. A yellow oil was left which was dissolved in ether and filtered free from the last traces of potassium chloride. The ether was then evaporated and the oil dissolved in chloroform. Petroleum ether was added to this solution until it was slightly turbid; subsequent addition of acetone gave a white crystalline precipitate which was identified as acetone-ε-piperidinoformylcarbohydrazone hydrate M.Pt. 145°.

2. A solution of hydrochloride (V11) in alcohol was treated with sodium ethoxide until it was almost neutralised; it was then/

then filtered free from sodium chloride and concentrated. Acetone and a few drops of water were added, and the whole was refluxed for six hours. The solution was then distilled at slightly reduced pressure into dilute hydrochloric acid, the heating being carried out in a glycerine bath which was gradually heated to 120°, while a current of air free from carbon dioxide was aspirated through the apparatus during the distillation. The presence of piperidine in the distillate was proved by the formation and identification of benzenesulphonpiperidide, M.Pt.92°. The yellow oil in the distilling flask was dissolved in chloroform, decolorised with charcoal, mixed with a little acetone, and excess petroleum ether added as before. Crystals of the abnormal acetone derivative (11) were obtained.

## PREPARATION OF BENZALDEHYDEPIPERIDINOFORMYLHYDRAZONE. (V111).

( 2nd. method.)

To an absolute alcoholic solution of hydrazine hydrate (slightly more than two mols.) piperidinoformyl chloride (Wallach and Lehmann, Ann. 1887, 237, 249) was added drop by drop. A vigorous reaction ensued with evolution of much heat and hydrazine monohydrochloride separated out and was filtered off. A portion/

A portion of the filtrate was diluted with water and benzaldehyde added. A yellowish solid was precipitated and recognised to be a mixture. Petroleum ether dissolved the yellow crystals which were identified as benzalazine, and left a white residue. The latter was purified by recrystallization from benzene- light petroleum and found to be identical with substance (V111).

A second portion was treated with acetone and evaporated to dryness in a desiccator. The residue ( a mixture ) was dissolved in alcohol, decolorised with charcoal and poured into excess of ether. Precipitation of piperidine hydrochloride took place immediately and this substance was filtered off at once. When the filtrate had stood for a short time, fine white crystals began to separate from it, and these were recognised as acetone-ε-piperidinoformylcarbohydrazone hydrate.

## THERMAL DECOMPOSITION OF PIPERIDINOFORMYLHYDRAZIDE HYDROCHLORIDE.

This hydrochloride melted with decomposition at 189°.
A quantity was accordingly heated in an oil bath at a temperature of 190°-200° for six hours. The melt was cooled and extracted with boiling absolute alcohol. The undissolved fraction/

fraction was recrystallized from water and was identified as 4-aminourazole by its characteristic reactions.

Ether was added in excess to the alcoholic extract causing precipitation of a white crystalline hydrochloride, M.Pt. 237° which was recognised by comparison with an authentic specimen, and by conversion into benzenesulphonpiperidide, to be piperidine hydrochloride.

## THE ACTION OF PIPERIDINE ON ACETONESEMICARBAZONE.

### ( Anhydrous conditions).

The piperidine was dried over potassium hydroxide and distilled, acetonesemicarbazone was kept in an evacuated desiccator over concentrated sulphuric acid, and the toluene used was dried over sodium. During the reaction moisture was prevented from entering by fitting a calcium chloride tube in the mouth of the condenser.

Equimolecular quantities were heated under reflux in toluene suspension as before. The reaction was first allowed to proceed at 130° for nine hours, ammonia being evolved rapidly. The solution was cooled and the toluene removed as completely as possible under reduced pressure. A small quantity of solid began to be deposited from the viscous oil, and rapid washing with dry ether removed the oil and left some cream-coloured crystals, M.Pt. 84°-88°. These crystals were extremely soluble in methyl and ethyl alcohols, water, chloroform, carbon tetrachloride and benzene, also readily soluble in ether and light petroleum. The yield was first crystallized from dry ether and, when washed with petroleum ether, a nearly white substance, M.Pt. 93° was obtained.

Ethereal mother liquors containing this substance, when left exposed/

exposed to the air slowly deposited crystals of acetone-ε-piperidinoformylcarbohydrazone hydrate formed due to the hygroscopic nature of the acetonepiperidinoformylhydrazone and its subsequent decomposition.
Crystallization of derivative, M.Pt. 93° from petroleum ether produced a white substance M.Pt. 101°, which gave the following results on analysis:- C, 59·1; H, 9·1; N, 22·9%; $C_5H_{10}:N\cdot CO\cdot NH\cdot N:C(CH_3)_2$ i.e. $C_9H_{17}ON_3$ requires :- C, 59·0; H, 9·3; N, 22·9%.

The preparation was repeated heating the substances together without solvent at 130° for ten hours. A small quantity of unchanged piperidine was removed by vacuum distillation, and the residue was then extracted with dry ether. The ethereal extract was evaporated to dryness in a desiccator, and the acetonepiperidinoformylhydrazone crystallized from the residue by means of warm petroleum ether. This method gave a better yield, but the extremely hygroscopic nature of the ethereal solutions of the product was a disadvantage.

Since the melting point of the substance required was comparatively low, viz. 101°, it was thought advisable to attempt the reaction at a lower temperature. Equimolecular quantities/

quantities were therefore heated at 100°-110° for 25 hours with toluene as solvent. At the end of this period no solid separated on cooling. The liquid was rapidly filtered, concentrated in vacuo, dry air being bubbled slowly through the oil, and the viscous residue was then extracted with warm dry petroleum ether. The resulting solution was filtered through decolorising carbon, and, after standing for a short time, it deposited compact rosettes of white prisms, M.Pt. 101°. The yield from this method was higher than from the previous preparations, and petroleum ether solutions being less hygroscopic, were more convenient to use.

When the substance was boiled with dilute acid, hydrolysis occurred with liberation of acetone. The residue reduced Fehling's solution rapidly indicating the presence of a hydrazine ~~residue~~ linkage.

A quantity of the substance was dissolved in water and shaken with a few drops of benzaldehyde, alcohol sufficient to give homogeneous solution having been added with the oil. A white precipitate separated out, and this proved to be identical with benzaldehydepiperidinoformylhydrazone, (V111) a compound of the normal series.

## PRODUCTION OF ε-PIPERIDINOFORMYLCARBOHYDRAZIDE (1X) FROM ACETONEPIPERIDINOFORMYLHYDRAZONE (1) AND ACETONE-ε-PIPERIDINOFORMYLCARBOHYDRAZONE HYDRATE (11) BY HYDROLYSIS WITH WATER.

When acetonepiperidinoformylhydrazone was left exposed to the air , it was noticed that it deliquesced forming an alkaline solution. It was accordingly boiled with water and the volatile portion distilled. Acetone was liberated very rapidly on boiling, and a portion of the residue removed at this stage and treated with benzaldehyde produced benzaldehyde-piperidinoformylhydrazone. On further boiling, piperidine distilled over and was identified by production of benzene-sulphonpiperidide. The residual solution was evaporated to dryness and a deposit of white crystalline plates obtained. (1X). Benzaldehyde was added to an aqueous alcoholic solution of a quantity of these crystals, and the precipitate which gradually separated was identified as benzaldehyde-ε-piperidinoformylcarbohydrazone. (111) The preparation of this latter derivative from acetone-ε-piperidinoformylcarbohydrazone hydrate in aqueous alcohol indicated that hydrolysis of (11) also takes place in water. A quantity of (11)was boiled with water and acetone was identified in the distillate. When/

When no further trace of the ketone distilled, the aqueous solution was evaporated to dryness. The residue consisted of white crystalline plates of the base, (1X) and these were identical with the substance obtained from the normal acetone derivative (1) on prolonged boiling with water.

The base, ε-piperidinoformylcarbohydrazide can therefore be obtained from hydrolysis of (11) with loss of acetone, or from hydrolysis of (1) with loss of acetone and elimination of piperidine from two molecules.

The crude base was dissolved in hot absolute alcohol and precipitated by the addition of light petroleum in excess. After repeated crystallization, plates, M.Pt. 106°-108°, of ε-piperidinoformylhydrazide were isolated.

This substance, when air-dried, contained one molecule of water of crystallization; but, when dried in a high vacuum over concentrated sulphuric acid until constant in weight, and then crystallized rapidly in the cold from absolute alcohol by precipitation with pure dry ether or petroleum ether, it yielded the anhydrous substance in plates melting at 106°-107°. The melting point of the anhydrous derivative fell considerably over a few days, indicating that the substance was decomposing on keeping, and for this reason, it was difficult to purify; the hydrate was more stable.

The/

The following results were obtained on analysis:–

(air-dried) N, 32·6, 32·8%; $C_7H_{15}O_2N_5,H_2O$ requires N, 32·0%.

(anhydrous substance) N, 34·9%; $C_7H_{15}O_2N_5$ requires N, 34·8%.

……

The ether used in the precipitation and washing of [illegible]-ε-piperidinoformylcarbohydrazide had to be very pure, and particular care had to be taken to remove acetone which is often present in commercial samples.

……

# METHYLANILINE.

# THE ACTION OF METHYLANILINE ON ACETOPHENONESEMICARBAZONE.

In the first paper published by Borsche on the action of amines on semicarbazones, he states that the action of methylaniline, which he had attempted, if it proceeded at all, did so very much less smoothly than that of aniline.

This experiment was done presumably with the amine as solvent, in which case decomposition of the semicarbazone would occur to a very great extent, before any marked reaction could set in. It was decided, therefore, to attempt a reaction between methylaniline and acetophenonesemicarbazone in equimolecular proportions , using a considerable volume of toluene as solvent. The reaction between amines and semicarbazones in solvent at 130°, although slower than when no solvent is employed, has the advantage that very little decomposition of the starting material occurs.

In the first preparation attempted, ordinary distilled methylaniline was employed. It was known to contain a little aniline, and the fact that one product isolated was acetophenone-$\delta$-phenylsemicarbazone showed that the semicarbazone reacted much more readily with aniline than with methylaniline.

The second product isolated, M.Pt. 194°, was a derivative of methylaniline and the semicarbazone, but not the normal derivative. /

derivative. The empirical formula deduced from analysis was $C_7H_8ON_2$, and an estimation of the percentage of acetophenone residue present indicated that the molecular formula,( based on the assumption that the substance contained one such residue ) would be $C_{21}H_{24}O_3N_6$.

Methylaniline which had been freed from aniline was used in the next experiments. Solvent naphtha, B.Pt.170°-190°, was substituted for the toluene and a slightly higher temperature maintained. Decomposition of the semicarbazone occurred, producing a considerable quantity of acetophenoneazine and some hydrazodicarbonamide. No yield of the derivative,M.Pt. 194°, which was obtained in the previous experiment was isolated here; on the contrary, a trace of another substance, M.Pt.196°-198°, was found, this , however, could not be identified.

Two further preparations were carried out with toluene as solvent, slightly increased yields of the product M.Pt. 194° were obtained, but in no case was the yield good.

A hydrolysis was attempted, but the hydrochloride obtained was very oily and difficult to crystallize, so the investigation was not continued.

## EXPERIMENTAL.

### THE ACTION OF METHYLANILINE ON ACETOPHENONESEMICARBAZONE.

22 gm. ordinary distilled methylaniline and 36 gm. acetophenonesemicarbazone were heated together in toluene under reflux at 130° for 28 hours. Ammonia was evolved during the heating. At the end of this period the liquid was cooled, and filtered free from the solid which was unchanged acetophenonesemicarbazone. The filtrate was evaporated to small bulk under reduced pressure, the oil was then dissolved in 96% alcohol, and the solution then mixed with as much water as possible without causing turbidity. A small precipitate, M.Pt. 175°–181°, separated which, when recrystallized from absolute alcohol and washed with petroleum ether, melted at 187° . This substance lost acetophenone on boiling with dilute sulphuric acid, and the hydrolysed residue reduced Fehling's solution. This product was identified as -acetophenone-δ-phenylsemicarbazone formed from aniline present in the methylaniline. ( Found:- N, 16·4, 16·7% ; $C_6H_5NH\cdot CO\cdot NH\cdot N{:}C(CH_3)C_6H_5$ requires:- N, 16·6%. )

The residues from the preparation were evaporated again under reduced pressure, and then ether was added in excess with gentle warming until the viscous oil dissolved. A small quantity/

quantity of crystals melting at approximately 167° separated slowly from the solution. Attempted purification was carried out by recrystallization from chloroform-petroleum ether, but no alteration in the melting point was observed. Two recrystallizations from absolute alcohol, however, raised the melting point to 194°, at which value it remained constant.
This substance contained an acetophenone residue which could be removed by boiling with dilute acid, a hydrazine linkage was also present. On analysis the following results were obtained:- C, 61·80; H, 5·99; N, 20·62, 20·44, 20·38%.
An empirical formula $C_7H_8ON_2$ requires:- C, 61·76, H, 5·88; N, 20·59% .

The product was hydrolysed with 4% hydrochloric acid, and the acetophenone estimated by the method of Marsh and Struthers ( Proc., 1908, 24, 267.) Acetophenone reacts with mercuric iodide dissolved in cold aqueous potassium hydroxide solution as shown in the following equation:-

$$PhCOMe + 6HgI_2 + 4KOH = HgI,PhCOCHg_3I_3 + 2K_2HgI_4 + 4H_2O$$

This compound of the ketone is formed as a yellow precipitate, and in absence of other ketone the acetophenone may be estimated either by determining volumetrically the amount of alkali absorbed in presence of excess of $HgI_2$ or by weighing the precipitate formed. In the present estimation the ketone was/

was distilled into a solution of $HgI_2$ in KOH and the precipitate formed was washed by decantation, filtered, and dried in a desiccator until constant in weight. The percentage of $C_6H_5(CH_3)C$: found in the substance was 24·94; the molecular weight of a derivative containing one acetophenone residue would therefore be 417. $C_{21}H_{24}O_3N_6$ gives a molecular weight of 408.

A quantity of methylaniline was purified by refluxing it with $CS_2$, KOH and alcohol according to the method described by Hepp (Ber., 10, 328 ); the reaction converted the aniline to thiocarbanilide, and the secondary amine which was unattacked was removed by extraction with dilute acid, reprecipitated by caustic soda , then extracted with ether. The ethereal extract, after drying over potassium carbonate, was fractionated, and the portion distilling at 192° collected.

The purified amine was now heated with acetophenonesemicarbazone, solvent naphtha was, however, used in place of the toluene, the temperature was maintained at 140° , and the time extended to 35 hours. Unchanged acetophenonesemicarbazone was again obtained and removed by filtration of the hot liquid. The filtrate was evaporated to a thick oil which was dissolved in/

in a small quantity of alcohol , the solution was then diluted with a large volume of water just insufficient to cause turbidity. A yellow precipitate of acetophenoneazine containing some hydrazodicarbonamide separated; this indicated considerable decomposition of the semicarbazone.
A small crop of white crystals separated after this, and these, when recrystallized from chloroform-petroleum ether, melted at 196°-198°. This was found to be a different product from the derivative, M.Pt. 194°, but being present only in a very small quantity, it was not identified.

The preparation with toluene as solvent was then repeated using the purified methylaniline. 25 gm. of the amine and 36 gm. of the semicarbazone were heated at 130° for 50 hours. Ammonia was again evolved; and, at the end of the period of heating, 18 gm. of unchanged semicarbazone were filtered off from the hot liquid. The filtrate was evaporated in vacuo, alcohol and water added as before, and a yellow crystalline precipitate separated. This product was chiefly acetophenoneazine, but some crystals melting at 155°-159° were carried down with the azine and separated from it by dissolving the latter in petroleum ether. This small fraction was recrystallized several times without purification being effected. It was/

was subsequently found to be a mixture of the derivative, M.Pt. 194°, with some unknown substance.

The filtrate was again evaporated to small bulk and ether added. After standing twelve hours, crystals separated from the solution. These were washed with ether, and recrystallized from absolute alcohol. The substance separated from solution in the form of rings of small crystals on the bottom of the flask, this formation had been already noticed and appeared to be a characteristic of the substance . ( M.Pt. 194°) A further crystallization from chloroform-petroleum ether left the melting point 194° unchanged. The yield was poor.

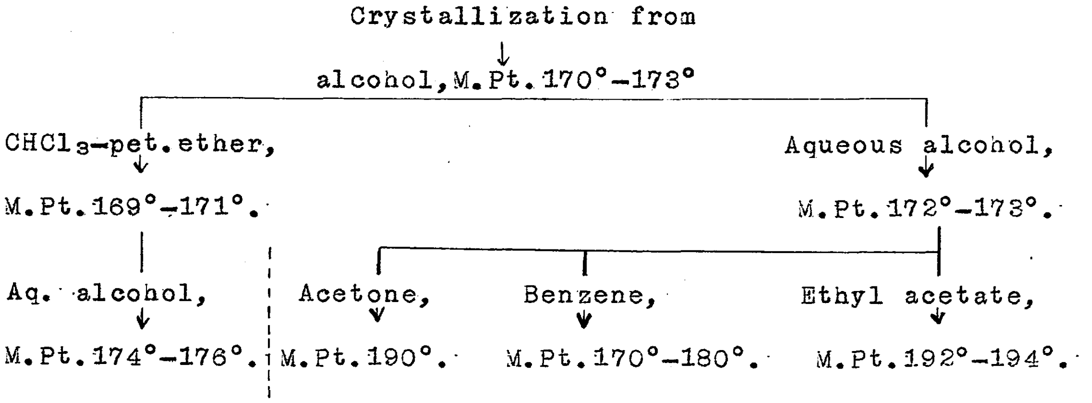
From the last residues, on evaporation and treatment again with mixed solvents , a second quantity of unchanged acetophenonesemicarbazone was recovered.

Another attempt was made to prepare the methylaniline acetophenonesemicarbazone derivative. The heating in toluene was continued for fifty hours at 125° and then forty hours at 125°-130°. The liquid was filtered while hot, leaving some unchanged semicarbazone. On cooling, a fairly bulky precipitate separated from the filtrate. This was removed and washed with ether until white; it was found to be a mixture melting at 165°-170°. ( Product 1 .)

The/

The toluene residues, after removal of Product 1. , deposited, on standing, a further crop of mealy solid. This was washed with ether, then crystallized twice from absolute alcohol to give derivative, M.Pt. 194°. Finally, concentration of the toluene residues and treatment with alcohol and water gave some acetophenoneazine and a quantity of acetophenonesemicarbazone.

Purification of Product 1., M.Pt. 165°-170°, by fractional crystallization, was attempted as shown in the following scheme.



The highest melting fraction was identified as impure acetophenonesemicarbazone. This product, M.Pt. 165°-170°, was therefore a mixture of acetophenonesemicarbazone and derivative, M.Pt. 194°, and the solubilities of the two substances were very similar, thereby rendering purification troublesome. The following plan was adopted: The solid (Product 1.) was extracted with cold ethyl acetate insufficient to dissolve it completely/

completely. The filtrate was evaporated to dryness, and the residue obtained was recrystallized from absolute alcohol. These crystals were then warmed with toluene on a water-bath, a quantity insufficient to dissolve all the solid being used. The toluene solution was filtered and allowed to crystallize, giving a substance, M.Pt. 189°-191°. A final crystallization from absolute alcohol gave the pure substance, M.Pt. 194°.

## HYDROLYSIS OF THE DERIVATIVE, M.Pt. 194°.

1 gm. of the substance, M.Pt. 194°, was hydrolysed by boiling for fifteen minutes with 100ccs. of 4% hydrochloric acid. The liquid was then evaporated to dryness under reduced pressure. Acetophenone was found in the distillate. The residue was dissolved in alcohol and decolorised with charcoal. No hydrazine hydrochloride separated on the addition of the alcohol. Addition of ether to this solution produced a turbidity but no precipitate. The liquid was again evaporated until only a yellow oil remained. This oil was insoluble in ether, it was kept for some time in an evacuated desiccator, and ether added ~~fr~~ at intervals to promote frothing. Some brownish solid and some hardened oil were obtained. The former was removed and washed with ether, but the melting point was not sharp, 75°-85°. The yield was too small to permit of purification and analysis.

# BENZYLANILINE.

## THE ACTION OF BENZYLANILINE ON ACETOPHENONESEMICARBAZONE.

The next secondary amine selected was benzylaniline, since it possessed both the benzyl residue, in presence of which the reaction under investigation appeared to proceed readily, and also the phenyl group which was very unfavourable to this reaction.

The action proceeded very slowly, ammonia was evolved slowly, and a small yield of the normal product, acetophenonebenzylphenylaminoformylhydrazone, was obtained.

$$C_6H_5CH_2{\cdot}NH{\cdot}C_6H_5 \quad + \quad NH_2{\cdot}CO{\cdot}NH{\cdot}N{:}C(CH_3)C_6H_5 \quad = \quad NH_3 \quad +$$
$$C_6H_5CH_2(C_6H_5)N{\cdot}CO{\cdot}NH{\cdot}N{:}C(CH_3)C_6H_5 \quad \text{, M.Pt. } 143^\circ{-}144^\circ.$$

The yield was so very poor (3%) that the experiment was repeated under varying conditions of time and temperature, but no further quantities of the substance were isolated.

The substance was hydrolysed with dilute hydrochloric acid, acetophenone was found in the distillate, and the presence of a hydrazine linkage in the residue was indicated by the reduction of Fehling's solution. This confirmed the structure given above. The hydrochloride left on evaporation of the residue was oily and appeared to be hygroscopic. Alcohol-ether solutions darkened on standing. On account of the small quantity obtainable, and the unstable nature of the hydrochloride, this investigation was not continued.

## EXPERIMENTAL.

### THE ACTION OF BENZYLANILINE ON ACETOPHENONESEMICARBAZONE.

18·3 gm. benzylaniline and 17·7 gm. acetophenonesemicarbazone were heated in toluene at 130°. There was a slight evolution of ammonia which ceased after about thirty hours heating, much of the semicarbazone was, however, still unchanged. A small additional quantity of the amine was poured into the hot liquid, and the evolution of ammonia recommenced. After fifty hours heating altogether, the unchanged acetophenonesemicarbazone ( 12 gm.) was filtered off from the partially cooled liquid. The filtrate was evaporated to small bulk, and portions of the residual oil dissolved in various solvents and mixed solvents, but in no case was a solid product obtained. Alcohol, chloroform, ether, petroleum ether and alcohol-water, alcohol-ether, and chloroform-petroleum ether were amongst those tried, but only oils were precipitated. The residue, combined with all the oils from the various attempts at crystallization, was then evaporated under a high vacuum at 140° to remove as much solvent as possible. The viscous oil remaining was dissolved in ether in a shallow basin, and kept in an evacuated desiccator . On evaporation of the ~~quantities of~~ ether, a solid was obtained; this was ground and washed several times/

times with ether. A creamy-white crystalline substance remained undissolved. This product which melted at 139° was crystallized from alcoholic solution after decolorisation by charcoal as a white substance , M.Pt. 139°–140°, a second crystallization and washing with ether gave white needles of the pure substance melting at 143°–144°. Hydrolysis with dilute acid indicated the presence of an acetophenone and a hydrazine residue. ( Found: N, 12·31, 12·31%; $C_{22}H_{21}ON_3$, i.e. $C_6H_5CH_2(C_6H_5)N\cdot CO\cdot NH\cdot N:C(CH_3)C_6H_5$ requires: N, 12·25%.

The ethereal washings were now evaporated to dryness, the solid obtained was dissolved in alcohol, boiled with decolorising carbon, and the solvent then removed in vacuo. Crystals, M.Pt. 37°–39°, and after further recrystallization from ether, M.Pt. 38°–39°, were obtained. The solubility, M.Pt., alkaline reaction and smell of this compound indicated that it was unchanged amine. This was confirmed by preparing from it the nitroso compound and also the benzenesulphonyl derivative, and comparing these with authentic specimens.

A second preparation was attempted, and in this the amine and the semicarbazone were heated in solvent naphtha(B.Pt. 170°–180°) for thirty hours, the temperature being maintained at 170°. At the end of this period, some brownish crystals remained suspended in the solution. These , when filtered and crystallized from/

from water, were identified as hydrazodicarbonamide by mixed melting point determinations with a previously prepared sample. The filtrate deposited yellow crystals on cooling, and these were removed and washed with ether. The yellow portion dissolved in the ether from which it crystallized on concentration, and the crystals were recognized as acetophenoneazine, M.Pt.122°. Some acetophenonesemicarbazone had been precipitated amongst this quantity of azine, and was identified when the latter had been removed by excess of ether. No yield of the acetophenonebenzylphenylaminoformylhydrazone was isolated from this experiment.

Toluene was used again in another endeavour to obtain this substance. 25 gm. of each of the starting materials were heated together at 125° for ninety hours. Some unchanged acetophenonesemicarbazone separated on cooling the solution. The filtrate was then evaporated to leave about 10ccs. of oil which was dissolved in ether and the solution then allowed to evaporate slowly in vacuo. Another quantity of semicarbazone was removed from the partially evaporated liquid, and complete evaporation of the ether left a residue which consisted only of acetophenoneazine and benzylaniline.

## HYDROLYSIS OF ACETOPHENONEBENZYLPHENYLAMINOFORMYLHYDRAZONE.

The normal derivative, M.Pt. 143°, was hydrolysed by rapid boiling with 1% hydrochloric acid. The solution was evaporated under reduced pressure, acetophenone being found in the distillate. A small quantity of viscous yellow oil remained, but this did not solidify, and decomposition, indicated by a gradual darkening of the solutions, set in when crystallization was attempted. This was not repeated since the yield of the semicarbazone had been so poor.

## ACETONESEMICARBAZONE AND BENZYLANILINE.

9 gm. amine was refluxed in toluene solution with the equivalent weight of acetonesemicarbazone at 150° for thirty hours. At the end of this time there was a considerable deposit of hydrazodicarbonamide. This was removed and the filtrate evaporated to very small bulk. Petroleum ether was added to the viscous residue, and the liquid was allowed to evaporate slowly in vacuo. Unchanged benzylaniline remained as a deposit of discoloured crystals, M.Pt. 37°.

# DIBENZYLAMINE.

## DIBENZYLAMINE.

It was decided to investigate the action on semicarbazones of this strongly basic secondary amine of high molecular weight, it being one which might, judging from its formula, behave similarly to di(naphthylbenzyl)amine.

## THE ACTION OF DIBENZYLAMINE ON ACETONESEMICARBAZONE.

It was thought that the amine and semicarbazone would react, with evolution of ammonia, to give acetonedibenzylaminoformylhydrazone. The reactants were accordingly mixed in equimolecular proportions and heated in toluene at 130° for seven hours. Ammonia was evolved and the reaction was carried on until the production of this gas weakened. Several unsuccessful attempts were made to cause separation of a solid from the viscous oil obtained after removal of the toluene: finally a small quantity of impure and sticky substance was isolated from ether-petroleum ether. Various fractions melted between 130° and 150°, but when recrystallized from acetone, a pure substance M.Pt. 196° was obtained. [1].

The addition of benzaldehyde in aqueous alcohol to the oily residue/

residue gave a white crystalline precipitate which, when purified melted also at 196° [11]. Mixed melting point determinations proved, however, that these substances were different.

[1] was not hydrolysed by dilute acid but reduced Fehling's solution.

[11] was hydrolysed by dilute acid losing benzaldehyde, it also contained a hydrazine residue.

By analysis [1] was identified as s-di(dibenzylaminoformyl)-hydrazide, and [11] as benzaldehydedibenzylaminoformylhydrazone.

[1] :- $(C_6H_5CH_2)_2:N\cdot CO\cdot NH\cdot NH\cdot CO\cdot N:(C_6H_5CH_2)_2$ .

[11] :- $C_6H_5CH:N\cdot NH\cdot CO\cdot N:(CH_2C_6H_5)_2$ .

Acetone ketazine was detected in the toluene distillate from ~~the~~ the preparation, so that [1] appears to have been formed by decomposition of two molecules of acetonedibenzylaminoformylhydrazone into acetoneketazine and s-di(dibenzylaminoformyl)-hydrazide.

$$2(CH_3)_2C:N\cdot NH\cdot CO\cdot NH_2 + 2NH:(CH_2C_6H_5)_2 = 2NH_3 +$$

$$2(CH_3)_2C:N\cdot NH\cdot CO\cdot N:(CH_2C_6H_5)_2 = \begin{array}{l} NH\cdot CO\cdot N:(CH_2C_6H_5)_2 \\ \cdot \\ NH\cdot CO\cdot N:(CH_2C_6H_5)_2 \end{array} + \begin{array}{l} N:C(CH_3)_2 \\ \cdot \\ N:C(CH_3)_2 \end{array}$$

The probability that acetonedibenzylaminoformylhydrazone exists, although not yet isolated in this first preparation, is indicated also by the formation of the corresponding benzaldehyde/

benzaldehyde compound. Benzaldehyde is presumably able to displace the acetone group in the molecule, as happened previously in the case of the piperidine derivative, and can also occur when acetonesemicarbazone is treated with benzaldehyde.

## THE ACTION OF DIBENZYLAMINE ON BENZALDEHYDESEMICARBAZONE.

This reaction was now investigated with a view to confirming the structure of the derivative previously obtained. Equimolecular quantities were heated at 145° for eight hours. The residue on treatment with alcohol gave crystals which were a mixture of unchanged benzaldehydesemicarbazone and the expected product, benzaldehydedibenzylaminoformylhydrazone. Repeated crystallization from alcohol was necessary to purify this substance from the unchanged starting material.

$C_6H_5CH{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + HN{:}(CH_2C_6H_5)_2 \quad = \quad NH_3 +$

$C_6H_5CH{:}N{\cdot}NH{\cdot}CO{\cdot}N{:}(CH_2C_6H_5)_2$ .

## THE ACTION OF DIBENZYLAMINE ON ACETOPHENONESEMICARBAZONE.

This reaction was carried out at 130° for twenty hours. A pure product, M.Pt. 153°-154°, was readily separated which, when hydrolysed, gave acetophenone, and a hydrazine residue was recognised by the reduction of Fehling's solution.

This substance was proved from analysis and the feregoing tests to be acetophenonedibenzylaminoformylhydrazone, $C_6H_5(CH_3)C:N\cdot NH\cdot CO\cdot N:(CH_2C_6H_5)_2$ .

## HYDROLYSIS OF DIBENZYLAMINOFORMYLHYDRAZONES.

It was hoped to obtain dibenzylaminoformylhydrazide hydrochloride by hydrolysis of either benzaldehydedibenzylaminoformylhydrazone or acetophenonedibenzylaminoformylhydrazone but, although repeated attempts were made with increasing dilutions of acid, no such intermediate stage was isolated; and the break-down of the molecule into aldehyde or ketone, hydrazine hydrochloride and dibenzylamine hydrochloride was practically complete each time.

## PREPARATION OF ACETONEDIBENZYLAMINOFORMYLHYDRAZONE.

The presence of acetonedibenzylaminoformylhydrazone in the preparation carried out at 160° for seven hours, was indicated by the corresponding benzaldehyde derivative being formed on treatment of the preparation residues. This compound also appears to have been decomposed to a much greater extent in a later preparation in which the temperature was raised from 145° to 165° in sixteen hours and heating continued at

165° for a further sixteen hours. In view of these observations an experiment was carried out in which the mixture was heated at 110° for fifteen hours only. From this preparation a substance was obtained which, on repeated crystallization from acetone, gave colourless crystalline plates, M.Pt. 130°–132°. This product contained an acetone and a hydrazine residue, and was identified as acetonedibenzylaminoformylhydrazone, $(CH_3)_2{:}N\cdot NH\cdot CO\cdot N(CH_2C_6H_5)_2$. The formation of benzaldehydedibenzylaminoformylhydrazone from the above on treatment with benzaldehyde in aqueous alcohol confirmed this structure, the aldehydic group having replaced the ketonic.

## 2nd. PREPARATION OF s-DI(DIBENZYLAMINOFORMYL)HYDRAZIDE.

Since a very poor yield of s-di(dibenzylaminoformyl)hydrazide had been obtained in the first preparation, the experiment was repeated and the temperature and time of heating increased to facilitate decomposition of the normal derivative. A very much larger yield separated from the concentrated toluene solution.

Analysis confirmed the formula:-

$$\begin{array}{l} NH\cdot CO\cdot N(CH_2C_6H_5)_2 \\ \cdot \\ NH\cdot CO\cdot N(CH_2C_6H_5)_2 \end{array} .$$

## HYDROLYSIS OF s-DI(DIBENZYLAMINOFORMYL)HYDRAZIDE.

As was to be expected this substance was difficult to hydrolyse. Boiling it with concentrated hydrochloric acid did not accomplish this, and it was necessary to decompose it in a sealed tube. Hydrazine hydrochloride and dibenzylamine hydrochloride were isolated from the hydrolysed residue.

$$\begin{array}{l} NH\cdot CO\cdot N(CH_2C_6H_5)_2 \\ \cdot \\ NH\cdot CO\cdot N(CH_2C_6H_5)_2 \end{array} + 2H_2O + 4HCl = NH_2\cdot NH_2,2HCl + 2CO_2 + 2[(C_6H_5CH_2)_2NH,HCl] .$$

## EXPERIMENTAL.

### THE ACTION OF DIBENZYLAMINE ON ACETONESEMICARBAZONE.

The dibenzylamine was dried over potassium hydroxide and distilled in vacuo. 7·9 gm. amine and 4·6gm. acetonesemicarbazone were heated under reflux in a small quantity of toluene at approximately 160° for seven hours. Ammonia was evolved during the period, and no solid separated from solution on cooling. The solution was evaporated under reduced pressure, the temperature being again raised to 160°. After evaporation only a viscous oil remained.

Various portions were treated with (1) alcohol-water, (2) acetic acid, (3) alcohol-ether and (4) benzene-petroleum ether but no solid products were obtained.

A part was then dissolved in ether, petroleum ether added in excess, and after standing two days, a deposit of very sticky crystals was obtained on the walls of the flask. M.Pt. 149°-154°. Recrystallization of these from acetone gave fine needle-like prisms ,M.Pt. 196° [1].

A second portion was dissolved in alcohol and mixed with benzaldehyde and as much water as could be added without causing/

causing turbidity. Precipitation of needle-like crystals took place fairly rapidly on shaking the liquid.
This substance was crystallized successively from alcohol, chloroform-light petroleum and acetone and melted at 196° [11].
A mixed melting point determination proved that [11] was a different substance from that previously obtained , [1].
Product [1] gave no acetone on boiling with hydrochloric acid and did not appear to be hydrolysed .
Product [11] hydrolysed readily with dilute hydrochloric acid losing benzaldehyde.
Analyses of these substances were carried out on samples produced from later experiments and are reported thereunder.

## THE ACTION OF DIBENZYLAMINE ON BENZALDEHYDESEMICARBAZONE.

5 gm. dibenzylamine and 9 gm. benzaldehydesemicarbazone were heated together in toluene at 145° for eight hours, and the solvent was then removed by distillation in vacuo.
The contents of the flask were dissolved in hot alcohol from which solution crystals separated on cooling.
After repeated crystallization of the product from alcohol, a pure sample of benzaldehydedibenzylaminoformylhydrazone [11] was obtained.

( Found :- N, 12·31, 12·22% ; $(C_6H_5CH_2)_2$:N·CO·NH·N:$CHC_6H_5$, i.e. $C_{22}H_{21}ON_3$ requires N, 12·22%.)
The molecular weight was determined by the ebullioscopic method using chloroform as solvent; The value obtained was 316, and theory requires 343.
This substance was readily soluble in alcohol, chloroform and acetone, and sparingly soluble in water and petroleum ether.
This derivative in the pure state was, however, obtained more readily by the action of benzaldehyde on the oil containing a large percentage of acetonedibenzylaminoformylhydrazone, as was done in the preceding preparation.
The direct preparation from benzaldehydesemicarbazone is troublesome on account of the repeated crystallization involved in separating the product from any traces of the unchanged semicarbazone.
16 gm. dibenzylamine and 20gm. acetonesemicarbazone were heated in toluene at 130°-135° for thirteen hours; the solution was evaporated in vacuo, and the residual oil extracted with ether, 0·5 gm. acetonesemicarbazone which separated at this stage was removed. The ether was then evaporated off and benzaldehyde, alcohol and a large volume of water added. Benzaldehydedibenzylaminoformylhydrazone was obtained in good yield and in a practically pure state.

## THE ACTION OF DIBENZYLAMINE ON ACETOPHENONESEMICARBAZONE.

### Preparation of Acetophenonedibenzylaminoformylhydrazone.

9 gm. acetophenonesemicarbazone and 10 gm. amine were heated in toluene for twenty hours at 130°. Solution of the semicarbazone was then complete, and the smell of ammonia was no longer strong. The liquid was filtered while hot, then allowed to cool ; the contents of the flask crystallized to form an almost solid mass. The solid was pressed free from toluene on a Büchner filter and washed with a little ether.

A sample was recrystallized as follows:-

from hot 96% alcohol (twice), M.Pt. 153°-154° ;
from chloroform-petroleum ether, M.Pt. 153°;
from acetone, M.Pt. 153°.

The total yield was therefore purified by two crystallizations from alcohol: the last fractions precipitated from the alcoholic mother liquors by addition of water contained a small quantity of unchanged acetophenonesemicarbazone.

( Found N, 11·77 , 11·88 % ; $C_{23}H_{23}ON_3$ requires N, 11·76%. Molecular weight by ebullioscopic method in chloroform was 362, theoretical is 357.)

These results confirm the formula :-

$$C_6H_5(CH_3)C:N\cdot NH\cdot CO\cdot N:(CH_2C_6H_5)_2 .$$

The crystals of acetophenonedibenzylaminoformylhydrazone were obtained as long prisms, almost thread-like; they were soluble in chloroform, benzene, alcohol, acetone, slightly soluble in ether, but insoluble in light petroleum, and sparingly soluble in water.

## HYDROLYSIS OF THE DIBENZYLAMINOFORMYLHYDRAZONES.

### Attempts to obtain Dibenzylaminoformylhydrazide Hydrochloride.

Benzaldehydedibenzylaminoformylhydrazone was boiled with 2% hydrochloric acid until solution was complete. Benzaldehyde was identified in the aqueous distillate which was removed under reduced pressure. The solid remaining was warmed with absolute alcohol, and a crystalline deposit of hydrazine dihydrochloride separated. The filtrate, on addition of ether gave a precipitate of dibenzylamine hydrochloride which was recognised by the formation of the benzenesulphonyl derivative, and by comparing it with an authentic sample of benzenesulphondibenzylamide. Hydrolysis appears to have decomposed the substituted formylhydrazide also, into its component parts. A later hydrolysis with 3% acid gave a trace of precipitate M.Pt. 78°-83° when caustic soda was added/

added to the hydrolysed residue. This substance gave a benzenesulphonyl derivative M.Pt. 124°, but so little was isolated that it could not be identified.

The acetophenonedibenzylaminoformylhydrazone hydrolysed more quickly, so that it was hoped to prevent complete hydrolysis by using this substance and boiling for a shorter period. 1 % hydrochloric acid hydrolysed the solid rapidly giving acetophenone, hydrazine hydrochloride and dibenzylamine hydrochloride without any trace of an intermediate stage. 0·5 % acid gave the same result. The hydrolysis was next carried out in a large volume of alcohol containing the theoretical quantity of acid, but again it appeared to be complete. 0·2 % hydrochloric acid was then used and a trace of a yellowish hydrochloride , M.Pt. 55° (approx.) was isolated from the concentrated aqueous residues, from these also a trace of a benzenesulphonyl derivative, M.Pt. 121° was formed. The remainder of the residues was treated with sodium hydroxide and extracted with ether; evaporation of the ether yielded some crystals, M.Pt. 157°-161°.

## PREPARATION OF ACETONEDIBENZYLAMINOFORMYLHYDRAZONE.

Acetonesemicarbazone and dibenzylamine in molecular proportions were heated together in toluene at 110° for fifteen hours. Ammonia was evolved and the solution, on cooling, deposited crystals. The first fraction which separated was unchanged acetonesemicarbazone, but the second portion when pressed free from toluene melted at 113°- 120°. This substance was very soluble in alcohol, and was evidently a mixture of starting material and the required acetonedibenzylaminoformylhydrazone. Purification by fractional crystallization was carried out in accordance with the following scheme, the results of which are shown :-

| | | | |
|---|---|---|---|
| Ether as solvent ... ... | 1st. | fraction | M.Pt. 114°-120° |
| | 2nd. | '' | M.Pt. 118°-122° |
| Benzene '' ... ... | 1st. | '' | M.Pt. 130°-160° |
| Alcohol-ether<br>+ excess petroleum ether. | 1st. | '' | M.Pt. 187°<br>(acetonesemicarbazone) |
| | 2nd. | '' | M.Pt. 120°-150° |
| | 3rd. | '' | M.Pt. 124°-126° |
| | 4th. | '' | M.Pt. 113°-117° |
| Chloroform- petroleum ether. | 1st. | '' | M.Pt. 118°-122° |
| Acetone | 1st. | '' | M.Pt. 124°-128° |

Fraction/

Fraction No. 4 from alcohol-ethers was recrystallized from acetone, M.Pt. 127°-130°. Fraction No.1 from acetone was precipitated from chloroform solution by petroleum ether, M.Pt. 125°-130°. All fractions except those which melted above 130° and were therefore largely acetonesemicarbazone, were combined and subjected to repeated crystallization from acetone : crystals in the form of irregular plates M.Pt. 130°-132° were finally obtained.

This substance was soluble in water from which it crystallized as a flocculent precipitate.

By hydrolysis with dilute acid, it was shown to contain an acetone residue.

( Found :- N, 14·0 %; $(C_6H_5CH_2)_2:N\cdot CO\cdot NH\cdot N:C(CH_3)_2$ i.e. $C_{18}H_{21}ON_3$ requires N, 14·2% .)

The identity of this substance was further confirmed by the following experiment. A small quantity was dissolved in alcohol , then a drop of benzaldehyde was introduced. Water was added with shaking until the alcohol was just sufficient to keep the oil in solution. After a very short time crystals separated, and these on examination proved to be benzaldehydedibenzylaminoformylhydrazone M.Pt. 196°

## PREPARATION OF s-DI(DIBENZYLAMINOFORMYL)HYDRAZIDE.. [1]

20 gm. acetonesemicarbazone and 30 gm. dibenzylamine were heated in toluene for eight hours at 145°, then the temperature was raised through another eight hours to 165° and the heating continued until evolution of ammonia had ceased, approximately 32 hours in all. The solution was partially distilled in vacuo, and the distillate then examined as follows:-

Dilute hydrochloric acid was added to the toluene, and the mixture was distilled from a glycerine bath, the two layers being mixed as much as possible by frequent shaking. Acetone was identified in the aqueous portion of the mixed distillate, and hydrazine hydrochloride in the acid layer of the mixed residue. This indicated the formation of acetoneketazine in the reaction, but this was apparently not due to decomposition of acetonesemicarbazone itself, since no hydrazodicarbonamide had been produced.

The preparation residues from which half of the solvent had already been removed, were allowed to stand for several days while a flocculent solid separated slowly. This substance was very easily soluble in most organic solvents, but it was possible to crystallize it from ethylene dichloride-petroleum ether, chloroform-petroleum ether and dekalin.

The/

The toluene mother-liquors were again concentrated and mixed with ether and petroleum ether; a second quantity of solid separated after another period of several days.

The pure product, melting at 196°-197°, was extremely light in weight, and the crystals were fine thread-like prisms which felted readily. Found:- N, 11·62, 11·65%; Mol. Wt. in chloroform by the ebullioscopic method, 487.

$$\begin{array}{l} NH\cdot CO\cdot N(CH_2C_6H_5)_2 \\ NH\cdot CO\cdot N(CH_2C_6H_5)_2 \end{array}, \quad C_{30}H_{30}O_2N_4 \text{ requires N, 11·71\%, and Mol. Wt., 478.}$$

## HYDROLYSIS OF s-DI(DIBENZYLAMINOFORMYL)HYDRAZIDE.

This substance was boiled with concentrated hydrochloric acid, but did not dissolve.

0·1 gm. was placed in a sealed tube with four ccs. of the acid and heated at 150° for three hours.
The tube, in which there was considerable pressure due to $CO_2$, was then opened, the contents washed out with water, filtered free from a trace of tar and evaporated to dryness. ( Acetone was tested for but not found.) The dry residue was warmed with absolute alcohol and filtered. Hydrazine hydrochloride remained undissolved, and was identified by formation of the characteristic yellow precipitate of benzalazine, M.Pt.93°.

The filtrate/

The filtrate was concentrated slightly, and ether added which caused separation of a crystalline precipitate, M.Pt. 245°. This did not lower the melting point of a sample of dibenzylamine hydrochloride, and its identity was confirmed by the formation of a benzenesulphonyl derivative, insoluble in alkali, M.Pt. 62° and identical with benzenesulphondibenzylamide.

Hydrolysis therefore produced $CO_2$, hydrazine hydrochloride and dibenzylamine hydrochloride.

# NOR d ψ EPHEDRINE.

## NOR d ψ EPHEDRINE.

Nor d ψ ephedrine, which is a primary amine containing an asymmetric carbon atom, was next studied: the object of the investigation being the production, if possible, of an optically active aminoformylhydrazide which could be used in the resolution of racemic aldehydes and ketones.

The dextrorotatory form can be obtained as the normal sulphate from which the base itself is easily isolated. ( Smith, J., 1928,51; Gibson and Levin, J., 1929,2754; Nagai and Kanao, Ann. 1929, 470, 157-182.)

The optical rotation of the base was determined in an aqueous solution of concentration 1·6368 gm. per 100ccs., using a four decimetre polarimeter tube and mercury-green light, λ5461. At 21·5° the observed rotation was 1·65°, making the specific rotation $[\alpha]^{21\cdot5}_{\lambda 5461} = +25\cdot2°$.

The value according to Gibson and Levin is + 24·7° at 20°C with light of the same wave length.

## THE ACTION OF NOR d $\psi$ EPHEDRINE ON ACETOPHENONESEMICARBAZONE.

This was the first reaction to be investigated, and equimolecular quantities of the amine and the semicarbazone were heated in toluene under reflux as in previous experiments, and, as before, the evolution of ammonia proceeded rapidly. No solid product could, however, be obtained from the pale yellow viscous oil which remained after evaporation of the toluene : but dilute hydrochloric acid left in contact with the oil for several days caused separation of a small quantity of a solid hydrochloride. This substance reduced Fehling's solution in the cold, and its melting point was 193° . This was therefore a slightly impure deposit of hydrazine dihydrochloride produced possibly from decomposition of an aminoformylhydrazide hydrochloride formed although not isolated. The remaining liquid, which was toluene mixed with acid, some acetophenone from hydrolysis, and various organic solvents used in attempts to separate a solid from the preparation, was evaporated under reduced pressure. Quantities of water were added at intervals, and the mixture distilled off. A mealy solid remained which, when purified, yielded a white substance M.Pt. 123°-123·5° crystallizing in tufts of very long prisms. It was soluble/

soluble in alcohol, ether, chloroform, hot water and benzene; very sparingly soluble in cold water, and insoluble in light petroleum.

## ELUCIDATION OF THE STRUCTURE OF THE SUBSTANCE, M.Pt. 123°

This substance was hydrolysed with concentrated hydrochloric acid, the distillate being tested for acetophenone, and the residue for hydrazine or a hydrazine linkage. Both were absent. The low percentage of nitrogen present ( 8% approx.) indicated that this must be derived from a nor ψ ephedrine residue alone. The substance was again hydrolysed, and nor ψ ephedrine shown to be present in the residue by the formation of the benzenesulphonyl derivative of the amine. (P. 109)

At a later stage, this same substance was obtained from some impure nor ψ ephedrinoformylhydrazide hydrochloride which was undergoing decomposition.

The compound was analysed, and a molecular formula, $C_{10}H_{11}O_2N$ obtained. Difficulty was experienced at first with macro-combustions for determination of nitrogen, but the values were carefully verified later.

Before reliable analytical data were established, it was thought that the substance might be a disubstituted urea which/

which could presumably be formed from decomposition of the nor ψ ephedrinoformylhydrazide hydrochloride in the following manner:-

$$\begin{array}{c} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH\cdot NH_2,HCl \\ + \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH\cdot NH_2,HCl \end{array} =$$

$$= \begin{array}{l} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot \end{array} CO \quad + \quad CO\begin{array}{l} \cdot NH\cdot NH_2,HCl \\ \cdot NH\cdot NH_2,HCl \end{array}$$

An experiment was carried out in accordance with a general method described by Davis and Blanchard, ( J. Am. C. S., 1923, 45, 1819.) for the preparation of ureas of this type.

Urea reacted with nor d ψ ephedrine sulphate when the dry materials were heated together at 160°-170°. Subsequent extraction of the residue with water separated a derivative identical with the substance under investigation. (M.Pt. 123°.)

A second method, that of Dixon, ( J., 1889, 55, 622; 1893, 63, 328. ) was then tried. The general outline of this method of synthesis is as follows. The amine, in ethereal or alcoholic solution, reacts with carbon disulphide to form a salt of the amine and the aminodithiocarbamic acid, this salt decomposes on prolonged boiling in alcoholic solution to give $H_2S$ and a disubstituted thiourea.

$$RNH\cdot CSSH,H_2NR \quad = \quad H_2S \quad + \quad RNH\cdot CS\cdot NHR\ .$$

The sulphur atom in this compound may then be replaced by oxygen on treating the thiourea with alcoholic silver nitrate. This method did not yield the product that the previous one had given.

Analysis, however, disproved the possibility of the substance (M.Pt. 123°) being a disubstituted urea, since the nitrogen percentage required for this was 8·5, and the value obtained was 7·9. Carbon and hydrogen values were also different.

---

The formation of a substance having an empirical formula, $C_{10}H_{12}O_2N$ from urea and the sulphate of the amine , might take place according to the following equations.

$$2NH_2\cdot CO\cdot NH_2 \quad + \quad [C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH_2]_2,H_2SO_4$$

$$= \quad (NH_4)_2SO_4 \quad + \quad 2C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH_2\ .$$

$$\begin{array}{c} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH_2 \\ + \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH_2 \end{array} = \begin{array}{c} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO \\ \cdot \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO \end{array}$$

$$+ \quad NH_2\cdot NH_2\ .$$

This substance would be an oxalyl derivative.

The action of urea on the amine did not, however, liberate hydrazine. The evolution of ammonia was noticed during the reaction, and it has already been shown ( P. 10a) that hydrazine can decompose to give ammonia.

An attempt to form an oxalyl derivative by heating the base with oxalic acid gave the oxalate, M.Pt. 235°.

A similar attempt to prepare a formyl derivative gave a formate melting over 200°.

Hydrolysis of the substance with dilute sulphuric acid gave no trace of either oxalic or formic acids. No oxalate was found/

found in another hydrolysis carried out with 50% caustic soda.

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The nor ψ ephedrinoformylhydrazide hydrochloride had now been definitely characterized, so the by-products in the preparation of the substance, M.Pt. 123°, from this hydrochloride were studied.

Carbohydrazide was absent, and this again negatived the possibility of the substance being a disubstituted urea. ( See equation on page 97a)

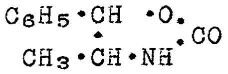
A decomposition of the hydrochloride in attempted dehydration yielded hydrazine hydrochloride as the only by-product. Decomposition by picric acid had also given hydrazine directly as the picrate.

---

The difference between the molecular formula found, viz. $C_{10}H_{11}O_2N$, and that of the nor ephedrine ( $C_9H_{13}ON$ ) which the substance gave on hydrolysis, was +1C, +1O, -2H.
The linkage -CO- was almost certain to be present since no carbon atom or oxygen atom occurred in the by-products from the decomposed hydrochloride.
It was thought that the action of phosphoric acid on the substance might show how this group was situated in the molecule. When warmed with phosphoric acid, the substance/

substance dissolved with loss of $CO_2$. A quantitative estimation of the proportion of the total carbon available as $CO_2$, was carried out, the ratio obtained being 1/10. This figure was incompatible with the suppositions that the substance could be an oxalyl derivative, a formyl derivative, or a disubstituted urea, since an oxalyl structure would give a ratio of 1/20, the urea a ratio of 1/19, and a formyl derivative would give no $CO_2$. ( See equations on following page, par. [3]. )

The mode of formation indicates the grouping $-NH-CO-$. To give $CO_2$ on hydrolysis this cannot be expanded to $-NH-CO-C$ or $-NH-CO-H$, it may, however, be $-NH-CO-O-$ or $-NH-CO-NH-$, but, since only one nitrogen atom is present the only possibility is $-NH-CO-O-$. This indicates that the hydrogen of the hydroxyl, (since this is where the second oxygen atom is situated) must be eliminated with the $-NH_2$ of the mono-substituted urea, and with the $-NH\cdot NH_2$ group of the $\delta$-substituted semicarbazide, to form ammonia and hydrazine respectively, leaving the same ring structure in each case. The substance would then be 2-oxo 4-methyl 5-phenyl oxazol tetrahydride, or 4-methyl 5-phenyl 2-oxazolidone,



$$\begin{array}{l} C_6H_5\cdot CH\cdot O. \\ CH_3\cdot CH\cdot NH \end{array}\cdot CO \quad .$$

This satisfies all the conditions as shown by the following equations :-

[1]. The molecular formula is $C_{10}H_{11}O_2N$.

[2]. Nor ψ ephedrine is obtainable on hydrolysis.

$$\begin{array}{l} C_6H_5\cdot CH\ \cdot O\cdot \\ \quad\ \ \cdot \\ \ CH_3\cdot CH\cdot NH \end{array}\!\!\cdot CO \quad + \quad H_2O \quad = \quad \begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad\ \ \cdot \\ \ CH_3\cdot CH\cdot NH_2 \end{array} \quad + \quad CO_2$$

[3]. One tenth of the total carbon is liberated as $CO_2$ on hydrolysis.

$$\begin{array}{l} C_6H_5\cdot CH\ \cdot O\cdot \\ \quad\ \ \cdot \\ \ CH_3\cdot CH\cdot NH \end{array}\!\!\cdot CO \quad + \quad H_2O \quad = \quad \begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad\ \ \cdot \\ \ CH_3\cdot CH\cdot NH_2 \end{array} \quad + \quad CO_2 \qquad (\ 1/10)$$

[ whereas the urea would give 1/19 ,

$$\begin{array}{l} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH \end{array}\!\!\cdot CO \quad + \quad H_2O \quad = \quad CO_2 \quad +$$

$$2C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH_2 \qquad (\ 1/19)$$

the oxalyl derivative would give 1/20 ,

$$\begin{array}{r} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO \\ \cdot \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO \end{array} \quad + \quad H_2O \quad = \quad CO \quad + \quad CO_2$$

$$+ \quad 2C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH_2 \qquad (\ 1/20)$$

~~and~~ and the formyl derivative would give no $CO_2$ when hydrolysed.

$$C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CHO \quad + \quad H_2O \quad = \quad CO \quad + \quad H_2O$$

$$+ \quad C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH_2\ ]$$

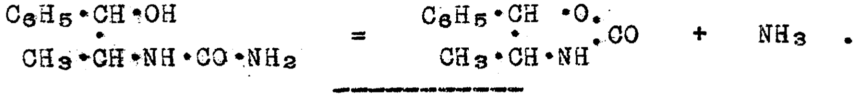
[4]. The substance can be formed from nor ψ ephedrinoformylhydrazide hydrochloride with loss of hydrazine hydrochloride.

$$\begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad\ \ \cdot \\ \ CH_3\cdot CH\cdot NH\cdot CO\cdot NH\cdot NH_2,HCl \end{array} \quad = \quad \begin{array}{l} C_6H_5\cdot CH\ \cdot O\cdot \\ \quad\ \ \cdot \\ \ CH_3\cdot CH\cdot NH \end{array}\!\!\cdot CO \quad + \quad NH_2\cdot NH_2,HCl\ .$$

[5]. The substance is obtainable by the action of urea on nor d $\psi$ephedrine sulphate.

$$[C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH_2]_2,H_2SO_4 \quad + \quad 2NH_2\cdot CO\cdot NH_2$$

$$= \quad 2C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH_2 \quad + \quad (NH_4)_2SO_4$$



$$\begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad\cdot \\ CH_3\cdot CH\cdot NH\cdot CO\cdot NH_2 \end{array} \quad = \quad \underline{\begin{array}{l} C_6H_5\cdot CH\ \cdot O\cdot \\ \quad\quad\ \cdot \qquad\quad \cdot CO \\ CH_3\cdot CH\cdot NH \end{array}} \quad + \quad NH_3 \ .$$

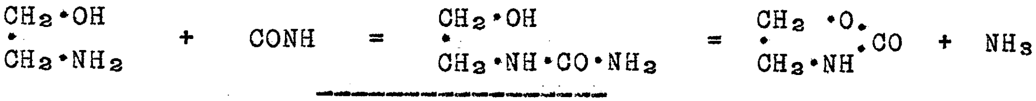
The resemblance of this structure to that of a lactone may explain the readiness with which the compound dissolved in dilute caustic soda solution.

## CONFIRMATION OF THE STRUCTURE BY SYNTHESIS.

A compound similar to substance, M.Pt. 123° was known. This was $\mu$- or 2-oxazolidone which had been prepared from $\alpha$-hydroxyethylamine by Knorr and Rössler, ( Ber. 1903, 36, 1280 ); the method being as follows.

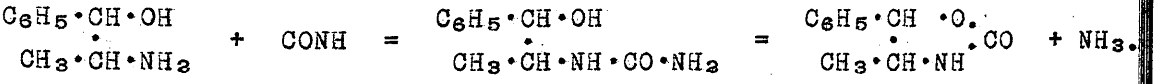
The sulphate of the amine was heated in aqueous solution with potassium cyanate , ( general reaction for the formation of mono-substituted ureas ). The water was slowly evaporated and the residue extracted with alcohol to remove potassium sulphate. The oily residue left after evaporation of the alcohol was decomposed at 200°, to give 2-oxazolidone with liberation/

liberation of ammonia.



$$\begin{array}{l}CH_2\cdot OH\\ \cdot\\ CH_2\cdot NH_2\end{array} + CONH = \underline{\begin{array}{l}CH_2\cdot OH\\ \cdot\\ CH_2\cdot NH\cdot CO\cdot NH_2\end{array}} = \begin{array}{l}CH_2\ \cdot O\cdot\\ \cdot\\ CH_2\cdot NH\cdot\end{array}CO + NH_3$$

A preparation exactly analogous to that of Knorr and Rössler was carried out, starting from nor d ψ ephedrine sulphate and potassium cyanate. The thermal decomposition was accompanied by loss of ammonia, and produced substance, M.Pt. 123°.



$$\begin{array}{l}C_6H_5\cdot CH\cdot OH\\ \quad\cdot\\ CH_3\cdot CH\cdot NH_2\end{array} + CONH = \begin{array}{l}C_6H_5\cdot CH\cdot OH\\ \quad\cdot\\ CH_3\cdot CH\cdot NH\cdot CO\cdot NH_2\end{array} = \begin{array}{l}C_6H_5\cdot CH\ \cdot O\cdot\\ \quad\cdot\\ CH_3\cdot CH\cdot NH\cdot\end{array}CO + NH_3.$$

This synthesis proved the substance to be 4-methyl 5-phenyl 2-oxazolidone.

## THE ACTION OF NOR d ψ EPHEDRINE ON ACETONESEMICARBAZONE.

A toluene solution of the amine was heated with acetonesemicarbazone at 110°-120°. Ammonia was evolved briskly for twelve hours, then the solution was evaporated. No solid product was obtained, only an oil being precipitated when petroleum ether was added to a benzene solution of the residue. The oil was left in contact with a small quantity of concentrated hydrochloric acid for several days, and a white precipitate separated which was removed and washed free from adhering oil by means of ether. This solid was recrystallized and identified as a hydrochloride M.Pt. 156°, the presence in it of a hydrazine residue being shown by the reduction of Fehling's solution. It was identical with the nor ψ ephedrinoformylhydrazide hydrochloride obtained later by the hydrolysis of the product from benzaldehydesemicarbazone and nor d ψ ephedrine.

It is practically certain that the oil obtained after heating contained acetone nor ψ ephedrinoformylhydrazone which was hydrolysed without being separated from the solvent.

## THE ACTION OF NOR d ψ EPHEDRINE ON BENZALDEHYDESEMICARBAZONE.

These two substances reacted much more slowly under similar conditions to the preceding, viz. in toluene at 110°-120°, the reaction requiring about 75 hours; a good yield was, however, obtained in a high degree of purity, directly from the toluene solution by shaking the latter in a wet flask.

This substance was purified by recrystallization from benzene and benzene-petroleum ether, M.Pt. 118°.
It was proved by hydrolysis to contain benzaldehyde, hydrazine and nor d ψ ephedrine residues, and analysis confirmed the formula :- $C_6H_5CH{:}N\cdot NH\cdot CO\cdot NH\cdot CH(CH_3)\cdot CH(OH)C_6H_5$ , i.e. benzaldehyde nor ψ ephedrinoformylhydrazone.

Benzaldehyde nor d ψ ephedrinoformylhydrazone was optically active to a far greater extent than the base itself; the specific rotation was determined in an alcoholic solution of concentration 1·9926 gm./100ccs. . $[\alpha]^{19^\circ}_{\lambda 5461} = +290\cdot5^\circ$.

## THE HYDROLYSIS OF BENZALDEHYDE NOR d ψ EPHEDRINOFORMYLHYDRAZONE.

This hydrolysis had to be carried out with very dilute acid (1%) to avoid complete hydrolysis of the substituted formylhydrazide to give hydrazine hydrochloride. The benzaldehyde/

The benzaldehyde which was easily liberated, required to be removed as rapidly as possible by steam distillation, since the benzaldehyde nor dψ ephedrinoformylhydrazone was reformed at once on cooling. Extraction methods for rapid removal of the aldehyde were tried, but steam-distillation proved the most effective means.

The residue left after evaporation of the acid under reduced pressure was completely soluble in cold alcohol, (no hydrazine). When the alcohol was evaporated in a desiccator, a yellowish sticky oil remained, which, after repeated addition and evaporation in vacuo of high-boiling petroleum ether (80°-90°), solidified to form a creamy-white solid, becoming sticky again on exposure to the air. This substance was the hydrochloride previously obtained from acetonesemicarbazone and nor dψ ephedrine reaction. Precipitation from alcoholic solution by the addition of excess of ether gave white crystals M.Pt. 156° of the norψ ephedrinoformylhydrazide hydrochloride which appeared stable.

The compound was hydrolysed qualitatively, and found to give hydrazine hydrochloride and norψ ephedrine, the latter being identified as the benzenesulphonamide. (P.109.)

A quantitative estimation of the hydrazine proved that 2/3 of the nitrogen came from the hydrazine residue, and consequently 1/3 was/

1/3 was in the amino residue. The substance was thus shown to be a hydrochloride of nor ψ ephedrinoformylhydrazide,

$H_2N\cdot NH\cdot CO\cdot NH\cdot CH(CH_3)\cdot CH(C_6H_5)OH$ .

From analysis the composition of the salt appeared to be :-

$3[C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH\cdot NH_2],4HCl,H_2O.$

The substance was dextrorotatory, $[\alpha]^{17°}_{\lambda 5461} = +37\cdot 8$, at concentration, $c = 2\cdot 842$ gm./ 100ccs. ( alcoholic solution.)

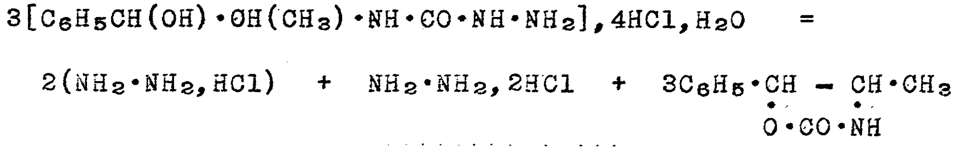
The benzaldehyde nor d ψ ephedrinoformylhydrazone was obtained by the action of benzaldehyde on this salt. but it formed very slowly, and, in one or two instances, precipitation occured only after the solution had been seeded with a crystal of the required substance.

Attempts to dehydrate the hydrochloride, M.Pt. 156°.

Some portions of the hydrolysed residue from the benzaldehyde nor d ψ ephedrinoformylhydrazone had been kept in a desiccator for a considerable time, and these were now treated with water. The substance appeared to be dissolving at first, but later, white crystals of the oxazolidone derivative M.Pt. 123° started to separate.

A quantity/

A quantity of the hydrochloride was kept for three hours at 100° and a pressure of 5mm.. The loss of weight was negligible. The experiment was repeated in presence of KOH at a temperature of 140°. The substance lost HCl and water, and the 4-methyl 5-phenyl 2-oxazolidone was identified in the residue. In a third experiment carried out at 140° but without KOH, a crystalline sublimate of the oxazol derivative containing some hydrazine hydrochloride was formed on the cooler surface of the outer containing bottle.



$$3[C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH\cdot NH_2],4HCl,H_2O \quad =$$

$$2(NH_2\cdot NH_2,HCl) \;+\; NH_2\cdot NH_2,2HCl \;+\; 3C_6H_5\cdot \underset{O\cdot CO\cdot NH}{CH - CH}\cdot CH_3$$

## TREATMENT OF NOR d ψ EPHEDRINOFORMYLHYDRAZIDE HYDROCHLORIDE WITH PICRIC ACID, AND WITH CHLOROPLATINIC ACID.

1). Since the composition of the hydrochloride was rather complex, it was decided to try to obtain some other salt more definite in its composition. Picric acid in alcohol when added to the hydrochloride, produced rosettes of long bright yellow needles which, however, proved to be hydrazine picrate.

2). Some of the hydrochloride was added to a 5% solution of chloroplatinic acid, but only a very small quantity of 4-methyl 5-phenyl 2-oxazolidone separated.

## PREPARATION OF BENZENESULPHONYL NOR ψ EPHEDRINE.

A suitable derivative was required by means of which nor ψ ephedrine, when present in small quantities, might be readily identified. When hydrolysis residues were being examined, the concentration of the nor ψ ephedrine salt in solution was in many cases too low to permit of its easy isolation in a pure state, and subsequent examination; and, in particular, if hydrochloric were the acid used, the extreme solubility of nor ψ ephedrine hydrochloride in water and alcohol necessitated the finding of such a derivative.

Nor d ψ ephedrine in aqueous solution was found to react with benzenesulphonyl chloride in presence of caustic soda. (General reaction for the characterisation of amines.)

When the solution was concentrated, a thick white precipitate of the sodium salt of the benzenesulphonyl derivative formed, but this dissolved on the addition of more water.

The sodium salt was then decomposed with hydrochloric acid, and the N benzenesulphonyl nor ψ ephedrine separated slowly, M.Pt. 103°. The melting point of the pure substance was 104°.

It was readily crystallized from alcohol-water and benzene-petroleum ether. The specific rotation in alcohol is expressed by , $[\alpha]^{17^\circ}_{\lambda 5461} = +8{\cdot}93$ at concentration, $c = 4{\cdot}4788$ gm./ 100 ccs.

The insolubility in water of this product, and the ease with which it could be obtained practically pure, rendered this compound very suitable for the identification of nor$\psi$ ephedrine in residues from hydrolyses and similar solutions.

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$$C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH_2 \quad + \quad C_6H_5\cdot SO_2Cl \quad + \quad 2NaOH$$

$$= \quad C_6H_5CH(OH)\cdot CH(CH_3)\cdot N(Na)\cdot SO_2C_6H_5 \quad + \quad 2H_2O \quad + \quad NaCl$$

$$\text{''} \qquad\qquad + \quad HCl$$

$$= \quad C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot SO_2C_6H_5 \quad + \quad NaCl$$

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# EXPERIMENTAL.

## THE ACTION OF NOR dψ EPHEDRINE ON SEMICARBAZONES.

Nor dψephedrine was obtained by the addition of a slight excess over the theoretical of potassium hydroxide solution to an aqueous solution of the pure sulphate. A small quantity of the base separated at this stage, and the filtrate was extracted thoroughly with ether to remove the rest. The ethereal solution was dried over potassium carbonate, filtered and evaporated. The crystalline residue, purified by further crystallization from benzene and benzene-petroleum ether, formed colourless plates, M.Pt. 77°. ( Gibson and Levin, J., 1929, 2754.)

The specific rotation was determined in an aqueous solution of concentration 1·6368 gm. / 100ccs. using a four decimetre polarimeter tube . The source of light used was a mercury-vapour lamp fitted with a colour filter to give green light of wavelength λ5461. $[\alpha]^{21\cdot5^\circ}_{\lambda5461} = +\ 25\cdot2^\circ$

A solution of barium hydroxide was also used to liberate the base from the solution of the normal sulphate. Barium sulphate was precipitated, filtered off, and the aqueous filtrate concentrated in vacuo before extraction with ether.

## THE ACTION OF NOR dψ EPHEDRINE ON ACETOPHENONESEMICARBAZONE.

17 gm. acetophenonesemicarbazone and 15 gm. nor dψ ephedrine were heated in 150 ccs. of toluene in a flask fitted with a ground-in condenser. The temperature of the heating-bath was maintained at 115°-125°. The reaction proceeded briskly accompanied by the evolution of ammonia, and, after six to seven hours heating, no acetophenonesemicarbazone remained undissolved. After nine hours heating the smell of ammonia diminished, and the reaction mixture was allowed to cool. The toluene was distilled off in vacuo leaving a thick and yellow viscous oil.

The oil was dissolved in ether and the solution allowed to stand; a trace of unchanged acetophenonesemicarbazone separated after two days, and after its removal, the solution was again concentrated.

Repeated attempts were made with various solvents and mixtures of solvents to induce crystallization of a solid product, but without result. Among the solvents tried were benzene, chloroform-petroleum ether, alcohol-water, carbon tetrachloride, dekalin and ethylene dichloride.

The oil was finally left in contact with a little dilute hydrochloric acid, and, after standing several days, a small quantity of a white solid had separated. This substance was removed/

removed and examined. It reduced Fehling's solution rapidly without heating, was a hydrochloride melting at 193°, and was practically insoluble in alcohol; it was recognised as a slightly impure precipitate of hydrazine dihydrochloride which must have been produced during the decomposition of the hydrolysis product from acetophenone norψ ephedrinoformylhydrazone which is presumably present although not isolated. [ Hydrazine hydrochloride was produced when the hydrolysis product from benzaldehyde norψ ephedrinoformylhydrazone decomposed. ( See page 108a) ]

The acid residues were then subjected to steam-distillation to remove traces of the organic solvents used in attempted crystallization, and also acetophenone liberated by the acid. The steam-distillation was continued for eight hours, and the aqueous residue from which all the oil had been separated was reduced to small bulk in vacuo to avoid concentration of the acid present. A pale brown mealy solid remained. This substance was soluble in boiling water, alcohol, ether, benzene, chloroform and dilute caustic soda solution, very sparingly soluble in cold water and insoluble in petroleum ether. It was obtained pure as long colourless prisms forming in rosettes when petroleum ether was added just in excess to a benzene solution; the crystals melted sharply at 123°. The constitution of this product which/

which was 4-methyl 5-phenyl 2-oxazolidone was not determined when it was first prepared, but proved later by synthesis; details of analyses and structure are accordingly given under the reactions of nor d ψ ephedrine with urea and potassium cyanate.

## THE ACTION OF NOR d ψ EPHEDRINE ON ACETONESEMICARBAZONE.

3 gm. nor d ψ ephedrine and 2·3 gm. acetonesemicarbazone were heated together under reflux in toluene at 110°–120° for twelve hours. Ammonia was evolved strongly.
The yellowish solution was evaporated under reduced pressure until all the solvent was removed. A viscous yellow mass remained which became very thick on cooling, but did not crystallize. The product was dissolved in benzene, but only an oil was precipitated on the addition of petroleum ether. The oil was mixed with light petroleum and kept in an evacuated desiccator for some time, but there was no separation of any solid. A few drops of concentrated hydrochloric acid was poured over the oil, and , after standing for several days a white precipitate separated. This precipitate was filtered off, and washed with ether until free from adhering oil on the filter. The substance, when recrystallized from alcohol-ether was obtained in/

in the form of prismatic needles , M.Pt. 156°. It was found to be a hydrochloride, and it reduced Fehling's solution rapidly indicating the presence of a hydrazine residue. This same substance was obtained later by the hydrolysis of the derivative from benzaldehydesemicarbazone and nor dψ ephedrine and the analyses are reported under that section.

## THE ACTION OF NOR dψ EPHEDRINE ON BENZALDEHYDESEMICARBAZONE.

This reaction proceeded very much more slowly than the two previous ones with acetophenonesemicarbazone and acetonesemicarbazone, but was the only one to yield a solid substituted semicarbazone.

The first reaction was carried out as follows: 5 gm. of the amine and 5·5 gm. benzaldehydesemicarbazone were heated in toluene at 120°-130° for 43 hours. Ammonia was produced slowly. The toluene was distilled off under reduced pressure to leave a thick oil; more toluene was added, and on removing this by a further distillation in vacuo, the oil began to crystallize. The solid mass in the flask was dissolved in benzene, and a crop of white crystals, M.Pt. 118° separated on cooling. The crystals, long prisms, were soluble in alcohol also, but insoluble in water and petroleum ether.

A small/

A small quantity was warmed with dilute sulphuric acid, and benzaldehyde vapour was detected; the presence of a hydrazine residue in the hydrolysed solution was shown by the reduction of Fehling's solution. The results obtained on analysis were:– C, 69·00; H, 6·47; N, 14·14%. $C_{17}H_{19}O_2N_3$ requires : C, 68·78; H, 6·40; N, 14·14%. The substance is therefore benzaldehyde nor d$\psi$ ephedrinoformylhydrazone , $C_6H_5CH{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}CH(CH_3){\cdot}CH(C_6H_5)OH$ .

The optical activity was determined in an alcoholic solution of concentration 1·9926 gm./100 ccs. solution, using a 10 cms. polarimeter tube and light of wave length λ5461, the mercury green line. $[\alpha]^{19^\circ}_{\lambda 5461} = + 290{\cdot}5^\circ$.

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The preparation was repeated, 9 gm. of the amine and 10 gm. of the semicarbazone being heated in toluene at 110°–120° for sixty hours. The liquid which was pale yellow in colour and contained no undissolved solid, was cooled and filtered through some decolorising carbon into a flask which had been rinsed in water, and the walls of which were still wet. Precipitation of the desired product took place very rapidly and the first crop of crystals represented about 66–70% of the theoretical yield. The mother-liquors were concentrated, then dissolved in benzene. Petroleum ether was added until the solution/

solution became turbid; it was set aside and a further crop of crystals, bringing the yield up to 80% was obtained. A third preparation in which the heating lasted 75 hours gave a yield of 83% in the first quantity of substance separated. These crystals were also practically pure.

## HYDROLYSIS OF BENZALDEHYDE NOR d $\psi$ EPHEDRINOFORMYLHYDRAZONE.

10 gm. of the benzaldehyde derivative were boiled with 150ccs. water containing 4 ccs. concentrated hydrochloric acid. The hydrolysis was not carried out under reflux but by rapid boiling in a wide-mouthed flask so that benzaldehyde could escape readily; the volume of liquid was not allowed to fall below 150 ccs. . After two hours' boiling, the liquid was decanted from some oil remaining at the bottom. This oil solidified, and on purification, was identified as unhydrolysed material. The aqueous solution became turbid on cooling due to the formation of the benzaldehyde derivative. After removal by filtration of the small quantity re-formed, the liquid was evaporated in vacuo leaving a glassy deposit. This deposit was washed with ether to remove any unchanged starting material , and then extracted with absolute alcohol. Some solid which did not dissolve in the alcohol, was identified as hydrazine hydrochloride by the formation of benzalazine ,

when it was shaken with benzaldehyde in aqueous alcohol. The absolute alcoholic extract was evaporated in a vacuum desiccator, and then mixed with ether. A sticky white mass was formed which did not dry when pressed on porous plate. Some of this substance, after standing overnight with benzaldehyde in an aqueous alcoholic solution, deposited crystals of benzaldehyde nor d$\psi$ ephedrinoformylhydrazone.

Another quantity of the benzaldehyde derivative was hydrolysed by rapid boiling with 1% hydrochloric acid, and an attempt was made to remove the benzaldehyde from the hot solution by rapid extraction with toluene. Toluene was chosen, since any cooling of the liquid to permit of ether or chloroform being used, caused the benzaldehyde to combine again with the base. The toluene extraction, however, did not prove successful as the original derivative formed again as a firm shell where the toluene came in contact with the wet wall of the extraction vessel and at the common surface of the two layers. Extraction with a high boiling fraction of petroleum ether ( 80°-90°) was also unsuccessful, recombination being again too rapid.

A further hydrolysis was carried out with 1% hydrochloric acid, and/

and the solution was boiled vigorously ( volume being maintained ) until the smell of benzaldehyde could no longer be detected. The solution was then evaporated to dryness in vacuo and the residue dissolved in alcohol. The substance obtained on evaporation of the alcohol was a creamy-white sticky solid which yielded the starting material when treated with benzaldehyde, but which could not be induced to crystallize. Water was added to it, and at first solution took place , then followed separation of white crystals M.Pt. 119°. These were recrystallized from boiling water and separated in branching tufts of needle-like prisms, M.Pt. 123°. This substance was found to be identical with that previously obtained from the steam-distillation of the nor d $\psi$ ephedrine and acetophenone-semicarbazone reaction residues, and was later identified as 4-methyl 5-phenyl 2-oxazolidone.

The aqueous solution from which the impure fraction of the oxazol derivative, M.Pt. 119°, had separated, was evaporated to dryness again in a desiccator over concentrated sulphuric acid. The residue was again dissolved in alcohol to remove a small quantity of hydrazine hydrochloride, ( it being insoluble in alcohol ) and this solution on evaporation yielded a deposit of white crystals, M.Pt. 153°. When recrystallized from alcohol-ether, this substance was obtained in the form of colourless prisms/

prisms, M.Pt. 156°, identical with those isolated from the acidified residues of the acetonesemicarbazone and nor d ψ ephedrine experiment. (P115a) This product was the required nor ψ ephedrineformylhydrazide hydrochloride , analysis of which is reported later.

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In the last hydrolysis, some of the available hydrochloride had been converted into the methyl phenyl oxazolidone which had hindered the separation of a crystalline hydrochloride besides decreasing the yield. Another hydrolysis was therefore carried out with weaker acid, and in the following manner.

12 gm. of the benzaldehyde nor d ψ ephedrinoformylhydrazone was placed in a two-litre flask with 250 ccs. water containing 5 ccs. of 33% hydrochloric acid. The liquid was heated to boiling, then a rapid current of steam was passed through for ten hours, ( volume being maintained ). At the end of this period no smell of benzaldehyde remained and no turbidity appeared on cooling the solution. The latter was evaporated under reduced pressure, leaving a colourless viscous mass. This residue dissolved completely in 120 ccs. cold alcohol, and the resulting solution was evaporated to dryness in a desiccator. Considerable frothing took place leaving a slightly yellowish hard viscous mass which, when ground, appeared/

appeared as cream coloured crystals, these, however became sticky again on exposure to the air. Mixing the crystals with petroleum ether ( B.Pt. 80°-90° ) , and subsequently removing this in an evacuated desiccator, considerably improved the dryness of the product. It was then purified by crystallization from cold absolute alcoholic solution by the addition of ether in excess. The crystals obtained, M.Pt. 156°, were soluble in water and alcohol, and insoluble in ether and petroleum ether. Combination with benzaldehyde in aqueous alcoholic solution gave a slight precipitate of benzaldehyde nor d $\psi$ ephedrinoformylhydrazone indicating that this was a hydrochloride of the corresponding base, nor $\psi$ ephedrinoformylhydrazide.

## HYDROLYSIS OF NOR $\psi$ EPHEDRINOFORMYLHYDRAZIDE HYDROCHLORIDE.

2 gm. of the salt was boiled for 5 hours with concentrated hydrochloric acid. On cooling the solution crystals separated. The solution was decanted, and the crystals washed with alcohol and identified as hydrazine dihydrochloride , by comparison with an authentic sample, and by formation of benzalazine.

The liquid and washings were evaporated to dryness, then extracted with cold absolute alcohol so that the remainder of the hydrazine hydrochloride/

hydrochloride was removed. A trace of ammonium chloride separated on concentration of this alcoholic solution. The filtrate was further evaporated to remove the alcohol, and the residue shaken with benzenesulphonyl chloride and caustic soda solution. On acidification, a white precipitate separated which, on examination, proved to be identical with a previously prepared sample of d-N benzenesulphonyl nor$\psi$ ephedrine.

A quantitative hydrolysis of nor$\psi$ ephedrinoformylhydrazide hydrochloride was carried out as follows:-

A weighed quantity of the salt ( 0·1567 gm.) was completely hydrolysed by boiling for three hours with 25ccs. concentrated hydrochloric acid. At the end of this period the contents of the flask were partially evaporated , and added to a volume of Fehling's solution. (cf. P 43b) The nitrogen evolved was collected in a nitrometer, being swept out from the reaction flask by a current of $CO_2$; it was measured over 50% caustic potash solution, and it was estimated that 2/3 of the total nitrogen in the substance was liberated by this means, indicating that the molecular proportions in the compound of hydrazine residue to amine residue were as 1 : 1 . This proves the hydrochloride to be a salt of the normal base, viz. nor$\psi$ ephedrinoformylhydrazide $C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH\cdot NH_2$ . The results of the/

the ultimate analysis were :- C, 45·4, 45·4; H, 6·5, 6·4; Cl, 17·9, 18·5; N, 15·9, 16·2%.

A formula, $3[C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH\cdot NH_2],4HCl,H_2O$ , requires:- C, 45·5; H, 6·4; Cl, 18·0; N, 15·9%.

The optical rotation was determined using a four decimetre polarimeter tube filled with an alcoholic solution of the salt of concentration 2·842 gm./100ccs., and light of wave length λ5461 ( Mercury green.). $[\alpha]^{17^\circ}_{\lambda 5461} = +37\cdot8^\circ$.

## DEHYDRATION OF NOR d ψ EPHEDRINOFORMYLHYDRAZIDE HYDROCHLORIDE.

0·4 gm. of the hydrochloride was weighed accurately into a weighing bottle supported inside a strong glass bottle with a tight-fitting rubber stopper through which a glass tube carrying a stop-cock passed. The latter was connected to an oil pump and a reduced pressure of 5-6 mms. maintained while the apparatus was heated to 100° on a water-bath. After three hours the substance was found to have lost only 2 mgs. weight.

The attempted dehydration was repeated with a piece of potassium hydroxide in the outer bottle to act as a dehydrating agent, and the temperature was raised to 140° by heating the outer vessel in a glycerol bath. The contents of the weighing /

weighing bottle melted and frothed losing hydrochloric acid and water which were held by the potassium hydroxide. After the decomposition had proceeded for about ten minutes, the apparatus was disconnected, and the contents examined. HCl was found to have been absorbed by the KOH which also appeared moist. The viscous residue in the small bottle was digested with water, and a white crystalline substance separated which, on examination, was identified as 4-methyl 5-phenyl 2-oxazolidone since it was identical with previous samples. The portion which dissolved in the water was shown to contain some undecomposed salt or base since the action of benzaldehyde produced benzaldehyde nor d ψ ephedrinoformylhydrazone.

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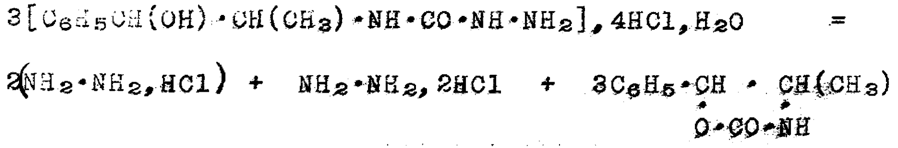
A second decomposition was carried out without the potassium hydroxide in the outer bottle. The substance was kept at 140° and 7mms. until the bubbling of the melt had abated. After three hours a crystalline deposit was observed on the upper wall of the larger bottle, and the oil in the weighing bottle started to solidify. The apparatus was disconnected and allowed to cool. The crystalline sublimate was a mixture of the methyl phenyl oxazolidone and hydrazine hydrochloride. The former remained undissolved on addition of/

of cold water, and was dried and recognised by melting point determinations. The latter in solution gave benzalazine, M.Pt. 93°, when mixed with a drop of benzaldehyde dissolved in alcohol. The residue in the bottle was extracted with benzene to remove 4-methyl 5-phenyl 2-oxazolidone which was recovered from the benzene solution by precipitation with petroleum ether; this left an impure hydrochloride which was washed with absolute alcohol to remove any traces of undecomposed nor dψ ephedrinoformylhydrazide hydrochloride. Only a very small quantity had not undergone decomposition. The remaining hydrochloride melted at 89°, was sparingly soluble in alcohol, reduced Fehling's solution rapidly even in the cold, and when shaken with benzaldehyde in aqueous alcohol formed a yellow precipitate of benzalazine. It was therefore recognised as hydrazine monohydrochloride.



$$3[C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH\cdot NH_2],4HCl,H_2O \quad = \quad 2(NH_2\cdot NH_2,HCl) + NH_2\cdot NH_2,2HCl + 3C_6H_5\cdot \underset{O\cdot CO\cdot NH}{\underbrace{CH\cdot CH}}(CH_3)$$

## TREATMENT OF THE HYDROCHLORIDE ( M.Pt. 156°) WITH PICRIC ACID.

A solution of picric acid in warm alcohol was prepared, and a quantity of nor dψephedrinoformylhydrazide hydrochloride added to it. By this means it was hoped to form a picrate of the base of simpler composition than the hydrochloride, which could be readily analysed. Bright yellow needles separated when the solution was allowed to cool. These were filtered from the yellow solution, washed with ether, and found to melt at 184°. The crystals were identified as hydrazine picrate by mixed melting point determinations with a prepared sample.

## TREATMENT OF THE HYDROCHLORIDE WITH CHLOROPLATINIC ACID.

After the failure to obtain a picrate, formation of a chloroplatinate was attempted. Some of the hydrochloride was added to a 5% solution of chloroplatinic acid, but, after standing overnight, a few crystals of the methyl phenyl oxazolidone had separated. In both this and the previous experiment, decomposition of the nor dψephedrinoformylhydrazide hydrochloride took place in accordance with the equation given on the previous page.

## EXPERIMENTS TO DETERMINE THE CONSTITUTION OF SUBSTANCE, M.Pt. 123°.

### ( 4-methyl 5-phenyl 2-oxazolidone )

When this derivative was first isolated from the steam-distilled residues of the acetophenonesemicarbazone and nor d ψ ephedrine experiment, a qualitative hydrolysis was carried out to discover if the acetophenone residue and the hydrazine residue remained in the molecule. Both were shown to be absent. Later experiments in which the derivative was obtained indicated that hydrazine was split off from the semicarbazide molecule in the formation of this substance. ( See dehydration of hydrochloride, M.Pt. 156°. Page125 ).

The comparatively low percentage of nitrogen (8% approx.) also indicated that only the nitrogen of the nor ψ ephedrine residue was retained in the new substance.

On hydrolysing 1gm. of the substance in a sealed tube with 4ccs. conc. hydrochloric acid for five hours at 135°, and examining the residue, the only substance identified was nor ψ ephedrine. This amine was readily recognised by the formation of its benzenesulphonyl derivative which is described on page 137. ( A trace of ammonium chloride also found was probably due to a decomposition of the nor ψ ephedrine molecule.)

The analysis was then carried out. Macro-nitrogen-estimations by the Dumas method tended to give high results even when complete combustion of any methane formed was facilitated by using CuO + 5%CoO as a tube filling, and in one case using $PbCrO_4$ on CuO and removing the oxygen from the gas in the nitrometer by the addition of a 10% solution of pyrogallic acid. ( Found; N, 8·15, 8·02, and 8·14%.) Micro-analysis by the Dumas-Pregl method, however gave results of 7·95% and 7·92%, and the author was also able to carry out Micro-Kjeldahl estimations on the substance, when the following values were obtained; N, 7·86, 7·78%.

The results of the carbon and hydrogen estimations were;- C, 68·1, 67·7, 68·0, 68·1; H, 6·3, 6·3, 6·2, 6·0%. The estimation of carbon by the wet combustion method using conc. sulphuric acid, and potassium and silver dichromates, ( Lieb-Krainik method) gave unsatisfactory results. The empirical formula requires: C, 67·78, H, 6·21, N, 7·90%. The molecular weight determination was made according to the Rast method, the author's results and that of an other investigator being, 201, 209, 204. $C_{10}H_{11}O_2N$ requires M.Wt., 177.

## THE ACTION OF NOR d ψ EPHEDRINE SULPHATE ON UREA.

It was thought earlier that this derivative might possibly be a disubstituted urea, and two general methods for the preparation of such carbamides were tried.

The first was that of Davis and Blanchard (J. Am. C. S. 1923, 45, 1816.). 5 gm. of nor d ψephedrine sulphate and 0·8 gm. of urea were heated together under reflux for three hours at 170°-180°. There was evolution of ammonia, but besides this and a little charring, there was no obvious reaction. ( In a later experiment some condensed liquid was noticed on the sides of the flask, and a small sublimate of the product was found in the tube of the condenser.)
The mixture was allowed to cool, and then heated on a water-bath with sufficient water to dissolve all the crystals. With the exception of a small quantity of yellowish oil, the contents of the flask dissolved completely in the hot water, but the solution became turbid at once when cooled, and the crystals grew rapidly as the liquid cleared. The crystals obtained melted at 123°, which melting point remained constant when they were recrystallized from benzene-petroleum ether. This product was again 4-methyl 5-phenyl 2-oxazolidone.
A disubstituted urea would, however, have the following composition/

composition : $[C_6H_5\cdot CH(OH)\cdot CH(CH_3)\cdot NH]_2CO$ corresponding to : C, 69·5; H, 7·3; N, 8·5%; M.Wt., 328.

The second general method of synthesis attempted was that described by Dixon ( J. 1889, 55, 622; 1893, 63, 328.) Two solutions of nor dψephedrine were prepared, one in dry ether and the other in alcohol. Carbon disulphide in slight excess over the theoretical was added to each. In both cases heat was evolved and the solutions became yellow. Alcohol was added to the ethereal solution and the ether and excess carbon disulphide distilled off. The two alcoholic solutions were boiled separately under reflux for several hours, until the presence of $H_2S$ in the condenser was no longer detected. Each solution was treated with alcoholic silver nitrate, and the precipitated silver sulphide removed. The filtrates were concentrated in an evacuated desiccator, but no solid product was obtained from either.

## FURTHER EXPERIMENTS TO DETERMINE THE STRUCTURE.

The formation of an oxalyl derivative of the nor dψephedrine was then tried as the possible structure of such a compound would be :

$$\begin{array}{l} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad\ \cdot \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO \end{array}$$

requiring an empirical formula , $C_{10}H_{12}O_2N$, a difference of one hydrogen atom from that found. Oxalic acid and nor d ψ ephedrine were heated together for two hours at 110°, but the product obtained melted at 235° and was found to be the oxalate.

The fact that no hydrazine was found in the aqueous filtrate from which crystals of the derivative had been separated in the reaction between urea and nor d ψ ephedrine, also tends to disprove the possibility of the substance being an oxalyl derivative, since , if it were, its formation might be expressed by the equations given below.

$$2[C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH_2],H_2SO_4 \quad + \quad 2NH_2\cdot CO\cdot NH_2 \quad =$$

$$2C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\cdot NH_2 \quad + \quad (NH_4)_2SO_4$$

$$\begin{array}{l} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\vdots\cdot NH_2 \\ \qquad\qquad\qquad\quad + \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO\vdots\cdot NH_2 \end{array} \quad = \quad \begin{array}{r} C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO \\ \cdot \\ C_6H_5CH(OH)\cdot CH(CH_3)\cdot NH\cdot CO \end{array} \quad +$$

$$NH_2\cdot NH_2 \,.$$

---

The empirical formula required by a formyl derivative of the amine would be, $C_{10}H_{13}O_2N$, a difference of two hydrogen atoms. The amine was heated with an aqueous solution of formic acid, and the solution was evaporated to dryness. The formate, a cream coloured solid melting at 264°–267°, was obtained.

The nor d ψ ephedrine sulphate was also heated with sodium formate according to a method for preparing formyl derivatives, ( Ber., 36, 2287.) but the substance did not sublime, and decomposition appeared to be taking place.

The derivative, M.Pt. 123°, was hydrolysed again, but with 25% sulphuric acid. The distillate was tested thoroughly for any trace of formic acid ~~or oxalic acid~~, but with no positive results.[illegible].

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Hydrolysis with alkali was then attempted as follows:- 1 gm. of the substance was boiled for 1½ hours with a 50% solution of caustic soda in a nickel crucible with a lid. Dense alkaline vapours similar to those of a solid undergoing sublimation were evolved from the crucible, and when these had ceased the liquid was cooled and diluted with much water. A clear solution was obtained, and this was just acidified to destroy carbonate. Some calcium chloride was added and the solution made alkaline with ammonia, then heated on the water-bath. A white precipitate separated which was filtered off and examined. Hydrochloric acid destroyed the substance with evolution of $CO_2$; and since further addition of ammonia to a solution which had been prepared by dissolving the precipitate in a large excess of 2N hydrochloric acid, gave no turbidity, oxalate was shown to be absent.

## THE ACTION OF PHOSPHORIC ACID ON THE SUBSTANCE, M.Pt. 123°.

### Estimation of carbon available as $CO_2$.

A weighed quantity of the substance under investigation was placed in a small tube supported inside a flask containing syrupy phosphoric acid, the apparatus being so arranged that the two substances could be brought into contact without opening the flask. Air freed from $CO_2$ by passing it over soda-lime, and dried over calcium chloride, was finally bubbled through concentrated sulphuric acid, then driven into the flask through a tube reaching almost to the surface of the phosphoric acid. Two U tubes containing pumice stone moistened with conc. $H_2SO_4$ were used to dry the gas issuing from the flask before it was passed into an absorption apparatus filled with 50% KOH. The apparatus was swept out by a current of air, the weighed absorption apparatus was connected, and the substance brought into contact with the phosphoric acid. The acid was warmed gently until all the $CO_2$ had been liberated and collected in the potash bulbs.

It was found that one tenth of the total carbon present in the compound had been liberated as $CO_2$ by the action of the phosphoric acid. C as $CO_2$, 6·7%, total carbon , 67·8%.

## THE ACTION OF POTASSIUM CYANATE ON NOR d$\psi$ EPHEDRINE SULPHATE.

From the foregoing experiments, it was deduced that the substance, M.Pt. 123°, must be an oxazol derivative, viz. 2-oxo 4-methyl 5-phenyl oxazoltetrahydride, or 4- methyl 5-phenyl 2-oxazolidone. This structure was now confirmed by the following synthesis analogous to that of 2-oxazolidone by Knorr and Rössler ( Ber. 1903, 36, 1280).

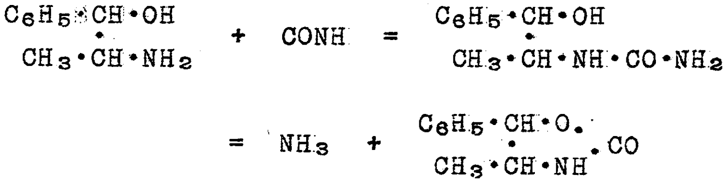
6 gm. of nor d$\psi$ ephedrine sulphate and 2·3 gm. of potassium cyanate were dissolved together in water, and the solution was heated for several hours on the water-bath. The water evaporated slowly, at a certain concentration some crystals of potassium sulphate separated, but, when the evaporation proceeded further, a viscous and slightly greenish oil remained. The flask was then heated in a phosphoric acid bath at 120°-130° until a hard glassy deposit remained on cooling. Ammonia had been evolved slightly during the heating on the water-bath, and more strongly during the evaporation at 130°. The mass was warmed with benzene and the extract examined. (Extract 1). The solvent was removed in an evacuated desiccator, and the oily residue dissolved in ether. Light petroleum was added and the liquid again evaporated. A sticky deposit containing some crystals was obtained/

obtained, but the latter decomposed forming a resinous and discoloured substance when pressed on porous plate.

Absolute alcohol was used to carry out the second extraction of the reaction residue which was still glassy in appearance. The alcohol dissolved the oily product causing separation of a white crystalline deposit of potassium sulphate. The filtered solution was then evaporated in a desiccator. (Extract 11). No crystallization took place in the oil which remained, so the latter was redissolved in alcohol, mixed with the residue from Extract 1 also dissolved in alcohol, and the whole transferred to a small distilling flask. The alcohol was distilled off, then the temperature of the heating-bath gradually raised to 200°.

The evolution of ammonia commenced slowly during the removal of the alcohol, but became very brisk between 200° and 210°, while the brown oil in the flask frothed vigorously. When the decomposition appeared complete, the liquid was cooled to 100°, and the receiver connected to the pump. At 250° some of the oil distilled but solidified in the side-tube of the flask. The remaining oil was then allowed to cool , when it solidified rapidly giving a light-brown mass. This crystalline residue was extracted with boiling water, all of the solid dissolving and leaving only a small quantity of/

of brown oil. The solution was filtered, it became milky immediately, and on further cooling deposited long white prismatic crystals, M.Pt. 123°. These were identical with the product from the decomposition of nor dψ ephedrinoformylhydrazide hydrochloride, and with that from the action of urea on nor dψ ephedrine sulphate.



$$\begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad\;\; \cdot \\ CH_3\cdot CH\cdot NH_2 \end{array} + CONH = \begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad\;\; \cdot \\ CH_3\cdot CH\cdot NH\cdot CO\cdot NH_2 \end{array}$$

$$= NH_3 + \begin{array}{l} C_6H_5\cdot CH\cdot O. \\ \quad\;\; \cdot \\ CH_3\cdot CH\cdot NH \end{array} .CO$$

i.e. 4-methyl 5-phenyl 2-oxazolidone.

## OPTICAL ROTATION OF 4-METHYL 5-PHENYL 2-OXAZOLIDONE.

A four decimetre polarimeter tube was used and filled with an alcoholic solution of concentration, 4·9764 gm./100ccs. The substance was levorotatory.

$$[\alpha]^{19^\circ}_{\lambda 5461} = -18{\cdot}0^\circ \;,\quad [\alpha]^{17^\circ}_{\lambda 5461} = -18{\cdot}5^\circ .(c = 3{\cdot}932\text{gm./100cc})$$

## PREPARATION OF d-N BENZENESULPHONYL NOR ψ EPHEDRINE.

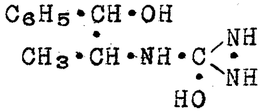
Some nor d ψ ephedrine sulphate was dissolved in a small quantity of water, and benzenesulphonyl chloride and caustic soda solution added. The mixture was shaken at intervals for two hours; no smell of unchanged benzenesulphonyl chloride remained, and the flask contained a bulky white precipitate. Water was added, and this sodium salt of the required derivative dissolved. The solution was acidified with hydrochloric acid and left to crystallize overnight. A large yield of white crystals, M.Pt. 103°, separated in tufts from the acid solution. Crystallization from benzene-petroleum ether, or alcohol-water gave the pure product as long prisms melting at 104°. ( Found : N, 4·78%; $C_6H_5\cdot CH(OH)\cdot CH(CH_3)\cdot NH\cdot SO_2\cdot C_6H_5$ i.e. $C_{15}H_{17}O_3NS$ requires: N, 4·81%.

The substance was dextrorotatory. An alcoholic solution of concentration 4·4788 gm./100 ccs. was used for the determination. $[\alpha]^{17^\circ}_{\lambda 5461} = +8\cdot 9^\circ$.

## ATTEMPTS TO COMBINE NOR d $\psi$ EPHEDRINOFORMYLHYDRAZIDE HYDROCHLORIDE WITH 1) BENZOIN 2) p-METHOXYHYDRATROPALDEHYDE. (Append. p.164)

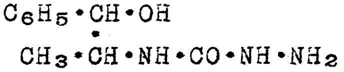
It was hoped that the optically active $\delta$-substituted semicarbazide hydrochloride synthesised from nor d $\psi$ ephedrine might combine with racemic aldehydes and ketones such as the two substances given above, and that, by this means, a resolution might be effected. This $\delta$-substituted semicarbazide hydrochloride, however, when once purified, seemed to combine very slowly even with benzaldehyde in aqueous alcohol, and in one or two cases the solution had to be seeded to promote separation of the semicarbazone in spite of the insolubility of the latter in water. This behaviour was rather exceptional, since the formation of benzaldehyde-$\delta$-substituted semicarbazones generally proceeds very readily.

In view of this, the necessity for speedy removal of benzaldehyde when this hydrochloride was being prepared by the hydrolysis of benzaldehyde nor d $\psi$ ephedrinoformylhydrazone is remarkable. It may be that an intra-molecular change takes place gradually, possibly to an equilibrium between a formula



$$\begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad \bullet \\ \quad CH_3\cdot CH\cdot NH\cdot C\langle\begin{smallmatrix} NH \\ \bullet \\ NH \end{smallmatrix} \\ \qquad\qquad\qquad HO \end{array}$$

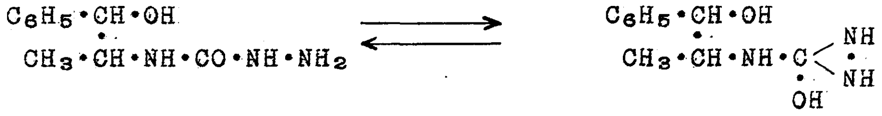
and



$$\begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad \bullet \\ \quad CH_3\cdot CH\cdot NH\cdot CO\cdot NH\cdot NH_2 \end{array}$$ .

When/

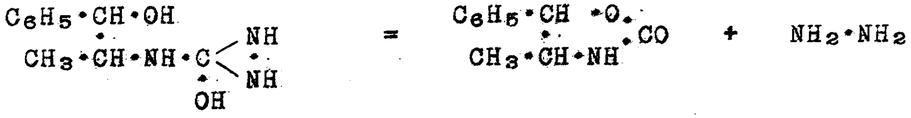
When first produced by hydrolysis of the benzaldehyde-δ-substituted semicarbazone, the substance would presumably have the structure of a δ-substituted semicarbazide hydrochloride, and would recombine rapidly with the aldehyde; if, however, an intra-molecular change occurred on keeping to produce equilibrium, as shown below, then only a portion would react with an aldehyde or ketone, since structure (2) possesses no $-NH_2$ group.



$$\begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad CH_3\cdot CH\cdot NH\cdot CO\cdot NH\cdot NH_2 \end{array} \rightleftharpoons \begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad CH_3\cdot CH\cdot NH\cdot C\left<\begin{array}{l} NH \\ NH \end{array}\right. \\ \qquad\qquad\qquad\quad OH \end{array}$$

(1) Semicarbazide structure. (2).

A compound having the second structure would probably decompose very readily with elimination of hydrazine to give the oxazol ring.



$$\begin{array}{l} C_6H_5\cdot CH\cdot OH \\ \quad CH_3\cdot CH\cdot NH\cdot C\left<\begin{array}{l} NH \\ NH \end{array}\right. \\ \qquad\qquad\qquad\quad OH \end{array} = \begin{array}{l} C_6H_5\cdot CH\cdot O\cdot \\ \quad CH_3\cdot CH\cdot NH\cdot \end{array} CO \quad + \quad NH_2\cdot NH_2$$

: : : : : : : : : :

## EXPERIMENTAL.

### NOR d $\psi$ EPHEDRINOFORMYLHYDRAZIDE HYDROCHLORIDE AND BENZOIN.

[ Method of Wilson and Hopper, J., 1928, 2483.]

A quantity (2gm.) of the hydrochloride was dissolved in 4ccs. water and added to a solution of the equivalent quantity of racemic benzoin dissolved in 18ccs. of pyridine. The mixture was shaken and allowed to stand for seven days, then it was poured into a large beaker of water, and a sticky dark yellow oil separated. The opalescent liquor was decanted after three hours, and boiling water poured on the residue. After cooling, this water was also poured off, and the contents of the beaker were dried and the last traces of pyridine removed by evaporation in vacuo in a desiccator over concentrated $H_2SO_4$. The residue was dissolved in dry ·720 ether and the solution filtered. On removal of the ether, the residue was sticky, and did not solidify when it was evaporated in a desiccator after mixing with petroleum ether. It was then dissolved in alcohol, and water was added slowly to the solution, but, again, an oil separated.

Combination was now attempted in aqueous alcoholic solution. The hydrochloride was dissolved in alcohol and mixed with the equivalent quantity of benzoin. A solution of potassium acetate/

acetate was then added, and the precipitated potassium chloride filtered off. A large quantity of water just insufficient to cause turbidity was then poured into the solution, but no precipitation occurred on standing. The liquid was evaporated in a desiccator under reduced pressure, leaving a yellowish oil. This was mixed with ether, and the slight excess of potassium acetate separated; the filtrate was evaporated, but no solid was obtained from the oily residue.

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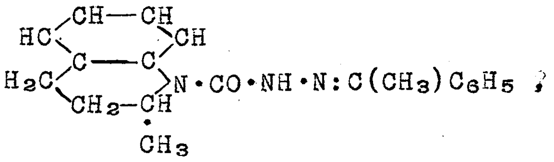
### 2). p-METHOXYHYDRATROPALDEHYDE.

A quantity of the hydrochloride (3·0gm.) and the equivalent of potassium acetate (1·5gm.) were mixed in alcoholic solution, and the precipitate of potassium chloride removed. 2·2 gm. of the aldehyde was added, and after standing some time the solution was diluted with water. As in the previous experiment with benzoin, only oils resulted.

## TETRAHYDROQUINALDINE.

## THE ACTION OF TETRAHYDROQUINALDINE ON ACETOPHENONESEMICARBAZONE.

Tetrahydroquinaldine and acetophenonesemicarbazone reacted only to a very small extent in toluene. Some ammoniacal vapour was evolved during the heating, but at no time was this strong. A trace of a derivative was obtained, but evidently in a rather impure state as several crystallizations were required, and even then no sharp melting-point resulted. An acetophenone residue was shown to be present by the formation of the ketone on hydrolysis. Had the reaction proceeded normally, a substance having the following structure would have been expected:



i.e. $C_{19}H_{21}ON_3$ .

The product was analysed, but the values obtained did not correspond to this formula. The product was apparently abnormal, and, the yield being so poor, the investigation was abandoned.

Two reactions were attempted with acetonesemicarbazone, one without solvent, the other in toluene; only decomposition products of the semicarbazone were found.

## EXPERIMENTAL.

Equimolecular quantities of acetophenonesemicarbazone and tetrahydroquinaldine were heated in toluene at 120°-120° for fifty hours. Ammonia was evolved in very small quantity, and when the reaction mixture was allowed to cool, a large proportion of the semicarbazone was recovered unchanged.

The residue obtained after evaporation of the filtrate was mixed with ether and light petroleum and placed in a desiccator. After standing for about two months, a sticky semi-crystalline mass resulted which consisted largely of acetophenoneazine. Repeated extraction with petroleum ether removed the azine leaving a cream-coloured solid which was finally washed with ether. The substance crystallized from benzene as a precipitate of fine needles almost flocculent in appearance, M.Pt. 195°-200°. After two crystallizations from 96% alcohol, the product melted at 206°-208°, but the yield was extremely small. Hydrolysis showed the presence of an acetophenone residue, the reduction of Fehling's solution by the hydrolysed residue was, however, very slow. (Found:- C,69·32, H,6·27, N,14·06%; but $C_{19}H_{21}ON_3$ (normal deriv.) required:- C,74·27, H,6·84, N,13·68%.)

A similar experiment was carried out using acetonesemicarbazone. The solution on cooling deposited hydrazodicarbonamide, but/

but this was the only solid isolated.

In another attempt to combine acetonesemicarbazone with tetrahydroquinaldine, the substances were heated without solvent at 150°. No reaction appeared to take place, so the temperature was raised to 180°-185° and maintained at that for two hours. There was a slight evolution of ammonia, the semicarbazone dissolved, and gradual separation of a crystalline substance occurred. This solid was removed, washed with ether, and recrystallized from hot water; it melted with strong decomposition at 253°, and was identified as hydrazodicarbonamide. The amine was recovered from the filtrate and ethereal washings; in this experiment it had apparently acted only as solvent during a thermal decomposition of the acetonesemicarbazone.

# DIPROPYLAMINE.

## THE ACTION OF DIPROPYLAMINE ON ACETONESEMICARBAZONE.

Dipropylamine was the next amine chosen for investigation. Being a strongly basic aliphatic amine, it was considered probable that it would react readily with semicarbazones in accordance with the general equation.

Acetonesemicarbazone was the substance employed, and a compound of the structure $(CH_3 \cdot CH_2 \cdot CH_2)_2 : N \cdot CO \cdot NH \cdot N : C(CH_3)_2$ was expected.

The product from the reaction, after the removal of the solvent, was extremely oily, and only after it had been twice mixed with petroleum ether, (B.Pt.80°-90°), and the solvent evaporated in vacuo each time, were any crystals formed. These separated as a flocculent deposit on the oil, and the yield was consequently poor. The pure crystals in the form of fine needles from benzene melted at 206°.

The substance did not dissolve on boiling with dilute acid, and this indicated that the structure was probably that of a hydrazodicarbonamide derivative, (cf. p. 81.) and not acetone-dipropylaminoformylhydrazone, since the latter would hydrolyse readily with loss of acetone. When boiled with Fehling's solution the latter was reduced showing the presence of a hydrazine linkage in the substance. Analysis confirmed the formula/

formula of the hydrazodicarbonamide derivative,

$$\begin{array}{l}(CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH \\ \phantom{(CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot N}\cdot \\ (CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH\end{array} \text{, s-di(dipropylaminoformyl)hydrazide.}$$

The following equations indicate the reactions by which this substance would be formed,

$$(CH_3\cdot CH_2\cdot CH_2)_2{:}NH \; + \; NH_2\cdot CO\cdot NH\cdot N{:}C(CH_3)_2 \; = \; NH_3$$

$$+ \; (CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH\cdot N{:}C(CH_3)_2$$

$$\begin{array}{c}(CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH\cdot N{:}C(CH_3)_2 \\ + \\ (CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH\cdot N{:}C(CH_3)_2\end{array} = \begin{array}{l}(CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH \\ \phantom{(CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot N}\cdot \\ (CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH\end{array}$$

$$+ \; (CH_3)_2C{:}N\cdot N{:}C(CH_3)_2 \; .$$

These reactions are analogous to those obtained with dibenzylamine and acetonesemicarbazone, in which the normal derivative was decomposed thermally to give acetoneketazine and s-di(dibenzylaminoformyl)hydrazide.

## EXPERIMENTAL.

### THE ACTION OF DIPROPYLAMINE ON ACETONESEMICARBAZONE.

6 gm. amine and 6·9 gm. semicarbazone were heated together in xylene at 150° for 33 hours, ammonia being evolved during the reaction. The xylene was distilled off under reduced pressure, ether was added to the residue and precipitation occurred. These crystals were identified as unchanged acetonesemicarbazone. The portion soluble in ether was kept in an evacuated desiccator for three days, but it still remained sticky. Petroleum ether (B.Pt.80°-90°) was added, and the oil again evaporated in vacuo. This procedure was repeated until a trace of solid appeared. More petroleum ether was then added, and some thread-like white crystals separated in a flocculent mass on the surface of the thick oily deposit. These were rinsed off from the lower layer by several washings with petroleum ether. No further yield could be obtained from the oil. The product was recrystallized from benzene-petroleum ether, and obtained as fine white needles, M.Pt. 206°, soluble in alcohol, ether and benzene, and insoluble in water and petroleum ether.

The substance did not dissolve on boiling with dilute acid, and therefore no acetone residue was present. It was then boiled with Fehling's solution which it reduced indicating the presence of a hydrazine linkage. (Found: C,58·79, H,10·39,

N/

(Found :- C, 58·79, H, 10·39, N, 19·51%;

$$\begin{array}{l}(CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH\\ \qquad\qquad\qquad\qquad\qquad\;\; \cdot \\ (CH_3\cdot CH_2\cdot CH_2)_2{:}N\cdot CO\cdot NH\end{array}$$

i.e. $C_{14}H_{30}O_2N_4$ requires :-

C, 58·73, H, 10·49, N, 19·58%.

# ETHYLBENZYLAMINE.

## THE ACTION OF ETHYLBENZYLAMINE ON ACETOPHENONESEMICARBAZONE.

Since this amine was a strong base containing both the benzyl residue with which the reaction under investigation seems to proceed readily, and an aliphatic residue which also tends to act normally, it was considered likely to produce $\delta$-substituted semicarbazones.

The reaction with acetophenonesemicarbazone was investigated, the reactants being heated in toluene. Ammonia was evolved, and the semicarbazone dissolved readily. A good yield of practically pure substance was isolated. When crystallized it was obtained in the form of long needle-like prisms, M.Pt. 119·5°, soluble in alcohol, acetone, chloroform, and insoluble in water, ether and petroleum ether. This substance was proved by hydrolysis to contain an acetophenone residue and a hydrazine linkage, the analysis corresponded to the formula, $C_6H_5CH_2(C_2H_5):N\cdot CO\cdot NH\cdot N:C(CH_3)C_6H_5$, that of acetophenoneethylbenzylaminoformylhydrazone, a normal derivative.

$$C_6H_5CH_2(C_2H_5):NH \quad + \quad NH_2\cdot CO\cdot NH\cdot N:C(CH_3)C_6H_5 \quad = \quad NH_3$$
$$+ \quad C_6H_5CH_2(C_2H_5):N\cdot CO\cdot NH\cdot N:C(CH_3)C_6H_5 \; .$$

(Acetophenoneethylbenzylaminoformylhydrazone.)

## EXPERIMENTAL.

### THE ACTION OF ETHYLBENZYLAMINE ON ACETOPHENONESEMICARBAZONE.

Ethylbenzylamine was prepared according to the method described by Zaunschirm (Ann., 1888, 245, 279.) except that the reduction of the benzylidene ethylamine was accomplished by means of sodium in alcohol. (Appendix p.162.)

7 gm. of the amine and 9 gm. acetophenonesemicarbazone were heated in toluene at 135°–140° for 8–9 hours. Ammonia was evolved briskly, and solution was practically complete after eight hours. The solution was cooled and allowed to stand overnight, when a quantity of white crystalline solid had separated. A portion of this was removed and recrystallized. Addition of a few drops of water to an alcoholic solution gave a precipitate, M.Pt.121°; further addition of water produced a second precipitate, M.Pt.190°, which was identified as impure acetophenonesemicarbazone. The reaction mixture was heated for another five hours at 130°, then allowed to cool overnight. 1·5 gm. of unchanged semicarbazone separated in a practically pure state. The filtrate deposited a further crop of crystals which melted at 118°. After removal of this second crop, the solution was concentrated by distillation in vacuo; petroleum ether/

ether was added in excess producing turbidity, and causing separation of a sticky solid. Ether was then added and the oil dissolved leaving white crystals, M.Pt. 119°. On the addition of more ether and light petroleum a second fraction also melting at 119° was precipitated. The total yield was dissolved in warm alcohol and allowed to crystallize, M.Pt. 119°-119·5°. A portion of this was recrystallized from acetone-ether, M.Pt. 119·5°, and a second portion from chloroform-petroleum ether, M.Pt. 119·5°. The crystals were in the form of long prisms generally arranged in rosettes, and melting without decomposition at 119·5°. The yield of pure product was approximately 80% of the theoretical calculated from the semicarbazone used.

Acetophenone was liberated when the substance was hydrolysed with dilute sulphuric acid, and the residue reduced Fehling's solution rapidly, thus proving the presence of a hydrazine residue. The estimated percentage of nitrogen was 14·37. $C_6H_5CH_2(C_2H_5){:}N{\cdot}CO{\cdot}NH{\cdot}N{:}C(CH_3)C_6H_5$ requires : N, 14·23%.

## THE ACTION OF ETHYLBENZYLAMINE ON ACETONESEMICARBAZONE.

7 gm. amine and 6 gm. acetonesemicarbazone were heated in toluene at 110°-120° for 18 hours. Ammonia was evolved fairly strongly/

strongly, but the evolution diminished after 17–18 hours. The solution was allowed to cool overnight, and 0·3 gm. of unchanged acetonesemicarbazone crystallized out. No hydrazodicarbonamide appeared to have been formed during the reaction. The toluene solution was evaporated to small bulk under reduced pressure, the residual oil being then dissolved in ether. A trace of acetonesemicarbazone separated at this stage and was removed. No solid product was obtained from this oil even after repeated evaporation.

# APPENDIX.

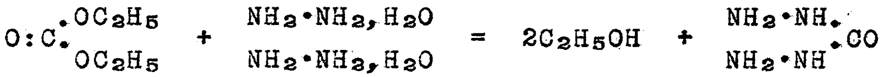
## PREPARATION OF SEMICARBAZONES.

Acetophenonesemicarbazone and benzaldehydesemicarbazone were prepared by the method of Baeyer, ( Ber.,1894,27,1918). To an aqueous solution of semicarbazide hydrochloride was added an alcoholic solution of the equivalent quantity of potassium acetate. Precipitated potassium chloride was filtered off, and then an alcoholic solution of the required quantity of ketone or aldehyde was poured in with stirring. The precipitated semicarbazone was filtered and washed with water. It was purified by crystallization from alcohol by addition of water. A trace of yellow azine was occasionally produced due to the presence of a hydrazine salt in the semicarbazide hydrochloride, this was removed by washing the product with ether.

In the preparation of acetonesemicarbazone water alone was used to dissolve the reagents, and the solution was cooled in ice to cause separation of the semicarbazone.

# PREPARATION OF CARBOHYDRAZIDE.

[ Kesting, Ber., 1924, 57, 1324. ]



$$O{:}C\begin{matrix}\cdot OC_2H_5\\ \cdot OC_2H_5\end{matrix} + \begin{matrix}NH_2\cdot NH_2,H_2O\\ NH_2\cdot NH_2,H_2O\end{matrix} = 2C_2H_5OH + \begin{matrix}NH_2\cdot NH\cdot\\ NH_2\cdot NH\cdot\end{matrix}CO$$

60 gm. diethyl carbonate and 52 gm. hydrazine hydrate ( 99% ) were heated under reflux on a water-bath for 48 hours. At the end of this period a considerable quantity of the carbohydrazide had separated out of solution. The alcohol liberated in the reaction was distilled off very slowly over a period of several hours, then the flask was heated in an oil-bath at 130°, and water and unchanged starting material distilled over. The residue was practically pure carbohydrazide. The pure product was obtained in the form of white needles, M.Pt. 152°-153°, by crystallization from aqueous alcohol.

## PREPARATION OF PIPERYL URETHANE.

[ Schotten, Ber., 1882, 15, 425. ]

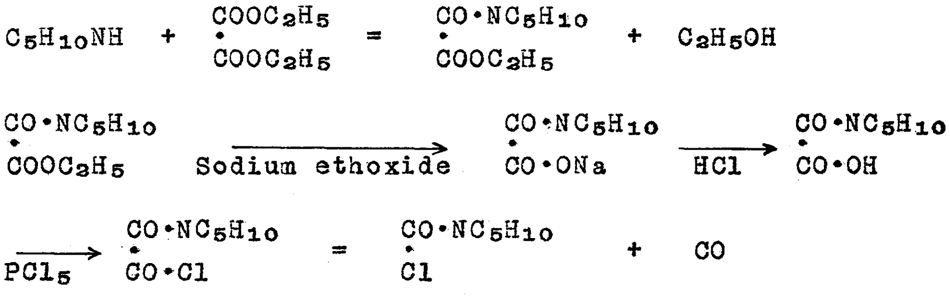
$2C_5H_{10}NH + ClCOOC_2H_5 = C_5H_{10}N \cdot CO \cdot OC_2H_5 + C_5H_{10}NH,HCl$ .

Ethlychlorformate (1 mol.) was dropped into a quantity of piperidine (2 mols.) in a long-necked flask. Heat was evolved and piperidine hydrochloride and piperyl urethane were formed. The mixture was allowed to cool, and water was added to extract the hydrochloride. The urethane which is insoluble in water, formed as an oily layer below the water and was separated, dried over potassium carbonate and distilled. It boiled without decomposition at 211° giving a colourless oil.

The yield by this method was very good.

## PREPARATION OF PIPERIDINOFORMYL CHLORIDE.

[ Wallach and Lehmann, Ann. 1887, 237, 249. ]



$$C_5H_{10}NH + \begin{array}{c}COOC_2H_5\\ \cdot\\ COOC_2H_5\end{array} = \begin{array}{c}CO\cdot NC_5H_{10}\\ \cdot\\ COOC_2H_5\end{array} + C_2H_5OH$$

$$\begin{array}{c}CO\cdot NC_5H_{10}\\ \cdot\\ COOC_2H_5\end{array} \xrightarrow[\text{Sodium ethoxide}]{} \begin{array}{c}CO\cdot NC_5H_{10}\\ \cdot\\ CO\cdot ONa\end{array} \xrightarrow[HCl]{} \begin{array}{c}CO\cdot NC_5H_{10}\\ \cdot\\ CO\cdot OH\end{array}$$

$$\xrightarrow[PCl_5]{} \begin{array}{c}CO\cdot NC_5H_{10}\\ \cdot\\ CO\cdot Cl\end{array} = \begin{array}{c}CO\cdot NC_5H_{10}\\ \cdot\\ Cl\end{array} + CO$$

Piperidine and ethyl oxalate in equimolecular quantities were boiled together under reflux for ten hours; the alcohol was distilled off on a water bath and the oil then fractionated. The ester distilled as a slightly coloured oily liquid, B.Pt. 288°–290° , the yield being almost theoretical.

The ester was diluted in a large evaporating basin with half its volume of alcohol, and a cold concentrated solution of the equivalent quantity of sodium dissolved in alcohol, added with constant stirring. The thick liquid was heated on a water-bath until all the alcohol had evaporated. The sodium salt which had formed as a cake was ground on a porous plate. It was then dissolved in approximately double its volume of water, and mixed with concentrated hydrochloric acid rather in excess of the theoretical quantity. The acid was precipitated as/

as fine needles which were practically pure, M.Pt. 128°-129°. The yield again was very good.

The oxamic acid was then dissolved in chloroform, and phosphorus pentachloride added to the solution in small quantities since the reaction is vigorous. After the equivalent quantity of the pentachloride had been added, the chloroform was distilled off on a water-bath, then the temperature was raised, and the phosphorus oxychloride removed leaving a viscous brown oil. This liquid was the oxamic chloride which required to be heated under reflux to bring about its decomposition to carbon monoxide and piperidinoformyl chloride. When the evolution of the gas had ceased the residue was fractionated and the portion boiling at 112°-114° at 13-14 mm. was collected.

The oil was colourless and had a disagreeable odour. A good deal of tarry matter was formed during the removal of the $POCl_3$ and CO, which decreased the yield considerably.

## PREPARATION OF ETHYLBENZYLAMINE.

[ Zaunschirm, Ann. 1888, 245, 279.]

$$C_6H_5CHO \quad + \quad H_2N\cdot C_2H_5 \qquad C_6H_5CH{:}N\cdot C_2H_5 \quad \underset{2H}{} \quad C_6H_5CH_2\cdot HNC_2H_5$$

Benzaldehyde was shaken with a 33% solution of ethylamine in water. ( Molecular proportions.) Some heat was evolved at the commencement of the reaction. The shaking was continued until the smell of the ethylamine could no longer be detected. The mixture was then extracted with ether, the extract dried over potassium carbonate, and fractionated.

The benzylidene ethylamine was a water-clear oily liquid with a disagreeable odour; it boiled without decomposition at 196°-197°. The yield was 80% of the theoretical.

The oil was dissolved in absolute alcohol, and the reduction attempted using 3% sodium amalgam. This method proved very unsatisfactory, the reaction being far from complete, with the result that subsequent acidification decomposed unchanged benzylidene ethylamine giving benzaldehyde. Steam-distillation was necessary to remove this benzaldehyde, and a good deal of decomposition also appeared to have taken place.

A good yield was, however, obtained when the reduction was effected by sodium and alcohol as follows :- 40 gm. of the benzylidene/

benzylidene ethylamine were dissolved in 250 ccs. absolute alcohol in a large two-necked flask. A reflux condenser was fitted in the short neck, and the sodium in small pieces was added through the long wide neck. The theoretical quantity of sodium was added, then some of the liquid was removed and tested by boiling with acid. The smell of benzaldehyde which was produced indicated that the reduction was incomplete. A 25% excess of sodium was required, and 50ccs. of alcohol had to be added to dissolve this. The resulting solution was acidified with hydrochloric acid, and the alcohol distilled off from a water-bath. The aqueous solution of the hydrochloride was made alkaline with caustic soda, then extracted with ether. The ethereal extract was dried over potassium carbonate, and fractionated. A colourless oil, B.Pt. 197°-199° was obtained.

This oil was used without further distillation in the preparation of the ethylbenzylamine derivative of acetophenone-semicarbazone.

* * *

## PREPARATION OF p-METHOXYHYDRATROPALDEHYDE.

[ Bougault, Ann. Chim. Phys. 1902 (7), 25, 483.]

$$C_6H_4(OCH_3)\cdot CH{:}CH\cdot CH_3 + HgO + I_2 = HgI_2 + C_6H_4(OCH_3)\cdot CH(CH_3)\cdot CHO$$

Anethole is oxidised by mercuric oxide and iodine to give p-methoxyhydratropaldehyde. The above reaction is quantitative. 10 gm. anethole were dissolved in 50 ccs. of pure ether saturated with water. 15 gm. of yellow mercuric oxide were suspended in the liquid and solid iodine was added in small quantities with shaking and cooling, each addition being absorbed before the next was made. The colour of the suspended solid changed gradually from the colour of the yellow oxide to the scarlet of the iodide. After 17·2 gm. of iodine had been added, the liquid was tested on wet starch paper to determine the point at which iodine was just present in excess. The mercuric iodide was then filtered off, and the ethereal solution mixed with a saturated aqueous solution containing a slight excess over the required quantity of sodium bisulphite. The ether was removed on the water-bath, leaving the bisulphite compound of the aldehyde, this was then decomposed by boiling with sodium carbonate solution, and the aldehyde steam-distilled. The latter was extracted with ether, dried , and fractionated, giving a colourless oil, B.Pt. 250°–254°.