ACTION OF AMINES

ON

SEMICARBAZONES.

A THESIS

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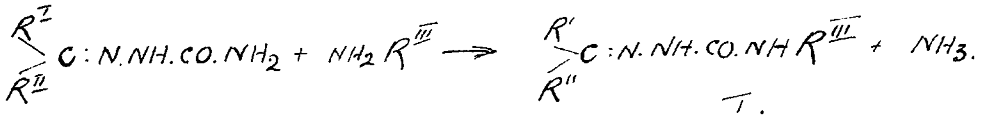
Part I of this thesis has already appeared in the Journal of the Chemical Society (Wilson, Hopper and Crawford, J.C.S. 121, 867), while Parts II and III have been accepted for publication in a forthcoming number of the Journal.

GENERAL INTRODUCTION.

GENERAL INTRODUCTION.

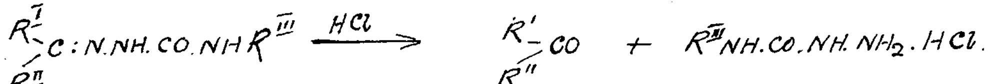
In a series of papers (Ber., (I90I), 34, 4299 ; 37, (I904), 3I77 ; 38, (I905) ; 83I,) Borsche and his co-workers have shown that purely aromatic ȧnimo-compounds react with semicarbazones mainly in the following way :



$$\genfrac{}{}{0pt}{}{R^{I}}{R^{II}}{>}C:N.NH.CO.NH_2 + NH_2R^{III} \longrightarrow \genfrac{}{}{0pt}{}{R'}{R''}{>}C:N.NH.CO.NHR^{III} + NH_3.$$

I.

forming a semicarbazone (I) with a substituent in the δ-position. This product, on acid hydrolysis, yields the salt of the δ-substituted semicarbazide (2).



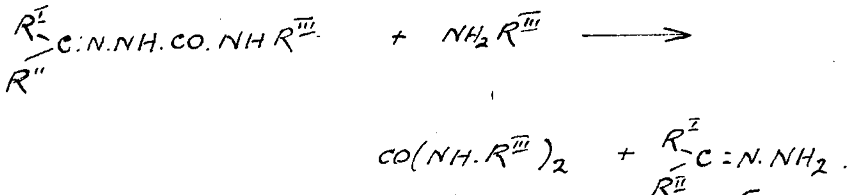
$$\genfrac{}{}{0pt}{}{R^{I}}{R^{II}}{>}C:N.NH.CO.NHR^{III} \xrightarrow{HCl} \genfrac{}{}{0pt}{}{R'}{R''}{>}CO + R^{III}NH.CO.NH.NH_2.HCl.$$

2.

From this, the free semicarbazide (3) can be easily obtained by means of dilute alkalis.

$$R^{III}NH.CO.NH.NH_2 \qquad 3.$$

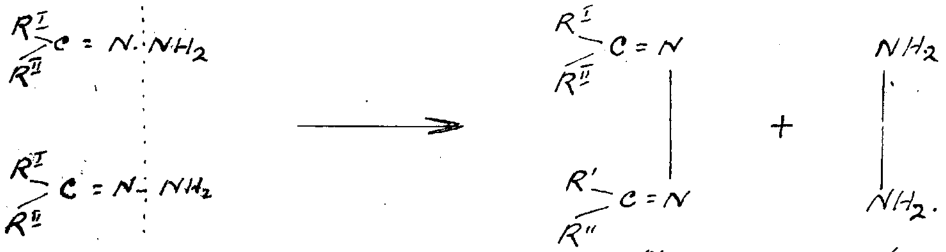
At the same time, various subsidiary reactions may occur, e.g. the δ-substituted semicarbazone formed may react with another molecule of the amine to give a carbamide derivative, (4) and a hydrazone. (5). Excess of amine, and prolonged high temperature favour this reaction.



$$\begin{matrix}R^{I}\\R''\end{matrix}\!>C:N.NH.CO.NHR^{III} + NH_2R^{III} \longrightarrow CO(NH.R^{III})_2 + \begin{matrix}R^{I}\\R^{II}\end{matrix}\!>C:N.NH_2.$$

4. 5.

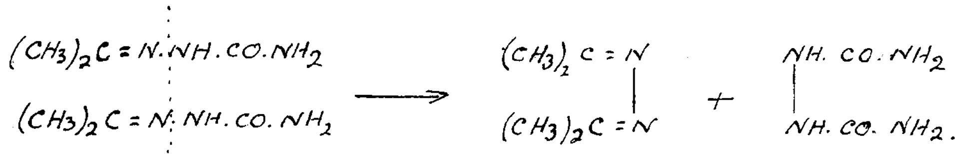
From the hydrazone, a further decomposition may give hydrazine (6) and a ketazine (7).



$$\begin{matrix}R^{I}\\R^{II}\end{matrix}\!>C=N.NH_2 + \begin{matrix}R^{I}\\R^{II}\end{matrix}\!>C=N.NH_2 \longrightarrow \begin{matrix}R^{I}\\R^{II}\end{matrix}\!>C=N-N=C\!<\begin{matrix}R'\\R''\end{matrix} + NH_2-NH_2.$$

7. 6.

The instability towards heat, of the semicarbazone used, may introduce further complications : <u>Acetonesemicarbazone,</u> when heated above its melting point, decomposes into dimethylketazine, (8) and hydrazodicarbonamide. (9).



$$\begin{matrix}(CH_3)_2C=N.NH.CO.NH_2\\(CH_3)_2C=N.NH.CO.NH_2\end{matrix} \longrightarrow \begin{matrix}(CH_3)_2C=N\\|\\(CH_3)_2C=N\end{matrix} + \begin{matrix}NH.CO.NH_2\\|\\NH.CO.NH_2.\end{matrix}$$

8. 9.

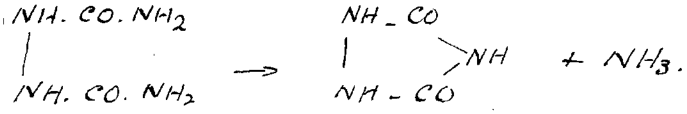
In the course of these investigations, ammonia has also been obtained as a decomposition product of acetonesemi-

-carbazone, perhaps due to decomposition of hydrazine.

$$3\begin{matrix}NH_2\\|\\NH_2\end{matrix} \longrightarrow 4\,NH_3 + N_2$$

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

or perhaps due to the formation of hydrazodicarbonimide (IO).



Benzophenonesemicarbazone, on heating also decomposes into hydrazodicarbonamide, and the corresponding azine, diphenylketazine.

$$(C_6H_5)_2C = N - N = C(C_6H_5)_2 .$$

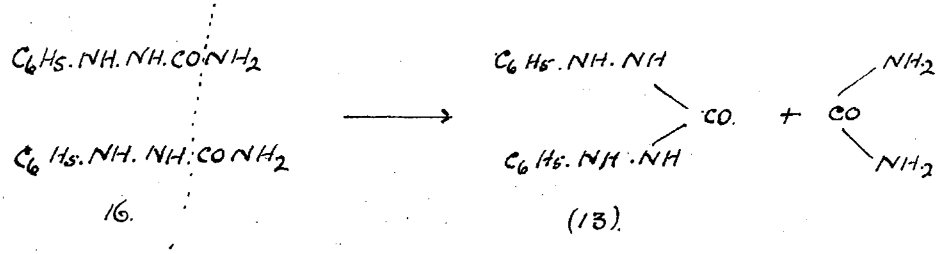
At the same time it yields another product, benzophenone-carbohydrazone, (II) to explain which Borsche (loc.cit.) assumed the formation of an intermediate hydrazone, (I2) which reacts with one molecule of the semicarbazone thus:

$$\underset{(12).}{(C_6H_5)C = N.NH_2} + NH_2.CO.NH.N = C(C_6H_5)_2 \longrightarrow$$

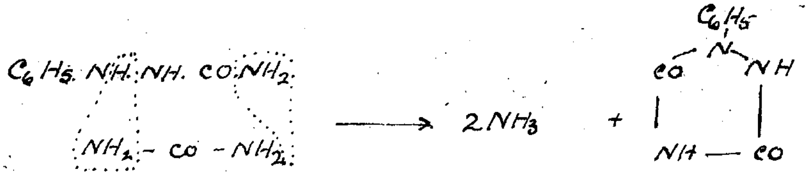
$$NH_3 + \underset{(11.)}{CO[NH.N = C(C_6H_5)_2]_2}$$

Further, Poth and Bailey (J.Am.Chem.Soc., 45, 3008) have shown that α-phenylsemicarbazide (I6) on heating, yields a variety of products ; diphenylcarbazide (I3), phenylurazole, (I4) and diphenylurazine (I5).

A.

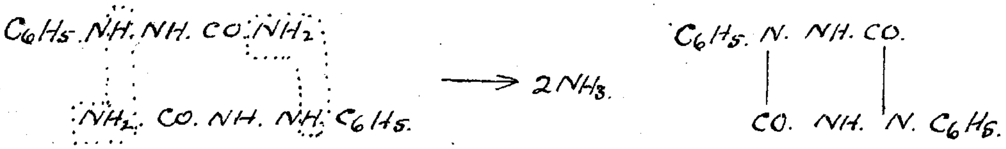


B.



14.

C.



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The reaction typified in equation A. is the only one possible in these investigations, where the ketone (acetone or benzophenone) is attached at the α -position, and the δ -position is either free, or accupied by a substituent.

$$(CH_3)_2C = \underset{\alpha}{N}\cdot\underset{\beta}{NH}\text{-}\underset{\gamma}{CO}.\underset{\delta}{NH_2}$$

This prevents the possibility of ring-formation by splitting off two molecules of ammonia as in equations B and C. Besides these, the reaction yielded ammonium carbamate, ammonia, nitrogen and carbon dioxide (no carbon monoxide) showing that drastic decomposition may occur.

Borsche, in his work, used such amines as aniline, the toluidines and the naphthylamines. The investigations recorded herein are an attempt to generalise this reaction of Borsche.

PART I.

THE ACTION OF BENZYLAMINE ON ACETONESEMICARBAZONE.

P A R T I.

THE ACTION OF BENZYLAMINE ON ACETONESEMICARBAZONE.

In view of the fact that Borsche used purely aromatic amino-bodies, it became interesting to find if the amino-group in a side chain, proved as reactive as a nuclear amino-group, thus extending the investigations to bodies of a more aliphatic nature. To this end, the action of benzylamine (Wilson and Crawford J.C.S., 121, 867.) and of α-phenylethylamine, (Wilson and Hopper. ibid.) on acetonesemicarbazone has been studied. Benzylamine reacted with ease, the condensation being complete in 5-10 minutes.

In his work, Borsche used a large excess of the amino-compounds for solvent purposes : here such excess was avoided, primarily from consideration of cost. Nor was the use of a solvent found necessary, the reaction temperature being below the boiling point of the amine, and the reaction products being soluble in the hot benzylamine.

By heating together acetonesemicarbazone (1 mol.), and benzylamine, (slightly more than 1 mol.)

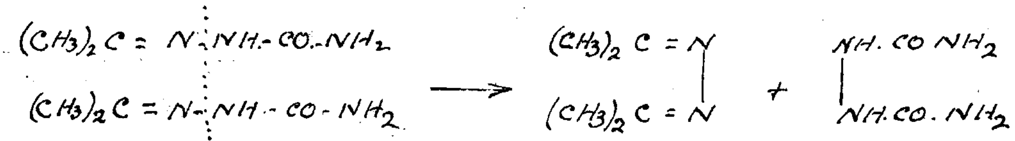
at 180°, there resulted a rapid evolution of ammonia, while the semicarbazone dissolved in the amine. The stream of gas bubbles never completely ceased, so the completion of solution was taken as the end of the reaction. The excess of the amine was removed from the melt by a slight excess of acetic acid, and from the residue were obtained, s-dibenzylcarbamide (12) needles from alcohol M.P. 167°) and acetone-δ-benzylsemicarbazone (11) (long prisms from alcohol M.P. 113°). The reaction also yielded dimethyl-ketazin (13) (liquid, characteristic smell, B.P. 131°) and hydrazodicarbonamide (14) (microcrystalline, almost insoluble in alcohol, M.P. 254°).

$$(CH_3)_2C=N.NH.CO.NH_2 + NH_2\cdot CH_2\cdot C_6H_5. \longrightarrow$$

$$NH_3 + (CH_3)_2C=N.NH.CO.NH.CH_2.C_6H_5 \qquad 11.$$

$$(CH_3)_2C=N.NH.CO.NH.CH_2.C_6H_5 + NH_2.CH_2.C_6H_5 \longrightarrow$$

$$\underset{12.}{CO(NH.CH_2.C_6H_5)_2} + (CH_3)_2C=N.NH_2$$



$$\begin{array}{l}(CH_3)_2C=N\vdots NH-CO-NH_2\\(CH_3)_2C=N-\vdots NH-CO-NH_2\end{array} \longrightarrow \begin{array}{l}(CH_3)_2C=N\\ \qquad\quad\;\, |\\(CH_3)_2C=N\end{array} + \begin{array}{l}NH.CO\,NH_2\\ |\\NH.CO.NH_2\end{array}$$

13. 14.

On hydrolysis with dilute hydrochloric acid, (11) gave the hydrochloride of δ-benzylsemicarbazide, (felted needles from alcohol, M.P. 225°), acetone being split off.

To avoid decomposition, the free δ-semicarbazide (small needles from toluene, M.P. 111°) (15) was obtained from the hydrochloride by means of sodium ethoxide, though Mr. Hopper (private communication) found that it could be obtained in the usual way by caustic soda.

$NH_2.NH.CO.NH.CH_2.C_6H_5.$ 15.

The hydrochloride reacted with benzaldehyde in the cold to give <u>benzylidene-δ-benzylsemicarbazone</u> (16) (lustrous prisms from alcohol, M.P. 139°). The strongly marked crystallising power of this compound suggested that the δ-substituted semicarbazide might be useful to characterise formaldehyde and acetaldehyde, but the somewhat oily condensation products obtained would not crystallise. On adding a few drops of sulphuric acid to an alcoholic solution of δ-benzylsemicarbazide, a white precipitate was obtained which melted at 239° with immediate decomposition. This is presumably the sulphate, but the quantity available was too small for accurate analysis.

$C_6H_5CH{:}N.NH.CO.NH\,CH_2\,C_6H_5$ 16.

EXPERIMENTAL.

PREPARATION OF ACETONE-δ-BENZYLSEMICARBAZONE.

$(CH_3)_2C=N.NH.CO.NH.CH_2.C_6H_5.$

Acetonesemicarbazone, (I mol.) and benzylamine, (rather more than I mol.) were heated separately in a glycerol bath to I80° C. The amine was then poured over the semicarbazone, whereupon a vigorous reaction ensued, ammonia being evolved and the solid quickly dissolving. When solution was complete the melt was cooled slightly, poured into cold water, and the viscous mass treated with dilute acetic acid in order to remove any unchanged amine. The product, which quickly solidified, was washed with water. On extraction with hot alcohol it all dissolved, with the exception of a little hydrazodicarbonamide (M.P. 254°). The alcoholic solution, on concentrating and cooling in ice, gave a small quantity of colourless needles. These, after recrystallisation and washing with carbon tetrachloride, melted at I69°, and were identified as s-dibenzylcarbamide (M.P. I67°).

Found N. = II·89%

$[(C_6H_5).CH_2.NH]_2CO.$ requires N = II·67%.

On concentrating the alcoholic extract, long colourless prisms were obtained which, after further recrystallisation from alcohol, melted at 113°.

The substance is acetone-δ-benzylsemi--carbazone.

	Found	N. = 20·35%
$(CH_3)_2C:N.NH.CO.NH.CH_2.C_6H_5$.	requires	N. = 20·48%.

This substance was moderately soluble in water, soluble in alcohol, and extremely soluble in benzene. It dissolved in concentrated sulphuric acid to give a colourless solution.

PREPARATION OF δ-BENZYLSEMICARBAZIDE.

$NH_2.NH.CO.NH.CH_2.C_6H_5$

Hydrolysis of Acetone-δ-benzylsemicarbazone.

The semicarbazone was heated at 50°, with twelve times its weight of N-hydrochl~~ine~~oric acid, until solution was effected. The solution was then extracted with ether, and the aqueous portion evaporated to dryness in a vacuum on the water bath. The white, flaky residue of the hydrochloride was dissolved in alcohol, whence it crystallised in a thick felted mass of white needles, soluble in water and in alcohol, soluble in ether and melting at 224°-225°.

Found Cl = 17·46%.

$(C_6H_5)CH_2.NH.CO.NH.NH_2.HCl.$ requires Cl=17·62%.

Crude acetone-δ-benzylsemicarbazone containing s-dibenzylcarbamide, may be used for the hydrolysis, since s-dibenzylcarbamide is sparingly soluble in hydrochloric acid, it may be conveniently separated by filtering the hydrolysis liquor on cooling.

Liberation of the Free Base, δ-Benzylsemicarbazide.

To a solution in absolute alcohol of the hydrochloride, an alcoholic solution of sodium ethoxide was added until the solution was alkaline to phenolphthalein. The precipitated sodium chloride was filtered off, and the filtrate evaporated to dryness at room temperature, by a current of dry air, free from carbon dioxide. The somewhat yellow residue was extracted with hot toluene and the filtrate, on cooling in ice, gave δ-benzylsemicarbazide as a white powder consisting of small needle-shaped crystals. These, on washing with petroleum spirit, and drying in a vacuum, melted at III°. The substance is moderately soluble in water, ether and chloroform, very soluble in alcohol, soluble in hot benzene and toluene, and insoluble in petroleum spirit. The aqueous solution is neutral to litmus.

Found N. =25·68% ; 25·64%.

$NH_2NH.CO.NH.CH_2.C_6H_5$. requires N =25·45%.

Benzylid~~i~~ene-δ-benzylsemicarbazone.

This substance was obtained on shaking an aqueous solution of the hydrochloride with a few drops of~~f~~ benzaldehyde and recrystallising the precipitate from alcohol. It crystallised in beautiful large lustrous prisms melting at I39°.

Found N = I6·77% ; I6·74%.

$(C_6H_5)CH:N.NH.CO.NH.CH_2C_6H_5$. requires N =I6·60%.

Formaldehyde and Acetaldehyde Derivatives of δ-Benzyl--semicarbazide.

Attempts were made to obtain these by

shaking up aqueous solutions of the aldehydes with an aqueous solution of the hydrochloride of δ-Benzylsemicarbazide. Oily products separated, which on much shaking solidified. Attempts to recrystallise these from alcohol yielded only syrupy products.

PART II.

ACTION OF *l*-MENTHYLAMINE ON ACETONESEMICARBAZONE.

PART II.

The Action of *l*-Menthylamine on Acetonesemicarbazone.

The ease with which benzylamine reacted with acetonesemicarbazone, would suggest that the acidic nature of the phenyl group has some effect on the activity of the positive amino-group.

With benzylamine, where the amino-group is in a side chain, the reaction would appear to go much more readily than in the case of aniline, where the amino-group is nuclear. Indeed, Mr. Hopper of this department, states (private communication) that benzylamine will commence reacting at 129° C., a temperature much lower than that required for aniline.

In the case of *l*-menthylamine, the ease of reaction is comparable to that of benzylamine. Here we have the amino-group attached to what is virtually a reduced benzene nucleus, giving a more basic molecule. Indeed, *l*-menthylamine will fume with air containing carbon dioxide or acid vapours ; to a lesser extent benzylamine does the same ; with aniline the effect is absent.

In both cases, the increased basic nature of the molecule has resulted in greater reactivity towards semicarbazones.

The first sample of *l*-menthylamine was obtained from Schuchardt, but when polarimetically examined was found to have an extremely low rotatinn.

$$[\alpha]_D^{19} = -23{\cdot}6^\circ$$

whereas for this compound, Wallach Ann., 276, 327, (I893) gives

$$[\alpha]_D^{19} = -38{\cdot}07^\circ \;;$$

Kenyon and Pickard (J.C.S., I07 36, 50, 55,) give

$$[\alpha]_D^{20} = -39{\cdot}97^\circ .$$

Pope and Read (J.C.S., (I9I0), 97, 997,) record a similar example of an optically impure menthylamine obtained from this firm.

The amine was converted to the hydrochloride, when the rotation of the salt in aqueous solution had the value,

$$[\alpha]_D^{19} = -I9{\cdot}2^\circ,$$

against the value $[\alpha]_D^{19} = -35{\cdot}66^\circ$ (Wallach loc.cit.)

Qualitative tests showed the absence of any "foreign" chemical body, e.g. menthoneoxime, menthol, hence it was certain that the low rotation was due to the presence of optically active *l*-menthylamines (Tutin and Kipping J.C.S., 85, (I904), 69.) the result of careless oxidation of *l*-menthol.

Four isomers are apparently possible, being formed by varying experimental conditions.

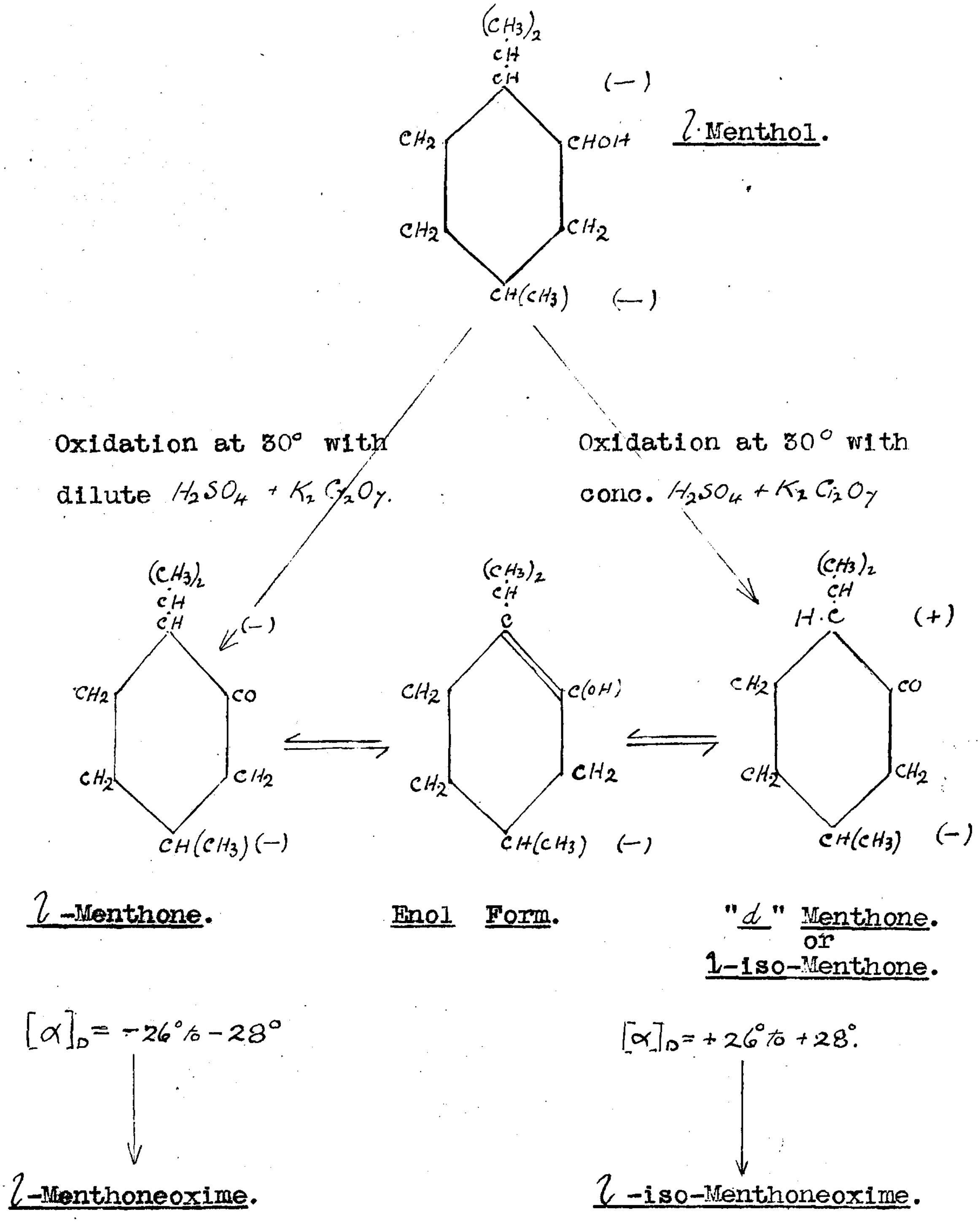
The starting product is *l*-menthol, which is oxidised by potassium dichromate and sulphuric acid to *l* -menthone. The active amine is then obtained by a sodium and alcohol reduction of menthoneoxime (see appendix p.84-87)

The use of strong acid or high temperatures during the oxidation, results in the formation of two isomeric *l*-menthones (Beckmann, Ann., (I889), 250, 322.). This change would tend to go further by the action of alkali during the preparation of the oxime.

The introduction of the amino-group by the oxime reduction, produces another asymmetric carbon atom, and consequently four *l* -menthylamines may result from the two *l* -menthones.

Although the rotation of these two menthones are of the same value, but opposite in sign, they are not enantiomorphously related, since their oximes are both laevo-rotatory. These authors (Tutin and Kipping) do not consider the change of rotation to be due to optical inversion, but rather to partial racemisation. They point out that the methyl groups undergo no change, otherwise inactive isomers should result : none were found.

The subjoined scheme outlines the course of the reaction suggested by these authors, the sign of rotation of each asymmetric carbon atom being indicated by (+) or (−).



l·Menthol.

Oxidation at 30° with dilute $H_2SO_4 + K_2Cr_2O_7$.

Oxidation at 30° with conc. $H_2SO_4 + K_2Cr_2O_7$

l-Menthone.

Enol Form.

"*d*" Menthone. or l-iso-Menthone.

$[\alpha]_D = -26°$ to $-28°$

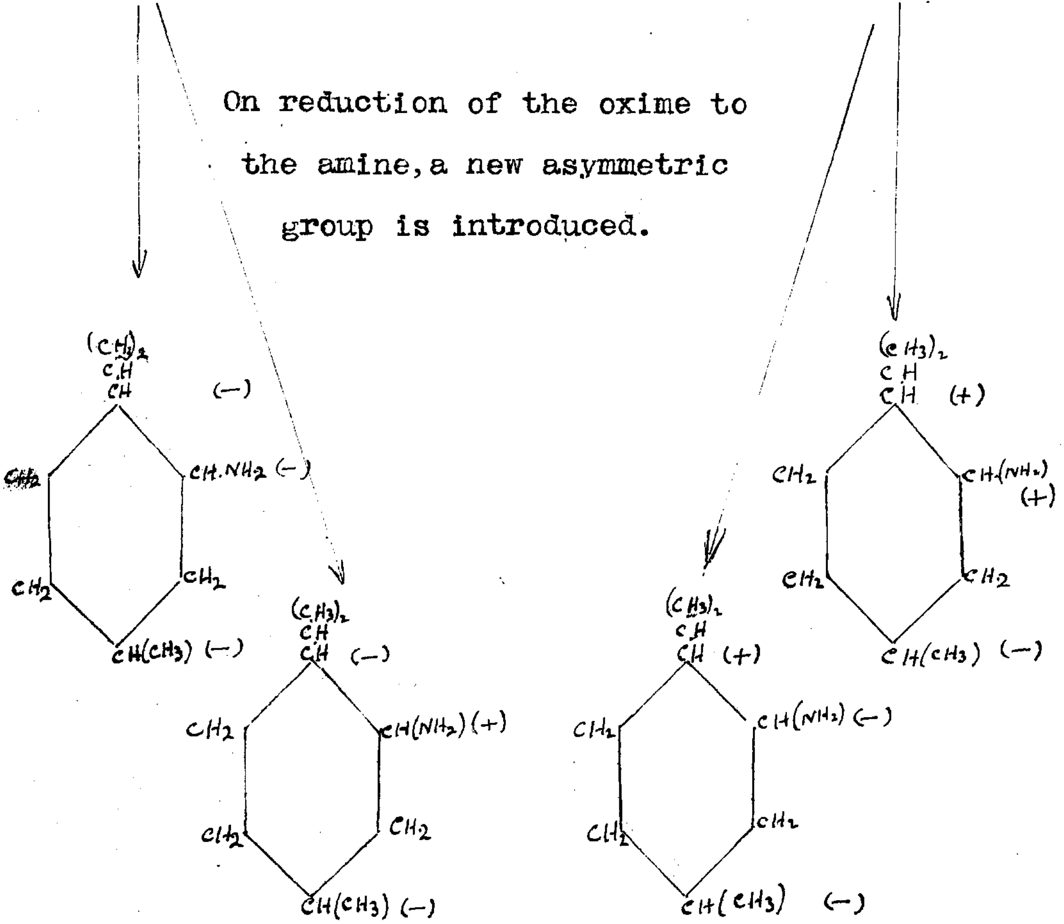
$[\alpha]_D = +26°$ to $+28°$.

l-Menthoneoxime.

l-iso-Menthoneoxime.

l-Menthoneoxime.

l-iso-menthoneoxime.



On reduction of the oxime to the amine, a new asymmetric group is introduced.

l-Menthylamine.

$[M]_D = -68{\cdot}8^{\circ}$

in chloroform.

l-isoneo-Menthylamine

$[M]_D =$ ——

l-neo-Menthylamine

$[M]_D = -6^{\circ}$.

in water.

l-iso-Menthylamine.

$[M]_D = +33^{\circ}$

in water.

Purification of *l*-Menthylamine Hydrochloride.

The hydrochloride was systematically fractionated from water, for according to Tutin and Kipping (loc. cit.), it is possible in this way to effect a separation of *l*-menthylamine hydrochloride from the other isomers. Estimations of the rotation of the various fractions, showed that progressive purification was being obtained. Towards the end it became evident that the increase in rotatory power per crystallisation was diminishing, and owing to scarcity of material the purification was stopped when the fraction gave $[\alpha]_D^{20} = -26\cdot 16°$. From this the free base was liberated in the usual way with caustic soda, and after drying and distilling in hydrogen, it gave $[\alpha]_D^{20} = -31\cdot 1°$.

Preliminary Reaction of *l*-Menthylamine and Acetonesemi-carbazone.

The partially pure amine was utilised in a preliminary investigation of the reaction. The two reactants, in equimolecular quantities, were heated separately to 165° and then mixed, when a vigorous evolution of ammonia occurred, and complete solution was obtained in 15 minutes. The product was worked in the usual way from acetic acid and yielded active acetone-δ-menthylsemicarbazone (needle clusters from alcohol, M.P. 128°). The absence of hydrazodicarbonamide was noticeable. There was no di-*l*-menthylcarbamide $CO(NHC_{10}H_{19})_2$ isolated. (long needles from alcohol, M.P. 258°. $[\alpha]_D = -91\cdot75°$) (Neville and Pickard J.C.S., (1904), <u>85</u>, 690.)

The acetone-δ-*l*-menthylsemicarbazone (1) derived from the partially pure amine gave, in alcohol solution, a value, $[\alpha]_D^{20} = -62\cdot13°$

On hydrolysis with N-hydrochloric acid at 70° the hydrochloride (2) was obtained as a gelatinous mass, which on drying assumed a somewhat fibrous appearance. It could not be obtained crystalline. (M.P. 203°-204°)

See p. 28 Solvent ? c ?

$$[\alpha]_D^{18} = -62\cdot66°.$$

$$(CH_3)_2C=N.NH.CO.NH_2 + NH_2C_{10}H_{19} \longrightarrow NH_3 + (CH_3)_2C=N.NH.CO.NH.C_{10}H_{19}. \quad 1.$$

$$(CH_3)_2C=N.NH.CO.NH.C_{10}H_{19}. \xrightarrow{HCl} (CH_3)_2CO + C_{10}H_{19}NH.CO.NH.NH_2.HCl. \quad 2.$$

Recovery of *l*-Menthylamine from Acetone-δ-*l*-Menthylsemicarbazide.

To find if any change had occurred in the rotatory power of the menthyl radicle, due either to the effect of heat, or to a selective action, utilising the l-amine to the exclusion of the isomers, the δ-substituted semicarbazone was first hydrolysed by dilute acid, and the semicarbaz~~one~~ide chain ruptured by means of Fehling's solution. The menthylamine was steam distilled from the reaction mixture, being recovered and polarimetrically examined as the hydrochloride. This method effected a rapid hydrolysis in marked contrast to the slower hydrochloric acid method, besides eliminating hydrazine immediately.

The hydrochloride thus obtained, after recrystallisation from moist, boiling, petroleum ether gave,

$[\alpha]_D^{20} = -32\cdot19^\circ$.

The increase of $[\alpha]_D$ from $-26\cdot16^\circ$ to $-32\cdot2^\circ$ for the active hydrochloride is probably due only to further purification during the recrystallisation of the various products.

Reaction Using Pure l-Menthylamine.

The active menthylamine was obtained sufficiently pure in the laboratory by careful oxidation of l-menthol to menthone, followed by subsequent reduction of l-menthoneoxime to l-menthylamine by sodium and absolute alcohol.

Beckmann Ann., 250., p.325., 1889.
Wallach loc.cit., p.296.
See also appendix p. 84.

The methylamine obtained was converted to the hydrochloride and twice recrystallised from water when it was unchanged at 280°, and gave $[\alpha]_D^{19} = -37\cdot25°$.

The amine was liberated in the usual manner by caustic soda, extracted with ether and dried over anhydrous ~~fused~~ sodium sulphate, and distilled in hydrogen. Examined polarimetrically, it gave :

$[\alpha]_D^{20} = -39\cdot41°$ [Wallach, $-38\cdot07°$. Tutin and Kipping, $-39\cdot92°$.]

The method worked exceedingly well and gave generally menthylamine hydrochloride of such purity that a recrystallisation only was necessary to give the rotation recorded in the literature (loc.cit.)

The rotation of each of the intermediate products was checked, but a satisfactory oxidation could always be judged by the formation of solid, crystalline menthoneoxime, for *l-iso* -menthoneoxime is a liquid, whereas the pure *l*- menthoneoxime melts at 59°.

The temperature of the oxidation should on no account rise above 55°C, while the menthone formed should be subjected as little as possible to heat, even to boiling water. Once the oxime is obtained there remains only the necessity of using absolute alcohol for the sodium-alcohol reduction.

On repeating the condensation with the pure active menthylamine, the acetone-δ-*l*-menthylsemicarbazone obtained had the rotation $[\alpha]_D^{20} = -64\cdot93°$ in absolute alcohol. M.P. 128°.

The hydrochloride obtained by hydrolysis with N-hydrochloric acid at 70° had the same characteristic gelatinous appearance (M.P. 203°-204°) and gave, in alcoholic solution :

$$[\alpha]_D^{20} = -65\cdot18°.$$

Liberation of δ-*l*-menthylsemicarbazide.

The free base was obtained by dissolving the hydrochloride in hot dilute alcohol, adding slight excess of caustic soda and cooling immediately. The δ-substituted semicarb~~en~~azide so obtained (small prisms from benzene-petroleum ether (M.P. 138°) gave, $[\alpha]_D^{20} = -77\cdot94°$ in absolute alcohol. $C_{10}H_{19}NH.CO.NH.NH_2$

Benzylidene δ-*l*-menthylsemicarbazone was obtained by shaking up the hydrochloride in alcoholic solution with benzaldehyde and diluting slightly (Rhombic prisms from alcohol M.P.III°). It gave $[\alpha]_D^{20} = -47{\cdot}18°$.

The solid semicarbazide is quite stable, but solutions in any solvent turn green on standing for more than a day, hence solutions should be freshly prepared. Long standing in presence of caustic soda e.g. in the liberation of the free base, should be avoided, for the solid assumes a pinkish tinge.

The Influence of Dilution on the Specific Rotation of *l*-Menthylamine Hydrochloride in Aqueous Solution.

During the work with *l*-menthylamine hydrochloride it became evident, in instances where only a small quantity of the salt was available, that very dilute solutions gave a smaller value for the specific rotation than could be accounted for by the limits of accuracy of the polarimeter used.

Hence, varying quantities of pure *l*-menthylamine hydrochloride were dissolved in 25 ccs. of distilled water, and values obtained for the specific rotation at the various concentrations.

The rotation of each solution was re-determined at intervals during the succeeding fortnight, but the small variations noted could ~~not~~ be accounted for as experimental error.

The temperature throughout was I5°C. It was found that concentrations from 5 grams per I00ccs. to I2 grams per I00ccs. of water gave practically constant values for the specific rotation, above a concentration of I2 the value tended to increase slightly. Solutions more dilute than 5 grams per I00ccs. gave rapidly diminishing values. of $[\alpha]_D$.

Hence, a solution of 5 grams per I00ccs. of water is quite suitable for determination of purity ; but a concentration of less than 5 should not be used ; nor is there any gain (other than a larger reading for α_D) from more concentrated solutions.

Impure samples of l-menthylamine show the same limiting concentration of 5 grams in I00ccs. water.

EXPERIMENTAL.

Purification of the Impure *l*-Menthylamine.

As noted in the introduction to this section (see page 17) the amine first obtained gave $[\alpha]_D^{19} = -23{\cdot}6^\circ$.

It was converted to the hydrochloride by neutralising an etherial solution by means of etherial hydrochloric acid. The reaction is quite violent in ether, hence the solutions should be dilute, and the addition of the acid made cautiously at first.

The salt is insoluble in ether, but if excess of acid be added it dissolves to a clear solution, from which it may be precipitated by drawing off the acid in a vacuum. On one occasion, the addition of a slight excess of etherial hydrochloric acid resulted in the formation of a heavier layer. This, on separating, was found to contain no water, but to consist of *l*-menthylamine hydrochloride, ether, and hydrochloric acid ; on standing in ice the hydrochloride separated out.

The hydrochloride obtained in this way from the impure amine, suffered no change on heating up to 280°, and when polarimetrically examined gave $\alpha_D =$ − ~~whence~~ 0·77°

for 0·9996 gram. in 25 ccs. water, whence $[\alpha]_D^{19} = -19\cdot2°$.

The method adopted in the fractionation was the usual one, whereby the least soluble fractions accumulate on the one hand, and the most soluble on the other.

It was observed that in any crystallisation, the purer fraction crystallised first in large coarse needles, (often one inch long), while the impurer mixtures separated later in a felted mass of small needles ; hence the aim was to obtain only the large coarse needles in any crystallisation.

The crystallisation was stopped when the purer fractions gave, for 2 grams in 25 ccs. water, $\alpha_D = -4\cdot19°$ ($l = 2$) whence $[\alpha]_D^{20} = -26\cdot16°$.

The amine was liberated from the hydrochloride by dissolving the salt in water and adding sufficient caustic soda solution. The base was ether-extracted and dried over ~~fused~~ anhydrous sodium sulphate. After distillation in an atmosphere of hydrogen it gave a rotation $[\alpha]_D^{20} = -31\cdot1°$.

Reaction with the Impure l-Menthylamine.

The amine reacted in the normal fashion to give, with evolution of ammonia, acetone-δ-l-menthylsemicarbazone.

(Details of the method are given later : see p. 31.)

This active semicarbazone gave, with ·5029 gms. in 25 ccs. absolute alcohol, a value $\alpha_D = -2·5°$ $(l=2)$ whence $[\alpha]_D^{18} = -62·13°$. (M.P. 128°)

The δ-l-menthylsemicarbazide hydrochloride obtained on hydrolysis gave $\alpha_D = -2·49°$ for ·4966gm. in 25 ccs. absolute alcohol, $(l=2)$ whence $[\alpha]_D^{19} = -62·66°$.

Recovery of l-Menthylamine Hydrochloride from Acetone-δ-l-Menthylsemicarbazone.

2·5 grams of the δ-substituted semicarbazone were hydrolysed in the heat with 2N-hydrochloric acid to liberate the acetone, and the hydrochloride solution almost neutralised with caustic soda. The warm solution was added to boiling Fehling's solution in a steam distilling flask, the addition being made at the same rate as the liberated menthylamine distilled over. The aqueous distillate was made faintly acid with hydrochloric acid, and the water removed in vacuo. The brownish residue was extracted with hot alcohol, and the solution brought to dryness in a vacuum desiccator. The l-menthylamine hydrochloride thus obtained was recrystallised twice from a large volume of moist boiling petroleum ether, when it remained unchanged at 280° (Wallach loc. cit.)

A solution of strength 4·9I grams per I00 ccs. of water gave $[\alpha]^{20}_{D} = -32{\cdot}19^\circ$.

Preparation of Acetone-δ-l-Menthylsemicarbazone.

The pure amine used in the preparation had a rotation $[\alpha]^{20}_{D} = -39{\cdot}4I^\circ$.

Acetonesemicarbazone (I mol.) and l-menthylamine (I mol.) were separately heated to I65° C in a glycerol bath. On mixing, vigorous evolution of ammonia occurred, and solution was complete in I5 minutes. The cooled melt was dissolved in a little alcohol, and on pouring into dilute acetic acid, quickly solidified. It dissolved completely in alcohol, (there being no hydrazodicarbonamide in this case) and, on ice-cooling, the acetone-δ-l-menthylsemicarbazone separated in clusters of small, colourless needles, which after well washing with dilute alcohol under suction, melted at 128°.

The substance is soluble in alcohol, acetone, chloroform, ether and petroleum spirit, and insoluble in water.

$C_{10}H_{19}.NH.CO.NH.N{=}C(CH_3)_2$ requires 16·60% N.
Found 16·62% N.
16·73% N.

0·5024 gram dissolved in 25 ccs. absolute alcohol gave $\alpha_D = -2{\cdot}612^\circ$ whence, $(l=2)\ [\alpha]^{20}_D = -64{\cdot}93^\circ$.

Yield of pure product, 65% on the acetone-semicarbazone used.

Hydrolysis of Acetone-δ-*l*-Menthylsemicarbazone.

The semicarbazone was heated at 70° with 5 times its weight of *N*-hydrochloric acid until solution was complete. The resulting mixture was vacuum distilled to dryness, and the residue dissolved in hot alcohol, whence it separated in a gelatinous form. On drying under suction, and well washing with ether, the somewhat fibrous mass of

δ-l-menthylsemicarbazide hydrochloride obtained melted at 203-204°.

$C_{10}H_{19}.NH.CO.NH.NH_2HCl$	requires	14·22% Cl.
	Found	14·02% Cl.
		14·22% Cl.

0·5024 gram in 25 ccs. absolute alcohol gave $\alpha_D = -2\cdot62^\circ$ ($l = 2$), whence $[\alpha]^{20}_D = -65\cdot18^\circ$.

The hydrochloride is soluble in alcohol and hot water, insoluble in ether and benzene. It was not found possible to obtain it in crystalline form. It is best prepared by adding etherial hydrochloric acid to an absolute alcohol solution of δ-l-menthylsemicarbazide until slight acidity, when it separates in the usual gelatinous form, drying to a white powder.

Preparation of δ-l- Menthylsemicarbazide.

$C_{10}H_{19}.NH.CO.NH.NH_2$.

The hydrochloride was dissolved in hot dilute alcohol, and caustic soda added in slight excess, the solution being immediately diluted and ice-cooled. The precipitated δ-l-menthylsemicarbazide was dried, and dissolved in petroleum ether containing a little benzene, from which it crystallised in microscopic prisms. On a second recrystallisation from the same mixture it melted at 138°.

In practice it is better to avoid the troublesome hydrochloride by hydrolysing the acetone-δ-l-menthylsemicarbazone with hydrochloric acid, and adding caustic soda to the hot solution as above.

On recrystallising from the benzene-petroleum spirit mixture, any unhydrolysed semicarbazone is retained in the mother liquors.

Long contact with caustic soda should be avoided, since the product tends to acquire a pinkish tinge.

$C_{10}H_{19}\cdot NH.CO.NH.NH_2$	requires	19·71% N.
	Found	19·89% N.
		19·83%. N.

Examined polarimetrically 0·4994 gram in 25 ccs, alcohol gave $\alpha_D = -3\cdot11°$ $(l=2)$, whence $[\alpha]_D^{20} = -77\cdot94°$.

δ-l-Menthylsemicarbazide is soluble in alcohol, ether, and in hot benzene, hot toluene and hot petroleum spirit, being only slightly soluble in the cold solvents. Solutions ~~solutions~~ should be made up only as required, for they invariably turn green on standing more than a day.

Benzylidene-δ-l-Menthylsemicarbazone.

δ-l-Menthylsemicarbazide hydrochloride in alcoholic solution was shaken up with a few drops of benzaldehyde, avoiding excess of the latter, and a few drops of water added. A syrupy mass separated, which crystallised on standing. It separates from alcohol, in which it is very soluble, in fine rhombic prisms, melting at 111°. Like the free base, a solution turns green on standing, and the crystals obtained may be deep olive green in tint.

$C_6H_5CH=N.NH.CO\,NH.C_{10}H_{19}$ requires 13·95% N.

Found 13·96% N.

1·898 grams in 100 ccs. absolute alcohol gave $\alpha_D = -1\cdot79°$ $(l=2)$, whence $[\alpha]_D^{20} = -47\cdot18°$

Effect of Dilution on the Specific Rotation of *l*-Menthylamine Hydrochloride.

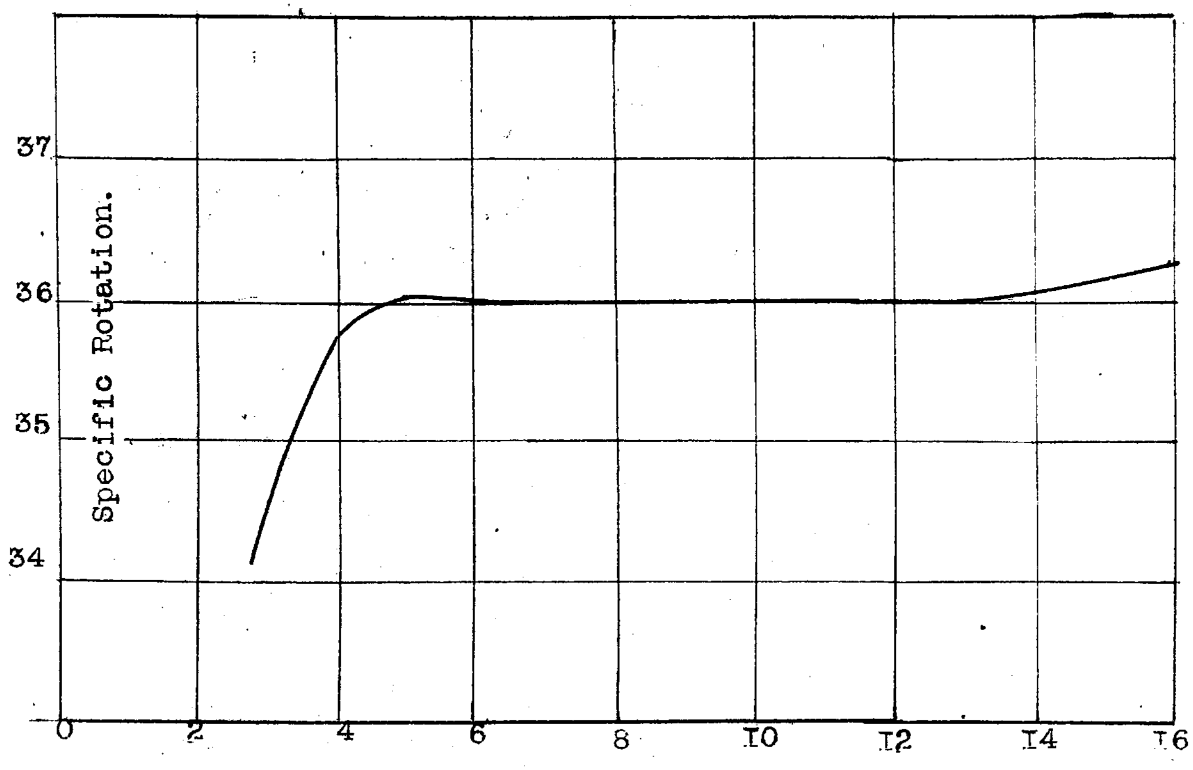
' The subjoined tables show the values obtained for the Specific Rotation of the salt at varying dilutions. The results given in the first table are for pure salt, those in the second table were obtained from an optically impure *l*-menthylamine hydrochloride.

Length of tube. (dcms.)	Concentration Grams per I00ccs.	α_D	$[\alpha]^{15}_D$	$[M]^{15}_D$
I	I5·94	$-5·79^{\circ}$	$-36·34^{\circ}$	$-69·58^{\circ}$
2	I2·004	$-8·64^{\circ}$	$-35·98^{\circ}$	$-68·89^{\circ}$
2	I0·0	$-7·22^{\circ}$	$-36·0I^{\circ}$	$-68·93^{\circ}$
2	7·999	$-5·76^{\circ}$	$-36·0^{\circ}$	$-68·93^{\circ}$
2	5·996	$-4·32^{\circ}$	$-36·0^{\circ}$	$-68·93^{\circ}$
2	4·994	$-3·57^{\circ}$	$-36·I^{\circ}$	$-69·II^{\circ}$
2	4·0	$-2·86^{\circ}$	$-35·75^{\circ}$	$-68·45^{\circ}$
2	3·0024	$-2·07^{\circ}$	$-34·47^{\circ}$	$-66·04^{\circ}$

Sample of Impure -Menthylamine Hydrochloride.

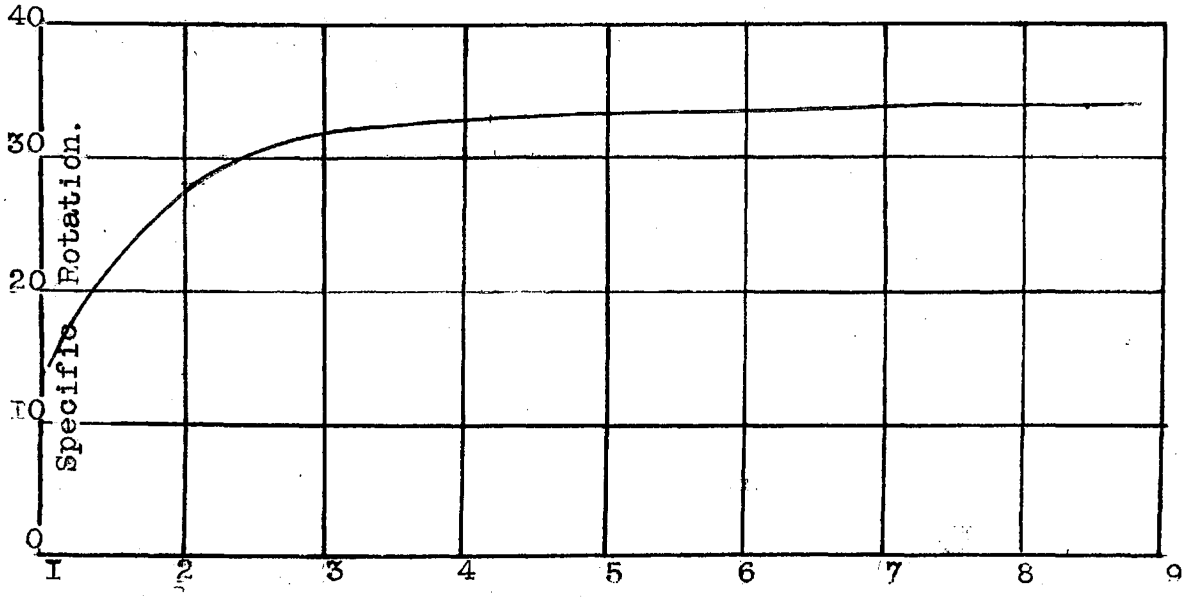
2	8·429	$-5·66^{\circ}$	$-33·8^{\circ}$
2	4·2I4	$-2·80^{\circ}$	$-33·2^{\circ}$
2	2·I07	$-I·I8^{\circ}$	$-28·0^{\circ}$
2	I·054	$-0·22^{\circ}$	$-I0·4^{\circ}$

Effect of Dilution on Specific Rotation of the Hydrochloride of *l*-Menthylamine (Pure Sample).



Concentration -- gms.per 100ccs.

Effect of Dilution on Specific Rotation of the Hydrochloride of *l*-Menthylamine (Impure Sample).



Concentration -- gms. per 100ccs.

PART III.

ACTION ON SEMICARBAZONES OF THE ESTERS OF ORTHO-, META-, AND PARA-AMINOBENZOIC ACIDS.

PART III.

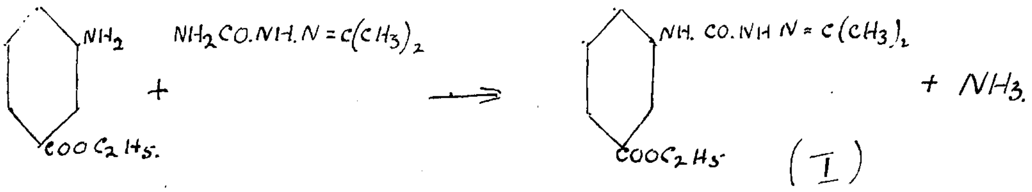
The Action on Semicarbazones of the Esters of ortho-,meta-, and para-aminobenzoic Acids.

The reaction having been established for amines such as benzylamine,and l-menthylamine,it was thought that the influence of substitution in the nucleus might repay study. To this end the reaction was carried out using the ethyl esters of meta- and para-aminobenzoic acids and methyl anthranilate.

Action of Ethyl *m*-Aminobenzoate on Acetonesemicarbazone.

The reaction followed the general reaction in detail.

I mol. of the aminoester and excess (I·6 mols.) of acetonesemicarbazone were heated for 20 mins. to I65° C. Since the amine did not readily dissolve in dilute acetic acid, the melt was recrystallised from alcohol, a small quantity of hydrazodicarbonamide remaining insoluble therein. The alcohol yielded first acetone-δ-3-carbethoxyphenylsemicarbazone (I) plates M.P. I46°) and finally unchanged ester.

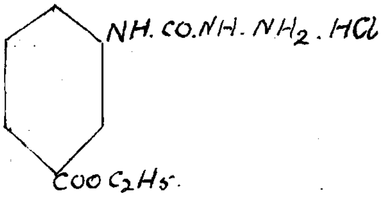


(I)

There was also a little dimethylketazine produced in the reaction, but no carbamide derivative was obtained.

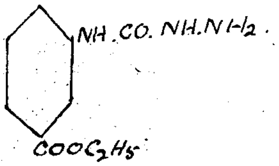
The product (I) on hydrolysis with 2N-hydrochloric acid at 70° C., yielded the hydrochloride of δ-3-carbethoxyphenylsemicarbazide II (prisms from alcohol.

M.P.172°.)

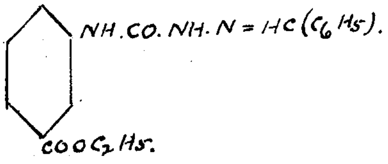


(II)

By neutralising the hydrochloride II with caustic soda, the free semicarbazide (III) δ-3-carbethoxy-phenysemicarbazide, was obtained (small prisms from benzene, M.P.119°). The hydrochloride II, on shaking with benzaldehyde, readily yielded benzylidene-δ-3-carbethoxy-phenylsemicarbazone (IV) (hair-like needles from alcohol M.P.144°)



III



IV.

The Action of Ethyl *p*-Aminobenzoate on Benzophenonesemicarbazone and Acetonesemicarbazone.

A Reaction with Benzophenonesemicarbazone.

In marked contrast to the *m*-ester, the condensation of the p-amino-ester with either semicarbazone proved remarkably difficult. With benzophenonesemicarbazone a slow reaction commenced at I45° which became faster at I65°. With I½ to 2 hours heating these reactions yielded only 22% of the δ-4-carbethoxysemicarbazone. By altering the detail of the method it was found possible to increase this yield to 57% calculated on the semicarbazone used.

Benzophenonesemicarbazone (Imol.) was added during I hour to excess (2mols.) of the ester at 230 ° C, heating being prolonged for I5 minutes longer. Only a moderate evolution of ammonia occurred. The melt was poured into acetic acid to remove ester, and the solid taken up in alcohol, leaving insoluble hydrazodicarbonamide.

The solid obtained from the alcoholic solution, on shaking up with cold toluene yielded a solution of diphenylketazine ~~benzophenoneazine~~(V) (yellow prisms from ether, M.P. 162°-4°) and benzophenonecarbohydrazone(VI.) (Long needles from alcohol, M.P. 221°-223°).

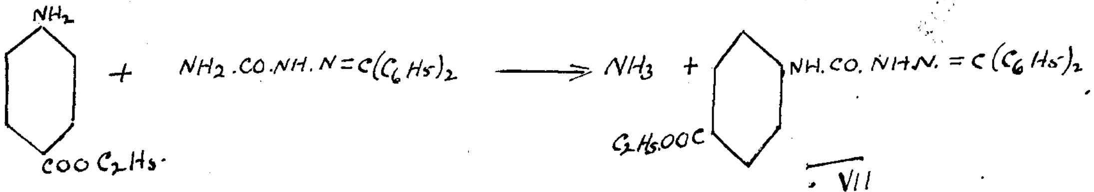
The solid insoluble in cold toluene was benzophenone-δ-4-carbethoxyphenylsemicarbazone(VII). This substance is markedly phototropic, turning yellow on standing. The colour is removed by solvents.

$$(C_6H_5)_2C=N\cdot N=C(C_6H_5)_2$$

(V).

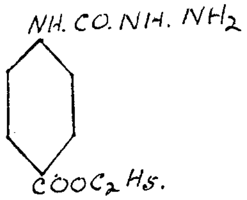
$$CO[NH.N=C(C_6H_5)_2]_2$$

(VI).



VII.

On hydrolysing(VII) with hydrochloric acid complete disruption of the molecule occurred, benzophenone, hydrazine, alcohol, and a little p-aminobenzoic acid being the only products recognised. The δ-substituted semi-carbazide(VIII) was not obtained.

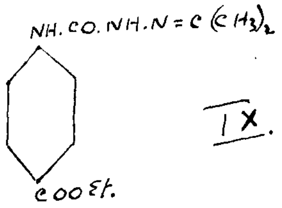


VIII.

B. Reaction of Ethyl-p-Aminobenzoate with Acetonesemicarbazone:

In the hope that the acetone derivative might yield to a milder hydrolysis, acetone-δ-4-carbethoxyphenylsemicarbazone was prepared. In this case the ease of reaction was in strong contrast to the somewhat slow condensation with benzophenonesemicarbazone.

The slow addition of 1 mol. of acetonesemicarbazone to 1 mol. of the amino-ester at 190-200 °C. during 20 minutes resulted in a brisk evolution of ammonia. The melt yielded acetone-δ-4-carbethoxyphenylsemicarbazone (IX), (hexagonal tablets from alcohol, M.P. 194°) hydrazodicarbonamide, a small amount of a substance melting at 210°, and an unidentified compound containing 14·2% N. (prisms from acetone M.P. 130°).



IX.

The yield was poor, being only 13% of the acetonesemicarbazone used.

On hydrolysis of (IX) with 2.N.-hydrochloric acid, disruption of the molecule occurred as with the benzophenone derivative; acetone and hydrazine being obtained. In view of this the hydrolysis was not further investigated.

It seems interesting to note that in both cases the ketone-semicarbazide chain should be stable to dilute acids (no apparent hydrolysis occurring with dilute acid)but that when 2N acid is used the ketone is removed,and at the same time the semicarbazide chain is broken.

Action of Methyl Anthranilate on Semicarbazones.

These reactions proved most interesting. As was to be expected, the ring-forming properties of the ortho-position resulted in bicyclic derivatives, but in the case of acetonesemicarbazone the reaction thereafter proved to be abnormal.

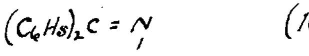
During this part of the work, dry reagents and solvents were used, unless otherwise stated.

A. Reaction with Benzophenonesemicarbazone.

Molecular quantities of the two reactants were heated together at 2I0° for 40 minutes. There was a slow evolution of ammonia, accompanied by a distillate of methyl alcohol. As in previous instances, benzophenone-semicarbazone gave a slow reaction.

From the melt were obtained :

diphenylketazine



$(C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2$ (10).

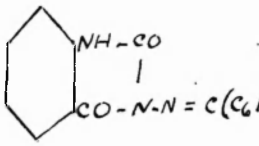
(Yellow prisms from ether M.P. I62°-I64°)

benzophenonecarbohydrazone. $CO[NH.N=C(C_6H_5)_2]_2$ (11).

(long needles from alcohol M.P.22I-223°)

3 – benzophenoneaminotetrahydro-quinazoline-2:4-dione.

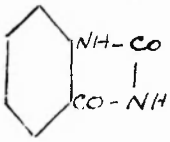
(large prisms from alcohol,M.P.240)



(12).

and tetrahydro-quinazoline-2:4-dione (o-benzoylene-urea).

(pearly plates from pyridine,M.P.354 corr.)

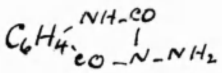


(13).

There was a little hydrazodicarbonamide,but the 3-aminotetrahydroquinazoline-2:4-dione (I4) obtained in the reaction with acetonesemicarbazone was not produced when dry reagents were used. It was obtained if the fusion was worked up in the usual way with acetic acid.

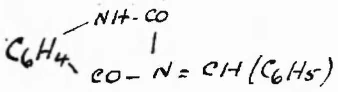
The benzophenone amino-compound (I2) on hydrolysis yielded the 3-aminoquinazoline compound (I4),not its hydrochloride. Kunckell,(Ber,43,I02I,(I9I0).

)states that the hydrochloride can be formed in alcoholic solution ; evidently it does not exist in aqueous solution. On boiling the compound (I4) thus obtained for two hours with alcoholic benzaldehyde,the benzylidene derivative was obtained (I5) (needles from alcohol.M.P.240°) Kunckell(loc.cit.) gives M.P.240°.



$C_6H_4\begin{matrix}NH-CO\\ |\\ CO-N-NH_2\end{matrix}$

(14).



$C_6H_4\begin{matrix}NH-CO\\ |\\ CO-N=CH(C_6H_5)\end{matrix}$

(15).

B. Reaction of Methyl Anthranilate with Acetonesemicarbazone.

When molecular quantities of the two substances were heated together in the usual way at 195°, copious evolution of ammonia occurred, heating being continued for 30-40 minutes. A distillate was obtained and the melt became solid.

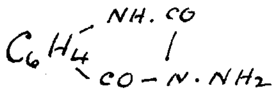
From the solid melt was obtained : 3.aminotetrahydroquinazoline-2:4-dione (14) (indefinite crystals from alcohol, M.P.288° or 290°) and an unidentified substance melting at 420° (uncorr.)

There was obtained besides tetrahydroquinazoline-2:4-dione (13)

The compound melting at 420°, which was not identified, separated from pyridine in prisms containing 32% of their weight of pyridine -they effloresced slowly in air.

The absence of hydrazodicarbonamide is to be noted. No solid acetone derivative was isolated.

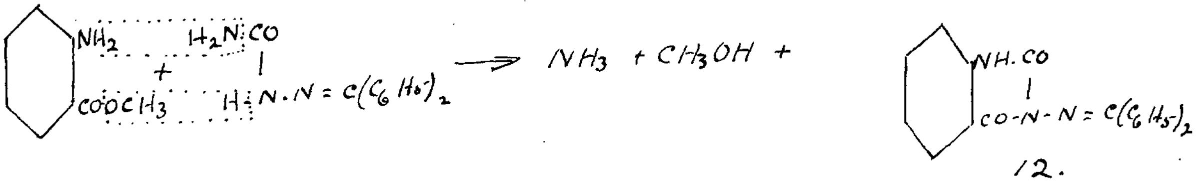
The distillate on fractionation yielded dimethylketazine and methyl alcohol. There was no free acetone, water, or hydrazine.



$C_6H_4\begin{cases}NH.CO \\ \quad | \\ CO-N.NH_2\end{cases}$ (14).

Discussion of the Probable Course of the Reaction.

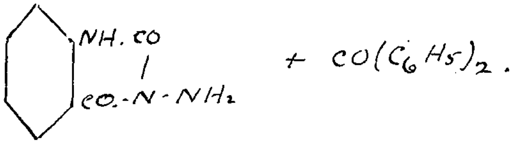
The reaction with benzophenonesemicarb-azone apparently proceeds according to this scheme :



12.

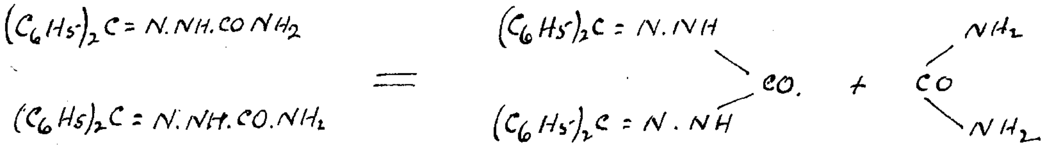
giving 3-benzophenoneaminotetrahydroquinazoline-2:4-dione (I2), On hydrolysis, either through working up with dilute acetic acid, or by hydrochloric acid hydrolysis, there results the 3 amino-compound (I4) and benzophenone.

(14).



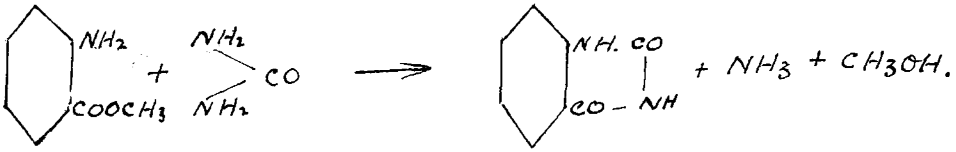
In this reaction, tetrahydroquinazoline-2:4-dione (I3) was present in much larger quantity than in the reaction with acetonesemicarbazone, and present, moreover, in the complete absence of the 3-amino-compound (I4) ; hence an explanation different from the one adopted in the reaction with acetonesemicarbazone (see later, p. 57) must be advanced to account for its presence in this instance.

Borsche has shown (see p. 3) that benzophenonecarbohydrazone (II) is a normal decomposition product of the action of heat on benzophenonesemicarbazone. It might possibly result in this case, along with urea, by such a reaction as this:

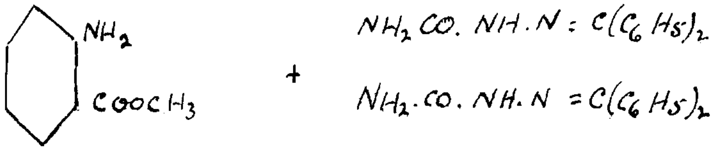


$$\begin{matrix}(C_6H_5)_2C=N.NH.CONH_2 \\ (C_6H_5)_2C=N.NH.CO.NH_2\end{matrix} = \begin{matrix}(C_6H_5)_2C=N.NH \\ (C_6H_5)_2C=N.NH\end{matrix}\!\!>CO. + CO<\!\!\begin{matrix}NH_2 \\ NH_2\end{matrix}$$

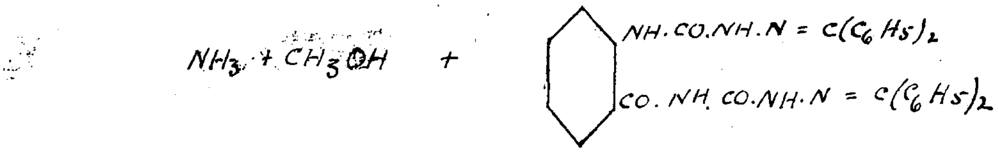
The urea might then react with the ester to give tetrahydroquinazoline-2:4-dione (I3) as shown originally by Griess (Ber., 2., 4I6. see also appendix p.91.)



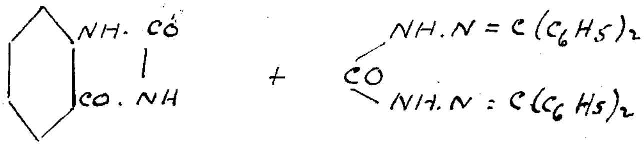
Borsche, however, makes no mention of urea among the decomposition products of benzophenone-semicarbazone, and indeed, suggests the formation of an intermediate hydrazone (see p. 3.) to explain the presence of the carbo-hydrazone. Hence, the formation of tetrahydroquinazoline-2:4-dione may be formulated in this fashion:-



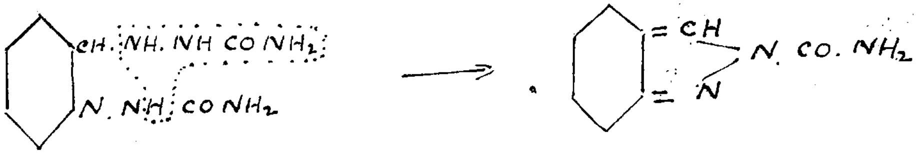
two molecules of benzophenone semicarbazone reacting with one molecule of the amino-ester, to give :



which immediately gives:

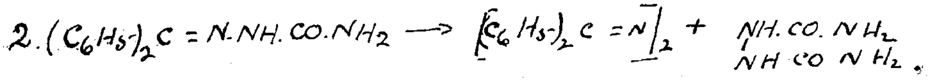


A somewhat similar di-semicarbazone has been isolated by Auwers Buschmann and Heidenreich (Ann. 435, 3, p. 277.) which, however, is unstable changing on acidification to a bicyclic carbonamide.



Tetrahydro-indazol-2-carbonamide.

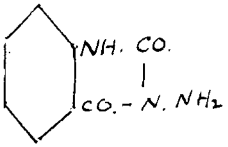
The ~~benzophenoneazine~~ diphenylketazine may possibly result, along with hydrazodicarbonamide from the decomposition of benzophenone semicarbazone already noticed (p. 3).



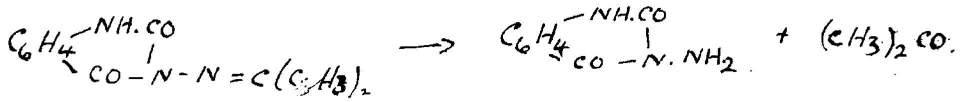
$$2.(C_6H_5)_2C = N.NH.CO.NH_2 \longrightarrow [(C_6H_5)_2C = N]_2 + \begin{array}{l} NH.CO.NH_2 \\ NH.CO.NH_2 \end{array}.$$

The Reaction with Acetonesemicarbazone.

The course of this reaction proved extremely difficult to elucidate. The production of the 3-amino-quinazoline compound.

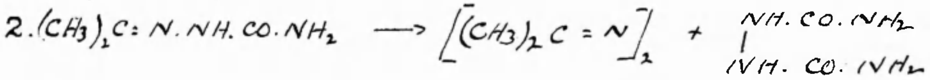

(14)

instead of its 3-acetoneamino derivative might suggest that hydrolysis occurs.



$$C_6H_4\begin{array}{l} NH.CO \\ \quad | \\ CO-N-N=C(CH_3)_2\end{array} \longrightarrow C_6H_4\begin{array}{l} NH.CO \\ \quad | \\ CO-N.NH_2\end{array} + (CH_3)_2CO.$$

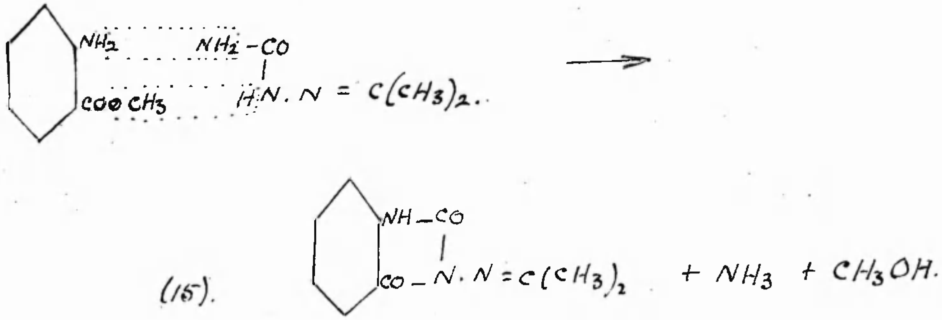
The use of dry reagents and solvents - together with the entire absence of free acetone -negatived this possibility. The acetone of the semicarbazone would seem to be removed as dimethylketazine and the quantities of this compound obtained from the distillate tended to confirm this idea, whilst the entire absence of any solid product containing the isopropylidene grouping also supported it. The noteworthy feature of the reaction is the entire absence of hydrazodicarbonamide, and when contrasted with the quantities of dimethylketazine produced; it is apparent that the latter substance can not be accounted for by the usual acetonesemicarbazone decomposition . (see p.2.)



$$2.(CH_3)_2C:N.NH.CO.NH_2 \longrightarrow \left[(CH_3)_2C=N\right]_2 + \begin{array}{l} NH.CO.NH_2 \\ | \\ NH.CO.NH_2 \end{array}$$

Further, the yield of the 3-amino-body, (14) (45% on the acetonesemicarbazone used) would seem to indicate that two molecules of acetonesemicarbazone are concerned in the formation of one molecule of this substance.

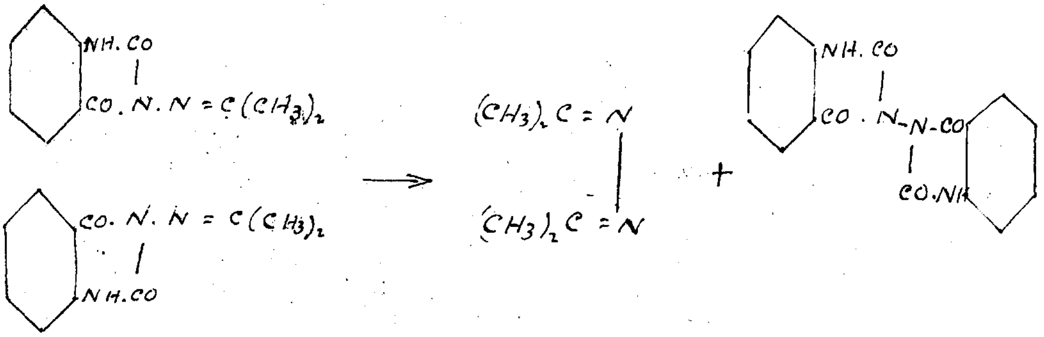
In previous instances it was found that if the amine reacted with benzophenonesemicarbazone, the reaction with acetonesemicarbazone went more readily ; hence it is almost certain that the reaction begins by the formation of the δ-substituted semicarbazone (15), accompanied by the closing of the ring due to elimination of alcohol.



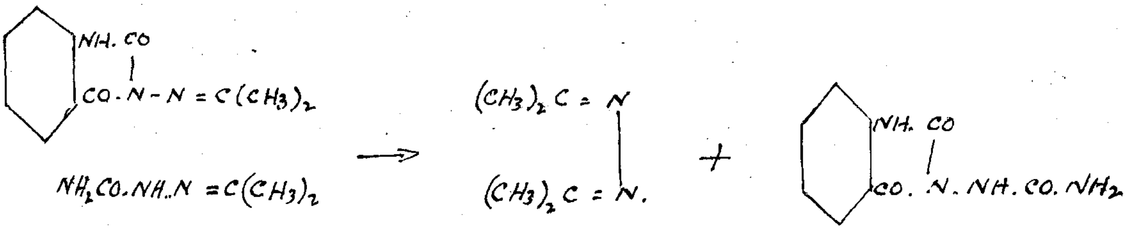
(15).

To provide dimethylketazine two reactions are possible. (a) Two molecules of this compound may react, or (b) one molecule may react with another molecule of acetonesemicarbazone.

a.

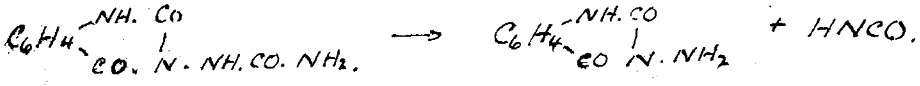


(b.)



The 3-acetoneamino-compound (I5) was later obtained by another method, and was shown not to behave as suggested in (a) when heated, so the dimethyl-ketazine must be produced as suggested in (b).

No such carbamino derivative was isolated, hence it must be assumed that this substance loses HNCO., giving the quinazoline body.

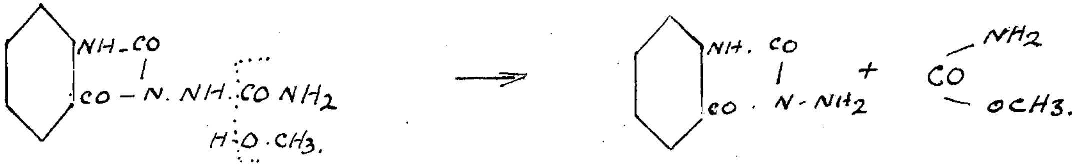


$$C_6H_4\left<\begin{matrix}NH.CO\\ |\\ CO.N.NH.CO.NH_2.\end{matrix}\right. \longrightarrow C_6H_4\left<\begin{matrix}NH.CO\\ |\\ CO\ N.NH_2\end{matrix}\right. + HNCO.$$

Free cyanuric acid could not be detected among the products of the reaction, but it does not seem possible to explain otherwise how the amino group becomes attached in the 3-position.

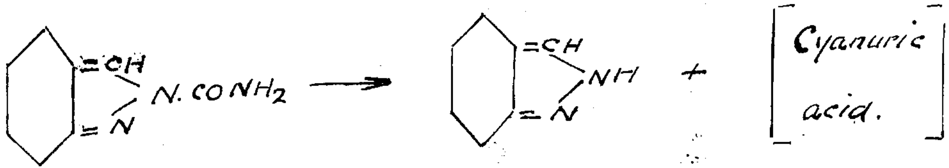
It is possible that alcoholysis

might result in the formation of methyl urethane and the 3-amino body (14), but no trace of this could be detected.

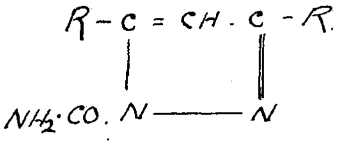


The elimination of the grouping HNCO has been demonstrated in several analagous cases.

Anwers and his collaborators (Ann. 435, 3, 277) have shown that tetrahydroindazol-2-carbonamide loses HNCO at 160 .

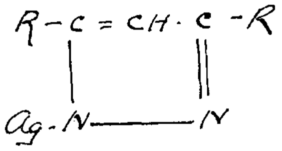


Posner, (Ber. 34, (~~1910~~ 1901) 3976) has noted a similar case where, by the action of diketones on semicarbazide, he obtained a ring system of this type:

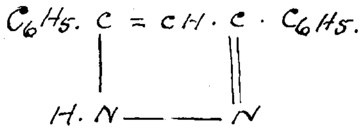


(R = alkyl group.)

which on treatment with silver nitrate gave:



when R was replaced by a phenyl group, the urea body was not obtained, but owing to the temperature of the reaction the product went immediately to 3:5-diphenylpyrazole



Attention has already been called (p. 3.) to the assumption made by Borsche of the intermediate formation of a hydrazone (16), whereby benzophenonecarbohydrazone results.

$$(C_6H_5)_2C=N.NH.CO.NH_2 \quad + \quad \underset{(16)}{H_2N.N=C(C_6H_5)_2} \longrightarrow$$

$$NH_3 + \quad CO[NH.N=C(C_6H_5)_2]_2.$$

The hydrazone might conceivably result by the elimination of HNCO from a molecule of benzophenone-semicarbazone.

The work of Poth and Bailey (loc.cit.) has shown also that this part of the molecule in α-substituted semicarbazides may undergo complete disruption. The evidence from these last two considerations is not directly applicable to the type of compound under discussion, but it is admissable in so far as each compound dealt with may be regarded as a substituted urea.

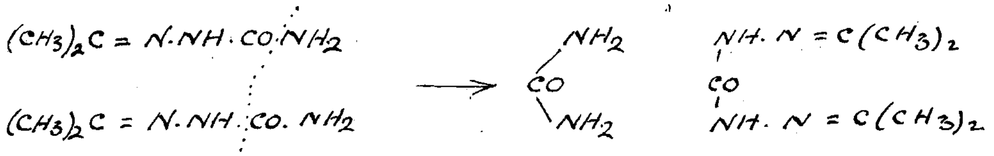
In the other cases the formation of the bicyclic grouping has weakened the binding forces of the carbamino- chain.

Since the preparation of 3-acetoneamino-tetrahydroquinazoline-2:4-dione (15) would shed some light on the problem, several attempts were made to obtain it. It was finally obtained by boiling the 3-aminoquinazoline compound (14) with ordinary acetone for 5 hours, when it dissolved. The compound separated from acetone in large efflorescent prisms M.P.212°. Strange to say, specially dried acetone did not react even after 6 hours boiling, nor did β β-dichleropropane prove reactive.

As was suspected, the acetone derivative proved to hydrolyse easily in aqueous solvents. When heated in molecular proportions with acetonesemicarbazone a copiuus distillate of dimethylketazine resulted, and the solid residue proved to be 3-aminotetrahydroquinazoline-2:4-dione (14). This experiment confirms the conclusions previously reached as to the course of the reaction.
(Cp. p.53(b))

Further proof of the intermediate formation of a carbamino-derivative is the presence of tetrahydroquinazoline-2:4-dione, due to the action of the ester on (a) urea, or (b) more probably on a carbamino-derivative.

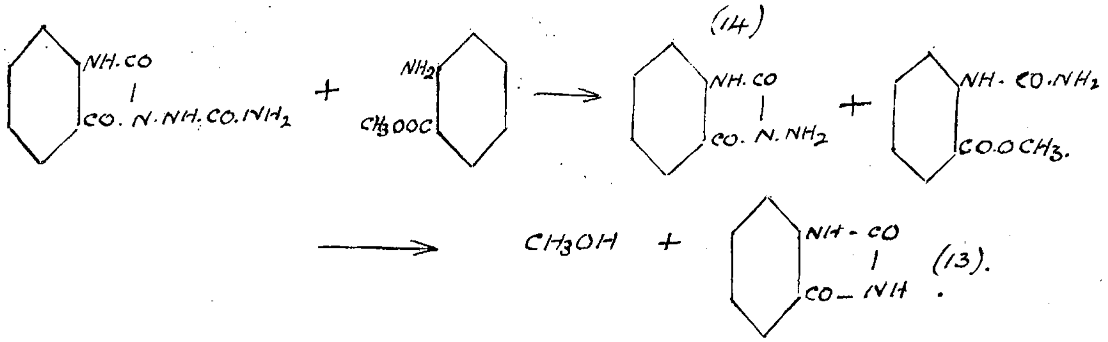
(a) The presence of free urea in reactions with acetonesemicarbazone has not been reported, nor was anything corresponding to the carbohydrazone (I7) obtained in the reaction which would produce urea.



$$\begin{matrix}(CH_3)_2C=N.NH.CO.NH_2\\(CH_3)_2C=N.NH.CO.NH_2\end{matrix}\longrightarrow CO\begin{matrix}NH_2\\NH_2\end{matrix}\quad \begin{matrix}NH.N=C(CH_3)_2\\CO\\NH.N=C(CH_3)_2\end{matrix}$$

(17).

Hence the reaction more probably follows the course suggested in (b).



This results in the formation of the 3-aminoquinazoline compound (I4) as well, but the quantity of tetrahydroquinazoline-2:4-dione obtained is much too small to account for all the 3-aminoquinazoline compound produced.

Experimental.

The Action of Ethyl m-Aminobenzoate on Acetonesemicarbazone.

1 mol. of the amino-ester and excess (1·6 mols of acetonesemicarbazone were rapidly heated together to 165° and kept at that temperature for 20 minutes, when the evolution of ammonia began to slacken. The melt was gently heated with a few ecs. of alcohol and the insoluble hydrazodicarbonamide filtered off. The solid which separated was washed with cold alcohol to free it from unchanged ester, and was then redissolved in moderately hot alcohol, when a little hydrazodicarbonamide was removed. On standing, well defined plates of *acetone-δ-3-carbethoxy-phenylsemicarbazone* separated - M.P. 146°.

It is insoluble in water and in cold petroleum spirit, only slightly soluble in cold benzene and in ether, moderately soluble in cold alcohol, but very soluble in pyridine.

The yield is about 80% of the acetonesemicarbazone used.

Found N = 15·94%

N = 16·02%

$C_6H_4(COOEt)NH.CO.NH.N=C(CH_3)_2$ Requires N=15·97%

Hydrolysis of Acetone-δ-3-carbethoxyphenylsemicarbazone.

The semicarbazone was just covered by 2 N. hydrochloric acid, and heated to 70° when hydrolysis was complete; on cooling in ice a solid mass separated. This was filtered, and washed with cold water till free from hydrochloric acid. On recrystallising from alcohol, the hydrochloride of δ-3-carbethoxyphenylsemicarbazide separated in prisms melting at 172°.

These are readily soluble in hot water or hot alcohol, only slightly soluble in cold ether, insoluble in cold petroleum spirit or tuluene, very soluble in pyridine. The substance reduces ammoniacal silver solution on heating, and Fehling's solution in the cold.

Found Cl. = 13·56%

Cl. = 13·72%

$C_6H_4(COOEt)NH.CO\,NH.NH_2.HCl$ requires Cl. = 13·68%

Acetone was identified in the filtrate from the hydrolysis by distilling a little and applying the iodoform and nitroprusside tests for acetone to the distillate.

Liberation of δ-3-Carbethoxyphenylsemicarbazide.

The hydrochloride was dissolved in hot water and caustic soda added to neutrality. On standing in ice, a white mass gradually separated from the milky solutinn. The product, after washing with water, was finally recrystallised from benzene, yielding small prisms melting at 119°. These are very soluble in cold alcohol and chloroform and in hot benzene : not very soluble in water or petroleum spirit.

Found N = 18·87%
N = 18·88%
$C_6H_4(COOEt)NH\,CO.NH.NH_2$ requires N = 18·83%

Benzylidene-δ-3-Carbethoxyphenylsemicarbazone.

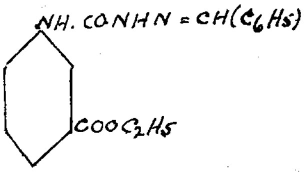
To a solution of the hydrochloride in hot water, a few drops of benzaldehyde were added and the mixture well shaken. The lumpy mass which separated was dissolved in alcohol, from which the benzylidene derivative separated in fine hair-like needles melting at 144°.

They are very soluble in cold ether, benzene, acetone, toluene, and pyridine, sparingly soluble in petroleum spirit and in water.

Found N = 13·62%.

N = 13·50%.

requires N = 13·50%.



The Action of Ethyl *p*-Aminobenzoate on Benzophenonesemicarbazone.

Benzophenonesemicarbazone (I mol.) was added in small quantities during one hour to excess (2 mols.) of the ester kept at 230° C in a glycerol bath, the heating being prolonged for I5 minutes after the last addition. The evolution of ammonia was never vigorous. On cooling, the melt was taken up with a little alcohol, and a small amount of hydrazodicarbonamide filtered off, the filtrate being poured into dilute acetic acid, whence the solid separated on standing. This was well washed with water, dried and shaken up with cold toluene. The insoluble portion, on recrystallisation from hot benzene, separated in pearly plates melting at I68°. This proved to be benzophenone-δ-4-carbethoxyphenylsemicarbazone.

On evaporating the toluene solution, the residue obtained was extracted with ether from which diphenylketazine crystallised in fine yellow prisms M.P. I62°-I64°. The crystals obtained from alcohol were long needle-like prisms some over an inch long. This compound was recognised by its appearance and properties (Borsche and Merkwitz loc.cit.)

The ether-insoluble portion was

dissolved in alcohol, boiled up with animal charcoal, and on cooling, benzophenonecarbohydrazone crystallised in long needles melting at 221°-223°. This was identified by its occurrence and properties. (Borsche and Merkwitz loc.cit.)

The excess ester was recovered by making the acetic acid solutinn alkaline, and recrystallising the precipitated ester from petroleum spirit.

Benzophenone-δ-4-carbethoxyphenyl-semicarbazone is soluble in most organic solvents, but almost insoluble in cold toluene, benzene, or petroleum spirit. The white pearly plates are markedly photo-tropic, turning a fine lemon yellow without change in melting point (168°). The colour is removed in solution.

Found N = 11·03%; 10·68%

$C_6H_4(COOEt).NH.CO.NH.N=C(C_6H_5)_2$. requires N = 10·85%

The yield varied somewhat according to the detail of the method, but the proceedure given above gave a yield of 57% on the acetonesemicarbazone used.

Hydrolysis of Benzophenone-δ-4-carbethoxyphenylsemicarbazone.

The semicarbazone was boiled with 10 times its weight of 2 N. hydrochloric acid until solution was effected, and a slight oily residue was then filtered off. Free alcohol could be detected at this stage by distilling a small quantity of the aqueous mixture and applying the iodoform test. On cooling the solution it was ether extracted to remove benzophenone, the presence of which was confirmed by the formation of its oxime (M.P. 140°). During the vacuum concentration of the aqueous solution a flocculent precipitate was obtained, which decomposed without melting at 240° C and immediately reduced cold ammoniacal silver solution, and Fehling's solution. Attempts to characterise it as the expected ~~4-carbethoxy---phenylsemicarbazide~~ δ-4-carbethoxyphenylsemicarbazide were unsuccessful, and it would seem to be a hydrazine derivative of some sort, but certainly not the hydrazide of p-amino-benzoic acid which crystallises in large needles (M.P. 220°) or its dihydrochloride. (Curtius J. Pr. (2) 94, 295).

From the concentrated solution

were obtained crystals of hydrazine dihydrochloride, recognised by their crystalline form, and their sudden decomposition at 200° as well as by their strong reducing properties. It was further confirmed by shaking with benzaldehyde, when benzalazine was obtained (M.P. 93°) and confirmed, by comparison with a known specimen.

On bringing the solution to complete dryness the residue was made just alkaline with caustic soda and glacial acetic acid added in slight excess. On standing, a few prisms separated, which melted at 185° ; these were probably p-aminobenzoic acid. For comparison, a dilute aqueous solution of a known sample of the acid was made alkaline with caustic soda, and then faintly acid with acetic acid. On being set aside prisms and needles appeared, both melting at 186° and showing no depressed melting point on mixing so that the acid is apparently dimorphous. The prisms obtained from the hydrolysis, when mixed with the prisms from the known sample showed no depression, hence they are probably p-aminobenzoic acid.

The hydrolysis is therefore very

drastic, yielding benzophenone, hydrazine and alcohol, while it is certain that free p-aminobenzoic acid (or its ester) are not present in any quantity among the products.

Action of Acetonesemicarbazone on Ethyl p-aminobenzoate.

To I mol. of the ester at a temperature of I90°-200° was added, in small portinns at a time, I mol. of acetonesemicarbazone, the reaction occupying 20 minutes, a steady stream of ammonia being obtained. On cooling, the melt was extracted with hot alcohol, a small residue of insoluble hydrazodicarbonamide remaining. The crude product, after extraction with ether to remove unchanged ester and after recrystallising from alcohol, was well washed with cold acetone which served to remove a product containing I4·2% N, and which on slow crystallisation from acetone gave well formed prisms melting at I30° C. This product was not identified.

The residue of crude acetone-δ-4-carbethoxyphenylsemicarbazone was recrystallised several times from alcohol and was obtained in well formed hexagonal tablets M.P.194°. There was some difficulty in separating it from a white powder of equal solubility melting at 210°.

The substituted semicarbazone is insoluble in petroleum spirit, ether and water, but is soluble in alcohol and hot benzene, slightly soluble in hot acetone.

The yield is very poor, only 13%, calculated on the acetonesemicarbazone used; nor was it found possible to increase it by altering the experimental details.

On analysis the product melting at 194° gave:

N = 16·18%

= 16·22%

$C_{13}H_{17}O_3N_3$. requires N = 15·97%.

The combustion proved very troublesome, results being 1-2% high and duplicates generally not concordant. Below are noted some of the combustion results.

Sample No.	I.	II.	III.	IV.
Melting point	I92°	I94°	I94°	I94°
Percentage of Nitrogen.	I6,98	I7·I	I6·20	I7·37
	I6·70	I7·5	I6·69	I6·68.

Each sample represents successive recrystallisations of sample No. I from alcohol, hence it was suspected that the discrepancy was due, not to impurity, but to the formation of methane and its incomplete combustion. It has been shown by Haas. (J.C.S. (I906) <u>59</u>, 570) and by Duhstan and Carr (P.I896, I2, 48) that two methyl groups attached to the same carbon atom may produce methane during the combustion, and that almost half of the methane may escape combustion.

The correct results given above were obtained by the use of a two metre tube filled with lead chromate, the empty tube being first freed from air by roasting it in a current of carbondioxide.

Hydrolysis of Acetone-δ-4-carbethoxyphenylsemicarbazide.

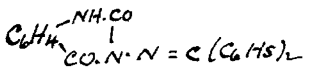
This proved to hydrolyse more quickly than the corresponding benzophenone derivative, giving acetone which was recognised by its smell. It also gave hydrazine however, so that the semicarbazide chain is ruptured in this case also. Hence, the hydrolysis was not further investigated.

The Action of Benzophenonesemicarbazone on Methyl Anthranilate.

Molecular quantities of methyl anthranilate and benzophenonesemicarbazone were heated together for 40 minutes in a glycerol bath at 210°, a moderate evolution of ammonia, together with a distillate of methyl alcohol occurring the while. The melt was cooled somewhat, a few ccs. of dry benzene added and the whole boiled. On cooling and filtering, the filtrate (1) contained diphenylketazine, benzophenonecarbohydrazone, and 3-benzophenoneaminotetrahydroquinazoline-2:4-dione. On concentrating, the two latter separated together. After drying, they were dissolved in hot chloroform (2) and the quinazoline body precipitated therefrom by petroleum spirit and filtered off. On recrystallising from alcohol, it separated in large coarse prisms melting at 240°.

Found N. =12·32%.

N. =12·54%



$C_6H_4{<}^{NH.CO}_{CO.N.N=C(C_6H_5)_2}$

requires N =12·31%.

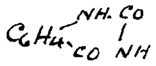
The substance is insoluble in ether, petroleum spirit, and water, slightly soluble in hot benzene, soluble in hot chloroform and in hot pyridine.

On concentrating, the chloroform solution (2) yielded benzophenonecarbohydrazone which on recrystallising from alcohol melted at 22I°. It was identified by its properties and by comparison with a sample previously obtained.

The benzene mother liquor (I) gave diphenylketazine which crystallised from ether in prisms (M.P. I62°-I64°), identified by their properties and comparison with a known specimen.

The benzene insoluble residue was extracted with chloroform and then dissolved in hot pyridine. On concentrating, small pearly plates separated which melted at 335° on gradual heating, but when plunged into the bath (molten sodium and potassium nitrates) melted at 340° (354° corrected). The substance crystallised from water and dilute mineral acids in needles, and from pyridine in pearly plates. It was slightly soluble in alcohol, soluble in caustic soda, and with concentrated sulphuric acid, gave a fine blue fluorescence. It reduced Fehling's solution slowly in the heat.

It was shown to be tetrahydroquinazoline-2:4-dione by its nitrogen content and by direct comparison with a sample prepared after the method of Griess (Ber.2. 416. See also appendix p.91.). Both samples melted at 335° on slow heating and a mixed melting point was unchanged.



$C_6H_4\begin{array}{l}\diagup NH.CO\\ \qquad\quad\ |\\ \diagdown CO\ \ NH\end{array}$

Found N = 17·17%

requires N = 17·28%.

It is interesting to note that this substance, like methyl anthranilate, gives blue fluorescent solutions, whereas the 3-amino-quinazoline compound does not fluoresce with concentrated sulphuric acid. The 3-amino body is more rapidly attacked by hot Fehling's solution than is tetrahydroquinazoline-2:4-dione.

Hydrolysis of 3-Benzophenoneaminotetrahydroquinazoline-2:4-dione.

The substance was boiled for 30 minutes with 2 N. hydrochloric acid, complete solution occurring. On cooling, clusters of large needles separated, which on washing with alcohol and ether, melted at 284°. This was the <u>3-aminotetrahydroquinazoline-2:4-dione</u> and not the hydrochloride, since the hydrolysis product did not give a precipitate with silver nitrate. For comparison, a known sample of the base was recrystallised from dilute hydrochloric acid and similar crystals were obtained. (M.P.286°) These two sets of crystals when compared with each other and with a known sample of 3-aminotetrahydroquinazoline-2:4-dione did not melt below 284°. Hence the hydrochloride is not formed from dilute hydrochloric acid.

With special purification (see later p. 75) the 3-amino compound melts at 289° but, as obtained in experiment, it generally melted at 284°-286°. Kunckell (loc.cit.) states that he obtained the hydrochloride from alcoholic solution melting at 290°, but he gives no analytical figures in support.

(3-aminotetrahydroquinazoline-2:4-dione being the main product in the reaction with acetonesemicarbazone is more fully dealt with under that heading. (See p.76,77).

For further characterisation, the hydrolysis product was boiled for two hours with alcoholic benzaldehyde solution. On cooling, needles separated, which when washed with ether, melted at 239°-240° That this was *3-benzalaminotetrahydroquinazoline-2:4-dione* was shown by comparison with a known specimen. See p.77).

The acid liquors from the hydrolysis were ether extracted to remove benzophenone, which was identified by its oxime (M.P.140°).

The Action of Acetonesemicarbazone on ~~Ethyl~~ Methyl o-Aminobenzoate.

Molecular quantities of the two reactants were heated in a glycerol bath at 195° for 30-40 minutes : copious evolution of ammonia ensued, accompanied by a distillate. After 20 minutes heating, a slight white sublimate generally appeared and the melt gradually went solid. It was cooled somewhat and boiled up with a little dry benzene. On cooling, the almost insoluble white powder was washed with petroleum spirit and fractionated from pyridine in which it was totally soluble, indicating the absence of hydrazodicarbonamide.

The first crop of crystals melted at 284°, but after rubbing up with benzene, boiling with benzene and finally recrystallising from alcohol they melted at 288° -- Crop A.

Further concentration gave a crop of large regular prisms which effloresced in air. These charred at 390°, but when plunged into a bath (mixed nitrates of sodium and potassium) melted at 420° ----Crop B.

On evaporating the pyridine mother liquor almost to dryness, a small quantity of pearly plates were obtained, which, recrystallised from pyridine, melted at 332°, but on plunging into the bath melted at 339°, and was shown by comparison with an authentic specimen,

(See appendix p. 91).

to be <u>tetrahydroquinazoline-2:4-dione</u>

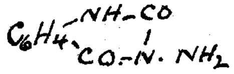
(See also p. 72.)

The product in Crop A -melting at 288° is the main reaction product and is identical with the 3-amino-2:4-dioxytetrahydroquinazoline (or 3-aminotetrahydroquinazoline-2:4-dione of the Chemical Society Nomenclature) described by Kunckell (Ber. 43 (1910) 1021).

Yield 45% on the acetonesemi-carbazone used.

Found N =23·63%.

N =23·70%



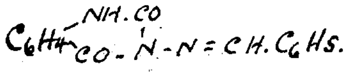
$C_6H_4\left\langle\begin{array}{l}NH-CO\\ \qquad\quad|\\ CO-N\cdot NH_2\end{array}\right.$

requires N =23·70%.

It is slightly soluble in alcohol, and water, fairly soluble in hot dilute mineral acids, crystallising therefrom in needles. It is moderately soluble in pyridine : insoluble in ether, petroleum spirit and chloroform ; readily ~~nearly~~ soluble in in caustic soda, to which solution the addition of iodine gives vigorous gas evolution. Reduces hot Fehling's solution slowly.

The further identification, the 3-benzalamino-derivative was prepared by boiling the compound with alcoholic benzaldehyde for two hours. On cooling, the needles which separated, after a futher recrystallisation from alcohol, melted at 240° C. (Kunckell loc.cit. gives M. .240°).

Found N =I5·85%



$C_6H_4\begin{matrix}\diagup NH.CO\\ \diagdown CO-\end{matrix}\overset{|}{N}-N=CH.C_6H_5.$ requires N =I5·85%.

Crop B. ---The Compound Melting at 420° C.

It has not been found possible to identify this substance. It is insoluble in alcohol, benzene and water. Moderately soluble in pyridine, it crystallises therefrom in prisms containing about 32% of their weight as pyridine of crystallisation - they effloresce slowly in air, pyridine being given off. It is insoluble in dilute acids, but soluble in caustic soda. With concentrated sulphuric acid it gives a clear solution which turns pink on standing.

After heating at 105° for two days it gave on analysis:

C.	H.	N.	O. (by difference).
60·53%	4·00%	17·41%	18 06.%
60·12%	4·00%	17·42%	18 36.%.

<u>The Distillate</u>.

The volatile distillate of several reactions was collected and fractionated. Two fractions were obtained, one containing methyl alcohol (65°-70°) which was characterised by the 3:5-dinitrobenzoate (M.P. 107°). The other fraction was di-methylketazine, a liquid with a characteristic smell B.P.131°.

The ketazine reduced ammoniacal silver nitrate solution <u>on standing</u> (hence there was no free hydrazine) and with benzaldehyde and barium hydroxide gave benzalazine (M.P. 95·5°) confirmed by comparison with a known specimen.

It gave the iodoform reaction only on standing and much more slowly than a comparison test with acetone; -hence it is concluded that there was no <u>free acetone</u> present.

The sublimate, small in quantity, could not be recognised. It volatilised at ordinary temperatures and was probably ammonium carbamate, ~~gradually~~ generally obtained on heating semicarbazones.

Preparation of 3-Acetoneaminotetrahydroquinazoline-2:4-dione.

A. From $\beta\beta$-Dichloropropane.

Molecular quantities of the 3-aminoquinazoline compound and $\beta\beta$-dichloropropane, together with just sufficient pyridine to dissolve the base, were gently boiled for two hours. On cooling, crystals separated which were entirely unchanged amino-compound, hence the reaction did not take place.

It was repeated with molecular quantities of the two reactants in quinoline as solvent, and the whole gently boiled for five hours. At the end the whole of the 3-amino-compound was recovered unchanged.

B. From Acetone.

The 3-aminoquinazoline compound was boiled up with dry acetone for six hours, but showed no sign of dissolving.

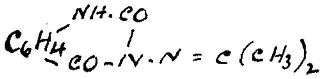
On repeating with ordinary acetone, solution was effected by five hours boiling, and on concentrating the bulk of the fluid to one third, the 3-acetoneamino-compound separated out in well formed prisms which on recrystallising several times from acetone melted at 212°.

As was suspected it proved rather unstable to aqueous solvents, being easily hydrolysed e.g. by undried pyridine or 90% alcohol.

It is soluble in alcohol, acetone and benzene, the crystals from benzene efflorescing in air, apparently due to the loss of a benzene addendum. Insoluble in ether and petroleum spirit.

Found N = 19·55%

N = 19·58%



$$C_6H_4\begin{matrix}\diagup NH.CO \\ \quad\;\; | \\ \diagdown CO-N.N=C(CH_3)_2\end{matrix}$$

requires N = 19·35%.

When heated to 220° for 2 hours the melted solid charred slightly, and a very slight smell of dimethylketazine was noticed. On extraction with hot benzene the greater part of the acetone compound was recovered unchanged, hence the dimethylketazine of the main reaction cannot be furnished by a reaction of this type.

The Action of Acetonesemicarbazone on 3:Acetoneamino-tetrahydroquinazoline-2:4-dione.

Molecular quantities of the two reactants were heated together at 190° for 35 minutes in a glycerol bath. There was a brisk effervescence and a copious distillate of dimethylketazine, together with evolution of ammonia. Solution was complete in five minutes and soon a solid separated, the melt gradually solidifying. This behaviour is exactly parallel with the main reaction. The melt was cooled down, and extracted with dry ether and dry benzene, which removed a sticky product, but left large prismatic crystals (apparently formed from the melt) which melted at 285°. This, by a comparison with a known specimen was proved to be 3-aminotetrahydro-quinazoline-2:4-dione.

On recrystallising from absolute alcohol they assumed the usual opaque, irregular, prismatic form, still melting at 285° and showing no depression with a known specimen melting at 287°.

The evolution of ammonia was shown to be due probably to the decomposition ~~of~~

of acetonesemicarbazone, by heating it alone under similar conditions, when a steady stream of ammonia was obtained.

APPENDIX.

APPENDIX.

Preparation of *l*-Menthylamine.

Preparation of *l*-Menthone from *l*-Menthol.

Beckmann Ann., 250, (I889), 325.

The success of the preparation is assured only by careful attention to the temperature and the concentration of the acid used during the oxidation. With careful control it is possible to obtain the menthone practically free from unchanged *l*-menthol, and uncontaminated by "*d*-" menthone.

The oxidising mixture consisted of 60 grams (I mol.) of potassium dichromate, and 50 grams (2½ mols.) of concentrated sulphuric acid in 300 grams of water. This was brought to a temperature of 30° (at which the salt is completely soluble), and to it was added, en bloc, 45 grams of crystalline *l*-menthol, which immediately turned black owing to the formation of a chromium compound. On shaking, the mixture spontaneously became warmer, and at 53° a transient softening of the menthol indicated the formation of menthone. When the thermometer stood at 55° the reaction was complete, and thereafter the temperature began to fall. This temperature should not be ~~extended~~ exceeded, otherwise the "*d*" isomer may be formed. In general it was found necessary to apply heat to bring the temperature to 55°, this occupying about 45 minutes, after which the mixture was allowed to cool spontaneously.

The menthone, which formed a brownish, oily layer, was extracted with ether, the etherial solution being washed with water and very dilute caustic soda ; a clear solution being thus obtained.

For final purification, the menthone was steam distilled, being added to the distillation flask at the same rate at which it distilled over, thus avoiding a large excess in contact with boiling water.

The mobile, oily layer was separated and dried over ~~fused~~ anhydrous sodium sulphate.

The boiling point of pure *l*-menthone is 207° (*l*-menthol B.P. 212°) and the rotation

$l = ?$

$$\alpha_D^{20} = -25 \cdot 25^\circ.$$

A value of α_D greater than $-25 \cdot 25^\circ$ indicates the presence of traces of unchanged *l*-menthol.

The substance is not very stable to alkali, or to heating in glass vessels, or heating with water - a diminution of rotation resulting.

Rotation obtained $\alpha_D^{20°} = -24·94°$.

Yield 95% on menthol used.

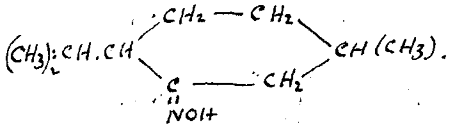
Rotation of *l*-Menthol used.

The fused compound at 50° gave $\alpha_D^{50} = -44°$ ($d = ·8769$) whence $[\alpha]_D^{50} = -50·19°$

The following figures are extracted from a table by Kenyon and Pickard (J.C.S., <u>107</u>, 36 etc.)

Temp.	Density.	α_D	$[\alpha]_D^t$	
20°	·9007		− 48·96°	
40°	·8848		− 49·55°	
[50°	·8769	−43·66°	− 49·80°	Interpolated.]
60°	·8690		− 50·02°	
80°			Falls after this.	

Preparation of *l*-Menthoneoxime.



20 parts of menthone (1 mol.) were dissolved in 2½

times this quantity of 90% alcohol, and to the mixture were added I2 parts (I·3 mols.) of hydroxylamine hydrochloride in a minimum quantity of water. Somewhat more than the calculated quantity of sodium bicarbonate was added slowly, and the mixture stood in ice overnight.

The oxime generally separated in a solid mass, but could be thrown by the addition of water, when, if sufficiently pure, it crystallised.

An oily mass difficult to crystallise indicated the presence of liquid *l*-iso-menthone.

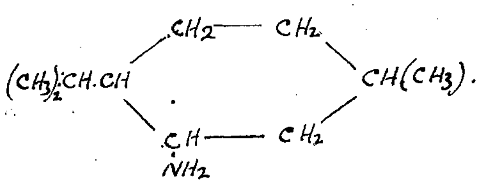
The oxime was filtered and pressed free from adherent liquid on a porous plate. Subsequent crystallisation from dilute alcohol gave a product melting at 58°.

Rotation $[\alpha]_D^{20} = -40\cdot75^\circ$ for 20% soln. in alcohol.

Yield 72% on menthone. used.

Reduction of *l*-Menthoneoxime to *l*-Menthylamine.

Wallach Ann. ~~275~~ 276. (I893), 296.



The reduction was carried out by means of sodium in boiling <u>absolute</u> alcohol, a good yield resulting only if the alcohol be water-free. The addition of sodium in small pieces was conveniently made through the upright limb of a  -shaped tube, to the sloping arm of which a condenser was attached.

20 grams of the oxime were dissolved in I50 ccs. of absolute alcohol, and to the boiling liquid about 30 grams of sodium were added, a few small pieces at a time. Towards the end of the reaction, as sodium ethoxide began to separate out, a little more alcohol was added as required.

The addition of sodium was continued until a test portion showed the absence of oxime by not reducing Fehling's solution.

The reduction mixture was then steam distilled. Alcohol passed over first, but when the distillate showed turbidity the receiver was changed. On standing, the *l*-menthylamine separated almost completely from the water and was dried over anhydrous sodium sulphate (or caustic potash sticks, Wallach loc.cit.) It was then distilled, in an atmosphere of purified hydrogen, directly into a polarimeter tube.

The alcoholic distillate contained a fair amount of the base which was recovered by adding hydrochloric acid to slight acidity and distilling off the solvent, when menthylamine hydrochloride separated in needles, from which the base was recovered by caustic soda in the usual manner.

Rotation obtained without further purification, $[\alpha]_D^{20} = -38\cdot7^\circ$.

Yield - 62% on oxime.used.

Overall yield =45-50% on menthol used.

l-Menthylamine is a colourless mobile liquid B.P. 206-7° and which fumes in ordinary laboratory air, combining readily with carbon dioxide.

$[\alpha]_D^{19} = -38\cdot07^\circ$ (Wallach loc.cit.)

$= -39\cdot97^\circ$ (Kenyon and Pickard J.C.S. 107, 36, 50, 55.)

l-Menthylamine hydrochloride crystallises in large needles from water and should not decompose below 280° (Wallach.)

$[\alpha]_D^{19} = -35\cdot66^\circ$ (Wallach.)

Preparation of Acetone-semicarbazone.

$(CH_3)_2C = N.NH.CO.NH_2$.

50 grams of semicarbazide hydrochloride were dissolved in a minimum quantity of water, and 43·5 grams of potassium acetate were dissolved in a small quantity of alcohol. The two solutions were mixed, shaken well and the precipitated sodium chloride filtered off, 30 grams of acetone being now added to the filtrate, and the mixture stood in the ice chest overnight. The precipitated semicarbazone was recrystallised from alcohol. A further crop could be obtained by adding more acetone.

M.P. 189° (decomposition.)
Yield 90% - 95%.

Preparation of Benzophenone Semicarbazone.

$(C_6H_5)_2C = N.NH.CO.NH_2$.

(Borsche and Merkwitz Ber. 37. 1904. 3177.)

31 grams of semicarbazide hydrochloride were dissolved in a small quantity of water, and 27 grams of potassium acetate dissolved in a minimum quantity of alcohol.

The two solutions were mixed and the precipitated potassium chloride filtered off. To the filtrate were added 50 grams of benzophenone and the whole boiled under a reflux for 6 -8 hours. On cooling white needles separated, which were filtered off and recrystallised from alcohol. The filtrate was reduced in bulk, when an oily layer separated; this crystallising on cooling. On recrystallising from alcohol a further crop of benzophenone semicarbazone was obtained. The mother liquors were worked up to recover the unchanged benzophenone.

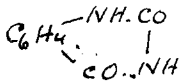
M.P. I64°-I65°.

Yield 65%.

Preparation of Tetrahydroquinazoline

(o -Benzoylene urea).

Griess Ber. 2 4I6,47.



$$C_6H_4\begin{cases} NH.CO \\ \quad\ \ | \\ CO.NH \end{cases}$$

Molecular proportions of urea and *o* -ammobenzoic acid were heated together for two hours at I40° . Ammonia was given off amid much frothing, and when cold the melt was extracted with hot alcohol to remove unchanged ammobenzoic acid and tarry matters. The insoluble residue was recrystallised from pyridine, giving pearly plates melting at 335° (uncorrected).

Preparation of ββ --Dichloropropane.

Friedel and Ladenberg Ann. 142, (1867), 315.
Herzfelder Ber. (1893), 1259.

To 200 grams of phosphorus pentachloride cooled in ice, were added, drop by drop during five hours, 50 grams of acetone, and the whole allowed to stand until all the solid phosphorus pentachloride had disappeared. The mixture was then gently warmed on the water bath and any distillate condensed in a cooled receiver. At this stage a low-boiling chlorinated propylene passed over between 25° and 35°.

To obtain the ββ-dichloropropane, the phosphorus oxychloride in the flask was slowly decomposed by adding water, and the resulting oil separated, washed and dried.

On distilling, the fraction passing over between 66° and 78° was collected and redistilled. It boiled at 69°.

SUMMARY.

SUMMARY.

The action of semicarbazones on aromatic amino-compounds, previously studied by Borsche, has been extended by the author to include amino-compounds of a more aliphatic nature. Benzylamine and active menthylamine react with ease, the increased basic nature of the molecule apparently giving an easier reaction than in the case of aniline.

Benzylamine gave acetone-δ-benzylsemicarbazone $(CH_3)_2C=N.NH.CO.NH.CH_2.C_6H_5$. when heated with acetonesemicarbazone.

This substance, on hydrolysis with hydrochloric acid, gave the hydrochloride of δ-benzylsemicarbazide from which the free base was obtained by sodium ethoxide.

$NH_2.NH.CO.NH.CH_2C_6H_5$.

It readily formed a benzylidene derivative with benzaldehyde.

l-Menthylamine also reacted easily with acetonesemicarbazone to give acetone-δ·*l*-menthyl-

-semicarbazone from which the active δ-substituted semicarbazide was obtained by hydrolysis.

$$NH_2.NH.CO\,NH.C_{10}H_9.$$

It readily reacted with benzaldehyde to give a benzylidene derivative.

It is expected that this active semicarbazide will be of service in the resolution of certain racemic aldehydes and ketones.

The reaction was next extended to the esters of o-, m-, and p-aminobenzoic acids.

Ethyl-m-aminobenzoate reacted readily with acetonesemicarbazone giving acetone-δ-3-carbethoxy-phenylsemicarbazone.

$$(CH_3)_2C=N.NH.CO.NH.C_6H_4.COOC_2H_5.$$

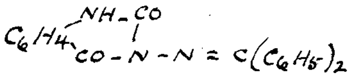
which on acid hydrolysis gave the corresponding δ-substituted semicarbazide:

$$NH_2.NH.CO\,NH.C_6H_4.COOC_2H_5.$$

Ethyl-p-aminobenzoate reacted with both acetonesemicarbazone and benzophenonesemicarbazone to give the corresponding δ-substituted semicarbazones, but on acid hydrolysis the δ-substituted semicarbazides were not obtained ; they apparently were unstable in the presence of the acid.

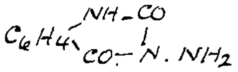
With Methylanthranilate both semicarbazones yielded quinazoline derivatives due to the elimination of alcohol and the formation of a bicylic molecule

Benzophenonesemicarbazone gave <u>3-benzophenoneaminotetrahydroquinazoline-2:4-dione</u>.



$$C_6H_4\begin{array}{l}\diagup NH-CO \\ \quad\quad\quad\quad\;\; | \\ \diagdown CO-N-N=C(C_6H_5)_2\end{array}$$

which when hydrolysed by dilute acid, gave <u>3-aminotetrahydroquinazoline-2:4-dione</u>.

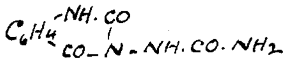


$$C_6H_4\begin{array}{l}\diagup NH-CO \\ \quad\quad\quad\quad\;\; | \\ \diagdown CO-N.NH_2\end{array}$$

Acetonesemicarbazone did not give the 3-acetoneamino-compound, but gave directly the 3-amino-compound and that under anhydrous conditions which precluded the possibility of hydrolysis of the acetone derivative.

This reaction was closely studied and an explanation of its probable course given.

This assumes the elision of $HNCO$ from an intermediate carbamino-derivative.



$$C_6H_4\left<\begin{array}{l}NH\cdot CO\\ \qquad\quad | \\ CO-N\cdot NH\cdot CO\cdot NH_2\end{array}\right.$$

which is derived from the interaction of the 3-acetone-amino-derivative, presumably formed in the reaction, and a molecule of acetonesemicarbazone.

The acetone derivative was finally obtained by boiling the 3-aminoquinazoline compound in ordinary acetone, and was shown to react with acetonesemicarbazone as suggested.

The argument is further supported by the behaviour of analogous carbamino-compounds recorded in the chemical literature.

It was noticed that acetonesemicarbazone in general, showed greater reactive power towards amines than did benzophenonesemicarbazone.

ABBREVIATIONS.

J.C.S.	Journal of the Chemical Society.
P.	Proceedings of the Chemical Society.
J.Am.C.Soc.	Journal of the American Chemical Society.
Ber.	Berichte der Deutschen Chemischen Gesellschaft.
Ann.	Liebig's Annalen der Chemie.

BIBLIOGRAPHY.

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Action of Amines on Semicarbazones.

Borsche etc. Ber., 34, (1901), 4299.
Ber., 37, (1904), 3177.
Ber., 38, (1905), 831.
Wilson, Hopper & Crawford J.C.S., 121, 867.

Hydrazine; Decomposition of.

Curtius Ber., 26, 405.
Ber., 27, 57.

α -Phenylsemicarbazide ; Action of. heat on.

Poth and Bailey J.Am.C.S. 45, 3008.

Benzophenonesemicarbazone,

Action of heat on:

Borsche & Merkwitz Ber., 37, (1904), 3177.

l-Menthylamine.

Wallach	Ann. 276, (1893), 327.
Kenyon & Pickard	J.C.S. 107 pp. 36, 50, 55.
Pope & Read	J.C.S., 97, (1910), 997.
Neville & Pickard	J.C.S., 85 (1904), 690.

Isomeric Menthylamines.

Tutin & Kipping	J.C.S., 85 (1904), 69.
Beckmann	Ann. 250, (1889), 322.

l-Menthylamine ; Preparation of:

Beckmann	Ann. 250, (1889), 325.
Wallach	Ann. 276, (1893), 296.

3 Aminotetrahydroquinazoline-2:4-dione.

Kunckell	Ber 43 (1910) 1021.

~~3-Amino~~Tetrahydroquinazoline-2:4-dione.

Kunckell	Loc. cit.
Griess	Ber., 2, 419.

Elimination of HNCO.

Auwers Buschmann, Heidenreich
Ann. 435 3 277.
Posner Ber., 34 (1901) 3976.

Hydrazide of p-Aminobenzoic Acid.

Curtius J.Pr. (2) 94, 296.

Methane, Combustion of

Dunstan & Carr P. 1896. 12 48.
Haas J.C.S. 1906, 59, 570.

BB Dichloropropane.

Friedel & Ladenberg Ann. 142 (1867), 315.
Herzfelder Ber., 26 (1893), 1259.